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APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
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Title of Invention

METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1503	FILED BY	Diana Sciamanna
PATENT CENTER #	70663120	AUTHORIZED BY	John Kozlowski
CUSTOMER #	58249	FILING DATE	-
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Neil M. COWEN

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 501283	E20255TJ39109640	Diana Sciamanna

FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
1011	BASIC FILING FEE - UTILITY (PAPER FILING ALSO REQUIRES NON-ELECTRONIC FILING FEE UNDER 1.16(T))	350.00	1	350.00
1111	UTILITY PATENT APPL. SEARCH FEE	770.00	1	770.00
1311	PATENT APPL. EXAMINATION FEE	880.00	1	880.00
1056	FILING AN APPLICATION OR PRESENTATION OF BENEFIT CLAIM MORE THAN NINE YEARS AFTER EARLIEST BENEFIT DATE	4000.00	1	4000.00
1817	REQUEST FOR PRIORITIZED EXAMINATION	4515.00	1	4515.00

1054	Non-DOCX Filing Surcharge	430.00	1	430.00
1830	PROCESSING FEE, EXCEPT IN PROVISIONAL APPLICATIONS	150.00	1	150.00
TOTAL AMOUNT:				\$11,095.00

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National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)			
First Named Inventor:	Neil M. COWEN	Nonprovisional Application Number (if known):	Not Yet Assigned
Title of Invention:	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME		
APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION. 1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently \$0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application. 2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed. 3. The applicable box is checked below: I. ☒ <u>Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)</u> i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via USPTO patent electronic filing system. ---OR--- (b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper. ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, <u>or</u> the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application. II. ☐ <u>Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)</u> i. A request for continued examination has been filed with, or prior to, this form. ii. If the application is a utility application, this certification and request is being filed via USPTO patent electronic filing system. iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371. iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination. v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).			
Signature /John Kozlowski/		Date May 30, 2025	
Name (Print/Typed) John Kozlowski		Practitioner Registration Number 82,124	
Note: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required. *			
☒ *Total of <u>1</u> forms are submitted.			

METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. Patent Application No. 18/988,636, filed December 19, 2024, which is a continuation of U.S. Patent Application No. 18/824,811, filed September 4, 2024, now U.S. Patent No. 12,178,823, which is a continuation of U.S. Patent Application No. 18/421,914, filed January 24, 2024, now U.S. Patent No. 12,109,216, which is a continuation of U.S. Patent Application No. 17/104,433, filed November 25, 2020, which is a continuation of U.S. Patent Application No. 16/573,965, filed September 17, 2019, now U.S. Patent No. 10,874,676, which is a continuation of U.S. Patent Application No. 16/041,237, filed July 20, 2018, now U.S. Patent No. 10,456,408, which is a continuation of U.S. Patent Application No. 15/671,792, filed August 8, 2017, now U.S. Patent No. 10,058,557, which is a divisional of U.S. Patent Application No. 14/940,018, filed November 12, 2015, now U.S. Patent No. 9,757,384, which claims priority to U.S. Provisional Patent Application No. 62/080,150, filed November 14, 2014, U.S. Provisional Patent Application No. 62/138,245, filed March 25, 2015, U.S. Provisional Patent Application No. 62/170,035, filed June 2, 2015, and U.S. Provisional Patent Application No. 62/221,359, filed September 21, 2015, each of which is incorporated herein in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to pharmaceutical formulations of potassium ATP (K_{ATP}) channel openers and their use for treatment of various diseases and conditions such as Prader-Willi Syndrome (PWS), Smith–Magenis syndrome (SMS), and the like.

BACKGROUND OF THE INVENTION

[0003] The following description of the background of the invention is provided simply as an aid in understanding the invention and is not admitted to describe or constitute prior art to the invention.

[0004] ATP-sensitive potassium (K_{ATP}) channels play important roles in a variety of tissues by coupling cellular metabolism to electrical activity. The K_{ATP} channel has been identified as an octameric complex of two unrelated proteins, which assemble in a 4:4 stoichiometry. The

first is a pore forming subunit, Kir6.x, which forms an inwardly rectifying K⁺ channel; the second is an ABC (ATP binding cassette) transporter, also known as the sulfonylurea receptor (SURx) (Babenko, et al., *Annu. Rev. Physiol.*, 60:667-687 (1998)). The Kir6.x pore forming subunit is common for many types of K_{ATP} channels, and has two putative transmembrane domains (identified as TM1 and TM2), which are linked by a pore loop (H5). The subunit that comprises the SUR receptor includes multiple membrane-spanning domains and two nucleotide-binding folds.

[0005] According to their tissue localization, K_{ATP} channels exist in different isoforms or subspecies resulting from the assembly of the SUR and Kir subunits in multiple combinations. The combination of the SUR1 with the Kir6.2 subunits (SUR1/Kir6.2) typically forms the adipocyte and pancreatic B-cell type K_{ATP} channels, whereas the SUR2A/Kir6.2 and the SUR2B/Kir6.2 or Kir6.1 combinations typically form the cardiac type and the smooth muscle type K_{ATP} channels, respectively (Babenko, et al., *Annu. Rev. Physiol.*, 60:667-687 (1998)). There is also evidence that the channel may include Kir2.x subunits. This class of potassium channels are inhibited by intracellular ATP and activated by intracellular nucleoside diphosphates. Such K_{ATP} channels link the metabolic status of the cells to the plasma membrane potential and in this way play a key role in regulating cellular activity. In most excitatory cells, K_{ATP} channels are closed under normal physiological conditions and open when the tissue is metabolically compromised (e.g. when the (ATP:ADP) ratio falls). This promotes K⁺ efflux and cell hyperpolarization, thereby preventing voltage-operated Ca²⁺ channels (VOCs) from opening. (*Prog Res Research*, (2001) 31:77-80).

[0006] Potassium channel openers (PCOs or KCOs) (also referred to as channel activators or channel agonists), are a structurally diverse group of compounds with no apparent common pharmacophore linking their ability to antagonize the inhibition of K_{ATP} channels by intracellular nucleotides. Diazoxide is a PCO that stimulates K_{ATP} channels in pancreatic β-cells (see Trube, et al., *Pfluegers Arch kEur J Physiol*, 407, 493-99 (1986)). Pinacidil and chromakalim are PCOs that activate sarcolemmal potassium channels (see Escande, et al., *Biochem Biophys Res Commun*, 154, 620-625 (1988); Babenko, et al., *J Biol Chem*, 275(2), 717-720 (2000)). Responsiveness to diazoxide has been shown to reside in the 6th through 11th predicted transmembrane domains (TMD6-11) and the first nucleotide-binding fold (NBF1) of the SUR1 subunit.

[0007] Diazoxide, which is a nondiuretic benzothiadiazine derivative having the formula 7-chloro-3-methyl-2H-1,2,4-benzothiadiazine 1.1-dioxide (empirical formula $C_8H_7ClN_2O_2S$), is commercialized in three distinct formulations to treat two different disease indications: 1) hypertensive emergencies and 2) hyperinsulinemic hypoglycemic conditions. Hypertensive emergencies are treated with Hyperstat IV, an aqueous formulation of diazoxide for intravenous use, adjusted to pH 11.6 with sodium hydroxide. Hyperstat IV is administered as a bolus dose into a peripheral vein to treat malignant hypertension or sulfonylurea overdose. In this use, diazoxide acts to open potassium channels in vascular smooth muscle, stabilizing the membrane potential at the resting level, and preventing vascular smooth muscle contraction.

[0008] Hyperinsulinemic hypoglycemic conditions are treated with Proglycem, an oral pharmaceutical version of diazoxide useful for administration to infants, children and adults. It is available as a chocolate mint flavored oral suspension, which includes 7.25% alcohol, sorbitol, chocolate cream flavor, propylene glycol, magnesium aluminum silicate, carboxymethylcellulose sodium, mint flavor, sodium benzoate, methylparaben, hydrochloric acid to adjust the pH, poloxamer 188, propylparaben and water. Diazoxide is also available as a capsule with 50 or 100 mg of diazoxide including lactose and magnesium stearate.

[0009] Several experimental formulations of diazoxide have been tested in humans and animals. These include an oral solution tested in pharmacodynamic and pharmacokinetic studies and a tablet formulation under development as an anti-hypertensive, but never commercialized (see Calesnick, et al., *J. Pharm. Sci.* 54:1277-1280 (1965); Reddy, et al., *AAPS Pharm Sci Tech* 4(4):1-98, 9 (2003); US Patent 6,361,795).

[0010] Current oral formulations of diazoxide are labeled for dosing two or three times per day at 8 or 12 hour intervals. Most patients receiving diazoxide are dosed three times per day. Commercial and experimental formulations of diazoxide are characterized by rapid drug release following ingestion with completion of release in approximately 2 hours.

[0011] Current oral formulations of diazoxide in therapeutic use result in a range of adverse side effects including dyspepsia, nausea, diarrhea, fluid retention, edema, reduced rates of excretion of sodium, chloride, and uric acid, hyperglycemia, vomiting, abdominal pain, ileus, tachycardia, palpitations, and headache (see current packaging insert for the Proglycem). Oral treatment with diazoxide is used in individuals experiencing serious disease where failing to treat

results in significant morbidity and mortality. The adverse side effects from oral administration are tolerated because the benefits of treatment are substantial. The adverse side effects profile of oral diazoxide limit the utility of the drug in treating obese patients at doses within the labeled range of 3 to 8 mg/kg per day.

[0012] The effect of diazoxide in animal models of diabetes and obesity (e.g. obese and lean Zucker rats) has been reported. See e.g. Alemzadeh et al. (*Endocrinology* 133:705-712 (1993)), Alemzadeh et al. (*Metabolism* 45:334-341 (1996)), Alemzadeh et al. (*Endocrinology* 140:3197-3202 (1999)), Stanridge et al. (*FASEB J* 14:455-460 (2000)), Alemzadeh et al. (*Med Sci Monit* 10(3): BR53-60 (2004)), Alemzadeh and Tushaus (*Endocrinology* 145(12):3476-3484 (2004)), Aizawa et al. (*J of Pharma Exp Ther* 275(1): 194-199 (1995)), and Surwit et al. (*Endocrinology* 141:3630-3637 (2000)).

[0013] The effect of diazoxide in humans with obesity or diabetes has been reported. See e.g., Wigand and Blackard (*Diabetes* 28(4):287-291 (1979); evaluation of diazoxide on insulin receptors), Ratzmann et al. (*Int J Obesity* 7(5):453-458 (1983); glucose tolerance and insulin sensitivity in moderately obese patients), Marugo et al. (*Boll Spec It Biol Sper* 53:1860-1866 (1977); moderate dose diazoxide treatment on weight loss in obese patients), Alemzadeh et al. (*J Clin Endocr Metab* 83:1911-1915 (1998); low dose diazoxide treatment on weight loss in obese hyperinsulinemic patients), Guldstrand et al. (*Diabetes and Metabolism* 28:448-456 (2002); diazoxide in obese type II diabetic patients), Ortqvist et al. (*Diabetes Care* 27(9):2191-2197 (2004); beta-cell function measured by circulating C-peptide in children at clinical onset of type 1 diabetes), Bjork et al. (*Diabetes Care* 21(3):427-430 (1998); effect of diazoxide on residual insulin secretion in adult type I diabetes patients), and Qvigstad et al., (*Diabetic Medicine* 21:73-76 (2004)).

[0014] U.S. Patent No. 5,284,845 describes a method for normalizing blood glucose and insulin levels in an individual exhibiting normal fasting blood glucose and insulin levels and exhibiting in an oral glucose tolerance test, elevated glucose levels and at least one insulin level abnormality selected from the group consisting of a delayed insulin peak, an exaggerated insulin peak and a secondary elevated insulin peak. According to this reference, the method includes administering diazoxide in an amount from about 0.4 to about 0.8 mg/kg body weight before each meal in an amount effective to normalize the blood glucose and insulin levels.

[0015] U.S. Patent No. 6,197,765 describes administration of diazoxide as a treatment for syndrome-X, and resulting complications, that include hyperlipidemia, hypertension, central obesity, hyperinsulinemia and impaired glucose intolerance. According to this reference, diazoxide interferes with pancreatic islet function by ablating endogenous insulin secretion resulting in a state of insulin deficiency and high blood glucose levels equivalent to that of diabetic patients that depend on exogenous insulin administration for normalization of their blood glucose levels.

[0016] U.S. Patent No. 2,986,573 describes diazoxide and alkali metal salts for the treatment of hypertension.

[0017] U.S. Patent no. 5,629,045 describes diazoxide for topical ophthalmic administration.

[0018] WO 98/10786 describes use of diazoxide in the treatment of X-syndrome including obesity associated therewith.

[0019] U.S. Patent publication no. 2003/0035106 describes diazoxide-containing compounds for reducing the consumption of fat-containing foods.

[0020] U.S. Patent publication no. 2004/0204472 describes the use of a Cox-2 inhibitor plus diazoxide in the treatment of obesity.

[0021] U.S. Patent publication no. 2002/0035106 describes the use of K_{ATP} channel openers including diazoxide and metal salts for reducing the consumption of fat containing food.

SUMMARY OF THE INVENTION

[0022] Provided herein are pharmaceutical formulations of K_{ATP} channel openers and their use (optionally in combination with growth hormone) for treatment of various diseases and conditions, including Prader-Willi Syndrome (PWS), Smith-Magenis syndrome (SMS), and the like. Such formulations are characterized as being bioavailable. A K_{ATP} channel opener as used herein has any one or more of the following properties: (1) opening SUR1/Kir6.2 potassium channels; (2) binding to the SUR1 subunit of K_{ATP} channels; and (3) inhibiting glucose induced release of insulin following administration of the compound *in vivo*. Preferably, K_{ATP} channel openers are K_{ATP} channel openers with all three properties. K_{ATP} channel openers as defined above preferably have the structure of compounds of Formulas I-VII as set forth below.

[0023] In accordance with one aspect of the present invention, it has been discovered that one or more K_{ATP} channel opener(s) (optionally in combination with growth hormone) is effective for the treatment of a subject having Prader-Willi Syndrome (PWS), Smith–Magenis syndrome (SMS), and the like, and is especially effective for increasing the lean body mass of such subjects. Therefore, in one aspect of the present invention, there are provided methods of increasing the lean body mass of a subject having Prader-Willi Syndrome (PWS), Smith–Magenis syndrome (SMS), and the like, said method comprising administering to said subject for at least 4 weeks an effective amount of a K_{ATP} channel opener (optionally in combination with growth hormone).

[0024] In some embodiments, the lean body mass of said subject is increased by at least 1%. In some embodiments, the lean body mass of said subject is increased by at least 2%. In some embodiments, the lean body mass of said subject is increased by at least 3%. In some embodiments, the lean body mass of said subject is increased by at least 4%. In some embodiments, the lean body mass of said subject is increased by at least 5%.

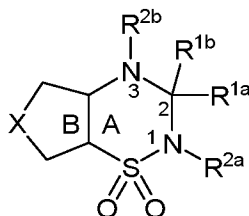
[0025] In addition to increasing the lean body mass of a subject, in some embodiments, invention methods also reduce the hyperphagia of a subject. In some embodiments, the hyperphagia of said subject is reduced by at least 10%. In some embodiments, the hyperphagia of said subject is reduced by at least 20%. In some embodiments, the hyperphagia of said subject is reduced by at least 30%.

[0026] In addition to increasing the lean body mass of a subject, in some embodiments, invention methods also reduce the body fat of a subject. In some embodiments, the body fat of said subject is reduced by at least 1%. In some embodiments, the body fat of said subject is reduced by at least 3%. In some embodiments, the body fat of said subject is reduced by at least 5%.

[0027] In another aspect, the present invention provides a method of increasing the lean body mass of a subject having Prader-Willi Syndrome (PWS), Smith–Magenis syndrome (SMS), and the like, wherein said subject is already being treated by administration thereto of growth hormone, said method comprising co-administering to said subject an effective amount of a K_{ATP} channel opener in addition to said growth hormone.

[0028] In yet another aspect, the present invention provides a method of increasing the lean body mass of a subject having Prader-Willi Syndrome (PWS), Smith–Magenis syndrome (SMS), and the like, wherein said subject is already being treated by administration thereto of an effective amount of a K_{ATP} channel opener, said method comprising co-administering to said subject an effective amount of growth hormone in addition to said K_{ATP} channel opener.

[0029] K_{ATP} channel openers defined by Formula I are as follows:



Formula I

wherein:

R^{1a} and R^{1b}, when present, are independently selected from the group consisting of hydrogen, lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, amino, and substituted amino;

R^{2a} and R^{2b}, when present, are independently selected from the group consisting of hydrogen, and lower alkyl;

X is a 1, 2 or 3 atom chain, wherein each atom is independently selected from carbon, sulfur or nitrogen, and each atom is optionally substituted with halogen, hydroxyl, lower alkyl, substituted lower alkyl, lower alkoxy, cycloalkyl, substituted cycloalkyl, substituted lower alkoxy, amino, or substituted amino;

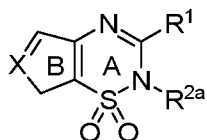
wherein rings A and B are each independently saturated, monounsaturated, polyunsaturated or aromatic;

and all bioequivalents including salts, prodrugs and isomers thereof.

[0030] In particular embodiments, compounds of Formula I may include a double bond between either positions 1 and 2 or positions 2 and 3 of Ring A. When a double bond is present between positions 1 and 2 of Ring A, R^{2a} is absent and one of R^{1a} and R^{1b} are absent. When a double bond is present between positions 2 and 3 of Ring A, R^{2b} is absent and one of R^{1a} and R^{1b}

are absent. In a preferred embodiment, R^{1a} and R^{1b} are not amino. In another preferred embodiment, Ring B does not include any heteroatoms.

[0031] K_{ATP} channel openers defined by Formula II being a subgenera of Formula I are as follows:



Formula II

wherein:

R^1 is selected from the group consisting of hydrogen, lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, amino, and substituted amino;

R^{2a} is selected from the group consisting of hydrogen, and lower alkyl;

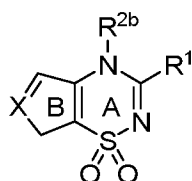
X is a 1, 2 or 3 atom chain, wherein each atom is independently selected from carbon, sulfur or nitrogen, and each atom is optionally substituted with halogen, hydroxyl, lower alkyl, substituted lower alkyl, lower alkoxy, cycloalkyl, substituted cycloalkyl, substituted lower alkoxy, amino, or substituted amino;

wherein ring B is saturated, monounsaturated, polyunsaturated or aromatic;

and all bioequivalents including salts, prodrugs and isomers thereof.

[0032] In particular embodiments of Formula II, X is $C(R^a)C(R^b)$, wherein R^a and R^b are independently selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, lower alkoxy, substituted lower alkoxy, amino, sulfonylamino, aminosulfonyl, sulfonyl, and the like. In further embodiments, R^a and R^b are independently selected from the group consisting of hydroxyl, substituted oxy, substituted thiol, alkylthio, substituted alkylthio, sulfinyl, sulfonyl, substituted sulfinyl, substituted sulfonyl, substituted sulfonylamino, substituted amino, substituted amine, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino, and the like. In a preferred embodiment, R^1 is not amino. In another preferred embodiment, Ring B does not include any heteroatoms.

[0033] K_{ATP} channel openers defined by Formula III being a subgenera of Formula I are as follows:



Formula III

wherein:

R¹ is selected from the group consisting of hydrogen, lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, amino, and substituted amino;

R^{2b} is selected from the group consisting of hydrogen, and lower alkyl;

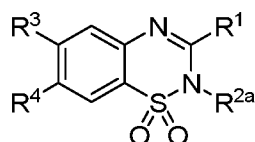
X is a 1, 2 or 3 atom chain, wherein each atom is independently selected from carbon, sulfur or nitrogen, and each atom is optionally substituted with halogen, hydroxyl, lower alkyl, substituted lower alkyl, lower alkoxy, cycloalkyl, substituted cycloalkyl, substituted lower alkoxy, amino, or substituted amino;

wherein ring B is saturated, monounsaturated, polyunsaturated or aromatic;

and all bioequivalents including salts, prodrugs and isomers thereof.

[0034] In particular embodiments of Formula III, X is C(R^a)C(R^b), wherein R^a and R^b are independently selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, lower alkoxy, substituted lower alkoxy, amino, sulfonylamino, aminosulfonyl, sulfonyl, and the like. In further embodiments, R^a and R^b are independently selected from the group consisting of hydroxyl, substituted oxy, substituted thiol, alkylthio, substituted alkylthio, sulfinyl, sulfonyl, substituted sulfinyl, substituted sulfonyl, substituted sulfonylamino, substituted amino, substituted amine, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino, and the like. In a preferred embodiment, R¹ is not amino. In another preferred embodiment, Ring B does not include any heteroatoms.

[0035] K_{ATP} channel openers defined by Formula IV being a subgenera of Formula I are as follows:



Formula IV

wherein:

R¹ is selected from the group consisting of hydrogen, lower alkyl, substituted lower alkyl, cycloalkyl, amino, and substituted lower amino;

R^{2a} is selected from the group consisting of hydrogen, lower alkyl, and substituted lower alkyl;

R³ is selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, amino, and substituted amino;

R⁴ is selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, amino, and substituted amino;

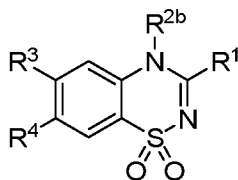
and all bioequivalents including salts, prodrugs and isomers thereof.

[0036] In particular embodiments of Formula IV, R¹ is a lower alkyl (preferably ethyl or methyl); R^{2a} is hydrogen; and R³ and R⁴ are each independently halogen.

[0037] In a preferred embodiment of Formula IV, R¹ is not amino.

[0038] In another embodiment of Formula IV, R¹ is methyl; R^{2a} is hydrogen; R³ is selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, amino, substituted amino, cycloalkyl, and substituted cycloalkyl; and R⁴ is chlorine.

[0039] K_{ATP} channel openers defined by Formula V being a subgenera of Formula I are as follows:



Formula V

wherein:

R^1 is selected from the group consisting of hydrogen, lower alkyl, substituted lower alkyl, cycloalkyl, amino, and substituted lower amino;

R^{2b} is selected from the group consisting of hydrogen, lower alkyl, and substituted lower alkyl;

R^3 is selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, amino, and substituted amino;

R^4 is selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, amino, and substituted amino;

and all bioequivalents including salts, prodrugs and isomers thereof.

[0040] In particular embodiments of Formula V, R^1 is a lower alkyl (preferably ethyl or methyl); R^{2b} is hydrogen; and R^3 and R^4 are each independently halogen.

[0041] In a preferred embodiment of Formula V, R^1 is not amino.

[0042] In another embodiment of Formula V, R^1 is methyl; R^{2b} is hydrogen; R^3 is selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, amino, substituted amino, cycloalkyl, and substituted cycloalkyl; and R^4 is chlorine.

[0043] K_{ATP} channel openers defined by Formula VI are as follows:



Formula VI

wherein:

R^1 is selected from the group consisting of hydrogen, lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, amino, and substituted lower amino, or R^1 can cooperate with R^5 or R^6 to form an additional ring;

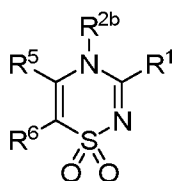
R^{2a} is selected from the group consisting of hydrogen, lower alkyl, and substituted lower alkyl;

R^5 is selected from the group consisting of hydrogen, halogen, hydroxyl, lower alkyl, substituted lower alkyl, amino, substituted amino, sulfonyl, aminosulfonyl, and sulfonylamino, or R^5 can cooperate with R^1 or R^6 to form an additional ring;
 R^6 is selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, amino, substituted amino, sulfonyl, aminosulfonyl, and sulfonylamino, or R^6 can cooperate with R^1 or R^5 to form an additional ring;
 wherein the ring formed by the cooperation of R^1 and R^5 , or R^1 and R^6 , or R^5 and R^6 is saturated, monounsaturated, polyunsaturated or aromatic;
 wherein the ring formed by the cooperation of R^1 and R^5 , or R^1 and R^6 , or R^5 and R^6 is optionally substituted with halogen, hydroxyl, lower alkyl, substituted lower alkyl, amino, substituted amino, sulfonyl, aminosulfonyl, or sulfonylamino;
 and all bioequivalents including salts, prodrugs and isomers thereof.

[0044] In a preferred embodiment, R^1 is not an amino substituent.

[0045] In another embodiment of Formula VI, R^5 and R^6 combine to form a 6 membered ring. In another embodiment, R^5 and R^6 combine to form a 6 membered ring wherein at least one nitrogen is present. Preferably, the ring formed by R^5 and R^6 does not include any heteroatoms.

[0046] K_{ATP} channel openers defined by Formula VII are as follows:



Formula VII

wherein:

R^1 is selected from the group consisting of hydrogen, lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, amino, and substituted lower amino, or R^1 can cooperate with R^5 or R^6 to form an additional ring;

R^{2b} is selected from the group consisting of hydrogen, lower alkyl, and substituted lower alkyl;

R⁵ is selected from the group consisting of hydrogen, halogen, hydroxyl, lower alkyl, substituted lower alkyl, amino, substituted amino, sulfonyl, aminosulfonyl, and sulfonylamino, or R⁵ can cooperate with R¹ or R⁶ to form an additional ring;

R⁶ is selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, amino, substituted amino, sulfonyl, aminosulfonyl, and sulfonylamino, or R⁶ can cooperate with R¹ or R⁵ to form an additional ring;

wherein the ring formed by the cooperation of R¹ and R⁵, or R¹ and R⁶, or R⁵ and R⁶ is saturated, monounsaturated, polyunsaturated or aromatic;

wherein the ring formed by the cooperation of R¹ and R⁵, or R¹ and R⁶, or R⁵ and R⁶ is optionally substituted with halogen, hydroxyl, lower alkyl, substituted lower alkyl, amino, substituted amino, sulfonyl, aminosulfonyl, or sulfonylamino; and all bioequivalents including salts, prodrugs and isomers thereof.

[0047] In a preferred embodiment, R¹ is not an amino substituent.

[0048] In another embodiment of Formula VI, R⁵ and R⁶ combine to form a 6 membered ring. In another embodiment, R⁵ and R⁶ combine to form a 6 membered ring wherein at least one nitrogen is present. Preferably, the ring formed by R⁵ and R⁶ does not include any heteroatoms.

[0049] Unless otherwise indicated, reference in this application to K_{ATP} channel openers should be understood to refer to K_{ATP} channel opener(s) having one or more and preferably all three of the following properties: (1) opening SUR1/Kir6.2 potassium channels; (2) binding to the SUR1 subunit of K_{ATP} channels; and (3) inhibiting glucose induced release of insulin following administration of the compound *in vivo*. Such K_{ATP} channel openers preferably have the structure of any of the compounds of Formulae I-VII, or more preferably Formulae I-VII where R¹ is not amino and also where ring B or its equivalent does not include any heteroatoms, or more preferably, any of the compounds of Formulae II or III, or more preferably, any of the compounds of Formulae II or III where R¹ is not amino and also where ring B or its equivalent

does not include any heteroatoms, or more preferably, the structure is diazoxide. Structural variants or bioequivalents of the compounds of any of Formulae I-VII such as derivatives, salts, prodrugs or isomers are also contemplated. Other K_{ATP} channel openers that are contemplated for use herein include BPDZ62, BPDZ 73, NN414, BPDZ 154.

[0050] *In vitro* analysis of glucose induced release of insulin via K_{ATP} channel openers can be determined using rat islets as provided by De Tullio, et al., *J. Med. Chem.*, 46:3342-3353 (2003) or by using human islets as provided by Björklund, et al., *Diabetes*, 49:1840-1848 (2000).

[0051] Provided herein are formulations, such as controlled release pharmaceutical formulations, of K_{ATP} channel openers and bioequivalents thereof. In one embodiment, the controlled release formulations are formulated for oral administration. Such formulations contain in a single administration dosage between 10 and 100 mg, between 25 and 100 mg, between 100 and 200 mg, between 200 and 300 mg, between 300 and 500 mg or between 500 and 2000 mg of the K_{ATP} channel openers. In certain embodiments, the dosage of the K_{ATP} channel openers contained in a formulation may be determined based on the weight of the patient for which it is to be administered, *i.e.*, the formulation may contain in a single administration dosage between 0.1-20 mg of the K_{ATP} channel opener per kg of the patient's body weight, or between 0.1-0.5 mg of the K_{ATP} channel opener per kg of the patient's body weight; or between 0.5-1 mg of the K_{ATP} channel opener per kg of the patient's body weight; or between 1-2 mg of the K_{ATP} channel opener per kg of the patient's body weight, or between 2-5 mg of the K_{ATP} channel opener per kg of the patient's body weight, or between 5-10 mg of the K_{ATP} channel opener per kg of the patient's body weight, or between 10-15 mg of the K_{ATP} channel opener per kg of the patient's body weight, or between 15-20 mg of the K_{ATP} channel opener per kg of the patient's body weight.

[0052] Also provided herein are controlled release pharmaceutical formulations containing K_{ATP} channel openers obtained by at least one of the following: (a) particle size reduction involving comminution, spray drying, or other micronising techniques, (b) use of a pharmaceutical salt of the K_{ATP} channel opener, (c) use of an ion exchange resin, (d) use of inclusion complexes, for example cyclodextrin, (e) compaction of the K_{ATP} channel opener with a solubilizing agent including a low viscosity hypromellose, low viscosity methylcellulose or

similarly functioning excipient or combinations thereof, (f) associating the K_{ATP} channel opener with a salt prior to formulation, (g) use of a solid dispersion of the K_{ATP} channel opener, (h) use of a self emulsifying system, (i) addition of one or more surfactants to the formulation, (j) use of nanoparticles, or (k) combinations of these approaches.

[0053] Further provided herein are controlled release pharmaceutical formulations containing K_{ATP} channel openers which include at least one component that substantially inhibits release of the K_{ATP} channel activator from the formulation until after gastric transit. As used herein, “substantially inhibits” means less than 15% release, more preferably at least less than 10% release, or more preferably at least less than 5% release of the drug from the formulation during gastric transport. Release can be measured in a standard USP based in-vitro gastric dissolution assay in a calibrated dissolution apparatus (see, for example, U.S. Pharmacopeia, Chapter 711 (2005)).

[0054] Also provided are oral pharmaceutical formulations of K_{ATP} channel openers which include at least one component that substantially inhibits release of the K_{ATP} channel opener from the formulation until after gastric transit. Substantial inhibition of drug release during gastric transit is achieved by inclusion of a component in the formulation selected from the group consisting of: (a) a pH sensitive polymer or co-polymer applied as a compression coating on a tablet, (b) a pH sensitive polymer or co-polymer applied as a thin film on a tablet, (c) a pH sensitive polymer or co-polymer applied as a thin film to an encapsulation system, (d) a pH sensitive polymer or co-polymer applied to encapsulated microparticles, (e) a non-aqueous-soluble polymer or co-polymer applied as a compression coating on a tablet, (f) a non-aqueous-soluble polymer or co-polymer applied as a thin film on a tablet, (g) a non-aqueous soluble polymer applied as a thin film to an encapsulation system, (h) a non-aqueous soluble polymer applied to microparticles, (i) incorporation of the formulation in an osmotic pump system, (j) use of systems controlled by ion exchange resins, and (k) combinations of these approaches, wherein the pH sensitive polymer or co-polymer is resistant to degradation under acid conditions.

[0055] Also provided herein are controlled release pharmaceutical formulations of K_{ATP} channel openers, wherein the formulation includes at least one component that contributes to sustained release of a K_{ATP} channel opener over a period of 2-4 hours following administration,

or over a period of 4-8 hours following administration, or over a period of more than 8-24 hours following administration. These formulations are characterized in having one of the following components: (a) a pH sensitive polymeric coating, (b) a hydrogel coating, (c) a film coating that controls the rate of diffusion of the drug from a coated matrix, (d) an erodable matrix that controls rate of drug release, (e) polymer coated pellets, granules or microparticles of drug which can be further encapsulated or compressed into a tablet, (f) an osmotic pump system containing the drug, (g) a compression coated tablet form of the drug, or (h) combinations of these approaches.

[0056] As used herein, an erodable matrix is the core of a tablet formulation that, upon exposure to an aqueous environment, begins a process of disintegration which facilitates the release of drug from the matrix. The rate of release of drug from the tablet is controlled both by the solubility of the drug and the rate of disintegration of the matrix.

[0057] The above formulations may further comprise one or more additional pharmaceutically active agents (other than K_{ATP} channel openers) useful for the treatment of a condition selected from the group consisting of obesity, prediabetes, diabetes, hypertension, depression, elevated cholesterol, fluid retention, other obesity associated comorbidities, ischemic and reperfusion injury, epilepsy, schizophrenia, mania, or other psychotic diseases.

[0058] Further provided is a controlled release pharmaceutical formulation of a K_{ATP} channel opener wherein administration to an obese, overweight or obesity prone individual results in at least one of the following: (a) inhibition of fasting insulin secretion (b) inhibition of stimulated insulin secretion, (c) elevation of energy expenditure, (d) elevation of beta oxidation of fat, (e) inhibition of hyperphagia for about 24 hours, or (f) increase in lean body mass.

[0059] Additionally provided is a controlled release pharmaceutical formulation of a K_{ATP} channel opener wherein administration to an obese, overweight or obesity prone individual results in at least one of the following: (a) inhibition of fasting insulin secretion (b) inhibition of glucose stimulated insulin secretion, (c) elevation of energy expenditure, (d) elevation of beta oxidation of fat, (e) inhibition of hyperphagia for about 18 hours, or (f) increase in lean body mass.

[0060] Still further provided is a controlled release pharmaceutical formulation of a K_{ATP} channel opener which upon administration to an obese, overweight or obesity prone individual results in at least one of the following: (a) inhibition of fasting insulin secretion (b) inhibition of glucose stimulated insulin secretion, (c) elevation of energy expenditure, (d) elevation of beta oxidation of fat, (e) inhibition of hyperphagia for about 24 hours, or (f) increase in lean body mass.

[0061] Additionally provided is a controlled release pharmaceutical formulation of a K_{ATP} channel opener that upon administration to an obese, overweight or obesity prone individual results in at least one of the following: (a) inhibition of fasting insulin secretion (b) inhibition of glucose stimulated insulin secretion, (c) elevation of energy expenditure, (d) elevation of beta oxidation of fat, (e) inhibition of hyperphagia for about 18 hours, or (f) increase in lean body mass.

[0062] Provided herein is a method of treating hypoglycemia, the method comprising orally administering a controlled release formulation of a K_{ATP} channel opener, optionally in combination with growth hormone.

[0063] Further provided herein is a method of treating obesity associated co-morbidities in an obese, overweight or obesity prone individual, the method comprising administering a therapeutically effective amount of a solid oral dosage form of a K_{ATP} channel opener, or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

[0064] Yet further provided herein is a method of achieving weight loss in an obese overweight, or obesity prone individual, the method comprising administering a therapeutically effective amount of a solid oral dosage form of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours. The daily dosage administered is preferably between 50 and 180 mg. In certain embodiments, the obese individual has a body mass index greater than 30 kg/m², or

greater than 35 kg/m², or greater than 40 kg/m², or greater than 50 kg/m², or greater than 60 kg/m² at the time the method commences.

[0065] Also provided is a method of maintaining a weight loss in an obese overweight, or obesity prone individual, the method comprising administering a therapeutically effective amount of a solid oral dosage form of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. It is preferable to maintain weight in an obese individual once some weight loss has occurred when the alternative is to regain weight. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

[0066] Further provided is a method of elevating energy expenditure in an overweight, obese or obesity prone individual, the method comprising administering an effective amount of a solid oral dosage form of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours. In certain embodiments, the individual has a body mass index greater than 20 kg/m², or greater than 25 kg/m², or greater than 30 kg/m², or greater than 35 kg/m², or greater than 40 kg/m², or greater than 50 kg/m², or greater than 60 kg/m² at the time the method commences.

[0067] Additionally provided is a method of elevating beta oxidation of fat in an overweight, obese or obesity prone individual, the method comprising administering an effective amount of a solid oral dosage form of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours. In certain embodiments, the individual has a body mass index greater than 20 kg/m², or greater than 25 kg/m², or greater than 30 kg/m², or greater than 35 kg/m², or greater than 40 kg/m², or greater than 50 kg/m², or greater than 60 kg/m² at the time the method commences.

[0068] Yet further provided is a method of reducing visceral fat in an overweight, obese or obesity prone individual, the method comprising administering an effective amount of a solid oral dosage form of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a

K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

[0069] Still further provided is a method of delaying or preventing the transition to diabetes of a prediabetic individual comprising administering an effective amount of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

[0070] Additionally provided is a method of restoring normal glucose tolerance in a prediabetic individual comprising administering an effective amount of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

[0071] Further provided is a method of restoring normal glucose tolerance in a diabetic individual comprising administering an effective amount of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

[0072] Still further provided is a method of delaying or preventing progression of diabetes in an individual comprising administering an effective amount of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

[0073] Also provided is a method to prevent or treat weight gain, impaired glucose tolerance or dyslipidemia associated with the use of anti-psychotics to treat patients comprising the co-administration of an effective amount of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

[0074] Further provided is a method to increase lean body mass in a Prader-Willi Syndrome patient, in a Smith–Magenis syndrome patient, in a Froelich’s Syndrome patient, in a Cohen Syndrome patient, in a Summit Syndrome patient, in an Alstrom Syndrome patient, in a Borjeson Syndrome patient or in a Bardet-Biedl Syndrome patient comprising the administration of an effective amount of a K_{ATP} channel opener (optionally in combination with growth hormone) or a controlled release pharmaceutical formulation of a K_{ATP} channel opener (optionally in combination with growth hormone). In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

[0075] Still further provided is a method to treat obesity or elevated triglycerides in a patient suffering hyperlipoproteinemia type I, type II, type III or type IV comprising administering an effective amount of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

[0076] Also provided is a method of reducing the incidence of adverse effects from administration of a K_{ATP} channel opener in the treatment of diseases of a subject achieved by any of the following: (a) use of a dosage form that on administration reduces C_{max} relative to the current Proglycem oral suspension or capsule products in order to reduce the incidence of adverse side effects that are associated with peak drug levels, (b) use of a dosage form that delays release until gastric transit is complete in order to reduce the incidence of adverse side effects that are associated with the release of drug in the stomach, (c) initiating dosing at subtherapeutic levels and in a stepwise manner increasing dose daily until the therapeutic dose is achieved wherein the number of steps is 2 to 10 to reduce the incidence of adverse side effects that occur transiently at the initiation of treatment, (d) use of the lowest effective dose to achieve the desired therapeutic effect in order to reduce the incidence of adverse side effects that are dose dependent, or (e) optimizing the timing of administration of dose within the day and relative to meals.

