(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 May 2015 (14.05.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/069956 A2

(51) **International Patent Classification**:
***C06B 43/00*** (2006.01)

(21) **International Application Number**:
PCT/US2014/064441

(22) **International Filing Date**:
6 November 2014 (06.11.2014)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:

| | | |
|---|---|---|
| 61/900,878 | 6 November 2013 (06.11.2013) | US |
| 61/900,946 | 6 November 2013 (06.11.2013) | US |
| 61/900,919 | 6 November 2013 (06.11.2013) | US |

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(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

**Published**:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2015/069956 A2

(54) **Title**: NOVEL FORMULATIONS

(57) **Abstract**: Provided are novel formulations of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4- chlorophenyl dihydrogen phosphate as described below and uses thereof.

# NOVEL FORMULATIONS

**[0001]** This application claims priority to U.S. Provisional Application No. 61/900,878 filed November 6, 2013, U.S. Provisional Application No. 61/900,946 filed November 6, 2013, and U.S. Provisional Application No. 61/900,919 filed November 6, 2013.

## TECHNICAL FIELD

**[0002]** Provided are novel formulations of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate as described below and uses thereof.

## BACKGROUND

**[0003]** Aquaporins are cell membrane proteins that act as molecular water channels to mediate the flow of water in and out of the cells. While there is some degree of passive diffusion or osmosis of water across cell membranes, the rapid and selective transport of water in and out of cells involves aquaporins. These water channels selectively conduct water molecules in and out of the cell, while blocking the passage of ions and other solutes, thereby preserving the membrane potential of the cell. Aquaporins are found in virtually all life forms, from bacteria to plants to animals. In humans, they are found in cells throughout the body.

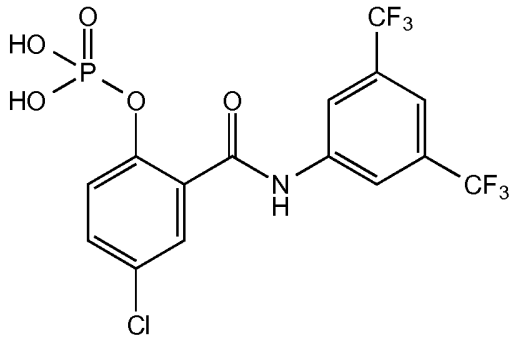
**[0004]** Aquaporin inhibitors, e.g., inhibitors of AQP4 and/or AQP2, may be of utility in the treatment or control of diseases of water imbalance, for example edema (particularly edema of the brain and spinal cord), hyponatremia, and excess fluid retention, as well as diseases such as epilepsy, retinal ischemia and other diseases of the eye, myocardial ischemia, myocardial ischemia/reperfusion injury, myocardial infarction, myocardial hypoxia, congestive heart failure, sepsis, and neuromyelitis optica, as well as migraines.

**[0005]** Prior to Applicants' filings, there have been no known specific, validated inhibitors of aquaporins, for example AQP4 or AQP2. Certain antiepileptic or sulfonamide drugs (e.g., acetylsulfanilamide, acetazolamide, 6-ethoxy-benzothiazole-2-sulfonamide, topiramate, zonisamide, phenytoin, lamotrigine, and sumatriptan) were at one point reported to be possible inhibitors of AQP4, but this later proved to be incorrect. Yang et al., Bioorganic and Medicinal Chemstry, 2008, 16, 7489-7493. No direct inhibitors of AQP2 have been reported.

**[0006]** Thus, there is a need for compounds that selectively inhibit aquaporins. In addition, there is a need for formulations that may be used to deliver compounds that selectively inhibit aquaporins and may be administered easily to patients.

## BRIEF SUMMARY

**[0007]** Provided are pharmaceutical compositions comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate (Formula I).




Formula I

and uses thereof.

**[0008]** Also provided are kits comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate.

**[0009]** Also provided is a method of treating or controlling a disease or condition mediated by an aquaporin, e.g., diseases or conditions of water imbalance and other diseases, for example,

edema of the brain or spinal cord, e.g., cerebral edema, e.g. cerebral edema consequent to head trauma, ischemic stroke, glioma, meningitis, acute mountain sickness, epileptic seizure, infection, metabolic disorder, hypoxia (including general systemic hypoxia and hypoxia due to cardiac arrest), water intoxication, hepatic failure, hepatic encephalopathy, diabetic ketoacidosis, abscess, eclampsia, Creutzfeldt-Jakob disease, lupus cerebritis, cardiac arrest, microgravity and/or radiation exposure, or an invasive central nervous system procedure, e.g., neurosurgery, endovascular clot removal, spinal tap, aneurysm repair, or deep brain stimulation or, e.g., spinal cord edema consequent to spinal cord trauma, e.g., spinal cord compression; or

optic nerve edema, e.g., optic nerve edema consequent to microgravity and/or radiation exposure; or

retinal edema; or

pulmonary edema; or

hyponatremia or excessive fluid retention, e.g., consequent to heart failure (HF), liver cirrhosis, nephrotic disorder, syndrome of inappropriate antidiuretic hormone secretion (SIADH), or infertility treatment; or

ovarian hyperstimulation syndrome; or

epilepsy, retinal ischemia or other diseases of the eye associated with abnormalities in intraocular pressure and/or tissue hydration, myocardial ischemia, myocardial ischemia/reperfusion injury, myocardial infarction, myocardial hypoxia, congestive heart failure, sepsis, neuromyelitis optica, or glioblastoma; or

fibromyalgia; or

multiple sclerosis; or

migraines,

comprising administering to a patient in need thereof a pharmaceutical composition comprising a therapeutically effective amount of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate.

**[0010]** Further areas of applicability of the present disclosure will become apparent from the detailed description provided hereinafter. It should be understood that the detailed description and specific examples, while indicating the preferred embodiment of the disclosure, are intended for purposes of illustration only and are not intended to limit the scope of the disclosure.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0011]** Figure 1 depicts percent survival curves for the water toxicity mouse model using 0.76 mg/kg N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide (Compound 1).

**[0012]** Figure 2 depicts inhibition of cerebral edema formation by N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide (Compound 1) in the mouse water toxicity model by MRI brain volume analysis, with n=14 mice/treatment. A time course of edema formation is shown comparing no drug vs. N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide (Compound 1) at 0.76 mg/kg. The first time point at 5.67 min coincides with the scan slice at the middle of the brain during the first post-injection scan. Other time points are placed in a similar manner. The data is fitted to a single exponential equation:

$V/V_0 = V_i + dV_{max}(1-e^{(-kt)})$; where $V/V_0$ = relative brain volume, $V_i$ = initial relative brain volume, $dV_{max}$ = maximum change in relative brain volume, k = first order rate constant ($min^{-1}$), and t = time in minutes.

**[0013]** Figure 3 depicts the calcein fluorescence end-point assay used for high throughput screening.

**[0014]** Figure 4 depicts hit validation using the Cell Bursting Aquaporin Assay; inset shows the structure of 5-chloro-*N*-(3,5-dichlorophenyl)-2-hydroxybenzamide (Compound 3).

**[0015]** Figure 5 depicts reduction in intracranial pressure (ICP) in the mouse water toxicity model with N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide (Compound 1) at 0.76 mg/kg.

**[0016]** Figure 6 depicts plasma and serum levels of N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide (Compound 1) converted from 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl phosphate bis ethanolamine salt.

**[0017]** Figure 7 depicts mouse middle cerebral artery occlusion (MCAo) model of ischemic stroke.

**[0018]** Figure 8 depicts relative change in hemispheric brain volume in the mouse middle cerebral artery occlusion (MCAo) model.

**[0019]** Figure 9 depicts neurological outcome following MCAo in mice treated with saline (no drug, •) or 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl phosphate disodium salt (o) (Compound 5).

**[0020]** Figure 10 depicts plasma and serum levels of N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide (Compound 1) converted from a solution of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate and Tris-Base.

## DETAILED DESCRIPTION

**[0021]** The following description of the preferred embodiments is merely exemplary in nature and is in no way intended to limit the present disclosure, its application, or uses.

**[0022]** As used herein, "therapeutically effective amount" refers to an amount effective, when administered to a human or non-human patient, to provide a therapeutic benefit such as amelioration of symptoms, slowing of disease progression, or prevention of disease. The specific dose of substance administered to obtain a therapeutic benefit will, of course, be determined by

the particular circumstances surrounding the case, including, for example, the specific substance administered, the route of administration, the condition being treated, and the individual being treated.

**[0023]** As used herein, "sodium phosphate" refers to sodium dihydrogen phosphate ($NaH_2PO_4$), disodium hydrogen phosphate ($Na_2HPO_4$), and trisodium phosphate ($Na_3PO_4$).

**[0024]** As used herein, "potassium phosphate" refers to potassium dihydrogen phosphate ($KH_2PO_4$), dipotassium hydrogen phosphate ($K_2HPO_4$), and tripotassium phosphate ($K_3PO_4$).

**[0025]** As used herein, "bolus" refers to administration of a therapeutic agent in a single injection that lasts for a relatively short period of time, e.g., about 60 minutes or less, about 30 minutes or less, about 20 minutes or less, about 10 minutes or less, about 5 minutes or less, e.g., about 3 minutes or less. A bolus may rapidly deliver a therapeutically effective amount of a therapeutic agent to the blood.

**[0026]** As used herein, "patient" includes human or non-human (i.e., animal) patient. In a particular embodiment, the invention encompasses both human and nonhuman. In another embodiment, the invention encompasses nonhuman. In another embodiment, the term encompasses human.

**[0027]** As used herein, "fairly rapid" with respect to onset of action means that the time it takes after a compound is administered for a response to be observed is 30 minutes or less, for example 20 minutes or less, for example 15 minutes or less, for example 10 minutes or less, for example 5 minutes or less, for example 1 minute or less.

**[0028]** As used herein, "alkyl" is a saturated hydrocarbon moiety, preferably having one to six carbon atoms, preferably having one to four carbon atoms, which may be linear or branched. A "$C_{1-4}$-alkyl" is an alkyl having one to four carbon atoms.

**[0029]** As used herein "alkylene" is a saturated hydrocarbon moiety, preferably having one to six carbon atoms, preferably having one to four carbon atoms, which may be linear or branched and which has two points of attachment. A $C_{1-4}$-alkylene is an alkylene having from one to four carbon atoms. For example, $C_1$-alkylene is methylene ($-CH_2-$).

**[0030]** As used herein, "alkoxy" is an alkyl ether radical, alkyl-O-, wherein the term alkyl is as defined above. A "$C_{1-4}$-alkoxy" is an alkoxy having one to four carbon atoms.

**[0031]** As used herein, "aryl" is a mono or polycyclic (e.g., bicyclic) aromatic hydrocarbon, preferably phenyl, which may be optionally substituted, e.g., optionally substituted with one or

more groups independently selected from $C_{1-6}$ alkyl (e.g., methyl), halogen (e.g., Cl or F), $C_{1-6}$-haloalkyl (e.g., trifluoromethyl), hydroxy, and carboxy. In some embodiments, aryl, in addition to being substituted with the groups disclosed herein, is further substituted with an aryl or a heteroaryl to form, e.g., biphenyl or pyridylphenyl.

**[0032]** As used herein, "heteroaryl" is an mono or polycyclic (e.g., bicyclic) aromatic moiety wherein one or more of the atoms making up the aromatic ring is sulfur or nitrogen rather than carbon, e.g., pyridyl or thiadiazolyl, which may be optionally substituted, e.g., optionally substituted with one or more groups independently selected from $C_{1-6}$ alkyl (e.g., methyl), halogen (e.g., Cl or F), $C_{1-6}$-haloalkyl (e.g., trifluoromethyl), hydroxy, and carboxy.

**[0033]** As used herein, "hydroxy" is -OH.

**[0034]** As used herein, "carboxy" is -COOH.

**[0035]** As used herein, "halogen" as used herein is F, Cl, Br, or I.

**[0036]** As used herein, "haloalkyl" is a saturated hydrocarbon moiety, preferably having one to six carbon atoms, preferably having one to four carbon atoms, which may be linear or branched, and is mono-, di- or tri- substituted with halogen. For di- or tri- substituted haloalkyl, the halogens may be the same (e.g., dichloromethyl) or different (e.g., chlorofluoromethyl).

**[0037]** Expression of Aquaporin-4 (AQP4) is upregulated in animal models of trauma, stroke and water intoxication, as well as around human malignant brain tumors. Aquaporin-4 (AQP4) has been shown to play a critical role in the development of cerebral and spinal cord edema. AQP4 provides the primary route for water movement across the blood-brain barrier (BBB) and *glia limitans*. AQP4 knockout mice, without the APQ4 gene, have improved survival compared to wild-type mice in models of ischemic stroke, water toxicity, bacterial meningitis, and spinal cord compression.

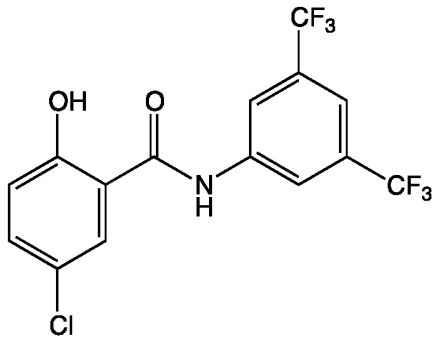
**[0038]** Cerebral edema (CE) may be generally divided into 2 major categories: vasogenic and cytotoxic. Vasogenic cerebral edema may occur when a breach in the BBB allows water and solutes to diffuse into the brain. It has been reported that AQP4-null mice have increased brain edema in a model of subarachnoid hemorrhage, suggesting that AQP4 may be required for the clearance of water collected in intercellular space. In contrast, cytotoxic cerebral edema may be initiated by ischemia which may result in reduced plasma osmolality rather than a disrupted BBB. Ischemia may lead to a drop in ATP levels, which is thought to slow the Na-K ATPase pump resulting in an uptake of $Na^+$ and $Cl^-$ through leakage pathways. The net effect may be a

cellular osmotic imbalance, drawing $H_2O$ into cells – astrocytes more so than neurons – and leading to increased intracranial pressure (ICP). Mouse models for ischemic stroke, water toxicity, bacterial meningitis, and spinal-cord compression fall into this category. In these models, AQP4-null mice have been reported to have reduced CE pointing to AQP4 as the central pathway for water movement into the brain during the formation of cytotoxic CE. However, cytotoxic and vasogenic edema are not sharply divided categories; an injury that initially causes cytotoxic edema may be followed later, e.g., within the next hours to days, by vasogenic edema. This may suggest different treatments for cerebral edema at different times.

**[0039]** AQP4 inhibitors may be of further utility for certain ailments where control of AQP4-medited water movement may augment neuroexcitation (by alteration of neuronal potassium homeostasis) and prove beneficial by reducing neuronal excitation, for example ailments such as fibromyalgia, multiple sclerosis, migraines and seizures (in particular but not limited to seizures associated with epilepsy).

**[0040]** Aquaporin-2 (AQP2) is the primary route of water movement at the collecting duct in the kidney. Blocking this water channel would lower water reabsorption without incurring electrolyte imbalances or interfering with vasopressin receptor-mediated signaling. Evidence that an AQP2 blocker would not produce electrolyte imbalances, and instead be an effective treatment for hyponatremia, comes from patients with diabetes insipidus who lack functional AQP2. They exhibit chronic aquaresis but – if normal hydration is maintained – do not demonstrate any other consequence of their long-term loss of AQP2 function.

**[0041]** 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is a prodrug of N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide (Compound 1, shown below).




Compound 1

**[0042]** Certain uses of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate and of N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide are described in International Patent Application No. PCT/US2013/040194, which is incorporated herein by reference in entirety.

**[0043]** In stroke or other severely debilitating diseases or conditions, for example where the patient may be unconscious or unable to swallow, an IV infusion or IV bolus may be preferred. In addition, when a patient has suffered a stroke, or traumatic brain or spinal cord injury, rapid achievement of therapeutically effective amounts of a therapeutic agent, may be important to a successful therapeutic outcome. In the acute care settings in the hospital, particularly for stroke, traumatic brain injury, and myocardial infarction, best practices are to administer drugs via IV. However, a therapeutic agent with only a limited solubility in water and/or physiological media and/or limited stability, may make parenteral administration, e.g., intravenous, intramuscular, intraperitoneal, subcutaneous, epidural, sublingual, or intracerbral, of the therapeutic agent challenging. While N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide is an aquaporin inhibitor, its solubility in water is 3.8 μg/ml. Alanine and di-alanine prodrugs of N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide are insoluble in water and pH 7.4 water (Example 16). A prodrug salt form of N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide does show improved solubility – specifically, the solubility of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl phosphate disodium salt in water is 1 mg/ml. However, prodrug salt forms of N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide may revert to N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide even in the solid state. For instance, 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl hydrogen phosphate mono sodium salt ("mono sodium salt"), 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl phosphate bis sodium salt ("bis sodium salt"), and 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl phosphate bis ethanolamine salt ("bis ethanolamine salt") show hydrolysis in the solid state at about 1% per day. Thus, stable pharmaceutical compositions which may allow rapid achievement of therapeutically effective amounts of N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide are needed.

**[0044]** Accordingly, in one embodiment, provided are novel formulations of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate which may allow

rapid achievement of therapeutically effective amounts of N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide.

**[0045]** In one embodiment, provided is a pharmaceutical composition (Composition I) comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate (Formula I) and a pharmaceutically acceptable excipient.

**[0046]** Further provided is Composition I as follows:

1.1 Composition I wherein the composition comprises 0.1 or 0.25 mg to 2.0 g of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate, e.g., from about 0.1 or 0.25 mg to 75 or 600 mg, e.g., from about 0.1 or 0.25 or 1 or 2 or 5 or 10 or 15 or 20 mg to 50, 75, 100, 125, 150, 200, 300, 350, 400, 500, or 600 mg, or 1 g, 1.5 g, or 2.0 g, e.g., from about 5 to 50, 75, 100, 125, 150, 200, 300, 350, 400, 500, or 600 mg, or 1 g, 1.5 g, or 2 g, e.g., from about 5 to 500 mg, e.g., from about 5 to 300 or 350 mg, e.g., from about 5 to 200 mg, e.g., from about 25 to 500 mg, e.g., from about 25 to 300 or 350 mg, e.g., from about 25 to 200 mg, e.g., from about 15, 20, 30, 35, 50, or 100 to 150, 200, 300, 350, 400, 450, 500, 550, or 600 mg, e.g., from about 0.5 or 1 mg to 50 mg, e.g., from about 0.5 or 1 mg to 20 mg, e.g., from about 0.5 or 1 mg to 10 mg, e.g., from about 1 or 2 or 5 mg to 10 or 20 mg, e.g., from about 1 or 2 or 3 or 4 to 5 mg, e.g., about 35 mg, e.g., about 350 mg, or wherein the composition comprises 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate in an amount sufficient to provide

0.1 or 0.25 mg to 2.0 g of N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide, e.g., in an amount sufficient to provide from about 0.1 or 0.25 mg to 75 or 600 mg, e.g., from about 0.1 or 0.25 or 1 or 2 or 5 or 10 or 15 or 20 mg to 50, 75, 100, 125, 150, 200, 300, 350, 400, 500, or 600 mg, or 1 g, 1.5 g, or 2.0 g, e.g., from about 5 to 50, 75, 100, 125, 150, 200, 300, 350, 400, 500, or 600 mg, or 1 g, 1.5 g, or 2 g, e.g., from about 5 to 500 mg, e.g., from about 5 to 300 or 350 mg, e.g., from about 5 to 200 mg, e.g., from about 25 to 500 mg, e.g., from about 25 to 300 or 350 mg, e.g., from about 25 to 200 mg, e.g., from about 15, 20, 30, 35, 50, or 100 to 150, 200, 300, 350, 400, 450, 500, 550, or 600 mg, e.g., from about 0.5 or 1 mg to 50 mg, e.g., from about 0.5 or 1 mg to 20 mg, e.g., from

about 0.5 or 1 mg to 10 mg, e.g., from about 1 or 2 or 5 mg to 10 or 20 mg, e.g., from about 1 or 2 or 3 or 4 to 5 mg, e.g., about 35 mg, e.g., about 350 mg.

1.2 Composition I wherein the composition comprises 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate in an amount sufficient to provide a dose of 0.01 or 0.1 or 0.5 mg/kg to 1 or 5 or 10 or 15 mg/kg of N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide, e.g., a dose of about 0.05 to 1 or 5 mg/kg, e.g., a dose of about 0.05 to 0.1, 0.2, 0.3, 0.4, 0.5, 1, 5, 10 or 20 mg/kg, e.g., a dose of about 0.5 to 1, 2, 3, 4, 5 or 10 or 20 mg/kg, e.g, a dose of about 1 to 2, 3, 4, 5, 10, 20 or 50 mg/kg.

1.3 Composition I, 1.1, or 1.2 wherein the pharmaceutically acceptable excipient comprises one or more bases, e.g., a base wherein upon dissolution of the composition in a solvent, e.g., an aqueous solution, the composition has a pH between 7, 7.5, or 8 and 10.5, e.g., between about 7, 7.5, or 8 and 9.5, e.g., between about 7 or 7.5 and 8, e.g., between about 7.5 and 8.5, e.g., about 7.5, e.g., about 8.5, e.g., between about 8 and 8.5, e.g., about 8.2, e.g., a base wherein a conjugate acid of the base has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, e.g., wherein the one or more bases are one or more of:

a) a $C_{1-8}$-alkyl mono-, di-, or tri- carboxylic acid salt, e.g., a citrate salt, e.g, a metal citrate salt (e.g., an alkali and/or alkaline citrate salt, e.g., an alkali citrate salt, e.g., sodium citrate and/or potassium citrate), e.g., a tartrate salt (e.g., a metal tartrate salt, an alkali tartrate, e.g., sodium tartrate), e.g., a succinate salt (e.g., a metal succinate salt, e.g., an alkali succinate, e.g., disodium succinate), and/or e.g., a lactate salt (e.g., a metal lactate salt, e.g., an alkali lactate, e.g., sodium lactate),

b) a phosphate salt, e.g., a metal phosphate salt (e.g., an alkali and/or alkaline phosphate salt, e.g., an alkali phosphate salt, e.g., sodium phosphate (e.g., $NaH_2PO_4$ and/or $Na_2HPO_4$) and/or potassium phosphate (e.g., $KH_2PO_4$ and/or $K_2HPO_4$)),

c) an amine and/or a salt thereof (e.g., morpholine, piperazine, benethamine, benzathine, trimethylglycine, chloroprocaine,

hydrabamine, an amino acid (e.g., arginine and/or lysine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, dimethylethanolamine, diethylamine, diethylethanolamine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9,

d) a metal chloride salt (e.g., zinc chloride),

e) an acetate salt, e.g., a metal acetate salt (e.g., an alkali and/or alkaline acetate salt, e.g., an alkali acetate salt, e.g., sodium acetate and/or potassium acetate),

f) a hydroxide and/or alkoxide salt, e.g., a metal hydroxide and/or metal alkoxide salt (e.g., a quarternary ammonium hydroxide, e.g., ammonium hydroxide and/or choline hydroxide, lithium hydroxide, aluminum hydroxide, e.g., an alkali and/or alkaline hydroxide salt, e.g., sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, and/or magnesium ethoxide, e.g., sodium hydroxide), and/or

g) a carbonate and/or bicarbonate salt, e.g., a metal carbonate and/or metal bicarbonate salt (e.g., an alkali and/or alkaline carbonate salt, e.g., an alkali and/or alkaline bicarbonate salt, e.g., sodium bicarbonate),

h) a borate salt, e.g., a metal borate salt (e.g., an alkali borate salt, e.g., sodium borate),

e.g., one or more of sodium citrate, $Na_2HPO_4$, tris(hydroxymethyl)aminomethane, and a tris(hydroxymethyl)aminomethane salt (e.g., tris acetate), e.g., one or more of sodium citrate, $Na_2HPO_4$, and tris(hydroxymethyl)aminomethane, e.g., one or more of sodium citrate and $Na_2HPO_4$, e.g., $Na_2HPO_4$, e.g., tris(hydroxymethyl)aminomethane.

1.4 Composition I, 1.1, or 1.2 wherein the pharmaceutically acceptable excipient comprises one or more bases, e.g., a base wherein upon dissolution of the composition in an aquous solution the composition has a pH between 7, 7.5, or 8 and 10.5, e.g., between about 7, 7.5, or 8 and 9.5, e.g., between about 7 or 7.5 and 8, e.g., between about 7.5 and 8.5, e.g., about 7.5, e.g., about 8.5, e.g., between about 8 and 8.5, e.g., about 8.2, e.g., a base wherein a conjugate acid of the base has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, e.g., wherein the one or more bases are one or more of:

a) a metal citrate salt (e.g., an alkali and/or alkaline citrate salt, e.g., an alkali citrate salt, e.g., sodium citrate and/or potassium citrate),

b) a metal phosphate salt (e.g., an alkali and/or alkaline phosphate salt, e.g., an alkali phosphate salt, e.g., sodium phosphate (e.g., $NaH_2PO_4$ and/or $Na_2HPO_4$) and/or potassium phosphate (e.g., $KH_2PO_4$ and/or $K_2HPO_4$), e.g., sodium phosphate (e.g., $Na_2HPO_4$)),

c) an amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a

salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9,

d) a metal acetate salt (e.g., an alkali and/or alkaline acetate salt, e.g., an alkali acetate salt, e.g., sodium acetate and/or potassium acetate),

e) a metal hydroxide salt (e.g., an alkali and/or alkaline hydroxide salt, e.g., sodium hydroxide, potassium hydroxide, calcium hydroxide, and/or magnesium hydroxide, e.g., sodium hydroxide),

f) a metal carbonate and/or bicarbonate salt (e.g., an alkali and/or alkaline carbonate salt, e.g., an alkali and/or alkaline bicarbonate salt, e.g., sodium bicarbonate), and/or

g) a metal borate salt (e.g., an alkali borate salt, e.g., sodium borate),

e.g., one or more of sodium citrate, $Na_2HPO_4$, tris(hydroxymethyl)aminomethane, and a tris(hydroxymethyl)aminomethane salt (e.g., tris acetate), e.g., one or more of sodium citrate, $Na_2HPO_4$, and tris(hydroxymethyl)aminomethane, e.g., one or more of sodium citrate and $Na_2HPO_4$, e.g., $Na_2HPO_4$, e.g., tris(hydroxymethyl)aminomethane.

1.5 Composition 1.3 or 1.4 wherein the composition comprises 1 or 5 mg to 200 or 500 mg of the one or more bases, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.6 Composition 1.3-1.5 wherein the one or more bases comprise one or more of a metal citrate salt (e.g., sodium citrate) and a metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$).

1.7 Composition 1.3-1.6 wherein the one or more bases comprise a metal citrate salt (e.g., sodium citrate).

1.8 Composition 1.7 wherein the composition comprises 1 or 5 mg to 200 or 500 mg of a metal citrate salt (e.g., sodium citrate), e.g., from about 1 or 5 or 10 mg to 15,

20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.9 Composition 1.3-1.8 wherein the one or more bases comprise a metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$).

1.10 Composition 1.9 wherein the composition comprises 1 or 5 mg to 200 or 500 mg of a metal phosphate salt, e.g., sodium phosphate, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.11 Composition 1.3-1.10 wherein the one or more bases comprise sodium phosphate, e.g., $Na_2HPO_4$.

1.12 Composition 1.11 wherein the composition comprises 1 or 5 mg to 200 or 500 mg sodium phosphate, e.g., $Na_2HPO_4$, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.13 Composition 1.3-1.12 wherein the one or more bases comprise an amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9.

1.14 Composition 1.13 wherein the composition comprises 1 or 5 mg to 200 or 500 mg of the amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.15 Composition 1.3-1.14 wherein the one or more bases comprise a mono- and/or poly-hydroxyalkylamine and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine).

1.16 Composition 1.15 wherein the composition comprises 1 or 5 mg to 200 or 500 mg of the mono- and/or poly-hydroxyalkylamine and/or salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., -

$CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., –$CH_2$–$CH_2$–, e.g., –$C(CH_2)_3$–, e.g., one $R^8$ is –$CH_3$ and another $R^8$ is –$(CH_2)_6$–) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.17 Composition 1.3-1.16 wherein the one or more bases comprise $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., -$CH_2CH_3$, e.g., -$CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., –$CH_2$–$CH_2$–, e.g., –$C(CH_2)_3$–, e.g., one $R^8$ is –$CH_3$ and another $R^8$ is –$(CH_2)_6$–) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine).

1.18 Composition 1.17 wherein the composition comprises 1 or 5 mg to 200 or 500 mg of $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., -$CH_2CH_3$, e.g., -$CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., –$CH_2$–$CH_2$–, e.g., –$C(CH_2)_3$–, e.g., one $R^8$ is –$CH_3$ and another $R^8$ is –$(CH_2)_6$–) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.19 Composition 1.3-1.18 wherein the one or more bases comprise tris(hydroxymethyl)aminomethane and/or meglumine, e.g., tris(hydroxymethyl)aminomethane, e.g., meglumine.

1.20 Composition 1.19 wherein the composition comprises 1 or 5 mg to 200 or 500 mg tris(hydroxymethyl)aminomethane, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg and/or wherein the composition comprises 1 or 5 mg to 200 or 500 mg meglumine, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.21 Composition 1.3-1.20 wherein the one or more bases comprise a tris(hydroxymethyl)aminomethane salt, e.g., tris(hydroxymethyl)aminomethane acetate.

1.22 Composition 1.21 wherein the composition comprises 1 or 5 mg to 200 or 500 mg of the tris(hydroxymethyl)aminomethane salt (e.g., tris(hydroxymethyl)aminomethane acetate), e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g, from about 15, 20, 30, or 50 to 100, 200, 250, 400, 450, 500, 600, or 700 mg, e.g., from about 1 or 5 mg to 200 or 500 mg tris(hydroxymethyl)aminomethane acetate, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.23 Composition 1.3-1.22 wherein the one or more bases comprise a base, e.g., an amine and/or a salt thereof, wherein a conjugate acid of the base has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9.

1.24 Composition 1.23 wherein the composition comprises 1 or 5 mg to 200 or 500 mg of a base, e.g., an amine and/or a salt thereof, wherein a conjugate acid of the base

has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.25 Composition 1.1-1.24 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to the one or more bases is at least 1:1, e.g, wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to the one or more bases is at least 2:1.

1.26 Composition 1.1-1.25 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to the one or more bases is at least 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.27 Composition 1.26 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to a metal citrate salt (e.g., sodium citrate) is at least 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.28 Composition 1.26 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to a metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$) is at least 1:1, e.g., at least 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.29 Composition 1.26 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to the amine and/or salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a

mono- and/or poly-hydroxyalkylamine, and/or salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, is at least 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.30 Composition 1.29 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to the mono- and/or poly-hydroxyalkylamine and/or salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), is at least 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.31 Composition 1.30 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to

$(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $-CH_2-CH_2-$, e.g., $-C(CH_2)_3-$, e.g., one $R^8$ is $-CH_3$ and another $R^8$ is $-(CH_2)_6-$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), is 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.32 Composition 1.31 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to tris(hydroxymethyl)aminomethane is at least 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.33 Composition 1.31 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to the tris(hydroxymethyl)aminomethane salt (e.g, tris(hydroxymethyl)aminomethane acetate) is at least 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10, e.g., wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to tris(hydroxymethyl)aminomethane acetate is at least 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.34 Composition 1.26 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to

a base, e.g., an amine and/or a salt thereof, wherein a conjugate acid of the base has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, is at least 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.35 Composition I or 1.1-1.34 wherein the composition comprises one or more bulking agents which may provide an adequate structure to the lyophilized cake, e.g., one or more of mannitol, lactose, sucrose, trehalose, sorbitol, glucose, raffinose, arginine, glycine, histidine, dextran (e.g., dextran 40), polyvinylpyrrolidone, polyethylene glycol, and polypropylene glycol, e.g., one or more of mannitol, glucose, sucrose, lactose, trehalose, and dextran (e.g., dextran 40).

1.36 Composition I or 1.1-1.35 wherein the composition comprises 5 or 10 or 50 mg to 2 or 5 g of one or more bulking agents, e.g., from about 50 or 100 mg to 200, 300, 500, or 800 mg, or 1, 1.5, 2, 3, 4, or 5 g of one or more bulking agents.

1.37 Composition I or 1.1-1.36 wherein the composition comprises dextran (e.g., dextran 40).

1.38 Composition 1.37 wherein the composition comprises 5 or 10 or 50 mg to 2 or 5 g dextran (e.g., dextran 40), e.g., from about 50 mg or 100 mg to 200, 300, 500, or 800 mg, or 1, 1.5, 2, 3, 4, or 5 g dextran (e.g., dextran 40).

1.39 Composition I or 1.1-1.38 wherein the composition comprises one or more solubilizing agents, e.g., ethylenediamine tetraacetic acid (EDTA) or a salt thereof (e.g., calcium disodium EDTA, disodium EDTA, sodium EDTA), alpha cyclodextrin, hydroxypropyl-β-cyclodextrin, polysorbate 80, tert-butanol, isopropanol, dichloromethane, ethanol, acetone, and glycerol; one or more collapse temperature modifiers which may shift the overall collapse temperature higher, e.g., one or more of dextran, Ficoll®, gelatin, and hydroxyethyl starch; one or more tonicity modifiers, e.g., one or more of sodium chloride, potassium chloride, sucrose, mannitol, glucose, and lactose; and one or more antimicrobial agents, e.g., one or more of benzyl alcohol, phenol, 2-phenoxyethanol, m-cresol,

chlorobutanol, parabens (e.g., methyl paraben, ethyl paraben, propyl paraben), benzalkonium chloride, benzethonium chloride, myristyl gamma-picolinium salt (e.g., myristyl gamma-picolinium chloride), and organomercury compounds and salts (e.g., phenyl mercuric acetate, phenyl mercuric borate, phenyl mercuric nitrate, and thimerosal).

1.40 Composition I or 1.1-1.39 wherein the composition is a solid, e.g., the pharmaceutically acceptable excipient, e.g, the one or more bases is a solid.

1.41 Composition I or 1.1-1.40 wherein the composition is lyophilized.

1.42 Composition I or 1.1-1.41 wherein 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is lyophilized, e.g., by freezing, primary drying, and secondary drying.

1.43 Composition 1.42 wherein 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is lyophilized, e.g., by freezing, primary drying, and secondary drying, prior to admixture with the pharmaceutically acceptable excipient.

1.44 Composition I or 1.1-1.43 wherein 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is crystalline.

1.45 Composition I or 1.1-1.44 wherein 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is amorphous.

1.46 Composition I or 1.1-1.45 which is suitable for constitution, or reconstitution if lyophilized, with a solvent, e.g., an aqueous solution, into a pharmaceutically acceptable liquid (e.g., a solution or suspension, e.g., a solution).

1.47 Composition I or 1.1-1.46 wherein the composition is admixed with a solvent, e.g., a sterile solution, e.g., sterile water for injection, a sterile solution comprising dextrose (e.g., dextrose injection 5%), a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection), a sterile solution comprising benzyl alcohol (e.g., bacteriostatic water for injection with benzyl alcohol or bacteriostatic sodium chloride for injection with benzyl alcohol), or Lactated Ringer's.

1.48 Composition I or 1.1-1.47 wherein the composition is admixed with 0.5 to 500 mL solvent, e.g., an aqueous solution, e.g., from about 1 or 2 mL to 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 30, 35, 50, 75, 100, 150, 200, 300 or 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 50, 75, 100, or 200 mL, e.g., from about 3.5 or 5 to 10, 25, 50, or 100 mL, e.g., about 3.5 or 35 mL.

1.49 Composition I or 1.1-1.48 wherein the composition is admixed with 0.5 to 500 mL sterile solution, e.g., sterile water for injection, a sterile solution comprising dextrose (e.g., dextrose injection 5%), a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection), a sterile solution comprising benzyl alcohol (e.g., bacteriostatic water for injection with benzyl alcohol or bacteriostatic sodium chloride for injection with benzyl alcohol), or Lactated Ringer's, e.g., from about 1 or 2 mL to 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 30, 35, 50, 75, 100, 150, 200, 300 or 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 50, 75, 100, or 200 mL, e.g., from about 3.5 or 5 to 10, 25, 50, or 100 mL, e.g., about 3.5 or 35 mL.

1.50 Composition I or 1.1-1.49 wherein the composition is admixed with sterile water for injection or a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection).

1.51 Composition I or 1.1-1.50 wherein the composition is admixed with sterile water for injection.

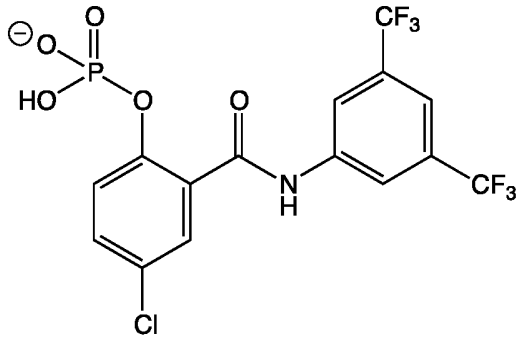
1.52 Composition 1.51 wherein the composition is admixed with 0.5 to 500 mL sterile water for injection, e.g., from about 1 or 2 mL to 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 30, 35, 50, 75, 100, 150, 200, 300 or 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 50, 75, 100, or 200 mL, e.g., from about 3.5 or 5 to 10, 25, 50, or 100 mL, e.g., about 3.5 or 35 mL.

1.53 Composition I or 1.1-1.52 wherein the composition is admixed with a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection).

1.54 Composition 1.53 wherein the composition is admixed with 0.5 to 500 mL a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection), e.g., from about 1 or 2 mL to 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 30, 35, 50, 75, 100, 150, 200, 300 or 500 mL, e.g., from about 1 or 2 mL

to 5, 10, 25, 50, 75, 100, or 200 mL, e.g., from about 3.5 or 5 to 10, 25, 50, or 100 mL, e.g., about 3.5 or 35 mL.

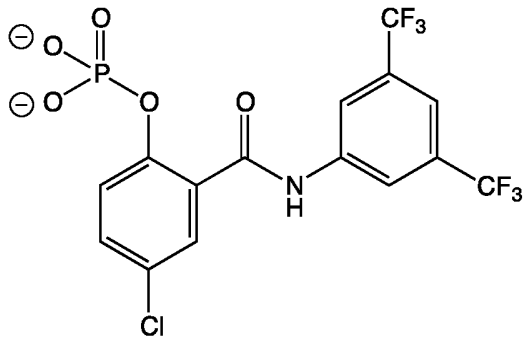
1.55 Composition 1.47-1.54 wherein the composition comprises Formula II



Formula II.

1.56 Composition 1.47-1.55 wherein the composition comprises at least a 1:1 molar ratio of Formula II to a cation of the base, e.g., at least a 2:1 molar ratio of Formula II to the cation of the base.

1.57 Composition 1.47-1.54 wherein the composition comprises Formula III



Formula III.

1.58 Composition 1.47-1.54 or 1.57 wherein the composition comprises at least a 1:2 molar ratio of Formula III to a cation of the base, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.59 Composition 1.47-1.58 wherein the concentration of Formula II or Formula III, e.g., the concentration of Formula II, e.g, the concentration of Formula III, is 0.01 or 0.02 or 0.05 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250 mM, or

1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM.

1.60 Composition 1.47-1.59 wherein the solvent, e.g., the sterile solution, comprises one or more pharmaceutically acceptable bases, e.g., a base wherein upon dissolution of the composition in the solvent, e.g, aqueous solution, the composition has a pH between 7, 7.5, or 8 and 10.5, e.g., between about 7, 7.5, or 8 and 9.5, e.g., between about 7 or 7.5 and 8, e.g., between about 7.5 and 8.5, e.g., about 7.5, e.g., about 8.5, e.g., between about 8 and 8.5, e.g., about 8.2, e.g., a base wherein a conjugate acid of the pharmaceutically acceptable base has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, e.g., wherein the one or more pharmaceutically acceptable bases are one or more of:

a) a $C_{1-8}$-alkyl mono-, di-, or tri- carboxylic acid salt, e.g., a citrate salt, e.g, a metal citrate salt (e.g., an alkali and/or alkaline citrate salt, e.g., an alkali citrate salt, e.g., sodium citrate and/or potassium citrate), e.g., a tartrate salt (e.g., a metal tartrate salt, an alkali tartrate, e.g., sodium tartrate), e.g., a succinate salt (e.g., a metal succinate salt, e.g., an alkali succinate, e.g., disodium succinate), and/or e.g., a lactate salt (e.g., a metal lactate salt, e.g., an alkali lactate, e.g., sodium lactate),

b) a phosphate salt, e.g., a metal phosphate salt (e.g., an alkali and/or alkaline phosphate salt, e.g., an alkali phosphate salt, e.g., sodium phosphate (e.g., $NaH_2PO_4$ and/or $Na_2HPO_4$) and/or potassium phosphate (e.g., $KH_2PO_4$ and/or $K_2HPO_4$)),

c) an amine and/or a salt thereof (e.g., morpholine, piperazine, benethamine, benzathine, trimethylglycine, hydrabamine, 4-(2-hydroxyethyl)morpholine, 1-2-hydroxyethyl)-pyrrolidine, an amino acid (e.g., arginine and/or lysine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., -

$CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, dimethylethanolamine, diethylamine, diethylethanolamine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9,

d) a metal chloride salt (e.g., zinc chloride),

e) an acetate salt, e.g., a metal acetate salt (e.g., an alkali and/or alkaline acetate salt, e.g., an alkali acetate salt, e.g., sodium acetate and/or potassium acetate),

f) a hydroxide and/or alkoxide salt, e.g., a metal hydroxide and/or alkoxide salt (.g., a quarternary ammonium hydroxide, e.g., ammonium hydroxide and/or choline hydroxide, lithium hydroxide, aluminum hydroxide, e.g., an alkali and/or alkaline hydroxide salt, e.g., sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, and/or magnesium ethoxide e.g., sodium hydroxide),

g) a carbonate and/or bicarbonate salt, e.g., a metal carbonate and/or metal bicarbonate salt (e.g., an alkali and/or alkaline carbonate salt, e.g., an alkali and/or alkaline bicarbonate salt, e.g., sodium bicarbonate), and/or

h) a metal borate salt (e.g., an alkali borate salt, e.g., sodium borate),

e.g., one or more of sodium citrate, $Na_2HPO_4$, tris(hydroxymethyl)aminomethane, and a tris(hydroxymethyl)aminomethane salt (e.g., tris acetate), e.g., one or more of sodium citrate, $Na_2HPO_4$, and tris(hydroxymethyl)aminomethane, e.g., one or

more of sodium citrate and $Na_2HPO_4$, e.g., $Na_2HPO_4$, e.g., tris(hydroxymethyl)aminomethane.

1.61 Composition 1.47-1.60 wherein the solvent, e.g., the sterile solution, comprises one or more pharmaceutically acceptable bases, e.g., a base wherein upon dissolution of the composition in the solvent, e.g., the sterile solution, the composition has a pH between 7, 7.5, or 8 and 10.5, e.g., between about 7, 7.5, or 8 and 9.5, e.g., between about 7 or 7.5 and 8, e.g., between about 7.5 and 8.5, e.g., about 7.5, e.g., about 8.5, e.g., between about 8 and 8.5, e.g., about 8.2, e.g., a base wherein a conjugate acid of the pharmaceutically acceptable base has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, e.g., wherein the one or more pharmaceutically acceptable bases is one or more of:

a) a metal citrate salt (e.g., an alkali and/or alkaline citrate salt, e.g., an alkali citrate salt, e.g., sodium citrate and/or potassium citrate),

b) a metal phosphate salt (e.g., an alkali and/or alkaline phosphate salt, e.g., an alkali phosphate salt, e.g., sodium phosphate (e.g., $NaH_2PO_4$ and/or $Na_2HPO_4$) and/or potassium phosphate (e.g., $KH_2PO_4$ and/or $K_2HPO_4$)),

c) an amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof

has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9,

d) a metal acetate salt (e.g., an alkali and/or alkaline acetate salt, e.g., an alkali acetate salt, e.g., sodium acetate and/or potassium acetate),

e) a metal hydroxide salt (e.g., an alkali and/or alkaline hydroxide salt, e.g., sodium hydroxide, potassium hydroxide, calcium hydroxide, and/or magnesium hydroxide, e.g., sodium hydroxide),

f) a metal carbonate and/or bicarbonate salt (e.g., an alkali and/or alkaline carbonate salt, e.g., an alkali and/or alkaline bicarbonate salt, e.g., sodium bicarbonate), and/or

g) a metal borate salt (e.g., an alkali borate salt, e.g., sodium borate),

e.g., one or more of sodium citrate, $Na_2HPO_4$, tris(hydroxymethyl)aminomethane, and a tris(hydroxymethyl)aminomethane salt (e.g., tris acetate), e.g., one or more of sodium citrate, $Na_2HPO_4$, and tris(hydroxymethyl)aminomethane, e.g., one or more of sodium citrate and $Na_2HPO_4$, e.g., $Na_2HPO_4$, e.g., tris(hydroxymethyl)aminomethane.

1.62 Composition 1.61 wherein the 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate and the base, e.g., sodium citrate, sodium phosphate (e.g., $Na_2HPO_4$), tris(hydroxymethyl)aminomethane, tris(hydroxymethyl)aminomethane salt (e.g., tris(hydroxymethyl)aminomethane acetate), and/or meglumine form a salt.

