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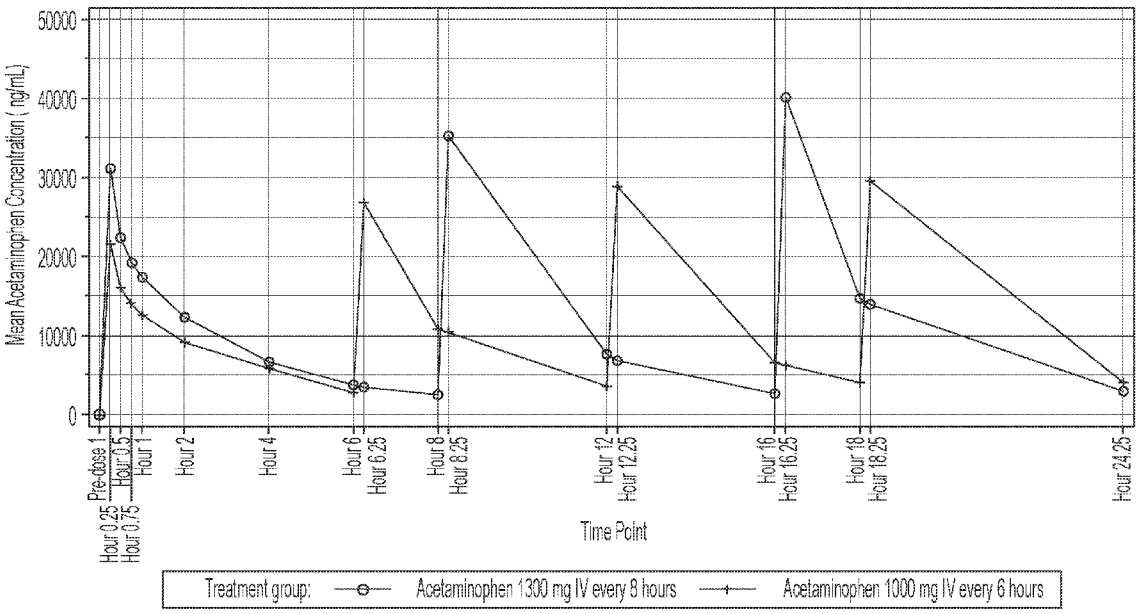

FIG. 1

(57) Abstract: Compositions, unit dosage forms thereof, and methods of use thereof for the treatment of pain are presented. The pharmaceutical compositions can contain a non-opioid analgesic and can be administered prior to surgery to reduce postoperative pain.

[Continued on next page]

WO 2022/178018 A1

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LIQUID UNIT DOSAGE FORMS FOR TREATMENT OF PAIN

[0001] This application claims priority to our copending US Provisional patent application with the serial number 63/151,265, filed 2/19/2021, incorporated by reference herein.

Field of the Invention

[0002] The field of the invention is compositions and methods of treating pain, and especially as it relates to treatment of pain using parenteral administration of acetaminophen from a single use container to a subject in need thereof.

Background of the Invention

[0003] The background description includes information that may be useful in understanding the present invention. It is not an admission that any of the information provided herein is prior art or relevant to the presently claimed invention, or that any publication specifically or implicitly referenced is prior art.

[0004] All publications and patent applications herein are incorporated by reference to the same extent as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Where a definition or use of a term in an incorporated reference is inconsistent or contrary to the definition of that term provided herein, the definition of that term provided herein applies and the definition of that term in the reference does not apply.

[0005] Pain management can involve the use of opioids or non-steroidal inflammatory drugs (NSAIDs) following surgery. However, the use of opioids or opioid-derived analgesics can lead to undesirable side effects including, for example, nausea, vomiting, constipation, and poor respiratory function. On the other hand, while NSAIDs are often used to control or reduce pain, significant side effects (*e.g.*, gastric upset, bleeding, and ulcers) can occur, particularly when administered at relatively high dosages and/or over extended periods of time. Notably, acetaminophen is a non-NSAID and non-opioid analgesic with a favorable safety profile at low dosages. However, the total daily dose for acetaminophen administration has been limited to 4,000 mg due to its potential hepatotoxic effect. Most commonly, acetaminophen is available in an oral tablet or capsule over the counter format for mild to moderate pain. However, such dosage form often performs less desirably where the pain is more severe such as for example, with post-operative pain after surgery. Among other reasons, the acetaminophen concentration

in cerebrospinal fluid after oral administration is typically significantly lower as compared to administration of the same dose by infusion.

[0006] Acetaminophen is also available in a liquid formulation for injection/infusion and a typical schedule of administration is infusion of 1,000 mg 4 times a day at 6 hour intervals. While such administration is common in various point-of care settings, the relatively high frequency of administration and accompanying administrative and billing generates a significant burden on personnel.

[0007] Thus, even though various systems and methods of pain management using acetaminophen are known in the art, all or almost all of them suffer from several drawbacks. Among other problems, oral dosing typically limits the drug concentration in cerebrospinal fluid to less than desirable levels, even at dosages as high as the daily maximum dose of 4,000mg, while administration via infusion adds to an already significant burden on care givers due to the frequent administration schedule. Therefore, there remains a need for improved compositions and methods for pain management, especially where the analgesic is acetaminophen and where the acetaminophen is administered by injection/infusion such as from a single use container at a ready-to-use concentration.

Summary of The Invention

[0008] The inventive subject matter is directed to various compositions and methods of parenteral administration of acetaminophen form a single use container at a ready-to-use concentration that does not require dilution or preparation of an injectable formulation. Most notably, the inventors discovered that a desirable pain relief could be achieved where a reduced schedule of administration (*e.g.*, 3 times per day at 8 hours intervals) was employed using somewhat higher concentrations (*e.g.*, about 1,300 mg) of acetaminophen.

[0009] In some embodiments, the invention provides a method of treating pain in a subject in need thereof, the method comprising administering to the subject a therapeutically-effective amount of a liquid unit dosage form, wherein the liquid unit dosage form comprises acetaminophen in an amount from about 1100 mg to about 1500 mg, wherein the administration of the liquid unit dosage form is from a single use container.

[0010] In some embodiments, the invention provides a method of treating pain in a subject in need thereof, the method comprising administering to the subject about 1300 mg

acetaminophen in a liquid unit dosage form about every 8 hours via intravenous injection, wherein the administration of the liquid unit dosage form is from a single use container.

[0011] For example, in one aspect of the inventive subject matter, the inventors contemplate a method of treating pain in a subject in need thereof that includes a step of administering to the subject a therapeutically-effective amount of a liquid unit dosage form, wherein the liquid unit dosage form comprises acetaminophen in an amount from about 1100 mg to about 1500 mg, and wherein the administration of the liquid unit dosage form is from a single use container.

[0012] In some embodiments, the liquid unit dosage form comprises acetaminophen in an amount from about 1200 mg to about 1400 mg (*e.g.*, about 1300 mg). Most typically, but not necessarily, the pain is dental pain, and/or the liquid unit dosage form is administered to the subject from one to three times per day. Furthermore, it is contemplated that the liquid unit dosage form is administered to the subject within 24 hours prior to the subject undergoing a surgical procedure, simultaneously with the subject undergoing a surgical procedure, and/or within 24 hours after the subject has undergone a surgical procedure. In preferred aspects the administration is parenteral administration, and especially intravenous administration.

[0013] In further embodiments, the liquid unit dosage form has an acetaminophen concentration of between 5-15 mg/mL (*e.g.*, about 10 mg/mL), and/or the liquid unit dosage form has a total volume of between 100 mL and 150 mL (*e.g.*, about 130 mL). It is also contemplated that the single use container is a polymer bag, which may be packaged in an aluminized over-pouch. The aluminum overwrap can optionally also contain an oxygen scavenger.

[0014] Therefore, one exemplary method of treating pain in a subject in need thereof may include a step of administering to the subject about 1300 mg acetaminophen in a liquid unit dosage form about every 8 hours via intravenous injection, wherein the administration of the liquid unit dosage form is from a single use container. Preferably, but not necessarily, the liquid unit dosage form is administered (*e.g.*, post-operatively) at a volume of about 130 mL.

[0015] Various objects, features, aspects, and advantages of the inventive subject matter will become more apparent from the following detailed description of preferred embodiments, along with the accompanying drawing figures in which like numerals represent like components.

Brief Description of The Drawing

[0016] **FIG.1** is a chart that depicts the average blood plasma concentration of acetaminophen over a period of 24 hours in patients administered 1300 mg acetaminophen IV every 8 hours or 1000 mg acetaminophen IV every 6 hours.

Detailed Description

[0017] The present application relates to methods for treatment of postoperative pain in a subject in need thereof. After surgery, patients can suffer from severe pain that can persist for days, weeks, or months. Postoperative pain can be managed by administering to the patient, for example, centrally-acting μ-opioid analgesics or non-opioid analgesics. However, the occurrence of undesirable side effects can lead to reduced patient compliance and ineffective pain treatment. The present application also describes unit dosage forms, pharmaceutical formulations, and methods of use thereof to alleviate postoperative pain by, for example, preoperatively administering the pharmaceutical formulation to the patient. A pharmaceutical formulation described herein can also reduce postoperative opioid consumption by a patient who has been administered the pharmaceutical formulation.

[0018] Unit dosage forms of the present disclosure can be administered with less frequency compared to other forms while providing similar efficacy for relief of postoperative pain, thereby reducing administrative burden and patient treatment time as compared to traditional modes of administration. Such advantage is especially beneficial in point-of-care settings such as hospital or at-home-care where nurses or other qualified medical personnel administer drugs for pain relief to a patient.

Pain.

[0019] The present disclosure provides pharmaceutical compositions for the treatment of pain.

[0020] Pain can be, for example, mild, moderate, severe, or agonizing. The pain of a subject can be assessed using a numeric scale, in which a patient can self-report pain on a scale from 0-10, where 0 indicates no pain, 1-3 suggests mild pain, 4-6 indicates moderate pain, and 7-10 suggests severe and disabling pain.

[0021] Pain of the subject can also be self-reported on a scale from 0-3, where 0 indicates no pain, 1 indicates mild pain, 2 indicates moderate pain, and 3 indicates severe pain.

[0022] Pain relief provided by a pharmaceutical composition or unit dosage form of the present disclosure can be evaluated using a numeric scale, in which a subject can self-report perceived pain relief on a scale from 0-4, where 0 indicates no pain relief, 1 indicates mild pain relief, 2 suggests some pain relief, 3 indicates considerable pain relief, and 4 indicates complete pain relief.

[0023] Pain can include, for example, angina pain, bone injury pain, central pain, chronic lower back pain, cluster headaches, dental pain, genitourinary tract- related pain including cystitis and nociceptive pain, herpes neuralgia, migraine, neuropathic pain, pain during labor and delivery, pain resulting from burns, phantom limb pain, postoperative pain, postpartum pain, surgical pain, renal colic pain, pain associated with fractures, pain associated with soft tissue injury, pain associated with would bandage changes, pain associated with joint dislocations, or visceral pain. In some embodiments, the pain is postoperative pain.

[0024] The pain can be chronic or acute. Postoperative pain can describe that occurs after a surgery and can be a direct or indirect result of the surgery.

[0025] A pharmaceutical formulation described herein can be administered to the patient during or prior to surgery to treat, for example, acute postoperative pain. The postoperative pain can be reduced by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 99%. The reduction is postoperative pain can happen after about 10 minutes, about 20 minutes, about 30 minutes, about 40 minutes, about 50 minutes, about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 8 hours, about 10 hours, or about 12 hours after the surgery.

[0026] A pharmaceutical formulation described herein can be administered to a subject disclosed herein to treat pain. The pain can be reduced by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 99%.

[0027] Time between administration of a pharmaceutical composition of the disclosure and onset of pain relief can be self-reported by the subject, in which the subject is given a stopwatch and asked to press the stopwatch when the subject first perceives any pain relief. The time to

onset of pain relief in subjects administered a pharmaceutical composition of the disclosure can be, for example, about 0.05 hours to about 2 hours, about 0.05 hours to about 1.75 hours, about 0.05 hours to about 1.5 hours, about 0.05 hours to about 1.25 hours, about 0.05 hours to about 1 hour, about 0.05 hours to about 0.75 hours, about 0.05 hours to about 0.25 hours, about 0.1 hours to about 0.25 hours, about 0.15 hours to about 0.25 hours, about 0.1 hours to about 0.2 hours, about 0.1 hours to about 0.18 hours, about 0.14 hours to about 0.23 hours, about 0.1 hours to about 0.23 hours, about 0.15 hours to about 0.23 hours, about 0.2 hours to about 0.25 hours, or about 0.2 hours to about 0.23 hours. In some embodiments, the subject self-reports pain of 2 on a scale from 0-3 before administration. In some embodiments, the subject self-reports pain of 3 on a scale from 0-3 before administration.

Non-Opioid Analgesic.

[0028] The present disclosure provides pharmaceutical formulations containing, for example, a non-opioid analgesic. A non-opioid analgesic can include, for example, an NSAID, an anti-convulsant, an anti-pyretic, acetylsalicylic acid, or acetaminophen (N-(4-hydroxyphenyl)acetamide); paracetamol; N-acetyl-para-aminophenol). Acetaminophen is an anti-pyretic agent, and can be used to treat mild to moderate pain in adults and children.

[0029] In some embodiments, a non-opioid analgesic in a pharmaceutical formulation described herein is acetaminophen.

[0030] The non-opioid analgesic can be, for example, aceclofenac, acemetacin, acetaminophen, acetylsalicylic acid, amoxiprin, azapropazone, benorilate, bromfenac, carprofen, choline magnesium salicylate, diflunisal, diclofenac, etodolac, faislamine, fenbuprofen, flubiprofen, ibuprofen, indometacin, ketaprofen, ketorolac, lomoxicam, loxoprofen, magnesium salicylate, meclofenamic, mefenamic acid, meloxicam, metamizole, methyl salicylate, nabumetone, naproxen, oxyphenbutazone, piroxicam, phenylbutazone, sulfinprazone, sulindac, suprofen, tenoxicam, tolmetin, or a pharmaceutically acceptable salt of any of the foregoing, or any combination thereof.

Pharmaceutically-Acceptable Salts.

[0031] The present disclosure provides the use of pharmaceutically-acceptable salts of any compound described herein. Pharmaceutically-acceptable salts include, for example, acid-addition salts and base-addition salts. The acid that is added to the compound to form an acid-

addition salt can be an organic acid or an inorganic acid. A base that is added to the compound to form a base-addition salt can be an organic base or an inorganic base. In some embodiments, a pharmaceutically-acceptable salt is a metal salt. In some embodiments, a pharmaceutically-acceptable salt is an ammonium salt.

[0032] Metal salts can arise from the addition of an inorganic base to a compound of the present disclosure. The inorganic base consists of a metal cation paired with a basic counterion, such as, for example, hydroxide, carbonate, bicarbonate, or phosphate. The metal can be an alkali metal, alkaline earth metal, transition metal, or main group metal. In some embodiments, the metal is lithium, sodium, potassium, cesium, cerium, magnesium, manganese, iron, calcium, strontium, cobalt, titanium, aluminum, copper, cadmium, or zinc.

[0033] In some embodiments, a metal salt is a lithium salt, a sodium salt, a potassium salt, a cesium salt, a cerium salt, a magnesium salt, a manganese salt, an iron salt, a calcium salt, a strontium salt, a cobalt salt, a titanium salt, an aluminum salt, a copper salt, a cadmium salt, or a zinc salt.

[0034] Ammonium salts can arise from the addition of ammonia or an organic amine to a compound of the present disclosure. In some embodiments, the organic amine is triethyl amine, diisopropyl amine, ethanol amine, diethanol amine, triethanol amine, morpholine, *N*-methylmorpholine, piperidine, *N*-methylpiperidine, *N*-ethylpiperidine, dibenzylamine, piperazine, pyridine, pyrazole, pyrrole, imidazole, or pyrazine.

[0035] In some embodiments, an ammonium salt is a triethyl amine salt, a trimethyl amine salt, a diisopropyl amine salt, an ethanol amine salt, a diethanol amine salt, a triethanol amine salt, a morpholine salt, an N-methylmorpholine salt, a piperidine salt, an N-methylpiperidine salt, an N-ethylpiperidine salt, a dibenzylamine salt, a piperazine salt, a pyridine salt, a pyrazole salt, a pyridazine salt, pyrrole salt, a pyrimidine salt, an imidazole salt, or a pyrazine salt.

[0036] Acid addition salts can arise from the addition of an acid to a compound of the present disclosure. In some embodiments, the acid is organic. In some embodiments, the acid is inorganic. In some embodiments, the acid is hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid, nitrous acid, sulfuric acid, sulfurous acid, a phosphoric acid, isonicotinic acid, lactic acid, salicylic acid, tartaric acid, ascorbic acid, gentisic acid, gluconic acid, glucuronic acid, saccharic acid, formic acid, benzoic acid, glutamic acid, pantothenic acid, acetic acid,

propionic acid, butyric acid, fumaric acid, succinic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, citric acid, oxalic acid, or maleic acid.

[0037] In some embodiments, the salt is a hydrochloride salt, a hydrobromide salt, a hydroiodide salt, a nitrate salt, a nitrite salt, a sulfate salt, a sulfite salt, a phosphate salt, isonicotinate salt, a lactate salt, a salicylate salt, a tartrate salt, an ascorbate salt, a gentisate salt, a gluconate salt, a glucuronate salt, a saccharate salt, a formate salt, a benzoate salt, a glutamate salt, a pantothenate salt, an acetate salt, a propionate salt, a butyrate salt, a fumarate salt, a succinate salt, a methanesulfonate salt, an ethanesulfonate salt, a benzenesulfonate salt, a p-toluenesulfonate salt, a citrate salt, an oxalate salt, or a maleate salt.