[0077] Further provided is a method of preventing weight gain, dyslipidemia or impaired glucose tolerance in a subject treated with an anti-psychotic drug, the method comprising

administering a pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone.

[0078] Yet further provided is a method of treating weight gain, dyslipidemia or impaired glucose tolerance in a subject treated with an anti-psychotic drug, the method comprising administering a pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone.

[0079] Also provided is a method of treating diseases characterized by obesity, hyperphagia, dyslipidemia, or decreased energy expenditure including (a) Prader Willi Syndrome, (b) Froelich's syndrome, (c) Cohen syndrome, (d) Summit Syndrome, (e) Alstrom, Syndrome, (f) Borjesen Syndrome, (g) Bardet-Biedl Syndrome, (h) hyperlipoproteinemia type I, II, III, and IV, or (i) Smith-Magenis syndrome (SMS), said method comprising administering a pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone.

[0080] Further provided is a pharmaceutical formulation of a K_{ATP} channel opener further comprising a pharmaceutically active agent other than the K_{ATP} channel opener. In this formulation, the other pharmaceutically active agent is an agent useful for the treatment of a condition selected from the group consisting of obesity, prediabetes, diabetes, hypertension, depression, elevated cholesterol, fluid retention, or other obesity associated comorbidities, ischemic and reperfusion injury, epilepsy, schizophrenia, mania, and other psychotic condition.

[0081] The formulations containing K_{ATP} channel openers described herein provide for improved compliance, efficacy and safety, and for co-formulations with other agents. Included are co-formulations of K_{ATP} channel openers with one or more additional pharmaceutically active agents that have complementary or similar activities or targets. Other pharmaceutical active agents that can be combined with K_{ATP} channel openers to treat obesity or to maintain weight loss in an obesity prone individual include, but are not limited to: sibutramine, orlistat, phentermine, rimonabant, a diuretic, an antiepileptic, or other pharmaceutical active whose therapeutic utility includes weight loss. It is preferable to maintain weight in an obese individual once some weight loss has occurred when the alternative is to regain weight. Other pharmaceutically active agents that may be combined with K_{ATP} channel openers to treat type II diabetes, or prediabetes include acarbose, miglitol, metformin, repaglinide, nateglinide,

rosiglitazone, proglitazone, ramipril, metaglidase, or any other pharmaceutical active that improves insulin sensitivity or glucose utilization or glycemic control where the mode of action is not enhanced insulin secretion. Other pharmaceutical active agents that can be combined with K_{ATP} channel openers to treat obesity associated co-morbidities include a drug active used to lower cholesterol, a drug active used to lower blood pressure, an anti-inflammatory drug that is not a cox-2 inhibitor, a drug that is an antidepressant, a drug used to treat urinary incontinence, or other drug routinely used to treat disease conditions the incidence of which is elevated in overweight or obese patients as compared to normal weight individuals including, but not limited to, drugs to treat atherosclerosis, osteoarthritis, disc herniation, degeneration of knees and hips, breast, endometrium, cervical, colon, leukemia and prostate cancers, hyperlipidemia, asthma/reactive airway disease, gallstones, GERD, obstructive sleep apnea, obesity hypoventilation syndrome, recurrent ventral hernias, menstrual irregularity, infertility, and the like.

[0082] In the present context, the term “therapeutically effective” or “effective amount” indicates that the materials or amount of material is effective to prevent, alleviate, or ameliorate one or more symptoms of a disease or medical condition, and/or to prolong the survival of the subject being treated.

[0083] The term “pharmaceutically acceptable” indicates that the identified material does not have properties that would cause a reasonably prudent medical practitioner to avoid administration of the material to a patient, taking into consideration the disease or conditions to be treated and the respective route of administration. For example, it is commonly required that such a material be essentially sterile, e.g., for injectibles.

[0084] As used herein, the term “composition” refers to a formulation suitable for administration to an intended animal subject for therapeutic purposes; exemplary formulations contain at least one pharmaceutically active compound and at least one pharmaceutically acceptable carrier or excipient. Other terms as used herein are defined below.

[0085] Adipocyte: An animal connective tissue cell specialized for the synthesis and storage of fat.

[0086] Agonist: A chemical compound that has affinity for and stimulates physiological activity at cell receptors normally stimulated by naturally occurring substances, triggering a biochemical response. An agonist of a receptor can also be considered an activator of the receptor.

[0087] About: is used herein to mean in quantitative terms plus or minus 10%.

[0088] Adipose tissue: Tissue comprised principally of adipocytes.

[0089] Adolescent: A person between 10 and 19 years of age.

[0090] Adiponectin: A protein hormone produced and secreted exclusively by adipocytes that regulates the metabolism of lipids and glucose. Adiponectin influences the body's response to insulin. Adiponectin also has anti-inflammatory effects on the cells lining the walls of blood vessels.

[0091] Amelioration of the symptoms of a particular disorder by administration of a particular pharmaceutical composition: refers to any lessening, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the composition.

[0092] Analog: a compound that resembles another in structure but differs by at least one atom.

[0093] Antagonist: A substance that tends to nullify the action of another, as a drug that binds to a cell receptor without eliciting a biological response.

[0094] Atherosclerotic Plaque: A buildup of cholesterol and fatty material within a blood vessel due to the effects of atherosclerosis

[0095] Bariatric Surgery: a range of surgical procedures which are designed to aid in the management or treatment of obesity and allied diseases.

[0096] Beta cell rest: Temporarily placing beta cells in a condition in which there is reduced metabolic stress due to suppressed secretion of insulin.

[0097] Bilaminate: A component of a pharmaceutical dosage form that consists of the lamination of two distinct materials.

[0098] Bioavailability: Refers to the amount or extent of therapeutically active substance that is released from the drug product and becomes available in the body at the intended site of drug action. The amount or extent of drug released can be established by the pharmacokinetic-parameters, such as the area under the blood or plasma drug concentration-time curve (AUC) and the peak blood or plasma concentration (C_{max}) of the drug.

[0099] Bioequivalent: Two formulations of the same active substance are bioequivalent when there is no significant difference in the rate and extent to which the active substance becomes available at the site of drug action when administered at the same molar dose under similar conditions. "Formulation" in this definition may include the free base of the active substance or different salts of the active substance. Bioequivalence may be demonstrated through several in vivo and in vitro methods. These methods, in descending order of preference, include pharmacokinetic, pharmacodynamic, clinical and in vitro studies. In particular, bioequivalence is demonstrated using pharmacokinetic measures such as the area under the blood or plasma drug concentration-time curve (AUC) and the peak blood or plasma concentration (C_{max}) of the drug, using statistical criteria.

[00100] Cannabinoid Receptor: Receptors in the endocannabinoid (EC) system associated with the intake of food and tobacco dependency. Blocking the cannabinoid receptor may reduce dependence on tobacco and the craving for food.

[00101] Combination: refers to any association between or among two or more items. The combination can be two or more separate items, such as two compositions or two collections. It can be a mixture thereof, such as a single mixture of the two or more items, or any variation thereof.

[00102] Composition: refers to any mixture. It can be a solution, a suspension, liquid, powder, a paste, aqueous, non-aqueous or any combination thereof.

[00103] Compression tablet: Tablet formed by the exertion of pressure to a volume of tablet matrix in a die.

[00104] Compression coated tablet: A tablet formed by the addition of a coating by compression to a compressed core containing the pharmaceutical active.

[00105] Derivative: a chemical substance derived from another substance by modification or substitution.

[00106] Daily dosage: the total amount of a drug taken in a 24 hour period whether taken as a single dose or taken in multiple doses.

[00107] Diazoxide: 7-chloro-3-methyl-2-H-1,2,4-benzothiadiazine 1,1 dioxide with the empirical formula $C_8H_7ClN_2O_2S$ and a molecular weight of 230.7.

[00108] Encapsulation system: a structural feature that contains drug within such as a pharmaceutical capsule. A gel into which drug is incorporated also is considered an encapsulation system.

[00109] Equivalent amount: an amount of a derivative of a drug that in assays or upon administration to a subject produces an equal effect to a defined amount of the non-derivatized drug.

[00110] Fatty acid synthase: The central enzyme of a multienzyme complex that catalyses the formation of palmitate from acetylcoenzyme A, malonylcoenzyme A, and NADPH.

[00111] Gastric Lipase: An enzyme secreted into the gastrointestinal tract that catalyzes the hydrolysis of dietary triglycerides.

[00112] Glidant: An inactive component of a pharmaceutical formulation that prevents caking of the matrix during processing steps.

[00113] Growth hormone: also known as somatotropin or somatropin, is a peptide hormone that stimulates growth, cell reproduction and regeneration in humans and other animals. It is a type of mitogen which is specific only to certain kinds of cells. Growth hormone is a 191-amino acid, single-chain polypeptide that is synthesized, stored, and secreted by somatotrophic cells within the lateral wings of the anterior pituitary gland. GH is a stress hormone that raises the concentration of glucose and free fatty acids. It also stimulates production of IGF-1.

[00114] Hyperinsulemia: Excessively high blood insulin levels, which is differentiated from hyperinsulinism, excessive secretion of insulin by the pancreatic islets. Hyperinsulinemia may be the result of a variety of conditions, such as obesity and pregnancy.

[00115] Hyperinsulinism: Excessive secretion of insulin by the pancreatic islets.

[00116] Hyperlipidemia: A general term for elevated concentrations of any or all of the lipids in the plasma, such as cholesterol, triglycerides and lipoproteins.

[00117] Hyperphagia: Ingestion of a greater than optimal quantity of food.

[00118] Ingredient of a pharmaceutical composition: refers to one or more materials used in the manufacture of a pharmaceutical composition. Ingredient can refer to an active ingredient (an agent) or to other materials in the compositions. Ingredients can include water and other solvents, salts, buffers, surfactants, water, non-aqueous solvents, and flavorings.

[00119] IGF-1, also called somatomedin C, is a protein that in humans is encoded by the *IGF1* gene. IGF-1 is a hormone similar in molecular structure to insulin. It plays an important role in childhood growth and continues to have anabolic effects in adults. IGF-1 consists of 70 amino acids in a single chain with three intramolecular disulfide bridges, and has a molecular weight of 7,649 daltons.

[00120] Insulin resistance: A condition in which the tissues of the body are diminished in their response to insulin.

[00121] Ischemic injury: injury to tissue that results from a low oxygen state usually due to obstruction of the arterial blood supply or inadequate blood flow leading to hypoxia in the tissue.

[00122] Ketoacidosis: Acidosis accompanied by the accumulation of ketone bodies (ketosis) in the body tissue and fluids, as in diabetic acidosis.

[00123] Kit: refers to a packaged combination. A packaged combination can optionally include a label or labels, instructions and/or reagents for use with the combination.

[00124] Kir: Pore forming subunit of the K_{ATP} channel. Also known as the inwardly rectifying subunit of the K_{ATP} channel. Typically existing as Kir6.x and infrequently as Kir2.x subspecies.

[00125] K_{ATP} channel: An ATP sensitive potassium ion channel across the cell membrane formed by the association of 4 copies of a sulfonylurea receptor and 4 copies of a pore forming subunit Kir. Agonizing the channel can lead to membrane hyperpolarization.

[00126] Lean body mass: Lean Body Mass is a component of body composition, calculated by subtracting body fat weight from total body weight: total body weight is lean plus fat. In equations:

Lean Body Mass equals Body Weight minus Body Fat ($LBM = BW - BF$)

Lean Body Mass plus Body Fat equals Body Weight ($LBM + BF = BW$)

The percentage of total body mass that is lean is usually not quoted – it would typically be 60–90%. Instead, the body fat percentage, which is the complement, is computed, and is typically 10–40%. The Lean body mass (LBM) has been described as an index superior to total body weight for prescribing proper levels of medications and for assessing metabolic disorders, as body fat is less relevant for metabolism.

[00127] Leptin: Product (16 kD) of the ob (obesity) locus. It is found in plasma of mammals and exerts a hormonal action, which reduces food uptake and increases energy expenditure.

[00128] Lipogenesis: The generation of new lipids, primarily triacylglycerides. It is dependent on the action of multiple distinct enzymes and transport molecules.

[00129] Lipolysis: The breakdown of fat by the coordinated action of multiple enzymes.

[00130] Lipoprotein lipase: An enzyme of the hydrolase class that catalyses the reaction of triacylglycerol and water to yield diacylglycerol and a fatty acid anion. The enzyme hydrolyses triacylglycerols in chylomicrons, very-low-density lipoproteins, low-density lipoproteins, and diacylglycerols.

[00131] Lubricant: An inactive component of a pharmaceutical formulation that provides for the flow of materials in various processing steps, particularly tableting.

[00132] Microparticle: A small particulate formed in the process of developing pharmaceutical formulations that may be coated prior to producing the final dosage form.

[00133] Obesity: An increase in body weight beyond the limitation of skeletal and physical requirement, as the result of an excessive accumulation of fat in the body. Formally defined as having a body mass index greater than 30 kg/m².

[00134] Obesity Prone: Individuals who because of genetic predisposition or prior history of obesity are at above average risk of becoming obese.

[00135] Obesity related co-morbidities: any disease or condition of animals or humans that are increased incidence in obese or overweight individuals. Examples of such conditions include hypertension, prediabetes, type 2 diabetes, osteoarthritis and cardiovascular conditions.

[00136] Osmotically controlled release: A pharmaceutical dosage form in which the release of the active drug is principally achieved by the hydration of a swellable component of the formulation.

[00137] Overweight: an individual whose weight is above that which is ideal for their height but who fails to meet the criteria for classification as obese. In humans using Body Mass Index (kg/m²) an overweight individual has a BMI between 25 and 30.

[00138] Oxidation of Fat: A series of reactions involving acyl-coenzyme A compounds, whereby these undergo beta oxidation and thioclastic cleavage, with the formation of acetyl-coenzyme A; the major pathway of fatty acid catabolism in living tissue.

[00139] Pharmaceutical composition: refers a composition that contains an agent and one or more other ingredients that is formulated for administration to a subject. An agent refers to an active ingredient of a pharmaceutical composition. Typically active ingredients are active for treatment of a disease or condition. For example, agents that can be included in pharmaceutical compositions include agents for treating obesity or diabetes. The pharmaceutically active agent can be referred to as “a pharmaceutical active.”

[00140] Pharmaceutical effect: refers to an effect observed upon administration of an agent intended for treatment of a disease or disorder or for amelioration of the symptoms thereof.

[00141] Pharmacodynamic: An effect mediated by drug action.

[00142] Pharmacokinetic: Relating to the absorption, distribution, metabolism and elimination of the drug in the body.

[00143] Polymorph: A compound that shares the same chemistry but a different crystal structure.

[00144] Prader–Willi syndrome (PWS): A complex neurobehavioral/metabolic disorder which is due to the absence of normally active, paternally expressed genes from the chromosome 15q11-q13 region. PWS is an imprinted condition with 70–75% of the cases due to a de novo deletion in the paternally inherited chromosome 15 11-q13 region, 20–30% from maternal uniparental disomy 15 (UPD), and the remaining 2–5% from either microdeletions or epimutations of the imprinting center (i.e., imprinting defects) (Bittel and Butler, *Expert Rev Mol Med* 7(14):1-20 (2005); Cassidy and Driscoll, *Eur J Hum Genet* 17(1):3-13(2009)).

[00145] The clinical manifestations of the condition begin in utero with diminished fetal activity (Miller *Am J Med Genet A* 155A(5):1-10 (2011)). Low lean body mass and hypotonia are universal in PWS and present throughout life (Brambilla *Am J Clin Nutr* 65(5):1369-1374 (1997), Lloret-lineras *Int J Obes* 37:1198-1203 (2013)). Mental retardation occurs to varying degrees with the average IQ being 70 (PWSUSA). PWS patients present with a range of behavioral complications including autistic-spectrum-disorder-like behaviors, compulsive behaviors, self-injurious behaviors, and aggressive, threatening and destructive behaviors. About 80% of PWS patients are growth hormone deficient (Goldstone, *Trends Endocrinol Metab* 15:12-120 (2004); Davies et al., *Front Neuroendocrinol* 29:413-427 (2008); Cassidy and Driscoll, 2009, *supra*). Nearly all PWS patients are hypogonadal, requiring sex hormone supplementation (Goldstone, 2004, *supra*; Davies et al., 2008, *supra*; Cassidy and Driscoll, 2009, *supra*). These patients have hypothalamic insufficiency/dysfunction (Goldstone *Am J Clin Nutr* 75(3):468-475 (2002)).

[00146] The accumulation of excess body fat may begin about age 2 and can continue into adulthood (Miller 2011, *supra*). The vast majority of body fat in PWS is subcutaneous (Brambilla 1997, *supra*; Sode-Carlson, Growth hormone and IGF research 20:179-184 (2010), Bedogni J Endocrinol Invest DOI 10.1007/s40618-015-0266-y (2015)). Obesity is not universal in PWS, unlike the universality of low lean body mass and hypotonia. For example, Sode-Carlson et al. (2010), *supra*, evaluated 46 adult PWS patients, 25 women and 21 men. The average BMI in these adult PWS patients was 27.2 kg/m². Thus, on average, these patients were overweight rather than obese, suggesting that more than half are not, in fact, obese by the best metric. Similarly, Brambilla et al. Nutr Metab Cardiovasc Dis 21(4):269-276 (2011) studied a population of 109 children with PWS. They found that 54% were not classified as obese by the best metric. Thus, both in adults and in children with PWS, obesity is not only not universal, but may, in fact, occur in less than half of the population. Subcutaneous fat makes up a greater percentage of total fat in PWS than it does in obese controls at all ages (Sode-Carlson 2010, *supra*).

[00147] Hyperphagia with the associated problematic food related behaviors begins on average about age 8 (Miller 2011, *supra*). These patients sense they are starving when they are not. Upon the onset of hyperphagia, PWS patients will eat any food in the line of sight, get up at night to eat, dig through the trash for food, steal food, consume frozen food, pet food, spoiled food and even consume non-food items (Miller 2011, *supra*). They will become angry or throw tantrums if denied food. At this stage and thereafter throughout life, access to food is strictly limited, with cabinets and refrigerators being locked. To limit food related anxiety, meal times and meal composition are strictly regimented.

[00148] The mortality rate for PWS patients is three times that of the general population at all ages (Cassidy Genet Med 14(1):10-26 (2012)), with the average age at death being about 29 years (PWSUSA mortality database, n=488). In contrast, being obese, but not morbidly obese has little impact on life expectancy (Anon (2011) National Research Council Panel on Understanding Divergent Trends in Longevity in High-Income Countries; Crimmons, EM, Preston, SH, Cohen, B, editors. National Academies Press).

[00149] Prader-Willi patients expend less energy and are more sedentary than either the general population, obese controls or patients with similar intellectual disabilities. Butler et al. Am J Med Gent A 143A(5):449-459 (2007)) compared the energy expenditure and total work of a group of 48 PWS patients with a group of 24 obese controls. Compared to the controls, PWS patients had significantly decreased total energy expenditure (-20%), resting energy expenditure (-16%) and mechanical work (-35%). After adjusting for group differences in lean body mass, the difference remained significant for mechanical work.

[00150] In a study by van Mil et al., Int J Obes Relat Metab Disord 24(4):429-434 (2000), the authors measured basal metabolic rate (BMR), average daily metabolic rate (ADMR), activity induced energy expenditure (AEE), and ADMR/BMR (PAL) in a group of PWS patients and matched controls. ADMR, AEE and PAL were significantly lower ($P < 0.01$) in the PWS group compared with the control group -28.2%, -58.2%, and -14.2%, respectively).

[00151] De Lind van Wijngaarden et al., J Clin Endocrinol Metab 95(4):1758-1766 (2010) evaluated cardiovascular and metabolic risk factors in children with PWS. They showed that 63% of infants and 73% of pre-pubertal children with PWS have at least one cardiovascular risk factor, defined as dyslipidemia or hypertension. Thus, the cardiometabolic risk in PWS is elevated even in younger children.

[00152] Preadipocyte: A progenitor cell to adipocytes.

[00153] Prediabetic: A condition that precedes diagnosis of type II diabetes. Type II diabetes is a form of diabetes mellitus which is characterized by insulin insensitivity or resistance.

[00154] Prodrug: refers to a compound which, when metabolized, yields the desired active compound. Typically, the prodrug is inactive, or less active than the active compound, but may provide advantageous handling, administration, or metabolic properties. For example, some prodrugs are esters of the active compound; during metabolism, the ester group is cleaved to yield the active drug. Also, some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound.

[00155] Prolonged Administration (prolonged basis): Administration of a pharmaceutically acceptable formulation of a drug for 7 or more days. Typically, prolonged administration is for

at least two weeks, preferably at least one month, and even more preferably at least two months (i.e. at least 8 weeks).

[00156] Quick dissolving formulation: a pharmaceutical formulation which upon oral administration may release substantially all of the drug active from the formulation within 10 minutes.

[00157] Release formulation (sustained), (or “sustained release formulation”): A formulation of pharmaceutical product that, upon administration to animals, provides for release of the active pharmaceutical over an extended period of time than provided by formulations of the same pharmaceutical active that result in rapid uptake. Similar terms are extended-release, prolonged-release, and slow-release. In all cases, the preparation, by definition, has a reduced rate of release of active substance.

[00158] Release formulation (delayed), (or “delayed release formulation”): Delayed-release products are modified-release, but are not extended-release. They involve the release of discrete amount(s) of drug some time after drug administration, e.g. enteric-coated products, and exhibit a lag time during which little or no absorption occurs.

[00159] Release formulation (controlled), (or “controlled release formulation”): A formulation of pharmaceutical product that may include both delay of release of pharmaceutical active upon administration and control of release in the manner described for sustained release.

[00160] Salt: the neutral, basic or acid compound formed by the union of an acid or an acid radical and a base or basic radical.

[00161] Smith–Magenis syndrome (SMS; OMIM #182290, *607642): A complex, generally sporadic, genetic disorder caused by haploinsufficiency of the retinoic acid induced 1 (RAI1) gene. caused by either a 17p11.2 deletion encompassing the retinoic acid-induced 1 (RAI1) gene or a mutation of RAI1.(see, for example, Burns et al., in Human Molecular Genetics, 2010, Vol. 19, No. 20, pp. 4026–4042).

[00162] Smith–Magenis syndrome is characterized by a clinically recognizable phenotype that includes physical, developmental, neurological, and behavioral features. Short stature (<5th

percentile) was observed in ~67% of young patients. Short stature resolves over time with most individuals reaching the 10–25th percentile by adulthood (see, for example, Burns et al. supra). A majority of children with SMS also have significant early-onset obesity (see, for example, European Journal of Human Genetics (2008) 16, 412–421). Obesity in teens and adults is common, typically with broad chests and truncal obesity. RAI1 haploinsufficiency represents a single-gene model of obesity with hyperphagia, abnormal fat distribution and altered hypothalamic gene expression associated with satiety, food intake, behavior and obesity.

[00163] Hearing loss is variable and is often associated with chronic ear infections. Ophthalmologic features are present in >60% of SMS patients and include myopia, iris anomalies, strabismus, microcornea, and, rarely, retinal detachment (often resulting from violent behaviors).

[00164] Prenatal history of SMS is notable for significantly decreased fetal movement in 50% of pregnancies. Early infancy is complicated by feeding difficulties leading to failure to thrive, marked oral sensory motor dysfunction with poor suckling reflex, gastroesophageal reflux, and hypotonia.

[00165] Most SMS individuals have mild-to-moderate mental retardation. IQ decreases as the child ages, ultimately placing the individual in the mild mental retardation range by adulthood. Delayed speech with or without hearing loss occurs in 96% of SMS patients. In addition, delayed fine/gross motor skills, problems with sensory integration, and poor adaptive function are seen. Other neurological features include pes cavus or pes planus, an abnormal ‘festinating’ gait, balance problems, and a decreased sensitivity to pain, which is often observed in association with self-injury in this disorder.

[00166] Sleep disturbance has been reported in 75–100% of SMS cases. Infants typically experience hypersomnolence during the first year of life. Sleep disturbances in older children include difficulties falling asleep, diminished REM sleep, reduced 24-h and night sleep, fragmented and shortened sleep cycles with frequent nocturnal and early-morning awakenings, and excessive daytime sleepiness.

[00167] Behavioral issues are one of the unique characteristic features of SMS. Maladaptive behaviors are a cause of major concern and include frequent outbursts/temper tantrums, attention seeking, aggression, disobedience, distraction, and self-injurious behaviors. Self-injurious behaviors include head banging, skin picking, wrist biting, onychotillomania and polyembolokoilamania. The behavioral phenotype of SMS escalates with age, typically with the onset of puberty. Age, degree of developmental delay, severity of any associated systemic disorder, and degree of sleep disturbance have a strong influence on maladaptive behaviors. Individuals also have a lack of respect for personal space during a conversation and are emotionally volatile.

[00168] SMS patients share many characteristics in common with PWS patients. These include: (1) diminished fetal activity; (2) hypotonia; (3) feeding difficulties in early infancy; (4) short stature; (5) early onset obesity which may include hyperphagia; (6) developmental delays; (7) mental retardation; (8) temper outbursts; (9) aggressive behavior; (10) self-injurious behavior; (11) hypersomnolence in infancy and similar sleep disturbances in older children and adults; (12) frequent ear infections; (13) scoliosis; and (14) strabismus. While the underlying genetic basis for these disorders is quite distinct, the presentation and natural history of the disease is very similar.

[00169] Solid oral dosage form: pharmaceutical formulations designed for oral administration including capsules and tablets.

[00170] Subject: refers to animals, including mammals, such as human beings.

[00171] Sulfonylurea receptor: A component of the K_{ATP} channel responsible for interaction with sulfonylurea, other K_{ATP} channel antagonists, diazoxide and other K_{ATP} channel agonists.

[00172] Tablet: Pharmaceutical dosage form that is produced by forming a volume of a matrix containing pharmaceutical active and excipients into a size and shape suitable for oral administration.

[00173] Thermogenesis: The physiological process of heat production in the body.

[00174] Threshold Concentration: The minimum circulating concentration of a drug required to exert a specific metabolic, physiological or compositional change in the body of a treated human or animal.

[00175] Treatment: means any manner in which the symptoms of a condition, disorder or disease or other indication, are ameliorated or otherwise beneficially altered.

[00176] Triglyceride: Storage fats of animal and human adipose tissue principally consisting of glycerol esters of saturated fatty acids.

[00177] Type I diabetes: A chronic condition in which the pancreas makes little or no insulin because the beta cells have been destroyed.

[00178] Uncoupling protein: A family of proteins that allow oxidation in mitochondria to proceed without the usual concomitant phosphorylation to produce ATP.

[00179] Visceral fat: Human adipose tissues principally found below the subcutaneous fat and muscle layer in the body.

BRIEF DESCRIPTION OF THE FIGURES

[00180] Figure 1 summarizes the change in hyperphagia score for all subjects who participated in clinical study PC025.

[00181] Figure 2 summarizes the percent change in lean body mass for all subjects who participated in clinical study PC025.

[00182] Figure 3 summarizes the percent change in body fat mass for all subjects who participated in clinical study PC025.

[00183] Figure 4 summarizes the percent change of the lean body mass/fat mass ratio for all subjects who participated in clinical study PC025.

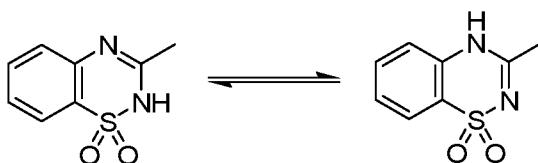
[00184] Figure 5 summarizes the clinical study treatment schedule for pediatric and adult patients who have PWS and are obese.

DETAILED DESCRIPTION OF THE INVENTION

[00185] Provided herein are pharmaceutical formulations of particular K_{ATP} channel openers that when administered to subjects achieve novel pharmacodynamic, pharmacokinetic, therapeutic, physiological, and metabolic outcomes. Also provided are pharmaceutical formulations, methods of administration and dosing of particular K_{ATP} channel openers, optionally in combination with growth hormone, that achieve therapeutic outcomes while reducing the incidence of adverse effects.

[00186] In particular, pharmaceutical formulations formulated for oral administration exhibit advantageous properties including: facilitating consistency of absorption, pharmacokinetic and pharmacodynamic responses across treated patients, contributing to patient compliance and improving the safety profile of the product, such as by reducing the frequency of serious adverse effects. Method of treatment of metabolic and other diseases of humans and animals by administering the formulations are also provided.

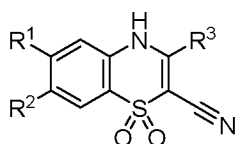
[00187] Compounds of formulas II and III, formulas IV and V, and formulas VI and VII, such as for example, diazoxide (shown below) can be proton tautomers. Proton tautomers are isomers that differ from each other only in the location of a hydrogen atom and a double bond. The hydrogen atom and double bond switch locations between a carbon atom and a heteroatom, such as for example N. Thus, when the nitrogen substituent is hydrogen, the two isomeric chemical structures may be used interchangeably.



[00188] The particular K_{ATP} channel openers that can be used in the invention formulations include any of those within formulae I to VII. Exemplary such compounds include diazoxide, BPDZ62, BPDZ 73, NN414 and BPDZ 154 (see, for example, Schou, et al., *Bioorg. Med. Chem.*, 13, 141-155 (2005)). Compound BPDZ 154 also is an effective K_{ATP} channel activator in patients with hyperinsulinism and in patients with pancreatic insulinoma. The synthesis of BPDZ compound is provided in Cosgrove, et al., *J. Clin. Endocrinol. Metab.*, 87, 4860-4868 (2002).

[00189] Analogs of diazoxide include 3-isopropylamino-7-methoxy-4H-1,2,4,-benzothiadiazine 1,1-dioxide, which is a selective Kir6.2/SUR1 channel opener (see Dabrowski, et al., *Diabetes*, 51, 1896-1906 (2002)). 2-alkyl substituted diazoxides are included (see, for example, Ouedraogo, et al., *Biol. Chem.*, 383, 1759-1768 (2002)); these channel openers show decreased activity in the inhibition of insulin release and increased activity in vascular smooth muscle tissue. Furthermore, 2-alkyl substituted diazoxides generally do not function as traditional potassium channel activators, but instead show potential as Ca^{2+} blockers.

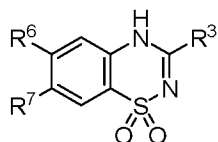
[00190] Other diazoxide analogs are described in Schou, et al., *Bioorg. Med. Chem.*, 13, 141-155 (2005), and are shown below.



R^1 , R^2 and R^3 are:

- a) H, Cl, $\text{NHCH}(\text{CH}_3)_2$
- b) CF_3 , H, $\text{NHCH}(\text{CH}_3)_2$
- c) H, Cl, $\text{NHCH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$
- d) H, Cl, NH-cyclobutyl

[00191] Diazoxide analogs having different alkyl substituents at the 3 position of the molecule (identified as R^3 shown below) are described in Bertolino, et al., *Receptors and Channels*, 1, 267-278 (1993).



R^3 , R^6 and R^7 are:

- | | |
|--|--|
| a) H, H, CH_3 | i) nC_7H_{15} , H, Cl |
| b) H, H, Cl | j) nC_3H_7 , Cl, H |
| c) CH_3 , Cl, H | k) nC_4H_9 , Cl, H |
| d) CH_2Cl , H, Cl | l) nC_5H_{11} , Cl, H |
| e) NH_2 , H, H | m) nC_7H_{15} , Cl, H |
| f) $\text{CH}_2\text{CH}_2\text{Cl}$, H, Cl | n) nC_3H_7 , Cl, Cl |
| g) nC_4H_9 , H, Cl | o) nC_4H_9 , Cl, Cl |
| h) nC_5H_{11} , H, Cl | p) nC_5H_{11} , Cl, Cl |
| | q) nC_7H_{15} , Cl, Cl |
| | r) H, Cl, H |

[00192] K_{ATP} channel activity of formulae I – VII and related compounds can be measured by membrane potential studies as described in Schou, et al., *Bioorg. Med. Chem.*, 13, 141-155 (2005) and Dabrowski, et al., *Diabetes*, 51, 1896-1906 (2002).

[00193] Measurement of the inhibition of glucose-stimulated insulin release from β TC6 cells is described in Schou, et al., *Bioorg. Med. Chem.*, 13, 141-155 (2005). The ability of particular K_{ATP} channel openers to inhibit release of insulin from incubated rat pancreatic islets can be performed as described by Ouedraogo, et al., *Biol. Chem.*, 383, 1759-1768 (2002).

[00194] Activation of recombinant K_{ATP} channels by K_{ATP} channel openers can be examined by monitoring macroscopic currents of inside-out membrane patches from *Xenopus* oocytes coexpressing Kir6.2 and either SUR1, SUR2A or SUR2B. SUR expressing membranes can be prepared by known methods. See, for example, Dabrowski, et al., *Diabetes*, 51, 1896-1906 (2002).

[00195] Binding experiments can be used to determine the ability of K_{ATP} channel openers to bind SUR1, SUR2A and SUR2B. See, for example, Schwanstecher, et al., *EMBO J.*, 17, 5529-5535 (1998).

[00196] Preparation of SUR1 and SUR2A chimeras, as described by Babenko et al., allows for comparison of pharmacologic profiles (i.e. sulfonyl sensitivity and responsiveness to diazoxide or other potassium channel openers) of the SUR1/Kir6.2 and SUR2A/Kir6.2 potassium channels. See Babenko, et al., *J. Biol. Chem.*, 275(2), 717-720 (2000). The cloning of a sulfonylurea receptor and an inwardly rectifying K^+ channel is described by Isomoto, et al., *J. Biol. Chem.*, 271 (40), 24321-24324 (1996); D'hahan, et al., *PNAS*, 96(21), 12162-12167 (1999).

[00197] Differences between the human SUR1 and human SUR2 genes are described and shown in Aguilar-Bryan, et al., *Physiological Review*, 78(1), 227-245 (1998).

[00198] "Halo" and "halogen" refer to all halogens, that is, chloro (Cl), fluoro (F), bromo (Br), or iodo (I).

[00199] "Hydroxyl" and "hydroxy" refer to the group -OH.

[00200] "Substituted oxy" refers to the group $-OR^f$, where R^f is alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aralkyl, substituted aralkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl.

[00201] “Substituted thiol” refers to the group -SR, where R is alkyl, substituted alkyl, acyl, substituted acyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aralkyl, substituted aralkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl.

[00202] “Alkyl” refers to an alkane-derived radical containing from 1 to 10, preferably 1 to 6, carbon atoms. Alkyl includes straight chain alkyl, branched alkyl and cycloalkyl, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and the like. Straight chain or branched alkyl groups contain from 1-10, preferably 1 to 6, more preferably 1-4, yet more preferably 1-2, carbon atoms. The alkyl group is attached at any available point to produce a stable compound.

[00203] A "substituted alkyl" is an alkyl group independently substituted with 1 or more, e.g., 1, 2, or 3, groups or substituents such as halo, hydroxy, optionally substituted alkoxy, optionally substituted alkylthio, alkylsulfinyl, alkylsulfonyl, optionally substituted amino, optionally substituted amido, amidino, urea optionally substituted with alkyl, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, alkylsulfonylamino, carboxyl, heterocycle, substituted heterocycle, nitro, cyano, thiol, sulfonylamino or the like attached at any available point to produce a stable compound. In particular, "fluoro substituted" refers to substitution by 1 or more, e.g., 1, 2, or 3 fluorine atoms. "Optionally fluoro substituted" means that substitution, if present, is fluoro.

[00204] “Lower alkyl” refers to an alkyl group having 1-6 carbon atoms.

[00205] A "substituted lower alkyl" is a lower alkyl which is substituted with 1 or more, e.g., 1, 2, or 3, groups or substituents as defined above, attached at any available point to produce a stable compound.

[00206] "Cycloalkyl" refers to saturated or unsaturated, non-aromatic monocyclic, bicyclic or tricyclic carbon ring systems of 3-8, more preferably 3-6, ring members per ring, such as cyclopropyl, cyclopentyl, cyclohexyl, adamantyl, and the like. "Cycloalkylene" is a divalent cycloalkyl.

[00207] “Alkoxy” denotes the group -OR^f, where R^f is lower alkyl.

[00208] “Substituted alkoxy” denotes the group -OR^f, where R^f is substituted lower alkyl.

[00209] “Alkylthio” or “thioalkoxy” refers to the group -S-R, where R is lower alkyl.

[00210] “Substituted alkylthio” or “substituted thioalkoxy” refers to the group -S-R, where R is substituted lower alkyl.

[00211] “Sulfinyl” denotes the group -S(O)-.

[00212] “Sulfonyl” denotes the group -S(O)₂-.

[00213] “Substituted sulfinyl” denotes the group -S(O)-R, where R is lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, cycloalkylalkyl, substituted cycloalkylalkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heteroaralkyl, substituted heteroaralkyl, aralkyl or substituted aralkyl.