1.63 Composition 1.60 -1.62 wherein the solvent, e.g., the sterile solution, comprises 1 or 5 mg to 200 or 500 mg of the one or more bases, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.64 Composition 1.60-1.63 wherein the concentration of each of the one or more bases is 0.01 or 0.02 or 0.05 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250 mM, or 1000 mM e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000

mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of each of the one or more bases is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of each of the one or more bases is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.65 Composition 1.60-1.64 wherein the one or more bases comprise one or more of a metal citrate salt (e.g., sodium citrate) and a metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$).

1.66 Composition 1.60-1.65 wherein the one or more bases comprise a metal citrate salt (e.g., sodium citrate).

1.67 Composition 1.66 wherein the solvent, e.g., the sterile solution, comprises 1 or 5 mg to 200 or 500 mg of the metal citrate salt (e.g., sodium citrate), e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.68 Composition 1.66 wherein the concentration of the metal citrate salt (e.g., sodium citrate) is 0.01 or 0.02 or 0.05 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, , e. e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of the metal citrate salt is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of the metal citrate salt is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.69 Composition 1.60-1.68 wherein the one or more bases comprise a metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$).

1.70 Composition 1.69 wherein the solvent, e.g., the sterile solution, comprises 1 or 5 mg to 200 or 500 mg of the metal phosphate salt (e.g., sodium phosphate, e.g.,

$Na_2HPO_4$), e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.71 Composition 1.69 wherein the concentration of the metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$), is 0.01 or 0.02 or 0.05 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of each of the metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$)is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of the metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.72 Composition 1.60-1.71 wherein the one or more bases comprise an amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9.

1.73 Composition 1.72 wherein the solvent, e.g., the sterile solution, comprises 1 or 5 mg to 200 or 500 mg of the amine and/or a salt thereof (e.g., morpholine, an

amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.74 Composition 1.72 wherein the concentration of the amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, is 0.01 or 0.02 or 0.05 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40,

50 or 60 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of each of the the amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9 is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of each of the the amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9 is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.75 Composition 1.60-1.74 wherein the one or more bases comprise a mono- and/or poly-hydroxyalkylamine and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine).

1.76 Composition 1.75 wherein the solvent, e.g., the sterile solution, comprises 1 or 5 mg to 200 or 500 mg of the mono- and/or poly-hydroxyalkylamine and/or salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.77 Composition 1.75 wherein the concentration of the mono- and/or poly-hydroxyalkylamine and/or salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also

known as tris acetate), meglumine, and/or diethanolamine), is 0.01 or 0.02 or 0.05 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of the mono- and/or poly-hydroxyalkylamine and/or salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of the mono- and/or poly-hydroxyalkylamine and/or salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.78 Composition 1.60-1.77 wherein the one or more bases comprise $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and

each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine).

1.79 Composition 1.78 wherein the solvent, e.g., the sterile solution, comprises 1 or 5 mg to 200 or 500 mg of $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.80 Composition 1.78 wherein the concentration of $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), is 0.01 or 0.02 or 0.05 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is

independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., -$CH_2CH_3$, e.g., -$CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., –$CH_2$–$CH_2$–, e.g., –$C(CH_2)_3$–, e.g., one $R^8$ is –$CH_3$ and another $R^8$ is –$(CH_2)_6$–) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., -$CH_2CH_3$, e.g., -$CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., –$CH_2$–$CH_2$–, e.g., –$C(CH_2)_3$–, e.g., one $R^8$ is –$CH_3$ and another $R^8$ is –$(CH_2)_6$–) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10

1.81 Composition 1.60-1.80 wherein the one or more bases comprise tris(hydroxymethyl)aminomethane and/or meglumine, e.g., tris(hydroxymethyl)aminomethane, e.g., meglumine.

1.82 Composition 1.81 wherein the solvent, e.g., the sterile solution, comprises 1 or 5 mg to 200 or 500 mg of tris(hydroxymethyl)aminomethane, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g, from about 15, 20, 30, or 50 to 100, 200, 250, 400, 450, 500, 600, or 700 mg and/or wherein the composition comprises 1 or 5 mg to 200 or 500 mg meglumine, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, , e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.83 Composition 1.81 wherein the concentration of tris(hydroxymethyl)aminomethane is 0.01 or 0.02 or 0.05 or 0.1 or 0.5 or 1 or 2 to

250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of tris(hydroxymethyl)aminomethane is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of tris(hydroxymethyl)aminomethane is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10 and/or wherein the concentration of tris(hydroxymethyl)aminomethane is 0.01 or 0.02 or 0.05 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of meglumine is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of meglumine is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.84 Composition 1.60-1.83 wherein the one or more bases comprise a tris(hydroxymethyl)aminomethane salt (e.g., tris(hydroxymethyl)aminomethane acetate).

1.85 Composition 1.84 wherein the solvent, e.g., the sterile solution, comprises 1 or 5 mg to 200 or 500 mg of a tris(hydroxymethyl)aminomethane salt (e.g., tris(hydroxymethyl)aminomethane acetate), e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.86 Composition 1.84 wherein the concentration of the tris(hydroxymethyl)aminomethane salt (e.g., tris(hydroxymethyl)aminomethane acetate) is 0.01 or 0.02 or 0.05 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about

0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of the tris(hydroxymethyl)aminomethane salt (e.g., tris(hydroxymethyl)aminomethane acetate) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of the tris(hydroxymethyl)aminomethane salt (e.g., tris(hydroxymethyl)aminomethane acetate) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.87 Composition 1.60-1.86 wherein the one or more bases comprise a buffeing agent, e.g., an amine and/or a salt thereof, wherein a conjugate acid of the base has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9.

1.88 Composition 1.87 wherein the solvent, e.g., the sterile solution, comprises 1 or 5 mg to 200 or 500 mg of the base, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.89 Composition 1.87 wherein the concentration of the base is 0.01 or 0.02 or 0.05 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of the one or more bases is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of the one or more bases is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.90 Composition 1.44-1.89 wherein the solvent, e.g., the sterile solution comprises one or more bulking agents, e.g., one or more of maltose, mannose, ribose,

cyclodextrin, mannitol, lactose, sucrose, trehalose, sorbitol, glucose, raffinose, arginine, glycine, histidine, dextran (e.g., dextran 40), polyvinylpyrrolidone, polyethylene glycol, and polypropylene glycol, e.g., one or more of mannitol, glucose, sucrose, lactose, trehalose, and dextran (e.g., dextran 40).

1.91 Composition 1.44-1.90 wherein the solvent, e.g., the sterile solution, comprises 5 or 10 or 50 mg to 2 or 5 g of one or more bulking agents, e.g., from about 50 or 100 mg to 200, 300, 500, or 800 mg, or 1, 1.5, 2, 3, 4, or 5 g of one or more bulking agents.

1.92 Composition 1.44-1.91 wherein the solvent, e.g., the sterile solution, comprises dextran (e.g., dextran 40).

1.93 Composition 1.92 wherein the solvent, e.g. the sterile solution, comprises 5 or 10 or 50 mg to 2 or 5 g dextran (e.g., dextran 40), e.g., from about 50 or 100 mg to 200, 300, 500, or 800 mg, or 1, 1.5, 2, 3, 4, or 5 g dextran (e.g., dextran 40).

1.94 Composition 1.44-1.93 wherein the solvent, e.g., the sterile solution, comprises one or more solubilizing agents, e.g., ethylenediamine tetraacetic acid (EDTA) or a salt thereof (e.g., calcium disodium EDTA, disodium EDTA, sodium EDTA), alpha cyclodextrin, hydroxypropyl-β-cyclodextrin, polysorbate 80, tert-butanol, isopropanol, dichloromethane, ethanol, acetone, and glycerol; one or more collapse temperature modifiers which may shift the overall collapse temperature higher, e.g., one or more of dextran, Ficoll®, gelatin, and hydroxyethyl starch; one or more tonicity modifiers, e.g., one or more of sodium chloride, potassium chloride, sucrose, mannitol, and glucose; and one or more antimicrobial agents, e.g., one or more of benzyl alcohol, phenol, 2-phenoxyethanol, m-cresol, chlorobutanol, parabens (e.g., methyl paraben, ethyl paraben, propyl paraben), benzalkonium chloride, benzethonium chloride, myristyl gamma-picolinium salt (e.g., myristyl gamma-picolinium chloride), and organomercury compounds and salts (e.g., phenyl mercuric acetate, phenyl mercuric borate, phenyl mercuric nitrate, and thimerosal).

1.95 Composition 1.44-1.94 wherein the pH after admixture with the solvent, e.g., the aqueous solution, is between pH 7 and pH 10.5, e.g., between pH 7 and pH 9.5,

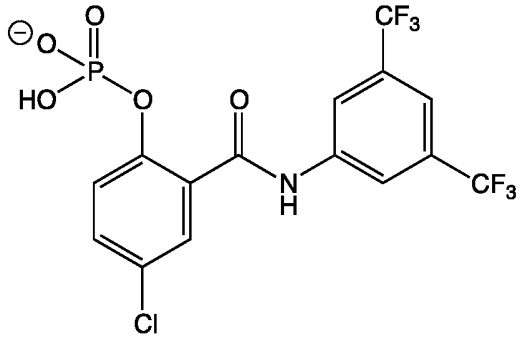
e.g., between pH 7 and pH 8, e.g., between 7.5 and 8.5, e.g., 7.5, e.g., 8.5, e.g., 8.2.

1.96 Composition 1.44-1.95 wherein the pH after admixture with the solvent, e.g., the aqueous solution, is further adjusted, e.g., adjusted to achieve a pH between pH 7 and pH 10.5, e.g., between pH 7 and pH 9.5, e.g., between pH 7 and pH 8, e.g., between 7.5 and 8.5, e.g., 7.5, e.g., 8.5, e.g., 8.2, e.g., wherein the pH is adjusted with NaOH.

1.97 Composition 1.44-1.96 wherein the composition is filtered after admixture with the solvent, e.g., the aqueous solution, to remove particles and microbes, e.g., filtered prior to injection.

1.98 Composition 1.44-1.97 wherein the composition is administered about 24 hours, 12 hours, 10 hours, 8 hours, 2 hours, 1 hour, 30 minutes, 20 minutes, 15 minutes, 10 minutes, 5 minutes, 3 minutes, 2 minutes or 1 minute or less after admixture.

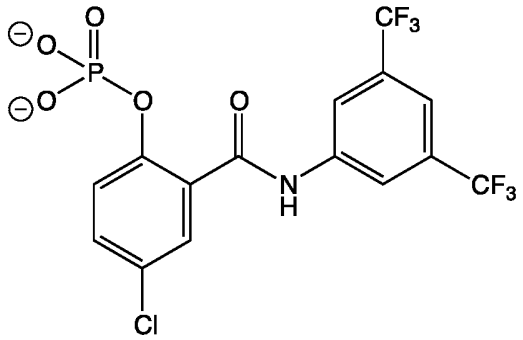
1.99 Composition 1.44-1.98 wherein the composition comprises Formula II




Formula II.

1.100 Composition 1.44-1.99 wherein the composition comprises at least a 1:1 molar ratio of Formula II to a cation of the base.

1.101 Composition 1.44-1.98 wherein the composition comprises Formula III



Formula III

1.102 Composition 1.44-1.98 or 1.101 wherein the composition comprises at least a 1:2 molar ratio of Formula III to a cation of the base, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.103 Composition I or 1.1-1.102 wherein the composition is for injection, e.g., subcutaneously, intramuscularly, intravenously, or intrathecally, e.g., intramuscularly or intravenously, e.g., a bolus injected subcutaneously, intramuscularly, intravenously, or intrathecally.

1.104 Composition 1.103 wherein the composition is for injection intravenously, e.g., IV bolus and/or IV infusion, e.g., IV bolus followed by IV infusion, e.g., a loading bolus (e.g., 10 or 20 to 30, 50, 70, 75, 100, 140, 150, 200, 300 or 400 mg per day administered by a loading bolus dose, e.g., about 50 to 200 or 250 mg per day administered by a loading bolus dose, e.g., about 70 to 140 mg per day administered by a loading bolus dose, e.g., a concentration of the dissolved salt administered by a loading bolus dose of 1 to 4, 5, 8, 10, 15, 20, 30, or 50 mM per day, e.g., a concentration of the dissolved salt administered by a loading bolus dose of about 2 to 5, 10, 15, or 20 mM per day, e.g., a concentration of the dissolved salt administered by a loading bolus dose of about 4 to 8 or 9 mM per day) and then an IV infusion over 24 hours for 3 days (e.g., at a rate of 1, 2, 3, 5, 6, 7, 8, 10, 15, 20, 25, 30, or 50 mg/hr for 24 hours, e.g., at a rate of 3, 6, or 15 mg/hr).

1.105 Composition 1.104 wherein the composition is for injection intramuscularly, e.g., IM bolus and/or IM infusion, e.g., IM bolus followed by IM infusion.

1.106 Composition 1.104 or 1.105 wherein the infusion, e.g., IV or IM, is administered over about 10 or 30 minutes to 72 hours, e.g., about 30 minutes to 24 hours, e.g, about 30 minutes to 12 hours, e.g., about 30 minutes to 8 hours, e.g., about 30 minutes to 6 hours, e.g., about 30 minutes to 4 hours, e.g., about 30 minutes to 2 hours, e.g., about 30 minutes to 1 hour, e.g., about 72 hours.

1.107 Composition 1.2-1.106 wherein the 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate and the one or more bases are milled together.

1.108 Composition I wherein the composition is formulated for oral administration.

1.109 Composition 1.108 wherein the composition is a tablet, capsule, solution, suspension, or the like.

1.110 Composition I wherein the composition comprises between 20 and 500 mg 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate (Formula I), e.g., between about 25 and 450 mg, e.g., between about 30 and 400 mg, e.g., between about 35 and 350 mg, and one or more bases, e.g., one or more of tris(hydroxymethyl)aminomethane, $Na_2HPO_4$, meglumine, and sodium citrate, e.g., between 10 and 1500 mg of one or more of tris(hydroxymethyl)aminomethane, $Na_2HPO_4$, meglumine, and sodium citrate, e.g., between about 15 and 1000 mg, e.g., between about 20 and 600 mg, e.g., between about 50 and 200 mg, e.g., between about 50 and 150 mg, e.g., between 10 and 1500 mg of the base, e.g., between about 15 and 1000 mg, e.g., between about 20 and 600 mg, e.g., between about 50 and 200 mg, e.g., between about 50 and 150 mg.

1.111 Composition 1.110 wherein the composition comprises between 20 and 500 mg 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate (Formula I), e.g., between about 25 and 450 mg, e.g., between about 30 and 400 mg, e.g., between about 35 and 350 mg, and tris(hydroxymethyl)aminomethane, e.g., between 10 and 600 mg tris(hydroxymethyl)aminomethane, e.g., between about 20 and 500, e.g., between about 40 and 500 mg.

1.112 Composition 1.110 wherein the composition comprises between 20 and 500 mg 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate (Formula I), e.g., between about 25 and 450 mg, e.g., between about 30 and 400 mg, e.g., between about 35 and 350 mg, and $Na_2HPO_4$, e.g., between 10 and 600 mg $Na_2HPO_4$, e.g., between about 20 and 500, e.g., between about 40 and 500 mg.

1.113 Composition 1.110 wherein the composition comprises between 20 and 500 mg 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate (Formula I), e.g., between about 25 and 450 mg, e.g., between about 30 and 400 mg, e.g., between about 35 and 350 mg, and meglumine, e.g., between 20 and 900 mg meglumine, e.g., between about 30 and 800, e.g., between about 60 and 500 mg, e.g, between about 70 and 400 mg.

1.114 Composition 1.110 wherein the composition comprises between 20 and 500 mg 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate (Formula I), e.g., between about 25 and 450 mg, e.g., between about 30 and 400 mg, e.g., between about 35 and 350 mg, and sodium citrate, e.g., between 30 and 1500 mg sodium citrate, e.g., between about 40 and 1200, e.g., between about 50 and 1000 mg, e.g, between about 80 and 600 mg, e.g., between about 100 and 500 mg.

1.115 Composition 1.110-1.115 wherein the composition is admixed with a solvent, e.g., sterile water for injection, a sterile solution comprising dextrose (e.g., dextrose injection 5%), a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection), a sterile solution comprising benzyl alcohol (e.g., bacteriostatic water for injection with benzyl alcohol or bacteriostatic sodium chloride for injection with benzyl alcohol), or Lactated Ringer's, e.g., wherein the composition is admixed with 1 mL to 100 mL, e.g., about 3 to 50 mL, e.g., about 3.5 to 35 mL.

1.116 Composition 1.110-1.115 wherein the composition is admixed with a sterile water for injection, e.g., wherein the composition is admixed with 1 mL to 100 mL, e.g., about 3 to 50 mL, e.g., about 3.5 to 35 mL.

1.117 Composition 1.110-1.115 wherein the composition is admixed with a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection), e.g., wherein the composition is admixed with 1 mL to 100 mL, e.g., about 3 to 50 mL, e.g., about 3.5 to 35 mL.

1.118 Composition I or 1.1-1.117 wherein the composition comprises one or more additional therapeutic agents, e.g., one or more additional therapeutic agents for cerebral edema, stroke, traumatic brain injury, glioma (e.g., glioblastoma),

meningitis, acute mountain sickness, infection, metabolic disorder, hypoxia, water intoxication, hepatic failure, hepatic encephalopathy, diabetic ketoacidosis, abscess, eclampsia, Creutzfeldt-Jakob disease, lupus cerebritis, optic nerve edema, hyponatremia, fluid retention, ovarian hyperstimulation syndrome, epilepsy, retinal ischemia or other diseases of the eye associated with abnormalities in intraocular pressure and/or tissue hydration, myocardial ischemia, myocardial ischemia/reperfusion injury, myocardial infarction, myocardial hypoxia, congestive heart failure, sepsis, neuromyelitis optica, or migraines.

1.119 Composition I or 1.1-1.118 wherein the composition comprises one or more additional therapeutic agents, e.g., one or more additional therapeutic agents for pulmonary edema, fibromyalgia, or multiple sclerosis.

1.120 Composition I or 1.1-1.119 wherein the composition is stable for at least one week at room temperature, e.g., for at least 1, 2, 4, 6, 8, or 12 months, e.g., the composition has < 20% N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide, < 15% N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide, < 10% N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide, < 5% N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide, < 2% N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide, 1% N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide, or < 1% N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide.

1.121 Composition I or 1.1-1.120 wherein the composition comprises less than 10%, 15%, or 20% of N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide, e.g., less than 5, 4, 3, or 2% of N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide for at least one week, e.g., for at least 1, 2, 4, 6, 8, or 12 months.

1.122 Composition I or 1.1-1.121 wherein the composition is administered concurrently or sequentially, in either order, with one or more additional therapeutic agents, e.g., one or more additional therapeutic agents for cerebral edema, stroke, traumatic brain injury, glioma (e.g., glioblastoma), meningitis, acute mountain

sickness, infection, metabolic disorder, hypoxia, water intoxication, hepatic failure, hepatic encephalopathy, diabetic ketoacidosis, abscess, eclampsia, Creutzfeldt-Jakob disease, lupus cerebritis, optic nerve edema, hyponatremia, fluid retention, ovarian hyperstimulation syndrome, epilepsy, retinal ischemia or other diseases of the eye associated with abnormalities in intraocular pressure and/or tissue hydration, myocardial ischemia, myocardial ischemia/reperfusion injury, myocardial infarction, myocardial hypoxia, congestive heart failure, sepsis, neuromyelitis optica, or migraines.

1.123 Composition I or 1.1-1.122 wherein the composition is administered concurrently or sequentially, in either order, with one or more additional therapeutic agents, e.g., one or more additional therapeutic agents for pulmonary edema, fibromyalgia, or multiple sclerosis.

1.124 Composition I or 1.1-1.123 wherein the composition is for use in any of the methods described herein, e.g., for use in Method A, e.g., Method A.1-A.58, for use in Method B, e.g., Method B.1-B.41, e.g., for use in Method C, e.g., C.1-C.8, e.g., for use in Method D, e.g., D.1-D.19, e.g., for use in Method E, e.g., E.1-E.59, e.g., for use in Method F, e.g., F.1-F.5, e.g., for use in Method G, e.g., G.1-G.58, e.g., for use in Method H, e.g., H.1-H.9, *vida infra*.

**[0047]** In some embodiments, when 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate, is provided as a solid that is to be admixed with a solvent, e.g., a sterile solution, to provide a pharmaceutically acceptable liquid, it is typically provided as a powder and admixed immediately or shortly before administration to the patient. In some embodiments, the powdered 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate may be packaged in a container, for example, in a vial to which is added the solvent, e.g., the sterile solution. Alternatively, the contents of the vial may be added to the solvent, e.g., the steril solution, in a separate container. In some embodiments, the powdered 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is packaged in a sachet, such as a foil package, that can be opened and the contents added to the solvent, e.g., the sterile solution. In some embodiments, the powdered 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is formulated as a tablet that dissolves when it is added to the solvent, e.g., the sterils solution.

**[0048]** In yet another embodiment, a pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate, e.g., Composition I, e.g., composition 1.1-1.124, is prepared by admixing 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate with a pharmaceutically acceptable excipient. In some embodiments, 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate and the pharmaceutically acceptable excipient are milled together. In some embodiments, 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is crystalline. In some embodiments, 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is amorphous. In some embodiments, 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is lyophilized. In some embodiments, 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate and the pharmaceutically acceptable excipient, e.g., Composition I, e.g., composition 1.1-1.124, are lyophilized.

**[0049]** In yet another embodiment, a pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate, e.g., Composition I, e.g., composition 1.1-1.124, is prepared by admixing 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate with a sterile solution, e.g., sterile water for injection or a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection), to form a pharmaceutically acceptable liquid. In some embodiments, 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is admixed with the sterile solution immediately or shortly before administration. In some embodiments, 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is admixed with a base, e.g., sodium citrate, sodium phosphate (e.g., $Na_2HPO_4$), tris(hydroxymethyl)aminomethane, and/or a tris(hydroxymethyl)aminomethane salt (e.g., tris acetate) prior to admixture with the sterile solution, e.g., sterile water for injection or a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection). In some embodiments, 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is admixed with a base, e.g., sodium citrate, sodium phosphate (e.g., $Na_2HPO_4$), tris(hydroxymethyl)aminomethane, and/or a tris(hydroxymethyl)aminomethane salt (e.g., tris acetate) and/or a bulking agent, e.g., dextran (e.g., dextran 40), prior to admixture with the sterile

solution, e.g., sterile water for injection or a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection). In some embodiments, 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate admixed with the base and/or the bulking agent is lyophilized. In some embodiments, 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate admixed with the base and/or the bulking agent are milled together. In some embodiments, 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is admixed with a sterile solution comprising a base, e.g., sodium citrate, sodium phosphate (e.g., $Na_2HPO_4$), tris(hydroxymethyl)aminomethane, and/or a tris(hydroxymethyl)aminomethane salt (e.g., tris acetate). In some embodiments, 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is admixed with a sterile solution comprising a base, e.g., sodium citrate, sodium phosphate (e.g., $Na_2HPO_4$), tris(hydroxymethyl)aminomethane base, and/or a tris(hydroxymethyl)aminomethane salt (e.g., tris(hydroxymethyl)aminomethane acetate) and/or a bulking agent. In some embodiments, the admixture of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate and the sterile solution is agitated, e.g., any mode of agitation that results in a clear liquid, e.g., mechanical agitation, sonication, conventional mixing, conventional stirring and the combinations thereof. In some embodiments, 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate admixed with the sterile solution is lyophilized. In some embodiments, 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate admixed with the sterile solution is crystalline. In some embodiments, 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate admixed with the sterile solution is amorphous.

**[0050]** In one embodiment, Composition I, e.g., composition 1.1-1.124, is prepared by admixing 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate with a solvent, e.g., a sterile water for injection or a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection). In some embodiments, 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is admixed with a base, e.g., sodium citrate, sodium phosphate (e.g., $Na_2HPO_4$), tris(hydroxymethyl)aminomethane, and/or a tris(hydroxymethyl)aminomethane salt (e.g., tris(hydroxymethyl)aminomethane acetate) and/or a bulking agent, e.g., dextran (e.g., dextran

40), prior to admixture with the solvent, e.g. an aqueous solution. In some embodiments, the solvent, e.g., the aqueous solution, comprises a base, e.g., sodium citrate, sodium phosphate (e.g., $Na_2HPO_4$), tris(hydroxymethyl)aminomethane, and/or a tris(hydroxymethyl)aminomethane salt (e.g., tris(hydroxymethyl)aminomethane acetate) and/or a bulking agent, e.g., dextran (e.g., dextran 40). In some embodiments, the admixture of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate and the solvent, e.g., the aqueous solution, is agitated after admixture, e.g., by any mode of agitation that results in a clear liquid, e.g., mechanical agitation, sonication, conventional mixing, conventional stirring and the combinations thereof. In some embodiments, 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is lyophilized. In some embodiments, the admixture of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate and the base and/or bulking agent is lyophilized. In some embodiments, the admixture of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate and the base and/or bulking agent is milled together. In some embodiments, 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is admixed with the solvent, e.g., the sterile solution, immediately or shortly before administration.

**[0051]** Pharmaceutical compositions disclosed herein, e.g., Composition I, e.g., composition 1.1-1.124, may be contained in a sterilized vessel such as syringes, vials or ampoules of various sizes and capacities.

**[0052]** The pH of the pharmaceutical compositions disclosed herein when dissolved in solvent, e.g., an aqueous solution, e.g., Composition I, e.g., composition 1.1-1.124, may be adjusted to achieve the desired pH by addition of a metal hydroxide salt (e.g., NaOH and/or KOH, e.g., NaOH) to the composition.

**[0053]** In some embodiments, the base is a solid.

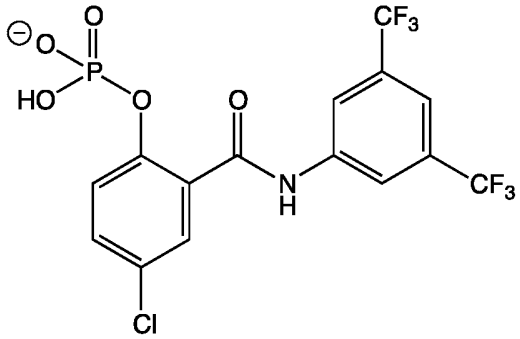
**[0054]** The bases used herein may form a buffer with the 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate. If a solution of the base described herein and bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is too basic, the phosphate group may be cleaved. On the other hand, if the solution is too acidic, the solubility of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate may decrease.

**[0055]** In some embodiments, "base" is any inorganic or organic Bronsted base.

**[0056]** Further provided is a method for increasing the stability of a solid state formulation comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate, wherein the method comprises milling 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate with a base, e.g., with tris(hydroxymethyl)aminomethane for later reconstitution as an aqueous solution for injection.

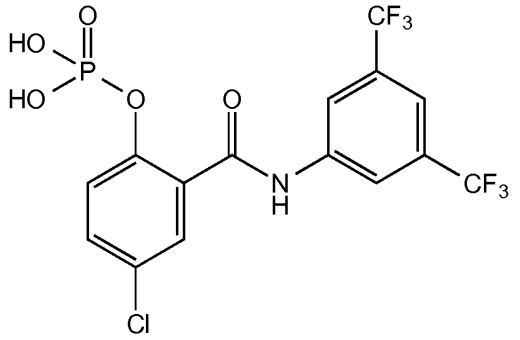
**[0057]** Further provided is a method for lessening the potential for precipitation of N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide and allows for IV administration comprising comprises milling 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate with a base, e.g., with tris(hydroxymethyl)aminomethane and reconstituting as an aqueous solution for injection.

**[0058]** Further provided is a method for increasing the aqueous solubility, dissolution and bioavailability of N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide comprising preparing Formula II



Formula II

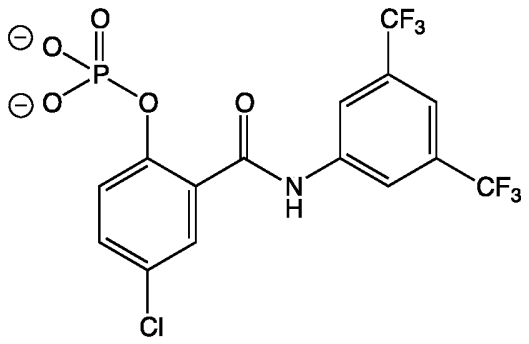
by reacting a compound of Formula I



Formula I

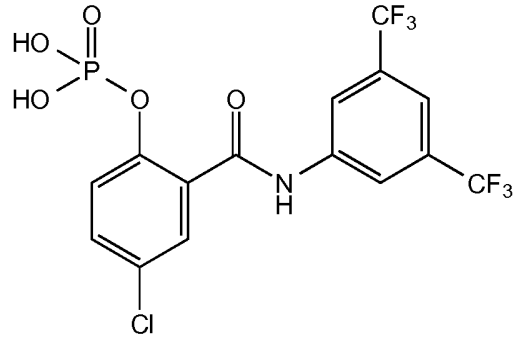
with a free base, e.g., tris(hydroxymethyl)aminomethane, e.g., meglumine.

**[0059]** Further provided is a method for increasing the aqueous solubility, dissolution and bioavailability of N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide comprising preparing Formula III



Formula III

by reacting a compound of Formula I



Formula I

with a free base, e.g., tris(hydroxymethyl)aminomethane, e.g., meglumine.

**[0060]** Further provided is a method (Method I) of making a pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate, e.g., Composition I, e.g., composition 1.1-1.124, wherein the method comprises admixing 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate and a pharmaceutically acceptable excipient.

**[0061]** Further provided is Method I as follows:

1.1 Method I wherein the pharmaceutically acceptable excipient comprises one or more bases.

1.2 Method I or 1.1 comprising admixing 0.1 or 0.25 mg to 2.0 g of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate,

e.g., from about 0.1 or 0.25 mg to 75 or 600 mg, e.g., from about 0.1 or 0.25 or 1 or 2 or 5 or 10 or 15 or 20 mg to 50, 75, 100, 125, 150, 200, 300, 350, 400, 500, or 600 mg, or 1 g, 1.5 g, or 2.0 g, e.g., from about 5 to 50, 75, 100, 125, 150, 200, 300, 350, 400, 500, or 600 mg, or 1 g, 1.5 g, or 2 g, e.g., from about 5 to 500 mg, e.g., from about 5 to 300 or 350 mg, e.g., from about 5 to 200 mg, e.g., from about 25 to 500 mg, e.g., from about 25 to 300 or 350 mg, e.g., from about 25 to 200 mg, e.g., from about 15, 20, 30, 35, 50 or 100 to 150, 200, 300, 350, 400, 450, 500, 550, or 600 mg, e.g., from about 0.5 or 1 mg to 50 mg, e.g., from about 0.5 or 1 mg to 20 mg, e.g., from about 0.5 or 1 mg to 10 mg, e.g., from about 1 or 2 or 5 mg to 10 or 20 mg, e.g., from about 1 or 2 or 3 or 4 to 5 mg, e.g., about 35 mg, e.g., about 350 mg, or wherein the composition admixing an amount of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate sufficient to provide 0.1 or 0.25 mg to 2.0 g of N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide, e.g., from about 0.1 or 0.25 mg to 75 or 600 mg, e.g., from about 0.1 or 0.25 or 1 or 2 or 5 or 10 or 15 or 20 mg to 50, 75, 100, 125, 150, 200, 300, 350, 400, 500, or 600 mg, or 1 g, 1.5 g, or 2.0 g, e.g., from about 5 to 50, 75, 100, 125, 150, 200, 300, 350, 400, 500, or 600 mg, or 1 g, 1.5 g, or 2 g, e.g., from about 5 to 500 mg, e.g., from about 5 to 300 or 350 mg, e.g., from about 5 to 200 mg, e.g., from about 25 to 500 mg, e.g., from about 25 to 300 or 350 mg, e.g., from about 25 to 200 mg, e.g., from about 15, 20, 30, 35, 50 or 100 to 150, 200, 300, 350, 400, 450, 500, 550, or 600 mg, e.g., from about 0.5 or 1 mg to 50 mg, e.g., from about 0.5 or 1 mg to 20 mg, e.g., from about 0.5 or 1 mg to 10 mg, e.g., from about 1 or 2 or 5 mg to 10 or 20 mg, e.g., from about 1 or 2 or 3 or 4 to 5 mg, e.g., about 35 mg, e.g., about 350 mg, with one or more bases.

1.3 Method I, 1.1 or 1.2 comprising admixing 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate in an amount sufficient to provide a dose of 0.01 or 0.1 or 0.5 mg/kg to 1 or 5 or 10 or 15 mg/kg of N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide, e.g., a dose of about 0.05 to 1 or 5 mg/kg, e.g., a dose of about 0.05 to 0.1, 0.2, 0.3, 0.4, or 0.5 mg/kg with one or more bases.

1.4 Method 1.1-1.3 wherein upon dissolution of the composition in a solvent, e.g., the aqueous solution, the composition has a pH between 7, 7.5, or 8 and 10.5, e.g., between about 7, 7.5, or 8 and 9.5, e.g., between about 7 or 7.5 and 8, e.g., between about 7.5 and 8.5, e.g., about 7.5, e.g., about 8.5, e.g., between about 8 and 8.5, e.g., about 8.2, e.g., a base wherein a conjugate acid of the base has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, e.g., wherein the one or more bases are one or more of:

a) a $C_{1-8}$-alkyl mono-, di-, or tri- carboxylic acid salt, e.g., a citrate salt, e.g, a metal citrate salt (e.g., an alkali and/or alkaline citrate salt, e.g., an alkali citrate salt, e.g., sodium citrate and/or potassium citrate), e.g., a tartrate salt (e.g., a metal tartrate salt, an alkali tartrate, e.g., sodium tartrate), e.g., a succinate salt (e.g., a metal succinate salt, e.g., an alkali succinate, e.g., disodium succinate), and/or e.g., a lactate salt (e.g., a metal lactate salt, e.g., an alkali lactate, e.g., sodium lactate),

b) a phosphate salt, e.g., a metal phosphate salt (e.g., an alkali and/or alkaline phosphate salt, e.g., an alkali phosphate salt, e.g., sodium phosphate (e.g., $NaH_2PO_4$ and/or $Na_2HPO_4$) and/or potassium phosphate (e.g., $KH_2PO_4$ and/or $K_2HPO_4$)),

c) an amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine and/or lysine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, dimethylethanolamine, diethylamine, diethylethanolamine, and/or diethanolamine), e.g., any

of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9,

d) a metal chloride salt (e.g., zinc chloride),

e) an acetate salt, e.g., a metal acetate salt (e.g., an alkali and/or alkaline acetate salt, e.g., an alkali acetate salt, e.g., sodium acetate and/or potassium acetate),

f) a hydroxide and/or alkoxide salt, e.g., a metal hydroxide and/or alkoxide salt (e.g., a quarternary ammonium hydroxide, e.g., ammonium hydroxide and/or choline hydroxide, lithium hydroxide, aluminum hydroxide, e.g., an alkali and/or alkaline hydroxide salt, e.g., sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, and/or magnesium ethoxide, e.g., sodium hydroxide),

g) a carbonate and/or bicarbonate salt, e.g., a metal carbonate and/or metal bicarbonate salt (e.g., an alkali and/or alkaline carbonate salt, e.g., an alkali and/or alkaline bicarbonate salt, e.g., sodium bicarbonate), and/or

h) a metal borate salt (e.g., an alkali borate salt, e.g., sodium borate),

e.g., one or more of sodium citrate, $Na_2HPO_4$, tris(hydroxymethyl)aminomethane, and a tris(hydroxymethyl)aminomethane salt (e.g., tris acetate), e.g., one or more of sodium citrate, $Na_2HPO_4$, and tris(hydroxymethyl)aminomethane, e.g., one or more of sodium citrate and $Na_2HPO_4$, e.g., $Na_2HPO_4$, e.g., tris(hydroxymethyl)aminomethane.

1.5 Method 1.1-1.4 wherein upon dissolution of the composition in a solvent, e.g., the aqueous solution, the composition has a pH between 7, 7.5, or 8 and 10.5, e.g., between about 7, 7.5, or 8 and 9.5, e.g., between about 7 or 7.5 and 8, e.g., between about 7.5 and 8.5, e.g., about 7.5, e.g., about 8.5, e.g., between about 8 and 8.5, e.g., about 8.2, e.g., a base wherein a conjugate acid of the base has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g.,

between about 7 and 9, e.g., between about 8 and 9, e.g., wherein the one or more bases are one or more of:

a) a metal citrate salt (e.g., an alkali and/or alkaline citrate salt, e.g., an alkali citrate salt, e.g., sodium citrate and/or potassium citrate),

b) a metal phosphate salt (e.g., an alkali and/or alkaline phosphate salt, e.g., an alkali phosphate salt, e.g., sodium phosphate (e.g., $NaH_2PO_4$ and/or $Na_2HPO_4$) and/or potassium phosphate (e.g., $KH_2PO_4$ and/or $K_2HPO_4$)),

c) an amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9,

d) a metal acetate salt (e.g., an alkali and/or alkaline acetate salt, e.g., an alkali acetate salt, e.g., sodium acetate and/or potassium acetate),

e) a metal hydroxide salt (e.g., an alkali and/or alkaline hydroxide salt, e.g., sodium hydroxide, potassium hydroxide, calcium hydroxide, and/or magnesium hydroxide, e.g., sodium hydroxide),

f) a metal carbonate and/or bicarbonate salt (e.g., an alkali and/or alkaline carbonate salt, e.g., an alkali and/or alkaline bicarbonate salt, e.g., sodium bicarbonate), and/or

g) a metal borate salt (e.g., an alkali borate salt, e.g., sodium borate),

e.g., one or more of sodium citrate, $Na_2HPO_4$, tris(hydroxymethyl)aminomethane, and a tris(hydroxymethyl)aminomethane salt (e.g., tris acetate), e.g., one or more of sodium citrate, $Na_2HPO_4$, and tris(hydroxymethyl)aminomethane, e.g., one or more of sodium citrate and $Na_2HPO_4$, e.g., $Na_2HPO_4$, e.g., tris(hydroxymethyl)aminomethane.

1.6 Method 1.1-1.5 comprising admixing 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate with 1 or 5 mg to 200 or 500 mg of the one or more bases, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.7 Method 1.1-1.6 wherein the one or more bases comprise one or more of a metal citrate salt (e.g., sodium citrate) and a metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$).

1.8 Method 1.1-1.7 wherein the one or more bases comprise a metal citrate salt (e.g., sodium citrate).

1.9 Method 1.8 wherein the 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is admixed with 1 or 5 mg to 200 or 500 mg of a metal citrate salt (e.g., sodium citrate), e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.10 Method 1.1-1.9 wherein the one or more bases comprise a metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$).

1.11 Method 1.10 wherein the 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is admixed with 1 or 5 mg to 200 or 500 mg of a metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$), e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.12 Method 1.1-1.11 wherein the one or more bases comprise $Na_2HPO_4$.

1.13 Method 1.12 wherein the 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is admixed with 1 or 5 mg to 200 or 500 mg $Na_2HPO_4$, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.14 Method 1.1-1.13 wherein the one or more bases comprise an amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9.

1.15 Method 1.14 wherein the 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is admixed with 1 or 5 mg to 200 or 500 mg of the amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., any of the preceding wherein a

conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.16 Method 1.1-1.15 wherein the one or more bases comprise a mono- and/or poly-hydroxyalkylamine and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine).

1.17 Method 1.16 wherein the 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is admixed with 1 or 5 mg to 200 or 500 mg of the mono- and/or poly-hydroxyalkylamine and/or salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.18 Method 1.1-1.17 wherein the one or more bases comprise $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine).

1.19 Method 1.18 wherein the 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is admixed with 1 or 5 mg to 200 or 500 mg of $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.20 Method 1.1-1.19 wherein the one or more bases comprise tris(hydroxymethyl)aminomethane and/or meglumine, e.g., tris(hydroxymethyl)aminomethane, e.g., meglumine.

1.21 Method 1.20 wherein the 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is admixed with 1 or 5 mg to 200 or 500 mg tris(hydroxymethyl)aminomethane, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg and/or wherein the 2-{[3,5-

bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is admixed with 1 or 5 mg to 200 or 500 mg meglumine, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.22 Method 1.1-1.21 wherein the one or more bases comprise a tris(hydroxymethyl)aminomethane salt, e.g., tris(hydroxymethyl)aminomethane acetate.

1.23 Method 1.22 wherein the 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is admixed with 1 or 5 mg to 200 or 500 mg of the tris(hydroxymethyl)aminomethane salt (e.g., tris(hydroxymethyl)aminomethane acetate), e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg, e.g., 1 or 5 mg to 200 or 500 mg tris(hydroxymethyl)aminomethane acetate, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg tris(hydroxymethyl)aminomethane acetate, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg tris(hydroxymethyl)aminomethane acetate.

1.24 Method 1.1-1.23 wherein the one or more bases comprise a base wherein a conjugate acid of the base has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9.

1.25 Method 1.24 wherein the 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is admixed with 1 or 5 mg to 200 or 500 mg of the base, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.26 Method 1.1-1.25 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to the one or more bases is at least 1:1.

1.27 Method 1.1-1.26 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to the one or more bases is at least 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.28 Method 1.27 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to a metal citrate salt (e.g., sodium citrate) is at least 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.29 Method 1.27 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to a metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$) is at least 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.30 Method 1.27 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to an amine and/or salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof

(e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, is at least 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.31 Method 1.27 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to the mono- and/or poly-hydroxyalkylamine and/or salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine) is at least 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.32 Method 1.27 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6)), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate),

meglumine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, is 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.33 Method 1.27 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to tris(hydroxymethyl)aminomethane is at least 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.34 Method 1.27 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to the tris(hydroxymethyl)aminomethane salt (e.g., tris(hydroxymethyl)aminomethane acetate) is at least 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.35 Method 1.27 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to a base wherein a conjugate acid of the base has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9 is at least 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.36 Method I or 1.1-1.35 further comprising admixing with one or more bulking agents which may provide an adequate structure to the lyophilized cake, e.g., one or more of mannitol, lactose, sucrose, trehalose, sorbitol, glucose, raffinose,

arginine, glycine, histidine, dextran (e.g., dextran 40), polyvinylpyrrolidone, polyethylene glycol, and polypropylene glycol, e.g., one or more of mannitol, glucose, sucrose, lactose, trehalose, and dextran (e.g., dextran 40).

1.37 Method I or 1.1-1.36 further comprising admixing with 5 or 10 or 50 mg to 2 or 5 g of one or more bulking agents, e.g., from about 50 or 100 mg to 200, 300, 500, or 800 mg, or 1, 1.5, 2, 3, 4, or 5 g of one or more bulking agents.

1.38 Method I or 1.1-1.37 further comprising admixing with dextran (e.g., dextran 40).

1.39 Method I or 1.1-1.38 further comprising admixing with 5 or 10 or 50 mg to 2 or 5 g dextran (e.g., dextran 40), e.g., from about 50 mg or 100 mg to 200, 300, 500, or 800 mg, or 1, 1.5, 2, 3, 4, or 5 g dextran (e.g., dextran 40).

1.40 Method I or 1.1-1.39 further comprising admixing with one or more solubilizing agents, e.g., ethylenediamine tetraacetic acid (EDTA) or a salt thereof (e.g., calcium disodium EDTA, disodium EDTA, sodium EDTA), alpha cyclodextrin, hydroxypropyl-β-cyclodextrin, polysorbate 80, tert-butanol, isopropanol, dichloromethane, ethanol, acetone, and glycerol; one or more collapse temperature modifiers which may shift the overall collapse temperature higher, e.g., one or more of dextran, Ficoll®, gelatin, and hydroxyethyl starch; one or more tonicity modifiers, e.g., one or more of sodium chloride, potassium chloride, sucrose, mannitol, glucose, and lactose; and one or more antimicrobial agents, e.g., one or more of benzyl alcohol, phenol, 2-phenoxyethanol, m-cresol, chlorobutanol, parabens (e.g., methyl paraben, ethyl paraben, propyl paraben), benzalkonium chloride, benzethonium chloride, myristyl gamma-picolinium salt (e.g., myristyl gamma-picolinium chloride), and organomercury compounds and salts (e.g., phenyl mercuric acetate, phenyl mercuric borate, phenyl mercuric nitrate, and thimerosal).

1.41 Method I or 1.1-1.40 further comprising milling the 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate and the one or more bases.

1.42 Method I or 1.1-1.41 further comprising lyophilizing the 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate and the one or more bases, e.g., by freezing, primary drying, and secondary drying.

1.43 Method I or 1.1-1.42 wherein 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is lyophilized, e.g., by freezing, primary drying, and secondary drying, prior to admixture with the pharmaceutically acceptable excipient.

1.44 Method I or 1.1-1.43 wherein 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is crystalline.

1.45 Method I or 1.1- 1.44 wherein 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is amorphous.

1.46 Method I or 1.1-1.45 further comprising constituting or reconstituting, if lyophilized, the composition with a solvent, e.g., the aqueous solution, into a pharmaceutically acceptable liquid (e.g., a solution or suspension, e.g., a solution).

1.47 Method I or 1.1-1.46 further comprising admixing the composition with a solvent, e.g., a sterile solution, e.g., sterile water for injection, a sterile solution comprising dextrose (e.g., dextrose injection 5%), a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection), a sterile solution comprising benzyl alcohol (e.g., bacteriostatic water for injection with benzyl alcohol or bacteriostatic sodium chloride for injection with benzyl alcohol), or Lactated Ringer's.