Formulations.

[0038] A pharmaceutical formulation of the disclosure can provide a therapeutically-effective amount of any compound disclosed herein. A pharmaceutical formulation of the disclosure can provide a therapeutically-effective amount of a non-opioid analgesic. In some embodiments, the additional non-opioid analgesic is acetaminophen.

[0039] The disclosed formulations can contain one or more pharmaceutically-acceptable agents, which alone or in combination solubilize a compound herein or a pharmaceutically-acceptable salt thereof. In some embodiments, the pharmaceutically-acceptable agent is a buffer. In some embodiments, the pharmaceutically-acceptable agent is a citrate buffer. In some embodiments, the pharmaceutically-acceptable agent is a phosphate buffer. In some embodiments, the pharmaceutically-acceptable agent is an acetate buffer. A buffer as described herein can be formed from a solution containing, for example, an acid and a conjugate base of the acid, or a base and a conjugate acid of the base. The acid in a buffer described herein can be a weak acid. A base in a buffer described herein can be a weak base. Any formulation described herein can contain, for example, an acid, and a conjugate base of the acid, or a base, and a conjugate acid of the base.

[0040] A formulation described herein can contain an isotonicity inducing agent. The isotonicity inducing agent can be, for example, sodium chloride or mannitol or dextrose.

[0041] In some embodiments, a compound disclosed herein or pharmaceutically-acceptable salt thereof is present in a formulation in an amount of from about 0.01 mg/mL to about 100 mg/mL, from about 0.1 mg/mL to about 1 mg/mL, from about 0.01 mg/mL to about 5 mg/mL,

from about 5 mg/mL to about 10 mg/mL, from about 10 mg/mL to about 15 mg/mL, from about 15 mg/mL to about 20 mg/mL, from about 20 mg/mL to about 25 mg/mL, from about 25 mg/mL to about 30 mg/mL, from about 30 mg/mL to about 35 mg/mL, from about 35 mg/mL to about 40 mg/mL, from about 40 mg/mL to about 45 mg/mL, about 45 mg/mL to about 50 mg/mL, from about 50 mg/mL to about 55 mg/mL, from about 55 mg/mL to about 60 mg/mL, from about 60 mg/mL to about 65 mg/mL, from about 65 mg/mL to about 70 mg/mL, from about 70 mg/mL to about 75 mg/mL, about 75 mg/mL to about 80 mg/mL, from about 80 mg/mL to about 85 mg/mL, from about 85 mg/mL to about 90 mg/mL, from about 90 mg/mL to about 95 mg/mL, or from about 95 mg/mL to about 100 mg/mL. The compound can be, for example, acetaminophen.

[0042] In some embodiments, a compound disclosed herein or pharmaceutically-acceptable salt thereof is present in a formulation in an amount of about 1 mg/mL, about 2 mg/mL, about 3 mg/mL, about 4 mg/mL, about 5 mg/mL, about 6 mg/mL, about 7 mg/mL, about 8 mg/mL, about 9 mg/mL, about 10 mg/mL, about 11 mg/mL, about 12 mg/mL, about 13 mg/mL, about 14 mg/mL, about 15 mg/mL, about 16 mg/mL, about 17 mg/mL, about 18 mg/mL, about 19 mg/mL, about 20 mg/mL, about 21 mg/mL about 22 mg/mL, about 23 mg/mL, about 24 mg/mL, about 25 mg/mL, about 26 mg/mL, about 27 mg/mL, about 28 mg/mL, about 29 mg/mL, about 30 mg/mL, about 31 mg/mL about 32 mg/mL, about 33 mg/mL, about 34 mg/mL, about 35 mg/mL, about 36 mg/mL, about 37 mg/mL, about 38 mg/mL, about 39 mg/mL, about 40 mg/mL, about 41 mg/mL about 42 mg/mL, about 43 mg/mL, about 44 mg/mL, about 45 mg/mL, about 46 mg/mL, about 47 mg/mL, about 48 mg/mL, about 49 mg/mL, about 50 mg/mL, about 51 mg/mL about 52 mg/mL, about 53 mg/mL, about 54 mg/mL, about 55 mg/mL, about 56 mg/mL, about 57 mg/mL, about 58 mg/mL, about 59 mg/mL, about 60 mg/mL, about 61 mg/mL about 62 mg/mL, about 63 mg/mL, about 64 mg/mL, about 65 mg/mL, about 66 mg/mL, about 67 mg/mL, about 68 mg/mL, about 69 mg/mL, about 70 mg/mL, about 71 mg/mL about 72 mg/mL, about 73 mg/mL, about 74 mg/mL, about 75 mg/mL, about 76 mg/mL, about 77 mg/mL, about 78 mg/mL, about 79 mg/mL, about 80 mg/mL, about 81 mg/mL about 82 mg/mL, about 83 mg/mL, about 84 mg/mL, about 85 mg/mL, about 86 mg/mL, about 87 mg/mL, about 88 mg/mL, about 89 mg/mL, about 90 mg/mL, about 91 mg/mL about 92 mg/mL, about 93 mg/mL, about 94 mg/mL, about 95 mg/mL, about 96 mg/mL, about 97 mg/mL, about 98 mg/mL, about 99 mg/mL, or about 100 mg/mL. The compound can be, for example, acetaminophen.

[0043] A pharmaceutical formulation described herein can contain, for example, acetaminophen, sodium chloride, and citric acid monohydrate. The pharmaceutical formulation can be at, for example, pH 5, 5.5, or 6. In some embodiments, the pH of the pharmaceutical formulation is 5.5. In some embodiments, the pH of the pharmaceutical formulation is 6. The acetaminophen can be present in the pharmaceutical formulation at a concentration of about 5 mg/mL, about 6 mg/mL, about 7 mg/mL, about 8 mg/mL, about 9 mg/mL, or about 10 mg/mL. In some embodiments, the acetaminophen is present in the pharmaceutical formulation at a concentration of 10 mg/mL. The sodium chloride can be present in the pharmaceutical formulation at a concentration of about 4 mg/mL, about 4.5 mg/mL, about 5 mg/mL, about 5.5 mg/mL, or about 6 mg/mL. In some embodiments, the sodium chloride is present in the pharmaceutical formulation at a concentration of 5 mg/mL. In some embodiments, the sodium chloride is present in the pharmaceutical formulation at a concentration of 4.5 mg/mL. The citric acid monohydrate can be present in the pharmaceutical formulation at a concentration of about 2 mg/mL, about 2.05 mg/mL, about 2.1 mg/mL, about 2.101 mg/mL, about 2.102 mg/mL, about 2.103 mg/mL, about 2.014 mg/mL, about 2.105 mg/mL, about 2.11 mg/mL, about 2.15 mg/mL, or about 2.2 mg/mL. In some embodiments, the citric acid monohydrate is present in the pharmaceutical formulation at a concentration of 2.101 mg/mL.

[0044] A pharmaceutical formulation described herein can contain, for example, acetaminophen, sodium chloride, and acetic acid. The pharmaceutical formulation can be at, for example, pH 5, 5.5, or 6. In some embodiments, the pH of the pharmaceutical formulation is 5.5. The acetaminophen can be present in the pharmaceutical formulation at a concentration of about 5 mg/mL, about 6 mg/mL, about 7 mg/mL, about 8 mg/mL, about 9 mg/mL, or about 10 mg/mL. In some embodiments, the acetaminophen is present in the pharmaceutical formulation at a concentration of 10 mg/mL. The sodium chloride can be present in the pharmaceutical formulation at a concentration of about 4 mg/mL, about 4.5 mg/mL, about 5 mg/mL, about 5.5 mg/mL, or about 6 mg/mL. In some embodiments, the sodium chloride is present in the pharmaceutical formulation at a concentration of 5 mg/mL. The acetic acid can be present in the pharmaceutical formulation at a concentration of about 0.5 mg/mL, about 0.6 mg/mL, about 0.7 mg/mL, about 0.8 mg/mL, about 0.9 mg/mL, or about 1 mg/mL. In some embodiments, the acetic acid is present in the pharmaceutical formulation at a concentration of 0.6 mg/mL.

[0045] A pharmaceutical formulation described herein can contain, for example, acetaminophen, sodium chloride, and citric acid. The pharmaceutical formulation can be at, for example, pH 5, 5.5, or 6. In some embodiments, the pH of the pharmaceutical formulation is 6. The acetaminophen can be present in the pharmaceutical formulation at a concentration of about 5 mg/mL, about 6 mg/mL, about 7 mg/mL, about 8 mg/mL, about 9 mg/mL, or about 10 mg/mL. In some embodiments, the acetaminophen is present in the pharmaceutical formulation at a concentration of 10 mg/mL. The sodium chloride can be present in the pharmaceutical formulation at a concentration of about 3.5 mg/mL, 4 mg/mL, about 4.5 mg/mL, about 5 mg/mL, about 5.5 mg/mL, about 6 mg/mL, about 6.5 mg/mL, about 7 mg/mL or about 7.5 mg/mL. In some embodiments, the sodium chloride is present in the pharmaceutical formulation at a concentration of 5.5 mg/mL. The citric acid can be present in the pharmaceutical formulation at a concentration of about1 mg/mL, about 0.1 mg/mL, 0.2 mg/mL, 0.3 mg/mL, 0.4mg/mL, 0.5 mg/mL, 0.6 mg/mL, 0.7 mg/mL, 0.8 mg/mL, 0.9 mg/mL, 1 mg/mL, 1.1 mg/mL, about 1.2 mg/mL, about 1.3 mg/mL, about 1.4 mg/mL, about 1.5 mg/mL, about 1.6 mg/mL, about 1.7 mg/mL, about 1.8 mg/mL, about 1.9 mg/mL, or about 2 mg/mL. In some embodiments, the citric acid is present in the pharmaceutical formulation at a concentration of 1.2 mg/mL.

[0046] Sodium chloride can be a present in a pharmaceutical formulation described herein at a concentration of about 0.1 mg/mL, about 0.2 mg/mL, about 0.3 mg/mL, about 0.4 mg/mL, about 0.5 mg/mL, about 0.6 mg/mL, about 0.7 mg/mL, about 0.8 mg/mL, about 0.9 mg/mL, about 1 mg/mL, about 1.1 mg/mL, about 1.2 mg/mL, about 1.3 mg/mL, about 1.4 mg/mL, about 1.5 mg/mL, about 1.6 mg/mL, about 1.7 mg/mL, about 1.8 mg/mL, about 1.9 mg/mL, about 2 mg/mL, about 2.1 mg/mL, about 2.2 mg/mL, about 2.3 mg/mL, about 2.4 mg/mL, about 2.5 mg/mL, about 2.6 mg/mL, about 2.7 mg/mL, about 2.8 mg/mL, about 2.9 mg/mL, about 3 mg/mL, about 3.1 mg/mL, about 3.2 mg/mL, about 3.3 mg/mL, about 3.4 mg/mL, about 3.5 mg/mL, about 3.6 mg/mL, about 3.7 mg/mL, about 3.8 mg/mL, about 3.9 mg/mL, about 4 mg/mL, about 4.1 mg/mL, about 4.2 mg/mL, about 4.3 mg/mL, about 4.4 mg/mL, about 4.5 mg/mL, about 4.6 mg/mL, about 4.7 mg/mL, about 4.8 mg/mL, about 4.9 mg/mL, about 5 mg/mL, about 5.1 mg/mL, about 5.2 mg/mL, about 5.3 mg/mL, about 5.4 mg/mL, about 5.5 mg/mL, about 5.6 mg/mL, about 5.7 mg/mL, about 5.8 mg/mL, about 5.9 mg/mL, or about 6 mg/mL. Sodium chloride can be present in a pharmaceutical formulation described herein at a concentration from about 0.1 mg/mL to about 0.5 mg/mL, about 0.2 mg/mL to about 0.6 mg/mL, about 0.3 mg/mL to about 0.7 mg/mL, about 0.4 mg/mL to about 0.8 mg/mL, about

0.5 mg/mL to about 1 mg/mL, about 0.6 mg/mL to about 1.1 mg/mL, about 0.7 mg/mL to about 1.2 mg/mL, about 0.8 mg/mL to about 1.3 mg/mL, about 0.9 mg/mL to about 1.4 mg/mL, about 1 mg/mL to about 1.5 mg/mL, about 1.1 mg/mL to about 1.6 mg/mL, about 1.2 mg/mL to about 1.7 mg/mL, about 1.3 mg/mL to about 1.8 mg/mL, about 1.4 mg/mL to about 1.9 mg/mL, about 1.5 mg/mL to about 2 mg/mL, about 1.6 mg/mL to about 2.1 mg/mL, about 2.2 mg/mL to about 2.7 mg/mL, about 2.3 mg/mL to about 2.8 mg/mL, about 2.4 mg/mL to about 2.9 mg/mL, about 2.5 mg/mL to about 3 mg/mL, about 2.6 mg/mL, about 3.1 mg/mL, about 2.7 mg/mL to about 3.2 mg/mL, about 2.8 mg/mL to about 3.3 mg/mL, about 2.9 mg/mL to about 3.4 mg/mL, about 3 mg/mL to about 3.5 mg/mL, about 3.1 mg/mL to about 3.6 mg/mL, about 3.2 mg/mL to about 3.7 mg/mL, about 3.3 mg/mL to about 3.8 mg/mL, about 3.4 mg/mL to about 3.9 mg/mL, about 3.5 mg/mL to about 4 mg/mL, about 3.6 mg/mL to about 4.1 mg/mL, about 3.7 mg/mL to about 4.2 mg/mL, about 3.8 mg/mL to about 4.3 mg/mL, about 3.9 mg/mL to about 4.4 mg/mL, about 4 mg/mL to about 4.5 mg/mL, about 4.1 mg/mL to about 4.6 mg/mL, about 4.2 mg/mL to about 4.7 mg/mL, about 4.3 mg/mL to about 4.8 mg/mL, about 4.4 mg/mL to about 4.9 mg/mL, about 4.5 mg/mL to about 5 mg/mL, about 4.6 mg/mL to about 5.1 mg/mL, about 4.7 mg/mL to about 5.2 mg/mL, about 4.8 mg/mL to about 5.3 mg/mL, about 4.9 mg/mL to about 5.4 mg/mL, about 5 mg/mL to about 5.5 mg/mL, about 5.1 mg/mL to about 5.6 mg/mL, about 5.2 mg/mL to about 5.7 mg/mL, about 5.3 mg/mL to about 5.8 mg/mL, about 5.4 mg/mL to about 5.9 mg/mL, or about 5.5 mg/mL to about 6 mg/mL.

[0047] l-Histidine can be present in a pharmaceutical formulation described herein at a concentration from about 0.1 mg/mL to about 6 mg/mL. Citric acid monohydrate or sodium dihydrogen phosphate can be present in a pharmaceutical formulation described herein at a concentration from about 0.1 mg/mL to about 6 mg/mL. Acetic acid can be present in a pharmaceutical formulation described herein at a concentration of about 0.1 mg/mL to about 5 mg/mL.

[0048] A pharmaceutical agent that is disclosed herein can be made more soluble in a formulation by the addition of an additive or agent. The improvement of solubility of the formulation can increase by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75% about 80%, about 85%, about 90%, about 95%, about 100%, about 110%, about 120%, about 130%, about 140%, about 150%, about 160%, about 170%, about 180%,

about 190%, about 200%, about 225%, about 250%, about 275%, about 300%, about 325%, about 350%, about 375%, about 400%, about 450%, or about 500%.

[0049] Pharmaceutical compositions described herein can be used, stored, tested, analyzed or assayed at any suitable temperature. Non-limiting examples of temperatures include about 0 °C, about 1 °C, about 2 °C, about 3 °C, about 4 °C, about 5 °C, about 6 °C, about 7 °C, about 8 °C, about 9 °C, about 10 °C, about 11 °C, about 12 °C, about 13 °C, about 14 °C, about 15 °C, about 16 °C, about 17 °C, about 18 °C, about 19 °C, about 20 °C, about 21 °C, about 22 °C, about 23 °C, about 24 °C, about 25 °C, about 26 °C, about 27 °C, about 28 °C, about 29 °C, about 30 °C, about 31 °C, about 32 °C, about 33 °C, about 34 °C, about 35 °C, about 36 °C, about 37 °C, about 38 °C, about 39 °C, about 40 °C, about 41 °C, about 42 °C, about 43 °C, about 44 °C, about 45 °C, about 46 °C, about 47 °C, about 48 °C, about 49 °C, about 50 °C, about 51 °C, about 52 °C, about 53 °C, about 54 °C, about 55 °C, about 56 °C, about 57 °C, about 58 °C, about 59 °C, about 60 °C, about 61 °C, about 62 °C, about 63 °C, about 64 °C, about 65 °C, about 66 °C, about 67 °C, about 68 °C, about 69 °C, about 70 °C, about 71 °C, about 72 °C, about 73 °C, about 74 °C, or about 75 °C.

[0050] Pharmaceutical compositions described herein can be used, stored, tested, analyzed or assayed at room temperature. The room temperature can be, for example, about 20.0 °C, about 20.1 °C, about 20.2 °C, about 20.3 °C, about 20.4 °C, about 20.5 °C, about 20.6 °C, about 20.7 °C, about 20.8 °C, about 20.9 °C, about 21.0 °C, about 21.1 °C, about 21.2 °C, about 21.3 °C, about 21.4 °C, about 21.5 °C, about 21.6 °C, about 21.7 °C, about 21.8 °C, about 21.9 °C, about 22.0 °C, about 22.1 °C, about 22.2 °C, about 22.3 °C, about 22.4 °C, about 22.5 °C, about 22.6 °C, about 22.7 °C, about 22.8 °C, about 22.9 °C, about 23.0 °C, about 23.1 °C, about 23.2 °C, about 23.3 °C, about 23.4 °C, about 23.5 °C, about 23.6 °C, about 23.7 °C, about 23.8 °C, about 23.9 °C, about 24.0 °C, about 24.1 °C, about 24.2 °C, about 24.3 °C, about 24.4 °C, about 24.5 °C, about 24.6 °C, about 24.7 °C, about 24.8 °C, about 24.9 °C, or about 25.0 °C.