[00214] “Substituted sulfonyl” denotes the group -S(O)₂-R, where R is lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, cycloalkylalkyl, substituted cycloalkylalkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heteroaralkyl, substituted heteroaralkyl, aralkyl or substituted aralkyl.

[00215] “Sulfonylamino” denotes the group -NRS(O)₂- where R is hydrogen or lower alkyl.

[00216] “Substituted sulfonylamino” denotes the group -NR^aS(O)₂-R^b, where R^a is hydrogen or lower alkyl and R^b is lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heteroaralkyl, substituted heteroaralkyl, aralkyl or substituted aralkyl.

[00217] “Amino” or “amine” denotes the group -NH₂. A “divalent amine” denotes the group -NH-. A “substituted divalent amine” denotes the group -NR- wherein R is lower alkyl, substituted lower alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, acyl, substituted acyl, sulfonyl or substituted sulfonyl.

[00218] “Substituted amino” or “substituted amine” denotes the group -NRⁱR^j, wherein Rⁱ and R^j are independently hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl,

heteroaryl, substituted heteroaryl, acyl, substituted acyl, sulfonyl, substituted sulfonyl, or cycloalkyl provided, however, that at least one of R^i and R^j is not hydrogen. R^iR^j in combination with the nitrogen may form an optionally substituted heterocyclic or heteroaryl ring.

[00219] “Alkylsulfinyl” denotes the group $-S(O)R^p$, wherein R^p is optionally substituted alkyl.

[00220] “Alkylsulfonyl” denotes the group $-S(O)_2R^p$, wherein R^p is optionally substituted alkyl.

[00221] “Alkylsulfonylamino” denotes the group $-NR^qS(O)_2R^p$, wherein R^p is optionally substituted alkyl, and R^q is hydrogen or lower alkyl.

[00222] Pharmaceutical formulations containing K_{ATP} channel openers include the free base of the drug or a salt of the drug. Such salts may have one or more of the following characteristics: (1) stability in solution during synthesis and formulation, (2) stability in a solid state, (3) compatibility with excipients used in the manufacture of tablet formulations, (4) quantitatively yield the K_{ATP} channel opener upon exposure to simulated or actual gastric and duodenal conditions, (5) release K_{ATP} channel opener from sufficiently small particles that are readily dissolved and absorbed, (6) provide, when incorporated into a pharmaceutical formulation, for absorption of greater than 80% of the administered dose, (7) present no elevated toxicological risk as compared to the free base of the K_{ATP} channel opener, (8) can be formulated into acceptable pharmaceutical formulations to treat obesity and other diseases of humans, (9) are acceptable to the FDA as the basis of a drug product, (10) can be recrystallized to improve purity, (11) can be used to form co-crystals of two or more salts of the K_{ATP} channel opener, (12) have limited hygroscopicity to improve stability, or (13) synthetic and crystallization conditions under which the salt is formed can be varied resulting in different crystal structures (polymorphs) can be controlled in the synthesis of the salt.

[00223] K_{ATP} channel openers can be formulated as pharmaceutically acceptable salts. Pharmaceutically acceptable salts are non-toxic salts in the amounts and concentrations at which they are administered. The preparation of such salts can facilitate the pharmacological use by altering the physical characteristics of a compound without preventing it from exerting its physiological effect. Useful alterations in physical properties include lowering the melting point

to facilitate transmucosal administration and increasing the solubility to facilitate administering lower effective doses of the drug.

[00224] Pharmaceutically acceptable salts include acid addition salts such as those containing sulfate, chloride, hydrochloride, fumarate, maleate, phosphate, sulfamate, acetate, citrate, lactate, tartrate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, cyclohexylsulfamate and quinate. Pharmaceutically acceptable salts can be obtained from acids such as hydrochloric acid, maleic acid, sulfuric acid, phosphoric acid, sulfamic acid, acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, cyclohexylsulfamic acid, fumaric acid, and quinic acid.

[00225] Pharmaceutically acceptable salts also include basic addition salts such as those containing benzathine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium, potassium, sodium, ammonium, alkylamine, and zinc, when acidic functional groups, such as carboxylic acid or phenol are present. For example, see Remington's Pharmaceutical Sciences, 19th ed., Mack Publishing Co., Easton, PA, Vol. 2, p. 1457, 1995. Such salts can be prepared using the appropriate corresponding bases.

[00226] Pharmaceutically acceptable salts can be prepared, for example, by dissolving the free-base form of a compound in a suitable solvent, such as an aqueous or aqueous-alcohol in solution containing the appropriate acid and then isolated by evaporating the solution. In another example, a salt is prepared by reacting the free base and acid in an organic solvent.

[00227] The pharmaceutically acceptable salt of the different compounds may be present as a complex. Examples of complexes include 8-chlorotheophylline complex (analogous to, *e.g.*, dimenhydrinate: diphenhydramine 8-chlorotheophylline (1:1) complex; Dramamine) and various cyclodextrin inclusion complexes.

[00228] Salts of K_{ATP} channel openers, and particular salts of diazoxide, may include, but are not limited to acetate, acetamide, acetyl, adipate, aspartate, besylate, biacetate, bitartrate, bromide, butoxide, butyrate, calcium, camsylate, caproate, carbonate, citrate, cyprionate, decaroate, diacetate, dimegulumine, dinitrate, dipotassium, dipropionate, disodium, disulfide,

edisylate, enanthate, estolate, etabonate, ethylsuccinate, fumarate, furoate, gluceptate, gluconate, hexacetone, hippurate, hyclate, hydrobromide, hydrochloride, isethionate, lactobionate, malate, maleate, meglumine, methylbromide, methylsulfate, metrizoate, nafate, napsylate, nitrate, oleate, palmitate, pamoate, phenpropionate, phosphate, pivalate, polistirex, polygalacturonate, probutate, propionate, saccharate, sodium glycinate, sodium phosphate, sodium succinate, state, succinate, sulfate, sulfonate, sulfosalicylate, tartrate, tebutate, terephthalate, terephthalate, tosylate, trifluate, trihydrate, trisilicate, tromethamine, valerate, xinafolate, or the like.

[00229] Formulations provided herein exhibit some or all the following characteristics: (1) they are stable at ambient temperatures for a minimum of one year; (2) they provide for ease of oral administration; (3) they facilitate patient compliance with dosing; (4) upon administration, they consistently facilitate high levels of absorption of the pharmaceutical active; (5) upon once or twice daily oral administration they allow release of the K_{ATP} channel opener over a sustained time frame such that the circulating concentration of the K_{ATP} channel opener or its metabolically active metabolites does not fall below a therapeutically effective concentration; (6) they achieve these results independent of the pH of the gastrointestinal tract of treated individuals, and (7) they delay release until gastric transit is complete or nearly complete.

[00230] Formulations designed for oral administration can be provided, for example, as capsules or tablets. Capsule or tablet formulations include a number of distinguishing components. One is a component to improve absorption of the K_{ATP} channel opener. Another sustains release of the drug over more than 2 hours. A third delays substantial release of the drug until gastric transit is completed.

[00231] The formulations disclosed herein exhibit improved solubility and absorption of the K_{ATP} channel opener compared to previous formulations of these drugs. These advantageous properties are achieved by any one or more of the following approaches: (1) reducing particle size of the formulation by comminution, spray drying, or other micronising techniques, (2) using a pharmaceutical salt of the K_{ATP} channel opener, (3) using an ion exchange resin in the formulation, (4) using inclusion complexes, for example using a cyclodextrin, (5) compaction of the K_{ATP} channel opener with a solubilizing agent including low viscosity hypromellose, low viscosity methylcellulose or similarly functioning excipient and combinations thereof, (6)

associating the K_{ATP} channel opener with a salt prior to formulation, (7) using a solid dispersion of the K_{ATP} channel opener, (8) using a self emulsifying system, (9) adding one or more surfactants to the formulation, (10) using nanoparticles in the formulation, or (11) combinations of these approaches. Preferably, when the K_{ATP} channel opener is a salt of diazoxide, the salt is not a sodium salt.

[00232] Release of K_{ATP} channel opener over a sustained period of time (2-24 hours) is achieved by the use of one or more approaches including, but not limited to: (1) the use of pH sensitive polymeric coatings, (2) the use of a hydrogel, (3) the use of a film coating that controls the rate of diffusion of the drug from a coated matrix, (4) the use of an erodable matrix that controls rate of drug release, (5) the use of polymer coated pellets, granules, or microparticles which can be further encapsulated or compressed into a tablet, (6) the use of an osmotic pump system, or (7) the use of a compression coated tablet, or (8) combinations of these approaches.

[00233] Delay of release of K_{ATP} channel openers from the formulation until gastric transit is complete is achieved in the formulations provided herein by any of several mechanisms. A pH sensitive polymer or co-polymer is used which when applied around the drug matrix functions as an effective barrier to release of active at pH 3.0 or lower and is unstable at pH 5.5 and above. This provides for control of release of the active compound in the stomach but rapidly allows release once the dosage form has passed into the small intestine. An alternative to a pH sensitive polymer or co-polymer is a polymer or co-polymer that is non-aqueous-soluble. The extent of resistance to release in the gastric environment can be controlled by coating with a blend of the non-aqueous-soluble and a aqueous soluble polymer. In this approach neither of the blended polymers or co-polymers are pH sensitive. One example of a pH sensitive co-polymer is the Eudragit methacrylic co-polymers, including Eudragit L100, S100 or L100-55 solids, L30 D-55 or FS 30D dispersions, or the L12,5 or S12,5 organic solutions.

[00234] Polymers that delay release can be applied to a tablet either by spray coating (as a thin film) or by compression coating. If a capsule is used, then the polymer(s) may be applied over the surface of the capsule or applied to microparticles of the drug, which may then be encapsulated such as in a capsule or gel. If the capsule is coated, then it will resist disintegration until after gastric transit. If microparticles are coated, then the capsule may disintegrate in the

stomach but little to no drug will be released until after the free microparticles complete gastric transit. Finally, an osmotic pump system that uses e.g., a swellable hydrogel can be used to delay drug release in the stomach. The swellable hydrogel takes up moisture after administration. Swelling of the gel results in displacement of the drug from the system for absorption. The timing and rate of release of the drug depend on the gel used, and the rate at which moisture reaches the gel, which can be controlled by the size of the opening in the system through which fluid enters. See Drug Delivery Technologies online article Dong et al. “L-OROS® SOFTCAP™ for Controlled Release of Non-Aqueous Liquid Formulations.”

[00235] Accordingly, delay of release of K_{ATP} channel openers from the invention formulations until after gastric transit is complete is achieved in the formulations provided herein by any of several mechanisms, including, but not limited to: (a) a pH sensitive polymer or co-polymer applied as a compression coating on a tablet; (b) a pH sensitive polymer or co-polymer applied as a thin film on a tablet; (c) a pH sensitive polymer or co-polymer applied as a thin film to an encapsulation system; (d) a pH sensitive polymer or co-polymer applied to encapsulated microparticles, (e) a non-aqueous-soluble polymer or co-polymer applied as a compression coating on a tablet; (f) a non-aqueous-soluble polymer or co-polymer applied as a thin film on a tablet; (g) a non-aqueous soluble polymer applied as a thin film to an encapsulation system; (h) a non-aqueous soluble polymer applied to microparticles; (i) incorporation of the formulation in an osmotic pump system, or (j) use of systems controlled by ion exchange resins, or (k) combinations of these approaches, wherein the pH sensitive polymer or co-polymer is resistant to degradation under acid conditions.

[00236] Formulations are provided that are designed for administration once daily (per 24 hours). These can contain between 25 and 500 mg of K_{ATP} channel openers. Formulations intended for administration twice daily (per 24 hours) are also provided. These can contain between 25 and 250 mg of K_{ATP} channel openers.

[00237] The formulations provided herein exhibit improved safety of the administered drug product. This improvement in safety occurs by at least two mechanisms. First, delay of release of active drug until gastric transit is complete can reduce the incidence of a range of gastrointestinal adverse side effects including nausea, vomiting, dyspepsia, abdominal pain,

diarrhea and ileus. Second, by sustaining release of the active drug over 2 or more hours to as long as 24 hours, peak drug levels are reduced relative to the peak drug levels observed for the same administered dose using any oral formulation that does not have sustained or controlled release. This reduction in peak drug levels can contribute to reductions in adverse effects that are partially or completely determined by peak drug levels. These adverse effects include: fluid retention with the associated reduced rates of excretion of sodium, chloride and uric acid, edema, hyperglycemia and the associated potential for progression to ketoacidosis, cataracts and non-ketotic hyperosmolar coma, headaches, tachycardia and palpitations.

[00238] Also provided herein are controlled release formulations of K_{ATP} channel openers, which have one feature from each of A-D as shown in Table 1.

Table 1: Controlled Release Formulation Characteristics and Properties

A. Unit Form:	Tablet or Capsule
B. Dosage/unit:	10-100 mg
	100-200 mg
	200-300 mg
	300-500 mg
	500-2000mg
C. Dosing	Once daily (24 hours)
	Twice daily (24 hours)
D. Release time:	2-4 hrs
	4-8 hrs
	8-24 hours

[00239] For example, a controlled release composition can be a tablet containing 25-100 mg of a K_{ATP} channel opener, such tablet administered once daily to achieve a controlled release time of 2-4 hours. All of these formulations can further include the feature of substantially delaying pharmaceutical active release until after gastric transit is complete.

[00240] In addition, any of the above formulations from Table 1 can include at least one feature that improves the solubility or absorption of the K_{ATP} channel opener.

[00241] The controlled release formulations provided herein comprise the active compound (e.g., K_{ATP} channel opener, optionally in combination with growth hormone) and a matrix which comprises a gelling agent that swells upon contact with aqueous fluid. The active compound(s) entrapped within the gel is(are) slowly released into the body upon dissolution of the gel. The active compound(s) can be evenly dispersed within the matrix or can be present as pockets of drug in the matrix. For example, the drug can be formulated into small granules which are dispersed within the matrix. In addition, the granules of drug also can include a matrix, thus, providing a primary and a secondary matrix as described in U.S. Pat. No. 4,880,830 to Rhodes.

[00242] The gelling agent preferably is a polymeric material, which can include, for example, any pharmaceutically acceptable water soluble or water insoluble slow releasing polymer such as xanthan gum, gelatin, cellulose ethers, gum arabic, locust bean gum, guar gum, carboxyvinyl polymer, agar, acacia gum, tragacanth, veegum, sodium alginate or alginic acid, polyvinylpyrrolidone, polyvinyl alcohol, or film forming polymers such as methyl cellulose (MC), carboxymethyl cellulose (CMC), hydroxypropyl methylcellulose, hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), ethylcellulose (EC), acrylic resins or mixtures of the above (see e.g., U.S. Pat. No. 5,415,871).

[00243] The gelling agent of the matrix also can be a heterodisperse gum comprising a heteropolysaccharide component and a homopolysaccharide component which produces a fast-forming and rigid gel as described in U.S. Pat. No. 5,399,359. The matrix also can include a crosslinking agent such as monovalent or multivalent metal cations to further add rigidity and decrease dissolution of the matrix, thus further slowing release of drug. The amount of crosslinking agent to add can be determined using methods routine to the ordinary skilled artisan.

[00244] The matrix of the controlled release composition also can include one or more pharmaceutically acceptable excipients recognized by those skilled in the art, i.e. formulation excipients. Such excipients include, for example, binders: polyvinylpyrrolidone, gelatin, starch paste, microcrystalline cellulose; diluents (or fillers): starch, sucrose, dextrose, lactose, fructose, xylitol, sorbitol, sodium chloride, dextrans, calcium phosphate, calcium sulphate; and lubricants:

stearic acid, magnesium stearate, calcium stearate, Precirol™ and flow aids for example talc or colloidal silicon dioxide.

[00245] The matrix of the controlled release composition can further include a hydrophobic material which slows the hydration of the gelling agent without disrupting the hydrophilic nature of the matrix, as described in U.S. Pat. No. 5,399,359. The hydrophobic polymer can include, for example, alkylcellulose such as ethylcellulose, other hydrophobic cellulosic materials, polymers or co-polymers derived from acrylic or methacrylic acid esters, co-polymers of acrylic and methacrylic acid esters, zein, waxes, shellac, hydrogenated vegetable oils, waxes and waxy substances such as carnauba wax, spermaceti wax, candellila wax, cocoa butter, cetosteryl alcohol, beeswax, ceresin, paraffin, myristyl alcohol, stearyl alcohol, cetylalcohol and stearic acid. and any other pharmaceutically acceptable hydrophobic material known to those skilled in the art.

[00246] The amount of hydrophobic material incorporated into the controlled release composition is that which is effective to slow the hydration of the gelling agent without disrupting the hydrophilic matrix formed upon exposure to an environmental fluid. In certain preferred embodiments, the hydrophobic material is included in the matrix in an amount from about 1 to about 20 percent by weight and replaces a corresponding amount of the formulation excipient. A solvent for the hydrophobic material may be an aqueous or organic solvent, or mixtures thereof.

[00247] Examples of commercially available alkylcelluloses are Aquacoat® (aqueous dispersion of ethylcellulose available from FMC) and Surelease® (aqueous dispersion of ethylcellulose available from Colorcon). Examples of commercially available acrylic polymers suitable for use as the hydrophobic material include Eudragit® RS and RL (co-polymers of acrylic and methacrylic acid esters having a low content (e.g., 1:20 or 1:40) of quaternary ammonium compounds).

[00248] The controlled release composition also can be coated to retard access of liquids to the active compound and/or retard release of the active compound through the film-coating. The film-coating can provide characteristics of gastroresistance and enterosolubility by resisting rapid dissolution of the composition in the digestive tract. The film-coating generally represents about

5-15% by weight of the controlled release composition. Preferably, the core by weight represents about 90% of the composition with the remaining 10% provided by the coating. Such coating can be a film-coating as is well known in the art and include gels, waxes, fats, emulsifiers, combination of fats and emulsifiers, polymers, starch, and the like.

[00249] Polymers and co-polymers are useful as thin film coatings. Solution coatings and dispersion coatings can be used to coat the active compound, either alone or combined with a matrix. The coating is preferably applied to the drug or drug and matrix combination as a solid core of material as is well known in the art.

[00250] A solution for coating can include polymers in both organic solvent and aqueous solvent systems, and typically further including one or more compounds that act as a plasticizer. Polymers useful for coating compositions include, for example, methylcellulose (Methocel ® A; Dow Chemical Co.), hydroxypropylmethylcellulose with a molecular weight between 1,000 and 4,000,000 (Methocel ® E; Dow Chemical Co. or Pharmacoat ®; Shin Etsu), hydroxypropyl cellulose with a molecular weight between 2,000 and 2,000,000, ethyl cellulose, cellulose acetate, cellulose triacetate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose acetate trimellitate (Eastman Kodak), carboxymethylethyl cellulose (Duodcel ®), hydroxypropyl methylcellulose phthalate, ethylcellulose, methylcellulose and, in general, cellulosic derivatives, polymethacrylic acid-methacrylic acid co-polymer (Type A 1:1 Eudragit L100; Type B 1:2 Eudragit S100; and Type C 1:1 Eudragit L100-55, aqueous dispersion 30% solids, Eudragit L30D), poly(meth)acryl ester: poly(ethyl acrylate, methyl methacrylate 2:1), Eudragit NE30D aqueous dispersion 30% solids, polyaminomethacrylate Eudragit E100, poly(trimethylammonioethyl methacrylate chloride)ammoniomethacrylate co-polymer, Eudragit RL30D and Eudragit RS30D, carboxyvinyl polymers, polyvinylalcohols, glucans scleroglucans, mannans, and xanthans.

[00251] Aqueous polymeric dispersions include Eudragit L30D and RS/RL30D, and NE30D, Aquacoat brand ethyl cellulose, Surelease brand ethyl cellulose, EC brand N-10F ethyl cellulose, Aquateric brand cellulose acetate phthalate, Coateric brand Poly(vinyl acetate phthalate), and Aquacoat brand hydroxypropyl methylcellulose acetate succinate. Most of these dispersions are latex, pseudolatex powder or micronized powder mediums.

[00252] A plasticizing agent may be included in the coating to improve the elasticity and the stability of the polymer film and to prevent changes in the polymer permeability over prolonged storage. Such changes may affect the drug release rate. Suitable conventional plasticizing agents include, for example, diethyl phthalate, glycerol triacetate, acetylated monoglycerides, acetyltributylcitrate, acetyltriethyl citrate, castor oil, citric acid esters, dibutyl phthalate, dibutyl sebacate, diethyloxalate, diethyl malate, diethylfumarate, diethylphthalate, diethylsuccinate, diethylmalonate, diethyltartarate, dimethylphthalate, glycerin, glycerol, glyceryl triacetate, glyceryltributyrate, mineral oil and lanolin alcohols, petrolatum and lanolin alcohols, phthalic acid esters, polyethylene glycols, propylene glycol, rape oil, sesame oil, triacetin, tributyl citrate, triethyl citrate, and triethyl acetyl citrate, or a mixture of any two or more of the foregoing. Plasticizers which can be used for aqueous coatings include, for example, propylene glycol, polyethylene glycol (PEG 400), triacetin, polysorbate 80, triethyl citrate, and diethyl d-tartrate.

[00253] A coating solution comprising a mixture of hydroxypropylmethylcellulose and aqueous ethylcellulose (e.g. Aquacoat brand) as the polymer and dibutyl sebacate as plasticizer can be used for coating microparticles. (Aquacoat is an aqueous polymeric dispersion of ethylcellulose and contains sodium lauryl sulfate and cetyl alcohol). Preferably, the plasticizer represents about 1-2% of the composition.

[00254] In addition to the polymers, the coating layer can include an excipient to assist in formulation of the coating solution. Such excipients may include a lubricant or a wetting agent. Suitable lubricants as excipients for the film coating include, for example, talc, calcium stearate, colloidal silicon dioxide, glycerin, magnesium stearate, mineral oil, polyethylene glycol, and zinc stearate, aluminum stearate or a mixture of any two or more of the foregoing. Suitable wetting agents include, for example, sodium lauryl sulfate, acacia, benzalkonium chloride, cetomacrogol emulsifying wax, cetostearyl alcohol, cetyl alcohol, cholesterol, diethanolamine, docusate sodium, sodium stearate, emulsifying wax, glyceryl monostearate, hydroxypropyl cellulose, lanolin alcohols, lecithin, mineral oil, onoethanolamine, poloxamer, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene stearates, propylene glycol alginate, sorbitan esters, stearyl alcohol and triethanolamine, or a mixture of any two or more of the foregoing.

[00255] The specified tablet or capsule formulations of Table 1 may include co-formulation with an obesity treating drug (in addition to the K_{ATP} channel opener). Obesity treating drugs that may be used include, but are not limited to, sibutramine hydrochloride (5-30 mg/unit), orlistat (50-360 mg/unit), phentermine hydrochloride or resin complex (15 to 40 mg/unit), zonisamide (100 to 600 mg/unit) topiramate (64 to 400 mg/unit), naltrexone hydrochloride (50 to 600 mg/unit), rimonabant (5 to 20 mg/unit), ADP356 (5 to 25 mg/unit), ATL962 (20 to 400 mg/unit), or AOD9604 (1 to 10 mg/unit). These formulations are preferably used once daily. For a twice daily dosing, the amount of K_{ATP} channel opener is one half the amount included in the once daily formulation and the coformulated obesity treating drug is half of the amount specified. Alternative obesity treating drugs may include: selective serotonin 2c receptor agonists, dopamine antagonists, cannabinoid-1 receptor antagonists, leptin analogues, leptin transport and/or leptin receptor promoters, neuropeptide Y and agouti-related peptide antagonists, proopiomelanocortin and cocaine and amphetamine regulated transcript promoters, melanocyte-stimulating hormone analogues, melanocortin-4 receptor agonists, and agents that affect insulin metabolism/activity, which include protein-tyrosine phosphatase-1B inhibitors, peroxisome proliferator activated receptor- receptor antagonists, short-acting bromocriptine (ergoset), somatostatin agonists (octreotide), and adiponectin, gastrointestinal-neural pathway agents, including those that increase cholecystokinin activity, increase glucagon-like peptide-1 activity (extendin 4, liraglutide, dipeptidyl peptidase IV inhibitors), and increase protein YY3-36 activity and those that decrease ghrelin activity, as well as amylin analogues, agents that may increase resting metabolic rate (“selective” β -3 stimulators/agonist, uncoupling protein homologues, and thyroid receptor agonists), melanin concentrating hormone antagonists, phytostanol analogues, amylase inhibitors, growth hormone fragments, synthetic analogues of dehydroepiandrosterone sulfate, antagonists of adipocyte 11 β hydroxysteroid dehydrogenase type 1 activity, corticotropin releasing hormone agonists, inhibitors of fatty acid synthesis, carboxypeptidase inhibitors, indanones/indanols, aminosterols, and other gastrointestinal lipase inhibitors.

[00256] The specified tablet or capsule formulations of Table 1 may include co-formulation with a diabetes treating drug (in addition to the K_{ATP} channel opener). Diabetes treating drugs that may be used include, but are not limited to acarbose (50 to 300 mg/unit), miglitol (25 to 300 mg/unit), metformin hydrochloride (300 to 2000 mg/unit), repaglinide (1-16 mg/unit),

nateglinide (200 to 400 mg/unit), rosiglitazone (5 to 50 mg/unit), metaglidasen (100 to 400 mg/unit) or any drug that improves insulin sensitivity, or improves glucose utilization and uptake. These formulations are preferably used once daily. For a twice daily dosing, the amount of the the K_{ATP} channel opener is half the amount included in the once daily formulation and the co-formulated diabetes treating drug is half of the amount specified.

[00257] The specified tablet or capsule formulations of Table 1 may include co-formulation with a cholesterol lowering drug. Cholesterol lowering drugs that may be used include, but are not limited to pravastatin or simvastatin or atorvastatin or fluvastatin or rosuvastatin or lovastatin (all at 10 to 80 mg/unit). These formulations are preferably used once daily. For a twice daily dosing, the amount of K_{ATP} channel opener is preferably 25 to 200 mg/unit and the coformulated cholesterol lowering drug is half of the amount specified.

[00258] The specified tablet or capsule formulations of Table 1 may include co-formulation with a depression treating drug. Depression treating drugs that may be used include, but are not limited to citalopram hydrobromide (10 to 80 mg/unit), escitalopram hydrobromide (5 to 40 mg/unit), fluvoxamine maleate (25 to 300 mg/unit), paroxetine hydrochloride (12.5 to 75 mg/unit), fluoxetine hydrochloride (30 to 100 mg/unit), setraline hydrochloride (25 to 200 mg/unit), amitriptyline hydrochloride (10 to 200 mg/unit), desipramine hydrochloride (10 to 300 mg/unit), nortriptyline hydrochloride (10 to 150 mg/unit), duloxetine hydrochloride (20 to 210 mg/unit), venlafaxine hydrochloride (37.5 to 150 mg/unit), phenelzine sulfate (10 to 30 mg/unit), bupropion hydrochloride (200 to 400 mg/unit), or mirtazapine (7.5 to 90 mg/unit). These formulations are preferably used once daily. For a twice daily dosing, the amount of K_{ATP} channel opener is preferably half the amount included in the once daily formulation and the coformulated depression treating drug is half of the amount specified.

[00259] The specified tablet or capsule formulations of Table 1 may include co-formulation with a hypertension treating drug. Hypertension treating drugs that may be used include, but are not limited to enalapril maleate (2.5 to 40 mg/unit), captopril (2.5 to 150 mg/unit), lisinopril (10 to 40 mg/unit), benazepril hydrochloride (10 to 80 mg/unit), quinapril hydrochloride (10 to 80 mg/unit), perindopril erbumine (4 to 8 mg/unit), ramipril (1.25 to 20 mg/unit), trandolapril (1 to 8 mg/unit), fosinopril sodium (10 to 80 mg/unit), moexipril hydrochloride (5 to 20 mg/unit),

losartan potassium (25 to 200 mg/unit), irbesartan (75 to 600 mg/unit), valsartan (40 to 600 mg/unit), candesartan cilexetil (4 to 64 mg/unit), olmesartan medoxamil (5 to 80 mg/unit), telmisartan (20 to 160 mg/unit), eprosartan mesylate (75 to 600 mg/unit), atenolol (25 to 200 mg/unit), propranolol hydrochloride (10 to 180 mg/unit), metoprolol tartrate, succinate or fumarate (all at 25 to 400 mg/unit), nadolol (20 to 160 mg/unit), betaxolol hydrochloride (10 to 40 mg/unit), acebutolol hydrochloride (200 to 800 mg/unit), pindolol (5 to 20 mg/unit), bisoprolol fumarate (5 to 20 mg/unit), nifedipine (15 to 100 mg/unit), felodipine (2.5 to 20 mg/unit), amlodipine besylate (2.5 to 20 mg/unit), nicardipine (10 to 40 mg/unit), nisoldipine (10 to 80 mg/unit), terazosin hydrochloride (1 to 20 mg/unit), doxazosin mesylate (4 to 16 mg/unit), prazosin hydrochloride (2.5 to 10 mg/unit), or alfuzosin hydrochloride (10 to 20 mg/unit). These formulations are preferably used once daily. For a twice daily dosing, the amount of K_{ATP} channel opener is preferably half the amount included in the once daily formulation and the coformulated hypertension treating drug is half of the amount specified.

[00260] The specified tablet or capsule formulations of Table 1 may include co-formulation with a diuretic to treat edema. Diuretics that may be used include, but are not limited to amiloride hydrochloride (1 to 10 mg/unit), spironolactone (10 to 100 mg/unit), triamterene (25 to 200 mg/unit), bumetanide (0.5 to 4 mg/unit), furosemide (10 to 160 mg/unit), ethacrynic acid or ethacrylate sodium (all at 10 to 50 mg/unit), tosemide (5 to 100 mg/unit), chlorthalidone (10 to 200 mg/unit), indapamide (1 to 5 mg/unit), hydrochlorothiazide (10 to 100 mg/unit), chlorothiazide (50 to 500 mg/unit), bendroflumethiazide (5 to 25 mg/unit), hydroflumethiazide (10 to 50 mg/unit), mythyclothiazide (1 to 5 mg/unit), or polythiazide (1 to 10 mg/unit). These formulations are preferably used once daily. For a twice daily dosing, the amount of K_{ATP} channel opener is preferably half the amount included in the once daily formulation and the coformulated diuretic is half of the amount specified.

[00261] The specified tablet or capsule formulations of Table 1 may include co-formulation with a drug to treat inflammation or pain. Drugs for treating inflammation or pain that may be used include, but are not limited to aspirin (100 to 1000 mg/unit), tramadol hydrochloride (25 to 150 mg/unit), gabapentin (100 to 800 mg/unit), acetaminophen (100 to 1000 mg/unit), carbamazepine (100 to 400 mg/unit), ibuprofen (100 to 1600 mg/unit), ketoprofen (12 to 200 mg/unit), fenprofen sodium (100 to 600 mg/unit), flurbiprofen sodium or flurbiprofen (both at 50

to 200 mg/unit), or combinations of any of these with a steroid or aspirin. These formulations are preferably used once daily. For a twice daily dosing, the amount of K_{ATP} channel opener is preferably half the amount included in the once daily formulation and the coformulated diuretic is half of the amount specified.

[00262] The specified tablet or capsule formulations of Table 1 may include co-formulation with a drug to treat obesity associated comorbidities include those specified above for treating diabetes, cholesterol, depression, hypertension and edema, or drugs to treat atherosclerosis, osteoarthritis, disc herniation, degeneration of knees and hips, breast, endometrial, cervical, colon, leukemia and prostate cancers, hyperlipidemia, asthma/reactive airway disease, gallstones, GERD, obstructive sleep apnea, obesity hypoventilation syndrome, recurrent ventral hernias, menstrual irregularity and infertility.

[00263] The specified tablet or capsule formulations of Table 1 may include co-formulation with an anti-psychotic drug the combination used to treat the psychotic condition and to treat or prevent weight gain, dyslipidemia or impaired glucose tolerance in the treated individual. Drugs for treating various psychotic conditions that may be used include, but are not limited to, lithium or a salt thereof (250 to 2500 mg/unit), carbamazepine or a salt thereof (50 to 1200 mg/unit), valproate, valproic acid, or divalproex (125 to 2500 mg/unit), lamotrigine (12.5 to 200 mg/unit), olanzapine (5 to 20 mg/unit), clozapine (12.5 to 450 mg/unit), or risperidone (0.25 to 4 mg/unit). These coformulations are preferably intended for once per day administration. For a twice daily dosing, the amount of K_{ATP} channel opener is preferably half the amount included in the once daily formulation and the coformulated anti-psychotic is half of the amount specified.

[00264] The specified tablet or capsule formulations of Table 1 may include co-formulation with a drug to treat or prevent ischemic or reperfusion injury. Drugs for treating or preventing ischemic or reperfusion injury that may be used include, but are not limited to: low molecular weight heparins (dalteparin, enoxaparin, nadroparin, tinzaparin or danaparoid), ancrd, pentoxifylline, nimodipine, flunarizine, ebselen, tirilazad, clomethiazole, an AMPA agonist (GYKI 52466, NBQX, YM90K, zonampanel, or MPQX), SYM 2081, selfotel, Cerestat, CP-101,606, dextrophan, dextromethorphan, MK-801, NPS 1502, remacemide, ACEA 1021, GV150526, eliprodil ifenprodil, lubeluzole, naloxone, nalfemene citicoline, acetyl-l-carnitine,

nifedipine, resveratrol, a nitron derivative, clopidogrel, dabigatram, prasugrel, troxoprodil, AGY-94806, or KAI-9803.

[00265] Provided are formulations administered once or twice daily to an obese or overweight subject continuously to result in a circulating concentration of K_{ATP} channel opener sufficient to induce weight loss. Weight loss occurs by the preferential loss of body fat. Additional weight loss can occur when the formulation is administered in combination with a reduced calorie diet.

[00266] Provided are formulations of K_{ATP} channel openers administered as a single dose to an obese, overweight or obesity-prone subject that result in the inhibition of fasting or glucose stimulated insulin secretion for about 24 hours or for about 18 hours.

[00267] Provided are formulations of K_{ATP} channel openers administered as a single dose to an obese, overweight or obesity-prone subject that result in the elevation of energy expenditure for about 24 hours or for about 18 hours.

[00268] Provided are formulations of K_{ATP} channel openers administered as a single dose to an obese, overweight or obesity-prone subject that result in the elevation of beta oxidation of fat for about 24 hours or for about 18 hours.

[00269] Provided are formulations of K_{ATP} channel openers administered as a single dose to an obese, overweight or obesity-prone hyperphagic subject that result in the inhibition of hyperphagia for about 24 hours or for about 18 hours.

[00270] Provided are formulations administered once or twice daily (per 24 hours) to a subject continuously result in a circulating concentration of K_{ATP} channel opener sufficient to induce either beta-cell rest or improved insulin sensitivity or both. Such beta-cell rest and improvements in insulin sensitivity can contribute to effective treatment of type I diabetes, type II diabetes and prediabetes. Such beta-cell rest and improvements in insulin sensitivity can contribute to effective restoration of normal glucose tolerance in type II diabetic and prediabetic subjects.

[00271] The various pharmaceutical K_{ATP} channel opener formulations have a variety of applications, including, but not limited to: (1) treatment of obesity; (2) prevention of weight gain

in individuals who are predisposed to obesity; (3) treatment of hyperinsulemia or hyperinsulinism; (4) treatment of hypoglycemia; (5) treatment of hyperlipidemia, (6) treatment of type II diabetes, (7) preservation of pancreatic function in type I diabetics; (8) treatment of metabolic syndrome (or syndrome X); (9) prevention of the transition from prediabetes to diabetes, (10) correction of the defects in insulin secretion and insulin sensitivity contributing to prediabetes and type II diabetes, (11) treatment of polycystic ovary syndrome, (12) prevention of ischemic or reperfusion injury, (13) treat weight gain, dyslipidemia, or impairment of glucose tolerance in subjects treated with antipsychotics drugs, (14) prevent weight gain, dyslipidemia, or impairment of glucose tolerance in subjects treated with antipsychotics drugs and (15) treatment of any disease where hyperlipidemia, hyperinsulemia, hyperinsulinism, hyperlipidemia, hyperphagia or obesity are contributing factors to the severity or progression of the disease, including but not limited to, Prader-Willi Syndrome, Smith–Magenis syndrome, Froelich’s syndrome, Cohen syndrome, Summit Syndrome, Alstrom, Syndrome, Borjesen Syndrome, Bardet-Biedl Syndrome, hyperlipoproteinemia type I, II, III, and IV, and the like.

[00272] In one embodiment, a K_{ATP} channel opener is administered to an overweight or obese individual as a solid oral dosage once per 24 hours, optionally in combination with growth hormone, to induce weight loss. In further embodiments, the individual (a) is not a type I diabetic, (b) is not a type II diabetic, (c) is not experiencing chronic, recurrent or drug-induced hypoglycemia, (d) does not have metabolic syndrome, or (e) is not experiencing malignant hypertension.

[00273] In one embodiment, a K_{ATP} channel opener is administered to an overweight or obese individual as a solid oral dosage twice per 24 hours, optionally in combination with growth hormone, to induce weight loss. This treatment can be the sole treatment to induce weight loss. In further embodiments, the overweight or obese individual (a) does not have an insulin secreting tumor, (b) is not suffering from Poly Cystic Ovary Syndrome, (c) is not a type I diabetic, (d) is not a type II diabetic, (e) does not have metabolic syndrome, (f) is not experiencing chronic recurrent or drug-induced hypoglycemia, (g) has not been treated for schizophrenia with haloperidol, or (h) is not experiencing malignant hypertension. In further embodiments, the overweight or obese adolescent (a) has not been diagnosed as being type I or type II diabetic, (b)

is not experiencing chronic, recurrent or drug-induced hypoglycemia, or (c) has not been diagnosed as having metabolic syndrome.