1.48 Method I or 1.1-1.47 further comprising admixing the composition with 0.5 to 500 mL solvent, e.g., an aqueous solution, e.g., from about 1 or 2 mL to 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 30, 35, 50, 75, 100, 150, 200, 300 or 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 50, 75, 100, or 200 mL, e.g., from about 3.5 or 5 to 10, 25, 50, or 100 mL, e.g., about 3.5 or 35 mL.

1.49 Method I or 1.1-1.48 further comprising admixing the composition with 0.5 to 500 mL sterile solution, e.g., sterile water for injection, a sterile solution comprising dextrose (e.g., dextrose injection 5%), a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection), a sterile solution comprising benzyl alcohol (e.g., bacteriostatic water for injection with benzyl alcohol or bacteriostatic sodium chloride for injection with benzyl alcohol), or Lactated Ringer's, e.g., from about 1 or 2 mL to 500 mL, e.g., from about 1 or 2

mL to 5, 10, 25, 30, 35, 50, 75, 100, 150, 200, 300 or 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 50, 75, 100, or 200 mL, e.g., from about 3.5 or 5 to 10, 25, 50, or 100 mL, e.g., about 3.5 or 35 mL.

1.50 Method I or 1.1-1.49 further comprising admixing the composition with sterile water for injection or a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection).

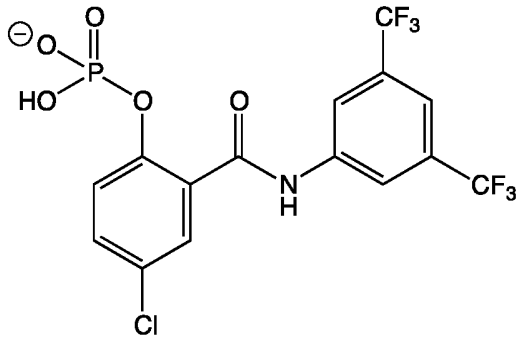
1.51 Method I or 1.1-1.50 further comprising admixing the composition with sterile water for injection.

1.52 Method 1.51 wherein the composition is admixed with 0.5 to 500 mL sterile water for injection, e.g., from about 1 or 2 mL to 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 30, 35, 50, 75, 100, 150, 200, 300 or 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 50, 75, 100, or 200 mL, e.g., from about 3.5 or 5 to 10, 25, 50, or 100 mL, e.g., about 3.5 or 35 mL.

1.53 Method I or 1.1-1.52 further comprising admixing the composition with a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection).

1.54 Method 1.53 wherein the composition is admixed with 0.5 to 500 mL a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection), e.g., from about 1 or 2 mL to 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 30, 35, 50, 75, 100, 150, 200, 300 or 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 50, 75, 100, or 200 mL, e.g., from about 3.5 or 5 to 10, 25, 50, or 100 mL, e.g., about 3.5 or 35 mL.

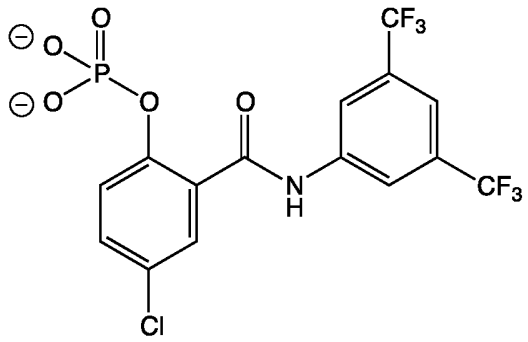
1.55 Method 1.47-1.54 wherein the composition comprises Formula II




Formula II.

1.56 Method 1.47-1.55 wherein the composition comprises at least a 1:1 molar ratio of Formula II to a cation of the base.

1.57 Method 1.47-1.54 wherein the composition comprises Formula III



Formula III.

1.58 Method 1.47-1.54 or 1.57 wherein the composition comprises at least a 1:2 molar ratio of Formula III to a cation of the base e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.59 Method 1.47-1.58 wherein the concentration of Formula II or Formula III, e.g., the concentration of Formula II, e.g, the concentration of Formula III, is 0.01 or 0.02 or 0.05 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250 mM, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM.

1.60 Method 1.47-1.59 wherein the solvent, e.g., the sterile solution, comprises a base, e.g., a base wherein upon dissolution of the composition in the solvent, e.g., the sterile solution, the composition has a pH between 7, 7.5, or 8 and 10.5, e.g., between about 7, 7.5, or 8 and 9.5, e.g., between about 7 or 7.5 and 8, e.g., between about 7.5 and 8.5, e.g., about 7.5, e.g., about 8.5, e.g., between about 8 and 8.5, e.g., about 8.2, e.g., a base with a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9 between 6 and 11, e.g., between 6.5 and 10, e.g., between 7 and 9, e.g., wherein the base is one or more of:

a) a $C_{1-8}$-alkyl mono-, di-, or tri- carboxylic acid salt, e.g., a citrate salt, e.g, a metal citrate salt (e.g., an alkali and/or alkaline citrate salt, e.g.,

an alkali citrate salt, e.g., sodium citrate and/or potassium citrate), e.g., a tartrate salt (e.g., a metal tartrate salt, an alkali tartrate, e.g., sodium tartrate), e.g., a succinate salt (e.g., a metal succinate salt, e.g., an alkali succinate, e.g., disodium succinate), and/or e.g., a lactate salt (e.g., a metal lactate salt, e.g., an alkali lactate, e.g., sodium lactate),

b) a phosphate salt, e.g., a metal phosphate salt (e.g., an alkali and/or alkaline phosphate salt, e.g., an alkali phosphate salt, e.g., sodium phosphate (e.g., $NaH_2PO_4$ and/or $Na_2HPO_4$) and/or potassium phosphate (e.g., $KH_2PO_4$ and/or $K_2HPO_4$)),

a) an amine and/or a salt thereof (e.g., morpholine, piperazine, benethamine, benzathine, trimethylglycine, hydrabamine, 4-(2-hydroxyethyl)morpholine, 1-2-hydroxyethyl)-pyrrolidine, an amino acid (e.g., arginine and/or lysine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., -$CH_2CH_3$, e.g., -$CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., –$CH_2$–$CH_2$–, e.g., –$C(CH_2)_3$–, e.g., one $R^8$ is –$CH_3$ and another $R^8$ is –$(CH_2)_6$–) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, dimethylethanolamine, diethylamine, diethylethanolamine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9,

b) a metal chloride salt (e.g., zinc chloride),

c) an acetate salt, e.g., a metal acetate salt (e.g., an alkali and/or alkaline acetate salt, e.g., an alkali acetate salt, e.g., sodium acetate and/or potassium acetate),

d) a hydroxide and/or alkoxide salt, e.g., a metal hydroxide and/or alkoxide salt (e.g., a quarternary ammonium hydroxide, e.g., ammonium hydroxide and/or choline hydroxide, lithium hydroxide, aluminum hydroxide, e.g., an alkali and/or alkaline hydroxide salt, e.g., sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, and/or magnesium ethoxide e.g., sodium hydroxide),

e) a carbonate and/or bicarbonate salt, e.g., a metal carbonate and/or metal bicarbonate salt (e.g., an alkali and/or alkaline carbonate salt, e.g., an alkali and/or alkaline bicarbonate salt, e.g., sodium bicarbonate), and/or

f) a metal borate salt (e.g., an alkali borate salt, e.g., sodium borate),

e.g., one or more of sodium citrate, $Na_2HPO_4$, tris(hydroxymethyl)aminomethane, and a tris(hydroxymethyl)aminomethane salt (e.g., tris acetate), e.g., one or more of sodium citrate, $Na_2HPO_4$, and tris(hydroxymethyl)aminomethane, e.g., one or more of sodium citrate and $Na_2HPO_4$, e.g., $Na_2HPO_4$, e.g., tris(hydroxymethyl)aminomethane.

1.61 Method 1.47-1.60 wherein the solvent, e.g., the sterile solution, comprises a base, e.g., a base wherein upon dissolution of the composition in the solvent, e.g., the sterile solution, the composition has a pH between 7, 7.5, or 8 and 10.5, e.g., between about 7, 7.5, or 8 and 9.5, e.g., between about 7 or 7.5 and 8, e.g., between about 7.5 and 8.5, e.g., about 7.5, e.g., about 8.5, e.g., between about 8 and 8.5, e.g., about 8.2, e.g., a base with a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, e.g., wherein the base is one or more of:

a) a metal citrate salt (e.g., an alkali and/or alkaline citrate salt, e.g., an alkali citrate salt, e.g., sodium citrate and/or potassium citrate),

b) a metal phosphate salt (e.g., an alkali and/or alkaline phosphate salt, e.g., an alkali phosphate salt, e.g., sodium phosphate (e.g., $NaH_2PO_4$ and/or $Na_2HPO_4$) and/or potassium phosphate (e.g., $KH_2PO_4$ and/or $K_2HPO_4$)),

c) an amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9,

d) a metal acetate salt (e.g., an alkali and/or alkaline acetate salt, e.g., an alkali acetate salt, e.g., sodium acetate and/or potassium acetate),

e) a metal hydroxide salt (e.g., an alkali and/or alkaline hydroxide salt, e.g., sodium hydroxide, potassium hydroxide, calcium hydroxide, and/or magnesium hydroxide, e.g., sodium hydroxide),

f) a metal carbonate and/or bicarbonate salt (e.g., an alkali and/or alkaline carbonate salt, e.g., an alkali and/or alkaline bicarbonate salt, e.g., sodium bicarbonate), and/or

g) a metal borate salt (e.g., an alkali borate salt, e.g., sodium borate),

e.g., one or more of sodium citrate, $Na_2HPO_4$, tris(hydroxymethyl)aminomethane, and a tris(hydroxymethyl)aminomethane salt (e.g., tris acetate), e.g., one or more of sodium citrate, $Na_2HPO_4$, and tris(hydroxymethyl)aminomethane, e.g., one or more of sodium citrate and $Na_2HPO_4$, e.g., $Na_2HPO_4$, e.g., tris(hydroxymethyl)aminomethane.

1.62 Method 1.61 wherein the 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate and the base, e.g., sodium citrate, sodium

phosphate (e.g., $Na_2HPO_4$), tris(hydroxymethyl)aminomethane, and/or a tris(hydroxymethyl)aminomethane salt (e.g., tris acetate), form a salt.

1.63 Method 1.60-1.62 wherein the solvent, e.g., the sterile solution, comprises 1 or 5 mg to 200 or 500 mg of the one or more base, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.64 Method 1.60-1.63 wherein the concentration of each of the one or more bases is 0.01 or 0.02 or 0.05 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of each of the one or more bases is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of each of the one or more bases is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.65 Method 1.60-1.64 wherein the one or more bases comprise one or more of a metal citrate salt (e.g., sodium citrate) and a metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$).

1.66 Method 1.60-1.65 wherein the one or more bases comprise a metal citrate salt (e.g., sodium citrate).

1.67 Method 1.66 wherein the solvent, e.g., the sterile solution, comprises 1 or 5 mg to 200 or 500 mg of a metal citrate salt (e.g., sodium citrate), e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.68 Method 1.67 wherein the concentration of the metal citrate salt (e.g., sodium citrate) is 0.01 or 0.02 or 0.05 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of the metal citrate salt is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of the metal citrate salt is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.69 Method 1.60-1.68 wherein the one or more bases comprise metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$).

1.70 Method 1.69 wherein the solvent, e.g., the sterile solution, comprises 1 or 5 mg to 200 or 500 mg of a metal phosphate salt (e.g, sodium phosphate, e.g., $Na_2HPO_4$), e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.71 Method 1.70 wherein the concentration of the metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$), is 0.01 or 0.02 or 0.05 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of the metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of the metal phosphate salt (e.g., sodium

phosphate, e.g., $Na_2HPO_4$) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.72 Method 1.60-1.71 wherein the one or more bases comprise an amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9.

1.73 Method 1.72 wherein the solvent, e.g., the sterile solution, comprises 1 or 5 mg to 200 or 500 mg of the amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6 and 11, e.g., between 6.5 and 10, e.g., between 7 and 9, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500

mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.74 Method 1.72 wherein the concentration of the amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, is 0.01 or 0.02 or 0.05 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of the amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof

(e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of the amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., -$CH_2CH_3$, e.g., -$CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., –$CH_2$–$CH_2$–, e.g., –$C(CH_2)_3$–, e.g., one $R^8$ is –$CH_3$ and another $R^8$ is –$(CH_2)_6$–) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.75 Method 1.60-1.74 wherein the one or more bases comprise a mono- and/or poly-hydroxyalkylamine and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., -$CH_2CH_3$, e.g., -$CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., –$CH_2$–$CH_2$–, e.g., –$C(CH_2)_3$–, e.g., one $R^8$ is –$CH_3$ and another $R^8$ is –$(CH_2)_6$–) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine).

1.76 Method 1.75 wherein the solvent, e.g., the sterile solution, comprises 1 or 5 mg to 200 or 500 mg of the mono- and/or poly-hydroxyalkylamine and/or salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., -$CH_2CH_3$, e.g., -$CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., –$CH_2$–$CH_2$–, e.g., –$C(CH_2)_3$–, e.g., one $R^8$ is –$CH_3$ and another $R^8$ is –$(CH_2)_6$–) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g.,

tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.77 Method 1.76 wherein the concentration of the mono- and/or poly-hydroxyalkylamine and/or salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), is 0.01 or 0.02 or 0.05 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of the mono- and/or poly-hydroxyalkylamine and/or salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of

Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of each of the mono- and/or poly-hydroxyalkylamine and/or salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., -$CH_2CH_3$, e.g., -$CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., –$CH_2$–$CH_2$–, e.g., –$C(CH_2)_3$–, e.g., one $R^8$ is –$CH_3$ and another $R^8$ is –$(CH_2)_6$–) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.78 Method 1.60-1.77 wherein the one or more bases comprise $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., -$CH_2CH_3$, e.g., -$CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., –$CH_2$–$CH_2$–, e.g., –$C(CH_2)_3$–, e.g., one $R^8$ is –$CH_3$ and another $R^8$ is –$(CH_2)_6$–) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine).

1.79 Method 1.78 wherein the solvent, e.g., the sterile solution, comprises 1 or 5 mg to 200 or 500 mg of $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., -$CH_2CH_3$, e.g., -$CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., –$CH_2$–$CH_2$–, e.g., –$C(CH_2)_3$–, e.g., one $R^8$ is –$CH_3$ and another $R^8$ is –$(CH_2)_6$–) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg,

e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.80 Method 1.78 wherein the concentration of $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), is 0.01 or 0.02 or 0.05 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and

another $R^8$ is $-(CH_2)_6-$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.81 Method 1.60-1.80 wherein the one or more bases comprise tris(hydroxymethyl)aminomethane and/or meglumine, e.g., tris(hydroxymethyl)aminomethane, e.g, meglumine.

1.82 Method 1.81 wherein the solvent, e.g., the sterile solution, comprises 1 or 5 mg to 200 or 500 mg of tris(hydroxymethyl)aminomethane, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg and/or wherein the solvent, e.g., the sterile solution, comprises 1 or 5 mg to 200 or 500 mg of meglumine, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.83 Method 1.81 wherein the concentration of tris(hydroxymethyl)aminomethane is 0.01 or 0.02 or 0.05 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of tris(hydroxymethyl)aminomethane is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of tris(hydroxymethyl)aminomethane is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10 and/or wherein the concentration of meglumine is 0.01 or 0.02 or 0.05 or 0.1 or 0.5 or 1 or 2 to 250

mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of meglumine is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of meglumine is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.84 Method 1.60-1.83 wherein the one or more bases comprise a tris(hydroxymethyl)aminomethane salt (e.g., tris(hydroxymethyl)aminomethane acetate).

1.85 Method 1.84 wherein the solvent, e.g., the sterile solution, comprises 1 or 5 mg to 200 or 500 mg of the tris(hydroxymethyl)aminomethane salt (e.g., tris(hydroxymethyl)aminomethane acetate), e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.86 Method 1.84 wherein the concentration of the tris(hydroxymethyl)aminomethane salt (e.g., tris(hydroxymethyl)aminomethane acetate) is 0.01 or 0.02 or 0.05 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM.

1.87 Method 1.60-1.86 wherein the one or more bases comprise a base wherein a conjugate acid of the base has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9.

1.88 Method 1.87 wherein the solvent, e.g., the sterile solution, comprises 1 or 5 mg to 200 or 500 mg of the base, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.89 Method 1.87 wherein the concentration of the base is 0.01 or 0.02 or 0.05 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of the base is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of the base is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.90 Method 1.47-1.89 wherein the solvent, e.g., the sterile solution comprises one or more bulking agents, e.g., one or more of maltose, mannose, ribose, cyclodextrin, mannitol, lactose, sucrose, trehalose, sorbitol, glucose, raffinose, arginine, glycine, histidine, dextran (e.g., dextran 40), polyvinylpyrrolidone, polyethylene glycol, and polypropylene glycol, e.g., one or more of mannitol, glucose, sucrose, lactose, trehalose, and dextran (e.g., dextran 40).

1.91 Method 1.47-1.90 wherein the solvent, e.g., the sterile solution, comprises 5 or 10 or 50 mg to 2 or 5 g of one or more bulking agents, e.g., from about 50 or 100 mg to 200, 300, 500, or 800 mg, or 1, 1.5, 2, 3, 4, or 5 g of one or more bulking agents.

1.92 Method 1.47-1.91 wherein the solvent, e.g., the sterile solution, comprises dextran (e.g., dextran 40).

1.93 Method 1.92 wherein the solvent, e.g. the sterile solution, comprises 5 or 10 or 50 mg to 2 or 5 g dextran (e.g., dextran 40), e.g., from about 50 or 100 mg to 200, 300, 500, or 800 mg, or 1, 1.5, 2, 3, 4, or 5 g dextran (e.g., dextran 40).

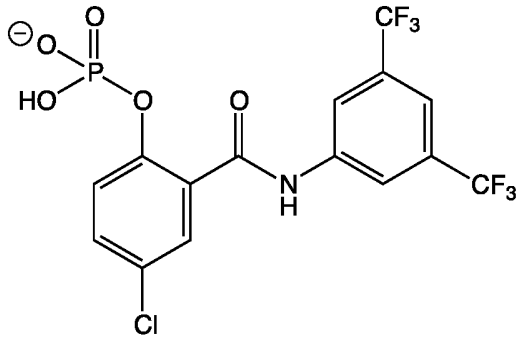
1.94 Method 1.47-1.93 wherein the solvent, e.g., the sterile solution, comprises one or more solubilizing agents, e.g., ethylenediamine tetraacetic acid (EDTA) or a salt thereof (e.g., calcium disodium EDTA, disodium EDTA, sodium EDTA), alpha cyclodextrin, hydroxypropyl-β-cyclodextrin, polysorbate 80, tert-butanol, isopropanol, dichloromethane, ethanol, acetone, and glycerol; one or more collapse temperature modifiers which may shift the overall collapse temperature higher, e.g., one or more of dextran, Ficoll®, gelatin, and hydroxyethyl starch; one or more tonicity modifiers, e.g., one or more of sodium chloride, potassium chloride, sucrose, mannitol, and glucose; and one or more antimicrobial agents, e.g., one or more of benzyl alcohol, phenol, 2-phenoxyethanol, m-cresol, chlorobutanol, parabens (e.g., methyl paraben, ethyl paraben, propyl paraben), benzalkonium chloride, benzethonium chloride, myristyl gamma-picolinium salt (e.g., myristyl gamma-picolinium chloride), and organomercury compounds and salts (e.g., phenyl mercuric acetate, phenyl mercuric borate, phenyl mercuric nitrate, and thimerosal).

1.95 Method 1.47-1.94 wherein the pH after admixture with the solvent, e.g., an aqueous solution, is between pH 7 and pH 10.5, e.g., between pH 7 and pH 9.5, e.g., between pH 7 and pH 8, e.g., between 7.5 and 8.5, e.g., 7.5, e.g., 8.5, e.g., 8.2.

1.96 Method 1.47-1.95 wherein the pH after admixture with the solvent, e.g., an aqueous solution, is further adjusted, e.g., adjusted to achieve a pH between pH 7 and pH 10.5, e.g., between pH 7 and pH 9.5, e.g., between pH 7 and pH 8, e.g., between 7.5 and 8.5, e.g., 7.5, e.g., 8.5, e.g., 8.2, e.g., wherein the pH is adjusted with NaOH.

1.97 Method 1.47-1.96 further comprising filtering after admixture with the solvent, e.g., an aqueous solution, to remove particles and microbes, e.g., filtered prior to injection.

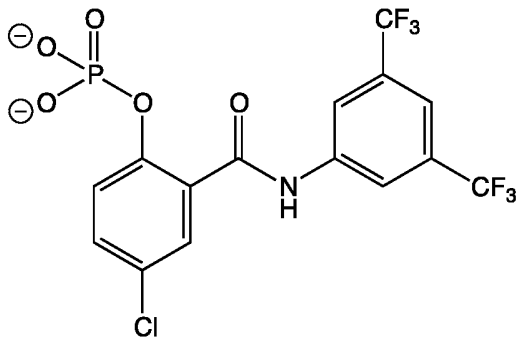
1.98 Method 1.47-1.97 wherein the composition comprises Formula II



Formula II.

1.99 Method 1.47-1.98 wherein the composition comprises at least a 1:1 molar ratio of Formula II to a cation of the base.

1.100 Composition 1.47-1.96 wherein the composition comprises Formula III



Formula III

1.101 Method 1.47-1.96 or 1.100 wherein the composition comprises at least a 1:2 ratio of Formula III to a cation of the base, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

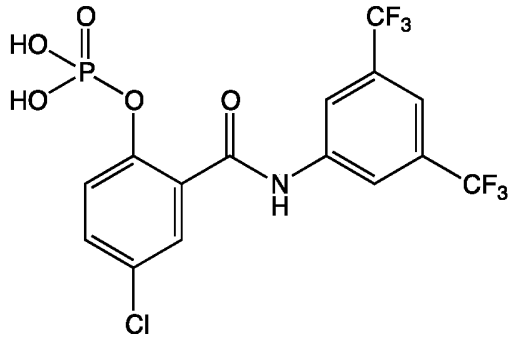
1.102 Method 1.47-1.101 wherein upon dissolution of the composition in the solvent, e.g., the aqueous solution, the composition has a pH between 7, 7.5, or 8 and 10.5, e.g., between about 7, 7.5, or 8 and 9.5, e.g., between about 7 or 7.5 and 8, e.g., between about 7.5 and 8.5, e.g., about 7.5, e.g., about 8.5, e.g., between about 8 and 8.5, e.g., about 8.2.

1.103 Method I or 1.1-1.102 further comprising admixing the composition with one or more additional therapeutic agents, e.g., one or more additional therapeutic agents for cerebral edema, stroke, traumatic brain injury, glioma (e.g., glioblastoma),

meningitis, acute mountain sickness, infection, metabolic disorder, hypoxia, water intoxication, hepatic failure, hepatic encephalopathy, diabetic ketoacidosis, abscess, eclampsia, Creutzfeldt-Jakob disease, lupus cerebritis, optic nerve edema, hyponatremia, fluid retention, ovarian hyperstimulation syndrome, epilepsy, retinal ischemia or other diseases of the eye associated with abnormalities in intraocular pressure and/or tissue hydration, myocardial ischemia, myocardial ischemia/reperfusion injury, myocardial infarction, myocardial hypoxia, congestive heart failure, sepsis, neuromyelitis optica, or migraines.

1.104 Method I or 1.1-1.103 further comprising admixing the composition with one or more additional therapeutic agents, e.g., one or more additional therapeutic agents for pulmonary edema, fibromyalgia, or multiple sclerosis.

**[0062]** In yet another embodiment, provided is a salt solution (Salt Solution I) comprising a solvent, e.g., an aqueous solution, and a salt formed from a compound of Formula I



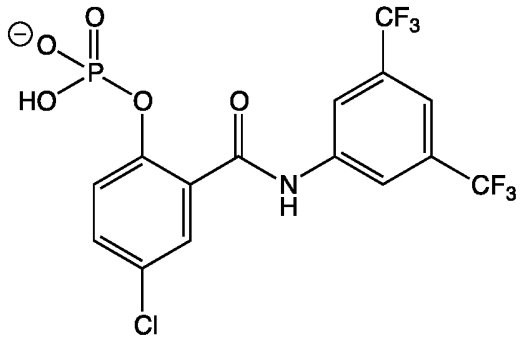
Formula I

and an amine and/or a salt thereof (e.g., morpholine, piperazine, benethamine, benzathine, trimethylglycine, hydrabamine, 4-(2-hydroxyethyl)morpholine, 1-2-hydroxyethyl)-pyrrolidine, an amino acid (e.g., arginine and/or lysine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, dimethylethanolamine, diethylamine, diethylethanolamine, and/or diethanolamine), e.g., any of

the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9.

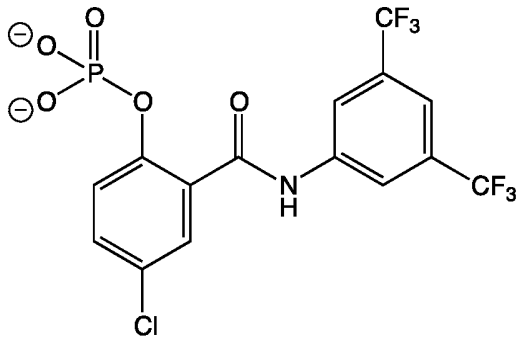
**[0063]** Further provided is Salt Solution I as follows:

1.1 Salt Solution I wherein the salt solution comprises Formula II



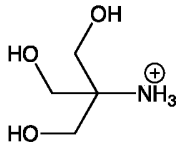
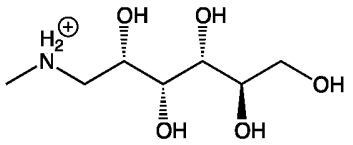
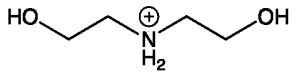
Formula II

1.2 Salt Solution I or 1.1 wherein the salt solution comprises Formula III

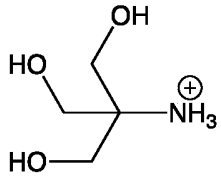


Formula III

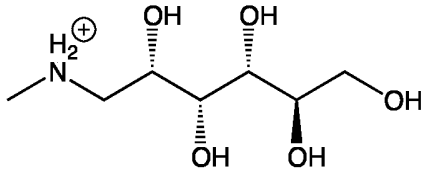
1.3 Salt Solution I, 1.1, or 1.2 wherein the salt solution comprises a protonated and/or unprotonated mono- and/or poly-hydroxyalkylamine, e.g., e.g., $(HO)_nR^8NH_3$, $[(HO)_nR^8]_2NH_2$, $[(HO)_nR^8]_3NH$, e.g., $(HO)_nR^8NH_3$, $[(HO)_nR^8]_2NH_2$, $[(HO)_nR^8]_3NH^+$, wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g.,



and/or


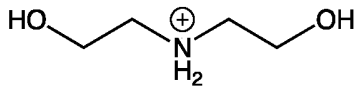
1.4 Salt Solution I or 1.1-1.3 wherein the salt solution comprises



1.5 Salt Solution I or 1.1-1.4 wherein the salt solution comprises



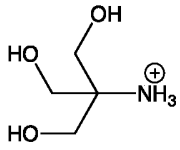
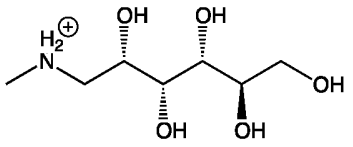
1.6 Salt Solution I or 1.1-1.5 wherein the salt solution comprises



1.7 Salt Solution I or 1.1-1.6 wherein the salt solution comprises at least a 1:1 molar ratio of Formula II to the protonated amine.

1.8 Salt Solution I or 1.1-1.7 wherein the salt solution comprises at least a 1:2 molar ratio of Formula II to the protonated amine, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.9 Salt Solution 1.8 wherein the salt solution comprises at least a 1:2 molar ratio of Formula II to the protonated mono- and/or poly-hydroxyalkylamine, e.g., $(HO)_nR^8NH_3^+$, $[(HO)_nR^8]_2NH_2^+$, $[(HO)_nR^8]_3NH^+$, wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $-CH_2-CH_2-$, e.g., $-C(CH_2)_3-$, e.g., one $R^8$ is $-CH_3$ and another $R^8$ is $-(CH_2)_6-$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g.,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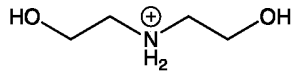
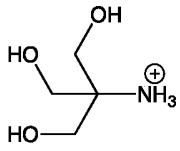
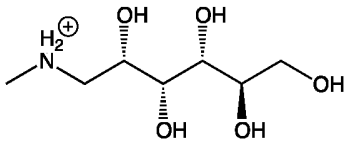


e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.10 Salt Solution 1.8-1.10 wherein the salt solution comprises at least a 1:2 molar ratio of Formula II to $(HO)_nR^8NH_3^+$, $[(HO)_nR^8]_2NH_2^+$, $[(HO)_nR^8]_3NH^+$, wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g.,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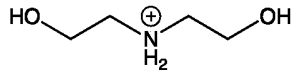
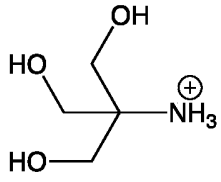
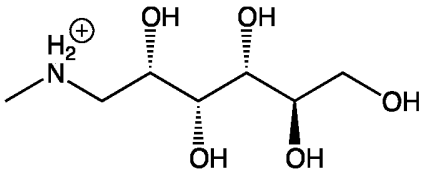


e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.11 Salt Solution 1.8-1.10 wherein the salt solution comprises at least a 1:2 molar ratio of Formula II to


, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

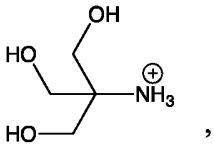
1.12 Salt Solution 1.8-1.10 wherein the salt solution comprises at least a 1:2 molar ratio of Formula II to



, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.13 Salt Solution I or 1.1-1.6 wherein the salt solution comprises at least a 1:2 molar ratio of Formula III to the protonated amine, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.14 Salt Solution 1.14 wherein the salt solution comprises at least a 1:2 molar ratio of Formula III to the protonated mono- and/or poly-hydroxyalkylamine, e.g., $(HO)_nR^8NH_3^+$, $[(HO)_nR^8]_2NH_2^+$, $[(HO)_nR^8]_3NH^+$, wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g.,



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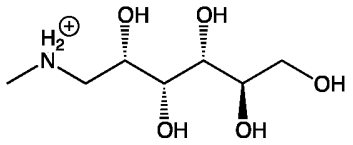

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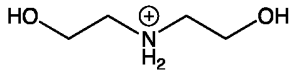

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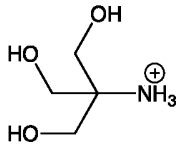
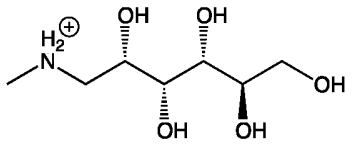
e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.15 Salt Solution 1.14-1.15 wherein the salt solution comprises at least a 1:2 molar ratio of Formula III to $(HO)_nR^8NH_3^+$, $[(HO)_nR^8]_2NH_2^+$, $[(HO)_nR^8]_3NH^+$, wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g.,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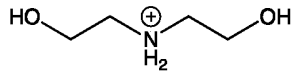
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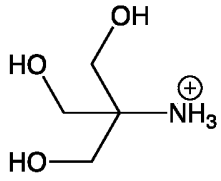
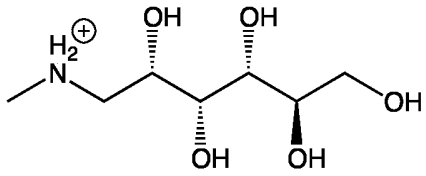
e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

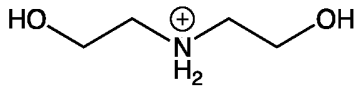
1.16 Salt Solution 1.14-1.16 wherein the salt solution comprises at least a 1:2 molar ratio of Formula III to


, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.17 Salt Solution 1.14-1.16 wherein the salt solution comprises at least a 1:2 molar ratio of Formula III to


, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.18 Salt Solution 1.14-1.16 wherein the salt solution comprises at least a 1:2 molar ratio of Formula III to


, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.19 Salt Solution I or 1.1-1.19 wherein the solvent is a sterile solution, e.g., sterile water for injection, a sterile solution comprising dextrose (e.g., dextrose injection 5%), a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection), a sterile solution comprising benzyl alcohol (e.g., bacteriostatic water for injection with benzyl alcohol or bacteriostatic sodium chloride for injection with benzyl alcohol), or Lactated Ringer's.

1.20 Salt Solution I or 1.1-1.20 wherein the salt solution comprises 0.5 to 500 mL solvent, e.g., an aqueous solution, e.g., from about 1 or 2 mL to 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 30, 35, 50, 75, 100, 150, 200, 300 or 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 50, 75, 100, or 200 mL, e.g., from about 3.5 or 5 to 10, 25, 50, or 100 mL, e.g., about 3.5 or 35 mL.

1.21 Salt Solution I or 1.1-1.21 wherein the salt solution comprises 0.5 to 500 mL sterile solution, e.g., sterile water for injection, a sterile solution comprising dextrose (e.g., dextrose injection 5%), a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection), a sterile solution comprising benzyl alcohol (e.g., bacteriostatic water for injection with benzyl alcohol or bacteriostatic sodium chloride for injection with benzyl alcohol), or Lactated Ringer's, e.g., from about 1 or 2 mL to 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 30, 35, 50, 75, 100, 150, 200, 300 or 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 50, 75, 100, or 200 mL, e.g., from about 3.5 or 5 to 10, 25, 50, or 100 mL, e.g., about 3.5 or 35 mL.

1.22 Salt Solution I or 1.1-1.22 wherein the salt solution comprises sterile water for injection or a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection).

1.23 Salt Solution I or 1.1-1.23 wherein the salt solution comprises sterile water for injection.

1.24 Salt Solution 1.24 wherein the salt solution comprises 0.5 to 500 mL sterile water for injection, e.g., from about 1 or 2 mL to 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 30, 35, 50, 75, 100, 150, 200, 300 or 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 50, 75, 100, or 200 mL, e.g., from about 3.5 or 5 to 10, 25, 50, or 100 mL, e.g., about 3.5 or 35 mL.

1.25 Salt Solution I or 1.1-1.25 wherein the salt solution comprises a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection).

1.26 Salt Solution 1.26 wherein the salt solution comprises 0.5 to 500 mL of a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection), e.g., from about 1 or 2 mL to 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 30, 35, 50, 75, 100, 150, 200, 300 or 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 50, 75, 100, or 200 mL, e.g., from about 3.5 or 5 to 10, 25, 50, or 100 mL, e.g., about 3.5 or 35 mL.

1.27 Salt Solution I or 1.1-1.27 wherein the concentration of Formula II or Formula III, e.g., the concentration of Formula II, e.g, the concentration of Formula III is 0.01 or 0.02 or 0.05 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM.

1.28 Salt Solution I or 1.1-1.28 wherein the salt solution comprises one or more bulking agents, e.g., one or more of maltose, mannose, ribose, cyclodextrin, mannitol, lactose, sucrose, trehalose, sorbitol, glucose, raffinose, arginine, glycine, histidine, dextran (e.g., dextran 40), polyvinylpyrrolidone, polyethylene glycol, and polypropylene glycol, e.g., one or more of mannitol, glucose, sucrose, lactose, trehalose, and dextran (e.g., dextran 40).

1.29 Salt Solution I or 1.1-1.29 wherein the salt solution comprises 5 or 10 or 50 mg to 2 or 5 g of one or more bulking agents, e.g., from about 50 or 100 mg to 200, 300, 500, or 800 mg, or 1, 1.5, 2, 3, 4, or 5 g of one or more bulking agents.

1.30 Salt Solution I or 1.1-1.30 wherein the salt solution comprises dextran (e.g., dextran 40).

1.31 Salt Solution 1.31 wherein the salt solution comprises 5 or 10 or 50 mg to 2 or 5 g dextran (e.g., dextran 40), e.g., from about 50 or 100 mg to 200, 300, 500, or 800 mg, or 1, 1.5, 2, 3, 4, or 5 g dextran (e.g., dextran 40).

1.32 Salt Solution I or 1.1-1.32 wherein the salt solution comprises one or more solubilizing agents, e.g., ethylenediamine tetraacetic acid (EDTA) or a salt thereof

(e.g., calcium disodium EDTA, disodium EDTA, sodium EDTA), alpha cyclodextrin, hydroxypropyl-β-cyclodextrin, polysorbate 80, tert-butanol, isopropanol, dichloromethane, ethanol, acetone, and glycerol; one or more collapse temperature modifiers which may shift the overall collapse temperature higher, e.g., one or more of dextran, Ficoll®, gelatin, and hydroxyethyl starch; one or more tonicity modifiers, e.g., one or more of sodium chloride, potassium chloride, sucrose, mannitol, and glucose; and one or more antimicrobial agents, e.g., one or more of benzyl alcohol, phenol, 2-phenoxyethanol, m-cresol, chlorobutanol, parabens (e.g., methyl paraben, ethyl paraben, propyl paraben), benzalkonium chloride, benzethonium chloride, myristyl gamma-picolinium salt (e.g., myristyl gamma-picolinium chloride), and organomercury compounds and salts (e.g., phenyl mercuric acetate, phenyl mercuric borate, phenyl mercuric nitrate, and thimerosal).

1.33 Salt Solution I or 1.1-1.33 wherein the pH of the salt solution is between pH 7 and pH 10.5, e.g., between pH 7 and pH 9.5, e.g., between pH 7 and pH 8, e.g., between 7.5 and 8.5, e.g., 7.5, e.g., 8.5, e.g., 8.2.

1.34 Salt Solution I or 1.1-1.34 wherein the salt solution is filtered to remove particles and microbes, e.g., filtered prior to injection.

1.35 Salt Solution I or 1.1-1.35 wherein the salt solution is for injection, e.g., subcutaneously, intramuscularly, intravenously, or intrathecally, e.g., intramuscularly or intravenously, e.g., a bolus injected subcutaneously, intramuscularly, intravenously, or intrathecally.

1.36 Salt Solution 1.36 wherein the salt solution is for injection intravenously, e.g., IV bolus and/or IV infusion, e.g., IV bolus followed by IV infusion, e.g., a loading bolus (e.g., 10 or 20 to 30, 50, 70, 75, 100, 140, 150, 200, 300 or 400 mg per day administered by a loading bolus dose, e.g., about 50 to 200 or 250 mg per day administered by a loading bolus dose, e.g., about 70 to 140 mg per day administered by a loading bolus dose, e.g., a concentration of the dissolved salt administered by a loading bolus dose of 1 to 4, 5, 8, 10, 15, 20, 30, or 50 mM per day, e.g., a concentration of the dissolved salt administered by a loading bolus dose of about 2 to 5, 10, 15, or 20 mM per day, e.g., a concentration of the

dissolved salt administered by a loading bolus dose of about 4 to 8 or 9 mM per day) and then an IV infusion over 24 hours for 3 days (e.g., at a rate of 1, 2, 3, 5, 6, 7, 8, 10, 15, 20, 25, 30, or 50 mg/hr for 24 hours, e.g., at a rate of 3, 6, or 15 mg/hr).

1.37 Salt Solution 1.36 wherein the salt solution is for injection intramuscularly, e.g., IM bolus and/or IM infusion, e.g., IM bolus followed by IM infusion.

1.38 Salt Solution 1.37 or 1.38 wherein the infusion, e.g., IV or IM, is administered over about 10 or 30 minutes to 72 hours, e.g., about 30 minutes to 24 hours, e.g, about 30 minutes to 12 hours, e.g., about 30 minutes to 8 hours, e.g., about 30 minutes to 6 hours, e.g., about 30 minutes to 4 hours, e.g., about 30 minutes to 2 hours, e.g., about 30 minutes to 1 hour, e.g., about 72 hours.

1.39 Salt Solution I or 1.1-1.39 wherein the salt solution comprises one or more additional therapeutic agents, e.g., one or more additional therapeutic agents for cerebral edema, stroke, traumatic brain injury, glioma (e.g., glioblastoma), meningitis, acute mountain sickness, infection, metabolic disorder, hypoxia, water intoxication, hepatic failure, hepatic encephalopathy, diabetic ketoacidosis, abscess, eclampsia, Creutzfeldt-Jakob disease, lupus cerebritis, optic nerve edema, hyponatremia, fluid retention, ovarian hyperstimulation syndrome, epilepsy, retinal ischemia or other diseases of the eye associated with abnormalities in intraocular pressure and/or tissue hydration, myocardial ischemia, myocardial ischemia/reperfusion injury, myocardial infarction, myocardial hypoxia, congestive heart failure, sepsis, neuromyelitis optica, or migraines.

1.40 Salt Solution I or 1.1-1.40 wherein the salt solution comprises one or more additional therapeutic agents, e.g., one or more additional therapeutic agents for pulmonary edema, fibromyalgia, or multiple sclerosis.

1.41 Salt Solution I or 1.1-1.41 wherein the salt solution is stable for at least one week, at room temperature, e.g., for at least 1, 2, 4, 6, 8, or 12 months, e.g., the composition has < 20% N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide, < 15% N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide, < 10% N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-

hydroxybenzamide, < 5% N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide, < 2% N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide, 1% N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide, or < 1% N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide.

1.42 Salt Solution I or 1.1-1.42 wherein the salt solution comprises less than 10%, 15%, or 20% of N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide, e.g., less than 5, 4, 3, or 2% of N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide for at least one week, e.g., for at least 1, 2, 4, 6, 8, or 12 months.

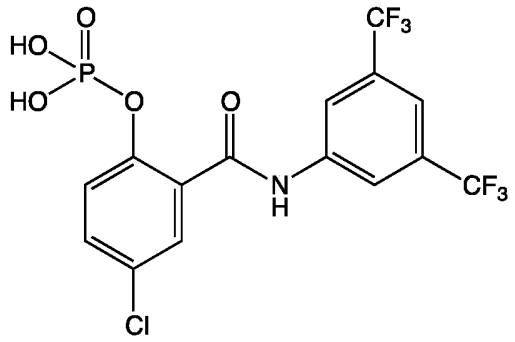
1.43 Salt Solution I or 1.1-1.43 wherein the salt solution is administered concurrently or sequentially, in either order, with one or more additional therapeutic agents, e.g., one or more additional therapeutic agents for cerebral edema, stroke, traumatic brain injury, glioma (e.g., glioblastoma), meningitis, acute mountain sickness, infection, metabolic disorder, hypoxia, water intoxication, hepatic failure, hepatic encephalopathy, diabetic ketoacidosis, abscess, eclampsia, Creutzfeldt-Jakob disease, lupus cerebritis, optic nerve edema, hyponatremia, fluid retention, ovarian hyperstimulation syndrome, epilepsy, retinal ischemia or other diseases of the eye associated with abnormalities in intraocular pressure and/or tissue hydration, myocardial ischemia, myocardial ischemia/reperfusion injury, myocardial infarction, myocardial hypoxia, congestive heart failure, sepsis, neuromyelitis optica, or migraines.

1.44 Salt Solution I or 1.1-1.44 wherein the salt solution is administered concurrently or sequentially, in either order, with one or more additional therapeutic agents, e.g., one or more additional therapeutic agents for pulmonary edema, fibromyalgia, or multiple sclerosis.

1.45 Salt Solution I or 1.1-1.45 wherein the salt solution is for use in any of the methods described herein, e.g., for use in Method A, e.g., Method A.1-A.58, for use in Method B, e.g., Method B.1-B.41, e.g., for use in Method C, e.g., C.1-C.8, e.g., for use in Method D, e.g., D.1-D.19, e.g., for use in Method E, e.g., E.1-E.59,

e.g., for use in Method F, e.g., F.1-F.5, e.g., for use in Method G, e.g., G.1-G.58, for use in Method H, e.g., H.1-H.9, *vida infra*.

**[0064]** In yet another embodiment, provided is a method (Method II) for making a salt solution, e.g., Salt Solution I, e.g., Salt Solution 1.1-1.46, comprising admixing a compound of Formula I



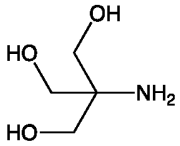
Formula I

and an amine and/or a salt thereof (e.g., morpholine, piperazine, benethamine, benzathine, trimethylglycine, hydrabamine, 4-(2-hydroxyethyl)morpholine, 1-2-hydroxyethyl)-pyrrolidine, an amino acid (e.g., arginine and/or lysine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$ and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, dimethylethanolamine, diethylamine, diethylethanolamine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, in a solvent, e.g., an aqueous solution,.

**[0065]** Further provided is Method II as follows:

2.1 Method II comprising admixing the compound of Formula I with a mono- and/or poly-hydroxyalkylamine and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, and/or $[(HO)_nR^8]_3N$ and/or a salt thereof, wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., –

$C(CH_2)_3$–, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g.,



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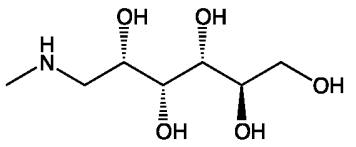
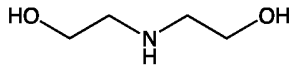
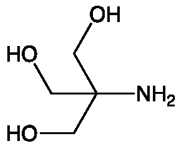


, and/or


,

and/or a salt thereof, e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9.