[0051] A liquid unit dosage form described herein can be administered to the patient one time a day, two times a day, three times a day, four times a day, five times a day, six times a day, seven times a day, eight times a day, nine times a day, or ten times a day. In some embodiments, the liquid unit dosage form is administered to the patient three times per day. A liquid unit dosage form described herein can be administered four times a day at 1300 mg every 8 hours or 1000 mg every 6 hours or 650 mg every 4 hours. A dosage administered herein can be adjusted based upon a patient's weight.

[0052] The liquid unit dosage form can be administered from a container or vessel, which can be sealed. The container or vessel can maintain the sterility of, or reduce the likelihood of contamination of, the pharmaceutical formulation. A liquid unit dosage form described herein can be formulated as, for example, a single use dosage or a multiple use dosage. The container or vessel can be, for example, a glass vial, an ampoule, or a plastic flexible container. The plastic flexible container can be made of, for example, PVC (polyvinyl chloride), or polypropylene. A container can be a prefilled syringe. A container can be a glass vial.

[0053] In some embodiments, a liquid unit dosage form disclosed herein is administered to the patient from one single use container. In some embodiments, the single use container is a glass vial. In some embodiments, the single use container is a polymer bag. In some embodiments, the polymer bag is a polypropylene bag. In some embodiments, the liquid unit dosage form comprises about 10 mg/mL acetaminophen and is about 130 mL in volume. The bag, such as a polypropylene bag, can be further packaged in an aluminum or aluminized over-pouch. A unit dosage form described herein can be supplied, stored, or delivered in a vial, tube, container, bag, or vessel that is, for example, about 0.5 mL, about 1 mL, about 2 mL, about 3 mL, about 4 mL, about 5 mL, about 6 mL, about 7 mL, about 8 mL, about 9 mL, about 10 mL, about 11 mL, about 12 mL, about 13 mL, about 14 mL, about 15 mL, about 16 mL, about 17 mL, about 18 mL, about 19 mL, about 20 mL, about 25 mL, about 30 mL, about 35 mL, about 40 mL, about 45 mL, about 50 mL, about 60 mL, about 70 mL, about 80 mL, about 90 mL, about 100 mL, about 110 mL, about 120 mL, about 130 mL, about 140 mL, about 150 mL, about 200 mL, about 400 mL, about 600 mL, about 800 mL, about 1000, about 1100 mL, about 1200 mL, about 1300 mL, about 1400 mL, or about 1500 mL in volume.

[0054] A pharmaceutical formulation described herein can be stored as a liquid in an aliquot having a total volume of between about 1 and about 1500 mL, between about 110 and 140 mL, between about 80 mL and about 120 mL, between about 90 mL and about 110 mL, between about 120 mL and about 140 mL, between about 90 mL and about 140 mL, between about 1 and about 250 mL, between about 1 and about 200 mL, between about 1 and about 150 mL, between about 1 and about 125 mL, between about 1 and about 120 mL, between about 1 and about 110 mL, between about 1 and about 100 mL, between about 1 and about 90 mL, between about 1 and about 80 mL, between about 1 and about 70 mL, between about 1 and about 60 mL, between about 1 and about 50 mL, between about 1 and about 40 mL, between about 1

and about 30 mL, between about 1 and about 20 mL, between about 1 and about 10 mL, or between about 1 and about 5 mL.

Dosage Amounts.

[0055] In practicing the methods of treatment or use provided herein, therapeutically-effective amounts of the compounds described herein are administered in pharmaceutical compositions to a subject having a disease or condition to be treated. A therapeutically-effective amount can vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compounds used, and other factors. Subjects can be, for example, humans, elderly adults, adults, adolescents, pre-adolescents, children, toddlers, infants, or neonates. A subject can be a patient.

[0056] Pharmaceutical compositions described herein can be formulated in any suitable volume. The formulation volume can be, for example, about 0.1 mL, about 0.2 mL, about 0.3 mL, about 0.4 mL, about 0.5 mL, about 0.6 mL, about 0.7 mL, about 0.8 mL, about 0.9 mL, about 1 mL, about 1.1 mL, about 1.2 mL, about 1.3 mL, about 1.4 mL, about 1.5 mL, about 1.6 mL, about 1.7 mL, about 1.8 mL, about 1.9 mL, about 2 mL, about 2.1 mL, about 2.2 mL, about 2.3 mL, about 2.4 mL, about 2.5 mL, about 2.6 mL, about 2.7 mL, about 2.8 mL, about 2.9 mL, about 3 mL, about 3.1 mL, about 3.2 mL, about 3.3 mL, about 3.4 mL, about 3.5 mL, about 3.6 mL, about 3.7 mL, about 3.8 mL, about 3.9 mL, about 4 mL, about 4.1 mL, about 4.2 mL, about 4.3 mL, about 4.4 mL, about 4.5 mL, about 4.6 mL, about 4.7 mL, about 4.8 mL, about 4.9 mL, about 5 mL, about 5.1 mL, about 5.2 mL, about 5.3 mL, about 5.4 mL, about 5.5 mL, about 5.6 mL, about 5.7 mL, about 5.8 mL, about 5.9 mL, about 6 mL, about 6.1 mL, about 6.2 mL, about 6.3 mL, about 6.4 mL, about 6.5 mL, about 6.6 mL, about 6.7 mL, about 6.8 mL, about 6.9 mL, about 7 mL, about 7.1 mL, about 7.2 mL, about 7.3 mL, about 7.4 mL, about 7.5 mL, about 7.6 mL, about 7.7 mL, about 7.8 mL, about 7.9 mL, about 8 mL, about 8.1 mL, about 8.2 mL, about 8.3 mL, about 8.4 mL, about 8.5 mL, about 8.6 mL, about 8.7 mL, about 8.8 mL, about 8.9 mL, about 9 mL, about 9.1 mL, about 9.2 mL, about 9.3 mL, about 9.4 mL, about 9.5 mL, about 9.6 mL, about 9.7 mL, about 9.8 mL, about 9.9 mL, about 10 mL, about 11 mL, about 12 mL, about 13 mL, about 14 mL, about 15 mL, about 16 mL, about 17 mL, about 18 mL, about 19 mL, about 20 mL, about 30 mL, about 40 mL, about 50 mL, about 60 mL, about 70 mL, about 80 mL, about 90 mL, about 100 mL, about 110 mL, about 120 mL, about 130 mL, about 140 mL, about 150 mL, about 200 mL, about 300 mL, about 400 mL, about 500 mL, about 600 mL, about 700 mL, about 800 mL, about 900

mL, about 1000 mL, about 1100 mL, about 1200 mL, about 1300 mL, about 1400 mL, or about 1500 mL. The formulation volume can be, for example, about 0.1 mL to about 1500 mL, such as about 100 mL to about 1500 mL, about 20 mL to about 150 mL, about 40 mL to about 150 mL, about 60 mL to about 150 mL, about 80 mL to about 150 mL, about 100 mL to about 150 mL, about 110 mL to about 140 mL, about 120 mL to about 150 mL, about 120 mL to about 140 mL, about 80 mL to about 140 mL, about 80 mL to about 130 mL, about 90 mL to about 120 mL, or about 90 mL to about 110 mL.

[0057] A therapeutically-effective amount of a compound described herein can be present in a composition described herein at a mass of, for example, about 0.01 μg, about 0.05 μg, about 0.1 μg, about 0.15 μg, about 0.2 μg, about 0.25 μg, about 0.3 μg, about 0.35 μg, about 0.4 μg, about 0.5 μg, about 0.6 μg, about 0.7 μg, about 0.8 μg, about 0.9 μg, about 1 μg, about 2 μg, about 3 μg, about 4 μg, about 5 μg, about 10 μg, about 15 μg, about 20 μg, about 25 μg, about 30 μg, about 35 μg, about 40 μg, about 45 μg, about 50 μg, about 60 μg, about 70 μg, about 80 μg, about 90 μg, about 100 μg, about 125 μg, about 150 μg, about 175 μg, about 200 μg, about 250 μg, about 300 μg, about 350 μg, about 400 μg, about 450 μg, about 500 μg, about 600 μg, about 700 μg, about 800 μg, about 900 μg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg, about 1400 mg, or about 1500 mg. A therapeutically-effective amount of a compound described herein can be present in a composition described herein at a mass of, for example, about 0.01 μg to about 20 mg, about 0.01 μg to about 1 mg, about 0.01 μg to about 100 μg, about 0.01 μg to about 10 μg, about 0.1 μg to about 10 μg, about 1 μg to about 10 μg, about 500 μg, to about 1 mg, about 1 mg to about 20 mg, about 1 mg to about 10 mg, about 1 mg to about 5 mg, about 1 mg to about 2 mg, about 5 mg to about 20 mg, about 10 mg to about 20 mg, about 100 mg to about 1500 mg, about 200 mg to about 1500 mg, about 400 mg to about 1500 mg, about 600 mg to about 1500 mg, about 800 mg to about 1500 mg, about 1000 mg to about 1500 mg, about 1100 mg to about 1400 mg, about 1200 mg to about 1500 mg, about 1200 mg to about 1400 mg, about 800 mg to about 1400 mg, about 800 mg to about 1300 mg, about 900 mg to about 1200 mg, or about 900 mg to about 1100 mg. In some embodiments, the compound is acetaminophen.

[0058] A therapeutically-effective amount of a compound described herein can be present in a composition described herein at a concentration of, for example, about 0.001 mg/mL, about 0.002 mg/mL, about 0.003 mg/mL, about 0.004 mg/mL, about 0.005 mg/mL, about 0.006 mg/mL, about 0.007 mg/mL, about 0.008 mg/mL, about 0.009 mg/mL, about 0.01 mg/mL, about 0.02 mg/mL, about 0.03 mg/mL, about 0.04 mg/mL, about 0.05 mg/mL, about 0.06 mg/mL, about 0.07 mg/mL, about 0.08 mg/mL, about 0.09 mg/mL, about 0.1 mg/mL, about 0.2 mg/mL, about 0.25 mg/mL, about 0.3 mg/mL, about 0.4 mg/mL, about 0.5 mg/mL, about 0.6 mg/mL, about 0.7 mg/mL, about 0.8 mg/mL, about 0.9 mg/mL, about 1 mg/mL, about 1.5 mg/mL, about 2 mg/mL, about 2.5 mg/mL, about 3 mg/mL, about 3.5 mg/mL, about 4 mg/mL, about 4.5 mg/mL, about 5 mg/mL, about 6 mg/mL, about 7 mg/mL, about 8 mg/mL, about 9 mg/mL, about 10 mg/mL, about 15 mg/mL, about 20 mg/mL, about 25 mg/mL, about 30 mg/mL, about 35 mg/mL, about 40 mg/mL, about 45 mg/mL, about 50 mg/mL, about 60 mg/mL, about 70 mg/mL, about 80 mg/mL, about 90 mg/mL, or about 100 mg/mL. A therapeutically-effective amount of a compound described herein can be present in a composition described herein at a concentration of, for example, from about 0.1 mg/mL to about 20 mg/mL, from about 0.1 mg/mL to about 50 mg/mL, from about 0.25 mg/mL to about 6 mg/mL, from about 1 mg/mL to about 20 mg/mL, from about 2 mg/mL to about 20 mg/mL, from about 5 mg/mL to about 15 mg/mL, from about 8 mg/mL to about 12 mg/mL, from about 9 mg/mL to about 11 mg/mL, from about 9.5 mg/mL to about 10.5 mg/mL, from about 9.9 mg/mL to about 10.1 mg/mL, from about 3 mg/mL to about 6 mg/mL, from about 3.5 mg/mL to about 5.5 mg/mL, from about 4 mg/mL to about 5 mg/mL, or from about 4.4 mg/mL to about 4.6 mg/mL. A therapeutically-effective amount of a compound described herein can be present in a composition described herein at a concentration of, for example, at least about 0.5 mg/mL, at least about 1 mg/mL, at least about 1.5 mg/mL, at least about 3 mg/mL, or at least about 5 mg/mL. In the same formulation, the therapeutically-effective amount of acetaminophen can be at least about 8 mg/mL, at least about 10 mg/mL, at least about 15 mg/mL, or at least about 20 mg/mL. In some embodiments, the compound is acetaminophen.

[0059] A therapeutically-effective amount of a compound described herein can be a dose based on the body mass of the subject, for example, about 0.5 mg/kg, about 1 mg/kg, about 1.25 mg/kg, about 1.5 mg/kg, about 1.75 mg/kg, about 2 mg/kg, about 2.25 mg/kg, about 2.5 mg/kg, about 2.75 mg/kg, about 3 mg/kg, about 3.25 mg/kg, about 3.5 mg/kg, about 3.75 mg/kg, about 4 mg/kg, about 4.25 mg/kg, about 4.5 mg/kg, about 4.75 mg/kg, about 5 mg/kg, about 5.25 mg/kg, about 5.5 mg/kg, about 5.75 mg/kg, about 6 mg/kg, about 6.25 mg/kg, about 6.5 mg/kg,

about 6.75 mg/kg, about 7 mg/kg, about 7.25 mg/kg, about 7.5 mg/kg, about 7.75 mg/kg, about 8 mg/kg, about 8.25 mg/kg, about 8.5 mg/kg, about 8.75 mg/kg, about 9 mg/kg, about 9.25 mg/kg, about 9.5 mg/kg, about 9.75 mg/kg, about 10 mg/kg, about 11 mg/kg, about 12 mg/kg, about 13 mg/kg, about 14 mg/kg, about 15 mg/kg, about 16 mg/kg, about 17 mg/kg, about 18 mg/kg, about 19 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, or about 50 mg/kg. A therapeutically-effective amount of a compound described herein can be a dose based on the body mass of the subject, for example, about 0.5 mg/kg to about 50 mg/kg, about 0.5 mg/kg to about 1 mg/kg, about 1 mg/kg to about 5 mg/kg, about 5 mg/kg to about 10 mg/kg, about 10 mg/kg to about 15 mg/kg, about 15 mg/kg to about 20 mg/kg, about 20 mg/kg to about 25 mg/kg, about 25 mg/kg to about 30 mg/kg, about 30 mg/kg to about 35 mg/kg, about 35 mg/kg to about 40 mg/kg, about 40 mg/kg to about 45 mg/kg, or about 45 mg/kg to about 50 mg/kg.

[0060] Pharmaceutical compositions described herein can be formulated at any suitable pH. The pH can be, for example, about 2, about 2.05, about 2.1, about 2.15, about 2.2, about 2.25, about 2.3, about 2.35, about 2.4, about 2.45, about 2.5, about 2.55, about 2.6, about 2.65, about 2.7, about 2.75, about 2.8, about 2.85, about 2.9, about 2.95, about 3, about 3.05, about 3.1, about 3.15, about 3.2, about 3.25, about 3.3, about 3.35, about 3.4, about 3.45, about 3.5, about 3.55, about 3.6, about 3.65, about 3.7, about 3.75, about 3.8, about 3.85, about 3.9, about 3.95, about 4, about 4.05, about 4.1, about 4.15, about 4.2, about 4.25, about 4.3, about 4.35, about 4.4, about 4.45, about 4.5, about 4.55, about 4.6, about 4.65, about 4.7, about 4.75, about 4.8, about 4.85, about 4.9, about 4.95, about 5, about 5.05, about 5.1, about 5.15, about 5.2, about 5.25, about 5.3, about 5.35, about 5.4, about 5.45, about 5.5, about 5.55, about 5.6, about 5.65, about 5.7, about 5.75, about 5.8, about 5.85, about 5.9, about 5.95, about 6, about 6.05, about 6.1, about 6.15, about 6.2, about 6.25, about 6.3, about 6.35, about 6.4, about 6.45, about 6.5, about 6.55, about 6.6, about 6.65, about 6.7, about 6.75, about 6.8, about 6.85, about 6.9, about 6.95, about 7, about 7.05, about 7.1, about 7.15, about 7.2, about 7.25, about 7.3, about 7.35, about 7.4, about 7.45, about 7.5, about 7.55, about 7.6, about 7.65, about 7.7, about 7.75, about 7.8, about 7.85, about 7.9, about 7.95, or about 8.