[00274] In another embodiment, a K_{ATP} channel opener is administered to an overweight or obese individual as a solid oral dosage form three times per 24 hours, optionally in combination with growth hormone, to induce weight loss. This treatment can be the sole treatment to induce weight loss. In further embodiments, the overweight or obese individual (a) does not have an insulin-secreting tumor, (b) is not suffering from Poly Cystic Ovary Syndrome, (c) is not a type I diabetic, (d) is not a type II diabetic, (e) does not have metabolic syndrome, or (f) is not experiencing chronic, recurrent or drug-induced hypoglycemia.

[00275] In another embodiment, a K_{ATP} channel opener is administered to an overweight or obese adolescent as a solid oral dosage form three times per 24 hours, optionally in combination with growth hormone, to induce weight loss. This treatment can be the sole treatment to induce weight loss. In further embodiments, the overweight or obese adolescent is (a) is a type I or type II diabetic, (b) is not experiencing chronic, recurrent or drug-induced hypoglycemia or (c) does not have metabolic syndrome.

[00276] In another embodiment, a K_{ATP} channel opener is administered as a solid oral dosage form three times per 24 hours, optionally in combination with growth hormone, to induce weight loss to an overweight or obese adult who (a) is not simultaneously receiving glucagon injections, triiodothyroxin or furosemide, (b) is not being treated for schizophrenia with haloperidol, or (c) is not experiencing malignant hypertension.

[00277] In another embodiment, a K_{ATP} channel opener is administered to an overweight or obese individual as a solid oral dosage form four times per 24 hours, optionally in combination with growth hormone, to induce weight loss.

[00278] In another embodiment, a K_{ATP} channel opener is administered to an overweight or obese individual as a solid oral dosage form administered from one, two, three or four times per 24 hours, optionally in combination with growth hormone, to induce weight loss at a daily dose of 50 to 275 mg. In a further embodiment, the overweight or obese individual individual (a) is

not type I diabetic, (b) is not type II diabetic, (c) is not suffering chronic, recurrent or drug-induced hypoglycemia, or (d) does not have metabolic syndrome.

[00279] In another embodiment, a K_{ATP} channel opener is administered to an overweight or obese individual as a solid oral dosage form administered from one, two, three or four times per 24 hours, optionally in combination with growth hormone, to induce weight loss at a daily dose of 130 to 275 mg. In a further embodiment, the overweight or obese individual (a) is not type I diabetic, (b) is not type II diabetic, (c) is not suffering chronic, recurrent or drug-induced hypoglycemia, or (d) does not have metabolic syndrome.

[00280] In another embodiment, a K_{ATP} channel opener is administered to an overweight or obesity prone individual as a solid oral dosage form one, two, three or four times per 24 hours, optionally in combination with growth hormone, to maintain a weight loss, as it is preferable to maintain weight in an obese individual once some weight loss has occurred when the alternative is to regain weight. In a further embodiment, the administered daily dose of the K_{ATP} channel opener is 50 to 275 mg.

[00281] In other embodiments, a K_{ATP} channel opener is administered as a solid oral dosage form to an overweight, obese, or obesity prone individual, optionally in combination with growth hormone, to (a) elevate energy expenditure, (b) elevate beta oxidation of fat, or (c) reduce circulating triglyceride concentrations.

[00282] In other embodiments, a solid oral dosage of a K_{ATP} channel opener is administered on a prolonged basis to an individual in need thereof to induce the loss of 25%, 50%, or 75% of initial body fat.

[00283] In another embodiment, a solid oral dosage of a K_{ATP} channel opener is administered on a prolonged basis to an individual in need thereof, optionally in combination with growth hormone, to induce (a) the preferential loss of body fat or (b) the preferential loss of visceral body fat.

[00284] In additional embodiments, a solid oral dosage of a K_{ATP} channel opener is administered on a prolonged basis one, two or three times per 24 hours at daily doses of 50 to 275 mg to an individual, optionally in combination with growth hormone, to (a) induce the loss

of 25%, 50% or 75% of initial body fat, (b) induce the preferential loss of body fat, or (c) induce the preferential loss of visceral fat.

[00285] In another embodiment, a solid oral dosage of a K_{ATP} channel opener is administered to an individual, optionally in combination with growth hormone, to induce the preferential loss of body fat and to induce reduction in circulating triglycerides.

[00286] In another embodiment, a solid oral dosage of a K_{ATP} channel opener is co-administered with growth hormone.

[00287] In yet another embodiment, a solid oral dosage of a K_{ATP} channel opener is co-administered with growth hormone and optionally one or more of sibutramine, orlistat, rimonabant, an appetite suppressant, an anti-depressant, an anti-epileptic, a diuretic that is not furosemide, a drug that induces weight loss by a mechanism that is distinct from a K_{ATP} channel opener, a drug that induces weight loss by a mechanism that is distinct from a K_{ATP} channel opener but is not metformin, furosemide or triiodothyroxin, or a drug that lowers blood pressure, to induce weight loss and/or treat obesity associated comorbidities in an overweight, obese, or obesity prone individual. In further embodiments, the overweight, obese, or obesity prone individual (a) is a type I diabetic, (b) is not a type II diabetic, (c) is not suffering from chronic, recurrent or drug-induced hypoglycemia, or (d) does not have metabolic syndrome.

[00288] In another embodiment a solid oral dosage of a K_{ATP} channel opener is co-administered with growth hormone and optionally one or more of an anti-depressant, a drug that lowers blood pressure, a drug that lowers cholesterol, a drug that raises HDL, an anti-inflammatory that is not a Cox-2 inhibitor, a drug that lowers circulating triglycerides, to an overweight, obese, or obesity prone individual to induce weight loss and/or treat obesity associated comorbidities. In further embodiments, the overweight, obese, or obesity prone individual (a) is not a type I diabetic, (b) is not a type II diabetic, (c) is not suffering from chronic, recurrent or drug-induced hypoglycemia, or (d) does not have metabolic syndrome.

[00289] In another embodiment, a solid oral dosage of a K_{ATP} channel opener is co-administered with growth hormone and optionally one or more of a drug that lowers blood pressure, a drug that lowers cholesterol, a drug that raises HDL, an anti-inflammatory that is not

a Cox-2 inhibitor, a drug that lowers circulating triglycerides, to maintain weight and/or treat obesity associated comorbidities in an overweight, obese, or obesity prone individual, as it is preferable to maintain weight in an obese individual once some weight loss has occurred when the alternative is to regain weight. In further embodiments, the overweight, obese, or obesity prone individual (a) is not a type I diabetic, (b) is not a type II diabetic, (c) is not suffering from chronic, recurrent or drug-induced hypoglycemia, or (d) does not have metabolic syndrome.

[00290] In additional embodiments, a tablet formulation of a K_{ATP} channel opener is used to administer a therapeutically effective dose of a K_{ATP} channel opener to an obese, overweight or obesity prone individual in need thereof to treat obesity, to (a) provide beta cell rest, (b) treat type I or type II diabetes, or (c) prevent the occurrence of diabetes.

[00291] In additional embodiments, a solid oral dosage form or tablet formulation of a K_{ATP} channel opener is co-administered with growth hormone and optionally one or more of Phentermine or a derivative thereof to an obese adult or adolescent to induce weight loss and/or treat obesity and obesity-associated co-morbidities. In further embodiments, a solid oral dosage form or tablet formulation of a K_{ATP} channel opener is co-administered with Phentermine or a derivative, optionally in combination with growth hormone, thereof to an obese adult or adolescent to treat metabolic syndrome in a patient in need thereof.

[00292] In further embodiments, a pharmaceutically acceptable formulation of a K_{ATP} channel opener at doses of 50 to 275 mg/day is co-administered with growth hormone and optionally one or more of Phentermine or a derivative thereof at daily doses of 15 to 37.5 mg to an overweight or obese individual to induce weight loss, to treat metabolic syndrome, or to induce weight loss and treat obesity-associated co-morbidities. In another embodiment, a tablet formulation is co-administered with growth hormone and optionally one or more of Phentermine or a derivative thereof to treat metabolic syndrome in a patient.

[00293] In another embodiment, a quick dissolving formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is used to provide a therapeutically effective dose to a patient in need thereof.

[00294] In further embodiments, a K_{ATP} channel opener is administered, optionally in combination with growth hormone, once per 24 hours at doses of 125 mg to 275 mg to an overweight or obese individual who is not type II diabetic and is not being treated for nighttime hypoglycemia.

[00295] In further embodiments, a K_{ATP} channel opener is formulated as a tablet or capsule for oral administration. The tablet or capsule may be co-formulated with metformin. In another embodiment, a K_{ATP} channel opener is formulated as an oral suspension, and the oral suspension may be further encapsulated in another embodiment.

[00296] In another embodiment, a pharmaceutical salt of a K_{ATP} channel opener is formulated as a tablet or capsule for oral administration, or as an oral suspension or as an oral solution, or as an oral solution that is encapsulated. If the opener is diazoxide, the salt, is preferably not a sodium salt.

[00297] In another embodiment a K_{ATP} channel opener is co-formulated with hydrochlorothiazide, chlorothiazide, cyclothiazide, benzthiazide, metyclothiazide, bendroflumethiazide, hydroflumethiazide, trichlormethiazide, or polythiazide in a pharmaceutical formulation suitable for oral administration.

[00298] Upon administration of the formulations provided herein to humans or animals, some or all of the following effects are observed: (1) the production of lipoprotein lipase by adipocytes is reduced; (2) enhanced lipolysis by adipocytes; (3) expression of fatty acid synthase by adipocytes is reduced; (4) glyceraldehydes phosphate dehydrogenase activity of adipocytes is reduced; (5) little or no new triglycerides are synthesized and stored by adipocytes; (6) enhanced expression of β_3 Adrenergic Receptor (β_3 AR) an improvement in the adrenergic function in adipocytes; (7) reduced glucose stimulated secretion of insulin by pancreatic B-cells; (8) decreased insulinemia; (9) enhanced blood glucose levels; (10) increased expression of Uncoupling Protein 1 in adipocytes; (11) enhanced thermogenesis in white and brown adipose tissue; (12) reduction of plasma triglyceride concentration; (13) decrease in circulating leptin concentrations; (14) up-regulation of insulin receptors; (15) enhanced glucose uptake; (16) reduced adipocyte hyperplasia; (17) reduced adipocyte hypertrophy; (18) reduced rates of conversion of preadipocytes to adipocytes; (19) reduced rates of hyperphagia, (20) increased

protection of CNS, cardiac and other tissues from ischemic or reperfusion injury, (21) improved insulin sensitivity, (22) elevated CSF insulin concentrations, (23) elevated circulating adiponectin concentrations, (25) reduced circulating triglyceride concentrations, (26) enhancement of beta-cell rest, and/or (27) increase in lean body mass.

[00299] Threshold concentrations of the current invention include those circulating concentrations of K_{ATP} channel openers, optionally in combination with growth hormone, resulting from the administration of the drug as an i.v. formulation, an immediate release oral formulation, a controlled release formulation, a transdermal formulation, or an intranasal formulation to an overweight or obese individual which results in (1) measurable suppression of fasting insulin levels, (2) suppression of fasting insulin levels by at least 20% from the baseline measurement in the same individual prior to treatment with a K_{ATP} channel openers, (3) suppression of fasting insulin levels by at least 30% from the baseline measurement in the same individual prior to treatment with K_{ATP} channel openers, (4) suppression of fasting insulin levels by at least 40% from the baseline measurement in the same individual prior to treatment with a K_{ATP} channel openers, (5) suppression of fasting insulin levels by at least 50% from the baseline measurement in the same individual prior to treatment with K_{ATP} channel openers, (6) suppression of fasting insulin levels by at least 60% from the baseline measurement in the same individual prior to treatment with K_{ATP} channel openers, (7) suppression of fasting insulin levels by at least 70% from the baseline measurement in the same individual prior to treatment with K_{ATP} channel openers, (8) suppression of fasting insulin levels by at least 80% from the baseline measurement in the same individual prior to treatment with K_{ATP} channel openers, (9) loss of weight, (10) elevation of resting energy expenditure, or (11) elevation of the oxidation of fat or fatty acids.

[00300] Threshold effects of the current invention include those circulating concentrations of K_{ATP} channel openers resulting from the administration of an i.v. formulation of the drug, or an immediate release oral formulation of the drug, or a controlled release formulation of the drug, or a sustained release formulation, or a transdermal formulation, or an intranasal formulation of the drug to an obesity prone individual which result in (1) the loss of weight, and (2) the maintenance of weight.

[00301] Threshold effects of the current invention include those circulating concentrations of K_{ATP} channel openers resulting from the administration of an i.v. formulation of the drug, or an immediate release oral formulation of the drug, or a controlled release formulation of the drug, or a sustained release formulation, or a transdermal formulation, or an intranasal formulation of the drug to a prediabetic individual which result in prevention of the transition to diabetes.

[00302] Threshold effects of the current invention include those circulating concentrations of K_{ATP} channel openers resulting from the administration of an i.v. formulation of the drug, or an immediate release oral formulation of the drug, or a controlled release formulation of the drug, or a sustained release formulation, or a transdermal formulation, or an intranasal formulation of the drug to a individual with type 1 diabetes which result in beta cell rest.

[00303] The mode of action by which weight is maintained or lost resulting from the prolonged administration of K_{ATP} channel openers to overweight, obese or obesity prone individuals as provided herein includes, but is not limited to one or more of (1) enhanced energy expenditure, (2) enhanced oxidation of fat and fatty acids, (3) the enhancement of lipolysis in adipose tissue, (4) enhanced glucose uptake by tissues, enhanced insulin sensitivity, (5) improved beta adrenergic response, and (6) increase in lean body mass. The mode of action by which weight is maintained or lost resulting from the prolonged administration of K_{ATP} channel openers to obese or obesity prone individuals as provided herein may also include the suppression of appetite.

[00304] Prolonged administration of pharmaceutical formulations of K_{ATP} channel openers to overweight or obese humans or animals, optionally in combination with growth hormone, results in substantial and sustained weight loss including some or all of the following effects: (1) preferential loss of body fat; (2) loss of greater than 25% of initial body fat mass; (3) loss of greater than 50% of initial body fat mass; (4) loss of greater than 75% of initial body fat mass; (5) significant increase in resting energy expenditure; (6) increase in the oxidation of fat and fatty acids; (7) reduction in blood pressure; (8) production of lipoprotein lipase by adipocytes is reduced; (9) enhanced lipolysis by adipocytes; (10) expression of fatty acid synthase by adipocytes is reduced; (11) glyceraldehydes phosphate dehydrogenase activity of adipocytes is reduced; (12) little or no new triglycerides are synthesized and stored by adipocytes; (13)

enhanced expression of β_3 Adrenergic Receptor (β_3 AR) and an improvement in the adrenergic function in adipocytes; (14) reduced glucose stimulated secretion of insulin by pancreatic B-cells; (15) decreased insulinemia; (16) enhanced blood glucose levels; (17) increased expression of Uncoupling Protein 1 in adipocytes; (18) enhanced thermogenesis in white and brown adipose tissue; (19) reduction of plasma triglyceride concentration; (20) decrease in circulating leptin concentrations; (21) up-regulation of insulin receptors; (22) enhanced glucose uptake; (23) reduced adipocyte hyperplasia; (24) reduced adipocyte hypertrophy; (25) reduced rates of conversion of preadipocytes to adipocytes; (26) reduced rates of hyperphagia; (27) the sequential loss first of the metabolically most active adipose tissue (visceral), followed by the loss of less metabolically active adipose tissue, (28) elevation of circulating adiponectin concentrations, (29) elevation of cerebrospinal fluid insulin levels, (30) enhanced islet insulin mRNA and insulin content, (31) enhanced metabolic efficiency of insulin, or (32) increase in lean body mass.

[00305] Prolonged administration of formulations of K_{ATP} channel openers, optionally in combination with growth hormone, to obesity prone humans or animals, including individuals who have undergone various types of bariatric surgery, results in sustained maintenance of weight including some or all of the following effects: (1) increased resting energy expenditure; (2) increase in the oxidation of fat and fatty acids; (3) reduction in blood pressure; (4) production of lipoprotein lipase by adipocytes is reduced; (5) enhanced lipolysis by adipocytes; (6) expression of fatty acid synthase by adipocytes is reduced; (7) glyceraldehyde phosphate dehydrogenase activity of adipocytes is reduced; (8) little or no new triglycerides are synthesized and stored by adipocytes; (9) enhanced expression of β_3 Adrenergic Receptor (β_3 AR) and improvement in the adrenergic function in adipocytes; (10) reduced glucose stimulated secretion of insulin by pancreatic B-cells; (11) decreased insulinemia; (12) enhanced blood glucose levels; (13) increased expression of Uncoupling Protein 1 in adipocytes; (14) enhanced thermogenesis in white and brown adipose tissue; (15) reduction of plasma triglyceride concentration; (16) decreased circulating leptin concentration; (17) up-regulation of insulin receptors; (18) enhanced glucose uptake; (19) reduced adipocyte hyperplasia; (20) reduced adipocyte hypertrophy; (21) reduced rates of conversion of preadipocytes to adipocytes; and (22) reduced rates of hyperphagia, (23) elevated circulating adiponectin concentration, (24) elevated cerebrospinal fluid insulin levels, (25) enhanced islet insulin mRNA and insulin content, or (26) enhanced metabolic efficiency of insulin.

[00306] Immediate or prolonged administration of formulations of K_{ATP} channel openers, optionally in combination with growth hormone, to prediabetic or type I diabetic humans or animals results in the prevention of beta cell failure, improved glycemic control, and prevention of the transition from prediabetes to diabetes including some or all of the following effects: (1) increase in resting energy expenditure; (2) increase in the oxidation of fat and fatty acids; (3) reduction in blood pressure; (4) production of lipoprotein lipase by adipocytes is reduced; (5) enhanced lipolysis by adipocytes; (6) expression of fatty acid synthase by adipocytes is reduced; (7) glyceraldehyde phosphate dehydrogenase activity of adipocytes is reduced; (8) little or no new triglycerides are synthesized and stored by adipocytes; (9) enhanced expression of β_3 Adrenergic Receptor (β_3AR) and an improvement in the adrenergic function in adipocytes; (10) reduced glucose stimulated secretion of insulin by pancreatic B-cells; (11) decreased insulinemia; (12) enhanced blood glucose levels; (13) increased expression of Uncoupling Protein 1 in adipocytes; (14) enhanced thermogenesis in white and brown adipose tissue; (15) reduction of plasma triglyceride concentration; (16) decreased circulating leptin concentrations; (17) up-regulation of insulin receptors; (18) enhanced glucose uptake; (19) reduced adipocyte hyperplasia; (20) reduced adipocyte hypertrophy; (21) reduced rates of conversion of preadipocytes to adipocytes; (22) reduced rates of hyperphagia, (23) elevated circulating adiponectin concentrations, (24) elevated cerebrospinal fluid insulin levels, (25) enhanced islet insulin mRNA and insulin content, or (26) enhanced metabolic efficiency of insulin.

[00307] Immediate or prolonged administration of formulations of K_{ATP} channel openers, optionally in combination with growth hormone, to humans or animals that are at risk for myocardial infarct, or stroke or undergoing a surgical procedure that restores blood flow to heart or brain results in improved therapeutic outcomes post-surgically, or following the occurrence of myocardial infarct or stroke by improving the survival of tissue after blood flow is restored, reduced stunning of tissue, and altering the nature of the inflammatory responses.

[00308] Pharmaceutical formulations as provided herein are designed to be used in the treatment of obesity, hyperlipidemia, hypertension, weight maintenance, type I diabetes, prediabetes, type II diabetes, or any condition where weight loss, reduction in circulating triglycerides or beta cell rest contributes to therapeutic outcomes provide for a range of critical changes in pharmacodynamic and pharmacokinetic responses to administered doses of K_{ATP}

channel openers, optionally in combination with growth hormone, which changes include one or more of the following: (1) extending the pharmacodynamic effect of an administered dose to greater than 24 hours as measured by the suppression of insulin secretion, (2) providing for substantial uptake of the active pharmaceutical ingredient in the small intestine, (3) providing for substantial uptake of the active pharmaceutical ingredient in the large intestine, (4) result in lowered C_{max} versus current oral suspension or capsule products for the same administered dose of active pharmaceutical ingredient, (5) provide for circulating concentrations of unbound active pharmaceutical ingredient above threshold concentrations for 24 or more hours from a single administered dose, and (6) provide for more consistent drug absorption by treated individuals as compared to existing capsule formulations.

[00309] Pharmaceutical co-formulations of the current invention designed to treat a range of conditions in humans and animals include the combination of K_{ATP} channel openers with growth hormone and optionally one or more of: (1) a diuretic, (2) a drug that lowers blood pressure, (3) a drug that suppresses appetite, (4) a cannabinoid receptor antagonist, (5) a drug that suppresses that action of gastric lipases, (6) any drug that is used to induce weight loss, (7) a drug that lowers cholesterol, (8) a drug that lowers LDL bound cholesterol, (9) a drug that improves insulin sensitivity, (10) a drug that improves glucose utilization or uptake, (11) a drug that reduces incidence of atherosclerotic plaque, (12) a drug that reduces inflammation, (13) a drug that is antidepressant, (14) a drug that is an anti-epileptic, or (15) a drug that is an anti-psychotic.

[00310] Treatment of humans or animals of the current invention using pharmaceutical formulations of K_{ATP} channel openers, optionally in combination with growth hormone, result in reduced incidence of adverse side effects including but not limited to edema, fluid retention, reduced rates of excretion of sodium, chloride, and uric acid, hyperglycemia, ketoacidosis, nausea, vomiting, dyspepsia, ileus and headaches. These reductions in frequency of adverse side effects are achieved by: (1) initiating dosing of individuals at subtherapeutic doses and in a step wise manner increasing the dose daily until the therapeutic dose is achieved where the number of days over which the step up in dose is effected is 2 to 10, (2) use of the lowest effective dose to achieve the desired therapeutic effect, (3) use of a pharmaceutical formulation that delays release of active until gastric transit is complete, (4) use of a pharmaceutical formulation that delays release of active until gastric transit is complete, (5) use of a pharmaceutical formulation that

results in lower circulating peak drug levels as compared to an immediate release oral suspension or capsule formulation for the same administered dose, and (6) optimizing the timing of administration of dose within the day and relative to meals.

[00311] Treatment of patients suffering from Prader-Willi Syndrome, Smith–Magenis syndrome, Froelich’s syndrome, Cohen syndrome, Summit Syndrome, Alstrom, Syndrome, Borjesen Syndrome, Bardet-Biedl Syndrome, and hyperlipoproteinemia type I, II, III, and IV with the current invention using pharmaceutical formulations of K_{ATP} channel openers, optionally in combination with growth hormone, result in some or all of the following therapeutic outcomes: (1) weight loss, (2) reduced rates of weight gain, (3) inhibition of hyperphagia, (4) reduced incidence of impaired glucose tolerance, prediabetes or diabetes, (5) reduced incidence of congestive heart failure, (6) reduced hypertension, and (7) reduced rates of all cause mortality.

[00312] Treatment of prediabetic subjects with the current invention using pharmaceutical formulations of K_{ATP} channel openers, optionally in combination with growth hormone, result in some or all of the following therapeutic outcomes: (1) weight loss, (2) restoration of normal glucose tolerance, (3) delayed rates of progression to diabetes, (4) reduced hypertension, and (5) reduced rates of all cause mortality.

[00313] Treatment of diabetic subjects with the current invention using pharmaceutical formulations of K_{ATP} channel openers, optionally in combination with growth hormone, result in some or all of the following therapeutic outcomes: (1) weight loss, (2) restoration of normal glucose tolerance, (3) delayed rates of progression of diabetes, (4) improvements in glucose tolerance, (5) reduced hypertension, and (6) reduced rates of all cause mortality.

[00314] Co-administration of drugs with formulations of K_{ATP} channel openers in the treatment of diseases of overweight, obese or obesity prone human and animal subjects involves the co-administration of a pharmaceutically acceptable formulation of K_{ATP} channel openers with an acceptable formulation of growth hormone and optionally one or more of: (1) Sibutramine, (2) orlistat, (3) Rimonabant, (4) a drug that is an appetite suppressant, (5) any drug used to induce weight loss in an obese or overweight individual, (6) a non-thiazide diuretic, (7) a drug that lowers cholesterol, (8) a drug that raises HDL cholesterol, (9) a drug that lowers LDL

cholesterol, (10) a drug that lowers blood pressure, (11) a drug that is an anti-depressant, (12) a drug that improves insulin sensitivity, (13) a drug that improves glucose utilization and uptake (14) a drug that is an anti-epileptic, (15) a drug that is an anti-inflammatory, or (16) a drug that lowers circulating triglycerides.

[00315] Co-administration of drugs with formulations of K_{ATP} channel openers in the treatment or prevention of weight gain, dyslipidemia, or impaired glucose tolerance in subjects treated with antipsychotics drugs involve the co-administration of a pharmaceutically acceptable formulation of K_{ATP} channel openers with growth hormone and optionally one or more of an acceptable formulation of: lithium, carbamazepine, valproic acid and divalproex, and lamotrigine, antidepressants generally classified as monoamine oxidase inhibitors including isocarboxazid, phenelzine sulfate and tranylcypromine sulfate, tricyclic antidepressants including doxepin, clomipramine, amitriptyline, maproline, desipramine, nortriptyline, desipramine, doxepin, trimipramine, imipramine and protriptyline, tetracyclic antidepressants including mianserin, mirtazapine, maprotiline, oxaprotiline, delequamine, levoprotline, triflucarbine, setipiline, lortalaline, azipramine, aptazapine maleate and pirlindole, and major tranquilizers and atypical antipsychotics including paloproxidol, perphenazine, thioridazine, risperidone, clozapine, olanzapine and chlorpromazine.

[00316] In one embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an overweight or obese individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation to reach and maintain the threshold concentration required to measurably reduce fasting insulin levels for a prolonged period. Preferably the K_{ATP} channel opener formulation reduces fasting insulin levels by at least 20%, more preferably by at least 30%, more preferably by at least 40%, more preferably by at least 50%, more preferably by at least 60% more preferably by at least 70%, and more preferably by at least 80%. Fasting insulin levels are commonly measured using the glucose tolerance test (OGTT). After an overnight fast, a patient ingests a known amount of glucose. Initial glucose levels are determined by measuring pre-test glucose levels in blood and urine. Blood insulin levels are measured by a blood is draw every hour after the glucose is consumed for up to three hours. In a fasting

glucose assay individuals with plasma glucose values greater than 200 mg/dl at 2 hours post-glucose load indicate an impaired glucose tolerance.

[00317] In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an overweight or obese individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation to reach and maintain the threshold concentration required to induce weight loss for a prolonged period.

[00318] In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an overweight or obese individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation to reach and maintain the threshold concentration required to elevate resting energy expenditure for a prolonged period.

[00319] In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an overweight or obese individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation to reach and maintain the threshold concentration required to elevate fat and fatty acid oxidation for a prolonged period.

[00320] In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an obesity prone individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation to reach and maintain the threshold concentration required to induce weight loss for a prolonged period.

[00321] In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an obesity prone individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation to reach and maintain the threshold concentration required to maintain weight for a prolonged period.

[00322] In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an overweight or obese individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation to reach and maintain a drug concentration above the threshold concentration required to induce weight loss for a prolonged period.

[00323] In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an overweight or obese individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation for a prolonged period of time to reduce body fat by more than 25%, more preferably by at least 50%, and more preferably by at least 75%.

[00324] In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an overweight or obese individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation for a prolonged period of time to preferentially reduce visceral fat deposits.

[00325] In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an overweight or obese individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation for a prolonged period of time to reduce visceral fat depots and other fat deposits.

[00326] In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to a normoinsulemic overweight or obese individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation to reach and maintain a drug concentration above the threshold concentration required to induce weight loss for a prolonged period.

[00327] In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to a prediabetic individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal

formulation or an intranasal formulation to reach and maintain a drug concentration above the threshold concentration required to prevent the transition to diabetes for a prolonged period.

[00328] In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to a type 1 diabetic individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation to reach and maintain a drug concentration above the threshold concentration required to induce beta cell rest for a prolonged period.

[00329] In another embodiment, a single dose of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an individual in need thereof that results in circulating concentration of active drug sufficient to diminish the secretion of insulin for 24 or more hours.

[00330] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is administered over a prolonged basis to an individual in need thereof no more than once per 24 hours that results in circulating concentration of active drug sufficient to diminish the secretion of insulin on a continuous basis.

[00331] In another embodiment, a single dose of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an individual in need thereof that results in circulating concentration of active drug sufficient to elevate non-esterified fatty acids in circulation for 24 or more hours.

[00332] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is administered over a prolonged basis to an individual in need thereof no more than once per 24 hours that results in circulating concentration of active drug sufficient to elevate non-esterified fatty acids in circulation on a continuous basis.

[00333] In another embodiment, a single dose of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an individual in need thereof that results in circulating concentration of active drug sufficient to treat hypoglycemia in circulation for 24 or more hours.

[00334] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is administered over a prolonged basis to an individual in need thereof no more than once per 24 hours that results in circulating concentration of active drug sufficient to treat hypoglycemia on a continuous basis.

[00335] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is administered over a prolonged basis to an individual in need thereof no more than once per 24 hours that results in circulating concentration of active drug sufficient to induce weight loss on a continuous basis.

[00336] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is administered over a prolonged basis to an individual in need thereof no more than once per 24 hours that results in circulating concentration of active drug sufficient to maintain weight on a continuous basis, as it is preferable to maintain weight in an obese individual once some weight loss has occurred when the alternative is to regain weight.

[00337] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is administered over a prolonged basis to an individual in need thereof no more than once per 24 hours that results in circulating concentration of active drug sufficient to reduce circulating triglyceride levels on a continuous basis.

[00338] In another embodiment, a single dose of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an individual in need thereof that results in circulating concentration of active drug sufficient to reduce or prevent ischemic or reperfusion injury in circulation for 24 or more hours.

[00339] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is administered over a prolonged basis to an individual in need thereof no more than once per 24 hours that results in circulating concentration of active drug sufficient reduce or prevent ischemic or reperfusion injury on a continuous basis.

[00340] In another embodiment, the adverse effects of frequent treatment with a K_{ATP} channel opener, optionally in combination with growth hormone, is reduced using a pharmaceutically acceptable formulation of diazoxide or its derivatives that is administered to an individual in need thereof on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached.

[00341] In another embodiment, the adverse effects of frequent treatment with a K_{ATP} channel opener, optionally in combination with growth hormone, is reduced using a pharmaceutically acceptable formulation of a K_{ATP} channel opener that is administered to an individual in need thereof on a daily basis in which the active ingredient is not released from the formulation until gastric transit is complete.

[00342] In another embodiment, the adverse effects of frequent treatment with a K_{ATP} channel opener, optionally in combination with growth hormone, is reduced using a pharmaceutically acceptable formulation of a K_{ATP} channel opener that is administered to an individual in need thereof on a daily basis in which the active ingredient is not released from the formulation until gastric transit is complete.

[00343] In another embodiment, the adverse effects of frequent treatment with a K_{ATP} channel opener, optionally in combination with growth hormone, is reduced using a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, that is administered to an individual in need thereof on a daily basis in which the maximum circulating concentration of active ingredient is lower than what would be realized by the administration of the same dose using an oral suspension or capsule formulation.

[00344] In another embodiment, the adverse effects of frequent treatment with a K_{ATP} channel opener, optionally in combination with growth hormone, is reduced using a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, that is administered to an individual in need thereof on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached, the active ingredient is not released from the formulation until gastric transit is complete and in which the maximum circulating concentration of active

ingredient is lower than what would be realized by the administration of the same dose using an oral suspension or capsule formulation.

[00345] In another embodiment, the adverse effects of frequent treatment with a K_{ATP} channel opener, optionally in combination with growth hormone, is reduced using a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, that is administered to an overweight or obese individual in need thereof on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached, the active ingredient is not released from the formulation until gastric transit is complete, in which the maximum circulating concentration of active ingredient is lower than what would be realized by the administration of the same dose using an oral suspension or capsule formulation, and in which the maximum dose is less than 2.5 mg/kg/day.

[00346] In another embodiment, the adverse effects of frequent treatment with a K_{ATP} channel opener, optionally in combination with growth hormone, is reduced using a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, that is administered to an overweight or obese individual in need thereof on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached, the active ingredient is not released from the formulation until gastric transit is complete, in which the maximum circulating concentration of active ingredient is lower than what would be realized by the administration of the same dose using an oral suspension or capsule formulation, and in which the maximum dose is less than 1.75 mg/kg/day.

[00347] In another embodiment, the treatment of an overweight or obese individual is optimized for weight loss by administration of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, once per 24 hours in which the release of the active ingredient from the formulation has been modified to provide near zero order release for at least 12 hours.

[00348] In another embodiment, the treatment of an overweight or obese individual is optimized for weight loss by administration of a pharmaceutically acceptable formulation of a

K_{ATP} channel opener, optionally in combination with growth hormone, once per 24 hours in which the release of the active ingredient from the formulation has been modified to provide near zero order release for at least 18 hours.

[00349] In another embodiment, the treatment of an overweight or obese individual is optimized for weight loss by administration of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, once per 24 hours in which the release of the active ingredient from the formulation has been modified to provide a rising drug concentration in circulation for at least 12 hours.

[00350] In another embodiment, the treatment of an overweight or obese individual is optimized for weight loss by administration of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, once per 24 hours in which the release of the active ingredient from the formulation has been modified to provide a rising drug concentration in circulation for at least 18 hours.

[00351] In another embodiment, the treatment of an overweight or obese individual is optimized for weight loss by administration of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, once per 24 hours in which the release of the active ingredient from the formulation has been modified to match the pattern of basal insulin secretion.

[00352] In another embodiment, the frequency of adverse effects upon treatment with a K_{ATP} channel opener is reduced using a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, that is administered to an obesity prone individual in need thereof on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached, the active ingredient is not released from the formulation until gastric transit is complete, in which the maximum circulating concentration of active ingredient is lower than what would be realized by the administration of the same dose using an oral suspension or capsule formulation, and in which the maximum dose is less than 2.5 mg/kg/day.

[00353] In another embodiment, the frequency of adverse effects upon treatment with a K_{ATP} channel opener, optionally in combination with growth hormone, is reduced using a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, that is administered to an obesity prone individual in need thereof on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached, the active ingredient is not released from the formulation until gastric transit is complete, in which the maximum circulating concentration of active ingredient is lower than what would be realized by the administration of the same dose using an oral suspension or capsule formulation, and in which the maximum dose is less than 1.75 mg/kg/day.

[00354] In another embodiment, the treatment of an obesity prone individual is optimized for weight maintenance by administration of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, once per 24 hours in which the release of the active ingredient from the formulation has been modified to provide near zero order release for at least 12 hours.

[00355] In another embodiment, the treatment of an obesity prone individual is optimized for weight maintenance by administration of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, once per 24 hours in which the release of the active ingredient from the formulation has been modified to provide near zero order release for at least 18 hours.

[00356] In another embodiment, the treatment of an obesity prone individual is optimized for weight maintenance by administration of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, once per 24 hours in which the release of the active ingredient from the formulation has been modified to provide a rising drug concentration in circulation for at least 12 hours.

[00357] In another embodiment, the treatment of an obesity prone individual is optimized for weight maintenance by administration of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, once per 24 hours in which the

release of the active ingredient from the formulation has been modified to provide a rising drug concentration in circulation for at least 18 hours.

[00358] In another embodiment, the treatment of an obesity prone individual is optimized for weight maintenance by administration of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, once per 24 hours in which the release of the active ingredient from the formulation has been modified to match the pattern of basal insulin secretion.

[00359] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with sibutramine to an overweight or obese individual to induce weight loss.

[00360] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with orlistat to an overweight or obese individual to induce weight loss.

[00361] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with rimonabant to an overweight or obese individual to induce weight loss.

[00362] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with an appetite suppressant to an overweight or obese individual to induce weight loss.

[00363] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with an anti-depressant to an overweight or obese individual to induce weight loss.

[00364] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with anti-epileptic to an overweight or obese individual to induce weight loss.

[00365] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with a non-thiazide diuretic to an overweight or obese individual to induce weight loss.

[00366] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with a drug that induces weight loss by a mechanism that is distinct from diazoxide to an overweight or obese individual to induce weight loss.

[00367] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with a drug that lowers blood pressure to an overweight, obesity prone or obese individual to induce weight loss and treat obesity associated comorbidities.

[00368] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with a drug that lowers cholesterol to an overweight, obesity prone or obese individual to induce weight loss and treat obesity associated comorbidities.

[00369] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with a drug that raises HDL associated cholesterol to an overweight, obesity prone or obese individual to induce weight loss and treat obesity associated comorbidities.

[00370] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with a drug that improves insulin sensitivity to an overweight, obesity prone or obese individual to induce weight loss and treat obesity associated comorbidities.

[00371] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with an anti-inflammatory to an overweight, obesity prone or obese individual to induce weight loss and treat obesity associated comorbidities.

[00372] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with a drug that lowers circulating triglycerides to an overweight, obesity prone or obese individual to induce weight loss and treat obesity associated comorbidities.

[00373] In another embodiment, K_{ATP} channel openers, optionally in combination with growth hormone, are co-formulated with sibutramine in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese individual to induce weight loss and treat obesity-associated co-morbidities.

[00374] In another embodiment, K_{ATP} channel openers, optionally in combination with growth hormone, are co-formulated with orlistat or other active that suppresses the action of gastric lipases in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese individual to induce weight loss and treat obesity-associated co-morbidities.