2.2 Method II or 2.1 comprising admixing the compound of Formula I with $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, and/or $[(HO)_nR^8]_3N$ and/or salt thereof (e.g., acetate, e.g., tris(hydroxymethyl)aminomethane acetate), wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g.,



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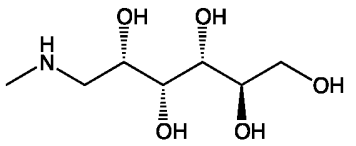

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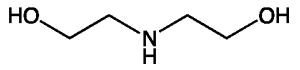
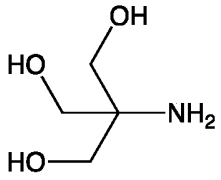


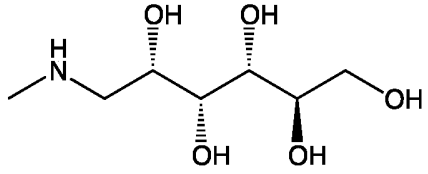

and/or a salt thereof.

2.3 Method II, 2.1, or 2.2 comprising admixing the compound of Formula I with



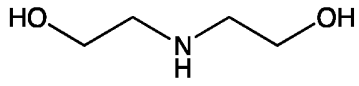
and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate).

2.4 Method II or 2.1-2.3 comprising admixing the compound of Formula I with



and/or a salt thereof.

2.5 Method II or 2.1-2.4 comprising admixing the compound of Formula I with

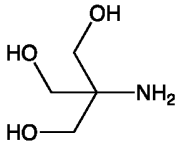


and/or a salt thereof.

2.6 Method II or 2.1-2.5 wherein Formula II and the amine and/or salt thereof are admixed in at least a 1:1 molar ratio.

2.7 Method II or 2.1-2.6 wherein Formula II and the amine and/or salt thereof are admixed in at least a 1:2 molar ratio, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

2.8 Method II or 2.1-2.7 wherein Formula II and the mono- and/or poly-hydroxyalkylamine and/or salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, and/or $[(HO)_nR^8]_3N$ and/or salt thereof and/or salt thereof (e.g., acetate, e.g., tris(hydroxymethyl)aminomethane acetate), wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g.,



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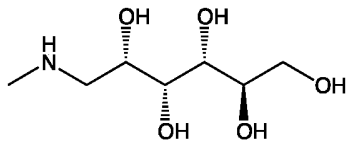
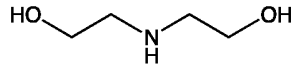


, and/or

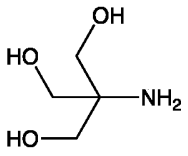


,

and/or a salt thereof, e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, are admixed in at least a 1:2 molar ratio, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

2.9 Method II or 2.1-2.8 wherein Formula II and $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, and/or $[(HO)_nR^8]_3N$ and/or salt thereof (e.g., acetate, e.g., tris(hydroxymethyl)aminomethane acetate), wherein each $R^8$ is independently $C_{1-}$

8alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $-CH_2-CH_2-$, e.g., $-C(CH_2)_3-$, e.g., one $R^8$ is $-CH_3$ and another $R^8$ is $-(CH_2)_6-$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g.,



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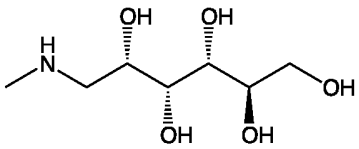
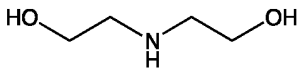
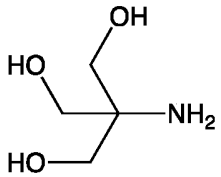


, and/or


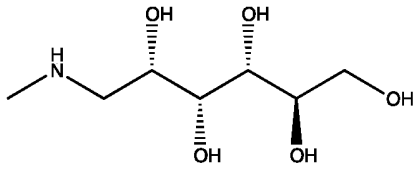

and/or a salt thereof are admixed in at least a 1:2 molar ratio, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

2.10 Method II or 2.1-2.9 wherein Formula II and



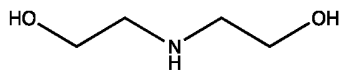

and/or a salt thereof are admixed in at least a 1:2 molar ratio, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

2.11 Method II or 2.1-2.10 wherein Formula II and




and/or a salt thereof are admixed in at least a 1:2 molar ratio, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

2.12 Method II or 2.1-2.11 wherein Formula II and



and/or a salt thereof are admixed in at least a 1:2 molar ratio, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

2.13 Method II or 2.1-2.12 wherein the solvent is a sterile solution, e.g., sterile water for injection, a sterile solution comprising dextrose (e.g., dextrose injection 5%), a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection), a sterile solution comprising benzyl alcohol (e.g., bacteriostatic water for injection with benzyl alcohol or bacteriostatic sodium chloride for injection with benzyl alcohol), or Lactated Ringer's.

2.14 Method II or 2.1-2.13 wherein there is 0.5 to 500 mL of solvent, e.g., an aqueous solution, e.g., from about 1 or 2 mL to 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 30, 35, 50, 75, 100, 150, 200, 300 or 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 50, 75, 100, or 200 mL, e.g., from about 3.5 or 5 to 10, 25, 50, or 100 mL, e.g., about 3.5 or 35 mL.

2.15 Method II or 2.1-2.14 wherein there is 0.5 to 500 mL of sterile solution, e.g., sterile water for injection, a sterile solution comprising dextrose (e.g., dextrose injection 5%), a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection), a sterile solution comprising benzyl alcohol (e.g., bacteriostatic water for injection with benzyl alcohol or bacteriostatic sodium chloride for injection with benzyl alcohol), or Lactated Ringer's, e.g., from about 1 or 2 mL to 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 30, 35, 50, 75, 100, 150, 200, 300 or 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 50, 75, 100, or 200 mL, e.g., from about 3.5 or 5 to 10, 25, 50, or 100 mL, e.g., about 3.5 or 35 mL.

2.16 Method II or 2.1-2.15 wherein the solvent comprises sterile water for injection or a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection).

2.17 Method II or 2.1-2.16 wherein the solvent comprises sterile water for injection.

2.18 Method II or 2.1-2.17 wherein the solvent comprises 0.5 to 500 mL sterile water for injection, e.g., from about 1 or 2 mL to 500 mL, e.g., from about 1 or 2 mL to

5, 10, 25, 30, 35, 50, 75, 100, 150, 200, 300 or 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 50, 75, 100, or 200 mL, e.g., from about 3.5 or 5 to 10, 25, 50, or 100 mL, e.g., about 3.5 or 35 mL.

2.19 Method II or 2.1-2.18 wherein the solvent comprises a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection).

2.20 Method 2.19 wherein the solvent comprises 0.5 to 500 mL of a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection), e.g., from about 1 or 2 mL to 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 30, 35, 50, 75, 100, 150, 200, 300 or 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 50, 75, 100, or 200 mL, e.g., from about 3.5 or 5 to 10, 25, 50, or 100 mL, e.g., about 3.5 or 35 mL.

2.21 Method II or 2.1-2.20 wherein the concentration of the compound of Formula I is 0.01 or 0.02 or 0.05 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM.

2.22 Method II or 2.1-2.21 wherein the solvent, e.g., an aqueous solution, comprises one or more bulking agents, e.g., one or more of maltose, mannose, ribose, cyclodextrin, mannitol, lactose, sucrose, trehalose, sorbitol, glucose, raffinose, arginine, glycine, histidine, dextran (e.g., dextran 40), polyvinylpyrrolidone, polyethylene glycol, and polypropylene glycol, e.g., one or more of mannitol, glucose, sucrose, lactose, trehalose, and dextran (e.g., dextran 40).

2.23 Method II or 2.1-2.22 wherein the solvent, e.g., an aqueous solution, comprises 5 or 10 or 50 mg to 2 or 5 g of one or more bulking agents, e.g., from about 50 or 100 mg to 200, 300, 500, or 800 mg, or 1, 1.5, 2, 3, 4, or 5 g of one or more bulking agents.

2.24 Method II or 2.1-2.23 wherein the solvent, e.g., an aqueous solution, comprises dextran (e.g., dextran 40).

2.25 Method II or 2.1-2.24 wherein the solvent, e.g., an aqueous solution, comprises 5 or 10 or 50 mg to 2 or 5 g dextran (e.g., dextran 40), e.g., from about 50 or 100 mg to 200, 300, 500, or 800 mg, or 1, 1.5, 2, 3, 4, or 5 g dextran (e.g., dextran 40).

2.26 Method II or 2.1-2.25 wherein the solvent, e.g., an aqueous solution, comprises one or more solubilizing agents, e.g., ethylenediamine tetraacetic acid (EDTA) or a salt thereof (e.g., calcium disodium EDTA, disodium EDTA, sodium EDTA), alpha cyclodextrin, hydroxypropyl-β-cyclodextrin, polysorbate 80, tert-butanol, isopropanol, dichloromethane, ethanol, acetone, and glycerol; one or more collapse temperature modifiers which may shift the overall collapse temperature higher, e.g., one or more of dextran, Ficoll®, gelatin, and hydroxyethyl starch; one or more tonicity modifiers, e.g., one or more of sodium chloride, potassium chloride, sucrose, mannitol, and glucose; and one or more antimicrobial agents, e.g., one or more of benzyl alcohol, phenol, 2-phenoxyethanol, m-cresol, chlorobutanol, parabens (e.g., methyl paraben, ethyl paraben, propyl paraben), benzalkonium chloride, benzethonium chloride, myristyl gamma-picolinium salt (e.g., myristyl gamma-picolinium chloride), and organomercury compounds and salts (e.g., phenyl mercuric acetate, phenyl mercuric borate, phenyl mercuric nitrate, and thimerosal).

2.27 Method II or 2.1-2.26 wherein the pH of the salt solution is between pH 7 and pH 10.5, e.g., between pH 7 and pH 9.5, e.g., between pH 7 and pH 8, e.g., between 7.5 and 8.5, e.g., 7.5, e.g., 8.5, e.g., 8.2.

2.28 Method II or 2.1-2.27 further comprising filter the salt solution to remove particles and microbes, e.g., filtered prior to injection.

2.29 Method II or 2.1-2.28 further comprising admixing the salt Solution with one or more additional therapeutic agents, e.g., one or more additional therapeutic agents for cerebral edema, stroke, traumatic brain injury, glioma (e.g., glioblastoma), meningitis, acute mountain sickness, infection, metabolic disorder, hypoxia, water intoxication, hepatic failure, hepatic encephalopathy, diabetic ketoacidosis, abscess, eclampsia, Creutzfeldt-Jakob disease, lupus cerebritis, optic nerve edema, hyponatremia, fluid retention, ovarian hyperstimulation syndrome, epilepsy, retinal ischemia or other diseases of the eye associated with

abnormalities in intraocular pressure and/or tissue hydration, myocardial ischemia, myocardial ischemia/reperfusion injury, myocardial infarction, myocardial hypoxia, congestive heart failure, sepsis, neuromyelitis optica, or migraines.

2.30 Method II or 2.1-2.29 further comprising admixing the salt solution with one or more additional therapeutic agents, e.g., one or more additional therapeutic agents for pulmonary edema, fibromyalgia, or multiple sclerosis.

**[0066]** In yet another embodiment, provided is a kit (Kit I) comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate.

**[0067]** Further provided is Kit I as follows:

1.1 Kit I wherein the kit comprises 0.1 or 0.25 mg to 2.0 g 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate, e.g., from about 0.1 or 0.25 mg to 75 or 600 mg, e.g., from about 0.1 or 0.25 or 1 or 2 mg to 50, 75, 100, 125, 150, 200, 300, 350, 400, 500, or 600 mg, or 1 g, 1.5 g, or 2.0 g, e.g., from about 5 to 50, 75, 100, 125, 150, 200, 300, 350, 400, 500, or 600 mg, or 1 g, 1.5 g, or 2, e.g., from about 5 to 500 mg, e.g., from about 5 to 300 or 350 mg, e.g., from about 5 to 200 mg, e.g., from about 25 to 500 mg, e.g., from about 25 to 300 or 350 mg, e.g., from about 25 to 200 mg, e.g., from about 15, 20, 30, 35, 50 or 100 to 150, 200, 300, 350, 400, 450, 500, 550, or 600 mg, e.g., from about 0.5 or 1 mg to 50 mg, e.g., from about 0.5 or 1 mg to 20 mg, e.g., from about 0.5 or 1 mg to 10 mg, e.g., from about 1 or 2 or 5 mg to 10 or 20 mg, eg., from about 1 or 2 or 3 or 4 or 5 mg, e.g., about 35 mg, e.g. about 35 mg, or wherein the kit comprises 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate in an amount sufficient to provide 0.1 or 0.25 mg to 2.0 g of N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide, e.g., from about 0.1 or 0.25 mg to 75 or 600 mg, e.g., from about 0.1 or 0.25 or 1 or 2 mg to 50, 75, 100, 125, 150, 200, 300, 350, 400, 500, or 600 mg, or 1 g, 1.5 g, or 2.0 g, e.g., from about 5 to 50, 75, 100, 125, 150, 200, 300, 350, 400, 500, or 600 mg, or 1 g, 1.5 g, or 2 g, e.g., from about 5 to 500 mg, e.g., from about 5 to 300 or 350 mg, e.g., from about 5 to 200 mg, e.g., from about 25 to 500 mg, e.g., from about 25 to 300 or 350 mg, e.g., from about 25 to 200 mg, e.g., from about

15, 20, 30, 35, 50 or 100 to 150, 200, 300, 350, 400, 450, 500, 550, or 600 mg, e.g., from about 0.5 or 1 mg to 50 mg, e.g., from about 0.5 or 1 mg to 20 mg, e.g., from about 0.5 or 1 mg to 10 mg, e.g., from about 1 or 2 or 5 mg to 10 or 20 mg, eg., from about 1 or 2 or 3 or 4 or 5 mg, e.g., about 35 mg, e.g. about 35 mg.

1.2 Kit I or 1.1 wherein the kit comprises one or more pharmaceutically acceptable excipients.

1.3 Kit 1.2 wherein the one or more pharmaceutically acceptable excipients comprise one or more of bases, bulking agents, solubilizing agents, collapse temperature modifiers, tonicity modifiers, and antimicrobial agents.

1.4 Kit 1.2 or 1.3 wherein the one or more pharmaceutically acceptable excipients comprise one or more bases, e.g., a base wherein upon dissolution of the composition in a solvent, e.g., an aqueous solution, the solution has a pH between 7, 7.5, or 8 and 10.5, e.g., between about 7, 7.5, or 8 and 9.5, e.g., between about 7 or 7.5 and 8, e.g., between about 7.5 and 8.5, e.g., about 7.5, e.g., about 8.5, e.g., between about 8 and 8.5, e.g., about 8.2, e.g., a base wherein a conjugate acid of the base has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, e.g., wherein the one or more bases are one or more of:

a) a $C_{1-8}$-alkyl mono-, di-, or tri- carboxylic acid salt, e.g., a citrate salt, e.g, a metal citrate salt (e.g., an alkali and/or alkaline citrate salt, e.g., an alkali citrate salt, e.g., sodium citrate and/or potassium citrate), e.g., a tartrate salt (e.g., a metal tartrate salt, an alkali tartrate, e.g., sodium tartrate), e.g., a succinate salt (e.g., a metal succinate salt, e.g., an alkali succinate, e.g., disodium succinate), and/or e.g., a lactate salt (e.g., a metal lactate salt, e.g., an alkali lactate, e.g., sodium lactate),

b) a phosphate salt, e.g., a metal phosphate salt (e.g., an alkali and/or alkaline phosphate salt, e.g., an alkali phosphate salt, e.g., sodium phosphate (e.g., $NaH_2PO_4$ and/or $Na_2HPO_4$) and/or potassium phosphate (e.g., $KH_2PO_4$ and/or $K_2HPO_4$)),

c) an amine and/or a salt thereof (e.g., morpholine, piperazine, benethamine, benzathine, trimethylglycine, hydrabamine, 4-(2-

hydroxyethyl)morpholine, 1-2-hydroxyethyl)-pyrrolidine, an amino acid (e.g., arginine and/or lysine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., -$CH_2CH_3$, e.g., -$CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., –$CH_2$–$CH_2$–, e.g., –$C(CH_2)_3$–, e.g., one $R^8$ is –$CH_3$ and another $R^8$ is –$(CH_2)_6$–) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, dimethylethanolamine, diethylamine, diethylethanolamine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9 between 6 and 11, e.g., between 6.5 and 10, e.g., between 7 and 9,

d) a metal chloride salt (e.g., zinc chloride),

e) an acetate salt, e.g., a metal acetate salt (e.g., an alkali and/or alkaline acetate salt, e.g., an alkali acetate salt, e.g., sodium acetate and/or potassium acetate),

f) a hydroxide and/or alkoxide salt, e.g., a metal hydroxide and/or alkoxide salt (e.g., a quarternary ammonium hydroxide, e.g., ammonium hydroxide and/or choline hydroxide, lithium hydroxide, aluminum hydroxide, e.g., an alkali and/or alkaline hydroxide salt, e.g., sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, and/or magnesium ethoxide, e.g., sodium hydroxide),

g) a carbonate and/or bicarbonate salt, e.g., a metal carbonate and/or metal bicarbonate salt (e.g., an alkali and/or alkaline carbonate salt,

e.g., an alkali and/or alkaline bicarbonate salt, e.g., sodium bicarbonate),

h) a metal borate salt (e.g., an alkali borate salt, e.g., sodium borate),

e.g., one or more of sodium citrate, $Na_2HPO_4$, tris(hydroxymethyl)aminomethane, and a tris(hydroxymethyl)aminomethane salt (e.g., tris acetate), e.g., one or more of sodium citrate, $Na_2HPO_4$, and tris(hydroxymethyl)aminomethane, e.g., one or more of sodium citrate and $Na_2HPO_4$, e.g., $Na_2HPO_4$, e.g., tris(hydroxymethyl)aminomethane.

1.5 Kit 1.2-1.4 wherein the one or more pharmaceutically acceptable excipients comprise one or more bases, e.g., a base wherein upon dissolution of the composition in a solvent, e.g., an aqueous solution, the solution has a pH between 7, 7.5, or 8 and 10.5, e.g., between about 7, 7.5, or 8 and 9.5, e.g., between about 7 or 7.5 and 8, e.g., between about 7.5 and 8.5, e.g., about 7.5, e.g., about 8.5, e.g., between about 8 and 8.5, e.g., about 8.2, e.g., a base wherein a conjugate acid of the base has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, e.g., wherein the one or more bases are one or more of:

a) a metal citrate salt (e.g., an alkali and/or alkaline citrate salt, e.g., an alkali citrate salt, e.g., sodium citrate and/or potassium citrate),

b) a metal phosphate salt (e.g., an alkali and/or alkaline phosphate salt, e.g., an alkali phosphate salt, e.g., sodium phosphate (e.g., $NaH_2PO_4$ and/or $Na_2HPO_4$) and/or potassium phosphate (e.g., $KH_2PO_4$ and/or $K_2HPO_4$)),

c) an amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g.,

tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9,

d) a metal acetate salt (e.g., an alkali and/or alkaline acetate salt, e.g., an alkali acetate salt, e.g., sodium acetate and/or potassium acetate),

e) a metal hydroxide salt (e.g., an alkali and/or alkaline hydroxide salt, e.g., sodium hydroxide, potassium hydroxide, calcium hydroxide, and/or magnesium hydroxide, e.g., sodium hydroxide),

f) a metal carbonate and/or bicarbonate salt (e.g., an alkali and/or alkaline carbonate salt, e.g., an alkali and/or alkaline bicarbonate salt, e.g., sodium bicarbonate), and/or

g) a metal borate salt (e.g., an alkali borate salt, e.g., sodium borate),

e.g., one or more of sodium citrate, $Na_2HPO_4$, tris(hydroxymethyl)aminomethane, and a tris(hydroxymethyl)aminomethane salt (e.g., tris acetate), e.g., one or more of sodium citrate, $Na_2HPO_4$, and tris(hydroxymethyl)aminomethane, e.g., one or more of sodium citrate and $Na_2HPO_4$, e.g., $Na_2HPO_4$, e.g., tris(hydroxymethyl)aminomethane.

1.6 Kit 1.3-1.5 wherein the kit comprises 1 or 5 mg to 200 or 500 mg of one or more bases, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.7 Kit 1.3-1.5 wherein the concentration of each of the one or more bases is 0.01 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5 to 50 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM,

e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of each of the one or more bases is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of each of the one or more bases is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.8 Kit 1.3-1.6 wherein the one or more bases comprise one or more of a metal citrate salt (e.g., sodium citrate) and a metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$).

1.9 Kit 1.3-1.8 wherein the one or more bases comprise a metal citrate salt (e.g., sodium citrate).

1.10 Kit 1.9 wherein the kit comprises 1 or 5 mg to 200 or 500 mg of the metal citrate salt (e.g., sodium citrate), e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.11 Kit 1.9 wherein the concentration of the metal citrate salt (e.g., sodium citrate) is 0.01 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, of 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5 to 50 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of the metal citrate salt (e.g., sodium citrate) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of the metal citrate salt (e.g., sodium citrate) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.12 Kit 1.3-1.11 wherein the one or more bases comprise a metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$).

1.13 Kit 1.12 wherein the kit comprises 1 or 5 mg to 200 or 500 mg of the metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$), e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.14 Kit 1.12 wherein the concentration of the metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$), is 0.01 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5 to 50 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM,e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of the metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of the metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.15 Kit 1.3-1.14 wherein the kit comprises $Na_2HPO_4$.

1.16 Kit 1.15 wherein the kit comprises 1 or 5 mg to 200 or 500 mg $Na_2HPO_4$, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.17 Kit 1.15 wherein the concentration of $Na_2HPO_4$ is 0.01 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5 to 50 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or

200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of each of $Na_2HPO_4$ is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of $Na_2HPO_4$ is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.18 Kit 1.3-1.17 wherein the one or more bases comprise an amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9.

1.19 Kit 1.18 wherein the kit comprises 1 or 5 mg to 200 or 500 mg of the amine and/or a salt thereof (e.g., morpholine, an amino (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10

and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.20 Kit 1.18 wherein the concentration of the amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, is 0.01 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5 to 50 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of each of the amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., –

$CH_2$–$CH_2$–, e.g., –$C(CH_2)_3$–, e.g., one $R^8$ is –$CH_3$ and another $R^8$ is –$(CH_2)_6$–) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of each of the amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., -$CH_2CH_3$, e.g., -$CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., –$CH_2$–$CH_2$–, e.g., –$C(CH_2)_3$–, e.g., one $R^8$ is –$CH_3$ and another $R^8$ is –$(CH_2)_6$–) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.21 Kit 1.3-1.20 wherein the one or more bases comprise a mono- and/or poly-hydroxyalkylamine and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., -$CH_2CH_3$, e.g., -$CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., –$CH_2$–$CH_2$–, e.g., –$C(CH_2)_3$–, e.g., one $R^8$ is –$CH_3$ and another $R^8$ is –$(CH_2)_6$–) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine).

1.22 Kit 1.21 wherein the kit comprises 1 or 5 mg to 200 or 500 mg of the mono- and/or poly-hydroxyalkylamine and/or salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., -$CH_2CH_3$, e.g., -

$CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., –$CH_2$–$CH_2$–, e.g., –$C(CH_2)_3$–, e.g., one $R^8$ is –$CH_3$ and another $R^8$ is –$(CH_2)_6$–) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.23 Kit 1.21 wherein the concentration of the mono- and/or poly-hydroxyalkylamine and/or salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., -$CH_2CH_3$, e.g., -$CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., –$CH_2$–$CH_2$–, e.g., –$C(CH_2)_3$–, e.g., one $R^8$ is –$CH_3$ and another $R^8$ is –$(CH_2)_6$–) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), is 0.01 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5 to 50 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of each of the mono- and/or poly-hydroxyalkylamine and/or salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., -$CH_2CH_3$, e.g., -$CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., –$CH_2$–$CH_2$–, e.g., –$C(CH_2)_3$–, e.g., one $R^8$ is –$CH_3$ and another $R^8$ is –$(CH_2)_6$–) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g.,

tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of the mono- and/or poly-hydroxyalkylamine and/or salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., -$CH_2CH_3$, e.g., -$CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., –$CH_2$–$CH_2$–, e.g., –$C(CH_2)_3$–, e.g., one $R^8$ is –$CH_3$ and another $R^8$ is –$(CH_2)_6$–) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine) agents is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.24 Kit 1.3-1.23 wherein the one or more bases comprise $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., -$CH_2CH_3$, e.g., -$CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., –$CH_2$–$CH_2$–, e.g., –$C(CH_2)_3$–, e.g., one $R^8$ is –$CH_3$ and another $R^8$ is –$(CH_2)_6$–) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine).

1.25 Kit 1.24 wherein the kit comprises 1 or 5 mg to 200 or 500 mg of the $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., -$CH_2CH_3$, e.g., -$CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., –$CH_2$–$CH_2$–, e.g., –$C(CH_2)_3$–, e.g., one $R^8$ is –$CH_3$ and another $R^8$ is –$(CH_2)_6$–) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate),

meglumine, and/or diethanolamine), e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.26 Kit 1.24 wherein the concentration of $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), is 0.01 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, of 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5 to 50 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene,

e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.27 Kit 1.3-1.26 wherein the one or more bases comprise tris(hydroxymethyl)aminomethane and/or meglumine, e.g, tris(hydroxymethyl)aminomethane, e.g., meglumine.

1.28 Kit 1.27 wherein the kit comprises 1 or 5 mg to 200 or 500 mg tris(hydroxymethyl)aminomethane, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg and/or wherein the kit comprises 1 or 5 mg to 200 or 500 mg meglumine, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.29 Kit 1.27 wherein the concentration of a tris(hydroxymethyl)aminomethane salt (e.g., tris(hydroxymethyl)aminomethane acetate) is 0.01 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5 to 50 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM.

1.30 Kit 1.3-1.29 wherein the one or more bases comprise the tris(hydroxymethyl)aminomethane salt, e.g., tris(hydroxymethyl)aminomethane acetate.

1.31 Kit 1.30 wherein the composition comprises 1 or 5 mg to 200 or 500 mg of the tris(hydroxymethyl)aminomethane salt (e.g., tris(hydroxymethyl)aminomethane acetate), e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg

tris(hydroxymethyl)aminomethane salt (e.g., tris(hydroxymethyl)aminomethane acetate), e.g., 1 or 5 mg to 200 or 500 mg tris(hydroxymethyl)aminomethane acetate, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.32 Kit 1.30 wherein the concentration of the tris(hydroxymethyl)aminomethane salt (e.g., tris(hydroxymethyl)aminomethane acetate) is 0.01 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5 to 50 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of the tris(hydroxymethyl)aminomethane salt (e.g., tris(hydroxymethyl)aminomethane acetate) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of the tris(hydroxymethyl)aminomethane salt (e.g., tris(hydroxymethyl)aminomethane acetate) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.33 Kit 1.3-1.33 wherein the one or more bases comprise a base, e.g., an amine and/or a salt thereof, wherein a conjugate acid of the base has a pKa between 6, 7, 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9.

1.34 Kit 1.34 wherein the kit comprises 1 or 5 mg to 200 or 500 mg of the base, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.35 Kit 1.34 wherein the concentration of the base is 0.01 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15,

20, 25, 40, 50 or 60 mM, e.g., from about 5 to 50 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of the base is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of of the base is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.36 Kit 1.3-1.35 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to the one or more bases is at least 1:1.

1.37 Kit 1.3-1.36 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to the one or more bases is at least 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.38 Kit 1.37 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to a metal citrate salt (e.g., sodium citrate) is at least 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.39 Kit 1.37 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to a metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$) is at least 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.40 Kit 1.37 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to the amine and/or salt thereof (e.g., morpholine, amino acid (e.g., arginine), mono- and/or poly-hydroxyalkylamine, and/or salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, is at least 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.41 Kit 1.40 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to the mono- and/or poly-hydroxyalkylamine and/or salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), is at least 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to

1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.42 Kit 1.41 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), is 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.43 Kit 1.42 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to tris(hydroxymethyl)aminomethane is at least 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.44 Kit 1.42 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to a tris(hydroxymethyl)aminomethane salt (e.g., tris(hydroxymethyl)aminomethane acetate) is at least 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.45 Kit 1.37 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to a base, e.g., an amine and/or a salt thereof, wherein a conjugate acid of the base

has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, is at least 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.46 Kit 1.2-1.45 wherein the kit comprises one or more bulking agents which may provide an adequate structure to the lyophilized cake, e.g., one or more of mannitol, lactose, sucrose, trehalose, sorbitol, glucose, raffinose, arginine, glycine, histidine, dextran (e.g., dextran 40), polyvinylpyrrolidone, polyethylene glycol, and polypropylene glycol, e.g., one or more of mannitol, glucose, sucrose, lactose, trehalose, and dextran (e.g., dextran 40).

1.47 Kit 1.46 wherein the kit comprises 5 or 10 or 50 mg to 2 or 5 g of one or more bulking agents, e.g., from about 50 or 100 mg to 200, 300, 500, or 800 mg, or 1, 1.5, 2, 3, 4, or 5 g of one or more bulking agents.

1.48 Kit 1.2-1.247 wherein the kit comprises dextran (e.g., dextran 40).

1.49 Kit 1.48 wherein the kit comprises 5 or 10 or 50 mg to 2 or 5 g dextran (e.g., dextran 40), e.g., from about 50 or 100 mg to 200, 300, 500, or 800 mg, 1, 1.5, 2, 3, 4, or 5 g dextran (e.g., dextran 40).

1.50 Kit 1.2-1.49 wherein the composition comprises one or more solubilizing agents, e.g., ethylenediamine tetraacetic acid (EDTA) or a salt thereof (e.g., calcium disodium EDTA, disodium EDTA, sodium EDTA), alpha cyclodextrin, hydroxypropyl-β-cyclodextrin, polysorbate 80, tert-butanol, isopropanol, dichloromethane, ethanol, acetone, and glycerol; one or more collapse temperature modifiers which may shift the overall collapse temperature higher, e.g., one or more of dextran, Ficoll®, gelatin, and hydroxyethyl starch; one or more tonicity modifiers, e.g., one or more of sodium chloride, potassium chloride, sucrose, mannitol, glucose, and lactose; and one or more antimicrobial agents, e.g., one or more of benzyl alcohol, phenol, 2-phenoxyethanol, m-cresol, chlorobutanol, parabens (e.g., methyl paraben, ethyl paraben, propyl paraben), benzalkonium chloride, benzethonium chloride, myristyl gamma-picolinium salt (e.g., myristyl gamma-picolinium chloride), and organomercury compounds and

salts (e.g., phenyl mercuric acetate, phenyl mercuric borate, phenyl mercuric nitrate, and thimerosal).

1.51 Kit 1.2-1.50 wherein 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate and the one pharmaceutically acceptable excipients are in the same container or in one or more different containers.

1.52 Kit 1.51 wherein the one or more pharmaceutically acceptable excipients comprise one or more bases, e.g., a base wherein upon dissolution of the composition in a solvent, e.g., an aqueous solution, e.g., an aqueous solution, the solution has a pH between 7, 7.5, or 8 and 10.5, e.g., between about 7, 7.5, or 8 and 9.5, e.g., between about 7 or 7.5 and 8, e.g., between about 7.5 and 8.5, e.g., about 7.5, e.g., about 8.5, e.g., between about 8 and 8.5, e.g., about 8.2, e.g., a base wherein a conjugate acid of the base has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, e.g., wherein the one or more bases are one or more of:

a) a $C_{1-8}$-alkyl mono-, di-, or tri- carboxylic acid salt, e.g., a citrate salt, e.g, a metal citrate salt (e.g., an alkali and/or alkaline citrate salt, e.g., an alkali citrate salt, e.g., sodium citrate and/or potassium citrate), e.g., a tartrate salt (e.g., a metal tartrate salt, an alkali tartrate, e.g., sodium tartrate), e.g., a succinate salt (e.g., a metal succinate salt, e.g., an alkali succinate, e.g., disodium succinate), and/or e.g., a lactate salt (e.g., a metal lactate salt, e.g., an alkali lactate, e.g., sodium lactate),

b) a phosphate salt, e.g., a metal phosphate salt (e.g., an alkali and/or alkaline phosphate salt, e.g., an alkali phosphate salt, e.g., sodium phosphate (e.g., $NaH_2PO_4$ and/or $Na_2HPO_4$) and/or potassium phosphate (e.g., $KH_2PO_4$ and/or $K_2HPO_4$)),

c) an amine and/or a salt thereof (e.g., morpholine, piperazine, benethamine, benzathine, trimethylglycine, hydrabamine, 4-(2-hydroxyethyl)morpholine, 1-2-hydroxyethyl)-pyrrolidine, an amino acid (e.g., arginine and/or lysine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is

independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., -$CH_2CH_3$, e.g., -$CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., –$CH_2$–$CH_2$–, e.g., –$C(CH_2)_3$–, e.g., one $R^8$ is –$CH_3$ and another $R^8$ is –$(CH_2)_6$–) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, dimethylethanolamine, diethylamine, diethylethanolamine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9,

d) a metal chloride salt (e.g., zinc chloride),

e) an acetate salt, e.g,. a metal acetate salt (e.g., an alkali and/or alkaline acetate salt, e.g., an alkali acetate salt, e.g., sodium acetate and/or potassium acetate),

f) a hydroxide and/or alkoxide salt, e.g., a metal hydroxide and/or alkoxdie salt (e.g., a quarternary ammonium hydroxide, e.g., ammonium hydroxide and/or choline hydroxide, lithium hydroxide, aluminum hydroxide, e.g., an alkali and/or alkaline hydroxide salt, e.g., sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, and/or magnesium ethoxide, e.g., sodium hydroxide),

g) a carbonate and/or bicarbonate salt, e.g., a metal carbonate and/or metal bicarbonate salt (e.g., an alkali and/or alkaline carbonate salt, e.g., an alkali and/or alkaline bicarbonate salt, e.g., sodium bicarbonate), and/or

h) a metal borate salt (e.g., an alkali borate salt, e.g., sodium borate),

e.g., one or more of sodium citrate, $Na_2HPO_4$, tris(hydroxymethyl)aminomethane, and a tris(hydroxymethyl)aminomethane salt (e.g., tris acetate), e.g., one or more of sodium citrate, $Na_2HPO_4$, and tris(hydroxymethyl)aminomethane, e.g., one or

more of sodium citrate and $Na_2HPO_4$, e.g., $Na_2HPO_4$, e.g., tris(hydroxymethyl)aminomethane, wherein the one or more bases are in the same container as 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate or in one or more different containers.

1.53 Kit 1.51 or 1.52 wherein the one or more pharmaceutically acceptable excipients comprise one or more bases, e.g., a base wherein upon dissolution of the composition in a solvent, e.g., an aqueous solution, the solution has a pH between 7, 7.5, or 8 and 10.5, e.g., between about 7, 7.5, or 8 and 9.5, e.g., between about 7 or 7.5 and 8, e.g., between about 7.5 and 8.5, e.g., about 7.5, e.g., about 8.5, e.g., between about 8 and 8.5, e.g., about 8.2, e.g., a base wherein a conjugate acid of the base has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, e.g., wherein the one or more bases are one or more of:

a) a metal citrate salt (e.g., an alkali and/or alkaline citrate salt, e.g., an alkali citrate salt, e.g., sodium citrate and/or potassium citrate),

b) a metal phosphate salt (e.g., an alkali and/or alkaline phosphate salt, e.g., an alkali phosphate salt, e.g., sodium phosphate (e.g., $NaH_2PO_4$ and/or $Na_2HPO_4$) and/or potassium phosphate (e.g., $KH_2PO_4$ and/or $K_2HPO_4$)),

c) an amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof

has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9,

d) a metal acetate salt (e.g., an alkali and/or alkaline acetate salt, e.g., an alkali acetate salt, e.g., sodium acetate and/or potassium acetate),

e) a metal hydroxide salt (e.g., an alkali and/or alkaline hydroxide salt, e.g., sodium hydroxide, potassium hydroxide, calcium hydroxide, and/or magnesium hydroxide, e.g., sodium hydroxide),

f) a metal carbonate and/or bicarbonate salt (e.g., an alkali and/or alkaline carbonate salt, e.g., an alkali and/or alkaline bicarbonate salt, e.g., sodium bicarbonate), and/or

g) a metal borate salt (e.g., an alkali borate salt, e.g., sodium borate),

e.g., one or more of sodium citrate, $Na_2HPO_4$, tris(hydroxymethyl)aminomethane, and a tris(hydroxymethyl)aminomethane salt (e.g., tris acetate), e.g., one or more of sodium citrate, $Na_2HPO_4$, and tris(hydroxymethyl)aminomethane, e.g., one or more of sodium citrate and $Na_2HPO_4$, e.g., $Na_2HPO_4$, e.g., tris(hydroxymethyl)aminomethane, wherein the one or more bases are in the same container as 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate or in one or more different containers.

1.54 Kit 1.52 or 1.53 wherein 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate and one or more of a metal citrate salt (e.g., sodium citrate) and a metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$) are in the same container or in one or more different containers.

1.55 Kit 1.54 wherein 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate and the metal citrate salt (e.g., sodium citrate) are in the same container or in different containers.

1.56 Kit 1.54 wherein 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate and the metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$) are in the same container or in different containers.

1.57 Kit 1.52 or 1.53 wherein 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate and one or more of an amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-

hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, are in the same container or in different containers.

1.58 Kit 1.57 wherein 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate and one or more of a mono- and/or poly-hydroxyalkylamine and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine) are in the same container or in different containers.

1.59 Kit 1.58 wherein 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate and one or more of $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris

base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine) are in the same container or in different containers.

1.60 Kit 1.59 wherein 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate and tris(hydroxymethyl)aminomethane are in the same container or in different containers.

1.61 Kit 1.59 wherein 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate and tris(hydroxymethyl)aminomethane acetate are in the same container or in different containers.

1.62 Kit 1.53 wherein 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate and a base, e.g., an amine and/or a salt thereof, wherein a conjugate acid of the base has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, are in the same container or in different containers.

1.63 Kit 1.51-1.62 wherein the kit comprises one or more bulking agents, e.g., one or more of mannitol, lactose, sucrose, trehalose, sorbitol, glucose, raffinose, arginine, glycine, histidine, dextran (e.g., dextran 40), polyvinylpyrrolidone, polyethylene glycol, and polypropylene glycol, e.g., one or more of mannitol, glucose, sucrose, lactose, trehalose, and dextran (e.g., dextran 40), wherein the one or more bulking agents are in the same container as 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate or any other component of the kit or in one or more different containers.

1.64 Kit 1.63 wherein 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate and dextran (e.g., dextran 40) are in the same container or in different containers.

1.65 Kit 1.51-1.64 wherein the kit comprises one or more solubilizing agents, e.g., ethylenediamine tetraacetic acid (EDTA) or a salt thereof (e.g., calcium disodium EDTA, disodium EDTA, sodium EDTA), alpha cyclodextrin, hydroxypropyl-β-cyclodextrin, polysorbate 80, tert-butanol, isopropanol, dichloromethane, ethanol, acetone, and glycerol; one or more collapse temperature modifiers, e.g., one or more of dextran, Ficoll®, gelatin, and hydroxyethyl starch; one or more tonicity

modifiers, e.g., one or more of sodium chloride, potassium chloride, sucrose, mannitol, glucose, and lactose; and one or more antimicrobial agents, e.g., one or more of benzyl alcohol, phenol, 2-phenoxyethanol, m-cresol, chlorobutanol, parabens (e.g., methyl paraben, ethyl paraben, propyl paraben), benzalkonium chloride, benzethonium chloride, myristyl gamma-picolinium salt (e.g., myristyl gamma-picolinium chloride), and organomercury compounds and salts (e.g., phenyl mercuric acetate, phenyl mercuric borate, phenyl mercuric nitrate, and thimerosal), wherein the one or more solubilizing agents, collapse temperature modifiers, tonicity modifiers, and antimicrobial agents are in the same container as 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate or any other component of the kit or in one or more different containers, e.g., in any combination in any number of different containers.

1.66 Kit I or 1.1-1.65 wherein 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is crystalline.

1.67 Kit I or 1.1-1.65 wherein 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is amorphous.

1.68 Kit I or 1.1-1.65 wherein 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is lyophilized, e.g., by freezing, primary drying, and secondary drying.

1.69 Kit 1.2-1.68 wherein 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate and the one or more pharmaceutically acceptable excipients are lyophilized.

1.70 Kit I or 1.1-1.69 wherein 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is suitable for constitution, or reconstitution if lyophilized, with a solvent, e.g., an aqueous solution, into a pharmaceutically acceptable liquid (e.g., a solution or suspension, e.g., a solution).

1.71 Kit I or 1.1-1.70 wherein the kit comprises a solvent, e.g., a sterile solution, e.g., sterile water for injection, a sterile solution comprising dextrose (e.g., dextrose injection 5%), a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection), a sterile solution comprising benzyl alcohol (e.g.,

bacteriostatic water for injection with benzyl alcohol or bacteriostatic sodium chloride for injection with benzyl alcohol), or Lactated Ringer's.

1.72 Kit I or 1.1-1.71 wherein the kit comprises 0.5 to 500 mL solvent, e.g., an aqueous solution, e.g., from about 1 or 2 mL to 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 30, 35, 50, 75, 100, 150, 200, 300 or 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 50, 75, 100, or 200 mL, e.g., from about 3.5 or 5 to 10, 25, 50, or 100 mL, e.g., about 3.5 or 35 mL.

1.73 Kit I or 1.1-1.72 wherein the kit comprises 0.5 to 500 mL sterile solution, e.g., sterile water for injection, a sterile solution comprising dextrose (e.g., dextrose injection 5%), a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection), a sterile solution comprising benzyl alcohol (e.g., bacteriostatic water for injection with benzyl alcohol or bacteriostatic sodium chloride for injection with benzyl alcohol), or Lactated Ringer's, e.g., from about 1 or 2 mL to 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 50, 75, 100, 150, 200, 300 or 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 30, 35, 50, 75, 100, or 200 mL, e.g., from about 3.5 or 5 to 10, 25, 50, or 100 mL, e.g., about 3.5 or 35 mL.

1.74 Kit I or 1.1-1.73 wherein the kit comprises sterile water for injection or a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection).

1.75 Kit 1.74 wherein the kit comprises 0.5 to 500 mL sterile water for injection, e.g., from about 1 or 2 mL to 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 30, 35, 50, 75, 100, 150, 200, 300 or 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 50, 75, 100, or 200 mL, e.g., from about 3.5 or 5 to 10, 25, 50, or 100 mL, e.g., about 3.5 or 35 mL.

1.76 Kit I or 1.1-1.75 wherein the kit comprises sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection).

1.77 Kit 1.76 wherein the kit comprises 0.5 to 500 mL of a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection), e.g., from about 1 or 2 mL to 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 50, 75, 100, 150, 200, 300 or 500 mL, e.g., from about 1 or 2 mL to 5, 10, 25, 30, 35, 50, 75, 100, or 200 mL, e.g., from about 3.5 or 5 to 10, 25, 50, or 100 mL, e.g., about 3.5 or 35 mL.

1.78 Kit 1.71-1.77 wherein the solvent, e.g., the sterile solution, comprises one or more bases, e.g., a base wherein upon dissolution of the composition in a solvent, e.g., an aqueous solution, the solution has a pH between 7, 7.5, or 8 and 10.5, e.g., between about 7, 7.5, or 8 and 9.5, e.g., between about 7 or 7.5 and 8, e.g., between about 7.5 and 8.5, e.g., about 7.5, e.g., about 8.5, e.g., between about 8 and 8.5, e.g., about 8.2, e.g., a base wherein a conjugate acid of the base has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, e.g., wherein the one or more bases are one or more of:

a) a $C_{1-8}$-alkyl mono-, di-, or tri- carboxylic acid salt, e.g., a citrate salt, e.g, a metal citrate salt (e.g., an alkali and/or alkaline citrate salt, e.g., an alkali citrate salt, e.g., sodium citrate and/or potassium citrate), e.g., a tartrate salt (e.g., a metal tartrate salt, an alkali tartrate, e.g., sodium tartrate), e.g., a succinate salt (e.g., a metal succinate salt, e.g., an alkali succinate, e.g., disodium succinate), and/or e.g., a lactate salt (e.g., a metal lactate salt, e.g., an alkali lactate, e.g., sodium lactate),

b) a phosphate salt, e.g., a metal phosphate salt (e.g., an alkali and/or alkaline phosphate salt, e.g., an alkali phosphate salt, e.g., sodium phosphate (e.g., $NaH_2PO_4$ and/or $Na_2HPO_4$) and/or potassium phosphate (e.g., $KH_2PO_4$ and/or $K_2HPO_4$)),

c) an amine and/or a salt thereof (e.g., morpholine, piperazine, benethamine, benzathine, trimethylglycine, hydrabamine, 4-(2-hydroxyethyl)morpholine, 1-2-hydroxyethyl)-pyrrolidine, an amino acid (e.g., arginine and/or lysine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., -$CH_2CH_3$, e.g., -$CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., –$CH_2$–$CH_2$–, e.g., –$C(CH_2)_3$–, e.g., one $R^8$ is –$CH_3$ and another $R^8$ is –$(CH_2)_6$–) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also

known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, dimethylethanolamine, diethylamine, diethylethanolamine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9,

d) a metal chloride salt (e.g., zinc chloride),

e) an acetate salt, e.g., a metal acetate salt (e.g., an alkali and/or alkaline acetate salt, e.g., an alkali acetate salt, e.g., sodium acetate and/or potassium acetate),

f) a hydroxide and/or alkoxide salt, e.g., a metal hydroxide and/or alkoxide salt (e.g., a quarternary ammonium hydroxide, e.g., ammonium hydroxide and/or choline hydroxide, lithium hydroxide, aluminum hydroxide, e.g., an alkali and/or alkaline hydroxide salt, e.g., sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, and/or magnesium ethoxide, e.g., sodium hydroxide),

g) a carbonate and/or bicarbonate salt, e.g., a metal carbonate and/or metal bicarbonate salt (e.g., an alkali and/or alkaline carbonate salt, e.g., an alkali and/or alkaline bicarbonate salt, e.g., sodium bicarbonate), and/or

h) a metal borate salt (e.g., an alkali borate salt, e.g., sodium borate),

e.g., one or more of sodium citrate, $Na_2HPO_4$, tris(hydroxymethyl)aminomethane, and a tris(hydroxymethyl)aminomethane salt (e.g., tris acetate), e.g., one or more of sodium citrate, $Na_2HPO_4$, and tris(hydroxymethyl)aminomethane, e.g., one or more of sodium citrate and $Na_2HPO_4$, e.g., $Na_2HPO_4$, e.g., tris(hydroxymethyl)aminomethane.