[0061] Pharmaceutical compositions described herein can be formulated at any suitable pH. The pH can be, for example, from about 2 to about 2.2, about 2.05 to about 2.25, about 2.1 to about 2.3, about 2.15 to about 2.35, about 2.2 to about 2.4, about 2.25 to about 2.45, about 2.3 to about 2.5, about 2.35 to about 2.55, about 2.4 to about 2.6, about 2.45 to about 2.65, about

2.5 to about 2.7, about 2.55 to about 2.75, about 2.6 to about 2.8, about 2.65 to about 2.85, about 2.7 to about 2.9, about 2.75 to about 2.95, about 2.8 to about 3, about 2.85 to about 3.05, about 2.9 to about 3.1, about 2.95 to about 3.15, about 3 to about 3.2, about 3.05 to about 3.25, about 3.1 to about 3.3, about 3.15 to about 3.35, about 3.2 to about 3.4, about 3.25 to about 3.45, about 3.3 to about 3.5, about 3.35 to about 3.55, about 3.4 to about 3.6, about 3.45 to about 3.65, about 3.5 to about 3.7, about 3.55 to about 3.75, about 3.6 to about 3.8, about 3.65 to about 3.85, about 3.7 to about 3.9, about 3.75 to about 3.95, about 3.8 to about 4, about 3.85 to about 4.05, about 3.9 to about 4.1, about 3.95 to about 4.15, about 4 to about 4.2, about 4.05 to about 4.25, about 4.1 to about 4.3, about 4.15 to about 4.35, about 4.2 to about 4.4, about 4.25 to about 4.45, about 4.3 to about 4.5, about 4.35 to about 4.55, about 4.4 to about 4.6, about 4.45 to about 4.65, about 4.5 to about 4.7, about 4.55 to about 4.75, about 4.6 to about 4.8, about 4.65 to about 4.85, about 4.7 to about 4.9, about 4.75 to about 4.95, about 4.8 to about 5, about 4.85 to about 5.05, about 4.9 to about 5.1, about 4.95 to about 5.15, about 5 to about 5.2, about 5.05 to about 5.25, about 5.1 to about 5.3, about 5.15 to about 5.35, about 5.2 to about 5.4, about 5.25 to about 5.45, about 5.3 to about 5.5, about 5.35 to about 5.55, about 5.4 to about 5.6, about 5.45 to about 5.65, about 5.5 to about 5.7, about 5.55 to about 5.75, about 5.6 to about 5.8, about 5.65 to about 5.85, about 5.7 to about 5.9, about 5.75 to about 5.95, about 5.8 to about 6, about 5.85 to about 6.05, about 5.9 to about 6.1, about 5.95 to about 6.15, about 6 to about 6.2, about 6.05 to about 6.25, about 6.1 to about 6.3, about 6.15 to about 6.35, about 6.2 to about 6.4, about 6.25 to about 6.45, about 6.3 to about 6.5, about 6.35 to about 6.55, about 6.4 to about 6.6, about 6.45 to about 6.65, about 6.5 to about 6.7, about 6.55 to about 6.85, about 6.6 to about 6.8, about 6.65 to about 6.85, about 6.7 to about 6.9, about 6.75 to about 6.95, about 6.8 to about 7, about 6.85 to about 7.05, about 6.9 to about 7.1, about 6.95 to about 7.15, about 7 to about 7.2, about 7.05 to about 7.25, about 7.1 to about 7.3, about 7.15 to about 7.35, about 7.2 to about 7.4, about 7.25 to about 7.45, about 7.3 to about 7.5, about 7.35 to about 7.55, about 7.4 to about 7.6, about 7.45 to about 7.65, about 7.5 to about 7.7, about 7.55 to about 7.75, about 7.6 to about 7.8, about 7.65 to about 7.85, about 7.7 to about 7.9, about 7.75 to about 7.95, about 7.8 to about 8, or about 7.85 to about 8.

[0062] In some embodiments, the pH of a pharmaceutical formulation described herein is about 4 to about 7. In some embodiments, the pH of a pharmaceutical formulation described herein is about 4 to about 6. In some embodiments, the pH of a pharmaceutical formulation described herein is about 5 to about 6. In some embodiments, the pH of a pharmaceutical formulation described herein is about 5.5 to about 6. In some embodiments, the pH of a pharmaceutical

formulation described herein is 5.5. In some embodiments, the pH of a pharmaceutical formulation described herein is 6.

[0063] A pharmaceutical composition of the disclosure can be a combination of any pharmaceutical compounds described herein with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. The pharmaceutical composition facilitates administration of the compound to an organism. Pharmaceutical compositions can be administered by therapeutically-effective routes, for example, oral, intravenous, subcutaneous, intramuscular, subdermal, transdermal, or parenteral administration. A pharmaceutical formulation described herein can be administered as an intravenous infusion.

[0064] Pharmaceutical preparations can be formulated for intravenous administration as injectable formulations. The pharmaceutical formulations can be in a form suitable for parenteral injection as a sterile suspension, solution, or emulsion in oily or aqueous vehicles, and can contain formulation agents such as suspending, stabilizing, and/or dispersing agents. Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Suspensions of the active compounds can be prepared as oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions can contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. The suspension can also contain suitable stabilizers or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, the active ingredient can be in powder form for constitution with a suitable vehicle, for example, sterile pyrogen-free water, before use.

[0065] Compositions described herein can be packaged as a kit. In some embodiments, a kit includes written instructions on the administration or use of the composition. The written material can be, for example, a label. The written material can suggest conditions methods of administration. The instructions provide the subject and the supervising physician with the best guidance for achieving the optimal clinical outcome from the administration of the therapy. In some embodiments, the label can be approved by a regulatory agency, for example the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), or other regulatory agencies.

[0066] A method of manufacture for a pharmaceutical composition described herein can involve manufacturing in a manufacturing tank. The manufacturing tank can contain water that has been, for example, deoxygenated. The deoxygenation of the water in the manufacturing tank can occur, via, for example, sparging using nitrogen, argon, or helium. The sparging can reduce the amount of oxygen in the water to about 0.01 ppm, about 0.02 ppm, about 0.03 ppm, about 0.04 ppm, about 0.05 ppm, about 0.1 ppm, about 0.15 ppm, about 0.2 ppm, about 0.25 ppm, about 0.3 ppm, about 0.35 ppm, about 0.4 ppm, about 0.45 ppm, about 0.5 ppm, about 0.6 ppm, about 0.7 ppm, about 0.8 ppm, about 0.9 ppm, about 1 ppm, about 1.5 ppm, or about 2 ppm.

Pharmaceutically-acceptable excipients.

[0067] Non-limiting examples of pharmaceutically-acceptable excipients can be found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins 1999), each of which is incorporated by reference in its entirety.

[0068] In some embodiments, the pharmaceutical composition provided herein comprises a buffer as an excipient. Non-limiting examples of buffers include potassium phosphate, sodium phosphate, phosphate buffer, citrate buffer, saline sodium citrate buffer (SSC), acetate, saline, physiological saline, phosphate buffer saline (PBS), 4-2-hydroxyethyl-1-piperazineethanesulfonic acid buffer (HEPES), 3-(N-morpholino)propanesulfonic acid buffer (MOPS), and piperazine-N,N′-bis(2-ethanesulfonic acid) buffer (PIPES), citric acid monohydrate, sodium dihydrogen phosphate, potassium dihydrogen phosphate, or any combination thereof.

[0069] In some embodiments, the pharmaceutical composition provided herein comprises an alcohol as an excipient. Non-limiting examples of alcohols include ethanol, propylene glycol, glycerol, polyethylene glycol, chlorobutanol, isopropanol, xylitol, sorbitol, maltitol, erythritol, threitol, arabitol, ribitol, mannitol, galactitol, fucitol, lactitol, or any combination thereof.

[0070] Pharmaceutical preparations can be formulated with polyethylene glycol (PEG). PEGs with molecular weights ranging from about 300 g/mol to about 10,000,000 g/mol can be

used. Non-limiting examples of PEGs include PEG 200, PEG 300, PEG 400, PEG 540, PEG 550, PEG 600, PEG 1000, PEG 1450, PEG 1500, PEG 2000, PEG 3000, PEG 3350, PEG 4000, PEG 4600, PEG 6000, PEG 8000, PEG 10,000, and PEG 20,000.

[0071] Further excipients that can be used in a composition described herein include, for example, benzalkonium chloride, benzethonium chloride, benzyl alcohol, butylated hydroxyanisole, butylated hydroxytoluene, chlorobutanol, dehydroacetic acid, ethylenediamine, ethyl vanillin, glycerin, hypophosphorous acid, phenol, phenylethyl alcohol, phenylmercuric nitrate, potassium benzoate, potassium metabisulfite, potassium sorbate, sodium bisulfite, sodium metabisulfite, sorbic acid, thimerasol, acetic acid, aluminum monostearate, boric acid, calcium hydroxide, calcium stearate, calcium sulfate, calcium tetrachloride, cellulose acetate phthalate, microcrystalline celluose, chloroform, citric acid, edetic acid, and ethylcellulose.

[0072] In some embodiments, the pharmaceutical composition provided herein comprises an aprotic solvent as an excipient. Non-limiting examples of aprotic solvents include perfluorohexane, α,α,α-trifluorotoluene, pentane, hexane, cyclohexane, methylcyclohexane, decalin, dioxane, carbon tetrachloride, freon-11, benzene, toluene, carbon disulfide, diisopropyl ether, diethyl ether, t-butyl methyl ether, ethyl acetate, 1,2-dimethoxyethane, 2-methoxyethyl ether, tetrahydrofuran, methylene chloride, pyridine, 2-butanone, acetone, N-methylpyrrolidinone, nitromethane, dimethylformamide, acetonitrile, sulfolane, dimethyl sulfoxide, and propylene carbonate.

[0073] The amount of the excipient in a pharmaceutical composition described herein can be about 0.01%, about 0.02%, about 0.03%, about 0.04%, about 0.05%, about 0.06%, about 0.07%, about 0.08%, about 0.09%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 1.5%, about 2%, about 2.5%, about 3%, about 3.5%, about 4%, about 4.5%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 60%, about 70%, about 80%, about 90%, about 100%, about 200%, about 300%, about 400%, about 500%, about 600%, about 700%, about 800%, about 900%, or about 1000% by mass of a compound in the pharmaceutical formulation.

[0074] The amount of the excipient in a pharmaceutical composition described herein can be about 0.01%, about 0.02%, about 0.03%, about 0.04%, about 0.05%, about 0.06%, about

0.07%, about 0.08%, about 0.09%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 1.5%, about 2%, about 2.5%, about 3%, about 3.5%, about 4%, about 4.5%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55% about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or about 100% by mass or by volume of the unit dosage form.

[0075] In some embodiments, the addition of an excipient can change the viscosity of a pharmaceutical composition described herein. In some embodiments the use of an excipient can increase or decrease the viscosity of a fluid by at least 0.001 Pascal-second (Pa.s), at least 0.001 Pa.s, at least 0.0009 Pa.s, at least 0.0008 Pa.s, at least 0.0007 Pa.s, at least 0.0006 Pa.s, at least 0.0005 Pa.s, at least 0.0004 Pa.s, at least 0.0003 Pa.s, at least 0.0002 Pa.s, at least 0.0001 Pa.s, at least 0.00005 Pa.s, or at least 0.00001 Pa.s.

[0076] In some embodiments, the addition of an excipient to a pharmaceutical composition described herein can increase or decrease the viscosity of the composition by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%. In some embodiments, the addition of an excipient to a pharmaceutical composition described herein can increase or decrease the viscosity of the composition by no greater than 5%, no greater than 10%, no greater than 15%, no greater than 20%, no greater than 25%, no greater than 30%, no greater than 35%, no greater than 40%, no greater than 45%, no greater than 50%, no greater than 55%, no greater than 60%, no greater than 65%, no greater than 70%, no greater than 75%, no greater than 80%, no greater than 85%, no greater than 90%, no greater than 95%, or no greater than 99%.

Pharmacokinetics and Pharmacodynamics.

[0077] A dose can be modulated to achieve a desired pharmacokinetic or pharmacodynamics profile, such as a desired or effective blood profile, as described herein.

[0078] Pharmacokinetic and pharmacodynamic data can be obtained by various experimental techniques. Appropriate pharmacokinetic and pharmacodynamic profile components describing a particular composition can vary due to variations in drug metabolism in human

subjects. Pharmacokinetic and pharmacodynamic profiles can be based on the determination of the mean parameters of a group of subjects. The group of subjects includes any reasonable number of subjects suitable for determining a representative mean, for example, 5 subjects, 10 subjects, 15 subjects, 20 subjects, 25 subjects, 30 subjects, 35 subjects, or more. The mean is determined, for example, by calculating the average of all subject's measurements for each parameter measured. A dose can be modulated to achieve a desired pharmacokinetic or pharmacodynamics profile, such as a desired or effective blood profile, as described herein.

[0079] The pharmacodynamic parameters can be any parameters suitable for describing compositions described herein. For example, the pharmacodynamic profile can be obtained at a time after dosing of, for example, about zero minutes, about 1 minute, about 2 minutes, about 3 minutes, about 4 minutes, about 5 minutes, about 6 minutes, about 7 minutes, about 8 minutes, about 9 minutes, about 10 minutes, about 11 minutes, about 12 minutes, about 13 minutes, about 14 minutes, about 15 minutes, about 16 minutes, about 17 minutes, about 18 minutes, about 19 minutes, about 20 minutes, about 21 minutes, about 22 minutes, about 23 minutes, about 24 minutes, about 25 minutes, about 26 minutes, about 27 minutes, about 28 minutes, about 29 minutes, about 30 minutes, about 31 minutes, about 32 minutes, about 33 minutes, about 34 minutes, about 35 minutes, about 36 minutes, about 37 minutes, about 38 minutes, about 39 minutes, about 40 minutes, about 41 minutes, about 42 minutes, about 43 minutes, about 44 minutes, about 45 minutes, about 46 minutes, about 47 minutes, about 48 minutes, about 49 minutes, about 50 minutes, about 51 minutes, about 52 minutes, about 53 minutes, about 54 minutes, about 55 minutes, about 56 minutes, about 57 minutes, about 58 minutes, about 59 minutes, about 60 minutes, about zero hours, about 0.5 hours, about 1 hour, about 1.5 hours, about 2 hours, about 2.5 hours, about 3 hours, about 3.5 hours, about 4 hours, about 4.5 hours, about 5 hours, about 5.5 hours, about 6 hours, about 6.5 hours, about 7 hours, about 7.5 hours, about 8 hours, about 8.5 hours, about 9 hours, about 9.5 hours, about 10 hours, about 10.5 hours, about 11 hours, about 11.5 hours, about 12 hours, about 12.5 hours, about 13 hours, about 13.5 hours, about 14 hours, about 14.5 hours, about 15 hours, about 15.5 hours, about 16 hours, about 16.5 hours, about 17 hours, about 17.5 hours, about 18 hours, about 18.5 hours, about 19 hours, about 19.5 hours, about 20 hours, about 20.5 hours, about 21 hours, about 21.5 hours, about 22 hours, about 22.5 hours, about 23 hours, about 23.5 hours, or about 24 hours.

[0080] The pharmacokinetic parameters can be any parameters suitable for describing a compound disclosed herein. The Cmax can be, for example, not less than about 1 ng/mL; not

less than about 5 ng/mL; not less than about 10 ng/mL; not less than about 15 ng/mL; not less than about 20 ng/mL; not less than about 25 ng/mL; not less than about 50 ng/mL; not less than about 75 ng/mL; not less than about 100 ng/mL; not less than about 200 ng/mL; not less than about 300 ng/mL; not less than about 400 ng/mL; not less than about 500 ng/mL; not less than about 600 ng/mL; not less than about 700 ng/mL; not less than about 800 ng/mL; not less than about 900 ng/mL; not less than about 1000 ng/mL; not less than about 1250 ng/mL; not less than about 1500 ng/mL; not less than about 1750 ng/mL; not less than about 2000 ng/mL; not less than about 5000 mg/mL; not less than about 10,000 ng/mL; not less than about 15,000 ng/mL; not less than about 20,000 ng/mL; not less than about 30,000 ng/mL; not less than about 40,000 n g/mL; or any other Cmax appropriate for describing a pharmacokinetic profile of a compound described herein. The Cmax can be, for example, about 1 ng/mL to about 5,000 ng/mL; about 1 ng/mL to about 4,500 ng/mL; about 1 ng/mL to about 4,000 ng/mL; about 1 ng/mL to about 3,500 ng/mL; about 1 ng/mL to about 3,000 ng/mL; about 1 ng/mL to about 2,500 ng/mL; about 1 ng/mL to about 2,000 ng/mL; about 1 ng/mL to about 1,500 ng/mL; about 1 ng/mL to about 1,000 ng/mL; about 1 ng/mL to about 900 ng/mL; about 1 ng/mL to about 800 ng/mL; about 1 ng/mL to about 700 ng/mL; about 1 ng/mL to about 600 ng/mL; about 1 ng/mL to about 500 ng/mL; about 1 ng/mL to about 450 ng/mL; about 1 ng/mL to about 400 ng/mL; about 1 ng/mL to about 350 ng/mL; about 1 ng/mL to about 300 ng/mL; about 1 ng/mL to about 250 ng/mL; about 1 ng/mL to about 200 ng/mL; about 1 ng/mL to about 150 ng/mL; about 1 ng/mL to about 125 ng/mL; about 1 ng/mL to about 100 ng/mL; about 1 ng/mL to about 90 ng/mL; about 1 ng/mL to about 80 ng/mL; about 1 ng/mL to about 70 ng/mL; about 1 ng/mL to about 60 ng/mL; about 1 ng/mL to about 50 ng/mL; about 1 ng/mL to about 40 ng/mL; about 1 ng/mL to about 30 ng/mL; about 1 ng/mL to about 20 ng/mL; about 1 ng/mL to about 10 ng/mL; about 1 ng/mL to about 5 ng/mL; about 10 ng/mL to about 4,000 ng/mL; about 10 ng/mL to about 3,000 ng/mL; about 10 ng/mL to about 2,000 ng/mL; about 10 ng/mL to about 1,500 ng/mL; about 10 ng/mL to about 1,000 ng/mL; about 10 ng/mL to about 900 ng/mL; about 10 ng/mL to about 800 ng/mL; about 10 ng/mL to about 700 ng/mL; about 10 ng/mL to about 600 ng/mL; about 10 ng/mL to about 500 ng/mL; about 10 ng/mL to about 400 ng/mL; about 10 ng/mL to about 300 ng/mL; about 10 ng/mL to about 200 ng/mL; about 10 ng/mL to about 100 ng/mL; about 10 ng/mL to about 50 ng/mL; about 25 ng/mL to about 500 ng/mL; about 25 ng/mL to about 100 ng/mL; about 50 ng/mL to about 500 ng/mL; about 50 ng/mL to about 100 ng/mL; about 100 ng/mL to about 500 ng/mL; about 100 ng/mL to about 400 ng/mL; about 100 ng/mL to about 300 ng/mL; or about 100 ng/mL to about 200 ng/mL.