[00375] In another embodiment, K_{ATP} channel openers, optionally in combination with growth hormone, are co-formulated with a non-thiazide diuretic in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese individual to induce weight loss and treat obesity-associated co-morbidities.

[00376] In another embodiment, K_{ATP} channel openers, optionally in combination with growth hormone, are co-formulated with an appetite suppressant in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese individual to induce weight loss and treat obesity-associated co-morbidities.

[00377] In another embodiment, K_{ATP} channel openers, optionally in combination with growth hormone, are co-formulated with a cannabinoid receptor antagonist in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese individual to induce weight loss and treat obesity-associated co-morbidities.

[00378] In another embodiment, K_{ATP} channel openers, optionally in combination with growth hormone, are co-formulated with an anti-cholesteremic active in a pharmaceutically acceptable

formulation that is administered to an overweight, obesity prone or obese individual to induce weight loss and treat obesity-associated co-morbidities.

[00379] In another embodiment, K_{ATP} channel openers, optionally in combination with growth hormone, are co-formulated with an antihypertensive active in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese individual to induce weight loss and treat obesity-associated co-morbidities

[00380] In another embodiment, K_{ATP} channel openers, optionally in combination with growth hormone, are co-formulated with an insulin sensitizing active in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese individual to induce weight loss and treat obesity-associated co-morbidities.

[00381] In another embodiment, K_{ATP} channel openers, optionally in combination with growth hormone, are co-formulated with an anti-inflammatory active in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese individual to induce weight loss and treat obesity-associated co-morbidities.

[00382] In another embodiment, K_{ATP} channel openers, optionally in combination with growth hormone, are co-formulated with an anti-depressant active in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese individual to induce weight loss and treat obesity-associated co-morbidities.

[00383] In another embodiment, K_{ATP} channel openers, optionally in combination with growth hormone, are co-formulated with an anti-epileptic active in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese individual to induce weight loss and treat obesity-associated co-morbidities.

[00384] In another embodiment, K_{ATP} channel openers, optionally in combination with growth hormone, are co-formulated with an active that reduces the incidence of atherosclerotic plaque in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese individual to induce weight loss and treat obesity-associated co-morbidities.

[00385] In another embodiment, K_{ATP} channel openers, optionally in combination with growth hormone, are co-formulated with an active that lowers circulating concentrations of triglycerides in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese individual to induce weight loss and treat obesity-associated co-morbidities.

[00386] The reduction of circulating triglycerides in an overweight, obese or obesity prone individual is achieved by the administration of an effective amount of a solid oral dosage form of a K_{ATP} channel opener, optionally in combination with growth hormone.

[00387] A solid oral dosage form of K_{ATP} channel opener can be used to administer a therapeutically effective dose of K_{ATP} channel opener to an overweight or obesity prone individual in need thereof to maintain weight, as it is preferable to maintain weight in an obese individual once some weight loss has occurred when the alternative is to regain weight.

[00388] A method of inducing loss of greater than 25% of initial body fat in an overweight or obese individual can be achieved by the prolonged administration of a solid oral dosage form of a K_{ATP} channel opener, optionally in combination with growth hormone.

[00389] A method of inducing loss of greater than 50% of initial body fat in an overweight or obese individual can be achieved by the prolonged administration of a solid oral dosage form of a K_{ATP} channel opener, optionally in combination with growth hormone.

[00390] A method of inducing loss of greater than 75% of initial body fat in an overweight or obese individual can be achieved by the prolonged administration of a solid oral dosage form of a K_{ATP} channel opener, optionally in combination with growth hormone.

[00391] A method of inducing preferential loss of visceral fat in an overweight or obese individual can be achieved by the prolonged administration of a solid oral dosage form of a K_{ATP} channel opener, optionally in combination with growth hormone.

[00392] A method of inducing loss of body fat and reductions in circulating triglycerides in an overweight or obese individual can be achieved by the prolonged administration of a solid oral dosage form of a K_{ATP} channel opener, optionally in combination with growth hormone.

[00393] The invention will now be described with reference to the following non-limiting examples.

EXAMPLES

Example 1: Potassium ATP channel activator containing formulations

1. *Compressed Tablet Formulations*

[00394] Diazoxide or a derivative thereof at about 15-30% by weight is mixed with hydroxypropyl methylcellulose at about 55-80% by weight, ethylcellulose at about 3-10 wt/vol % and magnesium stearate (as lubricant) and talc (as glidant) each at less than 3% by weight. The mixture is used to produce a compressed tablet as described in Reddy et al., *AAPS Pharm Sci Tech* 4(4):1-9 (2003). The tablet may be coated with a thin film as discussed below for microparticles.

[00395] A tablet containing 100 mg of diazoxide or a derivative thereof will also contain approximately 400 mg of hydroxypropyl cellulose and 10 mg of ethylcellulose. A tablet containing 50 mg of diazoxide or a derivative thereof will also contain approximately 200 mg of hydroxypropyl cellulose and 5 mg of ethylcellulose. A tablet containing 25 mg of diazoxide or a derivative thereof will also contain approximately 100 mg of hydroxypropyl cellulose and 2.5 mg of ethylcellulose.

2. *Encapsulated Coated Microparticle Formulation of Diazoxide*

[00396] Diazoxide or a derivative thereof is encapsulated into microparticles in accordance with well known methods (see, e.g. U.S. Patent No. 6,022,562). Microparticles of between 100 and 500 microns in diameter containing diazoxide or derivative, alone or in combination with one or more suitable excipient, is formed with the assistance of a granulator and then sieved to separate microparticles having the appropriate size. Microparticles are coated with a thin film by spray drying using commercial instrumentation (e.g. Uniglatt Spray Coating Machine). The thin film comprises ethylcellulose, cellulose acetate, polyvinylpyrrolidone and/or polyacrylamide. The coating solution for the thin film may include a plasticizer which may be castor oil, diethyl phthalate, triethyl citrate and salicylic acid. The coating solution may also include a lubricating

agent which may be magnesium stearate, sodium oleate, or polyoxyethylenated sorbitan laurate. The coating solution may further include an excipient such as talc, colloidal silica or of a mixture of the two added at 1.5 to 3% by weight to prevent caking of the film coated particles.

3. Formulation of a tableted form of diazoxide or a derivative for controlled release

[00397] Prior to mixing, both the active ingredient and hydroxypropyl methylcellulose (Dow Methocel K4M P) are passed through an ASTM 80 mesh sieve. A mixture is formed from 1 part diazoxide or a derivative thereof to 4 parts hydroxypropyl methylcellulose. After thorough mixing, a sufficient volume of an ethanolic solution of ethylcellulose as a granulating agent is added slowly. The quantity of ethylcellulose per tablet in the final formulation is about 1/10th part. The mass resulting from mixing the granulating agent is sieved through 22/44 mesh. Resulting granules are dried at 40° C for 12 hours and thereafter kept in a desiccator for 12 hours at room temperature. Once dry the granules retained on 44 mesh are mixed with 15% fines (granules that passed through 44 mesh). Talc and magnesium stearate are added as glidant and lubricant at 2% of weight each. A colorant is also added. The tablets are compressed using a single punch tablet compression machine.

4. Formulation of a compression tableted form of diazoxide or a derivative thereof that provides for controlled release

[00398] Diazoxide or a derivative thereof at 20-40% weight is mixed with 30% weight hydroxypropyl methylcellulose (Dow Methocel K100LV P) and 20-40% weight impalpable lactose. The mixture is granulated with the addition of water. The granulated mixture is wet milled and then dried 12 hours at 110° C. The dried mixture is dry milled. Following milling, 25% weight ethylcellulose resin is added (Dow Ethocel 10FP or Ethocel 100FP) followed by 0.5% weight magnesium stearate. A colorant is also added. The tablets are compressed using a single punch tablet compression machine (Dasbach, et al, Poster at AAPS Annual Meeting Nov 10-14 (2002)).

5. Formulation of a compression coated tableted form of diazoxide or a derivative thereof that provides for controlled release.

[00399] The core tablet is formulated by mixing either 100 mg of diazoxide or a derivative thereof with 10 mg of ethylcellulose (Dow Ethocel 10FP), or by mixing 75 mg of diazoxide or a

derivative thereof with 25 mg lactose and 10 mg of ethylcellulose (Dow Ethocel 10FP), or by mixing 50 mg of diazoxide or a derivative thereof with 50 mg of lactose and 10 mg of ethylcellulose (Dow Ethocel 10FP). The core tablets are formed on an automated press with concave tooling. The compression coating consisting of 400 mg of ethylene oxide (Union Carbide POLYOX WSR Coagulant) is applied and compressed to 3000 psi (Dasbach, et al., Poster at AAPS Annual Meeting Oct 26-30 (2003)).

6. A controlled release dosage form of diazoxide or a derivative thereof using an osmotically controlled release system

[00400] Diazoxide or a derivative thereof is formulated as an osmotically regulated release system. In general, two components, and expandable hydrogel that drives release of the active drug is assembled with diazoxide or a derivative thereof into a semipermeable bilaminate shell. Upon assembly a hole is drilled in the shell to facilitate release of active upon hydration of the hydrogel.

[00401] A dosage form adapted, designed and shaped as an osmotic delivery system is manufactured as follows: first, a diazoxide or a derivative thereof composition is provided by blending together into a homogeneous blend of polyethylene oxide, of diazoxide or a derivative thereof and hydroxypropyl methylcellulose. Then, a volume of denatured anhydrous ethanol weighing 70% of the dry mass is added slowly with continuous mixing over 5 minutes. The freshly prepared wet granulation is screened through a 20 mesh screen through a 20 mesh screen, dried at room temperature for 16 hours, and again screened through a 20 mesh screen. Finally, the screened granulation is mixed with 0.5% weight of magnesium stearate for 5 minutes.

[00402] A hydrogel composition is prepared as follows: first, 69% weight of polyethylene oxide weight, 25% weight of sodium chloride and 1% weight ferric oxide separately are screened through a 40 mesh screen. Then, all the screened ingredients are mixed with 5% weight of hydroxypropyl methylcellulose to produce a homogeneous blend. Next, a volume of denatured anhydrous alcohol equal to 50% of the dry mass is added slowly to the blend with continuous mixing for 5 minutes. The freshly prepared wet granulation is passed through a 20 mesh screen, allowed to dry at room temperature for 16 hours, and again passed through a 20 mesh screen.

The screened granulation is mixed with 0.5% weight of magnesium stearate 5 minutes (see U.S. Patent No. 6,361,795 by Kuczynski, et al.).

[00403] The diazoxide or a derivative thereof composition and the hydrogel composition are compressed into bilaminate tablets. First the diazoxide or a derivative thereof composition is added and tamped, then, the hydrogel composition is added and the laminae are pressed under a pressure head of 2 tons into a contacting laminated arrangement.

[00404] The bilaminate arrangements are coated with a semipermeable wall (i.e. thin film). The wall forming composition comprises 93% cellulose acetate having a 39.8% acetyl content, and 7% polyethylene glycol. The wall forming composition is sprayed onto and around the bilaminate.

[00405] Finally an exit passageway is drilled through the semipermeable wall to connect the diazoxide or a derivative thereof drug lamina with the exterior of the dosage system. The residual solvent is removed by drying at 50° C and 50% humidity. Next, the osmotic systems are dried at 50° C to remove excess moisture (see U.S. Patent No. 6,361,795 by Kuczynski, et al.).

7. Preparation of a salt of diazoxide

[00406] A hydrochloride salt of diazoxide is prepared by dissolving one mole of diazoxide (230.7 g) in 500 ml of Et₂O. Dry HCl is passed into the solution until the weight of the container is increased by 36g. During the addition of the HCl, the HCl salt of diazoxide precipitates as a powder. The salt is filtered off and washed with dry Et₂O.

Example 2: *In vivo* Obesity Testing

1. Obesity animal model

[00407] Formulations of diazoxide or derivatives prepared as described herein can be tested for efficacy in an animal model of obesity as described by Surwit et al. (*Endocrinology* 141:3630-3637 (2000)). Briefly, 4-week-old B6 male mice are housed 5/cage in a temperature-controlled (22°C) room with a 12-h light, 12-h dark cycle. The high fat (HF) and low fat (LF) experimental diets contain 58% and 11% of calories from fat, respectively. A group of mice are fed the HF diet for the first 4 weeks of the study; the remaining 15 mice are fed the LF diet. The mice assigned to the LF diet are maintained on this diet throughout the study as a reference

group of lean control mice. At week 4, all HF-fed mice are reassigned to 2 groups of mice. The first group remains on the HF diet throughout the study as the obese control group. The remaining 3 groups of mice are fed the HF diet and administered the controlled release formulation of diazoxide or derivative at about 150 mg of active per kg per day as a single dose administered by oral gavage. Animals are weighed weekly, and food consumption is measured per cage twice weekly until the diets are changed at week 4, whereupon body weight and food intake are determined daily. The feed efficiency (grams of body weight gained per Cal consumed) is calculated on a per cage basis. Samples for analysis of insulin, glucose, and leptin are collected on day 24 (4 days before the diets are changed), on day 32 (4 days after the change), and biweekly thereafter. In all cases food is removed 8 h before samples are collected. Glucose is analyzed by the glucose oxidase method. Insulin and leptin concentrations are determined by double antibody RIA. The insulin assay is based on a rat standard, and the leptin assay uses a mouse standard. At the termination of the study, a postprandial plasma sample is collected and analyzed for triglyceride and nonesterified fatty acid concentrations. After 4 weeks of drug treatment, a subset of 10 animals from each group is killed. The epididymal white adipose tissue (EWAT), retroperitoneal (RP) fat, interscapular brown adipose tissue (IBAT) fat pads, and gastrocnemius muscle are removed, trimmed, and weighed. The percent body fat is estimated from the weight of the epididymal fat pad. A subset of five animals from each group is injected ip with 0.5 g/kg glucose. At 30 min postinjection, a plasma sample is collected and analyzed for glucose content by the glucose oxidase method.

2. *Treatment of obesity in humans*

[00408] Formulations of diazoxide or derivatives prepared as described herein can be tested for efficacy in obese humans. The study is conducted as described by Alemzadeh (Alemzadeh, et al., *J Clin Endocr Metab* 83:1911-1915 (1998)). Subjects consist of moderate-to-morbidly obese adults with a body mass index (BMI) greater than or equal to 30 kg/m². Each subject undergoes a complete physical examination at the initial evaluation, body weight being measured on a standard electronic scale and body composition by DEXA.

[00409] Before the initiation of the study, all subjects are placed on a hypocaloric diet for a lead-in period of 1 week. This is designed to exclude individuals who are unlikely to be compliant and to ensure stable body weight before treatment. Up to 50 patients are tested at each

dosage of drug. Daily dosage is set at 100, 200, and 300 mg/day. The daily dose is divided into 2 doses for administration. The dose is administered as either one, two or three 50 mg capsules or tablets at each time of administration. Individual patients are dosed daily for up to 12 months. Patients are reviewed weekly, weighed, and asked about any side effects or concurrent illnesses.

[00410] Twenty-four-hour dietary recall is obtained from each patient. The dietary recalls are analyzed using a standard computer software program. All patients are placed on a hypocaloric diet and encouraged to participate in regular exercise.

[00411] Before commencing, and after completion of the study, the following laboratory tests are obtained: blood pressure fasting plasma glucose, insulin, cholesterol, triglycerides, free fatty acids (FFA), and glycohemoglobin and measures of rate of appearance and oxidation of plasma derived fatty acids. Additionally, routine chemistry profiles and fasting plasma glucose are obtained weekly to identify those subjects with evidence of glucose intolerance and/or electrolyte abnormalities. Glucose is analyzed in plasma, by the glucose oxidase method.

[00412] Insulin concentration is determined by RIA using a double-antibody kit. Cholesterol and triglycerides concentrations are measured by an enzymatic method. Plasma FFA is determined by an enzymatic colorimetric method. SI was assessed by an iv glucose tolerance test (IVGTT) using the modified minimal model. After an overnight fast, a glucose bolus (300 mg/kg) was administered iv, followed (20 min later) by a bolus of insulin. Blood for determination of glucose and insulin is obtained from a contra lateral vein at -30, -15, 0, 2, 3, 4, 5, 6, 8, 10, 19, 22, 25, 30, 40, 50, 70, 100, 140, and 180 min. SI and glucose effectiveness (SG) are calculated using Bergman's modified minimal-model computer program before and after the completion of the study. Acute insulin response to glucose is determined over the first 19 min of the IVGTT, and the glucose disappearance rate (Kg) is determined from 8–19 min of the IVGTT. Body composition is measured by bioelectrical impedance before and at the completion of the study. Resting energy expenditure (REE) is measured by indirect calorimetry after an overnight 12-h fast, with subjects lying supine for a period of 30 min. Urine is collected over the corresponding 24 h, for measurement of total nitrogen and determination of substrate use, before and after the study.

3. *Treatment of obesity in humans by coadministering diazoxide and phentermine*

[00413] Evaluation of a prolonged co-administration of solid oral dosage form of diazoxide or a derivative thereof and phentermine in obese humans with a moderate-to-morbidly and a body mass index (BMI) greater than or equal to 30 kg/m². Each subject undergoes a complete physical examination at the initial evaluation, body weight being measured on a standard electronic scale and body composition by DEXA.

[00414] Before the initiation of the study, all subjects are placed on a hypocaloric diet for a lead-in period of 1 week. This is designed to exclude individuals who are unlikely to be compliant and to ensure stable body weight before treatment. Up to 100 patients are tested. Daily dosage of diazoxide is set at 200 mg. The daily dose is divided into 2 doses for administration. The dose is administered as either a 100 mg capsule or a 100 mg tablet at each time of administration. Individual patients are dosed daily for up to 12 months. Phentermine is administered as a single daily dose of 15 mg. Patients are reviewed every two weeks, weighed, and asked about any side effects or concurrent illnesses.

[00415] All patients are continued on a hypocaloric diet and encouraged to participate in regular exercise. Before commencing, and after completion of the study, laboratory tests as described in the example above are obtained.

4. *Prevention of diabetes in prediabetic humans*

[00416] The example describes use of diazoxide in a prediabetic individual to prevent the occurrence of diabetes. Individuals included in the study all have elevated risk of developing diabetes as measured by one of two methods. In a fasting glucose assay they have plasma glucose values between 100 and 125 mg/dl indicating impaired fasting glucose, or in an oral glucose tolerance test they have plasma glucose values between 140 and 199 mg/dl at 2 hours post-glucose load indicating they have impaired glucose tolerance. Treatment is initiated in any individual meeting either criteria. Treated individuals receive either 200 mg diazoxide per day as a 100 mg capsule or tablet twice per day or as two 100 mg capsules or tablets once per day. Placebo treated individuals receive either one placebo capsule or tablet twice per day or two placebo capsules or tablets once per day.

[00417] Treatment is continued for one year with OGTT or fasting glucose measured monthly.

5. *A sustained release coformulation of diazoxide HCl and metformin HCl use to treat diabetic patients*

[00418] A sustained release co-formulation of diazoxide HCl and metformin HCl is produced by forming a compressed tablet matrix that includes 750 mg of metformin HCl and 100 mg of diazoxide HCl. These active ingredients are blended with sodium carboxymethyl cellulose (about 5% (w/w)), hypromellose (about 25% (w/w)), and magnesium stearate (<2% (w/w)). The compressed tablet is further coated with a combination of ethylcellulose (80% (w/w)) and methyl cellulose (20% (w/w)) as a thin film to control rate of hydration and drug release.

[00419] Type II diabetic patients are treated with the oral dosage form by administration of two tablets once per day or one tablet every 12 hours. Treatment of the patient with the drug is continued until one of two therapeutic endpoints is reached, or for so long as the patient derives therapeutic benefit from administration. The two therapeutic endpoints that would serve as the basis for the decision to cease treatment include the patient reaching a Body Mass Index (BMI (kg/m²)) between 18 and 25 or the re-establishment of normal glucose tolerance in the absence of treatment. The patient is monitored periodically for (a) glucose tolerance using an oral glucose tolerance test, (b) glycemic control using a standard blood glucose assay, (c) weight gain or loss,

(d) progression of diabetic complications, and (e) adverse effects associated with the use of these active ingredients.

6. Prevention or treatment of weight gain in a patient treated with olanzapine

[00420] Pharmacotherapy for schizophrenia is initiated for a patient meeting DSM III-R criteria for schizophrenia. The patient is administered 10 mg of olanzapine (Zyprexa, Lilly) once per day. Adjunctive therapy to the patient for schizophrenia includes 250 mg equivalent of valproic acid as divalproex sodium (Depakote, Abbott Labs). Weight gain, dyslipidemia and impaired glucose tolerance, and metabolic syndrome are high frequency adverse events in patients treated with this combination of anti-psychotics. Weight gain, dyslipidemia, impaired glucose tolerance or metabolic syndrome are treated by the co-administration of a therapeutically effective dose of a K_{ATP} channel opener. The patient is treated with administration of 200 mg/day of diazoxide as a once daily tablet formulation. Diazoxide administration continues until the weight gain, dyslipidemia, impaired glucose tolerance or metabolic syndrome is corrected or until treatment of the patient with olanzapine is discontinued. Dyslipidemia is detected by measuring circulating concentrations of total, HDL, and LDL cholesterol, triglycerides and non-esterified fatty acids. Impaired glucose tolerance is detected through the use of oral or IV glucose tolerance tests. Metabolic syndrome is detected by measuring its key risk factors including central obesity, dyslipidemia, impaired glucose tolerance, and circulating concentrations of key proinflammatory cytokines.

Example 3: Clinical Study in Obese Pediatric and Adult PWS Patients

[00421] A single-center, open-label, single-arm clinical study (PC025) with a double-blind, placebo-controlled, randomized withdrawal extension has been carried out. Patients were initiated on a DCCR dose of about 1.5 mg/kg (maximum starting dose of 145 mg) and were titrated every 14 days to about 2.4 mg/kg, 3.3 mg/kg, and 4.2 mg/kg (maximum dose of 507.5 mg). These DCCR doses are equivalent to diazoxide doses of 1.03, 1.66, 2.28, and 2.9 mg/kg, respectively. Patients were up-titrated at each visit at the discretion of the investigator. Any patient who showed an increase in resting energy expenditure and/or a reduction in hyperphagia from Baseline through Day 27 or Day 55 was designated a Responder and eligible to be randomized in the double-blind phase. Everyone who completed the open-label phase was a

Responder and was randomized in and completed the double-blind phase. During the double-blind, placebo-controlled, randomized withdrawal phase, Responders were randomized in a 1:1 ratio either to continue on active treatment at the dose they were treated with on Day 55 or to the placebo equivalent of that dose for an additional 4 weeks (29 days). Non-responders continued open label treatment with DCCR at the dose they were treated with on Day 55 for an additional 29 days. A total of 12 patients were enrolled in the study.

Inclusion Criteria: Basic requirements

- Ability to follow verbal and written instructions with or without assistance from caregiver
- Informed consent form signed by the subject or their legal guardian
- Completed the screening process between 2 and 4 weeks prior to Baseline Visit

General demographic characteristics

- Male and female patients 10 to 22 years of age, inclusive at the time of dosing
- Genetically confirmed Prader-Willi syndrome
- BMI exceeds the 95th percentile of the age specific BMI value on the CDC BMI charts or percent body fat $\geq 35\%$ (The body fat criteria will only be used if there were a measurement made within 12 months of the Screening Visit, and the patient has not lost weight since the measurement. Under all other circumstances, the BMI criteria will apply.)
- Generally healthy as documented by the medical history, physical examination, vital sign assessments, 12-lead electrocardiogram (ECG), and clinical laboratory assessments

Specific laboratory test results

- fasting glucose ≤ 126 mg/dL
- HbA1c $\leq 6.5\%$

Endpoints and Statistical Analysis

[00422] Every endpoint is measured in two timeframes: (1) during the open label treatment phase as change (or percent change) from Baseline to Day 69; and (2) during the double-blind, placebo-controlled, randomized withdrawal phase as change (or percent change) from Day 69 to Day 97.

[00423] Endpoints measured during the open label treatment phase were analyzed by paired t-test while those measured during the double-blind, placebo-controlled treatment phase are subjected to ANOVA and paired t-tests.

[00424] Efficacy endpoints include: hyperphagia (measured using parent/caregiver responses on a modified Dykens hyperphagia questionnaire – converted to a numeric score between 0 and 34); weight; body fat (measured by DEXA); lean body mass (measured by DEXA); resting energy expenditure (measured by indirect calorimetry); respiratory quotient (measured by indirect calorimetry); waist circumference; BMI; ghrelin; leptin; triglycerides; total cholesterol; HDL cholesterol; non-HDL cholesterol and LDL cholesterol. Additional information was collected in a behavioral questionnaire. Tables 2 and 3 summarize the visits at which each efficacy parameter was measured.

Table 2. Time points for assessment of efficacy parameters during open-label phase

Parameter	Screening	Baseline	Visit 3	Visit 4	Visit 5	Visit 6	End of Open label treatment
Hyperphagia	+	+	+	+	+	+	+
Body fat	Either at screening or baseline						+
Lean body mass							+
Weight	+	+	+	+	+	+	+
REE & RQ		+		+		+	+
Waist circumference	+	+	+	+	+	+	+
Ghrelin, leptin		+					+
Lipids		+					+
Behavioral questionnaire		+					+

Table 3. Time points for assessment of efficacy parameters during double-blind treatment

Parameter	Screening	Baseline	Day 69 End of Open label treatment	Day 97 End of double blind treatment
Hyperphagia	+	+	+	+
Body fat	Either at screening or baseline		+	
Lean body mass			+	

Weight	+	+	+	+
REE & RQ		+	+	+
Waist circumference	+	+	+	+
Ghrelin, leptin		+	+	
Lipids		+	+	+
Behavioral questionnaire		+	+	

Patients in the Study

[00425] Demographic information and relevant medical history for each patient are shown in **Table 4**. Eleven of the thirteen subjects enrolled in clinical study PC025 completed the open-label phase. All were identified as Responders and were, therefore, randomized in the double-blind phase of the study. All subjects randomized in the double-blind phase of the study completed the phase.

[00426] Baseline characteristics of patients enrolled in the study are provided in **Table 5**.

Table 4. Demographic information and relevant medical history for patients enrolled in PC025

Patient	Sex	Age	PWS sub-type	Age at diagnosis	GH trt*	Relevant medical history
BN-01	M	11.6	Deletion	4 wk	No	acanthosis nigricans, obesity @ 3 yr, asthma, undescended testes, fatty liver, sleep apnea
CP-02	M	16.5	Deletion	3 wk	Yes	cerebral palsy, obesity @ 2 yr, type 2 diabetes, gynecomastia, undescended testicle, sleep apnea, asthma @ 1 yr
TJ-03	M	18.6	Deletion	6 wk	No	obesity @ 3 yr with hyperphagia, psychiatric illness @ 2 yr, undescended testicle, osteopenia
AC-04	F	17.0	Deletion	15 yr	No	scoliosis, short stature, osteopenia
MR-05	F	17.8	Deletion	5.7 yr	No	scoliosis, strabismus, amenorrhea
SD-06	M	16.7	Deletion	3 yr	Yes	morbid obesity @ 6 yr, sleep apnea, scoliosis, pulmonary hypertension, undescended testes, strabismus
AS-08	M	11.9	Deletion	10 wk	Yes	hyperphagia @ 3 yr, dyslipidemia, ophthalmoplegia, osteopenia, scoliosis
SP-09	F	21.6	Deletion	6 wk	No	scoliosis, sleep apnea, osteopenia, amenorrhea
DD-10	M	12.5	UPD	16 wk	Yes	osteopenia
SM-11	F	15.4	Deletion	1 wk	Yes	psychiatric disease, osteopenia, scoliosis
AD-13	F	14.7	Deletion	4 wk	No	obesity @ 5 yr, osteopenia
JG-15	M	14.4	Deletion	2 wk	Yes	obesity @ 5 yr
NT-16	M	19.3	Deletion	2 wk	No	Scoliosis, strabismus, sleep apnea

Table 5. Baseline characteristics of subjects who were randomized in the double-blind phase of clinical study PC025.

Subject	Weight (kg)	Height (cm)	Percent body fat	BMI	Hyperphagia score	REE %RDA	RQ
CP-02	97.2	166	52.0	35.3	18.5	83%	0.86
AC-04	56.9	151	46.8	25.0	7	84%	0.78
MR-05	113.1	145	59.1	53.8	20.5	83%	0.87
SD-06	133.6	145	53.5	51.5	3	102%	0.84
AS-08	60.9	140	53.4	31.0	25.5	86%	1.03
SP-09	106.8	148	60.7	48.8	10.5	84%	0.72
DD-10	70.8	155	49.3	29.5	32	101%	0.97
SM-11	62.2	140	48.8	31.7	8	97%	0.81
AD-13	103.5	149	56.6	46.6	10	94%	0.85
JG-15	106.3	161	53.7	41.0	16	71%	0.79
NT-16	80.8	177	36.4	25.7	14	100%	0.78
Average	90.4	152.5	51.8	38.2	14.95	89.6%	0.85

Dosing

[00427] One subject, a treated type 2 diabetic, finished the open-label treatment period on a dose of 1.5 mg/kg. Of the remaining 10 subjects, 1 finished the open-label treatment period at a dose of 2.4 mg/kg, and 3 at 3.3 mg/kg. The last 6 subjects enrolled in the study finished the open-label treatment phase at a dose 4.2 mg/kg.

Changes in Body Composition, Waist Circumference and Weight

[00428] Body fat and lean body mass were measured by DEXA at baseline and again at the end of the open label treatment. Since DEXA was not run on Day 97, the only body composition measurements made on the subjects randomized in the double-blind phase occurred in the period from Baseline to Day 69. The body composition changes are outlined in Table 6. Changes in body composition by DEXA were evaluated separately for subjects who were growth hormone treated and growth hormone naïve. These results are shown in Table 6.

[00429] Weight by DEXA was calculated as the sum of body fat and lean body mass. The ratio of lean body mass to body fat was also calculated.

Table 6.**Changes in body composition by DEXA from Baseline through Day 69**

All subjects randomized in the double blind phase			
Parameter	n	Percent Change	p-value
Body fat	11	-3.8%	0.011
Lean body mass	11	5.41%	0.001
Lean body mass/fat mass ratio	11	9.82%	0.002
Weight	11	0.67%	0.150
Growth hormone treated subjects			
Parameter	n	Percent Change	p-value
Body fat	6	-3.31%	0.056
Lean body mass	6	5.50%	0.005
Lean body mass/fat mass ratio	6	9.37%	0.014
Weight	6	0.90%	0.189
Growth hormone naïve subjects			
Parameter	n	Percent Change	p-value
Body fat	5	-4.34%	0.083
Lean body mass	5	5.30%	0.055
Lean body mass/fat mass ratio	5	10.36%	0.043
Weight	5	0.39%	0.301

[00430] Treatment with DCCR for 10 weeks had a highly significant and clinically relevant impact on body composition including reductions in body fat, increases in lean body mass and a very marked increase in lean body mass to body fat ratio. Because these patients had almost equal lean body mass and fat mass at Baseline, parallel increases in lean body mass and reductions in body fat result in almost no net change in weight. In general, the changes in body composition were of similar magnitude in both growth hormone treated and growth hormone naïve subjects.

[00431] The changes in body composition were dose dependent. Those subjects who completed the open-label treatment phase at a dose of 4.2 mg/kg experienced a 6.3% decrease in fat mass, a 9.2% increase in lean body mass and a 16.6% increase in the lean body mass to fat mass ratio.

[00432] Three subjects in the study showed greater than 10% increase in lean body mass. Every subject showed an increase in lean body mass/fat mass ratio. More than half of the subjects in the study showed a > 10% increase in the lean body mass/fat mass ratio, and one showed more than a 20% increase.

[00433] Figures 1-4 summarize the percent change in body fat, lean body mass and lean body mass/fat mass ratio from Baseline through Day 69.

[00434] Weight and waist circumference were measured during the physical exam at each visit. This data can be used to evaluate the change from Baseline through Day 69 for all subjects randomized in the double-blind phase, by arm for the period from Day 69 through Day 97 and in those who continued on DCCR in the double-blind phase from Baseline through Day 97. The results from the period covering Baseline through Day 69 are summarized in Table 7. The results from the period covering Day 69 through Day 97 are shown in Table 8. The results for subjects who continued on DCCR in the double blind phase from baseline through Day 97 are shown in Table 9.

Table 7. Changes in weight and waist circumference from Baseline through Day 69

Parameter	n	Change/Percent change	p-value
Weight	11	0.53%	0.317
Waist circumference	11	-3.5 cm	0.003

Table 8. Changes in weight and waist circumference from Day 69 through Day 97

Parameter	Arm	n	Change/Percent change	p-value comparing arms
Weight	DCCR	5	-1.7%	0.723
Weight	Placebo	6	-1.1%	
Waist circumference	DCCR	5	-2.9 cm	0.047
Waist circumference	Placebo	5	0.25 cm	

Table 9. Changes in weight and waist circumference from Baseline through Day 97 for those treated with DCCR in the double-blind phase

Parameter	n	Change Through Day 97	p-value
Weight	5	0.4%	0.828
Waist circumference	5	-3.7cm	0.039

[00435] Interestingly, the change in weight from Baseline through day 69 by DEXA and by the standard weight measurement produces almost identical results (an increase of 0.67% by DEXA and 0.53% by the standard approach). In contrast to the lack of change in weight, there

was a statistically significant reduction in waist circumference through Day 69 in all subjects randomized in the double-blind phase; through Day 97 for those who continued on DCCR. The comparison of change in waist circumference between arms between Day 69 and Day 97, during which the placebo treated patients showed an incremental increase in waist circumference, while those who continued on DCCR, showed a notable reduction. The reduction in waist circumference is consistent with the explanation that DCCR treated subjects are losing visceral fat.

Changes in Hyperphagia

[00436] The hyperphagia questionnaire was administered at all visits. This data can be used to evaluate the change from Baseline through Day 69 for all subjects randomized in the double-blind phase, by arm for the period from Day 69 through Day 97 and in those who continued on DCCR in the double-blind phase from Baseline through Day 97. The results from the period covering Baseline through Day 69 are summarized in Table 10. The results from the period covering Day 69 through Day 97 are shown in Table 11. The results for subjects who continued on DCCR in the double blind phase from baseline through Day 97 are shown in Table 12.

Table 10. Changes in hyperphagia from Baseline through Day 69

Parameter	n	Percent change	p-value
Hyperphagia	11	-31.6%	0.003

Table 11. Changes in hyperphagia from Day 69 through Day 97

Parameter	Arm	n	Change	p-value comparing arms
Hyperphagia	DCCR	5	2.0	0.389
Hyperphagia	Placebo	6	0.33	

Table 12. Changes in hyperphagia from Baseline through Day 97 for those treated with DCCR in the double-blind phase

Parameter	n	Percent change through Day 97	p-value
Hyperphagia	5	-29.2%	0.006

[00437] There was a statistically significant reduction in hyperphagia in all subjects randomized in the double-blind phase from Baseline through Day 69 and in those who continued on DCCR through the double-blind phase from Baseline through Day 97.

[00438] DCCR treated patients at the end of 97 days of treatment showed an improvement in hyperphagia of 29.2% while those that were treated with DCCR for 69 days followed by 28 days of placebo treatment showed only a 13.9% improvement in hyperphagia on Day 97. Thus, at the end of the double-blind phase, DCCR treated patients showed more than twice the improvement in hyperphagia as did those who were randomized to placebo in the double-blind phase. Once patients discontinue from DCCR treatment, given the long half-life of DCCR (28-32 hours) it takes about 7-10 days to completely clear from circulation. Verbatim statements were obtained from parents of subjects in the study suggesting that they had seen their children's food related behavior deteriorate only in the last couple of weeks of the study, suggesting a longer double-blind phase might have resulted in further separation of the arms. In general, the magnitude of impact on how upset subjects became when denied food, how easy it was to get them to think about something else if once denied food, and the impact on the frequency of stealing food, digging through the trash for food and bargaining for food were of equivalent or greater magnitude as the overall impact on the hyperphagia score. DCCR appeared to have lesser impact on how sneaky or quick subjects were with respect to food and on how often they got up at night to seek food.

[00439] Improvements in hyperphagia were observed in subjects with baseline hyperphagia ranging from 29 (-45%) to less than 5 (-33%) on a 0 to 34 point scale.

[00440] About 25% of the subjects ended the open-label phase with very low levels of hyperphagia (2 or 3 on a 0 to 34 scale). These subjects tended to be able to lose more body fat than the average. Two such subjects, both females, one growth hormone treated and one growth hormone naïve, lost more than 10% of their initial body fat mass through 10 weeks.

[00441] Figure 1 shows the change in hyperphagia from Baseline through Day 69.

Changes in Lipids

[00442] A lipid panel was evaluated at Baseline, and again on Day 69 and Day 97. This data can be used to evaluate the change from Baseline through Day 69 for all subjects randomized in the double-blind phase, by arm for the period from Day 69 through Day 97 and in those who continued on DCCR in the double-blind phase from Baseline through Day 97. The results from the period covering Baseline through Day 69 are summarized in Table 13. The results for subjects who continued on DCCR in the double blind phase from baseline through Day 97 are shown in Table 14.