1.79 Kit 1.71-1.78 wherein the solvent, e.g., the sterile solution, comprises one or more pharmaceutically acceptable bases, e.g., one or more bases wherein upon dissolution of the composition in a solvent the solution has a pH between 7, 7.5,

or 8 and 10.5, e.g., between about 7, 7.5, or 8 and 9.5, e.g., between about 7 or 7.5 and 8, e.g., between about 7.5 and 8.5, e.g., about 7.5, e.g., about 8.5, e.g., between about 8 and 8.5, e.g., about 8.2, e.g., a base wherein a conjugate acid of the base has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, e.g., wherein the one or more base are one or more of:

a) a metal citrate salt (e.g., an alkali and/or alkaline citrate salt, e.g., an alkali citrate salt, e.g., sodium citrate and/or potassium citrate),

b) a metal phosphate salt (e.g., an alkali and/or alkaline phosphate salt, e.g., an alkali phosphate salt, e.g., sodium phosphate (e.g., $NaH_2PO_4$ and/or $Na_2HPO_4$) and/or potassium phosphate (e.g., $KH_2PO_4$ and/or $K_2HPO_4$)),

c) an amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9,

d) a metal acetate salt (e.g., an alkali and/or alkaline acetate salt, e.g., an alkali acetate salt, e.g., sodium acetate and/or potassium acetate),

e) a metal hydroxide salt (e.g., an alkali and/or alkaline hydroxide salt, e.g., sodium hydroxide, potassium hydroxide, calcium hydroxide, and/or magnesium hydroxide, e.g., sodium hydroxide),

f) a metal carbonate and/or bicarbonate salt (e.g., an alkali and/or alkaline carbonate salt, e.g., an alkali and/or alkaline bicarbonate salt, e.g., sodium bicarbonate), and/or

g) a metal borate salt (e.g., an alkali borate salt, e.g., sodium borate),

e.g., one or more of sodium citrate, $Na_2HPO_4$, tris(hydroxymethyl)aminomethane, and a tris(hydroxymethyl)aminomethane salt (e.g., tris acetate), e.g., one or more of sodium citrate, $Na_2HPO_4$, and tris(hydroxymethyl)aminomethane, e.g., one or more of sodium citrate and $Na_2HPO_4$, e.g., $Na_2HPO_4$, e.g., tris(hydroxymethyl)aminomethane.

1.80 Kit 1.78 or 1.79 wherein the solvent, e.g., the sterile solution, comprises 1 or 5 mg to 200 or 500 mg of the base, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.81 Kit 1.78 or 1.79 wherein the concentration of each of the one or more bases is 0.01 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5 to 50 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of each of the one or more bases is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of each of the one or more bases is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.82 Kit 1.78-1.81 wherein the solvent, e.g. the sterile solution, comprises one or more of a metal citrate salt (e.g., sodium citrate) and a metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$).

1.83 Kit 1.1.78-1.82 wherein the solvent, e.g. the sterile solution, comprises a metal citrate salt (e.g., sodium citrate).

1.84 Kit 1.83 wherein the solvent, e.g., the sterile solution, comprises 1 or 5 mg to 200 mg or 500 mg of the metal citrate salt (e.g., sodium citrate), e.g., from about 1 or 5 mg to 200 or 500 mg, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.85 Kit 1.83 wherein the concentration of the metal citrate salt (e.g., sodium citrate) is from about 0.01 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5 to 50 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of the metal citrate salt (e.g., sodium citrate) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of the metal citrate salt (e.g., sodium citrate) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.86 Kit 1.78-1.85 wherein the solvent, e.g., the sterile solution, comprises a metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$).

1.87 Kit 1.86 wherein the solvent, e.g., the sterile solution, comprises 1 or 5 mg to 200 mg or 500 mg of the metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$), e.g., from about 1 or 5 mg to 200 or 500 mg, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.88 Kit 1.86 wherein the concentration of the metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$), is from 0.01 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g.,

from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5 to 50 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of each of the metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of the metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.89 Kit 1.78-1.88 wherein the wherein the solvent, e.g., the sterile solution, comprises $Na_2HPO_4$.

1.90 Kit 1.89 wherein the solvent, e.g., the sterile solution, comprises 1 or 5 mg to 200 or 500 mg $Na_2HPO_4$, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.91 Kit 1.89 wherein the concentration of $Na_2HPO_4$ is 0.01 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5 to 50 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of $Na_2HPO_4$ is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of $Na_2HPO_4$ is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.92 Kit 1.78-1.91 wherein the solvent, e.g., the sterile solution, comprises an amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9.

1.93 Kit 1.92 wherein the wherein the solvent, e.g., the sterile solution, comprises 1 or 5 mg to 200 or 500 mg of the amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.94 Kit 1.92 wherein the concentration of the amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, is 0.01 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5 to 50 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of the amine and/or a salt thereof (e.g., morpholine, an amino acid a (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of

Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of the amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., -$CH_2CH_3$, e.g., -$CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., –$CH_2$–$CH_2$–, e.g., –$C(CH_2)_3$–, e.g., one $R^8$ is –$CH_3$ and another $R^8$ is –$(CH_2)_6$–) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.95 Kit 1.78-1.94 wherein the solvent, e.g., the sterile solution, comprises a mono- and/or poly-hydroxyalkylamine and/or a salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., -$CH_2CH_3$, e.g., -$CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., –$CH_2$–$CH_2$–, e.g., –$C(CH_2)_3$–, e.g., one $R^8$ is –$CH_3$ and another $R^8$ is –$(CH_2)_6$–) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine).

1.96 Kit 1.95 wherein the solvent, e.g., the sterile solution, comprises 1 or 5 mg to 200 or 500 mg of the mono- and/or poly-hydroxyalkylamine and/or salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., -$CH_2CH_3$, e.g., -$CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., –$CH_2$–$CH_2$–, e.g., –$C(CH_2)_3$–, e.g., one $R^8$ is –$CH_3$ and another $R^8$ is –$(CH_2)_6$–) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate),

meglumine, and/or diethanolamine), e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.97 Kit 1.95 wherein the concentration of the mono- and/or poly-hydroxyalkylamine and/or salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), is 0.01 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5 to 50 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of each of the mono- and/or poly-hydroxyalkylamine and/or salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of the mono- and/or poly-hydroxyalkylamine and/or salt

thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or a salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., -$CH_2CH_3$, e.g., -$CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., –$CH_2$–$CH_2$–, e.g., –$C(CH_2)_3$–, e.g., one $R^8$ is –$CH_3$ and another $R^8$ is –$(CH_2)_6$–) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.98 Kit 1.78-1.97 wherein the solvent, e.g., the sterile solution, comprises $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., -$CH_2CH_3$, e.g., -$CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., –$CH_2$–$CH_2$–, e.g., –$C(CH_2)_3$–, e.g., one $R^8$ is –$CH_3$ and another $R^8$ is –$(CH_2)_6$–) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine).

1.99 Kit 1.98 wherein the solvent, e.g., the sterile solution, comprises 1 or 5 mg to 200 or 500 mg of the $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., -$CH_2CH_3$, e.g., -$CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., –$CH_2$–$CH_2$–, e.g., –$C(CH_2)_3$–, e.g., one $R^8$ is –$CH_3$ and another $R^8$ is –$(CH_2)_6$–) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.100 Kit 1.98 wherein the concentration of the $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), is 0.01 or 0.1 or 0.5 or 1 or 2to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5 to 50 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of the $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of the $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris

acetate), meglumine, and/or diethanolamine) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.101 Kit 1.78-1.100 wherein the solvent, e.g., the sterile solution, comprises tris(hydroxymethyl)aminomethane.

1.102 Kit 1.101 wherein the solvent, e.g., the sterile solution, comprises 1 or 5 mg to 200 or 500 mg tris(hydroxymethyl)aminomethane, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.103 Kit 1.101 wherein the concentration of tris(hydroxymethyl)aminomethane is 0.01 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5 to 50 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of tris(hydroxymethyl)aminomethane is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of tris(hydroxymethyl)aminomethane is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.104 Kit 1.78-1.103 wherein the solvent, e.g., the sterile solution, comprises a tris(hydroxymethyl)aminomethane salt, e.g., tris(hydroxymethyl)aminomethane acetate.

1.105 Kit 1.104 wherein the solvent, e.g., the sterile solution, comprises 1 or 5 mg to 200 or 500 mg of the tris(hydroxymethyl)aminomethane salt (e.g., tris(hydroxymethyl)aminomethane acetate), e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75 100, 150, 200, 250, 300, 350, 400, 450, or 500 mg tris(hydroxymethyl)aminomethane salt (e.g., tris(hydroxymethyl)aminomethane acetate), e.g., 1 or 5 mg to 200 or 500 mg tris(hydroxymethyl)aminomethane

acetate, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.106 Kit 1.105 wherein the concentration of the tris(hydroxymethyl)aminomethane salt (e.g., tris(hydroxymethyl)aminomethane acetate) is 0.01 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5 to 50 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of the tris(hydroxymethyl)aminomethane salt (e.g., tris(hydroxymethyl)aminomethane acetate) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of the tris(hydroxymethyl)aminomethane salt (e.g., tris(hydroxymethyl)aminomethane acetate) is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.107 Kit 1.78-1.106 wherein the solvent, e.g., the sterile solution, comprises a base, e.g., an amine and/or a salt thereof, wherein a conjugate acid of the base has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9.

1.108 Kit 1.107 wherein the solvent, e.g., the sterile solution, comprises 1 or 5 mg to 200 or 500 mg of the base, e.g., from about 1 or 5 or 10 mg to 15, 20, 25, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 1000, or 1500 mg, e.g., from about 15, 20, 30, 50, or 100 to 200, 250, 400, 450, 500, 600, 700, 800, 1000, or 1500 mg.

1.109 Kit 1.107 wherein the concentration of the base is 0.01 or 0.1 or 0.5 or 1 or 2 to 250 mM, e.g., from about 0.01 or 0.1 or 0.5 to 1, 2, 5, 10, 15, 20, 25, 40, 50, 60, 75, 100, 125, 150, 175, 200, 250, or 1000 mM, e.g. from about 1 to 2, 5, 10, 15, 20, 25, 40, 50 or 60 mM, e.g., from about 5 to 50 mM, e.g., from about 5, 10, 15,

20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., from about 5, 10, 15, 20, 25, or 50 to 100, 200, 250, 300, 400, 500, or 1000 mM, e.g., about 2, 20, or 200 mM, e.g., about 5, 10, 50, 500, 500, or 1000 mM, e.g., wherein the concentration of the base is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula II, e.g., about 2.5 or 5 to 10, e.g. about 2.5, e.g., about 5, e.g., wherein the concentration of the base is 2 or 3 to 5, 6, 8, 10, 15 or 20 equivalents of Formula III, e.g., about 5 to 10, e.g. about 5, e.g., about 10.

1.110 Kit 1.78-1.109 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to the one or more bases is at least 1:1.

1.111 Kit 1.78-1.110 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to the one or more bases is at least 1:2, e e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.112 Kit 1.111 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to a metal citrate salt (e.g., sodium citrate) is at least 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.113 Kit 1.111 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to a metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$) is at least 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.114 Kit 1.111 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to

the amine and/or salt thereof (e.g., morpholine, amino acid (e.g., arginine), mono- and/or poly-hydroxyalkylamine, and/or salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, is at least 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.115 Kit 1.114 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to the mono- and/or poly-hydroxyalkylamine and/or salt thereof, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), is at least 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.116 Kit 1.115 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, and/or salt thereof wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), is 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.117 Kit 1.116 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to tris(hydroxymethyl)aminomethane is at least 1:2, e.g., at least about 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:10.

1.118 Kit 1.116 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to the tris(hydroxymethyl)aminomethane salt (e.g., tris(hydroxymethyl)aminomethane acetate) is at least 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.119 Kit 1.111 wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to a base, e.g., an amine and/or a salt thereof, wherein a conjugate acid of the base has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, is at least 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at

least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

1.120 Kit 1.71-1.119 wherein the solvent, e.g., the sterile solution, comprises one or more bulking agents, e.g., one or more of maltose, mannose, ribose, cyclodextrin, mannitol, lactose, sucrose, trehalose, sorbitol, glucose, raffinose, arginine, glycine, histidine, dextran (e.g., dextran 40), polyvinylpyrrolidone, polyethylene glycol, and polypropylene glycol, e.g., one or more of mannitol, glucose, sucrose, lactose, trehalose, and dextran (e.g., dextran 40).

1.121 Kit 1.71-1.120 wherein the solvent, e.g., the sterile solution, comprises 5 or 10 or 50 mg to 2 or 5 g of one or more bulking agents, e.g., from about 50 or 100 mg to 200, 300, 500, or 800 mg, or 1, 1.5, 2, 3, 4, or 5 g of one or more bulking agents.

1.122 Kit 1.71-1.121 wherein the solvent, e.g., the sterile solution, comprises dextran (e.g., dextran 40).

1.123 Kit 1.122 wherein the solvent, e.g. the sterile solution, comprises 5 or 10 or 50 mg to 2 or 5 g dextran (e.g., dextran 40), e.g., from about 50 or 100 mg to 200, 300, 500, or 800 mg, or 1, 1.5, 2, 3, 4, or 5 g dextran (e.g., dextran 40).

1.124 Kit 1.71-1.123 wherein the solvent, e.g., the sterile solution, comprises one or more solubilizing agents, e.g., ethylenediamine tetraacetic acid (EDTA) or a salt thereof (e.g., calcium disodium EDTA, disodium EDTA, sodium EDTA), alpha cyclodextrin, hydroxypropyl-β-cyclodextrin, polysorbate 80, tert-butanol, isopropanol, dichloromethane, ethanol, acetone, and glycerol; one or more collapse temperature modifiers which may shift the overall collapse temperature higher, e.g., one or more of dextran, Ficoll®, gelatin, and hydroxyethyl starch; one or more tonicity modifiers, e.g., one or more of sodium chloride, potassium chloride, sucrose, mannitol, and glucose; and one or more antimicrobial agents, e.g., one or more of benzyl alcohol, phenol, 2-phenoxyethanol, m-cresol, chlorobutanol, parabens (e.g., methyl paraben, ethyl paraben, propyl paraben), benzalkonium chloride, benzethonium chloride, myristyl gamma-picolinium salt (e.g., myristyl gamma-picolinium chloride), and organomercury compounds and salts (e.g., phenyl mercuric acetate, phenyl mercuric borate, phenyl mercuric nitrate, and thimerosal).

1.125 Kit 1.71-1.124 wherein 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is admixed with the solvent, e.g., an aqueous solution, to form a solution wherein the pH is between pH 7 and pH 10.5, e.g., between pH 7 and pH 9.5, e.g., between pH 7 and pH 8.

1.126 Kit 1.71-1.125 wherein the solution is filtered to remove particles and microbes, e.g., filtered prior to injection.

1.127 Kit 1.71-1.126 wherein the solution is administered about 24 hours, 12 hours, 10 hours, 8 hours, 2 hours, 1 hour, 30 minutes, 20 minutes, 15 minutes, 10 minutes, 5 minutes, 3 minutes, 2 minutes or 1 minute or less after admixture.

1.128 Kit I or 1.1-1.127 wherein the kit comprises one or more additional therapeutic agents, e.g., one or more additional therapeutic agents for cerebral edema, stroke, traumatic brain injury, glioma (e.g., glioblastoma), meningitis, acute mountain sickness, infection, metabolic disorder, hypoxia, water intoxication, hepatic failure, hepatic encephalopathy, diabetic ketoacidosis, abscess, eclampsia, Creutzfeldt-Jakob disease, lupus cerebritis, optic nerve edema, hyponatremia, fluid retention, ovarian hyperstimulation syndrome, epilepsy, retinal ischemia or other diseases of the eye associated with abnormalities in intraocular pressure and/or tissue hydration, myocardial ischemia, myocardial ischemia/reperfusion injury, myocardial infarction, myocardial hypoxia, congestive heart failure, sepsis, neuromyelitis optica, or migraines.

1.129 Kit I or 1.1-1.128 wherein the kit comprises one or more additional therapeutic agents, e.g., one or more additional therapeutic agents for pulmonary edema, fibromyalgia, or multiple sclerosis.

1.130 Kit I or 1.1-1.129 wherein the kit comprises instructions for using 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to treat or control a disease or condition mediated by an aquaporin, e.g., diseases or conditions of water imbalance and other diseases, for example, edema of the brain or spinal cord, e.g., cerebral edema, e.g. cerebral edema consequent to head trauma, ischemic stroke, glioma, meningitis, acute mountain sickness, epileptic seizure, infection, metabolic disorder, hypoxia (including general systemic hypoxia and hypoxia due to cardiac arrest), water intoxication, hepatic failure,

hepatic encephalopathy, diabetic ketoacidosis, abscess, eclampsia, Creutzfeldt-Jakob disease, lupus cerebritis, cardiac arrest, microgravity and/or radiation exposure, or an invasive central nervous system procedure, e.g., neurosurgery, endovascular clot removal, spinal tap, aneurysm repair, or deep brain stimulation or, e.g., spinal cord edema consequent to spinal cord trauma, e.g., spinal cord compression; or optic nerve edema, e.g., optic nerve edema consequent to microgravity and/or radiation exposure; or retinal edema; or hyponatremia or excessive fluid retention, e.g., consequent to heart failure (HF), liver cirrhosis, nephrotic disorder, syndrome of inappropriate antidiuretic hormone secretion (SIADH), or infertility treatment; or ovarian hyperstimulation syndrome; or epilepsy, retinal ischemia or other diseases of the eye associated with abnormalities in intraocular pressure and/or tissue hydration, myocardial ischemia, myocardial ischemia/reperfusion injury, myocardial infarction, myocardial hypoxia, congestive heart failure, sepsis, neuromyelitis optica, or glioblastoma; or migraines.

1.131 Kit I or 1.1-1.130 wherein the kit comprises instructions for using 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to treat or control a disease or condition mediated by an aquaporin, e.g., diseases or conditions of water imbalance and other diseases, for example, pulmonary edema, fibromyalgia, or multiple sclerosis.

1.132 Kit I or 1.1-1.131 wherein the kit comprises instructions for administering 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to a patient in need thereof.

1.133 Kit I or 1.1-1.132 wherein the kit comprises instructions for mixing 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate and one or more pharmaceutically acceptable excipients.

1.134 Kit I wherein the kit comprises a pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate, e.g., Composition I, e.g., a composition of 1.1-1.73.

1.135 Kit 1.134 wherein the kit comprises instructions for using the pharmaceutical composition to treat or control a disease or condition mediated by an aquaporin,

e.g., diseases or conditions of water imbalance and other diseases, for example, edema of the brain or spinal cord, e.g., cerebral edema, e.g. cerebral edema consequent to head trauma, ischemic stroke, glioma, meningitis, acute mountain sickness, epileptic seizure, infection, metabolic disorder, hypoxia (including general systemic hypoxia and hypoxia due to cardiac arrest), water intoxication, hepatic failure, hepatic encephalopathy, diabetic ketoacidosis, abscess, eclampsia, Creutzfeldt-Jakob disease, lupus cerebritis, cardiac arrest, microgravity and/or radiation exposure, or an invasive central nervous system procedure, e.g., neurosurgery, endovascular clot removal, spinal tap, aneurysm repair, or deep brain stimulation or, e.g., spinal cord edema consequent to spinal cord trauma, e.g., spinal cord compression; or optic nerve edema, e.g., optic nerve edema consequent to microgravity and/or radiation exposure; or retinal edema; or hyponatremia or excessive fluid retention, e.g., consequent to heart failure (HF), liver cirrhosis, nephrotic disorder, syndrome of inappropriate antidiuretic hormone secretion (SIADH), or infertility treatment; ovarian hyperstimulation syndrome; or epilepsy, retinal ischemia or other diseases of the eye associated with abnormalities in intraocular pressure and/or tissue hydration, myocardial ischemia, myocardial ischemia/reperfusion injury, myocardial infarction, myocardial hypoxia, congestive heart failure, sepsis, neuromyelitis optica, or glioblastoma; or migraines.

1.136 Kit 1.134 wherein the kit comprises instructions for using the pharmaceutical composition to treat or control a disease or condition mediated by an aquaporin, e.g., diseases or conditions of water imbalance and other diseases, for example, pulmonary edema, fibromyalgia, or multiple sclerosis.

1.137 Kit 1.134 wherein the kit comprises instructions for administering the pharmaceutical composition to a patient in need thereof.

1.138 Kit 1.134 wherein the kit comprises instructions for preparing the pharmaceutical composition.

1.139 Kit I or 1.1-1.138 wherein the kit is for use in any of the methods described herein, e.g., for use in Method A, e.g., Method A.1-A.58, for use in Method B, e.g., Method B.1-B.41, e.g., for use in Method C, e.g., C.1-C.8, e.g., for use in

Method D, e.g., D.1-D.19, e.g., for use in Method E, e.g., E.1-E.59, e.g., for use in Method F, e.g., F.1-F.5, e.g., for use in Method G, e.g., G.1-G.58, e.g., for use in Method H., e.g., H.1-H.9, *vida infra*.

**[0068]** In some embodiments, the kit is prepared by transferring a liquid comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to a container, e.g., a vial, in a predetermined volume first and then subjecting the liquid to a lyophilization process. Alternatively, liquid can be lyophilized in a large volume and then a predetermined amount of the lyophilized preparation can be placed in a container.

**[0069]** In yet another embodiment, provided is a method (Method A) of treating or controlling a disease or condition mediated by an aquaporin comprising administering to a patient in need thereof a pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate, e.g., Composition I, e.g., composition 1.1-1.124.

**[0070]** Further provided is Method A as follows:

A.1 Method A wherein the aquaporin is AQP4.

A.2 Method A or A.1 wherein the condition to be treated or controlled is edema, e.g. edema of the brain or spinal cord, e.g., cerebral edema, e.g. cerebral edema consequent to head trauma, ischemic stroke, glioma, meningitis, acute mountain sickness, epileptic seizure, infection, metabolic disorder, water intoxication, hepatic failure, hepatic encephalopathy, or diabetic ketoacidosis or, e.g., spinal cord edema, e.g., spinal cord edema consequent to spinal cord trauma, e.g., spinal cord compression.

A.3 Method A, A.1, or A.2 further comprising a treatment selected from one or more of the following: optimal head and neck positioning to facilitate venous outflow, e.g. head elevation 30°; avoidance of dehydration; systemic hypotension; maintenance of normothermia or hypothermia; aggressive measures; osmotherapy, e.g., using mannitol or hypertonic saline; hyperventilation; therapeutic pressor therapy to enhance cerebral perfusion; administration of barbiturates to reduce cerebral metabolism ($CMO_2$); hemicraniectomy; administration of aspirin; administration of amantadine; intravenous thrombolysis (e.g. using rtPA); mechanical clot removal; angioplasty; and/or stents.

A.4 Method A.2 wherein the patient is at elevated risk of cerebral edema, e.g., due to head trauma, ischemic stroke, glioma, meningitis, acute mountain sickness, epileptic seizure, infection, metabolic disorder, water intoxication, hepatic failure, hepatic encephalopathy, or diabetic ketoacidosis.

A.5 Method A.2 wherein the patient has suffered a stroke, head injury, or spinal injury.

A.6 Method A.5 wherein the patient has suffered a stroke, head injury or spinal injury within 12 hours, e.g. within 6 hours, preferably within 3 hours of commencing treatment.

A.7 Method A.2 wherein the patient is at elevated risk of suffering a stroke, head injury or spinal injury, e.g., in combat or in an athletic competition.

A.8 Method A or A.1-A.7 wherein the patient already has cerebral edema.

A.9 Method A or A.1-A.8 wherein the condition to be treated or controlled is cerebral edema consequent to a stroke or a traumatic brain injury.

A.10 Method A or A.1- A.9 wherein the condition to be treated or controlled is cerebral edema consequent to a middle cerebral artery stroke.

A.11 Method A or A.1-A.9 wherein the condition to be treated or controlled is cerebral edema consequent to closed head trauma.

A.12 Method A or A.1-A.4 wherein the condition to be treated or controlled is cerebral edema consequent to an epileptic seizure.

A.13 Method A or A.1-A.4 wherein the condition to be treated or controlled is cerebral edema consequent to an infection.

A.14 Method A or A.1-A.4 wherein the condition to be treated or controlled is cerebral edema consequent to a metabolic disorder.

A.15 Method A or A.1-A.4 wherein the condition to be treated or controlled is cerebral edema consequent to glioma.

A.16 Method A or A.1-A.4 wherein the condition to be treated or controlled is cerebral edema consequent to meningitis.

A.17 Method A or A.1-A.4 wherein the condition to be treated or controlled is cerebral edema consequent to acute mountain sickness.

A.18 Method A or A.1-A.4 wherein the condition to be treated or controlled is cerebral edema consequent to water intoxication.

A.19 Method A or A.1-A.4 wherein the condition to be treated or controlled is cerebral edema consequent to hepatic failure, hepatic encephalopathy, or diabetic ketoacidosis.

A.20 Method A or A.1-A.3 wherein the condition to be treated or controlled is cerebral edema consequent to an abscess.

A.21 Method A or A.1-A.3 wherein the condition to be treated or controlled is cerebral edema consequent to eclampsia.

A.22 Method A or A.1-A.3 wherein the condition to be treated or controlled is cerebral edema consequent to Creutzfeldt-Jakob disease.

A.23 Method A or A.1-A.3 wherein the condition to be treated or controlled is cerebral edema consequent to lupus cerebritis.

A.24 Method A or A.1-A.3 wherein the condition to be treated or controlled is edema consequent to hypoxia, e.g., general systemic hypoxia, e.g., hypoxia caused by an interruption of blood perfusion, for example wherein the edema is cerebral edema consequent to hypoxia caused by cardiac arrest, stroke, or other interruption of blood perfusion to the brain, or wherein the edema is cardiac edema consequent to cardiac ischemia or other interruption of blood flow to the heart.

A.25 Method A or A.1-A.3 wherein the condition to be treated or controlled is cerebral edema consequent to microgravity and/or radiation exposure, e.g., exposure from space flight or from working with radioactive materials or from working in radioactive areas.

A.26 Method A or A.1-A.3 wherein the condition to be treated or controlled is cerebral edema consequent to an invasive central nervous system procedure, e.g., neurosurgery, endovascular clot removal, spinal tap, aneurysm repair, or deep brain stimulation.

A.27 Method A.25 or A.26 wherein the patient is at elevated risk of edema, e.g., due to microgravity and/or radiation exposure, neurosurgery, endovascular clot removal, spinal tap, aneurysm repair, or deep brain stimulation.

A.28 Method A.25 or A.26 wherein the patient already has edema.

A.29 Method A or A.1-A.28 wherein the edema is cytotoxic cerebral edema or is primarily cytotoxic cerebral edema.

A.30 Method A, A.1-A.19, or A.24 wherein the edema is cytotoxic cerebral edema or is primarily cytotoxic cerebral edema.

A.31 Method A, A.1, or A.2 wherein the condition to be treated or controlled is spinal cord edema, e.g., spinal cord edema consequent to a spinal cord trauma, e.g., spinal cord compression.

A.32 Method A.31 wherein the condition to be treated or controlled is spinal cord edema consequent to spinal cord compression.

A.33 Method A, A.1, or A.2 wherein the condition to be treated or controlled is optic nerve edema, e.g., optic nerve edema consequent to microgravity and/or radiation exposure, e.g., exposure from space flight or from working with radioactive materials or from working in radioactive areas.

A.34 Method A, A.1, or A.2 wherein the condition to be treated or controlled is retinal edema.

A.35 Method A, A.1, or A.2 wherein the condition to be treated or controlled is pulmonary edema.

A.36 Method A or A.1 wherein the condition to be treated or controlled is epilepsy.

A.37 Method A or A.1 wherein the condition to be treated or controlled is retinal ischemia or other diseases of the eye associated with abnormalities in intraocular pressure and/or tissue hydration.

A.38 Method A or A.1 wherein the condition to be treated or controlled is myocardial ischemia.

A.39 Method A or A.1, wherein the condition to be treated or controlled is myocardial ischemia/reperfusion injury.

A.40 Method A or A.1 wherein the condition to be treated or controlled is myocardial infarction.

A.41 Method A or A.1 wherein the condition to be treated or controlled is myocardial hypoxia.

A.42 Method A or A.1 wherein the condition to be treated or controlled is congestive heart failure.

A.43 Method A or A.1 wherein the condition to be treated or controlled is sepsis.

A.44 Method A or A.1 wherein the condition to be treated or controlled is a migraine.

A.45 Method A or A.1 wherein the condition to be treated or controlled is neuromyelitis optica.

A.46 Method A or A.1 wherein the condition to be treated or controlled is glioblastoma.

A.47 Method A or A.1 wherein the condition to be treated or controlled is fibromyalgia.

A.48 Method A or A.1 wherein the condition to be treated or controlled is multiple sclerosis.

A.49 Method A wherein the aquaporin is AQP2.

A.50 Method A or A.49 wherein the condition to be treated or controlled is hyponatremia or excessive fluid retention, e.g., consequent to heart failure (HF), for example congestive heart failure, liver cirrhosis, nephrotic disorder, syndrome of inappropriate antidiuretic hormone secretion (SIADH), or infertility treatment.

A.51 Method A, A.49, or A.50 wherein the condition to be treated or controlled is ovarian hyperstimulation syndrome.

A.52 Method A, A.49, or A.50 further comprising one or more of restriction of dietary sodium, fluid and/or alcohol; and/or administration of one or more diuretics, vasopressin receptor antagonists, angiotensin converting enzyme (ACE) inhibitors, aldosterone inhibitors, angiotensin receptor blockers (ARBs), beta-adrenergic antagonists (beta-blockers), and/or digoxin.

A.53 Method A or A.1-A.42 wherein the pharmaceutical composition is administered orally.

A.54 Method A or A.1-A.52 wherein the pharmaceutical composition is administered parenterally.

A.55 Method A.54 wherein the pharmaceutical composition is administered by injection, e.g., subcutaneously, intramuscularly, intravenously, or intrathecally, e.g., a bolus injected subcutaneously, intramuscularly, intravenously, or intrathecally.

A.56 Method A.55 wherein the pharmaceutical composition is administered intravenously, e.g., IV bolus and/or IV infusion, e.g., IV bolus followed by IV infusion.

A.57 Method A or A.1-A.56 wherein the patient is human.

A.58 Method A or A.1-A.57 wherein the onset of action after administration of the pharmaceutical composition is fairly rapid.

**[0071]** In yet another embodiment, provided is a method (Method B) of treating or controlling edema, e.g. edema of the brain or spinal cord, e.g., cerebral edema, e.g. cerebral edema consequent to head trauma, ischemic stroke, glioma, meningitis, acute mountain sickness, epileptic seizure, infection, metabolic disorder, hypoxia, water intoxication, hepatic failure, hepatic encephalopathy, diabetic ketoacidosis, abscess, eclampsia, Creutzfeldt-Jakob disease, lupus cerebritis, cardiac arrest, microgravity and/or radiation exposure, or invasive central nervous system procedures, e.g., neurosurgery, endovascular clot removal, spinal tap, aneurysm repair, or deep brain stimulation or, e.g., optic nerve edema, e.g., optic nerve edema consequent to microgravity and/or radiation exposure or, e.g., retinal edema or, e.g., spinal cord edema, e.g., spinal cord edema consequent to spinal cord trauma, e.g., spinal cord compression, or e.g., pulmonary edema, comprising administering a pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate, e.g., Composition I, e.g., composition 1.1-1.124, to a patient in need thereof.

**[0072]** Further provided is Method B as follows:

B.1 Method B further comprising a treatment selected from one or more of the following: optimal head and neck positioning to facilitate venous outflow, e.g. head elevation 30°; avoidance of dehydration; systemic hypotension; maintenance of normothermia or hypothermia; aggressive measures; osmotherapy, e.g., using mannitol or hypertonic saline; hyperventilation; therapeutic pressor therapy to enhance cerebral perfusion; administration of barbiturates to reduce cerebral metabolism ($CMO_2$); hemicraniectomy; administration of aspirin; administration of amantadine; intravenous thrombolysis (e.g. using rtPA); mechanical clot removal; angioplasty; and/or stents.

B.2 Method B wherein the patient is at elevated risk of cerebral edema, e.g., due to head trauma, ischemic stroke, glioma, meningitis, acute mountain sickness,

epileptic seizure, infection, metabolic disorder, water intoxication, hepatic failure, hepatic encephalopathy, or diabetic ketoacidosis.

B.3 Method B wherein the patient has suffered a stroke, head injury, or spinal injury.

B.4 Method B.3 wherein the patient has suffered a stroke, head injury or spinal injury within 12 hours, e.g. within 6 hours, preferably within 3 hours of commencing treatment.

B.5 Method B wherein the patient is at elevated risk of suffering a stroke, head injury or spinal injury, e.g., in combat or in an athletic competition.

B.6 Method B or B.1-B.5 wherein the patient already has cerebral edema.

B.7 Method B or B.1-B.6 wherein the condition to be treated or controlled is cerebral edema consequent to a stroke or a traumatic brain injury.

B.8 Method B or B.1-B.7 wherein the condition to be treated or controlled is cerebral edema consequent to a middle cerebral artery stroke.

B.9 Method B or B.1-B.7 wherein the condition to be treated or controlled is cerebral edema consequent to a closed head trauma.

B.10 Method B, B.1, or B.2 wherein the condition to be treated or controlled is cerebral edema consequent to an epileptic seizure.

B.11 Method B, B.1, or B.2 wherein the condition to be treated or controlled is cerebral edema consequent to an infection.

B.12 Method B, B.1, or B.2 wherein the condition to be treated or controlled is cerebral edema consequent to a metabolic disorder.

B.13 Method B, B.1, or B.2 wherein the condition to be treated or controlled is cerebral edema consequent to glioma.

B.14 Method B, B.1, or B.2 wherein the condition to be treated or controlled is cerebral edema consequent to meningitis.

B.15 Method B, B.1, or B.2 wherein the condition to be treated or controlled is cerebral edema consequent to acute mountain sickness.

B.16 Method B, B.1, or B.2 wherein the condition to be treated or controlled is cerebral edema consequent to water intoxication.

B.17 Method B, B.1, or B.2 wherein the condition to be treated or controlled is cerebral edema consequent to hepatic failure, hepatic encephalopathy, or diabetic ketoacidosis.

B.18 Method B or B.1 wherein the condition to be treated or controlled is cerebral edema consequent to an abscess.

B.19 Method B or B.1 wherein the condition to be treated or controlled is cerebral edema consequent to eclampsia.

B.20 Method B or B.1 wherein the condition to be treated or controlled is cerebral edema consequent to Creutzfeldt-Jakob disease.

B.21 Method B or B.1 wherein the condition to be treated or controlled is cerebral edema consequent to lupus cerebritis.

B.22 Method B or B.1 wherein the condition to be treated or controlled is edema consequent to hypoxia, e.g., general systemic hypoxia, e.g., hypoxia caused by an interruption of blood perfusion, for example wherein the edema is cerebral edema consequent to hypoxia caused by cardiac arrest, stroke, or other interruption of blood perfusion to the brain, or wherein the edema is cardiac edema consequent to cardiac ischemia or other interruption of blood flow to the heart.

B.23 Method B or B.1 wherein the condition to be treated or controlled is cerebral edema consequent to microgravity exposure, e.g., exposure from space flight or from working with radioactive materials or from working in radioactive areas.

B.24 Method B or B.1 wherein the condition to be treated or controlled is cerebral edema consequent to invasive central nervous system procedures, e.g., neurosurgery, endovascular clot removal, spinal tap, aneurysm repair, or deep brain stimulation.

B.25 Method B.23 or B.24 wherein the patient is at elevated risk of edema, e.g., due to microgravity and/or radiation exposure, neurosurgery, endovascular clot removal, spinal tap, aneurysm repair, or deep brain stimulation.

B.26 Method B.23 or B.24 wherein the patient already has edema.

B.27 Method B or B.1-B.26 wherein the edema is cytotoxic cerebral edema or is primarily cytotoxic cerebral edema.

B.28 Method B, B.1-B.17, or B.22 wherein the edema is cytotoxic cerebral edema or is primarily cytotoxic cerebral edema.

B.29 Method B wherein the condition to be treated or controlled is spinal cord edema, e.g., spinal cord edema consequent to spinal cord trauma, e.g., spinal cord compression.

B.30 Method B.29 wherein the condition to be treated or controlled is spinal cord edema consequent to spinal cord compression.

B.31 Method B wherein the condition to be treated or controlled is optic nerve edema, e.g., optic nerve edema consequent to microgravity and/or radiation exposure, e.g., exposure from space flight or from working with radioactive materials or from working in radioactive areas.

B.32 Method B wherein the condition to be treated or controlled is retinal edema.

B.33 Method B wherein the condition to be treated or controlled is pulmonary edema.

B.34 Method B or B.1-B.33 wherein the duration of treatment with the pharmaceutical composition is less than 21 days, e.g., less than 2 weeks, e.g., one week or less.

B.35 Method B or B.1-B.34 wherein the pharmaceutical composition is administered orally.

B.36 Method B or B.1-B.34 wherein the pharmaceutical composition is administered parenterally.

B.37 Method B.36 wherein the pharmaceutical composition is administered by injection, e.g., subcutaneously, intramuscularly, intravenously, or intrathecally, e.g., a bolus administered subcutaneously, intramuscularly, intravenously, or intrathecally.

B.38 Method B.37 wherein the pharmaceutical composition is administered intravenously, e.g., IV bolus and/or IV infusion, e.g., IV bolus followed by IV infusion.

B.39 Method B or B.1-B.38 wherein the patient is human.

B.40 Method B or B.1-B.39 wherein the onset of action after administration of the pharmaceutical composition is fairly rapid.

B.41 Method B or B.1-B.40 wherein the 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate binds to AQP4.

**[0073]** In yet another embodiment, provided is a method (Method C) of treating or controlling a condition selected from hyponatremia and excessive fluid retention, e.g., consequent to heart failure (HF), for example congestive heart failure, liver cirrhosis, nephrotic disorder, syndrome of inappropriate antidiuretic hormone secretion (SIADH), or infertility treatment, comprising administering a pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate, e.g., Composition I, e.g., composition 1.1-1.124, to a patient in need thereof.

**[0074]** Further provided is Method C as follows:

C.1 Method C further comprising one or more of restriction of dietary sodium, fluid and/or alcohol; and/or administration of one or more diuretics, vasopressin receptor antagonists, angiotensin converting enzyme (ACE) inhibitors, aldosterone inhibitors, angiotensin receptor blockers (ARBs), beta-adrenergic antagonists (beta-blockers), and/or digoxin.

C.2 Method C or C.1 wherein the pharmaceutical composition is administered orally.

C.3 Method C or C.1 wherein the pharmaceutical composition is administered parenterally.

C.4 Method C.3 wherein the pharmaceutical composition is administered by injection, e.g., subcutaneously, intramuscularly, intravenously, or intrathecally, e.g., a bolus injected subcutaneously, intramuscularly, intravenously, or intrathecally.

C.5 Method C.4 wherein the pharmaceutical composition is administered intravenously, e.g., IV bolus and/or IV infusion, e.g., IV bolus followed by IV infusion.

C.6 Method C or C.1-C.5 wherein the patient is human.

C.7 Method C or C.1-C.6 wherein the onset of action after administration of the pharmaceutical composition is fairly rapid.

C.8 Method C or C.1-C.7 wherein 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate binds to AQP2.

**[0075]** In yet another embodiment, provided is a method (Method D) of treating or controlling a condition selected from epilepsy, retinal ischemia or other diseases of the eye associated with abnormalities in intraocular pressure and/or tissue hydration, myocardial ischemia, myocardial ischemia/reperfusion injury, myocardial infarction, myocardial hypoxia, congestive heart failure, sepsis, neuromyelitis optica, glioblastoma, fibromyalgia, multiple sclerosis, and a migraine comprising administering a pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate, e.g., Composition I, e.g., composition 1.1-1.124, to a patient in need thereof.

**[0076]** Further provided is Method D as follows:

D.1 Method D wherein the condition to be treated or controlled is retinal ischemia or other diseases of the eye associated with abnormalities in intraocular pressure and/or tissue hydration.

D.2 Method D wherein the condition to be treated or controlled is myocardial ischemia.

D.3 Method D wherein the condition to be treated or controlled is myocardial ischemia/reperfusion injury.

D.4 Method D wherein the condition to be treated or controlled is myocardial infarction.

D.5 Method D wherein the condition to be treated or controlled is myocardial hypoxia.

D.6 Method D wherein the condition to be treated or controlled is congestive heart failure.

D.7 Method D wherein the condition to be treated or controlled is sepsis.

D.8 Method D wherein the condition to be treated or controlled is neuromyelitis optica.

D.9 Method D wherein the condition to be treated or controlled is glioblastoma.

D.10 Method D wherein the condition to be treated or controlled is fibromyalgia.

D.11 Method D wherein the condition to be treated or controlled is multiple sclerosis.

D.12 Method D wherein the condition to be treated or controlled is a migraine.

D.13 Method D or D.1-D.12 wherein the pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is administered orally.

D.14 Method D or D.1-D.12 wherein the pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is administered parenterally.

D.15 Method D.14 wherein the pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is administered by injection, e.g., subcutaneously, intramuscularly, intravenously, or intrathecally, e.g., a bolus injected subcutaneously, intramuscularly, intravenously, or intrathecally.

D.16 Method D.15 wherein the pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is administered intravenously, e.g., IV bolus and/or IV infusion, e.g., IV bolus followed by IV infusion.

D.17 Method D or D.1-D.16 wherein the patient is human.

D.18 Method D or D.1-D.17 wherein the onset of action after administration of the pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is fairly rapid.

D.19 Method D or D.1-D.18 wherein 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate binds to AQP4.

**[0077]** In yet another embodiment, provided is a method (Method E) of treating or controlling a disease or condition mediated by an aquaporin comprising administering to a patient in need thereof a pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate, e.g., Composition I, e.g., composition 1.1-1.124, in an amount effective to inhibit the aquaporin, for example

**[0078]** Further provided is Method E as follows:

E.1 Method E wherein the aquaporin is AQP4.

E.2 Method E or E.1 wherein the condition to be treated or controlled is selected from edema, e.g. edema of the brain or spinal cord, e.g., cerebral edema, e.g. cerebral

edema consequent to head trauma, ischemic stroke, glioma, meningitis, acute mountain sickness, epileptic seizure, infection, metabolic disorder, water intoxication, hepatic failure, hepatic encephalopathy, or diabetic ketoacidosis or, e.g., spinal cord edema, e.g., spinal cord edema consequent to spinal cord trauma, e.g., spinal cord compression.

E.3 Method E, E.1, or E.2 further comprising a treatment selected from one or more of the following: optimal head and neck positioning to facilitate venous outflow, e.g. head elevation 30°; avoidance of dehydration; systemic hypotension; maintenance of normothermia or hypothermia; aggressive measures; osmotherapy, e.g., using mannitol or hypertonic saline; hyperventilation; therapeutic pressor therapy to enhance cerebral perfusion; administration of barbiturates to reduce of cerebral metabolism ($CMO_2$); hemicraniectomy; administration of aspirin; administration of amantadine; intravenous thrombolysis (e.g. using rtPA); mechanical clot removal; angioplasty; and/or stents.

E.4 Method E.2 wherein the patient is at elevated risk of cerebral edema, e.g., due to head trauma, ischemic stroke, glioma, meningitis, acute mountain sickness, epileptic seizure, infection, metabolic disorder, water intoxication, hepatic failure, hepatic encephalopathy, or diabetic ketoacidosis.

E.5 Method E.2 wherein the patient has suffered a stroke, head injury, or spinal injury.

E.6 Method E.5 wherein the patient has suffered a stroke, head injury or spinal injury within 12 hours, e.g. within 6 hours, preferably within 3 hours of commencing treatment.

E.7 Method E.2 wherein the patient is at elevated risk of suffering a stroke, head injury or spinal injury, e.g., in combat or in an athletic competition.

E.8 Method E or E.1-E.7 wherein the patient already has cerebral edema.

E.9 Method E or E.1-E.8 wherein the condition to be treated or controlled is cerebral edema consequent to a stroke or a traumatic brain injury.

E.10 Method E or E.1-E.9 wherein the condition to be treated or controlled is cerebral edema consequent to a middle cerebral artery stroke.

E.11 Method E or E.1-E.9 wherein the condition to be treated or controlled is cerebral edema consequent to a closed head trauma.

E.12 Method E or E.1-E.4 wherein the condition to be treated or controlled is cerebral edema consequent to an epileptic seizure.