[0081] The Tmax of a compound described herein can be, for example, not greater than about 0.5 hours, not greater than about 1 hours, not greater than about 1.5 hours, not greater than about 2 hours, not greater than about 2.5 hours, not greater than about 3 hours, not greater than about 3.5 hours, not greater than about 4 hours, not greater than about 4.5 hours, not greater than about 5 hours, or any other Tmax appropriate for describing a pharmacokinetic profile of a compound described herein. The Tmax can be, for example, about 0.1 hours to about 24 hours; about 0.1 hours to about 0.5 hours; about 0.5 hours to about 1 hour; about 1 hour to about 1.5 hours; about 1.5 hours to about 2 hour; about 2 hours to about 2.5 hours; about 2.5 hours to about 3 hours; about 3 hours to about 3.5 hours; about 3.5 hours to about 4 hours; about 4 hours to about 4.5 hours; about 4.5 hours to about 5 hours; about 5 hours to about 5.5 hours; about 5.5 hours to about 6 hours; about 6 hours to about 6.5 hours; about 6.5 hours to about 7 hours; about 7 hours to about 7.5 hours; about 7.5 hours to about 8 hours; about 8 hours to about 8.5 hours; about 8.5 hours to about 9 hours; about 9 hours to about 9.5 hours; about 9.5 hours to about 10 hours; about 10 hours to about 10.5 hours; about 10.5 hours to about 11 hours; about 11 hours to about 11.5 hours; about 11.5 hours to about 12 hours; about 12 hours to about 12.5 hours; about 12.5 hours to about 13 hours; about 13 hours to about 13.5 hours; about 13.5 hours to about 14 hours; about 14 hours to about 14.5 hours; about 14.5 hours to about 15 hours; about 15 hours to about 15.5 hours; about 15.5 hours to about 16 hours; about 16 hours to about 16.5 hours; about 16.5 hours to about 17 hours; about 17 hours to about 17.5 hours; about 17.5 hours to about 18 hours; about 18 hours to about 18.5 hours; about 18.5 hours to about 19 hours; about 19 hours to about 19.5 hours; about 19.5 hours to about 20 hours; about 20 hours to about 20.5 hours; about 20.5 hours to about 21 hours; about 21 hours to about 21.5 hours; about 21.5 hours to about 22 hours; about 22 hours to about 22.5 hours; about 22.5 hours to about 23 hours; about 23 hours to about 23.5 hours; or about 23.5 hours to about 24 hours.

[0082] The AUC(0-inf) or AUC(last) of a compound described herein can be, for example, not less than about 1 ng•hr/mL, not less than about 5 ng•hr/mL, not less than about 10 ng•hr/mL, not less than about 20 ng•hr/mL, not less than about 30 ng•hr/mL, not less than about 40 ng•hr/mL, not less than about 50 ng•hr/mL, not less than about 100 ng•hr/mL, not less than about 150 ng•hr/mL, not less than about 200 ng•hr/mL, not less than about 250 ng•hr/mL, not less than about 300 ng•hr/mL, not less than about 350 ng•hr/mL, not less than about 400 ng•hr/mL, not less than about 450 ng•hr/mL, not less than about 500 ng•hr/mL, not less than about 600 ng•hr/mL, not less than about 700 ng•hr/mL, not less than about 800 ng•hr/mL, not

less than about 900 ng•hr/mL, not less than about 1000 ng•hr/mL, not less than about 1250 ng•hr/mL, not less than about 1500 ng•hr/mL, not less than about 1750 ng•hr/mL, not less than about 2000 ng•hr/mL, not less than about 2500 ng•hr/mL, not less than about 3000 ng•hr/mL, not less than about 3500 ng•hr/mL, not less than about 4000 ng•hr/mL, not less than about 5000 ng•hr/mL, not less than about 6000 ng•hr/mL, not less than about 7000 ng•hr/mL, not less than about 8000 ng•hr/mL, not less than about 9000 ng•hr/mL, not less than about 10,000 ng•hr/mL, not less than about 15,000 ng•hr/mL, not less than about 20,000 ng•hr/mL, not less than about 25,000 ng•hr/mL, not less than about 30,000 ng•hr/mL, not less than about 40,000 ng•hr/mL, not less than about 50,000 ng•hr/mL, or any other AUC(0-inf) appropriate for describing a pharmacokinetic profile of a compound described herein. The AUC(0-inf) of a compound can be, for example, about 1 ng•hr/mL to about 10,000 ng•hr/mL; about 1 ng•hr/mL to about 10 ng•hr/mL; about 10 ng•hr/mL to about 25 ng•hr/mL; about 25 ng•hr/mL to about 50 ng•hr/mL; about 50 ng•hr/mL to about 100 ng•hr/mL; about 100 ng•hr/mL to about 200 ng•hr/mL; about 200 ng•hr/mL to about 300 ng•hr/mL; about 300 ng•hr/mL to about 400 ng•hr/mL; about 400 ng•hr/mL to about 500 ng•hr/mL; about 500 ng•hr/mL to about 600 ng•hr/mL; about 600 ng•hr/mL to about 700 ng•hr/mL; about 700 ng•hr/mL to about 800 ng•hr/mL; about 800 ng•hr/mL to about 900 ng•hr/mL; about 900 ng•hr/mL to about 1,000 ng•hr/mL; about 1,000 ng•hr/mL to about 1,250 ng•hr/mL; about 1,250 ng•hr/mL to about 1,500 ng•hr/mL; about 1,500 ng•hr/mL to about 1,750 ng•hr/mL; about 1,750 ng•hr/mL to about 2,000 ng•hr/mL; about 2,000 ng•hr/mL to about 2,500 ng•hr/mL; about 2,500 ng•hr/mL to about 3,000 ng•hr/mL; about 3,000 ng•hr/mL to about 3,500 ng•hr/mL; about 3,500 ng•hr/mL to about 4,000 ng•hr/mL; about 4,000 ng•hr/mL to about 4,500 ng•hr/mL; about 4,500 ng•hr/mL to about 5,000 ng•hr/mL; about 5,000 ng•hr/mL to about 5,500 ng•hr/mL; about 5,500 ng•hr/mL to about 6,000 ng•hr/mL; about 6,000 ng•hr/mL to about 6,500 ng•hr/mL; about 6,500 ng•hr/mL to about 7,000 ng•hr/mL; about 7,000 ng•hr/mL to about 7,500 ng•hr/mL; about 7,500 ng•hr/mL to about 8,000 ng•hr/mL; about 8,000 ng•hr/mL to about 8,500 ng•hr/mL; about 8,500 ng•hr/mL to about 9,000 ng•hr/mL; about 9,000 ng•hr/mL to about 9,500 ng•hr/mL; or about 9,500 ng•hr/mL to about 10,000 ng•hr/mL.

[0083] The plasma concentration of a compound described herein can be, for example, not less than about 1 ng/mL, not less than about 5 ng/mL, not less than about 10 ng/mL, not less than about 15 ng/mL, not less than about 20 ng/mL, not less than about 25 ng/mL, not less than about 50 ng/mL, not less than about 75 ng/mL, not less than about 100 ng/mL, not less than about 150 ng/mL, not less than about 200 ng/mL, not less than about 300 ng/mL, not less than

about 400 ng/mL, not less than about 500 ng/mL, not less than about 600 ng/mL, not less than about 700 ng/mL, not less than about 800 ng/mL, not less than about 900 ng/mL, not less than about 1000 ng/mL, not less than about 1200 ng/mL, or any other plasma concentration of a compound described herein. The plasma concentration can be, for example, about 1 ng/mL to about 2,000 ng/mL; about 1 ng/mL to about 5 ng/mL; about 5 ng/mL to about 10 ng/mL; about 10 ng/mL to about 25 ng/mL; about 25 ng/mL to about 50 ng/mL; about 50 ng/mL to about 75 ng/mL; about 75 ng/mL to about 100 ng/mL; about 100 ng/mL to about 150 ng/mL; about 150 ng/mL to about 200 ng/mL; about 200 ng/mL to about 250 ng/mL; about 250 ng/mL to about 300 ng/mL; about 300 ng/mL to about 350 ng/mL; about 350 ng/mL to about 400 ng/mL; about 400 ng/mL to about 450 ng/mL; about 450 ng/mL to about 500 ng/mL; about 500 ng/mL to about 600 ng/mL; about 600 ng/mL to about 700 ng/mL; about 700 ng/mL to about 800 ng/mL; about 800 ng/mL to about 900 ng/mL; about 900 ng/mL to about 1,000 ng/mL; about 1,000 ng/mL to about 1,100 ng/mL; about 1,100 ng/mL to about 1,200 ng/mL; about 1,200 ng/mL to about 1,300 ng/mL; about 1,300 ng/mL to about 1,400 ng/mL; about 1,400 ng/mL to about 1,500 ng/mL; about 1,500 ng/mL to about 1,600 ng/mL; about 1,600 ng/mL to about 1,700 ng/mL; about 1,700 ng/mL to about 1,800 ng/mL; about 1,800 ng/mL to about 1,900 ng/mL; or about 1,900 ng/mL to about 2,000 ng/mL.

[0084] The pharmacodynamic parameters can be any parameters suitable for describing compositions of the disclosure. For example, the pharmacodynamic profile can demonstrate an increased pain tolerance in a subject who has been administered a pharmaceutical formulation described herein.

[0085] Non-limiting examples of pharmacodynamic and pharmacokinetic parameters that can be calculated for a compound that is administered with the methods described herein include: a) the amount of drug administered, which can be represented as a dose D; b) the dosing interval, which can be represented as τ; c) the apparent volume in which a drug is distributed, which can be represented as a volume of distribution Vd, where Vd = D/C0; d) the amount of drug in a given volume of plasma, which can be represented as concentration C0 or Css, where C0 or Css = D/Vd and can be represented as a mean plasma concentration over a plurality of samples; e) the half-life of a drug t1/2, where t1/2 = ln(2)/ke ; f) the rate at which a drug is removed from the body ke, where ke = ln(2)/t1/2 = CL/Vd; g) the rate of infusion required to balance the equation Kin, where Kin = Css.CL; h) the integral of the concentration-time curve after administration of a single dose, which can be represented as AUC0-∞, wherein $\int_0^\infty C\,dt$,

or in steady-state, which can be represented as AUCτ, ss, wherein $\int_t^{t+\pi} C\ dt$; i) the volume of plasma cleared of the drug per unit time, which can be represented as CL (clearance), wherein CL = Vd.ke = D/AUC; j) the systemically available fraction of a drug, which can be represented as f, where $f = \frac{AUCpo.Div}{AUCiv.Dpo}$; k) the peak plasma concentration of a drug after administration Cmax; l) the time taken by a drug to reach Cmax, tmax; m) the lowest concentration that a drug reaches before the next dose is administered Cmin; and n) the peak trough fluctuation within one dosing interval at steady state, which can be represented as %PTF = 100. $\frac{(Cmax,ss-Cmin,ss)}{Cav,ss}$ where Cav,ss = $\frac{AUC\tau,ss}{\tau}$.

[0086] When administered via intravenous injection, a pharmaceutical composition described herein can exert an effect at a level of at least about 50%, at least about 70%, at least about 80%, or at least about 90% within less than about, for example, one hour or two hours of the administration. A pharmaceutical composition described herein can remain effective at a level of at least about 50%, at least about 70%, at least about 80%, or at least about 90% for at least about 1 hour, at least about 2 hours, at least about 3 hours, or at least about 6 hours after the administration.

[0087] A pharmaceutical formulation described herein can be administered to a subject about 1 minute, about 2 minutes, about 3 minutes, about 4 minutes, about 5 minutes, about 6 minutes, about 7 minutes, about 8 minutes, about 9 minutes, about 10 minutes, about 11 minutes, about 12 minutes, about 13 minutes, about 14 minutes, about 15 minutes, about 16 minutes, about 17 minutes, about 18 minutes, about 19 minutes, about 20 minutes, about 25 minutes, about 30 minutes, about 35 minutes, about 40 minutes, about 45 minutes, about 50 minutes, about 55 minutes, about 1 hour, about 1.5 hours, about 2 hours, about 2.5 hours, about 3 hours, about 3.5 hours, about 4 hours, about 4.5 hours, about 5 hours, about 5.5 hours, about 6 hours, about 6.5 hours, about 7 hours, about 7.5 hours, about 8 hours, about 8.5 hours, about 9 hours, about 9.5 hours, about 10 hours, about 10.5 hours, about 11 hours, about 11.5 hours, about 12 hours, about 18 hours, about 24 hours, about 30 hours, about 36 hours, about 42 hours, or about 48 hours prior to, or after, surgery. A pharmaceutical formulation described herein can be administered to a patient at the same time as when the surgery begins. A pharmaceutical formulation described herein can be administered to a patient during a surgery. A pharmaceutical formulation described herein can be administered to a patient right after a surgery is ended. A pharmaceutical formulation described herein can be administered one or

more times prior to, during, or after, surgery for a patient. For example, a pharmaceutical formulation described herein can be administered to a patient one time a day, two times a day, three times a day, four times a day, five times a day, six times a day, seven times a day, eight times a day, nine times a day, or ten times a day. A pharmaceutical formulation described herein can be administered to a patient every 1 hours, every 2 hours, every 3 hours, every 4 hours, every 5 hours, every 6 hours, every 7 hours, every 8 hours, every 9 hours, every 10 hours, every 11 hours, or every 12 hours.

[0088] The present disclosure provides several embodiments of pharmaceutical formulations that provide advantages in stability, administration, efficacy, and modulation of formulation viscosity. Any embodiments disclosed herein can be used in conjunction or individually. For example, any pharmaceutically-acceptable excipient, method, technique, solvent, or compound disclosed herein can be used together with any other pharmaceutically-acceptable excipient, method, technique, solvent, or compound disclosed herein to achieve any therapeutic result. Compounds, excipients, and other formulation components can be present at any amount, ratio, or percentage disclosed herein in any such formulation, and any such combination can be used therapeutically for any purpose described herein and to provide any viscosity described herein.

Methods Used Herein.

[0089] Pain intensity (PI): The Numerical Pain Rating Scale (PI-NPRS) can be used to assess self-reported pain intensity (PI) in human subjects, where a patient rates their pain on a defined scale from 0 to 10 (0= no pain; 10 = worst imaginable pain).

[0090] Pain Relief Rating (PR): The Pain Relief Rating can be used to assess self-reported pain relief in human subjects, where a patient rates perceived pain relief according to a 5-point Likert scale (0=no pain relief, 1=a little pain relief, 2=some pain relief, 3=a lot of pain relief, and 4=complete pain relief).

[0091] Time to perceptible pain relief confirmed (FPR-C): The time to perceptible pain relief confirmed can be used to assess time to self-reported onset of pain relief, in which a subject is given a stopwatch and asked to press the stopwatch when the subject first perceives any pain relief. FPR-C can be stratified according to patients who, before administration of Dose 1, reported moderate (2) pain intensity and patients who reported severe pain intensity (3) on a scale from 0 to 3 (0=no pain, 1=mild pain, 2=moderate pain, 3=severe pain).

[0092] Global Evaluation: Patient evaluation of the study medication can be assessed by Global Evaluation, where patients report an evaluation at an early termination timepoint or at 24.25 hours post-surgery, whichever is first, on a scale from 0 to 4 (0=Poor, 1=Fair, 2=Good, 3=Very Good, and 4=Excellent).

[0093] Pain Intensity Difference Rating (PID): Changes in patient evaluation of pain relief can be expressed as the Pain Intensity Difference Rating (PID), which can be calculated by taking the subtraction of baseline PI evaluated before Dose 1 administration from reported PI at different time points after administration of Dose 1.

[0094] Time to Treatment Failure: The time to treatment failure can be used to assess the period of time between administration of Dose 1 to administration of a rescue medication or subject withdrawal from the study for any reason. Subjects that did not withdraw from the study or take a rescue medication can be excluded.

Examples

Study of Acetaminophen Injection in Post-Surgical Dental Pain.

[0095] A randomized, double-blind, single-site, placebo-controlled, parallel-group study was conducted to assess similarities in safety, tolerability, efficacy, and pharmacokinetics of 1300 mg of injectable acetaminophen given in three doses, each 8 hours apart, relative to placebo, and 1000 mg of injectable acetaminophen given in four doses, each 6 hours apart, relative to placebo over a 24-hour period in patients experiencing moderate to severe postsurgical pain within 7 hours following surgical removal of 2 or more molars.

[0096] As is shown in more detail below, the inventors unexpectedly discovered that doses can be spaced apart significantly more than 6 hours with only a moderate increase of drug concentration per administration. For example, where the drug concentration was increased from 1,000 mg to 1,300 mg, administration of the acetaminophen could be spaced to 8 hours, which conveniently reduces daily administration from 4 to 3 times per day, thereby substantially reducing administrative burden and patient treatment time. Most notably, despite the relatively short serum half-life time of acetaminophen of about 3 hours, the therapeutic effect as measured in the pain scores indicated below was substantially the same as compared with 4 times daily acetaminophen infusion of 1,000 mg each. Moreover, it is noted that using the improved formulation and administration scheme potential issues with hepatotoxicity are

avoided as the total daily dose of acetaminophen remained unchanged to the conventional formulation and schedule (1,000 mg 4 times daily at 6 hour intervals). Still further, the increased dose (1,300 mg) per administration did not significantly alter the safety profile.

[0097] To maintain the double-blind conditions, patients received either a placebo (saline drip) or the active study medication every 2 hours (± 10 minutes) (infused over 15 minutes) over the first 18 hours after Dose 1. Patients underwent surgical removal of at least two third molars. Maxillary third molars were removed regardless of impaction level. The mandibular extractions met one of the following scenarios and must not result in a trauma rating of severe on the 4-point scale of mild, moderate, moderately severe, or severe:

[0098] -Two full bony impactions.