Table 13. Changes in Lipids from Baseline through Day 69

Parameter	n	Percent change	p-value
Total cholesterol	8	-4.0%	0.044
Triglycerides	7	-21.0%	0.084
HDL-C	8	10.8%	0.244
LDL-C	8	-7.0%	0.030
Non-HDL-C	8	-6.5%	0.019

Table 14. Median Percent Change in lipids from Baseline through Day 97 for those treated with DCCR in the double-blind phase

Parameter	Median Percent change from Baseline through Day 97
Total Cholesterol	-11.0%
Triglycerides	-41.8%
HDL-C	25.2%
LDL-C	-7.9%
Non-HDL-C	-13.4%

[00443] Consistent with previous studies involving DCCR, treatment of subjects randomized in the double-blind phase with DCCR from Baseline through Day 69 resulted in a number of statistically significant changes in lipids including reductions in total cholesterol, LDL cholesterol and non-HDL cholesterol. Even though the impact on triglycerides was of larger magnitude, it did not reach significance because of the smaller n and greater variability in the population. In general, greater reductions in triglycerides were seen in those with significant elevations in triglycerides at Baseline. A similar pattern was observed in those who were treated with DCCR through the end of the double-blind treatment. The decreases in total cholesterol,

triglycerides, LDL-C and non-HDL-C were all larger in those who were treated with DCCR longer.

Changes in Leptin and Ghrelin

[00444] Leptin and ghrelin were measured at Baseline and again on Day 69. The results from Baseline through Day 69 for leptin and ghrelin are provided in Table 15.

Table 15. Leptin and ghrelin changes from Baseline through Day 69

Parameter	n	Percent change	p-value
Leptin	6	-22.0%	0.061
Ghrelin	6	-15.0%	0.052

[00445] Further evidence for loss of body fat comes from the analysis of leptin, the results of which are consistent with the DEXA data and the data on waist circumference. Although not quite reaching statistical significance, leptin is down more than 20% from Baseline.

[00446] While ghrelin may or may not contribute substantially to hyperphagia in PWS, reductions in ghrelin are beneficial in PWS patients.

Behavioral Changes

[00447] A questionnaire, adapted from the PWS natural history study, was used to document the presence or absence of 23 PWS-associated behaviors at Baseline and again on Day 69.

These behaviors generally fell into 4 categories:

- (1) aggressive, threatening and destructive behaviors;
- (2) self-injurious behaviors;
- (3) compulsive behaviors; and
- (4) other behaviors.

The questionnaire was administered at Baseline and again on Day 69. Discontinuation rates for aggressive, threatening, destructive behaviors and for all other behaviors are shown in Table 16.

Table 16. Discontinuation rates for various classes of behavior in clinical study PC025

Behaviors	Discontinuation rate	p-value
Aggressive, threatening, destructive	-62.5%	0.01
All other PWS associated behaviors	-29.8%	

[00448] The impact on aggressive, threatening and destructive behaviors was independent of an impact on hyperphagia.

Changes in Resting Energy Expenditure and Respiratory quotient

[00449] The measurements for resting energy expenditure and respiratory quotient were quite variable from visit to visit. Despite the variability, resting energy expenditure and respiratory quotient appeared to be unchanged from Baseline through Day 69.

Changes in Insulin Sensitivity

[00450] Treatment with DCCR in other clinical studies was associated with improvements in insulin resistance as measured by changes in homeostatic model assessment of insulin resistance (HOMA-IR). Improvements in insulin sensitivity are well documented in the literature on diazoxide. The subjects enrolled in the double-blind phase of this study were quite insulin sensitive at Baseline, which is typical of PWS patients in this age range. Consistent with prior DCCR clinical studies and the historic diazoxide literature, treatment with DCCR for 10 weeks resulted in an improvement in HOMA-IR from 2.61 ± 1.85 at Baseline to 1.46 ± 1.36 on Day 69. The difference did not reach statistical significance ($p=0.095$).

Example 4: Clinical Studies with Smith–Magenis syndrome Patients

[00451] In a first example, a Smith-Magenis syndrome patient is treated with an oral suspension of diazoxide. The initial dose is approximately 1 mg/kg administered in divided doses. After the patient has been stably treated with 1 mg/kg for a period of 1 to 2 weeks, the dose is titrated to about 1.5 mg/kg. After the patient had been stably treated with 1.5 mg/kg for a period of 1 to 2 weeks, the dose is titrated to about 2.0 mg/kg. This process of increasing the dose by about 0.5 mg/kg at each titration step and the duration of treatment at each step of 1 to 2 weeks is continued until the patient displays an adequate response to treatment, or a maximal dose of 5 mg/kg is reached. Potential responses to treatment could include loss of body fat, reduction in hypotonia, an increase in the lean body mass to fat mass ratio, reduction in hyperphagia, reduction in waist circumference, loss of weight, reduction in temper outbursts and aggressive behavior, and improvements in cardiovascular risk factors. Treatment with the drug is chronic and may continue for life.

[00452] In a second example, a Smith-Magenis syndrome patient is treated with a controlled release tablet formulation of diazoxide choline. The initial dose is approximately 1.5 mg/kg administered once daily. After the patient has been stably treated with 1.5 mg/kg for a period of 1 to 2 weeks, the dose is titrated to about 2.1 mg/kg. After the patient has been stably treated with 2.1 mg/kg for a period of 1 to 2 weeks, the dose is titrated to about 2.7 mg/kg. This process of increasing the dose by about 0.6 mg/kg at each titration step and the duration of treatment at each step of 1 to 2 weeks is continued until the patient displays an adequate response to treatment, or a maximal dose of 5 mg/kg is reached. Potential responses to treatment could include loss of body fat, reduction in hypotonia, an increase in the lean body mass to fat mass ratio, reduction in hyperphagia, reduction in waist circumference, loss of weight, reduction in temper outbursts and aggressive behavior and improvements in cardiovascular risk factors. Treatment with the drug is chronic and may continue for life.

[00453] In a third example, a Smith-Magenis syndrome patient is treated with a controlled release tablet formulation of diazoxide choline. The initial dose is approximately 1.5 mg/kg administered once daily. After the patient has been stably treated with 1.5 mg/kg for a period of 1 to 2 weeks, the dose is titrated to about 2.2 mg/kg. After the patient has been stably treated with 2.2 mg/kg for a period of 1 to 2 weeks, the dose is titrated to about 2.9 mg/kg. This process of increasing the dose by about 0.7 mg/kg at each titration step and the duration of treatment at each step of 1 to 2 weeks is continued until the patient displays an adequate response to treatment or a maximal dose of 5 mg/kg is reached. In parallel, the patient may also be treated with beloranib. Potential responses to treatment could include loss of body fat, reduction in hypotonia, an increase in the lean body mass to fat mass ratio, reduction in hyperphagia, reduction in waist circumference, loss of weight, reduction in temper outbursts and aggressive behavior and improvements in cardiovascular risk factors. Treatment with the drug is chronic and may continue for life.

[00454] In a fourth example, a Smith-Magenis syndrome patient is treated with a controlled release tablet formulation of diazoxide choline. The initial dose is approximately 1.5 mg/kg administered once daily. After the patient has been stably treated with 1.5 mg/kg for a period of 1 to 2 weeks, the dose is titrated to about 2.3 mg/kg. After the patient has been stably treated with 2.3 mg/kg for a period of 1 to 2 weeks, the dose is titrated to about 3.0 mg/kg. This process

of increasing the dose by about 0.8 mg/kg at each titration step and the duration of treatment at each step of 1 to 2 weeks is continued until the patient displays an adequate response to treatment, or a maximal dose of 5 mg/kg is reached. In parallel, the patient may also be treated with an unacylated ghrelin analog. Potential responses to treatment could include loss of body fat, reduction in hypotonia, an increase in the lean body mass to fat mass ratio, reductions in hyperphagia, reductions in waist circumference, loss of weight, reductions in temper outbursts and aggressive behavior and improvements in cardiovascular risk factors. Treatment with the drug would be chronic and may continue for life.

[00455] In a fifth example, a Smith-Magenis syndrome patient is treated with a controlled release tablet formulation of diazoxide choline. The initial dose is approximately 1.5 mg/kg administered once daily. After the patient had been stably treated with 1.5 mg/kg for a period of 1 to 2 weeks, the dose would be titrated to about 2.4 mg/kg. After the patient has been stably treated with 2.4 mg/kg for a period of 1 to 2 weeks, the dose is titrated to about 3.3 mg/kg. This process of increasing the dose by about 0.9 mg/kg at each titration step and the duration of treatment at each step of 1 to 2 weeks is continued until the patient displays an adequate response to treatment, or a maximal dose of 5 mg/kg was reached. In parallel, the patient may also be treated with an MC4 agonist. Potential responses to treatment could include loss of body fat, reduction in hypotonia, an increase in the lean body mass to fat mass ratio, reductions in hyperphagia, reductions in waist circumference, loss of weight, reductions in temper outbursts and aggressive behavior and improvements in cardiovascular risk factors. Treatment with the drug would be chronic and may continue for life.

[00456] In a sixth example, a Smith-Magenis syndrome patient is treated with a controlled release tablet formulation of diazoxide choline. The initial dose is approximately 1.5 mg/kg administered once daily. After the patient had been stably treated with 1.5 mg/kg for a period of 1 to 2 weeks, the dose is titrated to about 2.5 mg/kg. After the patient has been stably treated with 2.5 mg/kg for a period of 1 to 2 weeks, the dose is titrated to about 3.5 mg/kg. This process of increasing the dose by about 1.0 mg/kg at each titration step and the duration of treatment at each step of 1 to 2 weeks is continued until the patient displays an adequate response to treatment, or a maximal dose of 5 mg/kg was reached. In parallel, the patient may also be treated with an MC4 agonist. Potential responses to treatment could include loss of body fat, reduction

in hypotonia, an increase in the lean body mass to fat mass ratio, reductions in hyperphagia, reductions in waist circumference, loss of weight, reductions in temper outbursts and aggressive behavior and improvements in cardiovascular risk factors. Treatment with the drug would be chronic and may continue for life.

[00457] All patents and other references cited in the specification are indicative of the level of skill of those skilled in the art to which the invention pertains, and are incorporated by reference in their entireties, including any tables and figures, to the same extent as if each reference had been incorporated by reference in its entirety individually.

[00458] One skilled in the art would readily appreciate that the present invention is well adapted to obtain the ends and advantages mentioned, as well as those inherent therein. The methods, variances, and compositions described herein as presently representative of preferred embodiments are exemplary and are not intended as limitations on the scope. Changes therein and other uses will occur to those skilled in the art, which are encompassed within the spirit of the invention, are defined by the scope of the claims.

[00459] Definitions provided herein are not intended to be limiting from the meaning commonly understood by one of skill in the art unless indicated otherwise.

[00460] The inventions illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein. Thus, for example, the terms “comprising”, “including,” “containing”, etc. shall be read expansively and without limitation. Additionally, the terms and expressions employed herein have been used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the inventions embodied therein herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention.

[00461] The invention has been described broadly and generically herein. Each of the narrower species and subgeneric groupings falling within the generic disclosure also form part of the invention. This includes the generic description of the invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

[00462] Other embodiments are within the following claims. In addition, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group.

CLAIMS

What is claimed is:

1. A method of treating a subject having Prader-Willi Syndrome (PWS) or Smith-Magenis syndrome (SMS), said method comprising administering to said subject for at least 10 weeks a pharmaceutical formulation comprising an effective amount of a KATP channel opener.
2. The method of claim 1 wherein said KATP channel opener is diazoxide or a pharmaceutically acceptable salt thereof.
3. The method of claim 2 wherein the pharmaceutically acceptable salt is diazoxide choline.
4. The method of claim 2 wherein said diazoxide or a pharmaceutically acceptable salt thereof is administered orally.
5. The method of claim 2 wherein the pharmaceutical formulation includes at least one excipient which affects the rate of release of diazoxide or a pharmaceutically acceptable salt thereof.
6. The method of claim 5 wherein the pharmaceutical formulation includes at least one excipient that delays release of diazoxide or a pharmaceutically acceptable salt thereof.
7. The method of claim 1 wherein the formulation further comprises at least one other active ingredient.
8. The method of claim 1 further comprising administering human growth hormone to the subject.
9. The method of claim 8 wherein said human growth hormone is administered by injection.
10. The method of claim 1 wherein the lean body mass or the lean body mass/fat mass ratio of said subject is increased by at least 1 %.
11. The method of claim 1 wherein the lean body mass or the lean body mass/fat mass ratio of said subject is increased by at least 2%.

12. The method of claim 1 wherein the lean body mass or the lean body mass/fat mass ratio of said subject is increased by at least 3%.

13. The method of claim 1 wherein the lean body mass or the lean body mass/fat mass ratio of said subject is increased by at least 4%.

14. The method of claim 1 wherein the lean body mass or the lean body mass/fat mass ratio of said subject is increased by at least 5%.

15. The method of claim 1 wherein said administering is carried out for 1 one or more years.

16. The method of claim 1 wherein hyperphagia of said subject is reduced by at least 10%.

17. The method of claim 1 wherein hyperphagia of said subject is reduced by at least 20%.

18. The method of claim 1 wherein hyperphagia of said subject is reduced by at least 30%.

19. The method of claim 1, wherein the circulating concentration of IGF-1 is not increased.

20. A method of increasing the lean body mass of a subject having Prader-Willi Syndrome, wherein said subject is already being treated by administration thereto of growth hormone, said method comprising co-administering to said subject an effective amount of a KATP channel opener in addition to said growth hormone.

21. A method of increasing the lean body mass of a subject having Prader-Willi Syndrome, wherein said subject is already being treated by administration thereto of an effective amount of a KATP channel opener, said method comprising co-administering to said subject an effective amount of growth hormone in addition to said KATP channel opener.

22. A method of increasing lower limb muscle mass of a subject having Smith- Magenis syndrome (SMS), said method comprising administering to said subject an effective amount of a KATP channel opener.

23. A kit comprising:

a unit dose of a KATP channel opener, and

a unit dose of growth hormone.

24. A method of reducing one or more aggressive behaviors in a subject having Prader-Willi syndrome (PWS) or Smith-Magenis syndrome (SMS), the method comprising administering to said subject for at least 10 weeks an effective amount of a KATP channel opener, wherein administration reduces one or more aggressive behaviors in the subject.

25. The method of claim 24 in which a second therapeutic product is administered, wherein the second product is intended to further reduce the one or more aggressive behaviors.

26. A method of reducing hyperghrelinemia in a subject having Prader-Willi syndrome (PWS) or Smith-Magenis syndrome (SMS), the method comprising administering to said subject for at least 10 weeks an effective amount of a KATP channel opener, wherein administration reduces one or more aggressive behaviors in the subject.

27. The method of claim 1 wherein the pharmaceutical formulation is administered twice per day.

28. The method of claim 1 wherein the pharmaceutical formulation is administered once per day.

ABSTRACT OF THE INVENTION

Provided are immediate or prolonged administration of certain potassium ATP (KATP) channel openers, optionally in combination with growth hormone, to a subject to achieve novel pharmacodynamic, pharmacokinetic, therapeutic, physiological, metabolic and compositional outcomes in the treatment of diseases or conditions involving KATP channels. Also provided are pharmaceutical formulations, methods of administration and dosing of KATP channel openers that achieve these outcomes and reduce the incidence of adverse effects in treated individuals. Further provided are methods of co-administering KATP channel openers with other drugs (e.g., in combination with growth hormone) to treat diseases of humans and animals (e.g., Prader-Willi Syndrome (PWS), Smith-Magenis syndrome (SMS), and the like.

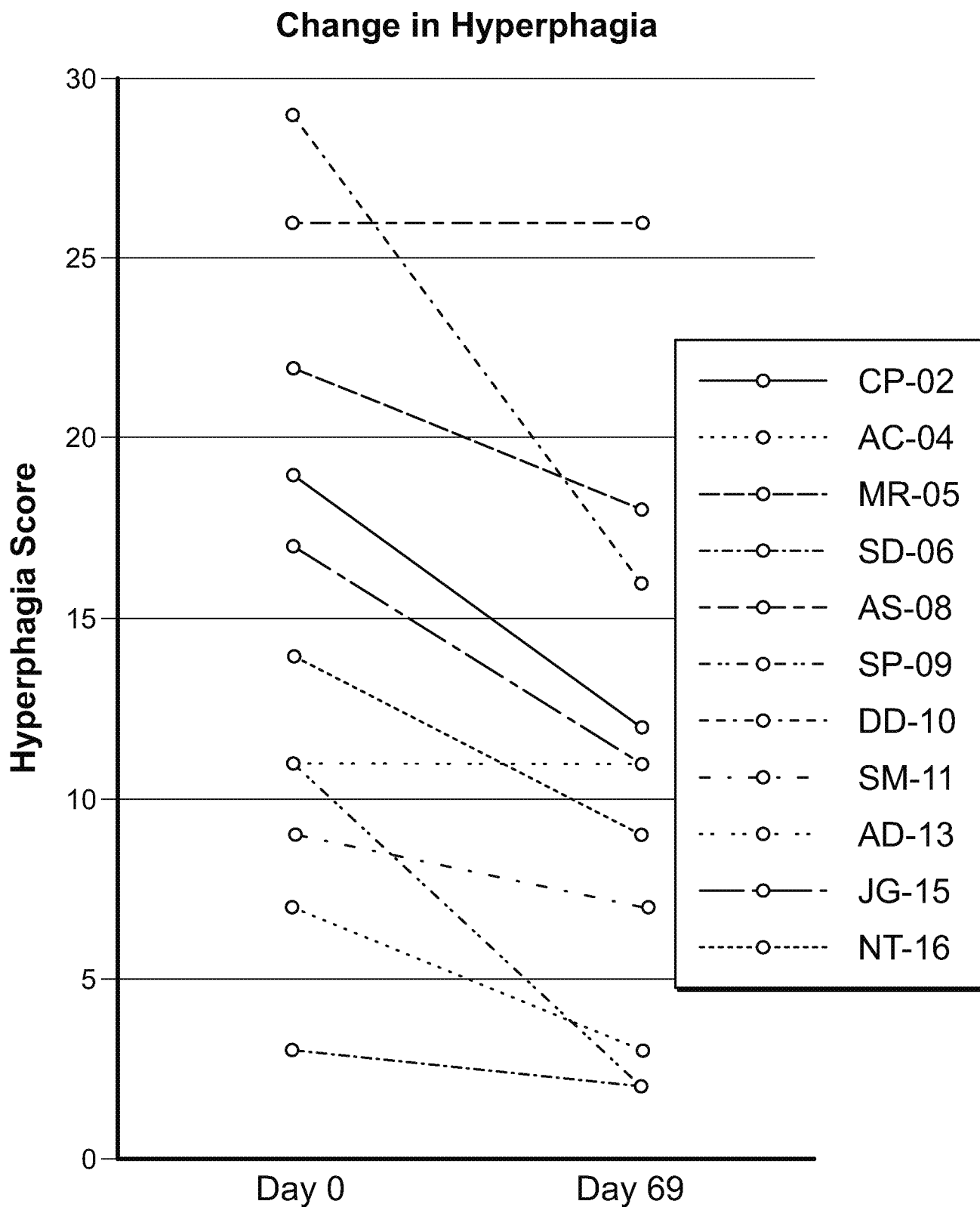


FIG. 1

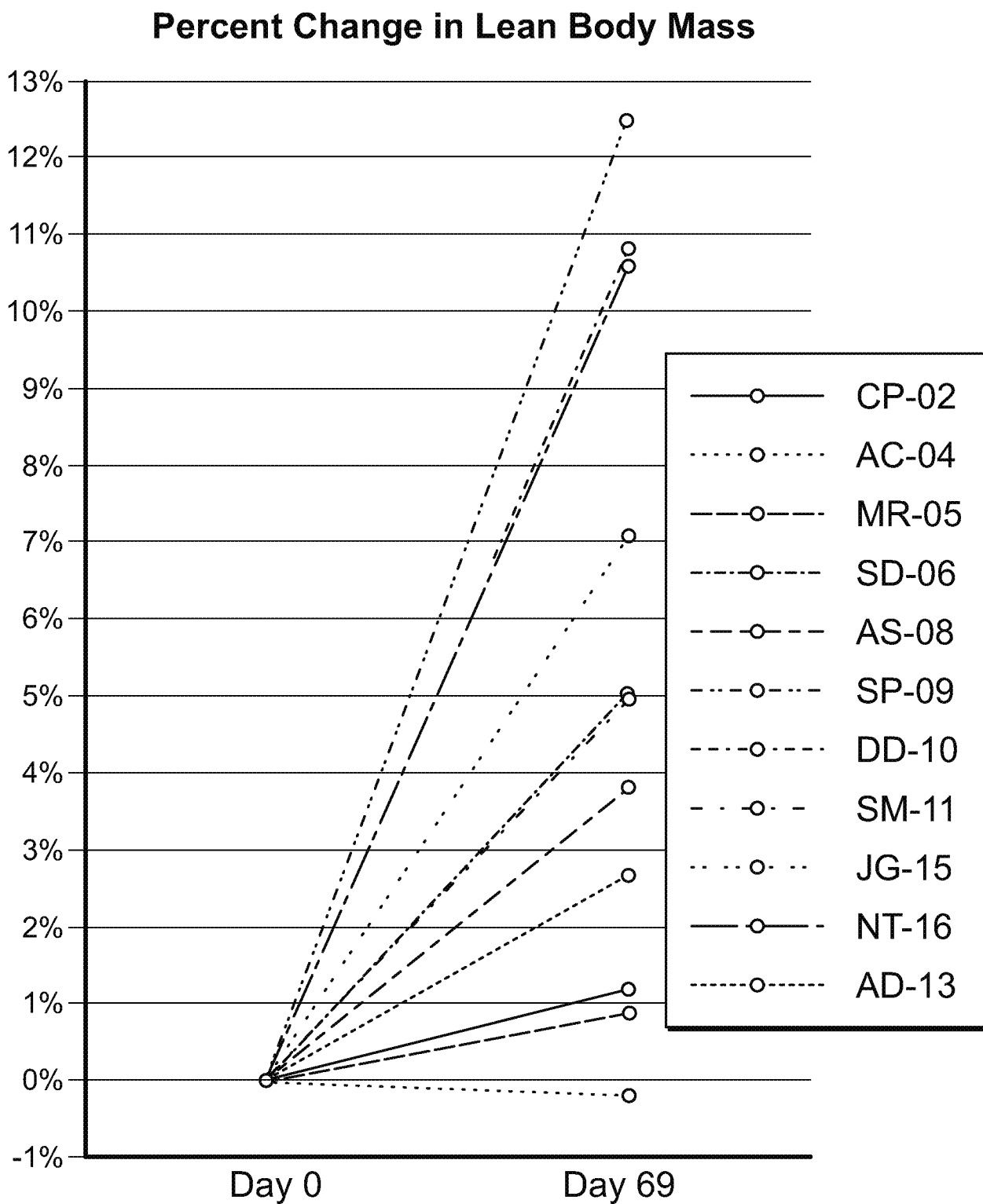


FIG. 2

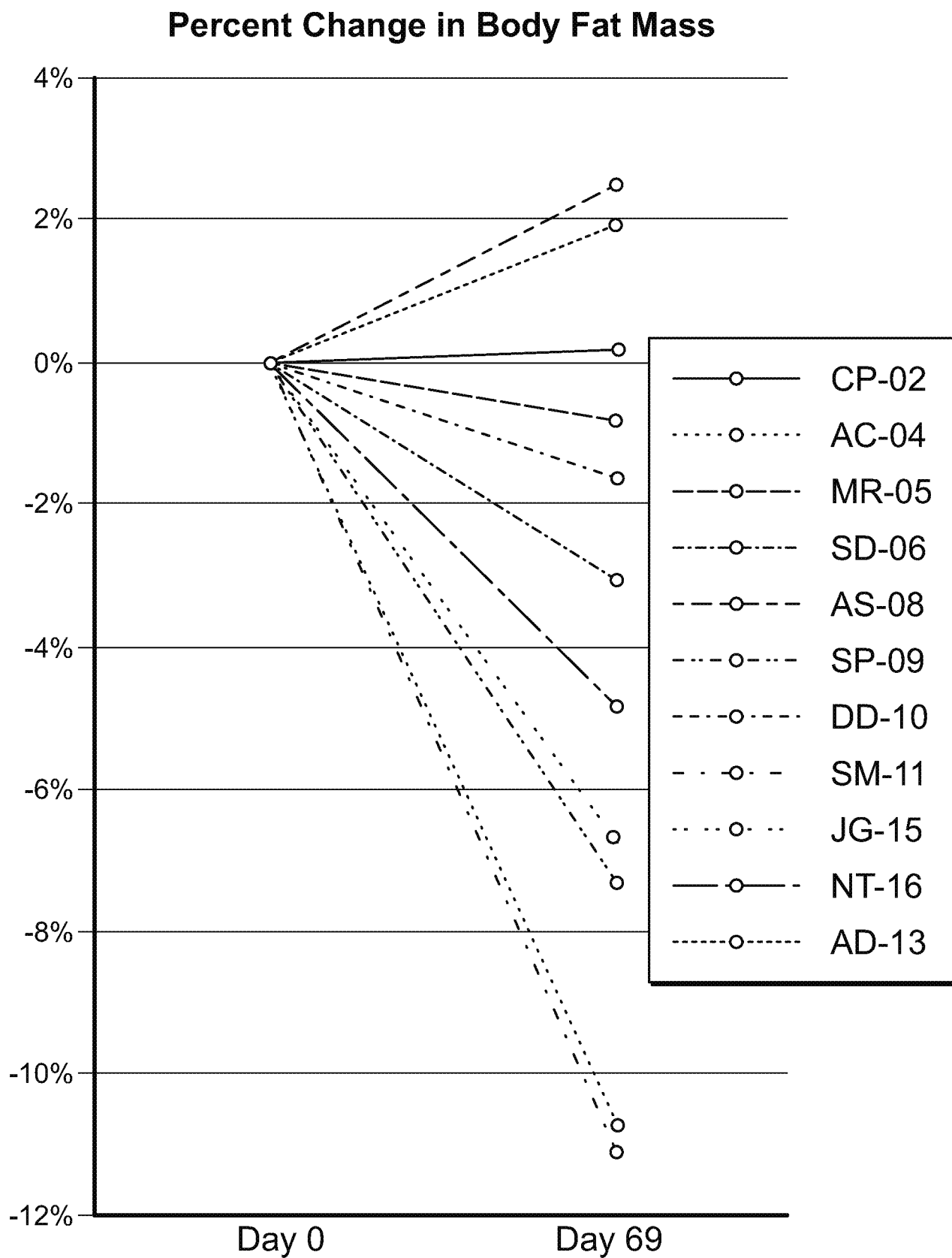


FIG. 3
APOTEX_EX1015_PGR2026-00034_Page 117

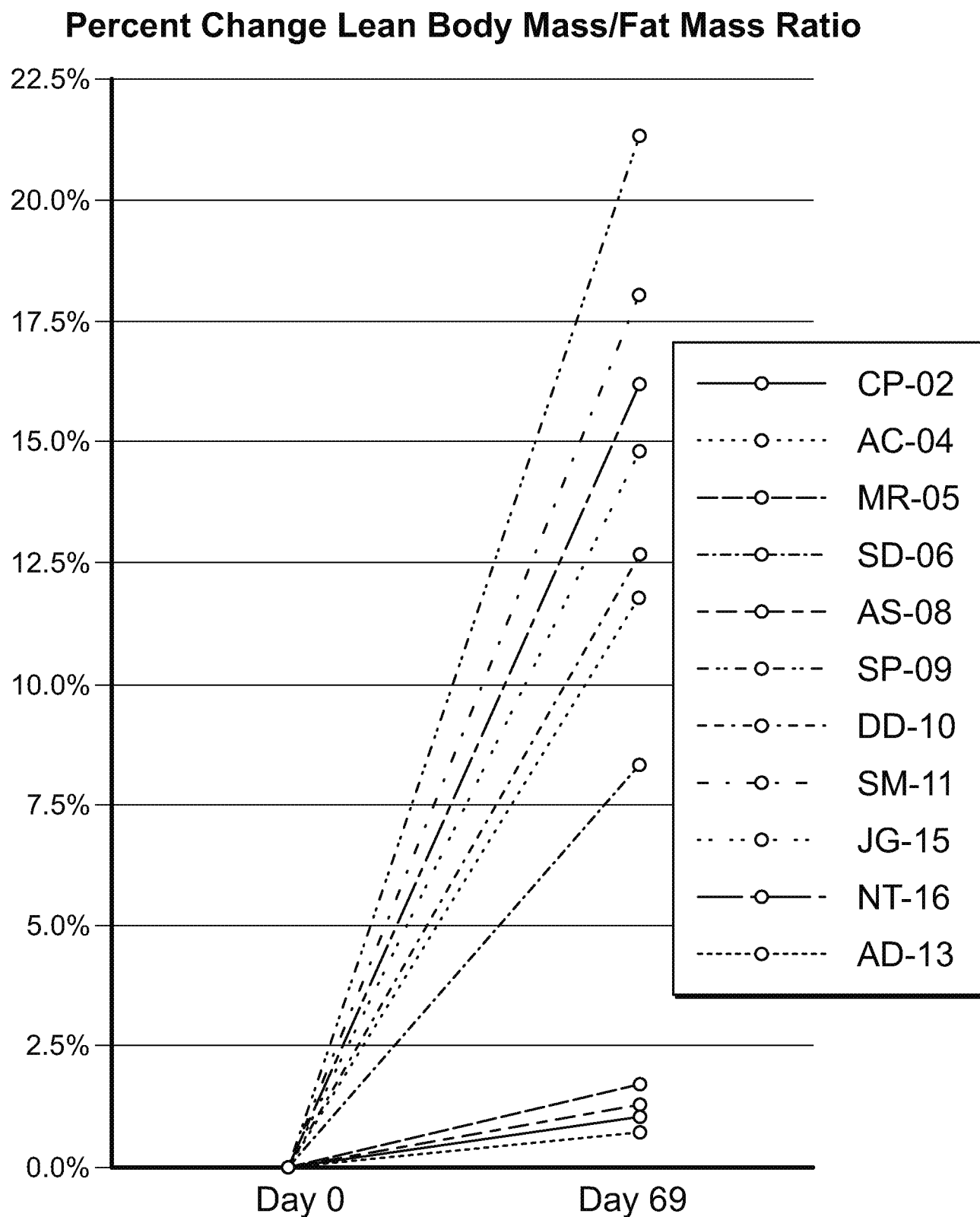


FIG. 4

Schematic

**Screening
(28 Days)***

**Open Label Treatment Period
(69 days)**

**Double-Blind,
Placebo-
Controlled,
Randomized
Withdrawal
Extension
(29 days)**

Day -28 to Day -1	Baseline Day 0	Day 13	Day 27	Day 41	Day 55	Day 69	Day 97
	1.5 mg/kg	2.4 mg/kg	3.3 mg/kg	4.2 mg/kg	5.1 mg/kg	Day 55 dose or Placebo Equivalent for Responders and Day 55 dose for Non- Responders	

*All screening procedures must be completed by Day -14

FIG. 5

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	SLNO-034/12US 333072-2199
		Application Number	
Title of Invention	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME		
The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76. This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.			

Secrecy Order 37 CFR 5.2:

☐	Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)
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Inventor Information:

Inventor 1 Remove				
Legal Name				
Prefix	Given Name	Middle Name	Family Name	Suffix
	Neil	M.	COWEN	
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service				
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Mailing Address of Inventor:				
Address 1	7915 Corte Cardo			
Address 2				
City	Carlsbad	State/Province	CA	
Postal Code	92009	Country	US	
All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the Add button. Add				

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).	
☐ An Address is being provided for the correspondence information of this application.	
Customer Number	58249
Email Address	Add Email Remove Email

Application Information:

Title of the Invention	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME		
Attorney Docket Number	SLNO-034/12US 333072-2199	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	5	Suggested Figure for Publication (if any)	

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	SLNO-034/12US 333072-2199
		Application Number	
Title of Invention	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME		

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	☒ Customer Number	☐ US Patent Practitioner	☐ Limited Recognition (37 CFR 11.9)
Customer Number	58249		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending	Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	18/988636	2024-12-19

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	SLNO-034/12US 333072-2199
		Application Number	
Title of Invention	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME		

Prior Application Status		Patented		Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
18/988636	Continuation of	18/824811	2024-09-04	12178823	2024-12-31
Prior Application Status		Patented		Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
18/824811	Continuation of	18/421914	2024-01-24	12109216	2024-10-08
Prior Application Status		Abandoned		Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
18/421914	Continuation of	17/104433	2020-11-25		
Prior Application Status		Patented		Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
17/104433	Continuation of	16/573965	2019-09-17	10874676	2020-12-29
Prior Application Status		Patented		Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
16/573965	Continuation of	16/041237	2018-07-20	10456408	2019-10-29
Prior Application Status		Patented		Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
16/041237	Continuation of	15/671792	2017-08-08	10058557	2018-08-28
Prior Application Status		Patented		Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15/671792	Division of	14/940018	2015-11-12	9757384	2017-09-12
Prior Application Status		Expired		Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
14/940018	Claims benefit of provisional	62/221359	2015-09-21		
Prior Application Status		Expired		Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
14/940018	Claims benefit of provisional	62/170035	2015-06-02		
Prior Application Status		Expired		Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
14/940018	Claims benefit of provisional	62/132445	2014-03-14		

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	SLNO-034/12US 333072-2199
		Application Number	
Title of Invention	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME		
Prior Application Status	Expired	Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
14/940018	Claims benefit of provisional	62/080150	2014-11-14
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the Add button.			Add

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)ⁱ the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Application Number	Country ⁱ	Filing Date (YYYY-MM-DD)	Access Code ⁱ (if applicable)	Remove
Additional Foreign Priority Data may be generated within this form by selecting the Add button.				Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	SLNO-034/12US 333072-2199
		Application Number	
Title of Invention	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME		

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	SLNO-034/12US 333072-2199
		Application Number	
Title of Invention	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME		

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.			
Applicant 1			Remove
If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.			
Clear			
☒ Assignee		☐ Legal Representative under 35 U.S.C. 117	
☐ Person to whom the inventor is obligated to assign.		☐ Joint Inventor	
☐ Person who shows sufficient proprietary interest			
If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:			
Name of the Deceased or Legally Incapacitated Inventor:			
If the Applicant is an Organization check here. ☒			
Organization Name	Essentialis, Inc.		
Mailing Address Information For Applicant:			
Address 1	100 Marine Parkway, Suite 400		
Address 2			
City	Redwood City	State/Province	CA
Country	US	Postal Code	94065
Phone Number		Fax Number	
Email Address			
Additional Applicant Data may be generated within this form by selecting the Add button. Add			

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	SLNO-034/12US 333072-2199
		Application Number	
Title of Invention	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME		

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	Given Name	Middle Name	Family Name	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		State/Province	
Country ⁱ		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.

Add

Signature:

Remove

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). However, if this Application Data Sheet is submitted with the **INITIAL** filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/John Kozlowski/		Date (YYYY-MM-DD)	2025-05-30
First Name	John	Last Name	Kozlowski	Registration Number
				82,124

Additional Signature may be generated within this form by selecting the Add button.

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	SLNO-034/12US 333072-2199
		Application Number	
Title of Invention	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME		

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

- 1 The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
- 2 A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
- 3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
- 4 A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
- 5 A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
- 6 A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
- 7 A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
- 8 A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
- 9 A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	Not Yet Assigned
Filing Date	Concurrently Herewith
First Named Inventor	Neil M. COWEN
Title	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	SLNO-034/12US 333072-2199

SIGNATURE of Applicant or Patent Practitioner

Signature	/John Kozlowski/	Date (Optional)	May 30, 2025
Name	John Kozlowski	Registration Number	82,124
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.



*Total of 1 forms are submitted.

POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☒ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above:

58249

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

☒ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

Firm or Individual Name			
Address			
City	State	Zip	
Country			
Telephone	Email		

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Essentialis, Inc.

☐ Inventor or Joint Inventor (title not required below)

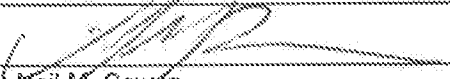
☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☒ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature		Date (Optional)	
Name	Neil M. Cowen		
Title	President and Chief Scientific Officer		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☒ Total of 1 forms are submitted.

Attorney Docket No.: 328512-2000



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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
19/224,580

RECEIPT DATE / TIME
05/30/2025 07:38:33 PM Z ET

ATTORNEY DOCKET #
SLNO-034/12US 333072-2199

Title of Invention

METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 1503

FILED BY Diana Sciamanna

PATENT CENTER # 70663120

FILING DATE -

CUSTOMER # 58249

FIRST NAMED
INVENTOR Neil M. COWEN

CORRESPONDENCE
ADDRESS -

AUTHORIZED BY John Kozlowski

Documents

TOTAL DOCUMENTS: 9

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
ADS.pdf		9	Application Data Sheet	2175 KB
Transmittal.pdf		1	Transmittal of New Application	104 KB
Track_One_Request.pdf		1	Track One Request	121 KB
POA.pdf		2	Power of Attorney	299 KB
Declaration.pdf		1	Oath or Declaration filed	183 KB
Application.pdf		110	-	502 KB
Application-SPEC.pdf	(1-106)	106	Specification	495 KB
Application-CLM.pdf	(107-109)	3	Claims	88 KB
Application-ABST.pdf	(110-	1	Abstract	85 KB

APOTEX_EX1015_PGR2026-00034_Page 131

110)

Drawings.pdf	5	Drawings-only black and white line drawings	376 KB
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Digest**DOCUMENT****MESSAGE DIGEST(SHA-512)**

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Drawings.pdf	D77FFB2FECEDB8CD6EEAAE06577AE0D049B53A409CD6CA3 C2CC9ED20A275B77B2E6C1AAC2DC52B0DC9E4C4D320E48A A2E4E47D8344638A3ED90FF10BB22E433A

described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UTILITY PATENT APPLICATION TRANSMITTAL (Only for new nonprovisional applications under 37 CFR 1.53(b))		Attorney Docket No. SLNO-034/12US 333072-2199	
		First Named Inventor Neil M. COWEN	
		Title METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME	
		Priority Mail Express® Label No.	