E.13 Method E or E.1-E.4 wherein the condition to be treated or controlled is cerebral edema consequent an infection.

E.14 Method E or E.1-E.4 wherein the condition to be treated or controlled is cerebral edema consequent to a metabolic disorder.

E.15 Method E or E.1-E.4 wherein the condition to be treated or controlled is cerebral edema consequent to glioma.

E.16 Method E or E.1-E.4 wherein the condition to be treated or controlled is cerebral edema consequent to meningitis.

E.17 Method E or E.1-E.4 wherein the condition to be treated or controlled is cerebral edema consequent to acute mountain sickness.

E.18 Method E or E.1-E.4 wherein the condition to be treated or controlled is cerebral edema consequent to water intoxication.

E.19 Method E or E.1-E.4 wherein the condition to be treated or controlled is cerebral edema consequent to hepatic failure, hepatic encephalopathy, or diabetic ketoacidosis.

E.20 Method E or E.1-E.3 wherein the condition to be treated or controlled is cerebral edema consequent to an abscess.

E.21 Method E or E.1-E.3 wherein the condition to be treated or controlled is cerebral edema consequent to eclampsia.

E.22 Method E or E.1-E.3 wherein the condition to be treated or controlled is cerebral edema consequent to Creutzfeldt-Jakob disease.

E.23 Method E or E.1-E.3 wherein the condition to be treated or controlled is cerebral edema consequent to lupus cerebritis.

E.24 Method E or E.1-E.3 wherein the condition to be treated or controlled is edema consequent to hypoxia, e.g., general systemic hypoxia, e.g., hypoxia caused by an interruption of blood perfusion, for example wherein the edema is cerebral edema consequent to hypoxia caused by cardiac arrest, stroke, or other interruption of

blood perfusion to the brain, or wherein the edema is cardiac edema consequent to cardiac ischemia or other interruption of blood flow to the heart.

E.25 Method E or E.1-E.3 wherein the condition to be treated or controlled is cerebral edema consequent to microgravity and/or radiation exposure, e.g., exposure from space flight or from working with radioactive materials or from working in radioactive areas.

E.26 Method E or E.1-E.3 wherein the condition to be treated or controlled is cerebral edema consequent to invasive central nervous system procedures, e.g., neurosurgery, endovascular clot removal, spinal tap, aneurysm repair, or deep brain stimulation.

E.27 Method E.25 or E.26 wherein the patient is at elevated risk of edema, e.g., due to microgravity and/or radiation exposure, neurosurgery, endovascular clot removal, spinal tap, aneurysm repair, or deep brain stimulation.

E.28 Method E.25 or E.26 wherein the patient already has edema.

E.29 Method E or E.1-E.28 wherein the edema is cytotoxic cerebral edema or is primarily cytotoxic cerebral edema.

E.30 Method E, E.1-E.19, or E.24 wherein the edema is cytotoxic cerebral edema or is primarily cytotoxic cerebral edema.

E.31 Method E, E.1, or E.2 wherein the condition to be treated or controlled is spinal cord edema, e.g., spinal cord edema consequent to spinal cord trauma, e.g., spinal cord compression.

E.32 Method E.31 wherein the condition to be treated or controlled is spinal cord edema consequent to spinal cord compression.

E.33 Method E, E.1 or E.2 wherein the condition to be treated or controlled is optic nerve edema, e.g., optic nerve edema consequent to microgravity and/or radiation exposure, e.g., exposure from space flight or from working with radioactive materials or from working in radioactive areas.

E.34 Method E, E.1, or E.2 wherein the condition to be treated or controlled is retinal edema.

E.35 Method E, E.1, or E.2 wherein the condition to be treated or controlled is pulmonary edema.

E.36 Method E or E.1 wherein the condition to be treated or controlled is epilepsy.

E.37 Method E or E.1 wherein the condition to be treated or controlled is retinal ischemia or other diseases of the eye associated with abnormalities in intraocular pressure and/or tissue hydration.

E.38 Method E or E.1 wherein the condition to be treated or controlled is myocardial ischemia.

E.39 Method E or E.1 wherein the condition to be treated or controlled is myocardial ischemia/reperfusion injury.

E.40 Method E or E.1 wherein the condition to be treated or controlled is myocardial infarction.

E.41 Method E or E.1 wherein the condition to be treated or controlled is myocardial hypoxia.

E.42 Method E or E.1 wherein the condition to be treated or controlled is congestive heart failure.

E.43 Method E or E.1 wherein the condition to be treated or controlled is sepsis.

E.44 Method E or E.1 wherein the condition to be treated or controlled is a migraine.

E.45 Method E or E.1 wherein the condition to be treated or controlled is neuromyelitis optica.

E.46 Method E or E.1 wherein the condition to be treated or controlled is glioblastoma.

E.47 Method E or E.1 wherein the condition to be treated or controlled is fibromyalgia.

E.48 Method E or E.1 wherein the condition to be treated or controlled is multiple sclerosis.

E.49 Method E wherein the aquaporin is AQP2.

E.50 Method E or E.49 wherein the condition to be treated is hyponatremia or excessive fluid retention, e.g., consequent to heart failure (HF), for example congestive heart failure, liver cirrhosis, nephrotic disorder, syndrome of inappropriate antidiuretic hormone secretion (SIADH), or infertility treatment.

E.51 Method E, E.49, or E.50 wherein the condition to be treated or controlled is ovarian hyperstimulation syndrome.

E.52 Method E, E.49, or E.50 further comprising one or more of restriction of dietary sodium, fluid and/or alcohol; and/or administration of one or more diuretics,

vasopressin receptor antagonists, angiotensin converting enzyme (ACE) inhibitors, aldosterone inhibitors, angiotensin receptor blockers (ARBs), beta-adrenergic antagonists (beta-blockers), and/or digoxin.

E.53 Method E or E.1-E.52 wherein the duration of treatment with the pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is less than 21 days, e.g., less than 2 weeks, e.g., one week or less.

E.54 Method E or E.1-E.53 wherein the pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate e is administered orally.

E.55 Method E or E.1-E.53 wherein the pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is administered parenterally.

E.56 Method E.55 wherein the pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is administered by injection, e.g., subcutaneously, intramuscularly, intravenously, or intrathecally, e.g., a bolus injected subcutaneously, intramuscularly, intravenously, or intrathecally.

E.57 Method E.56 wherein the pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is administered intravenously, e.g., IV bolus and/or IV infusion, e.g., IV bolus followed by IV infusion.

E.58 Method E or E.1-E.57 wherein the patient is human.

E.59 Method E or E.1-E.58 wherein the onset of action after administration of the pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is fairly rapid.

**[0079]** In a further embodiment, provided is a method (Method F) of inhibiting an aquaporin *in vivo* comprising administering a pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate, e.g., Composition I, e.g., composition 1.1-1.124, in an amount effective to inhibit the aquaporin.

**[0080]** Further provided is Method F as follows:

F.1 Method F wherein the aquaporin is AQP4.

F.2 Method F wherein the aquaporin is AQP2.

F.3 Method F, F.1, or F.2 wherein the pharmaceutical composition is administered orally.

F.4 Method F, F.1, or F.2 wherein the pharmaceutical composition is administered parenterally.

F.5 Method of F.4 wherein the pharmaceutical composition is administered intravenously, e.g., IV bolus and/or IV infusion, e.g., IV bolus followed by IV infusion.

**[0081]** In a further embodiment, provided is a method (Method G) to inhibit an aquaporin in a patient suffering from a disease or condition mediated by an aquaporin comprising administering an effective amount of a pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate, e.g., Composition I, e.g., composition 1.1-1.124, to inhibit the aquaporin.

**[0082]** Further provided is Method G as follows:

G.1 Method G wherein the aquaporin is AQP4.

G.2 Method G or G.1 wherein the condition to be treated or controlled is edema, e.g. edema of the brain or spinal cord, e.g., cerebral edema, e.g. cerebral edema consequent to head trauma, ischemic stroke, glioma, meningitis, acute mountain sickness, epileptic seizure, infection, metabolic disorder, water intoxication, hepatic failure, hepatic encephalopathy, or diabetic ketoacidosis or, e.g., spinal cord edema, e.g., spinal cord edema consequent to spinal cord trauma, e.g., spinal cord compression.

G.3 Method G, G.1, or G.2 further comprising a treatment selected from one or more of the following: optimal head and neck positioning to facilitate venous outflow, e.g. head elevation 30°; avoidance of dehydration; systemic hypotension; maintenance of normothermia or hypothermia; aggressive measures; osmotherapy, e.g., using mannitol or hypertonic saline; hyperventilation; therapeutic pressor therapy to enhance cerebral perfusion; administration of barbiturates to reduce cerebral metabolism ($CMO_2$); hemicraniectomy;

administration of aspirin; administration of amantadine; intravenous thrombolysis (e.g. using rtPA); mechanical clot removal; angioplasty; and/or stents.

G.4 Method G.2 wherein the patient is at elevated risk of cerebral edema, e.g., due to head trauma, ischemic stroke, glioma, meningitis, acute mountain sickness, epileptic seizure, infection, metabolic disorder, water intoxication, hepatic failure, hepatic encephalopathy, or diabetic ketoacidosis.

G.5 Method G.2 wherein the patient has suffered a stroke, head injury, or spinal injury.

G.6 Method G.5 wherein the patient has suffered a stroke, head injury or spinal injury within 12 hours, e.g. within 6 hours, preferably within 3 hours of commencing treatment.

G.7 Method G.2 wherein the patient is at elevated risk of suffering a stroke, head injury or spinal injury, e.g., in combat or in an athletic competition.

G.8 Method G or G.1-A.7 wherein the patient already has cerebral edema.

G.9 Method G or G.1-A.8 wherein the condition to be treated or controlled is cerebral edema consequent to a stroke or a traumatic brain injury.

G.10 Method G or G.1- A.9 wherein the condition to be treated or controlled is cerebral edema consequent to a middle cerebral artery stroke.

G.11 Method G or G.1-G.9 wherein the condition to be treated or controlled is cerebral edema consequent to closed head trauma.

G.12 Method G or G.1-G.4 wherein the condition to be treated or controlled is cerebral edema consequent to an epileptic seizure.

G.13 Method G or G.1-G.4 wherein the condition to be treated or controlled is cerebral edema consequent to an infection.

G.14 Method G or G.1-G.4 wherein the condition to be treated or controlled is cerebral edema consequent to a metabolic disorder.

G.15 Method G or G.1-G.4 wherein the condition to be treated or controlled is cerebral edema consequent to glioma.

G.16 Method G or G.1-G.4 wherein the condition to be treated or controlled is cerebral edema consequent to meningitis.

G.17 Method G or G.1-G.4 wherein the condition to be treated or controlled is cerebral edema consequent to acute mountain sickness.

G.18 Method G or G.1-G.4 wherein the condition to be treated or controlled is cerebral edema consequent to water intoxication.

G.19 Method G or G.1-G.4 wherein the condition to be treated or controlled is cerebral edema consequent to hepatic failure, hepatic encephalopathy, or diabetic ketoacidosis.

G.20 Method G or G.1-G.3 wherein the condition to be treated or controlled is cerebral edema consequent to an abscess.

G.21 Method G or G.1-G.3 wherein the condition to be treated or controlled is cerebral edema consequent to eclampsia.

G.22 Method G or G.1-G.3 wherein the condition to be treated or controlled is cerebral edema consequent to Creutzfeldt-Jakob disease.

G.23 Method G or G.1-G.3 wherein the condition to be treated or controlled is cerebral edema consequent to lupus cerebritis.

G.24 Method G or G.1-G.3 wherein the condition to be treated or controlled is edema consequent to hypoxia, e.g., general systemic hypoxia, e.g., hypoxia caused by an interruption of blood perfusion, for example wherein the edema is cerebral edema consequent to hypoxia caused by cardiac arrest, stroke, or other interruption of blood perfusion to the brain, or wherein the edema is cardiac edema consequent to cardiac ischemia or other interruption of blood flow to the heart.

G.25 Method G or G.1-G.3 wherein the condition to be treated or controlled is cerebral edema consequent to microgravity and/or radiation exposure, e.g., exposure from space flight or from working with radioactive materials or from working in radioactive areas.

G.26 Method G or G.1-G.3 wherein the condition to be treated or controlled is cerebral edema consequent to an invasive central nervous system procedure, e.g., neurosurgery, endovascular clot removal, spinal tap, aneurysm repair, or deep brain stimulation.

G.27 Method G.25 or G.26 wherein the patient is at elevated risk of edema, e.g., due to microgravity and/or radiation exposure, neurosurgery, endovascular clot removal, spinal tap, aneurysm repair, or deep brain stimulation.

G.28 Method G.25 or G.26 wherein the patient already has edema.

G.29 Method G or G.1-G.28 wherein the edema is cytotoxic cerebral edema or is primarily cytotoxic cerebral edema.

G.30 Method G, G.1-G.19, or G.24 wherein the edema is cytotoxic cerebral edema or is primarily cytotoxic cerebral edema.

G.31 Method G, G.1, or G.2 wherein the condition to be treated or controlled is spinal cord edema, e.g., spinal cord edema consequent to a spinal cord trauma, e.g., spinal cord compression.

G.32 Method G.31 wherein the condition to be treated or controlled is spinal cord edema consequent to spinal cord compression.

G.33 Method G, G.1, or G.2 wherein the condition to be treated or controlled is optic nerve edema, e.g., optic nerve edema consequent to microgravity and/or radiation exposure, e.g., exposure from space flight or from working with radioactive materials or from working in radioactive areas.

G.34 Method G, G.1, or G.2 wherein the condition to be treated or controlled is retinal edema.

G.35 Method G, G.1, or G.2 wherein the condition to be treated or controlled is pulmonary edema.

G.36 Method G or G.1 wherein the condition to be treated or controlled is epilepsy.

G.37 Method G or G.1 wherein the condition to be treated or controlled is retinal ischemia or other diseases of the eye associated with abnormalities in intraocular pressure and/or tissue hydration.

G.38 Method G or G.1 wherein the condition to be treated or controlled is myocardial ischemia.

G.39 Method G or G.1 wherein the condition to be treated or controlled is myocardial ischemia/reperfusion injury.

G.40 Method G or G.1 wherein the condition to be treated or controlled is myocardial infarction.

G.41 Method G or G.1 wherein the condition to be treated or controlled is myocardial hypoxia.

G.42 Method G or G.1 wherein the condition to be treated or controlled is congestive heart failure.

G.43 Method G or G.1 wherein the condition to be treated or controlled is sepsis.

G.44 Method G or G.1 wherein the condition to be treated or controlled is a migraine.

G.45 Method G or G.1 wherein the condition to be treated or controlled is neuromyelitis optica.

G.46 Method G or G.1 wherein the condition to be treated or controlled is glioblastoma.

G.47 Method G or G.1 wherein the condition to be treated or controlled is fibromyalgia.

G.48 Method G or G.1 wherein the condition to be treated or controlled is multiple sclerosis.

G.49 Method G wherein the aquaporin is AQP2.

G.50 Method G or G.49 wherein the condition to be treated or controlled is hyponatremia or excessive fluid retention, e.g., consequent to heart failure (HF), for example congestive heart failure, liver cirrhosis, nephrotic disorder, syndrome of inappropriate antidiuretic hormone secretion (SIADH), or infertility treatment.

G.51 Method G, G.49, or G.50 wherein the condition to be treated or controlled is ovarian hyperstimulation syndrome.

G.52 Method G, G.49, or G.50 further comprising one or more of restriction of dietary sodium, fluid and/or alcohol; and/or administration of one or more diuretics, vasopressin receptor antagonists, angiotensin converting enzyme (ACE) inhibitors, aldosterone inhibitors, angiotensin receptor blockers (ARBs), beta-adrenergic antagonists (beta-blockers), and/or digoxin.

G.53 Method G or G.1-G.52 wherein the pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is administered orally.

G.54 Method G or G.1-G.52 wherein the pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is administered parenterally.

G.55 Method G.54 wherein the pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is administered by injection, e.g., subcutaneously, intramuscularly, intravenously, or intrathecally, e.g., a bolus injected subcutaneously, intramuscularly, intravenously, or intrathecally.

G.56 Method G.55 wherein the pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is administered intravenously, e.g., IV bolus and/or IV infusion, e.g., IV bolus followed by IV infusion.

G.57 Method G or G.1-G.56 wherein the patient is human.

G.58 Method G or G.1-G.57 wherein the onset of action after administration of the pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is fairly rapid.

**[0083]** In yet another embodiment, provided is a method (Method H) of treating or controlling a condition selected from fibromyalgia and multiple sclerosis comprising administering a pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate, e.g., Composition I, e.g., composition 1.1-1.124, to a patient in need thereof.

**[0084]** Further provided is Method H as follows:

H.1 Method H wherein the condition to be treated or controlled is fibromyalgia.

H.2 Method H wherein the condition to be treated or controlled is multiple sclerosis.

H.3 Method H, H.1, or H.2 wherein the pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is administered orally.

H.4 Method H, H.1, or H.2 wherein the pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is administered parenterally.

H.5 Method H.4 wherein the pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is administered by injection, e.g., subcutaneously, intramuscularly, intravenously, or intrathecally, e.g., a bolus injected subcutaneously, intramuscularly, intravenously, or intrathecally.

H.6 Method H.5 wherein the pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is administered intravenously, e.g., IV bolus and/or IV infusion, e.g., IV bolus followed by IV infusion.

H.7 Method H or H.1-H.6 wherein the patient is human.

H.8 Method H or H.1-H.7 wherein the onset of action after administration of the pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is fairly rapid.

H.9 Method H or H.1-H.8 wherein 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate binds to AQP4.

**[0085]** In yet another embodiment, provided is a pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate, e.g., Composition I, e.g., composition 1.1-1.124, for use in treating or controlling a disease or condition mediated by an aquaporin.

**[0086]** In yet another embodiment, provided is a pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate, e.g., Composition I, e.g., composition 1.1-1.124, for use in any of Methods A, e.g., A.1-A.58, any of Methods B, e.g., B.1-B.41, any of Methods C, e.g., C.1-C.8, any of Methods D, e.g., D.1-D.19, any of Methods E, e.g., E.1-E.59, any of Methods F, e.g., F.1-F.5, any of Methods G, e.g., G.1-G.58, and any of Methods H, e.g., H.1-H.9.

**[0087]** A dose or method of administration of the dose of the present disclosure is not particularly limited. Dosages employed in practicing the present disclosure will of course vary depending, e.g. on the particular disease or condition to be treated, the particular compound used, the mode of administration, and the therapy desired. The pharmaceutical compositions may be administered by any suitable route, including orally, parenterally, transdermally, or by inhalation.

In stroke or other severely debilitating diseases or conditions, for example where the patient may be unconscious or unable to swallow, an IV infusion and/or IV bolus may be preferred. In general, satisfactory results, e.g. for the treatment of diseases as hereinbefore set forth are indicated to be obtained on oral administration at dosages of the order from about 0.01 to 15.0 mg/kg. In larger mammals, for example humans, an indicated daily dosage for oral administration will accordingly be in the range of from about 0.75 to 1000 mg per day, conveniently administered once, or in divided doses 2 to 3 times, daily or in sustained release form. Unit dosage forms for oral administration thus for example may comprise from about 0.2 to 75 mg or 150 mg, e.g. from about 0.2 or 2.0 mg to 50, 75, 100, 125, 150 or 200 mg of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate together with a pharmaceutically acceptable diluent or carrier therefor. When the pharmaceutical composition is used via injection (subcutaneously, intramuscularly or intravenously) the dose may be 0.1 or 0.25 mg to 500 mg per day, e.g., from about 0.25 mg to 75 or 150 mg, e.g., from about 0.1 or 0.25 or 2.0 mg to 50, 75, 100, 125, 150, 200, 300, 400, or 500 mg, by bolus or if IV by bolus or infusion.

**[0088]** The pharmaceutical compositions as hereinbefore described for use in the methods of the invention may be used as a sole therapeutic agent, but may also be used in combination or for co-administration with other active agents, for example in conjunction with conventional therapies for cerebral edema, stroke, traumatic brain injury, glioma (e.g., glioblastoma), meningitis, acute mountain sickness, infection, metabolic disorder, hypoxia, water intoxication, hepatic failure, hepatic encephalopathy, diabetic ketoacidosis, abscess, eclampsia, Creutzfeldt-Jakob disease, lupus cerebritis, optic nerve edema, hyponatremia, fluid retention, ovarian hyperstimulation syndrome, epilepsy, retinal ischemia or other diseases of the eye associated with abnormalities in intraocular pressure and/or tissue hydration, myocardial ischemia, myocardial ischemia/reperfusion injury, myocardial infarction, myocardial hypoxia, congestive heart failure, sepsis, neuromyelitis optica, or migraines.

**[0089]** Further provided is crystalline 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate.

**[0090]** 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate includes its polymorphs, hydrates, solvates and complexes.

**[0091]** 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate may be made using the methods as described and exemplified herein and by methods similar

thereto and by methods known in the chemical art. Such methods include, but not limited to, those described below. If not commercially available, starting materials for these processes may be made by procedures which are selected from the chemical art using techniques which are similar or analogous to the synthesis of known compounds.

**[0092]** As used throughout, ranges are used as shorthand for describing each and every value that is within the range. Any value within the range can be selected as the terminus of the range. In addition, all references cited herein are hereby incorporated by referenced in their entireties. In the event of a conflict in a definition in the present disclosure and that of a cited reference, the present disclosure controls.

**[0093]** Terms and abbreviations:

ala = alanine

Boc = *tert*-butyloxycarbonyl

DCC = dicyclohexylcarbodiimide

DMAP = 4-(dimethylamino)pyridine

DMF = dimethylformamide

Hünig's base = N,N-diisopropylethylamine

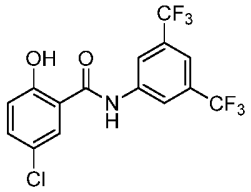
TFA = trifluoroacetic acid

## EXAMPLES

### EXAMPLE 1

### 2-{[3,5-Bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate

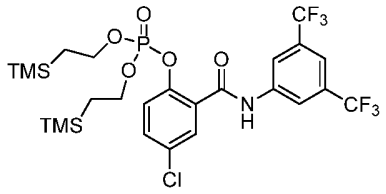
### Step 1: N-(3,5-bis(trifluoromethyl)phenyl)-5-chloro-2-hydroxybenzamide




**[0094]** 5-chloro salicylic acid (8.75 g, 50 mmol, 1 eq) is dissolved in toluene (300 mL) under $N_2$ atmosphere then phosphorus trichloride (2.2 mL, 25 mmol, 0.5 eq) is added dropwise followed by 3,5-bis(trifluoromethyl)aniline (10 g, 43.7 mmol, 0.87 eq). The reaction mixture is stirred under reflux for 12 h then cooled to room temperature. The reaction mixture is quenched with $NaHCO_3$ saturated solution and stirred for 10 min. To this solution is added 1M HCl (100mL)

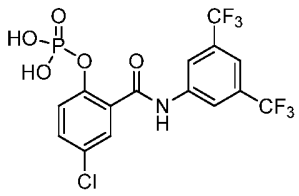
until the pH of the aqueous layer is 5 and the aqueous layer is extracted with ethyl acetate (2x300mL). The combined organics are then dried over sodium sulfate and concentrated *in vacuo* to yield the crude product which is purified by flash chromatography (5-20% EtOAc/hex). The yield of pure product as a white solid is 16 g (yield 85%) which is >95% pure by $^1$H NMR. $^1$H NMR (400 MHz, $CDCl_3$): δ 11.35 (bs, 1H), 10.85 (bs, 1H), 8.40 (s, 2H), 7.80-7.79 (m, 2H), 7.50 (dd, 1H), 7.00 (d, 1H).

**Step 2: 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl bis(2-(trimethylsilyl)ethyl) phosphate**




**[0095]** N-(3,5-bis(trifluoromethyl)phenyl)-5-chloro-2-hydroxybenzamide (4.0 g, 0.01 mol, 1 eq) is dissolved in $CH_3CN$ (104 mL) then DMAP (0.08 g, 0.001 mol, 0.06 eq), Hunig's base (7.36 mL, 0.021 mol, 2 eq) and $CCl_4$ (8.02 g, 0.052 mol, 5 eq) are added in this order. The solution is cooled to 0°C and bis[2-(trimethylsilyl)ethyl] phosphonate $(HP(O)(OCH_2CH_2Si(CH_3)_3)_2$ (4.66 g, 0.016 mol, 1.5 eq) in $CH_3CN$ (5 mL) is added dropwise. The reaction mixture is stirred at room temperature for 20 h then water is added and extracted twice with EtOAc. The combined organic layers are washed with a saturated solution of NaCl, dried over $Na_2SO_4$, filtered and the solvent is concentrated *in vacuo* to give the crude material which is used as such for next step. $^1$H NMR (200 MHz, $CDCl_3$): δ 10.20 (bs, 1H), 8.32 (s, 2H), 7.90 (s, 1H), 7.62 (s, 1H), 7.45-7.40 (m, 1H), 7.30-7.28 (m, 1H), 4.40-4.30 (m, 4H), 1.20-1.00 (m, 4H), 0.0 (s, 18H).

**Step 3: 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl dihydrogen phosphate**




**[0096]** 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl bis(2-(trimethylsilyl)ethyl) phosphate (6.64 g, 0.01 mol, 1 eq) is dissolved in a mixture TFA:Water (5:1, 50 mL). The reaction mixture is stirred at room temperature for 2 h then solvent is

concentrated *in vacuo*. The resulting white solid is dissolved in $Et_2O$ (20 mL) then concentrated *in vacuo*. This operation is repeated twice or until the compound becomes much less soluble in $Et_2O$.The resulting material is suspended in a mixture $Et_2O$:Hex (6:1, 50 mL) and filtered to give the desire material as light red solid. Finally, the solid is dissolved in water (100 mL), filtered and the resulting aqueous solution is freeze dried to give the desired product as a white solid (yield 76% over two steps, 97% pure by HPLC). $^1H$ NMR (400 MHz, $CD_3OD$): δ 8.38 (s, 2H), 7.78 (s, 1H), 7.70 (s, 1H), 7.55-7.50 (m, 1H), 7.45-7.43 (m, 1H).

**EXAMPLE 2**

**[0097]** A 95% pure lot of 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl dihydrogen phosphate is purified as follows. 15 g is dissolved in 1.2 L of water with 120 mM of sodium hydroxide and extracted with 500 ml ethyl acetate to remove phenol and non acid impurities. The aqueous layer is acidified with concentrated HCl to pH 1.2 and extracted with ethyl acetate 1 L followed by 600 ml. The ethyl acetate layer is dried $MgSO_4$ and sodium sulphate, filtered, and evaporated to give about 13 g of 98% pure 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl dihydrogen phosphate. NMR showed 1 mole of ethyl acetate trapped in solid. Ethyl acetate is removed by adding 100 ml of methanol and evaporating. 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl dihydrogen phosphate is stable at RT for a week or more. Sample kept at RT. It is soluble at 5 mg/mL in 1% $Na_2HPO_4$ giving pH of about 7. Dissolved in 2% $Na_2HPO_4$ at 5 mg/mL gives pH of 7.4

**EXAMPLE 3**

**[0098]** Mouse Water Toxicity Model - Survival Curves: The *in vivo* efficacies of the compounds are tested using the mouse water toxicity model, where a mouse is injected with water at 20% of its body weight. Manley, G. T. et al. *Aquaporin-4 deletion in mice reduces brain edema after acute water intoxication and ischemic stroke.* Nat Med 6, 159-163 (2000); Gullans, S. R. & Verbalis, J. G. *Control of brain volume during hyperosmolar and hypoosmolar conditions.* Annual Review of Medicine 44, 289-301 (1993). The resulting euvolemic hyponatremia rapidly leads to CE, making this a practical model to test an inhibitor of the CNS aquaporin, AQP4b.

**[0099]** The ability of mice to survive $H_2O$ toxicity is determined in three experiments using 10-12 mice each (16-19 weak old male/female). Deionized water is prepared for injection with

either 0.39 mg/kg phenylbenzamide (placebo) or 0.76 mg/kg with test compound. Figure 1 shows the combined results of these experiments (n=33 placebo, n=34 N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide). Percent survival of the N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide cohorts improves 3.2 fold and the time to 50% survival for animals treated with N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide is improved by roughly 52 min.

**[00100]** Mouse Water Toxicity Model - Brain Volume by Magnetic Resonance Imaging (MRI): MRI is used to measure changes in brain volume in response to water shock, using the water toxicity model. As described for the survival and brain water content studies above, mice are injected, IP, with a water bolus alone or water bolus and test compound at 0.76 mg/kg, and changes in brain volume as detected by MRI are monitored. Mouse brain volumes are assessed using MRI scans collected with a 9.4T Bruker Biospec MRI scanner at the Case Center for Imaging Research at Case Western Reserve University. This imaging method is found to provide sufficient contrast and resolution to sensitively detect changes in total brain volume in the mouse water toxicity model for cerebral edema. High resolution T2-weighted sagittal scans (resolution = 0.1mm x 0.1mm x 0.7mm) of the mouse head are obtained prior to water injection, 5.67 min post water injection, and then every 5.2 minutes until the animal expires from the water loading. Each scan contains twenty-five 0.7 mm contiguous imaging slices of which 14-15 slices contain a portion of the brain. The cross sectional area of the brain in each imaging slice is measured by manual region-of-interest selection using ImageJ. Brain volumes are then calculated for each scan by summing the individual cross sectional brain areas and multiplying by the slice thickness (0.7 mm).

**[00101]** Treatment with N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide (Compound 1) at 0.76 mg/kg reduces the rate of CE development from 0.081 to 0.032 $min^{-1}$ (or 2.5-fold) fit to a single exponential model (Figure 2). Also, the extent of CE during the period of observation is reduced (Figure 2). Moreover, plasma levels in the same assay are found to range between 0.03-0.06 μg as determined by LC-MS/MS (performed at Lerner Center, Cleveland Clinic, Cleveland, OH) and are sufficient to show efficacy in this model for CE.

Table 1. Efficacy of compounds on CE formation in the mouse water toxicity model

| Compound | AQP Inhibition Cell-Based Assay (%) | Cerebral Edema Rate by MRI ($min^{-1}$) |
|---|---|---|
| No Drug | 0 | 0.081 |

| | | |
|---|---|---|
| N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide | 47.9 | 0.032 |

For no drug and N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide, n = 14 mice each.

**EXAMPLE 4** – High throughput screening assay

**[00102]** Under hypotonic shock, both untransfected cells and cells expressing an unrelated transmembrane protein (CD81, at levels equivalent to AQP4b) swell slowly but remain intact. These observations are used to develop our high-throughput screening assay (HTS).

**[00103]** After hypotonic shock in a 384 well plate format, we return osmolality to normal (300 mOsm) by adding 2x concentrated phosphate buffered saline supplemented to 2 μM with a nonfluorescent acetoxymethyl derivative of calcein (calcein-AM) to each well. Intact cells take up calcein-AM and convert it to the fluorescent dye calcein – giving a quantitative measure of the remaining intact cells. Burst cells do not convert the precursor to the dye. Water uptake by AQP4-expressing cells is relatively rapid, with most test cells bursting within 4 min of hypotonic shock, whereas most cells expressing CD81 remain viable after 8 min. Intracellular conversion of calcein-AM provides a strong and easily detectable signal at 535 nM in our assay (Figure 3).

**[00104]** *Calcein fluorescence end-point assay:* Cells are seeded 24 hr before assay to reach 100% confluence. Culture medium is replaced with $H_2O$ for 5:30 min (osmotic shock). Osmolality is then normalized with the addition of 2x PBS plus 2 μM calcein-AM. Cells are then incubated at 37°C for an additional 30 min and fluorescence measured on a plate-reader. Rows 1-22 are seeded with CHO-AQP4 cells, and rows 23-24, with CHO-CD81 cells (384 well plate). Note, all plate edges are discarded. Relative Fluorescence Intensity is calculated as the fluorescence intensity (FI) of each well divided by the mean FI of AQP4 cells treated with DMSO (control). Criteria for a successful assay: coefficients of variation (CVs) < 15%, and Z-factors > 0.5. Statistical analysis shows that 5.5 min of osmotic shock provides the optimal signal-to-noise ratio.

Table 2. Statistics for endpoint 'calcein' assay in Figure 3; 5:30 min time point shown:

| | Mean | StDev | CV | Z′ | S/B |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| AQP4 | 581618 | 66311 | 11% | 0.629 | 5.0 |
| CD81 | 2910106 | 221240 | 8% | | |

**[00105]** As will be observed, the signal for the CD81 cells is ca. 5x higher than the signal for the APQ4 cells, because by 5.5 mins, most of the AQP4 cells have burst, while most of the CD81 cells remain intact. Inhibition of AQP4 would therefore be expected to provide a higher signal, more like the CD81 cells.

**[00106]** This assay is applied in a pilot screen of the MicroSource GenPlus 960 and the Maybridge Diversity™ 20k libraries (approximately 21,000 compounds tested, each compound at 10-20 μM).

**[00107]** From this assay, a specific chemical series is identified, phenylbenzamides, which represents 3 out of the top 234 hits.

**[00108]** Hits from the HTS are validated using the same assay using a different plating arrangement. In Figure 4, we show this validation assay used to examine 5-chloro-*N*-(3,5-dichlorophenyl)-2-hydroxybenzamide. Cells are seeded in a 96 well multiplate format with the plates edges omitted (lanes 1 and 24) and an entire column (n=16) is used to test the ability of a compound to block AQP4-mediated cell bursting upon $H_2O$ shock. CHO cells expressing CD81 are seeded in lanes 2-3 as a control, and CHO cells expressing AQP4, in lanes 4-23. Cells are treated with 0.1% DMSO in 10% FBS, DMEM (even numbered columns) or 10 μM N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide (odd number columns) in 0.1% DMSO, 10% FBS, DMEM for 30 minutes. The cells are shocked with $H_2O$ for 5:30 minutes, then osmolality returned to 300 mOsm in the presence of 1 μM calcein-AM, as described above. The cells are incubated at 37°C for 30 minutes and the relative fluorescence measured (ex 495/em 535 nM) on a fluorescence multiplate reader. The data in Figure 7 represents the average relative fluoresence units (RFU ± SEM, n=16).

**EXAMPLE 5** – Water Toxicity Model for CE: Intracranial Pressure (ICP)

**[00109]** ICP is monitored using a Samba 420 Sensor, pressure transducer, with a Samba 202 control unit (Harvard Apparatus, Holliston, MA). This ICP monitoring system consists of a 0.42 mm silicon sensor element mounted on an optical fiber. A 20-gauge syringe needle is implanted through the cisterna magna to a depth of ~ 1 cm. The needle then acts as a guide for

insertion of the Samba Sensor and the site of implantation and the open end of the needle are sealed with 100% silicone sealant. A baseline ICP reading is established followed by a water bolus IP injection (20% weight of animal) with or without N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide. ICP is monitored until the animal expires from the water load.

**[00110]** Adjusting for the slight rise in ICP observed in the animals when they are monitored without the water bolus injection (Figure 5, No Water Toxicity), N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide (Compound 1) at 0.76 mg/kg reduces the relative rate of ICP rise by 36%, from $3.6 \times 10^{-3}$ $min^{-1}$ to $2.3 \times 10^{-3}$ $min^{-1}$ (n = 6 mice/treatment, mean±SEM).

**EXAMPLE 5** – Conversion from 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl phosphate bis ethanolamine salt to N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide

**[00111]** Plasma or serum levels of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate are measured by LC-MS/MS at the Mass Spectrometry II Core facility at the Lerner Research Institute of the Cleveland Clinic Foundation. Measurements are taken at 15 minutes and 24 hours after a 10 mg/kg i.p. loading dose and 1 mg/ml at 8 μl/h maintenance dose (delivered by an Alzet i.p. osmotic pump, Durect Corp., Cupertino, CA) of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl phosphate bis ethanolamine salt (n = 5 mice/time point, mean±SEM) (Figure 6). After initial processing to remove proteins (75% acetonitrile extraction), 5-chloro-*N*-(3,5-dichlorophenyl)-2-hydroxybenzamide is introduced to improve quantitation using multiple reaction monitoring (MRM). Samples are analyzed by tandem LC-MS/MS using C18 reversed-phase chromatography and mass analysis with a triple-quadrapole mass spectrometer. The LC method is sufficient to separate N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide (Compound 1) from 5-chloro-*N*-(3,5-dichlorophenyl)-2-hydroxybenzamide and subsequent MRM gave reliable quantitation with a linear response from 0.004-0.4 ng of N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide (Compound 1) for its most abundant daughter ion. The dashed line in Figure 6 is the relative effective plasma concentration of N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide (Compound 1) observed in the mouse water toxicity model. Inclusion of an Alzet osmotic pump (Durect Corp., Cupertino, CA) containing 2-{[3,5-

bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl phosphate bis ethanolamine salt in the peritoneum is sufficient, in conjunction with an initial loading dose, to sustain N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide (Compound 1) above the expected efficacious plasma concentration of 20 ng/ml for 24 hours (Figure 6).

**[00112]** The solubility of N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide in water is 3.8 μg/ml. The solubility of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl phosphate disodium salt in water is 1 mg/ml.

Initial experiments show rapid bioconversion of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl phosphate bis ethanolamine salt to N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide when added to mouse plasma *in vitro*. Less than 5 minutes at 20°C is sufficient to render 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl phosphate bis ethanolamine salt undetectable. In addition, 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl phosphate bis ethanolamine salt is undetectable in plasma samples taken from mice injected IP with 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl phosphate bis ethanolamine salt. Instead, N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide is detected at a concentration consistent with good bioavailability and near-complete conversion of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl phosphate bis ethanolamine salt. With 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl phosphate bis ethanolamine salt doses of 10 mg/kg and IP injection volumes in saline (0.5 ml for a 30 g mouse), that give serum concentrations of N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide in excess of 400 ng/ml (Figure 6) can be used. Key PK parameters in mice are: rate of absorption 0.12 $min^{-1}$; rate of elimination 0.017 $min^{-1}$.

**EXAMPLE 6** – Animal Stroke Model

**[00113]** Most ischemic strokes (~ 80%) occur in the region of the middle cerebral artery (MCA). To mimic this injury in mice, an intraluminal monofilament model of middle cerebral artery occlusion (MCAo) is used. Occlusion is achieved by inserting a surgical filament into the external carotid artery (ECA) and threading it forward into the internal carotid artery (ICA) until the tip blocks the origin of the MCA. The resulting cessation of blood flow gives rise to subsequent brain infarction in the MCA territory (Longa, E.Z. et al., *Reversible Middle Cerebral*

*Artery Occlusion Without Craniectomy in Rats,* Stroke, 20, 84-91 (1989)). This technique is used to study a temporary occlusion in which the MCA is blocked for one hour. The filament is then removed allowing reperfusion to occur for 24 hours before the animal's brain is imaged using T2-weighted scans in a 9.4T Bruker MRI scanner at the Case Center for Imaging Research (Figure 7). Figure 7 shows a single slice from a T2-weighted MR image depicting the center of the brain showing cerebral cortex, hippocampus, thalamus, amygdala and hypothalamus for a "Normal" mouse (left panels) and a mouse which receives MCAo for one hour followed by 24 hours of reperfusion (right panels). Dashed lines mark the midline of the brain and show a large shift in the MCAo brain due to cerebral edema. Solid line highlights the region of infarct in the MCAo brain.

**[00114]** *Survival* – Mice are treated with 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl phosphate disodium salt (Compound 5) using a 2 mg/kg i.p. loading dose and 1mg/ml at 8 μl/h maintenance dose (delivered by an i.p. osmotic pump) of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl phosphate disodium salt, or given saline (controls; n = 17) using an identical approach. In this model, we observed a 29.4% improvement in overall survival at 24h when animals are treated with 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl phosphate disodium salt ($X^2(1) = 4.26$; $P < 0.05$).

**[00115]** *Cerebral Edema* – Mice are given saline or treated with 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl phosphate disodium salt (Compound 5) by multi-dosing at 5 mg/kg i.p. every three hours (n = 8 per treatment). This dosing regimen is sufficient to maintain a plasma concentration of N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide > 20 ng/ml for the duration of the study. Ipsilateral and contralateral hemispheric volume is measured from the T2-weighted MR images of mice 24 hours post-*icus*. Relative change in hemispheric volume is calculated as a percent of the difference between ipsilateral brain volume ($V_i$) and contralateral brain volume ($V_c$) relative to the contralateral brain volume (Percent Change in Hemispheric Brain Volume = $((V_i - V_c)/V_c) \times 100\%$.

**[00116]** Control animals show swelling in the ipsilateral hemisphere with a relative change in ipsilateral brain volume of 13.4% ± 1.9%, while animals given 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl phosphate disodium salt (Compound 5)

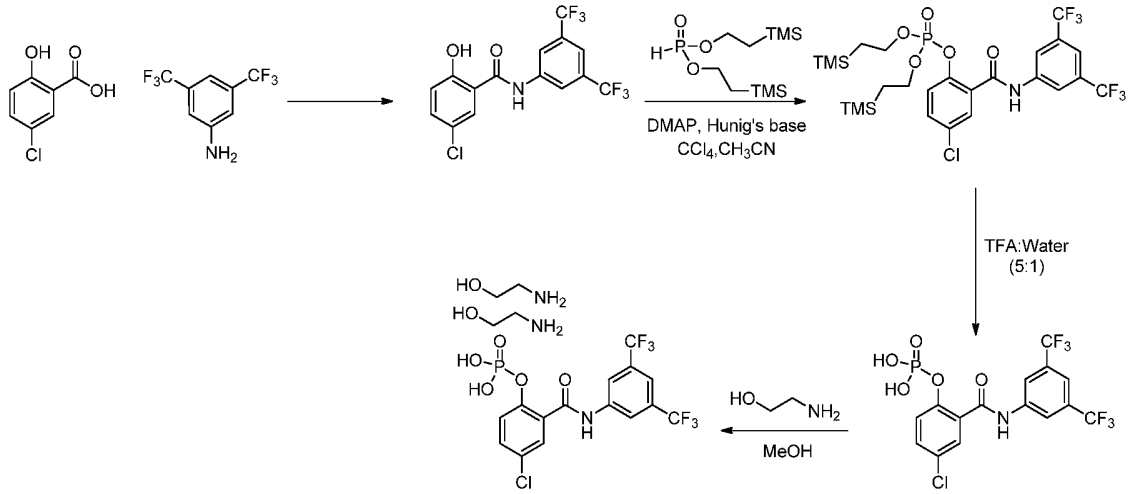
show a 4.2 ± 1.7% change (P = 0.003, ± SEM, see Figure 8). This represents a 3.2-fold reduction in brain swelling after MCAo.

**[00117]** *Neurological Outcome* – In the same experiment as above, animals are scored for neurological outcome on a simple 5 point scale described in Manley, G.T. et al., *Aquaporin-4 Deletion in Mice Reduces Brain Edema After Acute Water Intoxication and Ischemic Stroke*, Nature Medicine, 6, 159-163 (2000). An improvement in neurological outcome is observed for animals given 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl phosphate disodium salt (Compoudn 5). Control animals have an average neurological score of 2.77 ± 0.66, while animals given 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl phosphate disodium salt (Compound 5) have an average score of 0.88 ± 0.31 (Figure 9, inset, P = 0.025, n = 9 per treatment). Animals given 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl phosphate disodium salt (Compound 5) did not progress into a state of severe paralysis or death.

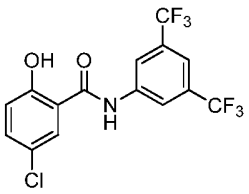
**[00118]** The data from the MCAo stroke model together with the water toxicity (brain edema) model link the pharmacology of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl phosphate disodium salt (Compound 5) / N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide (Compound 1) with improved outcomes in stroke.

## EXAMPLE 7

**2-{[3,5-Bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate**

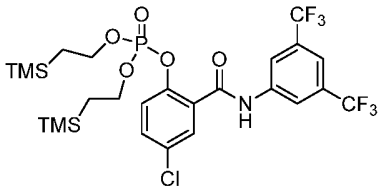



**Step 1: N-(3,5-bis(trifluoromethyl)phenyl)-5-chloro-2-hydroxybenzamide**



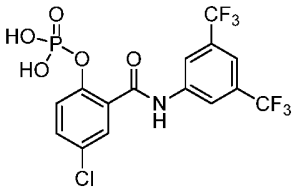
**[00119]** 5-chloro salicylic acid (8.75 g, 50 mmol, 1 eq) is dissolved in toluene (300 mL) under $N_2$ atmosphere then phosphorus trichloride (2.2 mL, 25 mmol, 0.5 eq) is added dropwise followed by aniline (10 g, 43.7 mmol, 0.87 eq). The reaction mixture is stirred under reflux for 12 h then cooled to room temperature. The reaction mixture is quenched with $NaHCO_3$ saturated solution and stirred for 10 min. To this solution is added 1M HCl (100mL) until the pH of the aqueous layer is 5 and the aqueous layer is extracted with ethyl acetate (2x300mL). The combined organics are then dried over sodium sulfate and concentrated *in vacuo* to yield the crude product which is purified by flash chromatography (5-20% EtOAc/hex). The yield of pure product as a white solid is 16 g (yield 85%) which is >95% pure by $^1H$ NMR. $^1H$ NMR (400 MHz, $CDCl_3$): δ 11.35 (bs, 1H), 10.85 (bs, 1H), 8.40 (s, 2H), 7.80-7.79 (m, 2H), 7.50 (dd, 1H), 7.00 (d, 1H).