[0099] -Two partial bony impactions.

[00100] -One full bony impaction in combination with one partial bony impaction.

[00101] Patients who met the randomization criteria (post-surgical pain of moderate to severe on the 4-point Categorical Pain Intensity scale, and at least a score of 5 on the 11-point (0-10) pain intensity numerical pain rating scale (PINPRS) at baseline within 7 hours of last stitch from dental extractions) were randomly assigned to one of three treatment groups in a 2:2:1 ratio of active to active to placebo treatments.

[00102] Approximately 110 patients received either IV APAP 1300 mg, three doses, each in 130 mL of total volume, 8 hours apart, or IV APAP 1000 mg, four doses, each in 130 mL of total volume, 6 hours apart, or placebo, 130 mL total volume of normal saline in a 2:2:1 allocation ratio. No less than approximately 30% of randomized patients were either male or female. In addition, no more than approximately 30% of patients were 17 years of age at the time of screening.

[00103] Infusion of the first dose of study medication began within 10 minutes of randomization. As a result of the different schedules for active drug administration (q6h versus q8h) and in order to maintain the double-blind conditions, every two hours thereafter randomized patients received either active drug or placebo infused over 15 minutes (by infusion pump) through hour 18. The maximum number of doses for an active drug was 4 doses of 1000

mg of acetaminophen or 3 doses of 1300 mg of acetaminophen. The maximum dose of acetaminophen over a 24-hour period was 4 grams.

[00104] Self-reported pain intensity was collected using a 11-point [0-10] PI-NPRS at baseline (time 0). NPRS and pain relief (PR) was collected at 0.5, 0.75, 1, 1.25, 1.75, 2.25 Hours (± 5 minutes), hourly from 3.25 through 12.25 Hours (± 5 minutes), then every two hours from 14.25 through 24.25 hours (± 10 minutes) after the infusion of the first dose of study medication was initiated (T0). In addition, efficacy scores (NPRS and PR) were collected prior to each use of rescue (if applicable). Time to perceptible pain relief and time to meaningful pain relief were collected using the double-stopwatch methodology as follows: For each randomized patient, two stopwatches were started immediately upon initiation of the first study dose infusion. The first stopwatch was given to each patient with the instructions to stop the watch when they first perceive pain relief to occur (time to perceptible relief). Once the first stopwatch was stopped, the second stopwatch was given to the patient with the instruction to stop the watch when they are first experiencing meaningful pain relief (time to meaningful relief). Time to perceptible pain relief was confirmed only if the patient experienced meaningful relief.

[00105] Rescue medication was one ibuprofen 200 mg tablet taken orally with at least 4 ounces of water. Prior to each dose of rescue medication, 11-point Pain Intensity (via 0-10 Numerical Pain Rating Scale) and Pain Relief (via 5-Point Categorical Pain Relief Assessment) measurements were performed. For statistical purposes, pain assessments performed after any dose of rescue were censored and imputed. Any subject requiring additional rescue medication was eligible to again receive ibuprofen 200 mg, and their data was similarly censored and imputed. Pain scores and safety data continued to be collected for the 24- hour observation period. Rescue medication did not exceed ibuprofen 200 mg q3h or 2400 mg in a 24-hour period. Patient Global Evaluation of the study medication was collected at Hour 24.25 or at the time of patient withdrawal (if applicable), whichever occurred first, using a 0-4 rating scale: (0) poor, (1) fair, (2) good, (3) very good, and (4) excellent.

[00106] A total of 226 participants were screened from 30 days before Day 0 to Day 0 before randomization. The number of subjects that started and completed the study in each cohort is summarized in **TABLE 1**.

Table 1

Arm/Group Title	High Dose IV APAP	Low Dose IV APAP	Placebo IV
Arm/Group Description	Acetaminophen (APAP) 10 mg/mL administered post-operatively at a dose of 1300 mg intravenously 3-times daily (q8h)	Acetaminophen (APAP) 10 mg/mL administered post-operatively at a dose of 1000 mg intravenously 4-times daily (q6h)	Placebo given intravenously post-operatively
Started	44	44	22
Completed	43	44	21
Not Completed	1	0	1
Withdrawal of consent	1	0	1

[00107] Baseline levels of reported pain in the study subjects are summarized in **TABLE 2**.

Table 2

Arm/Group Title	High Dose IV APAP	Low Dose IV APAP	Placebo IV	Total	Arm/Group Title
Arm/Group Description	Acetaminophen (APAP) 10 mg/mL administered post-operatively at a dose of 1300 mg intravenously 3-times daily (q8h)	Acetaminophen (APAP) 10 mg/mL administered post-operatively at a dose of 1000 mg intravenously 4-times daily (q6h)	Placebo given intravenously post-operatively		**Arm/Group Description**
NRS pain intensity n (%) Measure Type: Count of Participants Unit of measure: participants	*Number Analyzed*	44 participants	44 participants	22 participants	110 participants
0 = No pain		0	0	0	0
1		0	0	0	0
2		0	0	0	0
3		0	0	0	0
4		0	0	0	0
5		1 (2.3%)	1 (2.3%)	1 (4.5%)	3 (2.7%)
6		11 (25.0%)	7 (15.9%)	8 (36.4%)	26 (23.6%)
7		13 (29.5%)	12 (27.3%)	6 (27.3%)	31 (28.2%)
8		13 (29.5%)	18 (40.9%)	7 (31.8%)	38 (34.5%)
9		3 (6.8%)	5 (11.4%)	0	8 (7.3%)

10 = Worst imaginable pain		3 (6.8%)	1 (2.3%)	0	4 (3.6%)

Primary Outcome

[00108] During the course of the study, Pain Intensity was self-reported over 24 hours, using a pain rating of 0-10 on the Numerical Rating Scale (NRS), with score from 0 to10 (0= no pain; 10 = worst imaginable pain). The sum of pain intensity difference from 0 to 24 hours (SPID24) based on the 11 point numeric pain Rating scale in each cohort is summarized in **TABLE 3**. SPID was calculated as SUM([T(i) – T(i-1)] x (PID(i-1) + PID(i)) / 2), where T(0)=0, T(i) is the actual time, and PID(i) is the pain intensity difference (PID) score at time i. The Evaluable Population included all randomized patients who, as documented prior to the breaking of the study blind: (1) met all the inclusion and exclusion criteria and (2) were administered Dose 1.

Table 3

Arm/Group Title	**High Dose IV APAP**	**Low Dose IV APAP**	**Placebo IV**
Arm/Group Description:	Acetaminophen (APAP) 10 mg/mL administered post-operatively at a dose of 1300 mg intravenously 3-times daily (q8h)	Acetaminophen (APAP) 10 mg/mL administered post-operatively at a dose of 1000 mg intravenously 4-times daily (q6h)	Placebo given intravenously post-operatively
Overall Number of Participants Analyzed	43	44	22
Least Squares Mean SPID24 (Standard Error) *Unit of Measure: score on a 0-10 scale*	-96.80 (6.369)	-100.69 (6.333)	-74.96 (9.055)

[00109] For both experimental cohorts, SPID24 was analyzed using an analysis of covariance (ANCOVA) model with treatment group as a fixed effect and baseline PI-NPRS as a covariate. The lower limit of one-sided 90% CI was -∞. Statistical parameters for each cohort are summarized in **TABLE 4**.

Table 4

Statistical Analysis	*Comparison Group Selection*	**High Dose IV APAP, Placebo IV**	**Low Dose IV APAP, Placebo IV**

Overview (SPID24)	*Type of Statistical Test*	Superiority	
	Estimation Parameter	Other[LS Mean Difference] (SE)	
	Estimated Value	-21.84	-25.74
Method of Estimation (SPID24)	*Confidence Interval*	(1-Sided) 90% -INF, -7.53	(1-Sided) 90% -INF, -11.35
	Standard Error of the Mean	11.091	11.154
	One-Sided P Value for Diff.	0.0258	0.0115

[00110] The sum of pain relief from 0 to 24 hours (TOTPAR24) based on a 5-point Likert scale is summarized in **TABLE 5**. The Pain Relief Rating (PR) was scored on a 5-point scale (0=no-, 1=a little-, 2=some-, 3=a lot of-, and 4=complete- PR). TOTPAR24 was calculated as SUM([T(i) – T(i-1)] x (PR(i-1) + PR(i)) / 2), where T(0)=0, T(i) is the actual time, and PR(i) is the pain relief score at time i.

Table 5

Arm/Group Title	**High Dose IV APAP**	**Low Dose IV APAP**	**Placebo IV**
Arm/Group Description:	Acetaminophen (APAP) 10 mg/mL administered post-operatively at a dose of 1300 mg intravenously 3-times daily (q8h)	Acetaminophen (APAP) 10 mg/mL administered post-operatively at a dose of 1000 mg intravenously 4-times daily (q6h)	Placebo given intravenously post-operatively
Overall Number of Participants Analyzed	43	44	22
Least Squares Mean TOTPAR24 (Standard Error) *Unit of Measure: score on a 0-5 scale*	55.82 (3.024)	55.24 (3.007)	43.11 (4.300)

[00111] For both experimental cohorts, TOTPAR24 was analyzed using an ANCOVA model with treatment group as a fixed effect and baseline PI-NPRS as a covariate. The upper limit of one-sided 90% CI was $+\infty$. Statistical parameters for each cohort are summarized in **TABLE 6**.

Table 6

Statistical Analysis Overview	*Comparison Group Selection*	**High Dose IV APAP, Placebo IV**	**Low Dose IV APAP, Placebo IV**

(TOTPAR24)	*Type of Statistical Test*	Superiority	
	Estimation Parameter	Other [LS Mean Difference] (SE)	
	Estimated Value	12.72	12.14
Method of Estimation (TOTPAR24)	*Confidence Interval*	(1-Sided) 90% 5.92, INF	(1-Sided) 90% 5.31, INF
	Standard Error of the Mean	5.267	5.297
	One-Sided P Value for Diff.	0.0087	0.0120

[00112] The time to perceptible pain relief confirmed (FPR-C) after Dose 1 administration stratified by baseline pain score of moderate or severe for each cohort is summarized in **TABLE 7**. Upon initiation of the infusion of Dose 1, patients were given a stopwatch and asked to press the stopwatch when they first perceived any pain relief (first perceptible pain relief [FPR]).

[00113] If a subject did not record perceptible pain relief and prematurely discontinued from the study prior to 24 hours, then the subject was censored at time of drop out. If a subject did record perceptible pain relief prior to taking rescue medication, the subject was censored at 24 hours. The Evaluable Population included all randomized patients who, as documented prior to the breaking of the study blind: (1) met all the inclusion and exclusion criteria; and (2) were administered Dose 1. The number of subjects censored were 1 in High Dose IVAPAP group, 2 in Low Dose IVAPAP group, and 8 in IV placebo group.

Table 7

Arm/Group Title	High Dose IV APAP	Low Dose IV APAP	Placebo IV
Arm/Group Description:	Acetaminophen (APAP) 10 mg/mL administered post-operatively at a dose of 1300 mg intravenously 3-times daily (q8h)	Acetaminophen (APAP) 10 mg/mL administered post-operatively at a dose of 1000 mg intravenously 4-times daily (q6h)	Placebo given intravenously post-operatively
Overall Number of Participants Analyzed	43	44	22
n	42	42	14
Median time to FPR-C (hours)- for moderate baseline categorical pain intensity score	0.215	0.160	0.595

Median time to FPR-C (hours)- for severe baseline categorical pain intensity score	0.160	0.220	0.890
One-sided p-value	<0.0001	0.0004	

Secondary Outcome.

[00114] Time to meaningful perceptible relief (MPR) measure stratified by baseline pain score of moderate or severe for each cohort is summarized in **TABLE 8**. Upon initiation of the infusion of Dose 1, the patients were given a second stopwatch and asked to press the stopwatch if and when feeling any meaningful perceptible relief; a record of the time was noted in the patient record.

[00115] If a subject did not record perceptible pain relief and prematurely discontinued from the study prior to 24 hours, then the subject was censored at time of drop out. If a subject did not record perceptible pain relief prior to taking rescue medication, the subject was censored at 24 hours.

[00116] The Evaluable Population included all randomized patients who, as documented prior to the breaking of the study blind: (1) met all the inclusion and exclusion criteria and (2) were administered Dose 1. The number of subjects censored were 6 in High Dose IVAPAP group, 8 in Low Dose IVAPAP group, and 15 in IV placebo group.

Table 8

Arm/Group Title	High Dose IV APAP	Low Dose IV APAP	Placebo IV
Arm/Group Description:	Acetaminophen (APAP) 10 mg/mL administered post-operatively at a dose of 1300 mg intravenously 3-times daily (q8h)	Acetaminophen (APAP) 10 mg/mL administered post-operatively at a dose of 1000 mg intravenously 4-times daily (q6h)	Placebo given intravenously post-operatively
Overall Number of Participants Analyzed	43	44	22
n	37	36	7
Median time to MPR (hours)- for moderate baseline categorical pain intensity score	0.660	0.310	NE

Median time to MPR (hours)- for severe baseline categorical pain intensity score	0.680	0.870	NE
One-sided p-value	<0.0001	0.0013	

[00117] The average patient global evaluation of the study medication for each cohort is summarized in **TABLE 9**. The Global Evaluation was recorded at early termination or at 24.25 hours post-surgery, whichever was first. The scale was 0=Poor, 1=Fair, 2=Good, 3=Very Good, and 4=Excellent. The Evaluable Population included all randomized patients who, as documented prior to the breaking of the study blind: (1) met all the inclusion and exclusion criteria and; (2) were administered Dose 1.

Table 9

Arm/Group Title	**High Dose IV APAP**	**Low Dose IV APAP**	**Placebo IV**
Arm/Group Description:	Acetaminophen (APAP) 10 mg/mL administered post-operatively at a dose of 1300 mg intravenously 3-times daily (q8h)	Acetaminophen (APAP) 10 mg/mL administered post-operatively at a dose of 1000 mg intravenously 4-times daily (q6h)	Placebo given intravenously post-operatively
Overall Number of Participants Analyzed	43	44	22
n	42	44	21
Least Squares Mean Global Evaluation (Standard Error) *Unit of Measure: score on a 0-4 scale*	2.8 (0.16)	2.8 (0.16)	2.8 (0.16)

[00118] For both experimental cohorts, the patient global evaluation was analyzed using an ANCOVA model with treatment group as a fixed effect and baseline PI-NPRS as a covariate. The upper limit of one-sided 90% CI was $+\infty$. Statistical parameters for each cohort are summarized in **TABLE 10**.

Table 10

Statistical Analysis Overview (Patient Global Eval.)	*Comparison Group Selection*	**High Dose IV APAP, Placebo IV**	**Low Dose IV APAP, Placebo IV**
	Type of Statistical Test	Superiority	
	Estimation Parameter	Other [LS Mean Difference] (SE)	
	Estimated Value	0.4	0.4
Method of Estimation (Patient Global Eval.)	*Confidence Interval*	(1-Sided) 90% 0.1, INF	(1-Sided) 90% 0.1, INF
	Standard Error of the Mean	0.27	0.27
	One-Sided P Value for Diff.	0.0609	0.0766

[00119] The pain intensity difference rating (PID) at different timepoints after Dose 1 administration is summarized in **TABLE 11**. The Pain intensity difference was calculated from the scores reported on the 0-10 PI-NRS at each observation time after Dose 1 administration. Pain intensity was collected at 0.5, 0.75, 1, 1.25, 1.75, and 2.25 hours (± 5 minutes), 3.25, 4.25, 5.25, 6.25, 7.25, 8.25, 9.25, 10.25, 11.25, and 12.25 (± 5 minutes), 14.25, 16.25, 18.25, 20.25, 22.25, and 24.25 (± 10 minutes) post Dose 1. The Evaluable Population included all randomized patients who, as documented prior to the breaking of the study blind: (1) met all the inclusion and exclusion criteria and (2) were administered Dose 1.

Table 11

Arm/Group Title	**High Dose IV APAP**		**Low Dose IV APAP**		**Placebo IV**	
Arm/Group Description:	Acetaminophen (APAP) 10 mg/mL administered post-operatively at a dose of 1300 mg intravenously 3-times daily (q8h)		Acetaminophen (APAP) 10 mg/mL administered post-operatively at a dose of 1000 mg intravenously 4-times daily (q6h)		Placebo given intravenously post-operatively	
Overall Number of Participants Analyzed	43		44		22	
n	43		44		22	
PID / **Time (hrs)**	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
0.5	-2.5	1.65	-3.1	2.01	-0.7	1.28
0.75	-3.3	1.88	-3.5	2.1	-0.8	1.4
1	-3.7	1.89	-3.8	2.12	-0.8	1.44

1.25	-3.9	2.02	-4	2.29	-0.7	1.52
1.75	-3.9	1.97	-3.7	2.45	-0.7	1.59
2.25	-3.8	2.16	-3.6	2.44	-0.7	1.67
3.25	-3.4	2.32	-3	2.39	-0.9	1.95
4.25	-3.4	2.4	-2.9	2.32	-0.9	1.97
5.25	-3.3	2.48	-2.8	2.39	-2.4	2.59
6.25	-3.2	2.48	-3.5	2.49	-3.7	2.32
7.25	-3	2.61	-4.1	2.34	-4.2	1.99
8.25	-3.8	2.72	-4.4	2.29	-3.7	2.36
9.25	-4.5	2.89	-4.7	2.18	-3.6	2.26
10.25	-4.6	2.71	-5	1.98	-3.4	2.22
11.25	-4.7	2.44	-4.5	1.99	-3.3	2.28
12.25	-4.9	1.85	-4.5	2.31	-2.7	2.27
14.25	-3.7	2.13	-5	2.42	-2.9	1.97
16.25	-3.5	2.29	-4.4	2.08	-2.9	1.97
18.25	-4.4	2.34	-4.5	2.27	-3.5	1.97
20.25	-4.7	2.04	-4.9	2.37	-3.6	2.24
22.25	-4.7	2.25	-5	2.35	-3.9	2.19
24.25	-4.6	2.29	-5.1	2.42	-4.3	1.86

[00120] The pain intensity (PI) rating at different timepoints after dose 1 administration is summarized in **TABLE 12**. Pain intensity was reported using the 11-point Numerical Rating Scale (NRS), with score between 0-10 (0= no pain; 10 = worst imaginable pain). Pain intensity was collected at 0.5, 0.75, 1, 1.25, 1.75, and 2.25 hours (± 5 minutes), 3.25, 4.25, 5.25, 6.25, 7.25, 8.25, 9.25, 10.25, 11.25, and 12.25 (± 5 minutes), 14.25, 16.25, 18.25, 20.25, 22.25, and 24.25 (± 10 minutes) post Dose 1. The Evaluable Population included all randomized patients who, as documented prior to the breaking of the study blind: (1) met all the inclusion and exclusion criteria and (2) were administered Dose 1.