APPLICATION ELEMENTS See MPEP chapter 600 concerning utility patent application contents.	ADDRESS TO: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450
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1. ☐ Fee Transmittal Form (PTO/SB/17 or equivalent) 2. ☐ Applicant asserts small entity status. See 37 CFR 1.27 3. ☐ Applicant certifies micro entity status. See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent. 4. ☒ Specification [Total Pages <u>110</u>] Both the claims and abstract must start on a new page. (See MPEP § 608.01(a) for information on the preferred arrangement) 5. ☒ Drawing(s) (35 U.S.C. 113) [Total Sheets <u>5</u>] 6. Inventor's Oath or Declaration [Total Pages <u>1</u>] (including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e)) a. ☐ Newly executed (original or copy) b. ☒ A copy from a prior application (37 CFR 1.63(d)) 7. ☒ Application Data Sheet * See note below. See 37 CFR 1.76 (PTO/AIA/14 or equivalent) 8. CD-ROM or CD-R in duplicate, large table, or Computer Program (Appendix) ☐ Landscape Table on CD 9. Nucleotide and/or Amino Acid Sequence Submission (if applicable, items a. – c. are required) a. ☐ Computer Readable Form (CRF) b. ☐ Specification Sequence Listing on: i. ☐ CD-ROM or CD-R (2 copies); or ii. ☐ Paper c. ☐ Statements verifying identity of above copies	ACCOMPANYING APPLICATION PAPERS 10. ☐ Assignment Papers (cover sheet & document(s)) Name of Assignee 11. ☐ 37 CFR 3.73(c) Statement (when there is an assignee) ☒ Power of Attorney 12. ☐ English Translation Document (if applicable) 13. ☐ Information Disclosure Statement (PTO/SB/08 or PTO-1449) ☐ Copies of citations attached 14. ☐ Preliminary Amendment 15. ☐ Return Receipt Postcard (MPEP § 503) (Should be specifically itemized) 16. ☐ Certified Copy of Priority Document(s) (if foreign priority is claimed) 17. ☐ Nonpublication Request Under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent 18. ☒ Other: Certification and Request for Prioritized Examination Under 37 CFR 1.102(e)
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***Note:** (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 must be included in an Application Data Sheet (ADS).
 (2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).

19. CORRESPONDENCE ADDRESS			
☒ The address associated with Customer Number: <u>58249</u>		OR ☐ Correspondence address below	
Name			
Address			
City	State	Zip Code	
Country	Telephone	Email	
Signature	/John Kozlowski/		Date
Name (Print/Type)	John Kozlowski		Registration No. (Attorney/Agent)
		May 30, 2025	
		82,124	

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME
-----------------------	--

As the below named inventor, I hereby declare that:

This declaration

is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 14/940,018

filed on November 12, 2015

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

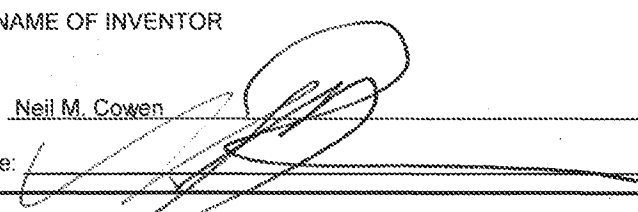
WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Neil M. Cowen

Date (Optional): 11/13/15

Signature: 

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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UNITED STATES
PATENT AND TRADEMARK OFFICEP.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov**ELECTRONIC ACKNOWLEDGEMENT RECEIPT**APPLICATION #
19/224,580RECEIPT DATE / TIME
06/03/2025 03:25:07 PM Z ETATTORNEY DOCKET #
SLNO-034/12US 333072-2199**Title of Invention**

METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME

Application InformationAPPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 1503

FILED BY Ricardo Lopez

PATENT CENTER # 70711794

FILING DATE -

CUSTOMER # 58249

FIRST NAMED INVENTOR Neil M. COWEN

CORRESPONDENCE ADDRESS -

AUTHORIZED BY John Kozlowski

Documents**TOTAL DOCUMENTS: 5**

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
IDS_Cover_Letter.pdf		3	-	108 KB
IDS_Cover_Letter-TRAN.LET.pdf	(1-2)	2	Transmittal Letter	103 KB
IDS_Cover_Letter-IDS.SIZEFEE.pdf	(3-3)	1	Assertion regarding Information Disclosure Statement (IDS) Size Fee (SB/08C)	98 KB
IDS_SB08.pdf		11	Information Disclosure Statement (IDS) Form (SB08)	242 KB

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NFOA_2_12_2025.pdf	11	Other reference-	916 KB
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APOTEX_EX1015_PGR2026-00034_Page 136

Patent/Application/Search
Documents

Other reference-
Patent/Application/Search
Documents

NOA_5_19_2025.pdf

8

884 KB

Digest

DOCUMENT

MESSAGE DIGEST(SHA-512)

IDS_Cover_Letter.pdf

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IDS_SB08.pdf

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NOA_5_19_2025.pdf

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This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security,

and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.



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PATENT AND TRADEMARK OFFICE

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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/224,580	06/03/2025 03:25:07 PM Z ET	SLNO-034/12US 333072-2199

Title of Invention

METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1503	FILED BY	Ricardo Lopez
PATENT CENTER #	70711794	AUTHORIZED BY	John Kozlowski
CUSTOMER #	58249	FILING DATE	-
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Neil M. COWEN

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 501283	E202563F26119885	Ricardo Lopez

FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
1833	FILING AN INFORMATION DISCLOSURE STATEMENT THAT CAUSES THE CUMULATIVE NUMBER OF APPLICANT-PROVIDED ITEMS OF INFORMATION TO EXCEED 100 BUT NOT EXCEED 200	500.00	1	500.00
TOTAL AMOUNT:				\$500.00

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d))

and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

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New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**

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Complete if Known

Application Number	19/224,580
Filing Date	May 30, 2025
First Named Inventor	Neil M. COWEN
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	SLNO-034/12US 333072-2199

Sheet

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of

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U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
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	2.	US-2003/0035106-A1	2/20/2003	Yeh et al.	
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	4.	US-2003/0211123-A1	11/13/2003	Shukla et al.	
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	11.	US-2009/0062264-A1	3/5/2009	Cowen et al.	
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	15.	US-2010/0256360-A1	10/7/2010	Cowen et al.	
	16.	US-2012/0053172-A1	3/1/2012	De Boer	
	17.	US-2012/0238554-A1	9/20/2012	Cowen	
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	22.	US-2019/0117665-A1	4/25/2019	Cowen et al.	
	23.	US-2020/0237772-A1	7/30/2020	Cowen	
	24.	US-2021/0322434-A1	10/21/2021	Cowen	
	25.	US-2024/0252507-A1	8/1/2024	Cowen et al.	
	26.	US-2025/0120979-A1	4/17/2025	Cowen	

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First Named Inventor	Neil M. COWEN
Art Unit	Not Yet Assigned
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		Number-Kind Code ² (if known)			
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	29.	US-5,284,845-A	2/8/1994	Paulsen	
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				First Named Inventor	Neil M. COWEN
				Art Unit	Not Yet Assigned
				Examiner Name	Not Yet Assigned
				Attorney Docket Number	SLNO-034/12US 333072-2199

FOREIGN PATENT DOCUMENTS

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		Country Code ³ "Number" "Kind Code ⁵ (if known)				
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				Application Number	19/224,580
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				First Named Inventor	Neil M. COWEN
				Art Unit	Not Yet Assigned
				Examiner Name	Not Yet Assigned
Sheet	4	of	11	Attorney Docket Number	SLNO-034/12US 333072-2199

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
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				First Named Inventor	Neil M. COWEN
				Art Unit	Not Yet Assigned
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				Art Unit	Not Yet Assigned
				Examiner Name	Not Yet Assigned
Sheet	8	of	11	Attorney Docket Number	SLNO-034/12US 333072-2199

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
	116.	LANG, Y. (2005). "World Drug News (77th)," Tianjin Pharmacy, No. 5, Vol. 17, pp. 73-75 (with English Translation), 10 total pages.	
	117.	LEE, P.D. (2002). "Disease management of Prader-Willi syndrome," Expert Opin. Pharmacother. 3:1451-1459.	
	118.	LIU, J. et al. (April 18, 2006). "The Role of Early Intensive Insulin Therapy in the Treatment of Diabetes," Journal of New Medicine 37(3):144-146 (with English Translation).	
	119.	MARUGO, M. et al. (1977). "Diazoxide in the treatment of obesity," Boll Spec It Biol Sper 53:1860-1866.	
	120.	MCCANDLESS, S.E. et al. (2017). "Effects of MetAP2 inhibition on hyperphagia and body weight in Prader-Willi syndrome: A randomized, double-blind, placebo-controlled trial," Diabetes Obes. Metab. 19:1751-1761.	
	121.	MELE, A. et al. (2014). "Dual response of the KATP channels to staurosporine: a novel role of SUR2B, SUR1 and Kir6.2 subunits in the regulation of the atrophy in different skeletal muscle phenotypes," Biochem. Pharmacol. 91:266-275.	
	122.	MENG, Z. et al. (2018). "Diazoxide ameliorates severity of experimental osteoarthritis by activating autophagy via modulation of the osteoarthritis-related biomarkers," J. Cell Biochem. 119:8922-8936.	
	123.	NOLAN, B.J. et al. (2022). "Single-center real-life experience with testosterone treatment in adult men with Prader-Willi syndrome," Am. J. Med. Genet. A. 188:2637-2641.	
	124.	Non-Final Office Action mailed on November 16, 2016, for U.S. Patent Application Number 14/940,018, filed on November 12, 2015, 13 pages.	
	125.	Non-Final Office Action mailed on September 17, 2009, for U.S. Patent Application Number 11/212,130, filed on August 25, 2005, 14 pages.	
	126.	Non-Final Office Action mailed on August 1, 2013, for U.S. Patent Application Number 12/368,215, filed on February 9, 2009, 12 pages.	
	127.	Non-Final Office Action mailed on December 8, 2009, for U.S. Patent Application Number 12/368,215, filed on February 9, 2009, 8 pages.	
	128.	Non-Final Office Action mailed on May 28, 2014, for U.S. Patent Application Number 12/370,456, filed on February 12, 2009, 17 pages.	
	129.	Non-Final Office Action mailed on September 8, 2011, for U.S. Patent Application Number 12/370,456, filed on February 12, 2009, 11 pages.	

Examiner Signature		Date Considered	
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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449B/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	19/224,580
				Filing Date	May 30, 2025
				First Named Inventor	Neil M. COWEN
				Art Unit	Not Yet Assigned
				Examiner Name	Not Yet Assigned
Sheet	9	of	11	Attorney Docket Number	SLNO-034/12US 333072-2199

NON PATENT LITERATURE DOCUMENTS				
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²	
	130.	Non-Final Office Action mailed on June 30, 2016, for U.S. Patent Application Number 14/458,032, filed on August 12, 2014, 12 pages.		
	131.	Non-Final Office Action mailed on July 31, 2015, for U.S. Patent Application Number 14/458,032, filed on August 12, 2014, 16 pages.		
	132.	Non-Final Office Action mailed on February 22, 2018, for U.S. Patent Application Number 15/671,792, filed on August 8, 2017, 13 pages.		
	133.	Non-Final Office Action mailed on January 8, 2019, for U.S. Patent Application Number 16/041,237, filed on July 20, 2018, 15 pages.		
	134.	Non-Final Office Action mailed on February 19, 2020, for U.S. Patent Application Number 16/573,965, filed on September 17, 2019, 14 pages.		
	135.	Non-Final Office Action mailed on May 11, 2022, for U.S. Patent Application Number 17/104,433, filed on November 25, 2020, 16 pages.		
	136.	Non-Final Office Action mailed on May 8, 2024, for U.S. Patent Application Number 18/421,914, filed on January 24, 2024, 22 pages.		
	137.	Non-Final Office Action mailed on October 18, 2024, for U.S. Patent Application Number 18/824,811, filed on September 4, 2024, 19 pages.		
	138.	Non-Final Office Action mailed on February 12, 2025, for U.S. Patent Application Number 18/988,636, filed on December 19, 2024, 11 pages.		
	139.	Notice of Allowance mailed on February 1, 2017, for U.S. Patent Application Number 14/940,018, filed on November 12, 2015, 8 pages.		
	140.	Notice of Allowance mailed on June 28, 2017, for U.S. Patent Application Number 14/940,018, filed on November 12, 2015, 8 pages.		
	141.	Notice of Allowance mailed on June 26, 2018, for U.S. Patent Application Number 15/671,792, filed on August 8, 2017, 7 pages.		
	142.	Notice of Allowance mailed on June 19, 2019, for U.S. Patent Application Number 16/041,237, filed on July 20, 2018, 7 pages.		
	143.	Notice of Allowance mailed on August 31, 2020, for U.S. Patent Application Number 16/573,965, filed on September 17, 2019, 7 pages.		

Examiner Signature		Date Considered	
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Substitute for form 1449B/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	19/224,580
				Filing Date	May 30, 2025
				First Named Inventor	Neil M. COWEN
				Art Unit	Not Yet Assigned
				Examiner Name	Not Yet Assigned
Sheet	10	of	11	Attorney Docket Number	SLNO-034/12US 333072-2199

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
	144.	Notice of Allowance mailed on August 1, 2024, for U.S. Patent Application Number 18/421,914, filed on January 24, 2024, 7 pages.	
	145.	Notice of Allowance mailed on November 8, 2024, for U.S. Patent Application Number 18/824,811, filed on September 4, 2024, 10 pages.	
	146.	Notice of Allowance mailed on May 19, 2025, for U.S. Patent Application Number 18/988,636, filed on December 19, 2024, 8 pages.	
	147.	ORTQVIST, E. et al. (2004). "Temporary preservation of beta-cell function by diazoxide treatment in childhood type 1 diabetes," Diabetes Care 27(9):2191-2197.	
	148.	OUEDRAOGO, R. et al. (2002). "2-alkyl-3-Alkylamino-2H-Benzo- and pyridothiadiazine 1,1-dioxides: from K ⁺ ATP channel openers to Ca ⁺⁺ channel blockers?" Biol. Chem. 383:1759-1768.	
	149.	QVIGSTAD, E. et al. (2004). "Nine weeks of bedtime diazoxide is well tolerated and improves beta-cell function in subjects with Type 2 diabetes," Diabetic Medicine 21:73-76.	
	150.	Partial Supplementary European Search Report mailed on March 28, 2018, for EP Application Number 15 859 169.3, filed on November 12, 2015, 8 pages.	
	151.	PROGLYCEM® (2003). Pharmaceutical Information, Diazoxide Hyperglycemic Agent, 5 total pages.	
	152.	RATZMANN, K.P. et al. (1983). "Effect of pharmacological suppression of insulin secretion on tissue sensitivity to insulin in subjects with moderate obesity," Int J Obesity 7(5):453-458.	
	153.	REDDY, K.R. et al. (2003). "Once-daily sustained-release matrix tablets of nicorandil: formulation and in vitro evaluation," AAPS Pharm Sci Tech 4(4):E61, 9 total pages.	
	154.	RUSSELL, S. et al. (November 2003). "The assessment of food-related problems in individuals with Prader-Willi syndrome," Br. J. Clin. Psychol. 42(Pt. 4):379-392.	
	155.	SCHOU, S.C. et al. (2005). "Synthesis and pharmacological evaluation of 4H-1,4-benzothiazine-2-carbonitrile 1,1-dioxide and N-(2-cyanomethylsulfonylphenyl)acylamide derivatives as potential activators of ATP sensitive potassium channels," Bioorg. Med. Chem. 13:141-155.	
	156.	SCHWANSTECHER, M. et al. (1998). "Potassium channel openers require ATP to bind to and act through sulfonylurea receptors," EMBO J. 17:5529-5535.	
	157.	STANRIDGE, M. et al. (2000). "Diazoxide down-regulates leptin and lipid metabolizing enzymes in adipose tissue of Zucker rats," FASEB J 14:455-460.	

Examiner Signature		Date Considered	
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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449B/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	19/224,580
				Filing Date	May 30, 2025
				First Named Inventor	Neil M. COWEN
				Art Unit	Not Yet Assigned
				Examiner Name	Not Yet Assigned
Sheet	11	of	11	Attorney Docket Number	SLNO-034/12US 333072-2199

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
	158.	SURWIT, R.S. et al. (2000). "Diazoxide Restores β 3-Adrenergic Receptor Function in Diet-Induced Obesity and Diabetes," Endocrinology 141:3630-3637.	
	159.	TRUBE, G. et al. (1986). "Opposite effects of tolbutamide and diazoxide on the ATP-dependent K ⁺ channel in mouse pancreatic beta-cells," Pfluegers Arch. 407:493-499.	
	160.	VAN BOEKEL, G. et al. (2008). "Weight loss in obese men by caloric restriction and high-dose diazoxide-mediated insulin suppression," Diabetes Obes. Metab. 10:1195-1203.	
	161.	VAN MIL, E.G. et al. (2000). "Activity related energy expenditure in children and adolescents with Prader-Willi syndrome," Int J Obes Relat Metab Disord 24(4):429-434.	
	162.	WIGAND, J.P. et al. (1979). "Downregulation of insulin receptors in obese man," Diabetes 28(4):287-291.	
	163.	Written Opinion of the International Searching Authority mailed on February 2, 2016, for PCT Application Number PCT/US2015/60455, filed on November 12, 2015, 8 pages.	
	164.	Written Opinion of the International Searching Authority mailed on June 16, 2006, for PCT Application Number PCT/US2005/30481, filed on August 25, 2005, 3 pages.	
	165.	Written Opinion of the International Searching Authority mailed on December 6, 2007, for PCT Application Number PCT/US2006/48711, filed on December 20, 2006, 8 pages.	
	166.	Written Opinion of the International Searching Authority mailed on September 30, 2008, for PCT Application Number PCT/US2008/68936, filed on July 1, 2008, 7 pages.	
	167.	Written Opinion of the International Searching Authority mailed on June 21, 2013, for PCT Application Number PCT/US2013/027676, filed on February 25, 2013, 6 pages.	
	168.	U.S. Patent Application Number 18/545,764, filed on December 19, 2023, by Cowen (Copy not attached).	
	169.	U.S. Patent Application Number 18/792,416, filed on August 1, 2024, by Cowen (Copy not attached).	

Examiner Signature		Date Considered	
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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
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NOTICE OF ALLOWANCE AND FEE(S) DUE

58249 7590 05/19/2025
COOLEY LLP
ATTN: IP Docketing Department
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

EXAMINER	
OH, TAYLOR V	
ART UNIT	PAPER NUMBER

1625

DATE MAILED: 05/19/2025

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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18/988,636

12/19/2024

Neil M. COWEN

SLNO-034/11US

6955

333072-2188

TITLE OF INVENTION: METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1290	\$0.00	\$0.00	\$1290	08/19/2025

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

58249 7590 05/19/2025
COOLEY LLP
ATTN: IP Docketing Department
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
-----------------	-------------	----------------------	---------------------	------------------

18/988,636 12/19/2024 Neil M. COWEN SLNO-034/11US 6955

TITLE OF INVENTION: METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1290	\$0.00	\$0.00	\$1290	08/19/2025

EXAMINER	ART UNIT	CLASS-SUBCLASS
OH, TAYLOR V	1625	514-005100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

1 _____

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☐ Issue Fee ☐ Publication Fee (if required)

4b. Method of Payment: (Please first reapply any previously paid fee shown above)

☐ Electronic Payment via the USPTO patent electronic filing system ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. Change in Entity Status (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____

Date _____

Typed or printed name _____

Registration No. _____



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/988,636	12/19/2024	Neil M. COWEN	SLNO-034/11US 333072-2188	6955
58249	7590	05/19/2025	EXAMINER OH, TAYLOR V	
COOLEY LLP ATTN: IP Docketing Department 1299 Pennsylvania Avenue, NW Suite 700 Washington, DC 20004			ART UNIT 1625	PAPER NUMBER
DATE MAILED: 05/19/2025				

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).

<https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf>

Routine uses of the information in this record may include disclosure to:

- 1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;
- 2) a federal, state, local, or international agency, in response to its request;
- 3) a contractor of the USPTO having need for the information in order to perform a contract;
- 4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;
- 5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;
- 6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
- 7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;
- 8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c));
- 9) the Office of Personnel Management (OPM) for personnel research purposes; and
- 10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

Notice of Allowability	Application No. 18/988,636	Applicant(s) COWEN, Neil M.	
	Examiner TAYLOR V OH	Art Unit 1625	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to 5/06/2025.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☒ The allowed claim(s) is/are See Continuation Sheet. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov**.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
Certified copies:
a) ☐ All b) ☐ Some* c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).
* Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.
Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)
1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 5/06/2025.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____.
5. ☐ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/TAYLOR V OH/ Primary Examiner, Art Unit 1625	
--	--

Continuation of 3. The allowed claim(s) is/are: 29-31,34-46 and 50-58

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Reasons of Allowance

The Status of Claims:

Claims 29-31, 34-46, and 50-58 are pending.

Claims 29-31, 34-46, and 50-58 are allowed.

I. The following is an examiner's statement of reasons for allowance:

- The IDS filed on 5/06/25 were reviewed, but they are unrelated to the claimed invention.
- The objection of Claims 46-47 is withdrawn.
- The rejection of Claims 31-45 and 48-49 under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, is withdrawn due to the modification of the claims.
- The rejection of Claims 29-45 on the ground of nonstatutory double patenting as being unpatentable over claims 1,3, 6-7, 12-13, 16-24 of U.S. Patent No. 12,178,823 B1 is withdrawn due to filing the Terminal Disclaimer on 5/06/25.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably

accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning the communication after allowance such as sending all post-allowance correspondence should be directed to " Box Issue Fee" or faxed directly to PUBS at 703-305-8755. This will expedite the process of these papers.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/TAYLOR V OH/
Primary Examiner, Art Unit 1625
5/09/2025

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor:	Neil M. COWEN	Confirmation No.:	1503
Application No.:	19/224,580	Group Art Unit:	Not Yet Assigned
Filed:	May 30, 2025	Examiner:	Not Yet Assigned
For:	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

In accordance with the duty of disclosure set forth in 37 CFR § 1.56, Applicant hereby submits this Information Disclosure Statement (“IDS”) along with the attached Form used in lieu of PTO/SB/08 (“SB/08”) and Written Assertion used in lieu of PTO/SB/08C in compliance with 37 CFR §§ 1.97 and 1.98. It is respectfully requested that the information be expressly considered during the prosecution of the above-identified Application, and the references be made of record therein and appear among the “References Cited” on any patent to issue therefrom.

In accordance with 37 CFR § 1.97(b), no additional fee for submission of this Information Disclosure Statement is required, as it is filed within any one of the time periods:

- ☒ [X] within three months from the filing date of this national Application other than a CPA under 37 CFR § 1.53(d);
- ☐ [] within three months from the date of entry of the national stage as set forth in 37 CFR § 1.491 in this international Application;
- ☐ [] before the mailing date of a first Office action on the merits; or

[] before the mailing of a first Office action after the filing of a request for continued examination under 37 CFR § 1.114.

In agreement with 37 CFR § 1.97(g), this Information Disclosure Statement shall not be construed as a representation that a search has been made.

In agreement with 37 CFR § 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that the information cited in the statement is, or is considered to be, relevant, analogous, or material to patentability as defined by 37 CFR § 1.56(b).

In accordance with 37 CFR §§ 1.98(a)(2) and (d)(1), Applicant submits a copy of any foreign patent and non-patent literature document cited on the SB/08 (including any English translation, abstract, or explanation submitted therewith) other than those which were previously submitted to, or cited by, the Office in any of the following Applications, which the above-identified Application relies on for an earlier effective filing date under 35 U.S.C. § 120: U.S. Patent Application Nos. 18/988,636; 18/824,811; 18/421,914; 17/104,433; 16/573,965; 16/041,237; 15/671,792 and/or 14/940,018.

As authorized by 37 CFR § 1.98(a)(2)(ii), Applicant does not submit a copy of any U.S. publication or patent information cited on the SB/08.

As authorized by the Waiver of the Copy Requirement set forth in 37 CFR § 1.98(a) for cited pending U.S. patent applications, issued October 19, 2004, Applicant does not submit a copy of any pending unpublished U.S. patent application cited on the SB/08, because a copy is stored in the USPTO's Image File Wrapper system and can be readily viewed by Examiners and the Applicant.

IDS SIZE FEE - WRITTEN ASSERTION UNDER 37 CFR § 1.98

As required by 37 CFR § 1.98(a)(4), Applicant asserts that this Information Disclosure Statement is accompanied by the IDS size fee under 37 CFR § 1.17(v)(2), less any amount previously paid.

The Director is hereby authorized to charge the IDS size fee indicated above in the amount of \$500.00, as well as any appropriate fee under 37 CFR § 1.17(p) that may be required by this Information Disclosure Statement, and to credit any overpayment, to Deposit Account No. 50-1283, referencing Docket No. SLNO-034/12US 333072-2199.

It is respectfully requested that the Examiner consider the above-noted information and return an initialed copy of the SB/08 to the undersigned. The Examiner is encouraged to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present Application.

Dated: June 3, 2025

Respectfully submitted,
COOLEY LLP

USPTO CUSTOMER No. 58249

COOLEY LLP
ATTN: IP Docketing Department
1299 Pennsylvania Avenue NW, Suite 700
Washington, DC 20004

Electronic signature: /John Kozlowski/
John Kozlowski
Reg. No. 82,124

Tel: (858) 550-6056
Fax: (202) 842-7899



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/988,636	12/19/2024	Neil M. COWEN	SLNO-034/11US 333072-2188	6955
58249	7590	02/12/2025	EXAMINER	
COOLEY LLP			OH, TAYLOR V	
ATTN: IP Docketing Department				
1299 Pennsylvania Avenue, NW				
Suite 700				
Washington, DC 20004				
			ART UNIT	PAPER NUMBER
			1625	
			NOTIFICATION DATE	DELIVERY MODE
			02/12/2025	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

zIPPatentDocketingMailboxUS@cooley.com

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Non-Final Rejection

The Status of Claims:

Claims 29-56 are pending.

Claims 29-45 and 48-49 are rejected.

Claims 46-47 and 50-56 are objected.

DETAILED ACTION

1. Claims 29-56 are under consideration in this Office Action.

Priority

2. It is noted that this application is a continuation of 18824811 09/04/2024 (PAT 12178823), which is a continuation of 18421914 01/24/2024 (PAT 12109216), which is a continuation of 17104433 (11/25/2020ABN), which is a continuation of 16573965 09/17/2019 (PAT 10874676), which is a continuation of 16041237 07/20/2018 (PAT 10456408), which is a continuation of 15671792 08/08/2017 (PAT 10058557), which is a division of 14/940,018(11/12/2015)(US 9,757,384), which claims benefit of 62/080,150(11/14/2014) and claims benefit

of 62/138,245(03/25/2015) and claims benefit of 62/170,035(06/02/2015) and claims benefit of 62/221,359(09/21/2015).

Drawings

3. The drawings filed on 12/19/24 are accepted by the examiner.

IDS

4. The IDS filed on 12/20/24 are reviewed by the examiner.

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

Claim Objections

Claims 46-47 and 50-56 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 112

1. The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31-45 and 48-49 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor (or for applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention.

In claims 31-45 and 48-49, the term "about" is recited. This expression is vague and indefinite because of the following reason:

A. "About"

The term "about" used to define the area of the lower end of a mold as between 25 to about 45% of the mold entrance was held to be clear, but flexible. *Ex parte Eastwood*,

163 USPQ 316 (Bd. App. 1968). Similarly, in *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), the court held that a limitation defining the stretch rate of a plastic as "exceeding about 10% per second" is definite because infringement could clearly be assessed through the use of a stopwatch.

The examiner recommends to remove the term "about" from the claims.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double

patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit <http://www.uspto.gov/forms/>. The filing date of the application will determine what form should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to <http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp>.

1. Claims 29-45 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1,3, 6-7, 12-13, 16-24 of U.S. Patent No. 12,178,823 B1. Although the claims at issue are not identical, they are not patentably distinct from each other because of some difference between the scope of the claimed invention with respect to treating a subject having Prader-Willi Syndrome (PWS) vs. treating hyperphagia in a subject having Prader-Willi Syndrome (PWS).

The claims 1 , 7 and 16 of U.S. Patent No. describe the following:

1. A method of treating a subject having Prader-Willi Syndrome (PWS), the method comprising administering to said subject for at least 10 weeks a pharmaceutical formulation comprising an effective amount of diazoxide, or a pharmaceutically acceptable salt thereof, wherein administration reduces one or more aggressive behaviors in the subject.
3. The method of claim 1, wherein said pharmaceutical formulation is administered orally.
7. The method of claim 1, wherein the pharmaceutical formulation is administered once per day.
16. The method of claim 1, wherein hyperphagia of the subject is reduced by at least 10% after at least 10 weeks of administering the diazoxide, or a pharmaceutically acceptable salt thereof.

Similarly, the current claim 29 does disclose the following method as shown below:

29. (New): A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising orally administering to said subject once per day a

pharmaceutical formulation comprising an effective amount of diazoxide choline, wherein administration reduces hyperphagia and one or more aggressive behaviors in the subject.

However, the current claims differ from the U.S. Patent No. 12,178,823 in that the claimed method of treating hyperphagia in the subject having Prader-Willi Syndrome (PWS), the method comprising orally administering to said subject once per day is not present in the claim 1 of the U.S. Patent No..

Even so, the dependent claims disclose the limitations of hyperphagia of the subject as in claim 16 and the pharmaceutical formulation being orally administered once per day as in claims 3 and 7.

From these, it seems reasonable that the limitations of hyperphagia and orally administered once per day can be incorporated into the claim 1 instead of at least 10 weeks, which can be placed on the dependent claim in order to make the claim narrower. Moreover, such limitations can be anticipated; there is very little difference as to the patentable distinction.

So, it would have been obvious to the skilled artisan to be motivated to add those limitations to the claim in order to make the scope of the claimed method narrower.. This is because the skilled artisan in the art would expect such a manipulation to be feasible and successful as guidance shown in the application.

Conclusion

Claims 29-45 and 48-49 are rejected.

Claims 46-47 and 50-56 are objected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TAYLOR V OH whose telephone number is (571)272-0689. The examiner can normally be reached on 8:00-5:00.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Kosar can be reached on 571-272-0913. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic

Art Unit: 1625

Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/TAYLOR V OH/

Primary Examiner, Art Unit 1625

2/7/2025

Notice of References Cited	Application/Control No. 18/988,636		Applicant(s)/Patent Under Reexamination COWEN, Neil M.	
	Examiner TAYLOR V OH		Art Unit 1625	Page 1 of 1

U.S. PATENT DOCUMENTS						
*		Document Number Country Code-Number-Kind Code	Date YYYY-MM-DD	Name	CPC Classification	US Classification
*	A	US-12178823-B1	2024-12-31	Cowen; Neil M.	A61K9/2054	1/1
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS						
*		Document Number Country Code-Number-Kind Code	Date YYYY-MM-DD	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS		
*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in YYYY-MM-DD format are publication dates. Classifications may be US or foreign.



UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
19/224,580

RECEIPT DATE / TIME
06/03/2025 05:45:26 PM Z ET

ATTORNEY DOCKET #
SLNO-034/12US 333072-2199

Title of Invention

METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
 under 35 USC 111(a)

PATENT # -

CONFIRMATION # 1503

FILED BY Diana Sciamanna

PATENT CENTER # 70717109

FILING DATE -

CUSTOMER # 58249

FIRST NAMED INVENTOR Neil M. COWEN

CORRESPONDENCE ADDRESS -

AUTHORIZED BY John Kozlowski

Documents

TOTAL DOCUMENTS: 5

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
Prelim_Amendment.pdf		9	-	165 KB
Prelim_Amendment-A.PE.pdf	(1-1)	1	Preliminary Amendment	95 KB
Prelim_Amendment-SPEC.pdf	(2-2)	1	Specification	148 KB
Prelim_Amendment-CLM.pdf	(3-6)	4	Claims	130 KB
Prelim_Amendment-REM.pdf	(7-9)	3	Applicant Arguments/Remarks Made in an Amendment	130 KB
Corrected_ADS.pdf		8	Application Data Sheet	512 KB

Warning: This is not a USPTO supplied ADS fillable form. Data in the form cannot be

automatically loaded to other USPTO systems.

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
Prelim_Amendment.pdf	E9C4B977515C0913DC2715C3CD62617FA09334B0F3370B384 E4FC67D15A2FCB26022D381B8F73A76CB25D92B75C011BCF 5FF4F15A2D061DF9649FA99BADCCFB8
Prelim_Amendment-A.PE.pdf	AAE005A2020AB50CF7C56A823CAB5A4C4106FCCCAEC19E5 268564C77DC72891779B95B72DBB18FDE7EBA71DA0B000279 94363059F225F5101DD542B8CAE8F32F
Prelim_Amendment-SPEC.pdf	528455FE3EC8EB948ACE9BCB60D72F17507A8F73F4C7AAD8 AA9D57D52C86AE61AB1FA859CD84CF4705BB63965622383F0 050C37F9EC8A8F7900B8D137CE9F1C7
Prelim_Amendment-CLM.pdf	D5503ACF066375D24909BB55761F3C141FDAB3313DB072AEA 6491C81B7A53B5288A504D24A0761C21059631593FA6AC81E4 8F422F725ED35421FCED0A188A1F9
Prelim_Amendment-REM.pdf	F4A8A87A1E2F2231D9269965DB8B6794A7D582FC91DE2AE5A 9439F265CC6ECEBF7A645C8240B2FB4FC76D032C5C69DBA1 A93022021880E7AD7B85172A595BB9D
Corrected_ADS.pdf	07E83FC3C6AD13595230566025C8EAC368459704B766EFD4D 3B4979470784DA1A4C40FAE03A33FFAB628E8CC946D551775 6F1986EB81139EFA6AA656F7C82E80

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	SLNO-034/12US 333072-2199
		Application Number	19/224,580
Title of Invention	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH MAGENIS SYNDROME		
The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76. This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.			

Secrecy Order 37 CFR 5.2:

☐	Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)
--------------------------	---

Inventor Information:

Inventor 1 Remove				
Legal Name				
Prefix	Given Name	Middle Name	Family Name	Suffix
	Neil	M.	COWEN	
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service				
City	Carlsbad	State/Province	CA	Country of Residence
				US
Mailing Address of Inventor:				
Address 1		7915 Corte Cardo		
Address 2				
City	Carlsbad	State/Province	CA	
Postal Code	92009	Country	US	
All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the Add button. Add				

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).	
☐ An Address is being provided for the correspondence information of this application.	
Customer Number	58249
Email Address	Add Email Remove Email

Application Information:

Title of the Invention	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH MAGENIS SYNDROME		
Attorney Docket Number	SLNO-034/12US 333072-2199	Small Entity Status Claimed ☐	
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	5	Suggested Figure for Publication (if any)	

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	SLNO-034/12US 333072-2199
		Application Number	<u>19/224,580</u>
Title of Invention	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME ~~OR SMITH MAGENIS SYNDROME~~		

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	☒ Customer Number	☐ US Patent Practitioner	☐ Limited Recognition (37 CFR 11.9)
Customer Number	58249		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending	Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	18/988636	2024-12-19

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	SLNO-034/12US 333072-2199
		Application Number	<u>19/224,580</u>
Title of Invention	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH MAGENIS SYNDROME		

Prior Application Status		Patented		Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
18/988636	Continuation of	18/824811	2024-09-04	12178823	2024-12-31
Prior Application Status		Patented		Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
18/824811	Continuation of	18/421914	2024-01-24	12109216	2024-10-08
Prior Application Status		Abandoned		Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
18/421914	Continuation of	17/104433	2020-11-25		
Prior Application Status		Patented		Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
17/104433	Continuation of	16/573965	2019-09-17	10874676	2020-12-29
Prior Application Status		Patented		Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
16/573965	Continuation of	16/041237	2018-07-20	10456408	2019-10-29
Prior Application Status		Patented		Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
16/041237	Continuation of	15/671792	2017-08-08	10058557	2018-08-28
Prior Application Status		Patented		Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15/671792	Division of	14/940018	2015-11-12	9757384	2017-09-12
Prior Application Status		Expired		Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
14/940018	Claims benefit of provisional	62/221359	2015-09-21		
Prior Application Status		Expired		Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
14/940018	Claims benefit of provisional	62/170035	2015-06-02		
Prior Application Status		Expired		Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
14/940018	Claims benefit of provisional	62/118245	2015-03-25		

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	SLNO-034/12US 333072-2199
		Application Number	<u>19/224,580</u>
Title of Invention	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH MAGENIS SYNDROME		
Prior Application Status	Expired	Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
14/940018	Claims benefit of provisional	62/080150	2014-11-14
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the Add button.			

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)ⁱ the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Application Number	Country ⁱ	Filing Date (YYYY-MM-DD)	Remove
			Access Code ⁱ (if applicable)
Additional Foreign Priority Data may be generated within this form by selecting the Add button.			

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

☐ NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	SLNO-034/12US 333072-2199
		Application Number	19/224,580
Title of Invention	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH MAGENIS SYNDROME		

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	SLNO-034/12US 333072-2199
		Application Number	19/224,580
Title of Invention	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH MAGENIS SYNDROME		

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

[Clear](#)

☒ Assignee
 ☐ Legal Representative under 35 U.S.C. 117
 ☐ Joint Inventor

☐ Person to whom the inventor is obligated to assign.
 ☐ Person who shows sufficient proprietary interest

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name Essentialis, Inc.

Mailing Address Information For Applicant:

Address 1	100 Marine Parkway, Suite 400		
Address 2			
City	Redwood City	State/Province	CA
Country	US	Postal Code	94065
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button.