**Step 2: 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl bis(2-(trimethylsilyl)ethyl) phosphate**



**[00120]** N-(3,5-bis(trifluoromethyl)phenyl)-5-chloro-2-hydroxybenzamide (4.0 g, 0.01 mol, 1 eq) is dissolved in $CH_3CN$ (104 mL) then DMAP (0.08 g, 0.001 mol, 0.06 eq), Hunig's base (7.36 mL, 0.021 mol, 2 eq) and $CCl_4$ (8.02 g, 0.052 mol, 5 eq) are added in this order. The solution is cooled to 0°C and $HP(O)(OCH_2CH_2Si(CH_3)_3)_2$ (4.66 g, 0.016 mol, 1.5 eq) in $CH_3CN$ (5 mL) is added dropwise. The reaction mixture is stirred at room temperature for 20 h then water is added and extracted twice with EtOAc. The combined organic layers are washed with a saturated solution of NaCl, dried over $Na_2SO_4$, filtered and the solvent is concentrated *in vacuo* to give the crude material which is used as such for next step. $^1H$ NMR (200 MHz, $CDCl_3$): δ 10.20 (bs, 1H), 8.32 (s, 2H), 7.90 (s, 1H), 7.62 (s, 1H), 7.45-7.40 (m, 1H), 7.30-7.28 (m, 1H), 4.40-4.30 (m, 4H), 1.20-1.00 (m, 4H), 0.0 (s, 18H).

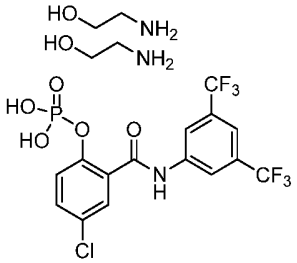
**Step 3: 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl dihydrogen phosphate**



**[00121]** 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl bis(2-(trimethylsilyl)ethyl) phosphate (6.64 g, 0.01 mol, 1 eq) is dissolved in a mixture TFA:Water (5:1, 50 mL). The reaction mixture is stirred at room temperature for 2 h then solvent is concentrated *in vacuo*. The resulting white solid is dissolved in $Et_2O$ (20 mL) then concentrated *in vacuo*. This operation is repeated twice or until the compound becomes much less soluble in $Et_2O$.The resulting material is suspended in a mixture $Et_2O$:Hex (6:1, 50 mL) and filtered to give the desire material as light red solid. Finally, the solid is dissolved in water (100 mL), filtered and the resulting aqueous solution is freeze dried to give the desired product as a white solid (yield 76% over two steps, 97% pure by HPLC). $^1H$ NMR (400 MHz, $CD_3OD$): δ 8.38 (s, 2H), 7.78 (s, 1H), 7.70 (s, 1H), 7.55-7.50 (m, 1H), 7.45-7.43 (m, 1H).

**EXAMPLE 8**

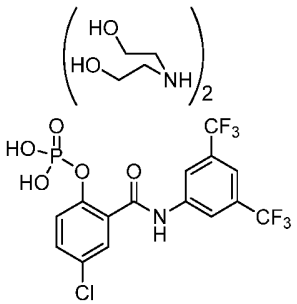
**2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl phosphate bis ethanolamine salt**



**[00122]** 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl dihydrogen phosphate (2.14 g, 0.005 mol, 1 eq) is dissolved in MeOH (46 mL) then ethanolamine (0.56 mL, 0.009 mol, 2 eq) is added. The reaction mixture is stirred at room temperature for 2 h then solvent is concentrated *in vacuo* to give the desired product as a white solid (yield 84%, 97% pure by HPLC). $^1H$ NMR (300 MHz, $D_2O$): δ 8.15 (s, 2H), 7.85 (d, 2H), 7.37-7.34 (m, 2H), 3.62 (t, 4H), 2.95 (t, 4H).

**EXAMPLE 9**

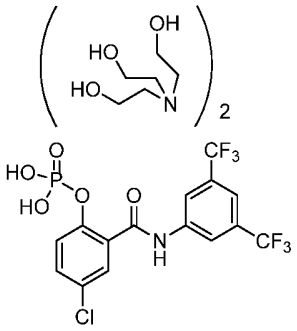
**2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl phosphate bis diethanolamine salt**



**[00123]** 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl dihydrogen phosphate (300 mg, 0.647 mmol, 1 eq) is dissolved in MeOH (3.2 mL) then diethanolamine (0.124 mL, 1.294 mmol, 2 eq) is added. The reaction mixture is stirred at room temperature for 2 h then solvent is concentrated *in vacuo* to give the desire product as a yellow foam (yield 100%, 95% pure by HPLC). $^1$H NMR (500 MHz, DMSO-d$_6$): δ 8.52 (s, 2H), 7.76 (s, 1H), 7.62 (s, 1H), 7.48 (d, 1H), 7.37 (d, 1H), 3.55 (s, 8H), 2.80 (s, 8H).

**EXAMPLE 10**

**2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl phosphate bis triethanolamine salt**

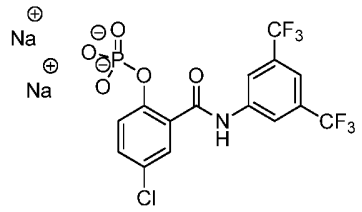


**[00124]** 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl dihydrogen phosphate (300 mg, 0.647 mmol, 1 eq) is dissolved in MeOH (3.2 mL) then triethanolamine (0.172 mL, 1.294 mmol, 2 eq) is added. The reaction mixture is stirred at room temperature for 2 h then solvent is concentrated *in vacuo* to give the desired product as a yellow oil (yield 100%,

98% pure by HPLC). $^1$H NMR (500 MHz, DMSO-d$_6$): δ 8.50 (s, 2H), 7.76 (s, 1H), 7.62 (s, 1H), 7.52 (d, 1H), 7.29 (d, 1H), 3.55 (s, 12H), 2.82 (s, 12H).

**EXAMPLE 11**

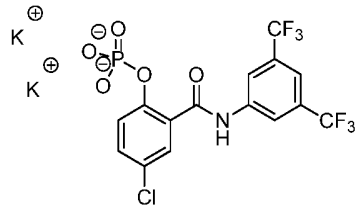
**2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl phosphate bis sodium salt (Compound 5)**



**[00125]** 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl dihydrogen phosphate (300 mg, 0.647 mmol, 1 eq) is suspended in water (6.4 mL) then NaOH (1M) (1.29 mL, 1.294 mmol, 2 eq) is added. The reaction mixture is stirred at room temperature for 2 h then the solution is filtered and freeze dried to give the desired product as a white solid (yield 100%, 93% pure by HPLC).

**EXAMPLE 12**

**2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl phosphate bis potassium salt**



**[00126]** 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl dihydrogen phosphate (300 mg, 0.647 mmol, 1 eq) is suspended in water (6.4 mL) then KOH (1M) (1.29 mL, 1.294 mmol, 2 eq) is added. The reaction mixture is stirred at room temperature for 2 h then the solution is filtered and freeze dried to give the desired product as a white solid (yield 100%, 82% pure by HPLC).

**EXAMPLE 13**

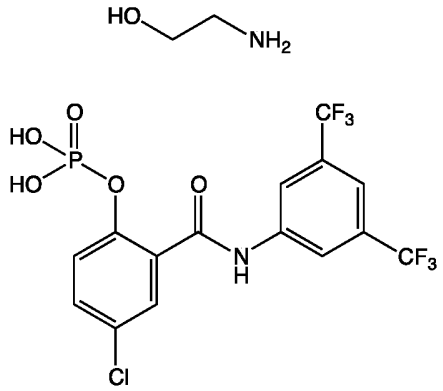
**2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl hydrogen phosphate mono sodium salt, 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl phosphate bis**

**sodium salt, and 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl phosphate bis ethanolamine salt**

**[00127]** 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl hydrogen phosphate mono sodium salt, 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl phosphate bis sodium salt, and 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl phosphate bis ethanolamine salt are made as follows: 2mM of 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl dihydrogen phosphate is dissolved in ethanol 50 ml and appropriate equivalents of each base are added. Evaporation gives salts which are dissolved in water and freeze dried.

**EXAMPLE 14**

**2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl hydrogen phosphate mono ethanolamine salt**




**[00128]** 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl hydrogen phosphate mono ethanolamine salt is made as follows: 1 g of 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl dihydrogen phosphate is dissolved in isopropanol and 1 eq ethanol amine is added. Evaporation gave 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl hydrogen phosphate mono ethanolamine salt.

**EXAMPLE 15**

**Stability and Solubility**

**[00129]** To understand the stability and solubility of the novel prodrug salts a 95% pure lot of 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl dihydrogen phosphate is

purified as follows. 15 g is dissolved in 1.2 L of water with 120 mM of sodium hydroxide and extracted with 500 ml ethyl acetate to remove phenol and non acid impurities. The aqueous layer is acidified with concentrated HCl to pH 1.2 and extracted with ethyl acetate 1 L followed by 600 ml. The ethyl acetate layer is dried $MgSO_4$ and sodium sulphate, filtered, and evaporated to give about 13 g of 98% pure 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl dihydrogen phosphate. NMR showed 1 mole of ethyl acetate trapped in solid. Ethyl acetate is removed by adding 100 ml of methanol and evaporating. 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl dihydrogen phosphate is stable at RT for a week or more. Sample kept at RT. It is soluble at 5 mg/mL in 1% $Na_2HPO_4$ giving pH of about 7. Dissolved in 2% $Na_2HPO_4$ at 5 mg/mL gives pH of 7.4

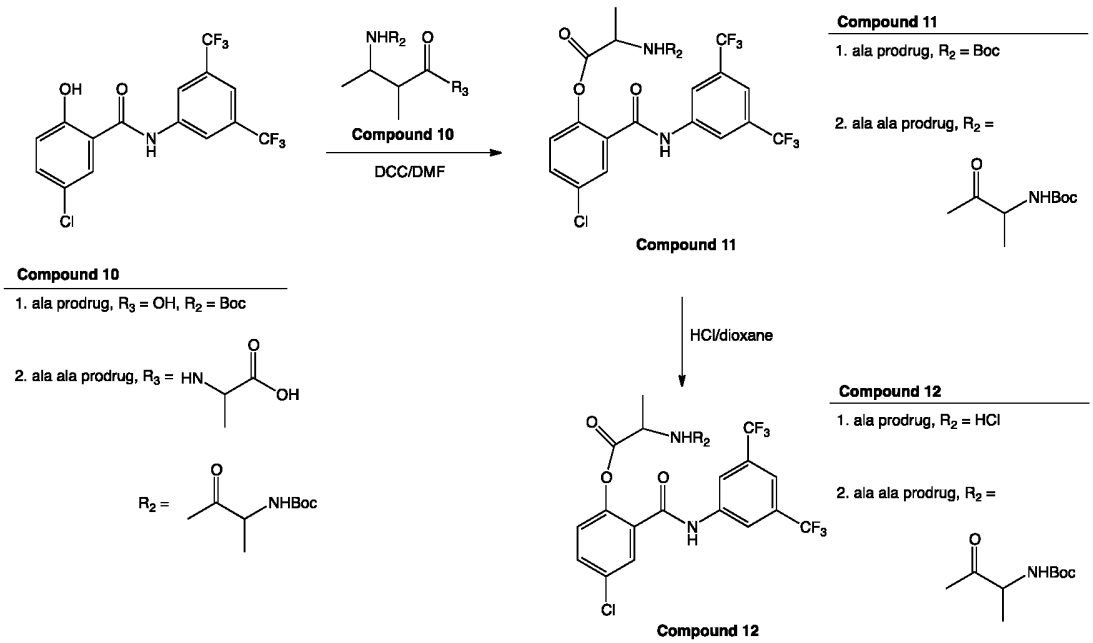
**[00130]** 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl hydrogen phosphate mono sodium salt ("mono sodium salt"), 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl phosphate bis sodium salt ("bis sodium salt"), and 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl phosphate bis ethanolamine salt ("bis ethanolamine salt") are made and freeze dried as in Example 7. In all cases stability studies show hydrolysis in the solid state at about 1% per day. Solubilities are about 5 mg/mL for mono sodium salt and 10 mg/mL for both bis sodium and bis ethanolamine salt in water.

**[00131]** Final pH of solutions are about 7.5 for the bis ethanolamine salt, pH 8.5 for mono sodium salt, and pH 9.5 for bis sodium salt in water. In all cases solutions of these salts show less than 1% phenol over 12 hrs. Longer term their stability is the same as the solid samples (about 1% per day at RT). Hydrolysis rate is expected to be faster at higher pH.

**[00132]** 2-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)-4-chlorophenyl dihydrogen phosphate mono ethanolamine salt ("mono ethanolamine salt") is made as in Example 8. Surprisingly, the mono ethanolamine salt only shows about 1% hydrolysis after 5 days at RT. Its solubility in water is about 5 mg/ml. Solubility is expected to be higher at higher pH.

## EXAMPLE 16

**Synthesis of ala and ala ala prodrugs of N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide**




**[00133]** To 750 mg of N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide (2 mM) in 10ml of DMF was added 360 mg (2 mM) of boc ala followed by 400 mg DCC (2 mM). Reaction is stirred for 3 hrs. and then filtered. To DMF is added 200 ml water and extracted with ethyl acetate. Extract is dried and evaporated. Purified on combi flash hexane to 50% ethyl acetate. Yield 800 mg of Compound 11 wherein $R_2$ = Boc.

**[00134]** To 800 mg Compound 11 wherein $R_2$ = Boc in 6ml THF is added 3 ml of 4N HCl in dioxane and stirred overnight. Product precipitates. 30 ml ether is added and product is filtered off, washed with ether, and dried to give 500 mg of Compound 12 as an HCl salt as a white powder.

**[00135]** Compound 12 wherein $R_2$ is $CH_3C(O)CH(CH3)NHBoc$ is synthesized using the same method but when tried to filter off, solid it turned into an oil. Ether is added and decanted several times. Finally compound solidifies. The solid is sticky and hygroscopic. Yield is about 100mg.

**[00136]** *Solubility*

**[00137]** Both prodrugs are insoluble in water and pH 7.4 water even after stirring for 4-5 hrs., as determined by HPLC analysis of filtrate.

**EXAMPLE 17** – 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate (Formula I) and tris(hydroxymethyl)aminomethane

**[00138]** 2.5 to 5 equivalents of tris(hydroxymethyl)aminomethane is added to 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate (Formula I). Water is added and the mixture is stirred or sonicated. Yields 10 mg/ml to 20 mg/ml solutions stable for at least 24 hrs.

**[00139]** HPLC conditions for assaying the stability of compositions formed from 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate and a base, e.g., tris(hydroxymethyl)aminomethane are as follows:

Hplc condition c18 SB Agilent 4.6 x 125 mm column 3 or 5u

At 1.5 ml per min 10% to 100 % acetonitrile with 2g ammonium acetate per 4 l of water

Using waters 2695 hplc running millennium 32 software

No baseline subtraction

**[00140]** Solid state compositions of the invention falling under Composition I show about 1% of N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide over a four month period at room temperature as measured under the HPLC conditions above.

**[00141]** Reconsistuted compositions of the invention falling under Composition I show 1-2% degradation over a 24 hour period.

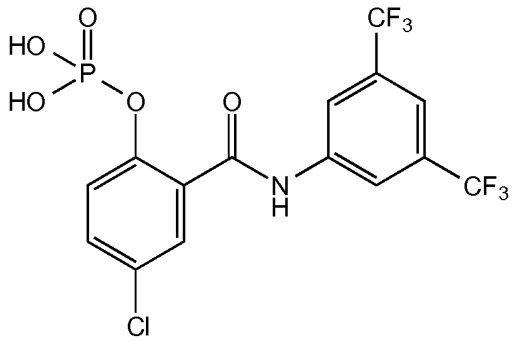
**EXAMPLE 18** – Conversion from 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl phosphate Tris-Base solution to N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide

**[00142]** The 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate is dissolved at 10 mg/mL in 0.07% aqueous Tris-Base. This solution is then diluted to 5mg/ml with water and used to fill an Alzet osmotic pump (DURECT, Corp., model 2001D, delivery at 8 ul/hr for 24 hrs). Surgery is performed on an anesthetized mouse under sterile conditions to implant the pump in the peritoneal cavity. Once the abdominal incision is closed with sutures, muscle layer followed by skin, an IP bolus of 10 mg/kg is given. For this bolus the 10 mg/mL 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate solution is diluted to 1 mg/ml with water and the appropriate volume administered. At 15 min, 6 hr, 18 hr and 24 hr post injection blood is drawn by tail laceration, serum prepared and stored at -20C for later processing. In preparation for LC-MS/MS, an aliquot of the serum sample is diluted 4-fold with acetonitrile to precipitate proteins and ensure soluble release of the parent compound

N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide. The protein is removed by centrifugation and the supernatant diluted to 37.5% acetonitrile using water. 5-chloro-*N*-(3,5-dichlorophenyl)-2-hydroxybenzamide is added as an internal standard and the sample run on LC-MS/MS. In this experiment n=3. See Figure 10. The dashed line in Figure 10 is the relative effective plasma concentration of N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide (Compound 1) observed in the mouse water toxicity model.

## CLAIMS

1. A pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate (Formula I)




Formula I

and a pharmaceutically acceptable excipient.

2. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition comprises 10 to 600 mg of Formula I.

3. The pharmaceutical composition of claim 1 or 2, wherein the pharmaceutically acceptable excipient comprises one or more bases.

4. The pharmaceutical composition of claim 3, wherein upon dissolution of the composition in an aqueous solution the composition has a pH between 7, 7.5, or 8 and 10.5, e.g., between about 7, 7.5, or 8 and 9.5, e.g., between about 7 or 7.5 and 8, e.g., between about 7.5 and 8.5, e.g., about 7.5, e.g., about 8.5, e.g., between about 8 and 8.5, e.g., about 8.2.

5. The pharmaceutical composition of claim 3 or 4, wherein a conjugate acid of the one or more bases has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9.

6. The pharmaceutical composition of any one of claims 3-5, wherein the one or more bases are one or more of:

a) a $C_{1-8}$-alkyl mono-, di-, or tri- carboxylic acid salt, e.g., a citrate salt, e.g, a metal citrate salt (e.g., an alkali and/or alkaline citrate salt, e.g., an alkali citrate salt, e.g., sodium citrate and/or potassium citrate), e.g., a tartrate salt (e.g., a metal tartrate salt, an alkali tartrate, e.g., sodium tartrate), e.g., a succinate salt (e.g., a metal succinate salt, e.g., an alkali succinate, e.g., disodium succinate), and/or e.g., a lactate salt (e.g., a metal lactate salt, e.g., an alkali lactate, e.g., sodium lactate),

b) a phosphate salt, e.g., a metal phosphate salt (e.g., an alkali and/or alkaline phosphate salt, e.g., an alkali phosphate salt, e.g., sodium phosphate (e.g., $NaH_2PO_4$ and/or $Na_2HPO_4$) and/or potassium phosphate (e.g., $KH_2PO_4$ and/or $K_2HPO_4$)),

c) an amine and/or a salt thereof (e.g., morpholine, piperazine, benethamine, benzathine, trimethylglycine, hydrabamine, an amino acid (e.g., arginine and/or lysine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $H_2NR^{20}$, $HNR^{20}R^{21}$, $NR^{20}R^{21}R^{22}$, and/or a salt thereof wherein each $R^{20}$, $R^{21}$, and $R^{22}$ are independently $C_{1-8}$ alkyl (e.g., $C_{1-6}$-alkyl, e.g. $C_{1-4}$-alkyl, e.g., $C_2$-alkyl, e.g., $-CH_3$) optionally substituted with one or more -OH (e.g., optionally substituted with 1-8 -OH, e.g., 1, 2, 3, 4, 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, dimethylethanolamine, diethylamine, diethylethanolamine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9,

d) an acetate salt, e.g., a metal acetate salt (e.g., an alkali and/or alkaline acetate salt, e.g., an alkali acetate salt, e.g., sodium acetate and/or potassium acetate),

e) a hydroxide and/or alkoxide salt, e.g., a metal hydroxide and/or metal alkoxide salt (e.g., choline hydroxide, lithium hydroxide, aluminum hydroxide, e.g., an alkali and/or alkaline hydroxide salt, e.g., sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, and/or magnesium ethoxide, e.g., sodium hydroxide),

f) a carbonate and/or bicarbonate salt, e.g., a metal carbonate and/or metal bicarbonate salt (e.g., an alkali and/or alkaline carbonate salt, e.g., an alkali and/or alkaline bicarbonate salt, e.g., sodium bicarbonate), and/or

g) a borate salt, e.g., a metal borate salt (e.g., an alkali borate salt, e.g., sodium borate), e.g., one or more of sodium citrate, $Na_2HPO_4$, tris(hydroxymethyl)aminomethane, and a tris(hydroxymethyl)aminomethane salt (e.g., tris acetate), e.g., one or more of sodium citrate, $Na_2HPO_4$, and tris(hydroxymethyl)aminomethane, e.g., one or more of sodium citrate and $Na_2HPO_4$, e.g., $Na_2HPO_4$, e.g., tris(hydroxymethyl)aminomethane.

7. The pharmaceutical composition of any one of claims 3-5, wherein the one or more bases are one or more of:

a) a metal citrate salt (e.g., an alkali and/or alkaline citrate salt, e.g., an alkali citrate salt, e.g., sodium citrate and/or potassium citrate),

b) a metal phosphate salt (e.g., an alkali and/or alkaline phosphate salt, e.g., an alkali phosphate salt, e.g., sodium phosphate (e.g., $NaH_2PO_4$ and/or $Na_2HPO_4$) and/or potassium phosphate (e.g., $KH_2PO_4$ and/or $K_2HPO_4$), e.g., sodium phosphate (e.g., $Na_2HPO_4$)),

c) an amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $H_2NR^{20}$, $HNR^{20}R^{21}$, $NR^{20}R^{21}R^{22}$, and/or a salt thereof wherein each $R^{20}$, $R^{21}$, and $R^{22}$ are independently $C_{1-8}$ alkyl (e.g., $C_{1-6}$-alkyl, e.g. $C_{1-4}$-alkyl, e.g., $C_2$-alkyl, e.g., $-CH_3$) optionally substituted with one or more -OH (e.g., optionally substituted with 1-8 -OH, e.g., 1, 2, 3, 4, 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), .g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9,

d) a metal acetate salt (e.g., an alkali and/or alkaline acetate salt, e.g., an alkali acetate salt, e.g., sodium acetate and/or potassium acetate),

e) a metal hydroxide salt (e.g., an alkali and/or alkaline hydroxide salt, e.g., sodium hydroxide, potassium hydroxide, calcium hydroxide, and/or magnesium hydroxide, e.g., sodium hydroxide),

f) a metal carbonate and/or bicarbonate salt (e.g., an alkali and/or alkaline carbonate salt, e.g., an alkali and/or alkaline bicarbonate salt, e.g., sodium bicarbonate), and/or

g) a metal borate salt (e.g., an alkali borate salt, e.g., sodium borate),

e.g., one or more of sodium citrate, $Na_2HPO_4$, tris(hydroxymethyl)aminomethane, and a tris(hydroxymethyl)aminomethane salt (e.g., tris acetate), e.g., one or more of sodium citrate, $Na_2HPO_4$, and tris(hydroxymethyl)aminomethane, e.g., one or more of sodium citrate and $Na_2HPO_4$, e.g., $Na_2HPO_4$, e.g., tris(hydroxymethyl)aminomethane.

8. The pharmaceutical omposition of any one of claims 3-7, wherein the composition comprises 10 to 1500 mg of the one or more bases.

9. The pharmaceutical composition of any one of claims 3-8, wherein the one or more bases comprise a metal citrate salt (e.g., sodium citrate), a metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$), and an amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $H_2NR^{20}$, $HNR^{20}R^{21}$, $NR^{20}R^{21}R^{22}$, and/or a salt thereof wherein each $R^{20}$, $R^{21}$, and $R^{22}$ are independently $C_{1-8}$-alkyl (e.g., $C_{1-6}$-alkyl, e.g. $C_{1-4}$-alkyl, e.g., -$C_2$-alkyl, e.g., -$CH_3$) optionally substituted with one or more -OH (e.g., optionally substituted with 1-8 -OH, e.g., 1, 2, 3, 4, 5, or 6),, e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine).

10. The pharmaceutical composition of any one of claims 3-9, wherein the one or bases comprise an amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $H_2NR^{20}$, $HNR^{20}R^{21}$, $NR^{20}R^{21}R^{22}$, and/or a salt thereof wherein each $R^{20}$, $R^{21}$, and $R^{22}$ are independently $C_{1-8}$-alkyl (e.g., $C_{1-6}$-alkyl, e.g. $C_{1-4}$-alkyl, e.g., -$C_2$-alkyl, e.g., -$CH_3$) optionally substituted with one or more -OH (e.g., optionally substituted with 1-8 -OH, e.g., 1, 2, 3, 4, 5, or 6),, e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine).

11. The pharmaceutical composition of any one of claims 3-10, wherein the one or more bases comprise a mono- and/or poly-hydroxyalkylamine and/or a salt thereof, e.g., $H_2NR^{20}$, $HNR^{20}R^{21}$, $NR^{20}R^{21}R^{22}$, and/or a salt thereof wherein each $R^{20}$, $R^{21}$, and $R^{22}$ are independently $C_{1-8}$ alkyl (e.g., $C_{1-6}$-alkyl, e.g. $C_{1-4}$-alkyl, e.g., -$C_2$-alkyl, e.g., -$CH_3$) optionally substituted with one or more -OH (e.g., optionally substituted with 1-8 -OH, e.g., 1, 2, 3, 4, 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine).

12. The pharmaceutical composition of any one of claims 3-11, wherein the one or more bases comprise $H_2NR^{20}$, $HNR^{20}R^{21}$, $NR^{20}R^{21}R^{22}$, and/or a salt thereof wherein each $R^{20}$, $R^{21}$, and $R^{22}$ are independently $C_{1-8}$ alkyl (e.g., $C_{1-6}$-alkyl, e.g. $C_{1-4}$-alkyl, e.g., -$C_2$-alkyl, e.g., -$CH_3$) optionally substituted with one or more -OH (e.g., optionally substituted with 1-8 -OH, e.g., 1, 2, 3, 4, 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine).

13. The pharmaceutical composition of any one of claims 3-12, wherein the one or more bases comprise tris(hydroxymethyl)aminomethane, meglumine, and or a tris(hydroxymethyl)aminomethane salt (e.g., tris(hydroxymethyl)aminomethane acetate).

14. The pharmaceutical composition of any one of claims 3-13, wherein the one or more bases comprise a base, wherein a conjugate acid of the base has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9.

15. The pharmaceutical composition of any one of claims 3-14, wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to the one or more bases is at least 1:1.

16. The pharmaceutical composition of any one of claims 3-15, wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to the one or more bases is at least 1:2, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

17. The pharmaceutical composition of any one of claims 1-16, wherein the pharmaceutical composition is a solid, e.g., the pharmaceutically acceptable excipient, e.g, the one or more bases is a solid.

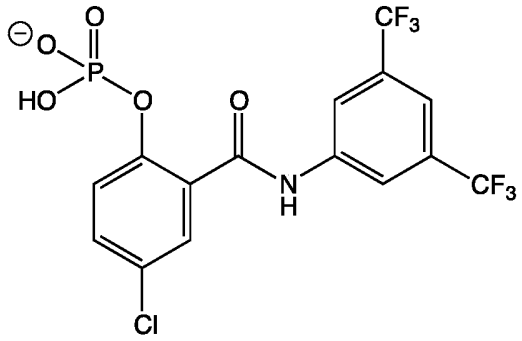
18. The pharmaceutical composition of any one of claims 3-17, wherein the 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate and the one or more bases are milled together.

19. The pharmaceutical composition of any one of claims 1-18, wherein the pharmaceutical composition is suitable for constitution, or reconstitution if lyophilized, with a aqueous solution into a pharmaceutically acceptable liquid (e.g., a solution or suspension, e.g., a solution).

20. The pharmaceutical composition of any one of claims 1-19, wherein the composition is admixed with an aqueous solution, e.g., a sterile solution, e.g., sterile water for injection, a sterile solution comprising dextrose (e.g., dextrose injection 5%), a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection), a sterile solution comprising benzyl alcohol (e.g., bacteriostatic water for injection with benzyl alcohol or bacteriostatic sodium chloride for injection with benzyl alcohol), or Lactated Ringer's.

21. The pharmaceutical composition of claim 20, wherein the composition is admixed with 0.5 to 500 mL of an aqueous solution.

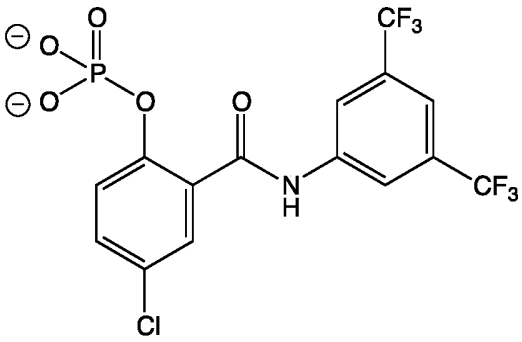
22. The pharmaceutical composition of claim 20 or 21, wherein the pharmaceutical composition comprises Formula II



Formula II.

23. The pharmaceutical composition of any one of claims 20-22, wherein the composition comprises at least a 1:1 molar ratio of Formula II to a cation of the base.

24. The pharmaceutical composition of claim 20 or 21, wherein the composition comprises Formula III



Formula III.

25. The pharmaceutical composition of any one of claims 20, 21, or 24, wherein the composition comprises at least a 1:2 molar ratio of Formula III to a cation of the base, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

26. The pharmaceutical composition of any one of claims 20-25, wherein the concentration of Formula II or Formula III, e.g., the concentration of Formula II, e.g, the concentration of Formula III, is 1 to 250 mM.

27. The pharmaceutical composition of any one of claims 20-26, wherein the aqueous solution, e.g., the sterile solution, comprises one or more bases.

28. The pharmaceutical composition of claim 27, wherein upon dissolution of the composition in an aqueous solution the composition has a pH between 7, 7.5, or 8 and 10.5, e.g., between about 7, 7.5, or 8 and 9.5, e.g., between about 7 or 7.5 and 8, e.g., between about 7.5 and 8.5, e.g., about 7.5, e.g., about 8.5, e.g., between about 8 and 8.5, e.g., about 8.2.

29. The pharmaceutical composition of claim 27 or 28, wherein a conjugate acid of the base has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9.

30. The pharmaceutical composition of any one of claims 27-29, wherein the one or more bases are one or more of:

a) a $C_{1-8}$-alkyl mono-, di-, or tri- carboxylic acid salt, e.g., a citrate salt, e.g, a metal citrate salt (e.g., an alkali and/or alkaline citrate salt, e.g., an alkali citrate salt, e.g., sodium citrate and/or potassium citrate), e.g., a tartrate salt (e.g., a metal tartrate salt, an alkali tartrate, e.g., sodium tartrate), e.g., a succinate salt (e.g., a metal succinate salt, e.g., an alkali succinate, e.g., disodium succinate), and/or e.g., a lactate salt (e.g., a metal lactate salt, e.g., an alkali lactate, e.g., sodium lactate),

b) a phosphate salt, e.g., a metal phosphate salt (e.g., an alkali and/or alkaline phosphate salt, e.g., an alkali phosphate salt, e.g., sodium phosphate (e.g., $NaH_2PO_4$ and/or $Na_2HPO_4$) and/or potassium phosphate (e.g., $KH_2PO_4$ and/or $K_2HPO_4$)),

c) an amine and/or a salt thereof (e.g., morpholine, piperazine, benethamine, benzathine, trimethylglycine, hydrabamine, an amino acid (e.g., arginine and/or lysine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $H_2NR^{20}$, $HNR^{20}R^{21}$, $NR^{20}R^{21}R^{22}$, and/or a salt thereof wherein each $R^{20}$, $R^{21}$, and $R^{22}$ are independently $C_{1-8}$ alkyl (e.g., $C_{1-6}$-alkyl, e.g. $C_{1-4}$-alkyl, e.g., $C_2$-alkyl, e.g., $-CH_3$) optionally substituted with one or more -OH (e.g., optionally substituted with 1-8 -OH, e.g., 1, 2, 3, 4, 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or

a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, dimethylethanolamine, diethylamine, diethylethanolamine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9,

d) an acetate salt, e.g., a metal acetate salt (e.g., an alkali and/or alkaline acetate salt, e.g., an alkali acetate salt, e.g., sodium acetate and/or potassium acetate),

e) a hydroxide and/or alkoxide salt, e.g., a metal hydroxide and/or metal alkoxide salt (e.g., a quarternary ammonium hydroxide, e.g., ammonium hydroxide and/or choline hydroxide, lithium hydroxide, aluminum hydroxide, e.g., an alkali and/or alkaline hydroxide salt, e.g., sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, and/or magnesium ethoxide, e.g., sodium hydroxide),

f) a carbonate and/or bicarbonate salt, e.g., a metal carbonate and/or metal bicarbonate salt (e.g., an alkali and/or alkaline carbonate salt, e.g., an alkali and/or alkaline bicarbonate salt, e.g., sodium bicarbonate), and/or

g) a borate salt, e.g., a metal borate salt (e.g., an alkali borate salt, e.g., sodium borate), e.g., one or more of sodium citrate, $Na_2HPO_4$, tris(hydroxymethyl)aminomethane, and a tris(hydroxymethyl)aminomethane salt (e.g., tris acetate), e.g., one or more of sodium citrate, $Na_2HPO_4$, and tris(hydroxymethyl)aminomethane, e.g., one or more of sodium citrate and $Na_2HPO_4$, e.g., $Na_2HPO_4$, e.g., tris(hydroxymethyl)aminomethane.

31. The pharmaceutical composition of any one of claims 27-30, wherein the one or more bases are one or more of:

a) a metal citrate salt (e.g., an alkali and/or alkaline citrate salt, e.g., an alkali citrate salt, e.g., sodium citrate and/or potassium citrate),

b) a metal phosphate salt (e.g., an alkali and/or alkaline phosphate salt, e.g., an alkali phosphate salt, e.g., sodium phosphate (e.g., $NaH_2PO_4$ and/or $Na_2HPO_4$) and/or potassium phosphate (e.g., $KH_2PO_4$ and/or $K_2HPO_4$), e.g., sodium phosphate (e.g., $Na_2HPO_4$)),

c) an amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $H_2NR^{20}$, $HNR^{20}R^{21}$,

$NR^{20}R^{21}R^{22}$, and/or a salt thereof wherein each $R^{20}$, $R^{21}$, and $R^{22}$ are independently $C_{1-8}$ alkyl (e.g., $C_{1-6}$-alkyl, e.g. $C_{1-4}$-alkyl, e.g., $C_2$-alkyl, e.g., $-CH_3$) optionally substituted with one or more -OH (e.g., optionally substituted with 1-8 -OH, e.g., 1, 2, 3, 4, 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9,

d) a metal acetate salt (e.g., an alkali and/or alkaline acetate salt, e.g., an alkali acetate salt, e.g., sodium acetate and/or potassium acetate),

e) a metal hydroxide salt (e.g., an alkali and/or alkaline hydroxide salt, e.g., sodium hydroxide, potassium hydroxide, calcium hydroxide, and/or magnesium hydroxide, e.g., sodium hydroxide),

f) a metal carbonate and/or bicarbonate salt (e.g., an alkali and/or alkaline carbonate salt, e.g., an alkali and/or alkaline bicarbonate salt, e.g., sodium bicarbonate), and/or

g) a metal borate salt (e.g., an alkali borate salt, e.g., sodium borate),

e.g., one or more of sodium citrate, $Na_2HPO_4$, tris(hydroxymethyl)aminomethane, and a tris(hydroxymethyl)aminomethane salt (e.g., tris acetate), e.g., one or more of sodium citrate, $Na_2HPO_4$, and tris(hydroxymethyl)aminomethane, e.g., one or more of sodium citrate and $Na_2HPO_4$, e.g., $Na_2HPO_4$, e.g., tris(hydroxymethyl)aminomethane.

32. The pharmaceutical composition of any one of claims 27-31, wherein the one or more bases comprise a metal citrate salt (e.g., sodium citrate), a metal phosphate salt (e.g., sodium phosphate, e.g., $Na_2HPO_4$), and an amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $H_2NR^{20}$, $HNR^{20}R^{21}$, $NR^{20}R^{21}R^{22}$, and/or a salt thereof wherein each $R^{20}$, $R^{21}$, and $R^{22}$ are independently $C_{1-8}$ alkyl (e.g., $C_{1-6}$-alkyl, e.g. $C_{1-4}$-alkyl, e.g., $C_2$-alkyl, e.g., $-CH_3$) optionally substituted with one or more -OH (e.g., optionally substituted with 1-8 -OH, e.g., 1, 2, 3, 4, 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g.,

tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine).

33. The pharmaceutical composition of any one of claims 27-32, wherein the one or more bases comprise an amine and/or a salt thereof (e.g., morpholine, an amino acid (e.g., arginine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $H_2NR^{20}$, $HNR^{20}R^{21}$, $NR^{20}R^{21}R^{22}$, and/or a salt thereof wherein each $R^{20}$, $R^{21}$, and $R^{22}$ are independently $C_{1-8}$ alkyl (e.g., $C_{1-6}$-alkyl, e.g. $C_{1-4}$-alkyl, e.g., $C_2$-alkyl, e.g., $-CH_3$) optionally substituted with one or more -OH (e.g., optionally substituted with 1-8 -OH, e.g., 1, 2, 3, 4, 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine).

34. The pharmaceutical composition of any one of claims 27-33, wherein the one or more bases comprise a mono- and/or poly-hydroxyalkylamine and/or a salt thereof, e.g., $H_2NR^{20}$, $HNR^{20}R^{21}$, $NR^{20}R^{21}R^{22}$, and/or a salt thereof wherein each $R^{20}$, $R^{21}$, and $R^{22}$ are independently $C_{1-8}$ alkyl (e.g., $C_{1-6}$-alkyl, e.g. $C_{1-4}$-alkyl, e.g., $C_2$-alkyl, e.g., $-CH_3$) optionally substituted with one or more -OH (e.g., optionally substituted with 1-8 -OH, e.g., 1, 2, 3, 4, 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine).

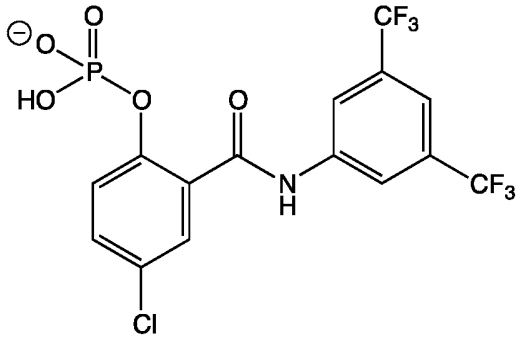
35. The pharmaceutical composition of any one of claims 27-34, wherein the one or more bases comprise e.g., $H_2NR^{20}$, $HNR^{20}R^{21}$, $NR^{20}R^{21}R^{22}$, and/or a salt thereof wherein each $R^{20}$, $R^{21}$, and $R^{22}$ are independently $C_{1-8}$ alkyl (e.g., $C_{1-6}$-alkyl, e.g. $C_{1-4}$-alkyl, e.g., $C_2$-alkyl, e.g., $-CH_3$) optionally substituted with one or more -OH (e.g., optionally substituted with 1-8 -OH, e.g., 1, 2, 3, 4, 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, and/or diethanolamine).

36. The pharmaceutical composition of any one of claims 27-35, wherein the one or more bases comprise tris(hydroxymethyl)aminomethane, meglumine, and or a tris(hydroxymethyl)aminomethane salt (e.g., tris(hydroxymethyl)aminomethane acetate).

37. The pharmaceutical composition of any one of claims 27-36, wherein the one or more bases comprise a base, wherein a conjugate acid of the base has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9.

38. The pharmaceutical composition of any one of claims 27-37, wherein the pH after admixture with the aqueous solution is between pH 7 and pH 10.5, e.g., between pH 7 and pH 9.5, e.g., between pH 7 and pH 8, e.g., between 7.5 and 8.5, e.g., 7.5, e.g., 8.5, e.g., 8.2.

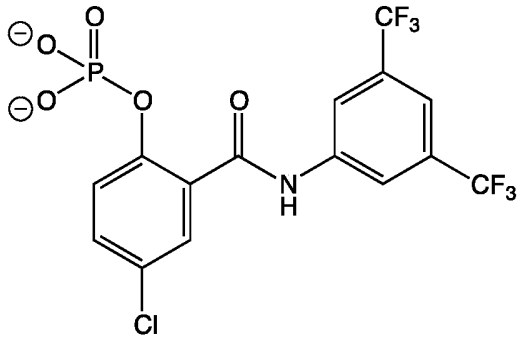
39. The pharmaceutical composition of any one of claims 27-38, wherein the pharmaceutical composition comprises Formula II




Formula II.

40. The pharmaceutical composition of claim 39, wherein the pharmaceutical composition comprises at least a 1:1 molar ratio of Formula II to cation of the base.

41. The pharmaceutical composition of claim 39, wherein the pharmaceutical composition comprises Formula III



Formula III.

42. The pharmaceutical composition of claim 41, wherein the composition comprises at least a 1:2 molar ratio of Formula III to a cation of the base, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

43. The pharmaceutical composition of any one of claims 1-42, wherein the composition is for injection, e.g., subcutaneously, intramuscularly, intravenously, or intrathecally, e.g., intramuscularly or intravenously, e.g., a bolus injected subcutaneously, intramuscularly, intravenously, or intrathecally.

44. The pharmaceutical composition of any one of claims 1-43, wherein the composition is for injection intravenously, e.g., IV bolus and/or IV infusion, e.g., IV bolus followed by IV infusion, e.g., a loading bolus (e.g., 10 or 20 to 30, 50, 70, 75, 100, 140, 150, 200, 300 or 400 mg per day administered by a loading bolus dose, e.g., about 50 to 200 or 250 mg per day administered by a loading bolus dose, e.g., about 70 to 140 mg per day administered by a loading bolus dose, e.g., a concentration of the dissolved salt administered by a loading bolus dose of 1 to 4, 5, 8, 10, 15, 20, 30, or 50 mM per day, e.g., a concentration of the dissolved salt administered by a loading bolus dose of about 2 to 5, 10, 15, or 20 mM per day, e.g., a concentration of the dissolved salt administered by a loading bolus dose of about 4 to 8 or 9 mM per day) and then an IV infusion over 24 hours for 3 days (e.g., at a rate of 1, 2, 3, 5, 6, 7, 8, 10, 15, 20, 25, 30, or 50 mg/hr for 24 hours, e.g., at a rate of 3, 6, or 15 mg/hr).

45. The pharmaceutical composition of any one of claims 1-43, wherein the composition is for injection intramuscularly, e.g., IM bolus and/or IM infusion, e.g., IM bolus followed by IM infusion.

46. The pharmaceutical composition of any one of claims 44 or 45, wherein the infusion, e.g., IV or IM, is administered over about 10 or 30 minutes to 72 hours, e.g., about 30 minutes to 24 hours, e.g, about 30 minutes to 12 hours, e.g., about 30 minutes to 8 hours, e.g., about 30 minutes to 6 hours, e.g., about 30 minutes to 4 hours, e.g., about 30 minutes to 2 hours, e.g., about 30 minutes to 1 hour, e.g., about 72 hours.

47. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition comprises between 20 and 500 mg 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate (Formula I), e.g., between about 25 and 450 mg, e.g., between about 30 and 400 mg, e.g., between about 35 and 350 mg, and a base, e.g., one or more of tris(hydroxymethyl)aminomethane, $Na_2HPO_4$, meglumine, and sodium citrate, e.g., between 10 and 1500 mg of one or more of tris(hydroxymethyl)aminomethane, $Na_2HPO_4$, meglumine, and sodium citrate, e.g., between about 15 and 1000 mg, e.g., between about 20 and 600 mg, e.g., between about 50 and 200 mg, e.g., between about 50 and 150 mg, e.g., between 10 and 1500 mg of the base, e.g., between about 15 and 1000 mg, e.g., between about 20 and 600 mg, e.g., between about 50 and 200 mg, e.g., between about 50 and 150 mg.

48. The pharmaceutical composition of claim 47, wherein the pharmaceutical composition comprises between 20 and 500 mg 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate (Formula I), e.g., between about 25 and 450 mg, e.g., between about 30 and 400 mg, e.g., between about 35 and 350 mg, and tris(hydroxymethyl)aminomethane, e.g., between 10 and 600 mg tris(hydroxymethyl)aminomethane, e.g., between about 20 and 500, e.g., between about 40 and 500 mg.

49. The pharmaceutical composition of claim 47, wherein the pharmaceutical composition comprises between 20 and 500 mg 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-

4-chlorophenyl dihydrogen phosphate (Formula I), e.g., between about 25 and 450 mg, e.g., between about 30 and 400 mg, e.g., between about 35 and 350 mg, and $Na_2HPO_4$, e.g., between 10 and 600 mg $Na_2HPO_4$, e.g., between about 20 and 500, e.g., between about 40 and 500 mg.

50. The pharmaceutical composition of claim 47, wherein the pharmaceutical composition comprises between 20 and 500 mg 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate (Formula I), e.g., between about 25 and 450 mg, e.g., between about 30 and 400 mg, e.g., between about 35 and 350 mg, and meglumine, e.g., between 20 and 900 mg meglumine, e.g., between about 30 and 800, e.g., between about 60 and 500 mg, e.g, between about 70 and 400 mg.