Table 12

Arm/Group Title	**High Dose IV APAP**		**Low Dose IV APAP**		**Placebo IV**	
Arm/Group Description:	Acetaminophen (APAP) administered post-operatively at a dose of 1300 mg intravenously 3-times daily (q8h)		Acetaminophen (APAP) administered post-operatively at a dose of 1000 mg intravenously 4-times daily (q6h)		Placebo given intravenously post-operatively	
Overall Number of Participants Analyzed	43		44		22	
n	43		44		22	
PI / **Time (hrs)**	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
0.5	4.8	1.83	4.4	1.97	6.1	1.42
0.75	4	2.12	4	1.98	6	1.7
1	3.6	1.98	3.7	2.01	6	1.68

1.25	3.4	2.16	3.5	2.14	6.2	1.89
1.75	3.5	2.24	3.8	2.33	6.2	1.94
2.25	3.6	2.4	3.9	2.39	6.2	1.97
3.25	3.9	2.53	4.5	2.48	6	2.17
4.25	4	2.58	4.6	2.33	6	2.21
5.25	4	2.48	4.7	2.44	4.5	2.56
6.25	4.2	2.52	4	2.59	3.2	2.11
7.25	4.3	2.46	3.4	2.22	2.7	1.86
8.25	3.5	2.58	3.1	2.2	3.2	2.3
9.25	2.9	2.71	2.8	1.95	3.3	2.25
10.25	2.8	2.48	2.5	1.68	3.5	2.15
11.25	2.7	2.27	3	1.66	3.5	2.24
12.25	2.5	1.83	3	2.09	4.1	2.32
14.25	3.6	2.29	2.5	2.11	4	2.08
16.25	3.8	2.55	3.1	2.01	4	2.21
18.25	2.9	2.58	3	2.23	3.4	1.99
20.25	2.7	2.28	2.6	2.14	3.2	2.22
22.25	2.6	2.58	2.5	1.96	3	2.16
24.25	2.8	2.38	2.4	2.06	2.6	1.71

[00121] The pain relief (PR) ratings at each observation time after dose 1 administration are summarized in **TABLE 13**. Pain Relief was reported on a 5-Point Categorical Pain Relief Assessment scale: 0 = No Pain Relief, 1 = A Little Pain Relief, 2 = Some Pain Relief, 3 = A Lot of Pain Relief, 4 = Complete Pain Relief. Pain relief was collected at 0.5, 0.75, 1, 1.25, 1.75, and 2.25 hours (± 5 minutes), 3.25, 4.25, 5.25, 6.25, 7.25, 8.25, 9.25, 10.25, 11.25, and 12.25 (± 5 minutes), 14.25, 16.25, 18.25, 20.25, 22.25, and 24.25 (± 10 minutes) post Dose 1. The Evaluable Population included all randomized patients who, as documented prior to the breaking of the study blind: (1) met all the inclusion and exclusion criteria and (2) were administered Dose 1.

Table 13

Arm/Group Title	**High Dose IV APAP**		**Low Dose IV APAP**		**Placebo IV**	
Arm/Group Description:	Acetaminophen (APAP) 10 mg/mL administered post-operatively at a dose of 1300 mg intravenously 3-times daily (q8h)		Acetaminophen (APAP) 10 mg/mL administered post-operatively at a dose of 1000 mg intravenously 4-times daily (q6h)		Placebo given intravenously post-operatively	
Overall Number of Participants Analyzed	43		44		22	
n	43		44		22	
PR / **Time (hrs)**	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
0.5	1.7	0.95	1.8	0.94	0.6	0.85

0.75	2	1.02	2	0.98	0.6	0.85
1	2.1	0.93	2.2	0.96	0.6	0.85
1.25	2.3	0.97	2.2	0.99	0.6	0.85
1.75	2.3	0.97	2	1.07	0.6	0.9
2.25	2.2	1.09	2	1.05	0.6	0.9
3.25	2	1.18	1.7	1.12	0.8	1.15
4.25	2	1.21	1.6	1.12	0.7	1.08
5.25	1.9	1.2	1.5	1.21	1.5	1.44
6.25	1.9	1.23	1.9	1.15	2.1	1.25
7.25	1.8	1.21	2.2	1.03	2.5	1.1
8.25	2.2	1.15	2.4	1.06	2.2	1.27
9.25	2.6	1.22	2.5	0.93	2.1	1.19
10.25	2.6	1.1	2.7	0.8	2	1.2
11.25	2.7	0.97	2.5	0.87	2	1.31
12.25	2.7	0.83	2.4	1.04	1.6	1.33
14.25	2.1	1	2.6	1.04	1.8	1.11
16.25	2.1	1.14	2.3	1.06	1.8	1.14
18.25	2.5	1.1	2.4	1.02	2.1	1.17
20.25	2.7	1	2.6	0.95	2.2	1.18
22.25	2.7	1.11	2.6	0.94	2.3	1.09
24.25	2.5	1.12	2.7	0.99	2.5	0.91

[00122] The time to treatment failure for each cohort is summarized in **TABLE 14**. The time to treatment failure is defined as time to first dose of rescue medication after Dose 1 or withdrawal from the study for any reason. If a subject did not take rescue medication or withdraw from the study prior to 24 hours, the subject was censored at 24 hours. The Evaluable Population included all randomized patients who, as documented prior to the breaking of the study blind: (1) met all the inclusion and exclusion criteria and (2) were administered Dose 1. The number of subjects censored were 31 in High Dose IV APAP group, 32 in Low Dose IV APAP group and 6 in IV Placebo group.

Table 14

Arm/Group Title	High Dose IV APAP	Low Dose IV APAP	Placebo IV
Arm/Group Description:	Acetaminophen (APAP) 10 mg/mL administered post-operatively at a dose of 1300 mg intravenously 3-times daily (q8h)	Acetaminophen (APAP) 10 mg/mL administered post-operatively at a dose of 1000 mg intravenously 4-times daily (q6h)	Placebo given intravenously post-operatively
Overall Number of Participants Analyzed	43	44	22
N	12	12	16

Median time to treatment failure- for moderate baseline categorical pain intensity score	NE	NE	3.680
Median time to treatment failure for severe baseline categorical pain intensity score	NE	NE	1.335
Unit of Measure: hours			
One-sided p-value	<.0001	<.0001	

Safety Outcome.

[00123] The mean change from baseline to 24-hours in systolic and diastolic blood pressure, temperature, pulse rate, and respiration rate observed in each cohort is summarized in **TABLE 15**. Changes from Baseline in the vital parameters are defined as the values at 24 hours minus values at Baseline. Baseline was defined as the last non-missing result prior to administration of the first dose of study drug. Vital signs were obtained at screening, prior to surgery and at Hours 4, 8, 12, 16, 20 and 24 following T0 (±10 min). The Safety Population included all randomized patients who received the study medication. The Safety Population was used for all safety summaries.

Table 15

Arm/Group Title	**High Dose IV APAP**	**Low Dose IV APAP**	**Placebo IV**
Arm/Group Description:	Acetaminophen (APAP) 10 mg/mL administered post-operatively at a dose of 1300 mg intravenously 3-times daily (q8h)	Acetaminophen (APAP) 10 mg/mL administered post-operatively at a dose of 1000 mg intravenously 4-times daily (q6h)	Placebo given intravenously post-operatively
Overall Number of Participants Analyzed	44	44	22
n	43	44	21
Systolic (mm Hg)			
Mean	1.6	1.0	9.2
SD	10.78	11.39	10.99
Diastolic (mm Hg)			
Mean	-0.2	2.3	5.2
SD	8.82	9.56	11.08
Temperature (°C)			
Mean	0.12	0.21	0.06

SD	0.336	0.275	0.347
Pulse Rate (beats/min)			
Mean	5.0	4.2	5.7
SD	11.85	11.58	11.17
Resp. Rate (breaths/min)			
Mean	0.3	-0.6	-1.3
SD	3.39	4.12	3.68

Pharmacokinetic Outcome.

[00124] Prior to surgery, patients had two indwelling catheters placed in the largest available arm veins - one catheter for PK draws and one catheter for IV administration of the study medication. At pre-set time points, a blood sample of approximately 6 mL (collected in K3EDTA tube) was collected, spun down and divided into 2 cryotubes (primary and backup), labeled and frozen.

[00125] An initial baseline PK blood sample was collected at least 5 minutes before administration of Dose 1 of study medication. The time of initiation of Dose 1 was designated as T0. After administration of Dose 1, samples were drawn at 0.25 hr.±3 min (end of infusion), 0.5 hr. ±3 min, 0.75 hr. ± 3 min, 1 hr. ± 5 min, 2 hr. ± 5min , 4 hr.± 5 min, 6 hr.- 5 min (prior to the next planned infusion), 6.25 hr. ± 3 min (end of the infusion), 8hr. - 5 min (prior to the next scheduled infusion), 8.25 hr. ± 3min (end of the infusion), 12 hr. - 5 min (prior to the next scheduled infusion), 12.25 hr. ± 3 min (end of the infusion), 16 hr. - 5 min (prior to the next scheduled infusion), 16.25 hr. ±3 min(end of the infusion), 18 hr. - 5 min (prior to the next scheduled infusion), 18.25 hr. ± 3min (end of the infusion), and at 24.25 hr.± 15 min (after starting the very first infusion).

[00126] The mean area under the plasma concentration-time curve from time of administration to 24 hours after dosing (AUC 0-24h) observed for each cohort is summarized in **TABLE 16**. The Area Under the Plasma Concentration-Time Curve (AUC) is a measure of the plasma concentration of the drug over time used to characterize drug absorption. An ANOVA analysis of daily drug exposure was performed. The PK Evaluable Population included all randomized subjects who, as documented prior to the breaking of the study blind: (1) met all the inclusion and exclusion criteria and (2) were administered Dose 1 resulting in an adequate number of quantifiable concentrations to calculate PK parameters. Subjects with positive pre-dose concentrations were excluded. Geometric LS mean, GMR (1300 mg IV q8hr

/ 1000 mg IV q6hr), 80% CI, 90% CI and p-value were obtained from an ANOVA model with treatment group as a fixed effect.

Table 16

Arm/Group Title	**High Dose IV APAP**	**Low Dose IV APAP**
Arm/Group Description:	Acetaminophen (APAP) 10 mg/mL administered post-operatively at a dose of 1300 mg intravenously 3-times daily (q8h)	Acetaminophen (APAP) 10 mg/mL administered post-operatively at a dose of 1000 mg intravenously 4-times daily (q6h)
Overall Number of Participants Analyzed	43/33	44/39
n	31	38
AUC 0-24h		
Geometric LS Mean	236326.3081	231104.0073
SE	1.06026	1.05427
80% CI	219089.0703, 254919.7174	215823.9573, 247465.8645
Comparison between treatment		
GMR (SE)	1.0226 (1.08204)	
80% CI for GMR	0.9234, 1.1325	
90% CI for GMR	0.8966, 1.1663	
One-Sided Upper-Tailed P Value for GMR	0.3889	

[00127] The mean area under the plasma concentration-time curve from time zero to infinite time (AUC[0-infinity]) and mean half-life ($t_{1/2}$) observed for each cohort is summarized in **TABLE 17**. AUC(0-infinity) is the area under the plasma concentration-time curve from time zero to infinite time. Half-life (t 1/2) is the time measured for the plasma concentration to decrease by 1 half to its original concentration. The PK Evaluable Population included all randomized subjects who, as documented prior to the breaking of the study blind: (1) met all the inclusion and exclusion criteria and; (2) were administered Dose 1 resulting in an adequate number of quantifiable concentrations to calculate PK parameters.

Table 17

Arm/Group Title	**High Dose IV APAP**	**Low Dose IV APAP**
Arm/Group Description:	Acetaminophen (APAP) 10 mg/mL	Acetaminophen (APAP) 10 mg/mL

	administered post-operatively at a dose of 1300 mg intravenously 3-times daily (q8h)	administered post-operatively at a dose of 1000 mg intravenously 4-times daily (q6h)
Overall Number of Participants Analyzed	43	44
n	42	43
AUC(0-∞) (hr*ng/mL)		
Geometric Mean	75925.2553	55018.1382
Geometric CV%	22.405	27.089
$t_{1/2}$ (hrs)		
Mean	2.565	2.360
SD	0.5774	0.4134
CV%	22.51	17.52
Geometric Mean	2.509	2.325
Geometric CV%	21.15	17.73
Median	2.325	2.310
Min	1.84	1.53
Max	4.36	3.31

[00128] The mean maximum observed plasma concentration (Cmax) last dose observed for each cohort is summarized in **TABLE 18**. The PK Evaluable Population included all randomized subjects who, as documented prior to the breaking of the study blind: (1) met all the inclusion and exclusion criteria and (2) were administered Dose 1 resulting in an adequate number of quantifiable concentrations to calculate PK parameters.

Table 18

Arm/Group Title	**High Dose IV APAP**	**Low Dose IV APAP**
Arm/Group Description:	Acetaminophen (APAP) 10 mg/mL administered post-operatively at a dose of 1300 mg intravenously 3-times daily (q8h)	Acetaminophen (APAP) 10 mg/mL administered post-operatively at a dose of 1000 mg intravenously 4-times daily (q6h)
Overall Number of Participants Analyzed	33	39
n	31	39
Cmax (ng/ml)		
Geometric Mean	39531.4	28495.6
Geometric CV%	26	30

Embodiments

[00129] The following non-limiting embodiments provide illustrative examples of the invention, but do not limit the scope of the invention.

[00130] Embodiment 1. A method of treating pain in a subject in need thereof, the method comprising administering to the subject a therapeutically-effective amount of a liquid unit dosage form, wherein the liquid unit dosage form comprises acetaminophen in an amount from about 1100 mg to about 1500 mg, wherein the administration of the liquid unit dosage form is from a single use container.

[00131] Embodiment 2. The method of embodiment 1, wherein the liquid unit dosage form comprises acetaminophen in an amount from about 1200 mg to about 1400 mg.

[00132] Embodiment 3. The method of any one of embodiments 1-2, wherein the liquid unit dosage form comprises acetaminophen in an amount of about 1300 mg.

[00133] Embodiment 4. The method of any one of embodiments 1-3, wherein the pain is dental pain.

[00134] Embodiment 5. The method of any one of embodiments 1-4, wherein the liquid unit dosage form is administered to the subject from one to three times per day.

[00135] Embodiment 6. The method of any one of embodiments 1-5, wherein the liquid unit dosage form is administered to the subject three times per day.

[00136] Embodiment 7. The method of any one of embodiments 1-6, wherein the liquid unit dosage form is administered to the subject within 24 hours prior to the subject undergoing a surgical procedure.

[00137] Embodiment 8. The method of any one of embodiments 1-6, wherein the liquid unit dosage form is administered to the subject simultaneously with the subject undergoing a surgical procedure.

[00138] Embodiment 9. The method of any one of embodiments 1-6, wherein the liquid unit dosage form is administered to the subject within 24 hours after the subject has undergone a surgical procedure.

[00139] Embodiment 10. The method of any one of embodiments 1-9, wherein the administration is parenteral administration.

[00140] Embodiment 11. The method of any one of embodiments 1-9, wherein the administration is intravenous.

[00141] Embodiment 12. A method of treating pain in a subject in need thereof, the method comprising administering to the subject about 1300 mg acetaminophen in a liquid unit dosage form about every 8 hours via intravenous injection, wherein the administration of the liquid unit dosage form is from a single use container.

[00142] Embodiment 100. A pharmaceutical composition comprising, in a liquid unit dosage form, acetaminophen in an amount from about 1100 mg to about 1500 mg, wherein the pharmaceutical composition is formulated for packaging in a single use container.

[00143] Embodiment 101. The pharmaceutical composition of embodiment 100, wherein the liquid unit dosage form further comprises water.

[00144] Embodiment 102. The pharmaceutical composition of any one of embodiments 100-101, wherein the liquid unit dosage form further comprises a pH-adjusting agent.

[00145] Embodiment 103. The pharmaceutical composition of any one of embodiments 100-102, wherein the acetaminophen is present in the liquid unit dosage form in an amount from about 2 mg/mL to about 20 mg/mL.

[00146] Embodiment 104. The pharmaceutical composition of any one of embodiments 100-103, wherein the acetaminophen is present in the liquid unit dosage form in an amount from about 8 mg/mL to about 12 mg/mL.

[00147] Embodiment 105. The pharmaceutical composition of any one of embodiments 100-104, wherein the liquid unit dosage form further comprises an acid, a conjugate base of the acid, or both the acid and conjugate base of the acid.

[00148] Embodiment 106. The pharmaceutical composition of any one of embodiments 100-105, wherein the liquid unit dosage form has a pH of about 4 to about 7.

[00149] Embodiment 107. The pharmaceutical composition of any one of embodiments 100-106, wherein the liquid unit dosage form has a pH of about 5.

[00150] Embodiment 108. The pharmaceutical composition of any one of embodiments 100-106, wherein the liquid unit dosage form has a pH of about 5.5.

[00151] Embodiment 109. The pharmaceutical composition of any one of embodiments 100-106, wherein the liquid unit dosage form has a pH of about 6.

[00152] In some embodiments, the numbers expressing quantities of ingredients, properties such as concentration, reaction conditions, and so forth, used to describe and claim certain embodiments of the invention are to be understood as being modified in some instances by the term "about." Accordingly, in some embodiments, the numerical parameters set forth in the written description and attached claims are approximations that can vary depending upon the desired properties sought to be obtained by a particular embodiment. The recitation of ranges of values herein is merely intended to serve as a shorthand method of referring individually to each separate value falling within the range. Unless otherwise indicated herein, each individual value is incorporated into the specification as if it were individually recited herein.

[00153] As used herein, the term "administering" a pharmaceutical composition or drug refers to both direct and indirect administration of the pharmaceutical composition or drug, wherein direct administration of the pharmaceutical composition or drug is typically performed by a health care professional (e.g., physician, nurse, etc.), and wherein indirect administration includes a step of providing or making available the pharmaceutical composition or drug to the health care professional for direct administration (e.g., via injection, infusion, oral delivery, topical delivery, etc.). It should further be noted that the terms "prognosing" or "predicting" a condition, a susceptibility for development of a disease, or a response to an intended treatment is meant to cover the act of predicting or the prediction (but not treatment or diagnosis of) the condition, susceptibility and/or response, including the rate of progression, improvement, and/or duration of the condition in a subject.

[00154] All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (*e.g.*, "such as") provided with respect to certain embodiments herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention otherwise claimed. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the invention.

[00155] As used in the description herein and throughout the claims that follow, the meaning of "a," "an," and "the" includes plural reference unless the context clearly dictates otherwise. Also, as used in the description herein, the meaning of "in" includes "in" and "on" unless the context clearly dictates otherwise.

[00156] It should be apparent to those skilled in the art that many more modifications besides those already described are possible without departing from the inventive concepts herein. The inventive subject matter, therefore, is not to be restricted except in the scope of the appended claims. Moreover, in interpreting both the specification and the claims, all terms should be interpreted in the broadest possible manner consistent with the context. In particular, the terms "comprises" and "comprising" should be interpreted as referring to elements, components, or steps in a non-exclusive manner, indicating that the referenced elements, components, or steps may be present, or utilized, or combined with other elements, components, or steps that are not expressly referenced. Where the specification claims refers to at least one of something selected from the group consisting of A, B, C .... and N, the text should be interpreted as requiring only one element from the group, not A plus N, or B plus N, etc.

CLAIMS

What is claimed is:

1. A method of treating pain in a subject in need thereof, the method comprising:
   administering to the subject a therapeutically-effective amount of a liquid unit dosage form;
   wherein the liquid unit dosage form comprises acetaminophen in an amount from about 1100 mg to about 1500 mg; and
   wherein the administration of the liquid unit dosage form is from a single use container.

2. The method of claim 1, wherein the liquid unit dosage form comprises acetaminophen in an amount from about 1200 mg to about 1400 mg.

3. The method of claim 1, wherein the liquid unit dosage form comprises acetaminophen in an amount of about 1300 mg.

4. The method of claim 1, wherein the pain is dental pain.

5. The method of claim 1, wherein the liquid unit dosage form is administered to the subject from one to three times per day.

6. The method of claim 1, wherein the liquid unit dosage form is administered to the subject three times per day.

7. The method of claim 1, wherein the liquid unit dosage form is administered to the subject within 24 hours prior to the subject undergoing a surgical procedure.

8. The method of claim 1, wherein the liquid unit dosage form is administered to the subject simultaneously with the subject undergoing a surgical procedure.

9. The method of claim 1, wherein the liquid unit dosage form is administered to the subject within 24 hours after the subject has undergone a surgical procedure.

10. The method of claim 1, wherein the administration is parenteral administration.

11. The method of claim 1, wherein the administration is intravenous.

12. The method of claim 1, wherein the liquid unit dosage form has an acetaminophen concentration of between 5-15 mg/mL.

13. The method of claim 1, wherein the liquid unit dosage form has an acetaminophen concentration of about 10 mg/mL.

14. The method of claim 1, wherein the liquid unit dosage form has a total volume of between 100 mL and 150 mL.

15. The method of claim 1, wherein the liquid unit dosage form has a total volume of about 130 mL.

16. The method of claim 1, wherein the single use container is a polymer bag.

17. The method of claim 16, wherein the polymer bag is packaged in an aluminized over-pouch.

18. A method of treating pain in a subject in need thereof, the method comprising:
administering to the subject about 1300 mg acetaminophen in a liquid unit dosage form about every 8 hours via intravenous injection, wherein the administration of the liquid unit dosage form is from a single use container.

19. The method of claim 18, wherein the liquid unit dosage form is administered at a volume of about 130 mL.

20. The method of claim 18, wherein the acetaminophen is administered post-operatively.

AMENDED CLAIMS
received by the International Bureau on 28 July 2022 (28.07.2022)

What is claimed is:

1. A method of treating pain in a subject in need thereof, the method comprising:
   administering to the subject a therapeutically-effective amount of a liquid unit dosage form;
   wherein the liquid unit dosage form comprises acetaminophen in an amount from about 1100 mg to about 1500 mg;
   wherein the administration of the liquid unit dosage form is from a single use container; and
   wherein the liquid unit dosage form is administered to the subject only three times per day.

2. The method of claim 1, wherein the liquid unit dosage form comprises acetaminophen in an amount from about 1200 mg to about 1400 mg.

3. The method of claim 1, wherein the liquid unit dosage form comprises acetaminophen in an amount of about 1300 mg.

4. The method of claim 1, wherein the pain is dental pain.

5. (canceled)

6. (canceled)

7. The method of claim 1, wherein the liquid unit dosage form is administered to the subject within 24 hours prior to the subject undergoing a surgical procedure.

8. The method of claim 1, wherein the liquid unit dosage form is administered to the subject simultaneously with the subject undergoing a surgical procedure.

9. The method of claim 1, wherein the liquid unit dosage form is administered to the subject within 24 hours after the subject has undergone a surgical procedure.

10. The method of claim 1, wherein the administration is parenteral administration.

11. The method of claim 1, wherein the administration is intravenous.

12. The method of claim 1, wherein the liquid unit dosage form has an acetaminophen concentration of between 5-15 mg/mL.

13. The method of claim 1, wherein the liquid unit dosage form has an acetaminophen concentration of about 10 mg/mL.

14. The method of claim 1, wherein the liquid unit dosage form has a total volume of between 100 mL and 150 mL.

15. The method of claim 1, wherein the liquid unit dosage form has a total volume of about 130 mL.

16. The method of claim 1, wherein the single use container is a polymer bag.

17. The method of claim 16, wherein the polymer bag is packaged in an aluminized over-pouch.

18. A method of treating pain in a subject in need thereof, the method comprising:
administering to the subject about 1300 mg acetaminophen in a liquid unit dosage form about every 8 hours via intravenous injection, wherein the administration of the liquid unit dosage form is from a single use container.

19. The method of claim 18, wherein the liquid unit dosage form is administered at a volume of about 130 mL.

20. The method of claim 18, wherein the acetaminophen is administered post-operatively.

STATEMENT UNDER ARTICLE 19(1)

PCT Article 33(2) Novelty

Applicant has amended independent claim 1 to recite the subject matter of dependent claim 6. The Office indicated in the Search Report that claims 4-9 and 12-17 are novel. See, Box No. V of the Written Opinion of the International Searching Authority.

PCT Article 33(3) Inventive Step Rejection

The Office asserts that **D1** (US 2013/0096201) represents the most relevant state of the art for the subject application. The Office admits that the subject matter of claim 6, now recited in independent claim 1, is different from **D1**. With respect to claim 6, the Office asserts that **D2** (US 2020/0230091) remedies the deficiencies of **D1**. Applicant respectfully disagrees.

Applicant submits that the Office's assertions and conclusions over **D1** in view of **D2** are wholly conclusory and are not supported by any specific reasoning. Indeed, neither **D1** or **D2** teaches, suggests, or even contemplates a method of treating pain comprising administering to the subject a therapeutically-effective amount of a liquid unit dosage comprising acetaminophen in an amount from about 1100 mg to about 1500 mg wherein the liquid unit dosage form is administered to the subject only three times per day, as now recited in claim 1. To the extent the Office asserts that administration of the liquid unit dosage form three times per day would be easily derived from **D2**'s disclosure of administration one to ten times per day, Applicant disagrees. As disclosed throughout the present disclosure, methods of treating pain using liquid unit dosages comprising acetaminophen in an amount of equal to or less than 1000 mg with administration being more than three times per day (*i.e.*, higher frequency and lower dosage amounts) are known in the art to: (1) perform less desirably where the pain is more severe such as for example, with post-operative pain after surgery, and (2) leads to administrative burden due to the increased frequency of administration. *See, e.g.*, instant paragraphs [0005] and [0006]. It is important to note that administration of acetaminophen in an amount of greater than 4,000 mg is not therapeutically acceptable due to the potential hepatotoxic effect. *See, e.g.*, instant paragraph 0005. In contrast to the presently claimed method, none of the cited references solve the problem of improving pain management by decreasing the pain level of a subject and decreasing the administrative burden on the provider

and administration. Such improvement is evidenced in the Examples section of the instant application. *See, e.g.,* instant paragraph [0095]-[00128].

Instead, **D2** appears to disclose a pharmaceutical composition comprising, in a liquid unit dosage form, a gabapentinoid and acetaminophen to improve postoperative pain. *See, e.g., D2 Abstract and Para. [0004].* As described in instant paras. [0023]-[0025], pregabalin, a gabapentinoid, is used in combination with acetaminophen to improve postoperative pain. In support of the effectiveness of this combination, **D2** references to Example 6 to show that the combination "had a synergistic analgesic effect that exceeded the effect and duration of analgesia provided by morphine." As compared to doses of pregabalin with or without acetaminophen. *See, e.g.,* D2 para. [0150]. Furthermore, while **D2** appears to also disclose a variety of dosage amounts and dosage frequencies, none of the dosage amounts or frequencies comprise acetaminophen on its own.

For at least the reasons presented herein, **D1** and **D2** considered alone or in combination do not teach or suggest a method of treating pain comprising administering to the subject a therapeutically-effective amount of a liquid unit dosage comprising acetaminophen in an amount from about 1100 mg to about 1500 mg wherein the liquid unit dosage form is administered to the subject only three times per day, as now recited in claim 1. Accordingly, independent claim 1, and all claims depending therefrom, including claims 2-4 and 7-17, are allowable over **D1** in view of **D2**. Additionally, for at least the reasons presented here, unexamined claims 18-20, which claim subject matter that aligns with claim 1, are also allowable over the cited references.

///

Conclusion

Claims **1-4** and **7-20** are pending in this application. Applicant requests allowance of all pending claims.

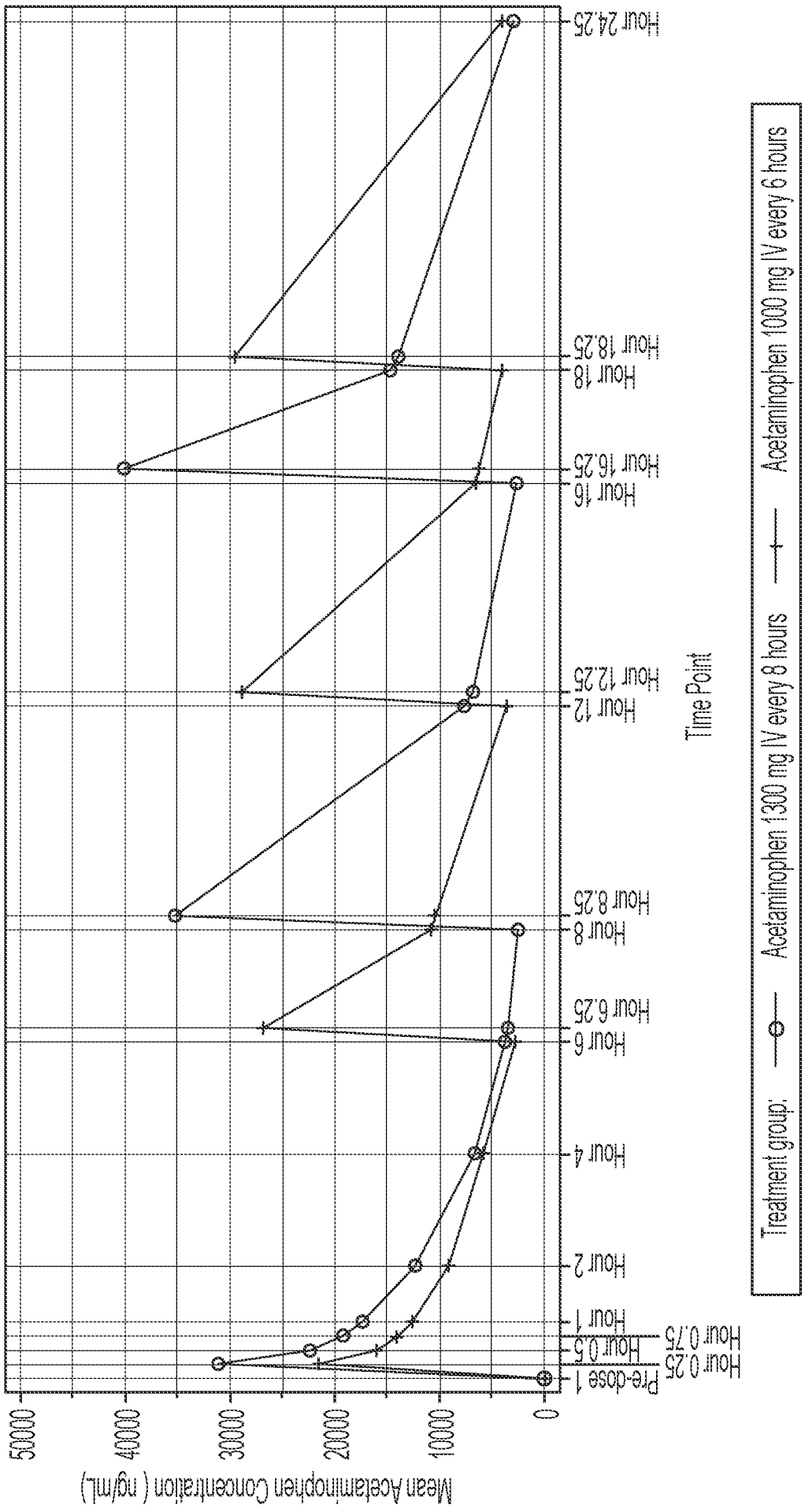
Mean Acetaminophen Concentration (ng/mL)
50000
40000
30000
20000
10000
0
Pre-dose 1
Hour 0.25
Hour 0.5
Hour 0.75
Hour 1
Hour 2
Hour 4
Hour 6
Hour 6.25
Hour 8
Hour 8.25
Hour 12
Hour 12.25
Hour 16
Hour 16.25
Hour 18
Hour 18.25
Hour 24.25
Time Point
Treatment group:
Acetaminophen 1300 mg IV every 8 hours
Acetaminophen 1000 mg IV every 6 hours

FIG. 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/016636

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/167(2006.01)i; **A61K 9/00**(2006.01)i; **A61P 29/00**(2006.01)i; **A61J 1/10**(2006.01)i; **A61J 1/14**(2006.01)i

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)

A61K 31/167(2006.01); A61K 31/197(2006.01); A61K 47/02(2006.01); A61K 47/22(2006.01); A61K 47/40(2006.01); A61K 9/08(2006.01); A61K 9/10(2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal) & Keywords: acetaminophen (paracetamol), analgesic, pain, liquid unit dosage form, high concentration, parenteral administration, single use container

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2013-0096201 A1 (KETAN R. PATEL et al.) 18 April 2013 (2013-04-18) claims 1, 21; and paragraphs [0003], [0057]-[0059]	1-3,10,11
Y		4-9,12-17
Y	US 2020-0230091 A1 (NEVAKAR INC.) 23 July 2020 (2020-07-23) claims 14-66; and paragraphs [0015]-[0104]	4-9,12-17
A	EP 3656377 A1 (HYLORIS PHARMACEUTICALS SA) 27 May 2020 (2020-05-27) abstract; and claims 1, 13	1-17
A	WO 2020-043587 A1 (GSK CONSUMER HEALTHCARE S.A.) 05 March 2020 (2020-03-05) abstract; and claim 1	1-17
A	WO 2009-098716 A2 (APTUIT LAURUS PRIVATE LIMITED et al.) 13 August 2009 (2009-08-13) abstract; and claims 1, 13	1-17

☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"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
30 May 2022	**31 May 2022**

Name and mailing address of the ISA/KR	Authorized officer
Korean Intellectual Property Office **189 Cheongsa-ro, Seo-gu, Daejeon** **35208, Republic of Korea**	**HEO, Joo Hyung**
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/016636

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.: **18-20**
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 18-20 pertain to methods for treatment of the human body by surgery or therapy, as well as diagnostic methods (PCT Article 17(2)(a)(i) and Rule 39.1(iv)).

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.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US2022/016636

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US2022/016636

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