51. The pharmaceutical composition of claim 47, wherein the pharmaceutical composition comprises between 20 and 500 mg 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate (Formula I), e.g., between about 25 and 450 mg, e.g., between about 30 and 400 mg, e.g., between about 35 and 350 mg, and sodium citrate, e.g., between 30 and 1500 mg sodium citrate, e.g., between about 40 and 1200, e.g., between about 50 and 1000 mg, e.g, between about 80 and 600 mg, e.g., between about 100 and 500 mg.

52. The pharmaceutical composition of any one of claims 47-51, wherein the pharmaceutical composition is admixed with an aqueous solution, e.g., sterile water for injection, a sterile solution comprising dextrose (e.g., dextrose injection 5%), a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection), a sterile solution comprising benzyl alcohol (e.g., bacteriostatic water for injection with benzyl alcohol or bacteriostatic sodium chloride for injection with benzyl alcohol), or Lactated Ringer's, e.g., wherein the composition is admixed with 1 mL to 100 mL of an aqueous solution e.g., about 3 to 50 mL, e.g., about 3.5 to 35 mL.

53. The pharmaceutical composition of any one of claims 47-52, wherein the pharmaceutical composition is admixed with a sterile water for injection, e.g., wherein the composition is admixed with 1 mL to 100 mL sterile water for injection, e.g., about 3 to 50 mL, e.g., about 3.5 to 35 mL.

54. The pharmaceutical composition of any one of claims 47-53, wherein the pharmaceutical composition is admixed with a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection), e.g., wherein the composition is admixed with 1 mL to 100 mL a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection), e.g., about 3 to 50 mL, e.g., about 3.5 to 35 mL.

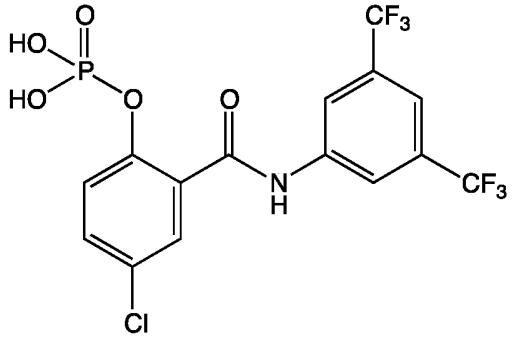
55. The pharmaceutical composition of any one of claims 1-54, wherein the composition is stable for at least one week at room temperature, e.g., for at least 1, 2, 4, 6, 8, or 12 months, e.g., the composition has < 20% N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide, < 15% N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide, < 10% N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide, < 5% N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide, < 2% N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide, 1% N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide, or < 1% N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide.

56. The pharmaceutical composition of any one of claims 1-55, wherein the pharmaceutical composition is for use in any of the methods described herein, e.g., for use in Method A, e.g., Method A.1-A.58, for use in Method B, e.g., Method B.1-B.41, e.g., for use in Method C, e.g., C.1-C.8, e.g., for use in Method D, e.g., D.1-D.19, e.g., for use in Method E, e.g., E.1-E.59, e.g., for use in Method F, e.g., F.1-F.5, e.g., for use in Method G, e.g., G.1-G.58, e.g., for use in Method H, e.g., H.1-H.9.

57. A method of making the pharmaceutical composition of any one of claims 1-56 comprising admixing 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate and a pharmaceutically acceptable excipient.

58. A kit comprising the pharmaceutical composition of any one of claims 1-56.

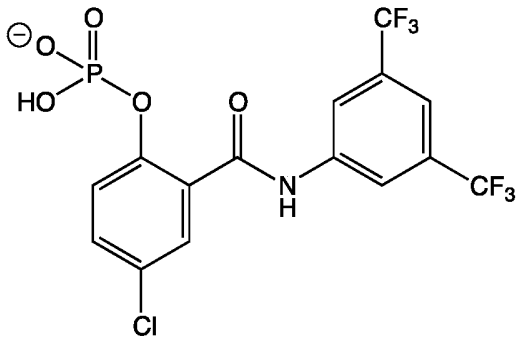
59. A salt solution comprising water and a salt formed from a compound of Formula I



Formula I

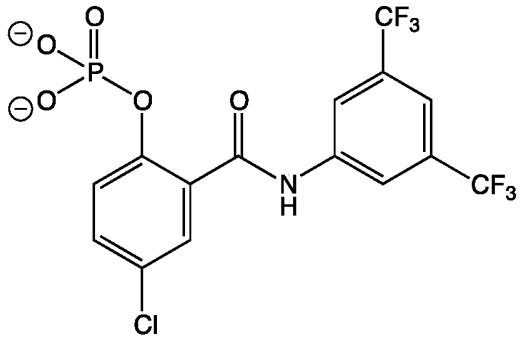
and an amine and/or a salt thereof (e.g., morpholine, piperazine, benethamine, benzathine, trimethylglycine, hydrabamine, 4-(2-hydroxyethyl)morpholine, 1-2-hydroxyethyl)-pyrrolidine, an amino acid (e.g., arginine and/or lysine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $H_2NR^{20}$, $HNR^{20}R^{21}$, $NR^{20}R^{21}R^{22}$, and/or a salt thereof wherein each $R^{20}$, $R^{21}$, and $R^{22}$ are independently $C_{1-8}$ alkyl (e.g., $C_{1-6}$-alkyl, e.g. $C_{1-4}$-alkyl, e.g., $C_2$-alkyl, e.g., $-CH_3$) optionally substituted with one or more -OH (e.g., optionally substituted with 1-8 -OH, e.g., 1, 2, 3, 4, 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, dimethylethanolamine, diethylamine, diethylethanolamine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9.

60. A salt solution comprising Formula II



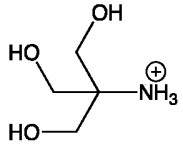
Formula II.

61. A salt solution comprising Formula III



Formula III.

62. The salt solution of any one of claims 59-61, wherein the salt solution comprises a a protonated and/or unprotonateed mono- and/or poly-hydroxyalkylamine, e.g., $(HO)_nR^8NH_2$, $[(HO)_nR^8]_2NH$, $[(HO)_nR^8]_3N$, e.g., $(HO)_nR^8NH_3^+$, $[(HO)_nR^8]_2NH_2^+$, $[(HO)_nR^8]_3NH^+$, wherein each $R^8$ is independently $C_{1-8}$alkyl (e.g., $C_{1-6}$-alkyl, e.g., $C_{1-4}$-alkyl, e.g., $-CH_2CH_3$, e.g., $-CH_3$) and n is 0 or $C_{1-8}$-alkylene (e.g., $C_{1-6}$-alkylene, e.g., $C_{1-4}$-alkylene, e.g., $–CH_2–CH_2–$, e.g., $–C(CH_2)_3–$, e.g., one $R^8$ is $–CH_3$ and another $R^8$ is $–(CH_2)_6–$) and each n is independently 1-8 (e.g., 1, 2, 3, 4 , 5, or 6), e.g.,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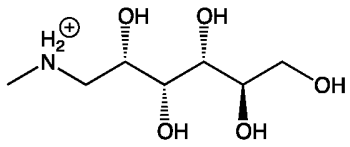
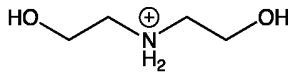

, and/or

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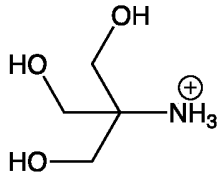
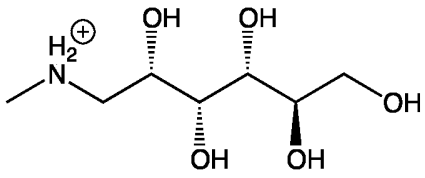
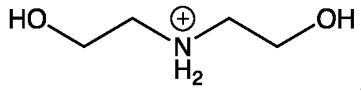
63. The salt solution of any one of claims 59-62, wherein the salt solution comprises


.

64. The salt solution of any one of claims 59-62, wherein the salt solution comprises


.

65. The salt solution I of any one of claims 59-62, wherein the salt solution comprises

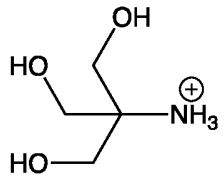


.

66. The salt solution of any one of claims 59-65, wherein the salt solution comprises at least a 1:1 molar ratio of Formula II to the protonated amine.

67. The salt solution of any one of claims 59-65, wherein the salt solution comprises at least a 1:2 molar ratio of Formula II to the protonated amine, e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

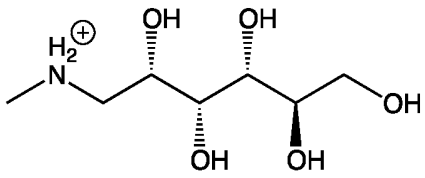
68. The salt solution of any one of claims 59-62, wherein the salt solution comprises at least a 1:2 molar ratio of Formula II to



,

e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

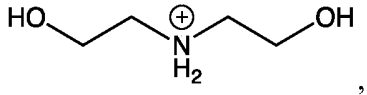
69. The salt solution of any one of claims 59-62, wherein the salt solution comprises at least a 1:2 molar ratio of Formula II to



,

e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

70. The salt solution of any one of claims 59-62, wherein the salt solution comprises at least a 1:2 molar ratio of Formula II to




,

e.g., at least about 1:2, 1:3, 1:4, or 1:5 to 1:6, 1:7, 1:8 to 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5 to 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, or 1:30, e.g., at least about 1:2.5, e.g., at least about 1:5, e.g. at least about 1:10.

71. The salt solution of any one of claims 59-70, wherein the salt solution comprises a sterile solution, e.g., sterile water for injection, a sterile solution comprising dextrose (e.g., dextrose injection 5%), a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection), a sterile solution comprising benzyl alcohol (e.g., bacteriostatic water for injection with benzyl alcohol or bacteriostatic sodium chloride for injection with benzyl alcohol), or Lactated Ringer's.

72. The salt solution of any one of claims 59-71, wherein the salt solution comprises 0.5 to 500 mL water.

73. The salt solution of any one of claims 59-72, wherein the salt solution comprises sterile water for injection.

74. The salt solution of any one of claims 59-73, wherein the salt solution comprises sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection).

75. The salt solution of any one of claims 59-74, wherein the concentration of Formula II or Formula III, e.g., the concentration of Formula II, e.g, the concentration of Formula III is 1 to 250 mM.

76. The salt solution of any one of claims 59-75, wherein the pH of the salt solution is between pH 7 and pH 10.5, e.g., between pH 7 and pH 9.5, e.g., between pH 7 and pH 8, e.g., between 7.5 and 8.5, e.g., 7.5, e.g., 8.5, e.g., 8.2.

77. The salt solution of any one of claims 59-76, wherein the salt solution is for injection, e.g., subcutaneously, intramuscularly, intravenously, or intrathecally, e.g., intramuscularly or intravenously, e.g., a bolus injected subcutaneously, intramuscularly, intravenously, or intrathecally.

78. The salt solution of claim 77, wherein the salt solution is for injection intravenously, e.g., IV bolus and/or IV infusion, e.g., IV bolus followed by IV infusion.

79. The salt solution of claim 77, wherein the salt solution is for injection intramuscularly, e.g., IM bolus and/or IM infusion, e.g., IM bolus followed by IM infusion.

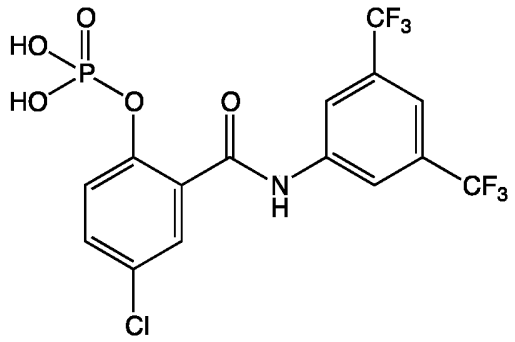
80. The salt solution of any one of claims 59-79, wherein the salt solution is stable for at least one week, e.g., for at least 1, 2, 4, 6, 8, or 12 months.

81. The salt solution of any one of claims 59-80, wherein the salt solution is stable for at least one week, at room temperature, e.g., for at least 1, 2, 4, 6, 8, or 12 months, e.g., the composition has < 20% N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide, < 15% N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide, < 10% N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide, < 5% N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide, < 2% N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide, 1% N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide, or < 1% N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide.

82. The salt solution of any one of claims 59-81, wherein the salt solution is for use in any of the methods described herein, e.g., for use in Method A, e.g., Method A.1-A.58, for use in Method B, e.g., Method B.1-B.41, e.g., for use in Method C, e.g., C.1-C.8, e.g., for use in

Method D, e.g., D.1-D.19, e.g., for use in Method E, e.g., E.1-E.59, e.g., for use in Method F, e.g., F.1-F.5, e.g., for use in Method G, e.g., G.1-G.58, for use in Method H, e.g., H.1-H.9.

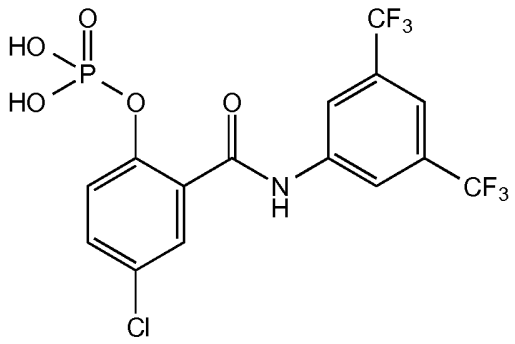
83. A method for making the salt solution of any one of claims 59-82 comprising admixing a compound of Formula I



Formula I

and an amine and/or a salt thereof (e.g., morpholine, piperazine, benethamine, benzathine, trimethylglycine, hydrabamine, 4-(2-hydroxyethyl)morpholine, 1-2-hydroxyethyl)-pyrrolidine, an amino acid (e.g., arginine and/or lysine), a mono- and/or poly-hydroxyalkylamine, and/or a salt thereof, e.g., $H_2NR^{20}$, $HNR^{20}R^{21}$, $NR^{20}R^{21}R^{22}$, and/or a salt thereof wherein each $R^{20}$, $R^{21}$, and $R^{22}$ are independently $C_{1-8}$ alkyl (e.g., $C_{1-6}$-alkyl, e.g. $C_{1-4}$-alkyl, e.g., $C_2$-alkyl, e.g., $-CH_3$) optionally substituted with one or more -OH (e.g., optionally substituted with 1-8 -OH, e.g., 1, 2, 3, 4, 5, or 6), e.g., tris(hydroxymethyl)aminomethane (also known as tris base) and/or a salt thereof (e.g., tris(hydroxymethyl)aminomethane acetate (also known as tris acetate), meglumine, dimethylethanolamine, diethylamine, diethylethanolamine, and/or diethanolamine), e.g., any of the preceding wherein a conjugate acid of the amine and/or salt thereof has a pKa between 6, 7 , 8, 9, or 10 and 11, e.g., between about 6, 7, 8, or 9 and 10, e.g., between about 7 and 9, e.g., between about 8 and 9, in an aqueous solution.

84. A pharmaceutical composition comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate (Formula I)



Formula I

and tris(hydroxymethyl)aminomethane.

85. The pharmaceutical composition of claim 84, wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to tris(hydroxymethyl)aminomethane is 1:2 to 1:10.

86. The pharmaceutical composition of claim 84 or 85, wherein the molar ratio of 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate to tris(hydroxymethyl)aminomethane is 1:2.5 to 1:5.

87. The pharmaceutical composition of any one of claims 84-86, wherein the wherein the composition is admixed with an aqueous solution, e.g., a sterile solution, e.g., sterile water for injection, a sterile solution comprising dextrose (e.g., dextrose injection 5%), a sterile solution comprising sodium chloride (e.g., 0.9% sodium chloride injection), a sterile solution comprising benzyl alcohol (e.g., bacteriostatic water for injection with benzyl alcohol or bacteriostatic sodium chloride for injection with benzyl alcohol), or Lactated Ringer's.

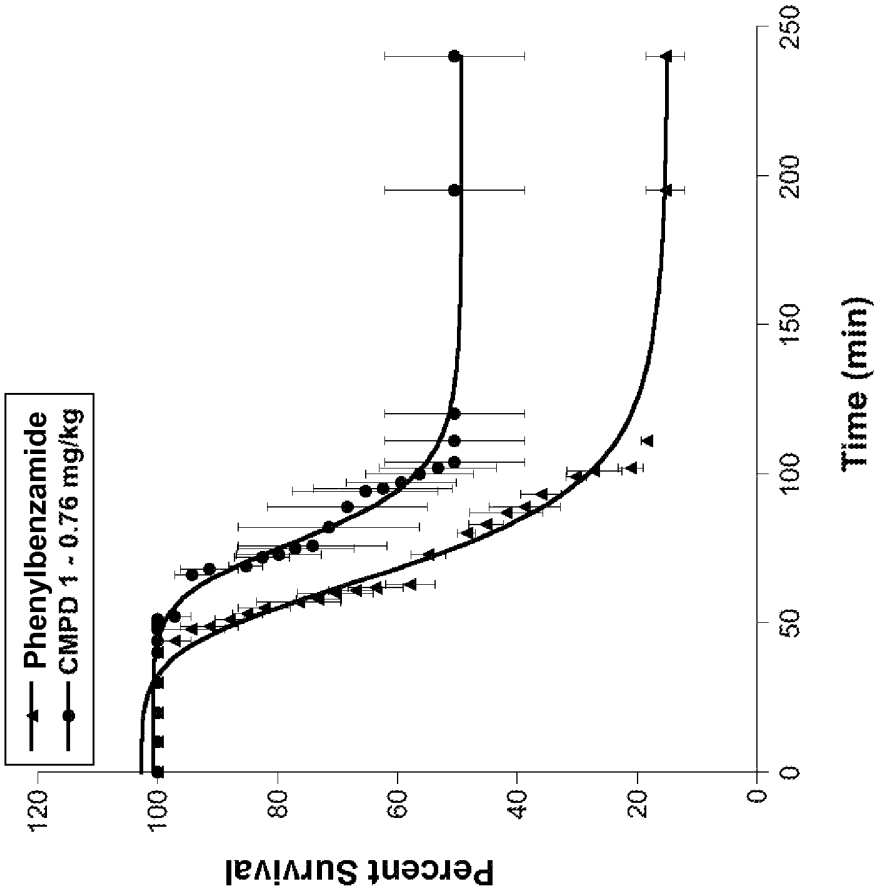

Phenylbenzamide
CMPD 1 - 0.76 mg/kg
Percent Survival
Time (min)
120
100
80
60
40
20
0
0
50
100
150
200
250

FIGURE 1

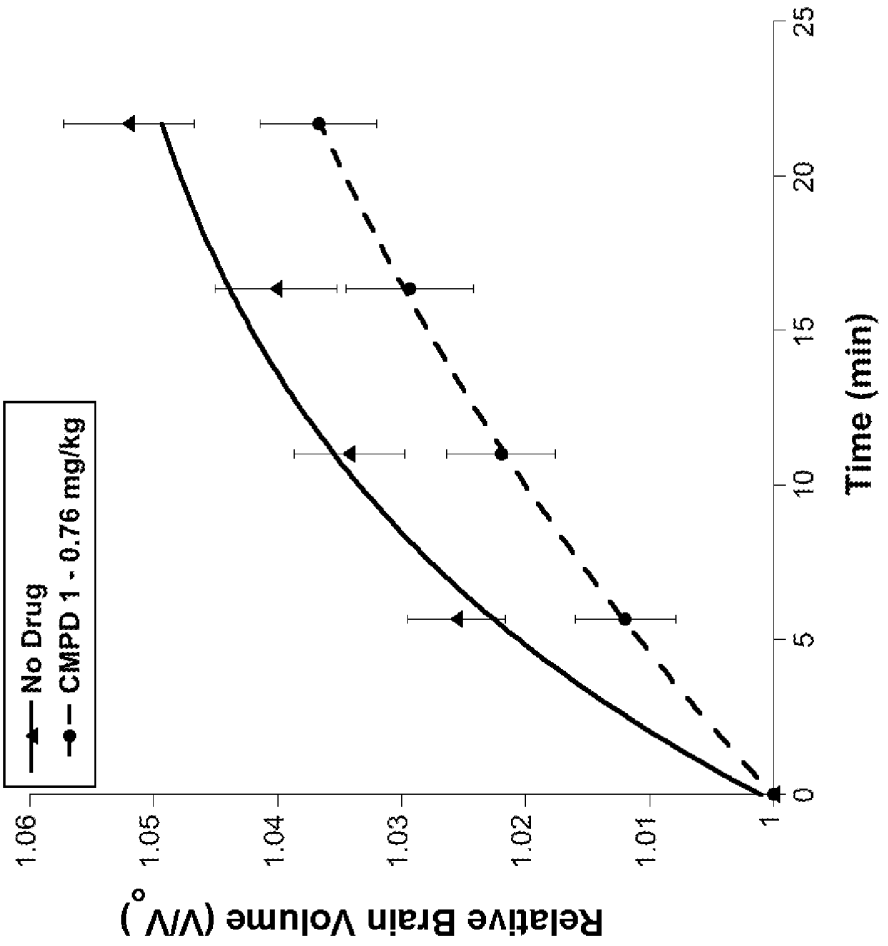

No Drug
CMPD 1 - 0.76 mg/kg
Relative Brain Volume (V/V$_o$)
1.06
1.05
1.04
1.03
1.02
1.01
1
0
5
10
15
20
25
Time (min)

FIGURE 2

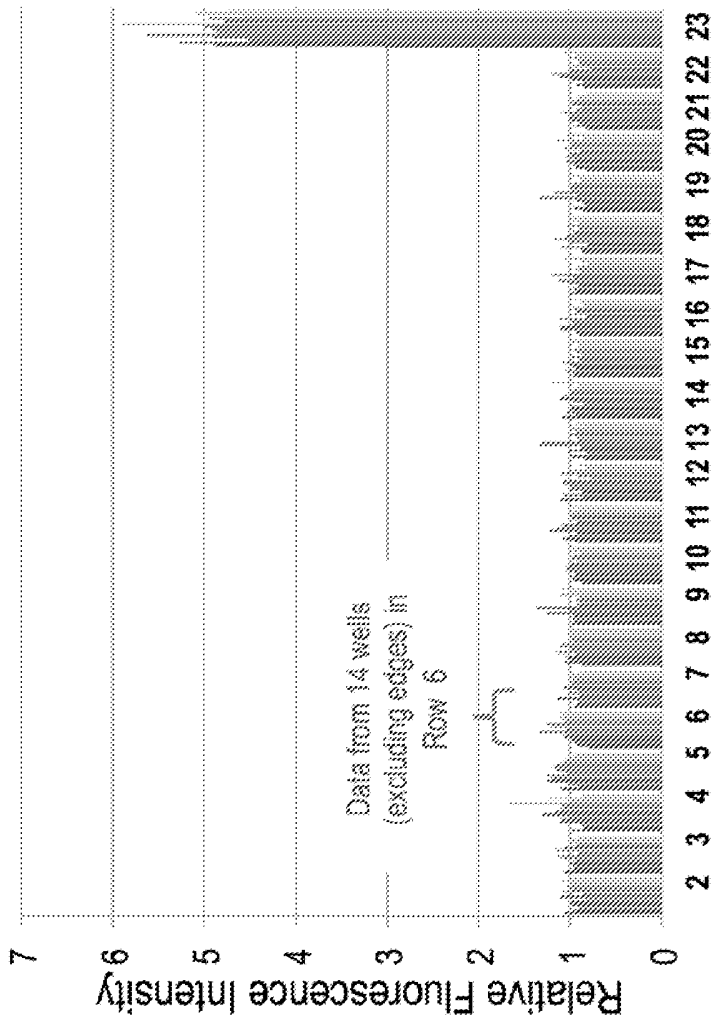

Relative Fluorescence Intensity
0
1
2
3
4
5
6
7
Data from 14 wells
(excluding edges) in
Row 6
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
ROW

FIGURE 3

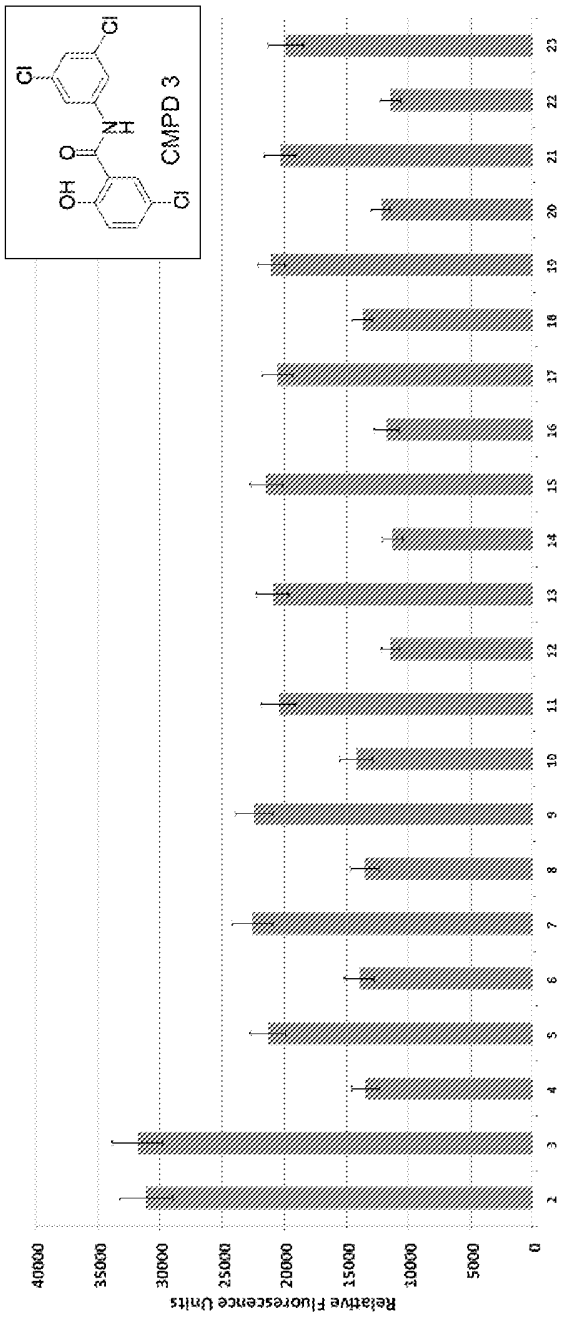

CMPD 3
Relative Fluorescence Units
40000
35000
30000
25000
20000
15000
10000
5000
0
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23

FIGURE 4

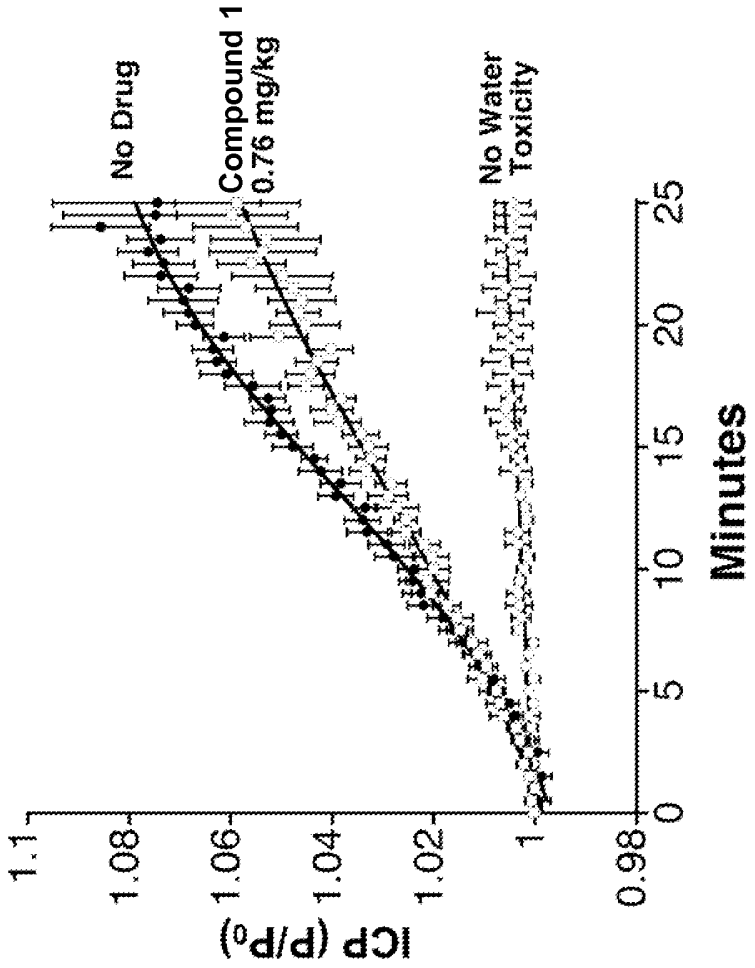

No Drug
Compound 1
0.76 mg/kg
No Water
Toxicity
ICP (P/P0)
Minutes
1.1
1.08
1.06
1.04
1.02
1
0.98
0
5
10
15
20
25

FIGURE 5

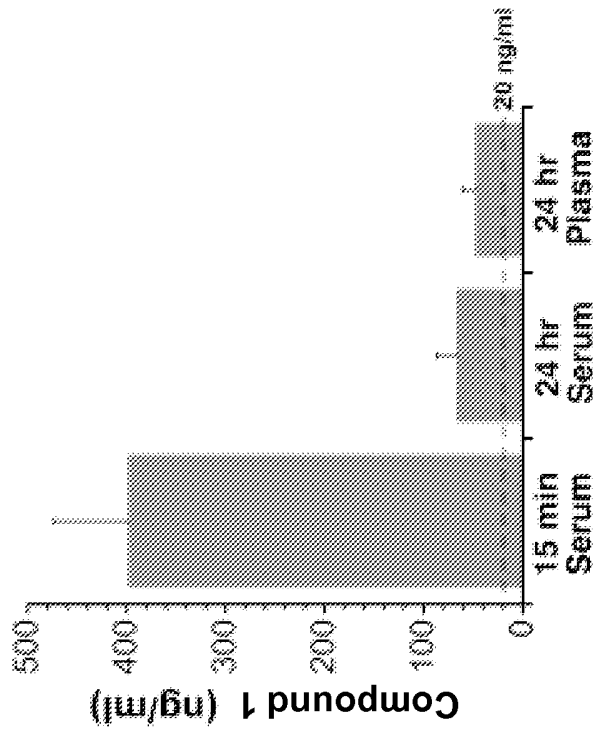

Compound 1 (ng/ml)
500
400
300
200
100
0
15 min Serum
24 hr Serum
24 hr Plasma
20 ng/ml

FIGURE 6

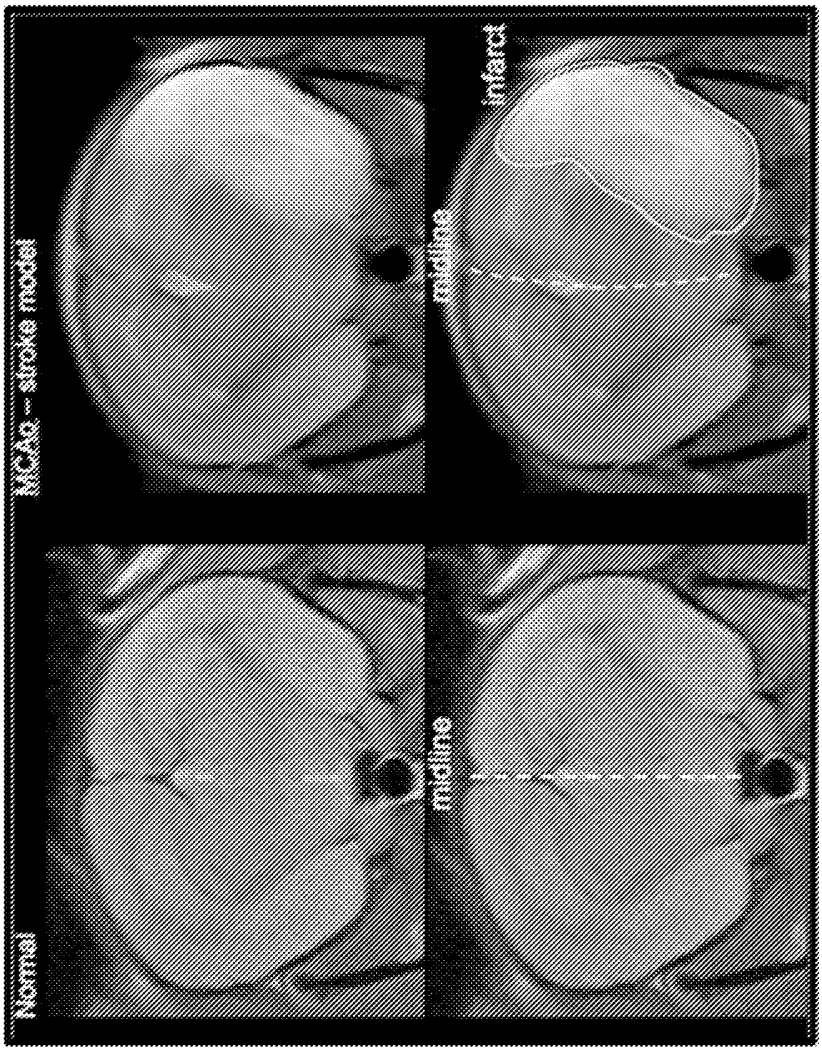



FIGURE 7

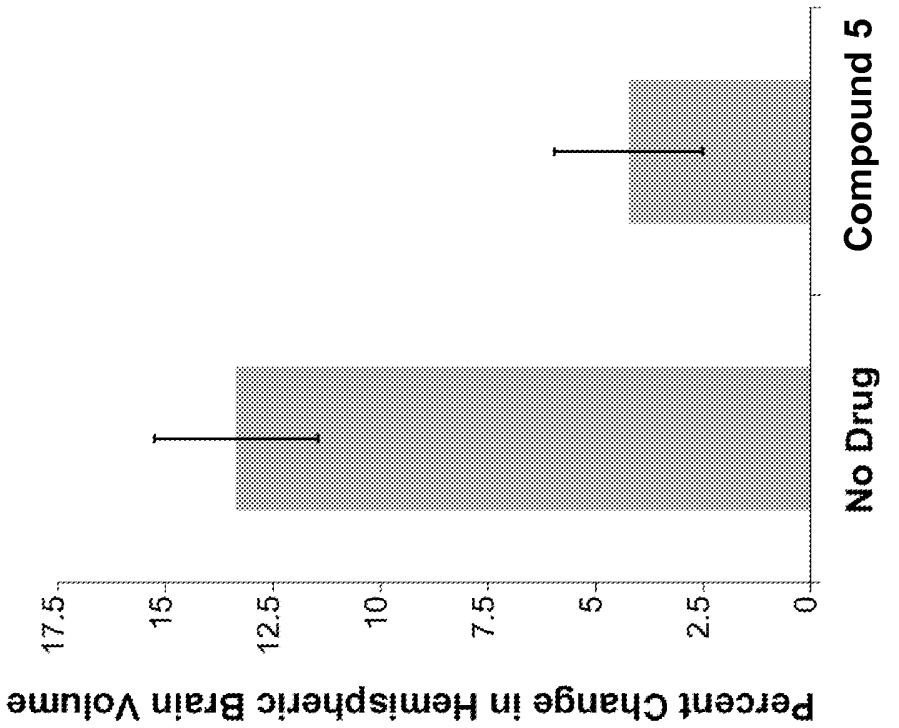

Percent Change in Hemispheric Brain Volume
17.5
15
12.5
10
7.5
5
2.5
0
No Drug
Compound 5

FIGURE 8

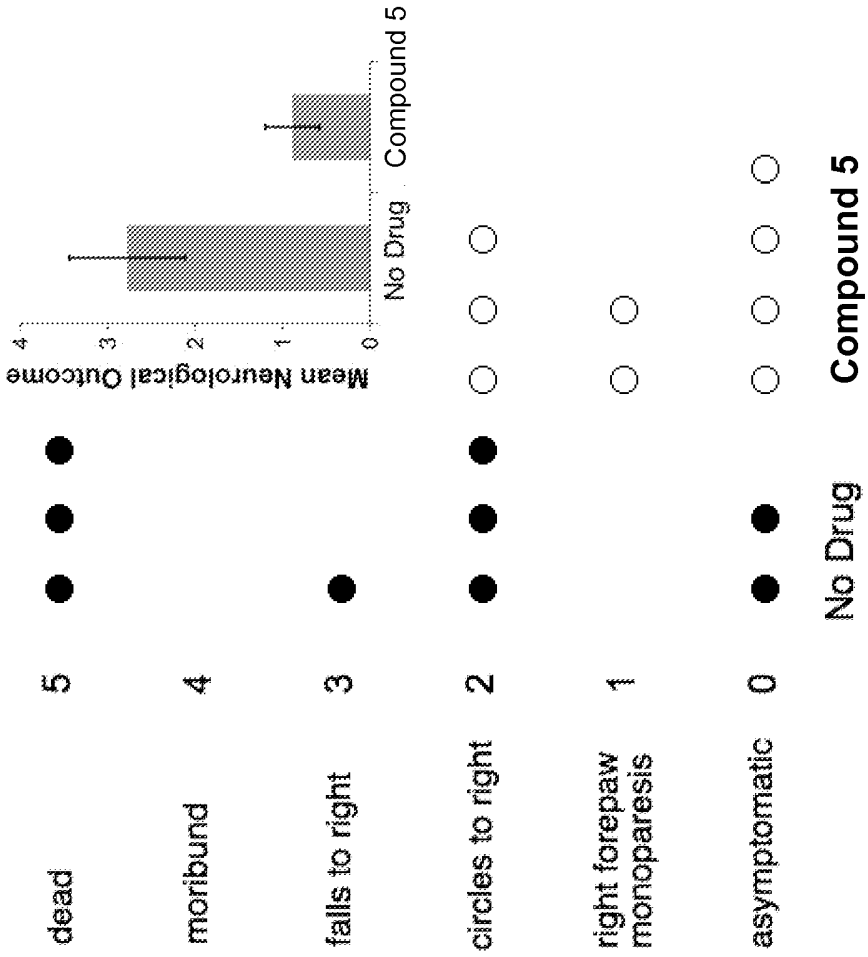

Mean Neurological Outcome
4
3
2
1
0
No Drug
Compound 5
dead
5
moribund
4
falls to right
3
circles to right
2
right forepaw monoparesis
1
asymptomatic
0
No Drug
Compound 5

FIGURE 9

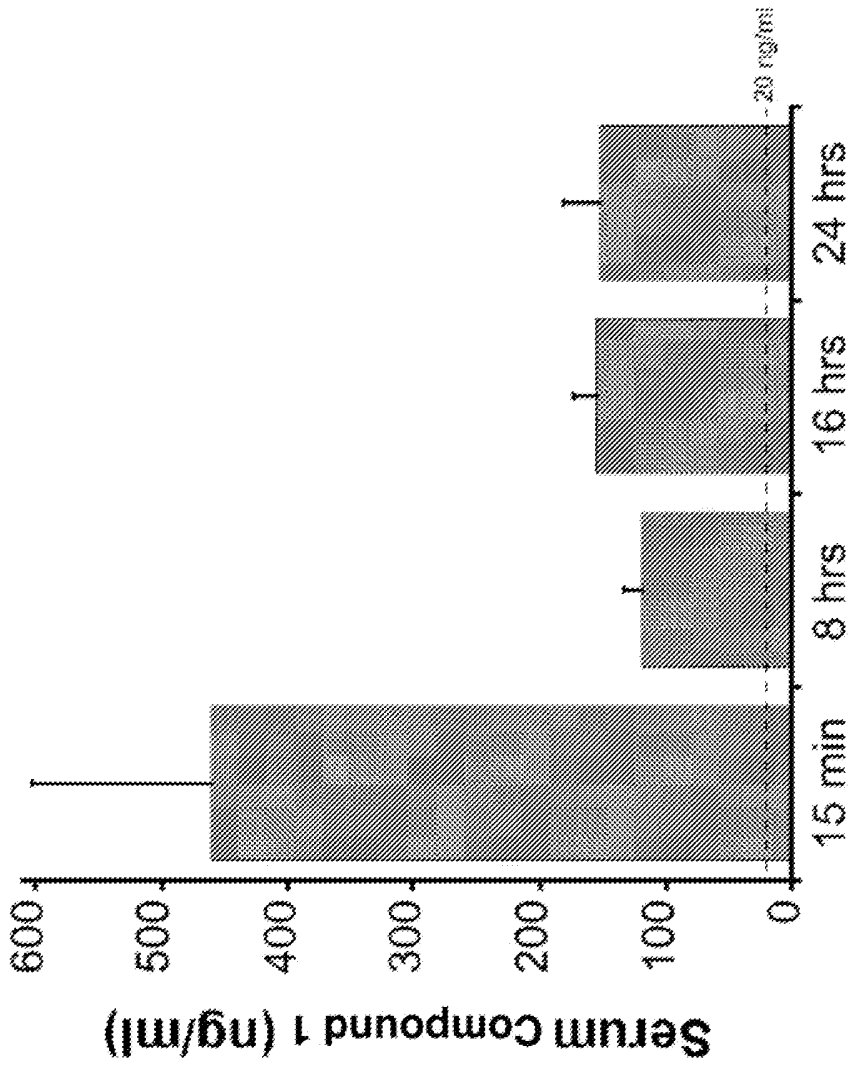

Serum Compound 1 (ng/ml)
600
500
400
300
200
100
0
15 min
8 hrs
16 hrs
24 hrs
20 ng/ml

FIGURE 10

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 May 2015 (14.05.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/069956 A3

(51) **International Patent Classification**:
*A61K 31/167* (2006.01)

(21) **International Application Number**:
PCT/US2014/064441

(22) **International Filing Date**:
6 November 2014 (06.11.2014)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:

| | | |
|---|---|---|
| 61/900,878 | 6 November 2013 (06.11.2013) | US |
| 61/900,946 | 6 November 2013 (06.11.2013) | US |
| 61/900,919 | 6 November 2013 (06.11.2013) | US |

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(74) **Agent**: **JONES, Marya K.**; HOXIE & ASSOCIATES, LLC, 75 Main Street, Suite 203, Millburn, New Jersey 07041 (US).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

*[Continued on next page]*

(54) **Title**: NOVEL FORMULATIONS

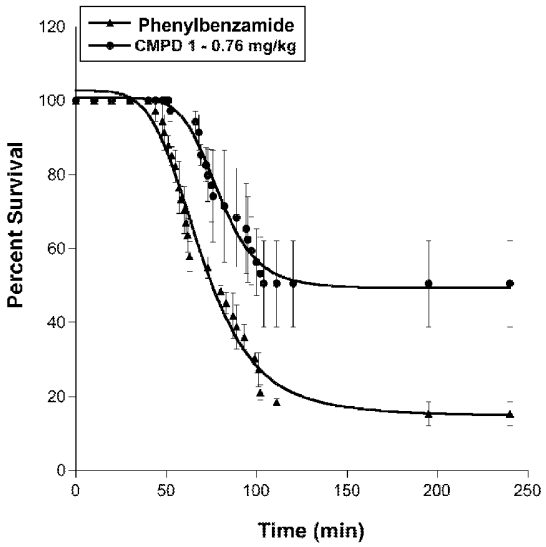


FIGURE 1

(57) **Abstract**: Provided are novel formulations of 2-{ [3,5-bis( trifluoromethyl)phenyl ]carbamoyl} -4-chlorophenyl dihydrogen phosphate as described below and uses thereof. Also provided are kits comprising 2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-4-chlorophenyl dihydrogen phosphate. Also provided is a method of treating or controlling a disease or condition mediated by an aquaporin, e.g., diseases or conditions of water imbalance and other diseases.

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**Published**:

— *with international search report (Art. 21(3))*

**(88) Date of publication of the international search report**:
12 November 2015

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/064441

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/167 (2015.01)
CPC - A61K 31/167 (2014.11)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 31/167, 31/24, 31/5375, 31/661, 31/6615 (2015.01)
CPC - A61K 31/167, 31/24, 31/5375, 31/661, 31/6615 (2014.11) (keyword delimited)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/235.2, 544/124, 139 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Orbit, Google Patents, STN, Google, PubChem, SureChem
Search terms used: Meglumine, phenyl, tris hydroxymethyl

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br>---<br>Y | US 2006/0094718 A1 (MUTO et al) 04 May 2006 (04.05.2006) entire document | 1-4, 47, 49, 51, 52, 59, 60<br>---<br>48, 50, 62, 84-86 |
| Y | RASLAN et al. Medical Management of Cerebral Edema. Neurosurg Focus. 22(5):E12, 2007. [Retrieved on 02 January 2015]. Retrieved from the Internet. <URL: http://www.medscape.com/viewarticle/559004_6>. entire document | 48, 62, 84-86 |
| Y | INTERVET. Banamine (flunixin meglumine). 2011. [Retrieved on 02 January 2015]. Retrieved from the Internet. <URL: https://web.archive.org/web/20110711140225/http://www.banamine.com/research/FlunixinMeglumine.asp>. entire document | 50 |
| X, P | WO 2013/169939 A2 (AEROMICS LLC) 14 November 2013 (14.11.2013) entire document | 1-4, 47-52, 59-62, 84-86 |

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 06 January 2015 | 13 FEB 2015 |

| Name and mailing address of the ISA/US | Authorized officer: |
|---|---|
| Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | Blaine R. Copenheaver<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

Form PCT/ISA/210 (second sheet) (July 2009)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/064441

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 5-46, 53-58, 63-83, 87
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

# 摘要

本发明提供了如下描述的 2-{[3,5-双(三氟甲基)苯基]氨基甲酰基}-4-氯苯基磷酸二氢酯的新型制剂及其应用。