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	SLNO-034/12US 333072-2199
		Application Number	<u>19/224,580</u>
Title of Invention	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH MAGENIS SYNDROME		

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	Given Name	Middle Name	Family Name	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		State/Province	
Country ¹		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). However, if this Application Data Sheet is submitted with the **INITIAL** filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/John Kozlowski/		Date (YYYY-MM-DD)	2025-06-03
First Name	John	Last Name	Kozlowski	Registration Number
82,124				

Additional Signature may be generated within this form by selecting the Add button.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	SLNO-034/12US 333072-2199
		Application Number	<u>19/224,580</u>
Title of Invention	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME ~~OR SMITH MAGENIS SYNDROME~~		

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**



UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/224,580	06/03/2025 05:45:26 PM Z ET	SLNO-034/12US 333072-2199

Title of Invention

METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1503	FILED BY	Diana Sciamanna
PATENT CENTER #	70717109	AUTHORIZED BY	John Kozlowski
CUSTOMER #	58249	FILING DATE	-
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Neil M. COWEN

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 501283	E202563H46079721	Diana Sciamanna

FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
1202	EACH CLAIM IN EXCESS OF 20	200.00	7	1400.00
TOTAL AMOUNT:				\$1,400.00

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C.

371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE TITLE:

Please replace the title with the following amended title.

-- METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME --

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor:	Neil M. COWEN	Confirmation No.:	1503
Application No.:	19/224,580	Group Art Unit:	Not Yet Assigned
Filed:	May 30, 2025	Examiner:	Not Yet Assigned
For:	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT

Prior to examination of the above-identified application, please amend the above-captioned application as follows:

Amendments to the Title begin on page 2 of this paper.

Amendments to the Claims are reflected on the listing of the claims, which begins on page 3 of this paper.

Remarks begin on page 7 of this paper.

An Information Disclosure Statement and Corrected Application Data Sheet are submitted on even date herewith.

IN THE CLAIMS:

Set forth below in ascending order, with status identifiers, is a complete listing of all claims currently under examination. Changes to any amended claims are indicated by [[double brackets]], ~~striketrough~~ and/or underlining. This listing also reflects any cancellation and/or addition of claims.

1-28. (Canceled)

29. (New): A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising administering to said subject once per day a pharmaceutical formulation comprising an effective amount of diazoxide choline, wherein administration reduces hyperphagia and one or more food related behaviors in the subject.

30. (New): The method of claim 29, wherein the diazoxide choline is administered for at least 10 weeks.

31. (New): The method of claim 29, wherein the diazoxide choline is administered for one or more years.

32. (New): The method of claim 29, wherein the once-daily administration of diazoxide choline is in an amount from 25 mg to 100 mg.

33. (New): The method of claim 29, wherein the once-daily administration of diazoxide choline is in an amount from 50 mg to 180 mg.

34. (New): The method of claim 29, wherein the once-daily administration of diazoxide choline is in an amount from 50 mg to 275 mg.

35. (New): The method of claim 29, wherein the once-daily administration of diazoxide choline is in an amount from 300 mg to 500 mg.

36. (New): The method of claim 29, wherein the once-daily administration of diazoxide choline is in an amount from 500 mg to 2000 mg.

37. (New): The method of claim 29, wherein the once-daily administration of diazoxide choline is in an amount from 25 mg to 500 mg.

38. (New): The method of claim 31, wherein the once-daily administration of diazoxide choline is in an amount from 25 mg to 100 mg.

39. (New): The method of claim 31, wherein the once-daily administration of diazoxide choline is in an amount from 50 mg to 180 mg.

40. (New): The method of claim 31, wherein the once-daily administration of diazoxide choline is in an amount from 50 mg to 275 mg.

41. (New): The method of claim 31, wherein the once-daily administration of diazoxide choline is in an amount from 300 mg to 500 mg.

42. (New): The method of claim 31, wherein the once-daily administration of diazoxide choline is in an amount from 500 mg to 2000 mg.

43. (New): The method of claim 31, wherein the once-daily administration of diazoxide choline is in an amount from 25 mg to 500 mg.

44. (New): The method of claim 29, wherein the administration of diazoxide choline is initiated at a starting dose of diazoxide choline and then titrated every two weeks to reach a maintenance dose of diazoxide choline.
45. (New): The method of claim 44, wherein the starting dose of diazoxide choline is between 25-100 mg of diazoxide choline.
46. (New): The method of claim 44, wherein the starting dose of diazoxide choline is between 50-180 mg of diazoxide choline.
47. (New): The method of claim 45, wherein the maintenance dose of diazoxide choline is between 100-200 mg of diazoxide choline.
48. (New): The method of claim 46, wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline.
49. (New): The method of claim 46, wherein the maintenance dose of diazoxide choline is between 300-500 mg of diazoxide choline.
50. (New): The method of claim 46, wherein the maintenance dose of diazoxide choline is between 500-2000 mg of diazoxide choline.
51. (New): The method of claim 46, wherein the maintenance dose of diazoxide choline is between 100-500 mg of diazoxide choline.
52. (New): The method of claim 45, wherein the maintenance dose of diazoxide choline is between 25-250 mg of diazoxide choline.

53. (New): The method of claim 45, wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline.

54. (New): The method of claim 29, wherein the one or more food related behaviors is an aggressive behavior.

55. (New): The method of claim 54, wherein the pharmaceutical formulation is administered orally.

REMARKS

The title of the application is being amended herewith to more accurately reflect the subject matter being claimed in the present application. No new matter is added.

Claims 1-28 were pending in the present application. By virtue of this amendment, claims 1-28 are canceled, without prejudice or disclaimer, and new claims 29-55 are added. Support for the new claims can be found throughout the application as originally filed, for example, in at least Example 3; paragraphs [0051], [0079], [00145], [00147], [00157], [00168], [00236]-[00241], [00311], [00436]-[00441], [00447]-[00448], [00451]-[00456]; Tables 1, 6, 15-16; FIGS. 1 and 5; and the claims as originally filed. No new matter is added.

Upon entry of these amendments, claims 29-55 will be pending in the present application.

The claims as amended total no more than 30 claims and no more than 4 independent claims. The claims as amended are therefore compliant with Track One examination requirements.

Amendment and cancelation of certain claims is not to be construed as a dedication to the public of any of the subject matter of the claims as previously presented. Applicant expressly reserves the right to pursue the presently unclaimed subject matter disclosed in the present application in one or more divisional and/or continuation applications or an application claiming benefit of the present application.

Entry and consideration of the foregoing amendments is respectfully requested.

Regarding the Information Disclosure Statement

An Information Disclosure Statement (IDS) is submitted on even date herewith. Applicant thanks the Examiner in advance for review of the cited references and return of the initialed form SB/08. Should any of the references be unavailable to the Examiner, the Examiner is requested to

contact the undersigned prior to the issuance of the next action and additional copies will be provided.

Regarding Examiner Interviews

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone Dr. Kimberly A. Bolin (Reg. No. 44,546) at (650) 843-5387 or the undersigned at the number given below.

CONCLUSION

Although amendments have been made, no acquiescence or estoppel is or should be implied thereby. Rather, the amendments are made only to expedite prosecution of the present application, and without prejudice to presentation or assertion, in the future, of claims on the subject matter affected thereby.

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced documents, Applicant is not conceding in this application that previously pending claims are not patentable. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue, at a later date, any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child, or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 50-1283 referencing Docket No. SLNO-034/12US 333072-2199. However, the Director is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: June 3, 2025

Respectfully submitted,
COOLEY LLP

USPTO CUSTOMER NO. 58249

COOLEY LLP
ATTN: IP Docketing Department
1299 Pennsylvania Avenue NW, Suite 700
Washington, DC 20004

By: /John Kozlowski/
John Kozlowski
Reg. No. 82,124

Tel: (858) 550-6056
Fax: (202) 842-7899



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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
19/224,580	05/30/2025		3830	SLNO-034/12US 333072-2199	27	1

CONFIRMATION NO. 1503

58249

COOLEY LLP

ATTN: IP Docketing Department

1299 Pennsylvania Avenue, NW

Suite 700

Washington, DC 20004

FILING RECEIPT



0000000090026866

Date Mailed: 06/12/2025

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Neil M. COWEN, Carlsbad, CA;

Applicant(s)

Essentialis, Inc., Redwood City, CA;

Power of Attorney: The patent practitioners associated with Customer Number 58249

Domestic Applications for which benefit is claimed

This application is a CON of 18/988,636 12/19/2024
which is a CON of 18/824,811 09/04/2024 PAT 12,178,823
which is a CON of 18/421,914 01/24/2024 PAT 12,109,216
which is a CON of 17/104,433 11/25/2020 ABN
which is a CON of 16/573,965 09/17/2019 PAT 10,874,676
which is a CON of 16/041,237 07/20/2018 PAT 10,456,408
which is a CON of 15/671,792 08/08/2017 PAT 10,058,557
which is a DIV of 14/940,018 11/12/2015 PAT 9,757,384
which claims benefit of 62/221,359 09/21/2015
and claims benefit of 62/170,035 06/02/2015
and claims benefit of 62/138,245 03/25/2015
and claims benefit of 62/080,150 11/14/2014

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see <http://www.uspto.gov> for more information.) - **None.**

Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 06/11/2025

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 19/224,580**

Projected Publication Date: 09/18/2025

Non-Publication Request: No

Early Publication Request: No

Title

METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

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page 2 of 4

patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at <http://www.uspto.gov/web/offices/pac/doc/general/index.html>.

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number
19/224,580

APPLICATION AS FILED - PART I

(Column 1)		(Column 2)		SMALL ENTITY		OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE(\$)	FEE(\$)	RATE(\$)	FEE(\$)	
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A		N/A	350	
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A		N/A	770	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A		N/A	880	
TOTAL CLAIMS (37 CFR 1.16(i))	27	minus 20 =	*	7	x	200 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1	minus 3 =	*		x	=	
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).					0	
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))						0	
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL		TOTAL	3400	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY		OTHER THAN SMALL ENTITY	
AMENDMENT A		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)	RATE(\$)	ADDITIONAL FEE(\$)		
	Total (37 CFR 1.16(i))	*	Minus	**	=	x	=	x	=		
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x	=	x	=		
	Application Size Fee (37 CFR 1.16(s))										
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))										
						TOTAL ADD'L FEE		TOTAL ADD'L FEE			
AMENDMENT B		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)	RATE(\$)	ADDITIONAL FEE(\$)		
	Total (37 CFR 1.16(i))	*	Minus	**	=	x	=	x	=		
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x	=	x	=		
	Application Size Fee (37 CFR 1.16(s))										
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))										
						TOTAL ADD'L FEE		TOTAL ADD'L FEE			

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
19/224,580	05/30/2025	Neil M. COWEN	SLNO-034/12US 333072-2199	1503
58249	7590	07/02/2025	EXAMINER	
COOLEY LLP			CENTRAL, DOCKET	
ATTN: IP Docketing Department			ART UNIT	
1299 Pennsylvania Avenue, NW			PAPER NUMBER	
Suite 700			OPAP	
Washington, DC 20004			NOTIFICATION DATE	
			DELIVERY MODE	
			07/02/2025	
			ELECTRONIC	

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The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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<i>Decision Granting Request for Prioritized Examination (Track I)</i>	Application No. 19/224,580	Applicant(s) COWEN, Neil M.	
	Examiner ANGELA E WALKER	Art Unit OPET	AIA (FITF) Status Yes
1. THE REQUEST FILED <u>30 May 2025</u> IS GRANTED . The above-identified application has met the requirements for prioritized examination A. ☒ for an original nonprovisional application (Track I). B. ☐ for an application undergoing continued examination (RCE). 2. The above-identified application will undergo prioritized examination. The application will be accorded special status throughout its entire course of prosecution until one of the following occurs: A. filing a <u>petition for extension of time</u> to extend the time period for filing a reply; B. filing an <u>amendment to amend the application to contain more than four independent claims, more than thirty total claims</u>, or a multiple dependent claim; C. filing a <u>request for continued examination</u> ; D. filing a notice of appeal; E. filing a request for suspension of action; F. mailing of a notice of allowance; G. mailing of a final Office action; H. completion of examination as defined in 37 CFR 41.102; or I. abandonment of the application. Telephone inquiries with regard to this decision should be directed to ANGELA WALKER at (571) 272-1058. In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.			
/ANGELA E WALKER/ Paralegal Specialist, OPET			

<i>Notice of References Cited</i>	Application/Control No. 19/224,580		Applicant(s)/Patent Under Reexamination COWEN, Neil M.	
	Examiner TAYLOR V OH		Art Unit 1625	Page 1 of 1

U.S. PATENT DOCUMENTS						
*		Document Number Country Code-Number-Kind Code	Date YYYY-MM-DD	Name	CPC Classification	US Classification
*	A	US-12343348-B2	2025-07-01	Cowen; Neil M.	A61K31/551	1/1
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
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FOREIGN PATENT DOCUMENTS						
*		Document Number Country Code-Number-Kind Code	Date YYYY-MM-DD	Country	Name	CPC Classification
	N					
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	R					
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 Dates in YYYY-MM-DD format are publication dates. Classifications may be US or foreign.

Search Notes 	Application/Control No. 19/224,580	Applicant(s)/Patent Under Reexamination COWEN, Neil M.
	Examiner TAYLOR V OH	Art Unit 1625

CPC - Searched*		
Symbol	Date	Examiner
C07D285/18 , C07D285/22 , A61K2300/00	07/07/2025	t.o.
A61K9/5026 , A61K9/5042 , A61K9/5047 , A61K31/137	07/07/2025	t.o.
A61K31/155 , A61K31/551 , A61K38/27 , A61K45/06	07/07/2025	t.o.
(A61K31/549 , A61K9/00 , A61K9/0004 , A61K9/2054	07/07/2025	t.o.

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
514	5.100	07/07/2025	t.o.

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Search Notes		
Search Notes	Date	Examiner
The IDS filed on 6/3/25 were reviewed.	07/07/2025	t.o.
PE2E search including cpc classes/subclasses limited by the text search done. p.2	07/07/2025	t.o.
STNNext search done .p.1	07/07/2025	t.o.
Inventor's name search done .p.1	07/07/2025	t.o.

/TAYLOR V OH/ Primary Examiner, Art Unit 1625	
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<i>Search Notes</i> 	Application/Control No. 19/224,580	Applicant(s)/Patent Under Reexamination COWEN, Neil M.
	Examiner TAYLOR V OH	Art Unit 1625

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/TAYLOR V OH/ Primary Examiner, Art Unit 1625	
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Bibliographic Data

Application No: 19/224,580

Foreign Priority claimed: ☐ Yes ☒ No

35 USC 119 (a-d) conditions met: ☐ Yes ☐ No ☐ Met After Allowance

Verified and Acknowledged:

/TAYLOR V OH/

Examiner's Signature

Initials

Title:

METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
05/30/2025	514	1625	SLNO-034/12US 333072-2199
RULE			

APPLICANTS

Essentialis, Inc., Redwood City, CA, UNITED STATES

INVENTORS

Neil M. COWEN, Carlsbad, CA, UNITED STATES

CONTINUING DATA

This application is a CON of 18988636 12/19/2024 PAT 12343348

18988636 is a CON of 18824811 09/04/2024 PAT 12178823

18824811 is a CON of 18421914 01/24/2024 PAT 12109216

18421914 is a CON of 17104433 11/25/2020ABN

17104433 is a CON of 16573965 09/17/2019 PAT 10874676

16573965 is a CON of 16041237 07/20/2018 PAT 10456408

16041237 is a CON of 15671792 08/08/2017 PAT 10058557

15671792 is a DIV of 14940018 11/12/2015 PAT 9757384

14940018 has PRO of 62221359 09/21/2015

14940018 has PRO of 62170035 06/02/2015

14940018 has PRO of 62138245 03/25/2015

14940018 has PRO of 62080150 11/14/2014

FOREIGN APPLICATIONS

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Sheet	1	of	11	Application Number	19/224,580
				Filing Date	May 30, 2025
				First Named Inventor	Neil M. COWEN
				Art Unit	Not Yet Assigned
				Examiner Name	Not Yet Assigned
				Attorney Docket Number	SLNO-034/12US 333072-2199

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
	1.	US-2002/0035106-A1	3/21/2002	Hansen et al.	
	2.	US-2003/0035106-A1	2/20/2003	Yeh et al.	
	3.	US-2003/0068366-A1	4/10/2003	Chungi et al.	
	4.	US-2003/0211123-A1	11/13/2003	Shukla et al.	
	5.	US-2004/0143213-A1	7/22/2004	Hunter et al.	
	6.	US-2004/0204472-A1	10/14/2004	Briggs et al.	
	7.	US-2006/0051418-A1	3/9/2006	Cowen et al.	
	8.	US-2006/0128673-A1	6/15/2006	Firnges et al.	
	9.	US-2007/0191351-A1	8/16/2007	Cowen et al.	
	10.	US-2007/0293552-A1	12/20/2007	Gorczyński	
	11.	US-2009/0062264-A1	3/5/2009	Cowen et al.	
	12.	US-2009/0148525-A1	6/11/2009	Cowen	
	13.	US-2009/0149451-A1	6/11/2009	Cowen	
	14.	US-2010/0028429-A1	2/4/2010	Cowen et al.	
	15.	US-2010/0256360-A1	10/7/2010	Cowen et al.	
	16.	US-2012/0053172-A1	3/1/2012	De Boer	
	17.	US-2012/0238554-A1	9/20/2012	Cowen	
	18.	US-2013/0040942-A1	2/14/2013	Cowen et al.	
	19.	US-2013/0309301-A1	11/21/2013	Cowen et al.	
	20.	US-2014/0364367-A1	12/11/2014	Cotter	
	21.	US-2018/0280405-A1	10/4/2018	Cowen	
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	24.	US-2021/0322434-A1	10/21/2021	Cowen	
	25.	US-2024/0252507-A1	8/1/2024	Cowen et al.	
	26.	US-2025/0120979-A1	4/17/2025	Cowen	

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Examiner Signature	/TAYLOR V OH/	Date Considered	07/07/2025
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Application Number	19/224,580
Filing Date	May 30, 2025
First Named Inventor	Neil M. COWEN
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	SLNO-034/12US 333072-2199

Sheet

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U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
	27.	US-2,986,573	5/30/1961	Topliss et al.	
	28.	US-4,880,830	11/14/1989	Rhodes	
	29.	US-5,284,845-A	2/8/1994	Paulsen	
	30.	US-5,399,359-A	3/21/1995	Baichwal	
	31.	US-5,415,871-A	5/16/1995	Pankhania et al.	
	32.	US-5,629,045-A	5/13/1997	Veech et al.	
	33.	US-6,022,562-A	2/8/2000	Autant et al.	
	34.	US-6,225,310-B1	5/1/2001	Nielsen et al.	
	35.	US-6,197,765-B1	3/6/2001	Vardi et al.	
	36.	US-7,572,789-B2	8/11/2009	Cowen et al.	
	37.	US-7,799,777-B2	9/21/2010	Cowen et al.	
	38.	US-9,381,202-B2	7/5/2016	Cowen et al.	
	39.	US-9,757,384-B2	9/12/2017	Cowen	
	40.	US-9,765,043-B2	9/19/2017	Cowen et al.	
	41.	US-9,782,416-B2	10/10/2017	Cowen	
	42.	US-10,058,557-B2	8/28/2018	Cowen	
	43.	US-10,085,998-B2	10/2/2018	Cowen et al.	
	44.	US-10,456,408-B2	10/29/2019	Cowen	
	45.	US-10,874,676-B2	12/29/2020	Cowen	
	46.	US-11,045,478-B2	6/29/2021	Cowen et al.	
	47.	US-11,786,536-B2	10/17/2023	Cowen et al.	
	48.	US-12,109,216-B2	10/8/2024	Cowen	
	49.	US-12,178,823-B1	12/31/2024	Cowen	

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Examiner Signature	/TAYLOR V OH/	Date Considered	07/07/2025
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STATEMENT BY APPLICANT**

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Complete if Known

Application Number	19/224,580
Filing Date	May 30, 2025
First Named Inventor	Neil M. COWEN
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	SLNO-034/12US 333072-2199

Sheet

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of

11

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T ⁶
		Country Code ³ "Number" ⁴ Kind Code ⁵ (if known)				
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	51.	CN-101257897-A	9/3/2008	Sirtris Pharmaceuticals, Inc.		
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	56.	WO-2006/000607-A1	1/5/2006	Universidad de Barcelona		
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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /T.V.O/

Examiner Signature	/TAYLOR V OH/	Date Considered	07/07/2025
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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449B/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	19/224,580
				Filing Date	May 30, 2025
				First Named Inventor	Neil M. COWEN
				Art Unit	Not Yet Assigned
				Examiner Name	Not Yet Assigned
Sheet	11	of	11	Attorney Docket Number	SLNO-034/12US 333072-2199

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
	158.	SURWIT, R.S. et al. (2000). "Diazoxide Restores β 3-Adrenergic Receptor Function in Diet-Induced Obesity and Diabetes," Endocrinology 141:3630-3637.	
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	162.	WIGAND, J.P. et al. (1979). "Downregulation of insulin receptors in obese man," Diabetes 28(4):287-291.	
	163.	Written Opinion of the International Searching Authority mailed on February 2, 2016, for PCT Application Number PCT/US2015/60455, filed on November 12, 2015, 8 pages.	
	164.	Written Opinion of the International Searching Authority mailed on June 16, 2006, for PCT Application Number PCT/US2005/30481, filed on August 25, 2005, 3 pages.	
	165.	Written Opinion of the International Searching Authority mailed on December 6, 2007, for PCT Application Number PCT/US2006/48711, filed on December 20, 2006, 8 pages.	
	166.	Written Opinion of the International Searching Authority mailed on September 30, 2008, for PCT Application Number PCT/US2008/68936, filed on July 1, 2008, 7 pages.	
	167.	Written Opinion of the International Searching Authority mailed on June 21, 2013, for PCT Application Number PCT/US2013/027676, filed on February 25, 2013, 6 pages.	
	168.	U.S. Patent Application Number 18/545,764, filed on December 19, 2023, by Cowen (Copy not attached).	
	169.	U.S. Patent Application Number 18/792,416, filed on August 1, 2024, by Cowen (Copy not attached).	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /T.V.O/

Examiner Signature	/TAYLOR V OH/	Date Considered	07/07/2025
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itle: METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME

Application number: 19/224,580

T.O.

V

Inventor name	City	State/country	Inventor oath compliant?
COWEN, Neil M.	Carlsbad	CALIFORNIA, UNITED STATES	N/A

T.O.
7/7/25

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	2071412	(A61K31/549 OR A61K9/00 OR A61K9/0004 OR A61K9/2054 OR A61K9/5026 OR A61K9/5042 OR A61K9/5047 OR A61K31/137 OR A61K31/155 OR A61K31/551 OR A61K38/27 OR A61K45/06 OR C07D285/18 OR C07D285/22 OR A61K2300/00).cpc. OR 514/\$.ccls.	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/07/07 08:51 PM
L2	7881668	Essentialis, Inc.as. OR Neil M. COWEN.in.	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/07/07 08:52 PM
L3	201417	L1 AND L2	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	AND	ON	ON	2025/07/07 08:52 PM
L4	351	L1 AND L2 AND TREATING SUBJECTS WITH PRADER-WILLI	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY,	AND	ON	ON	2025/07/07 08:54 PM

		SYNDROME OR SMITH-MAGENIS SYNDROME AND diazoxide AND choline AND hyperphagia	CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L5	1398	L1 AND TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME AND diazoxide AND choline AND aggressive behavior\$3 AND hyperphagia	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	AND	ON	ON	2025/07/07 08:56 PM
L6	46	L1 AND (TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME) AND diazoxide AND choline AND aggressive behavior\$3 AND hyperphagia	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	AND	ON	ON	2025/07/07 08:57 PM

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

d his

(FILE 'HOME' ENTERED AT 20:59:01 ON 07 JUL 2025)

FILE 'REGISTRY' ENTERED AT 21:00:50 ON 07 JUL 2025

L1 1 S DIAZOXIDE/CN
L2 0 S CHOLINE/RN
L3 1 S CHOLINE/CN

FILE 'HCAPLUS' ENTERED AT 21:02:50 ON 07 JUL 2025
S CHOINE OR 62-49-7/REG#

FILE 'REGISTRY' ENTERED AT 21:03:39 ON 07 JUL 2025
L4 1 S 62-49-7/RN

FILE 'HCAPLUS' ENTERED AT 21:03:40 ON 07 JUL 2025
L5 32259 S L4
L6 32260 S CHOINE OR L5
S 364-98-7/REG# OR DIAZOXIDE

FILE 'REGISTRY' ENTERED AT 21:04:24 ON 07 JUL 2025
L7 1 S 364-98-7/RN

FILE 'HCAPLUS' ENTERED AT 21:04:24 ON 07 JUL 2025

L8 2318 S L7
L9 3913 S L8 OR DIAZOXIDE
L10 2318 S L8 AND L9
L11 1687 S L10 AND PY<2014
L12 3 S L11 AND (PWS OR PRADER WILLI SYNDROME)
L13 0 S L12 AND (HYPERPHAGIA AND AGGRESSIVE BEHAVIOR)



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
19/224,580	05/30/2025	Neil M. COWEN	SLNO-034/12US 333072-2199	1503
58249	7590	07/09/2025	EXAMINER	
COOLEY LLP			OH, TAYLOR V	
ATTN: IP Docketing Department				
1299 Pennsylvania Avenue, NW				
Suite 700				
Washington, DC 20004				
			ART UNIT	PAPER NUMBER
			1625	
			NOTIFICATION DATE	DELIVERY MODE
			07/09/2025	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

zIPPatentDocketingMailboxUS@cooley.com

Office Action Summary	Application No. 19/224,580	Applicant(s) COWEN, Neil M.	
	Examiner TAYLOR V OH	Art Unit 1625	AIA (First Inventor to File) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 6/3/25.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

- 5) ☒ Claim(s) 29-55 is/are pending in the application.
5a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 6) ☐ Claim(s) ____ is/are allowed.
- 7) ☒ Claim(s) 29-55 is/are rejected.
- 8) ☐ Claim(s) ____ is/are objected to.
- 9) ☐ Claim(s) ____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☒ The drawing(s) filed on 5/30/25 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

- a) ☐ All b) ☐ Some** c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)
Paper No(s)/Mail Date 6/3/25.
- 3) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date ____.
- 4) ☐ Other: ____.

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Non-Final Rejection

The Status of Claims:

Claims 29-55 are pending.

Claims 29-55 are rejected.

DETAILED ACTION

1. Claims 29-55 are under consideration in this Office Action.

Priority

2. It is noted that this application is a continuation of 18988636 12/19/2024 (PAT 12343348), which is a continuation of 18824811 09/04/2024 (PAT 12178823), which is a continuation of 18421914 01/24/2024 (PAT 12109216), which is a continuation of 17104433 (11/25/2020ABN) , which is a continuation of 16573965 09/17/2019 (PAT 10874676), which is a continuation of of 16041237 07/20/2018 (PAT 10456408), which is a continuation of 15671792 08/08/2017 (PAT 10058557), which is a division of 14/940,018(11/12/2015)(US 9,757,384), which claims benefit of 62/080,150(11/14/2014) and claims benefit of

62/138,245(03/25/2015) and claims benefit of 62/170,035(06/02/2015) and claims benefit of 62/221,359(09/21/2015).

Drawings

3. The drawings filed on 5/30/25 are accepted by the examiner.

IDS

4. The IDS filed on 6/03/25 are reviewed by the examiner.

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

Double Patenting

1. A rejection based on double patenting of the “same invention” type finds its support in the language of 35 U.S.C. 101 which states that “whoever invents or discovers any new and useful process... may obtain a patent therefor...” (Emphasis added). Thus, the term “same invention,” in this context, means an invention drawn to

identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the claims that are directed to the same invention so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

2. Claims 29-53 are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-25 of prior U.S. Patent No. 12,343,348 B2. This is a statutory double patenting rejection.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit <http://www.uspto.gov/forms/>. The filing date of the application will determine what form should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to <http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp>.

1. Claims 29 and 54-55 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1,3, 6-7, 12-13, 16-24 of U.S. Patent No. 12,178,823 B1. Although the claims at issue are not identical, they are not patentably distinct from each other because of some difference between the scope of the claimed invention with respect to treating a subject having Prader-Willi Syndrome (PWS) vs. treating hyperphagia in a subject having Prader-Willi Syndrome (PWS).

The claims 1 , 7 and 16 of U.S. Patent No. describe the following:

1. A method of treating a subject having Prader-Willi Syndrome (PWS), the method comprising administering to said subject for at least 10 weeks a pharmaceutical formulation comprising an effective amount of diazoxide, or a pharmaceutically acceptable salt thereof, wherein administration reduces one or more aggressive behaviors in the subject.
3. The method of claim 1, wherein said pharmaceutical formulation is administered orally.
7. The method of claim 1, wherein the pharmaceutical formulation is administered once per day.
16. The method of claim 1, wherein hyperphagia of the subject is reduced by at least 10% after at least 10 weeks of administering the diazoxide, or a pharmaceutically acceptable salt thereof.

Similarly, the current claims 29 and 54-55 do disclose the following method as shown below:

29. (New): A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising orally administering to said subject once per day a pharmaceutical formulation comprising an effective amount of diazoxide choline, wherein administration reduces hyperphagia and one or more aggressive behaviors in the subject.

54. (New): The method of claim 29, wherein the one or more food related behaviors is an aggressive behavior.

55. (New): The method of claim 54, wherein the pharmaceutical formulation is administered orally.

However, the current claims differ from the U.S. Patent No. 12,178,823 in that the claimed method of treating hyperphagia in the subject having Prader-Willi Syndrome (PWS), the method comprising orally administering to said subject once per day is not present in the claim 1 of the U.S. Patent No..

Even so, the dependent claims disclose the limitations of hyperphagia of the subject as in claim 16 and the pharmaceutical formulation being orally administered once per day as in claims 3 and 7.

From these, it seems reasonable that the limitations of hyperphagia and orally administered once per day can be incorporated into the claim 1 instead of at least 10 weeks, which can be placed on the dependent claim in order to make the claim narrower. Moreover, such limitations can be anticipated; there is very little difference as to the patentable distinction.

So, it would have been obvious to the skilled artisan to be motivated to add those limitations to the claim in order to make the scope of the claimed method narrower.. This is because the skilled artisan in the art would expect such a manipulation to be feasible and successful as guidance shown in the application.

Conclusion

Claims 29-55 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TAYLOR V OH whose telephone number is (571)272-0689. The examiner can normally be reached on 8:00-5:00.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Kosar can be reached on 571-272-0913. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/TAYLOR V OH/
Primary Examiner, Art Unit 1625
7/07/2025

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 19/224,580	Filing Date 05/30/2025	☐ To be Mailed
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ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE (\$)	FEE (\$)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 = *		x \$200 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 = *		x \$ 600 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED - PART II

	(Column 1)		(Column 2)	(Column 3)	RATE (\$)	ADDITIONAL FEE (\$)
AMENDMENT	08/07/2025		CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	
	Total (37 CFR 1.16(i))	* 26	Minus	** 27	= 0	x \$ 200 = 0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0	x \$ 600 = 0
	☐ Application Size Fee (37 CFR 1.16(s))					
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					
TOTAL ADD'L FEE						0
AMENDMENT			CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	
	Total (37 CFR 1.16(i))	*	Minus	**	=	x \$ 0 =
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x \$ 0 =
	☐ Application Size Fee (37 CFR 1.16(s))					
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					
TOTAL ADD'L FEE						
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.						LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".						/CHRISTINE V MOORE/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".						
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.						

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.



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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/224,580	08/07/2025 02:20:37 PM Z ET	SLNO-034/12US 333072-2199

Title of Invention

METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1503	FILED BY	John Kozlowski
PATENT CENTER #	71740934	FILING DATE	05/30/2025
CUSTOMER #	58249	FIRST NAMED INVENTOR	Neil M. COWEN
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	John Kozlowski

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
petition-request.pdf	3	Terminal Disclaimer-Filed (Electronic)	45 KB
grantLetter.pdf	1	Terminal Disclaimer-Electronic- Approved	18 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
petition-request.pdf	0A2535A5CBDAAAF4445B3D63B306664A2DBD998ABC4FECC 9829EF36B998DBFAF21224DC904212158020043C319C8E3F38 98B7416B091E324C665A3850F47C123
grantLetter.pdf	DD5C0A8D3B5DB4DD26C99B880F75A87868111B1D525AEBA2

7D3E81EC95C0C1281B21DA9C79631A9CC3ED5C12A2D73533
D4DB603833983F8B4263F1C0E09ED757

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.



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APPROVAL LETTER

APPLICATION #
19/224,580

FILING DATE
05/30/2025

APPLICANT/PATENT UNDER REEXAMINATION
Neil COWEN

Title of Invention

METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME

Electronic terminal disclaimer filed on 08/07/2025



Approved

This patent is subject to a Terminal Disclaimer

Approved / Disapproved by: Electronic Terminal Disclaimer automatically approved



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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/224,580	08/07/2025 02:20:37 PM Z ET	SLNO-034/12US 333072-2199

Title of Invention

METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1503	FILED BY	John Kozlowski
PATENT CENTER #	71740934	AUTHORIZED BY	John Kozlowski
CUSTOMER #	58249	FILING DATE	05/30/2025
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Neil M. COWEN

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 501283	E202587E21166726	John Kozlowski

FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
1814	STATUTORY DISCLAIMER, INCLUDING TERMINAL DISCLAIMER	183.00	1	183.00
TOTAL AMOUNT:				\$183.00

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

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371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

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TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A PRIOR PATENT

APPLICATION #	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET #
19224580	05/30/2025	Neil COWEN	SLNO-034/12US 333072-2199

Title of Invention

METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME



Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action



This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.

Owner	Percent interest
Essentialis, Inc.	100%
Total	100%

The owner(s) of percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number(s)

Application #	Filing Date
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as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that any such patent granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

The owner(s) of percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of prior patent number(s)

Patent #
12343348
12178823
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as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later:

- expires for failure to pay a maintenance fee;
- is held unenforceable;
- is found invalid by a court of competent jurisdiction;
- is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
- has all claims canceled by a reexamination certificate;
- is reissued; or
- is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.



Terminal disclaimer fee under 37 CFR 1.20(d) included with Electronic Terminal Disclaimer request.

Applicant claims the following entity status:

Regular Undiscounted

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I certify, in accordance with 37 CFR 1.4(d)(4) that I am: An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application

Signature	Name	Registration #
/John Kozlowski/	John Kozlowski	82124

* Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner). Form PTO/SB/96 may be used for making this certification. See MPEP 324.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor:	Neil M. COWEN	Confirmation No.:	1503
Application No.:	19/224,580	Group Art Unit:	1625
Filed:	May 30, 2025	Examiner:	Taylor V. Oh
For:	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE TO OFFICE ACTION

In response to the non-final Office Action dated July 9, 2025, to which the deadline for responding is October 9, 2025, Applicant submits the following Amendments and Remarks, and respectfully requests reconsideration of the application in view thereof.

Any extensions of time necessary to prevent abandonment of this application are hereby petitioned for under 37 C.F.R. §1.136(a), and any additional fees required (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 50-1283.

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of the claims which begins on page 3 of this paper.

Remarks begin on page 7 of this paper.

An electronic Terminal Disclaimer is submitted on even date herewith.

IN THE SPECIFICATION:

Please replace paragraph no. [0001] with the following amended paragraph. The amendments to paragraph no. [0001] are indicated by ~~striketrough~~ and underlining.

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. Patent Application No. 18/988,636, filed December 19, 2024, now U.S. Patent No. 12,343,348, which is a continuation of U.S. Patent Application No. 18/824,811, filed September 4, 2024, now U.S. Patent No. 12,178,823, which is a continuation of U.S. Patent Application No. 18/421,914, filed January 24, 2024, now U.S. Patent No. 12,109,216, which is a continuation of U.S. Patent Application No. 17/104,433, filed November 25, 2020, which is a continuation of U.S. Patent Application No. 16/573,965, filed September 17, 2019, now U.S. Patent No. 10,874,676, which is a continuation of U.S. Patent Application No. 16/041,237, filed July 20, 2018, now U.S. Patent No. 10,456,408, which is a continuation of U.S. Patent Application No. 15/671,792, filed August 8, 2017, now U.S. Patent No. 10,058,557, which is a divisional of U.S. Patent Application No. 14/940,018, filed November 12, 2015, now U.S. Patent No. 9,757,384, which claims priority to U.S. Provisional Patent Application No. 62/080,150, filed November 14, 2014, U.S. Provisional Patent Application No. 62/138,245, filed March 25, 2015, U.S. Provisional Patent Application No. 62/170,035, filed June 2, 2015, and U.S. Provisional Patent Application No. 62/221,359, filed September 21, 2015, each of which is incorporated herein in its entirety.

IN THE CLAIMS:

Set forth below in ascending order, with status identifiers, is a complete listing of all claims currently under examination. Changes to any amended claims are indicated by [[double brackets]], ~~strike through~~ and/or underlining. This listing also reflects any cancellation and/or addition of claims.

1-28. (Canceled)

29. (Previously Presented): A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising administering to said subject once per day a pharmaceutical formulation comprising an effective amount of diazoxide choline, wherein administration reduces hyperphagia and one or more food related behaviors in the subject.

30. (Previously Presented): The method of claim 29, wherein the diazoxide choline is administered for at least 10 weeks.

31. (Previously Presented): The method of claim 29, wherein the diazoxide choline is administered for one or more years.

32. (Previously Presented): The method of claim 29, wherein the once-daily administration of diazoxide choline is in an amount from 25 mg to 100 mg.

33. (Previously Presented): The method of claim 29, wherein the once-daily administration of diazoxide choline is in an amount from 50 mg to 180 mg.

34. (Previously Presented): The method of claim 29, wherein the once-daily administration of diazoxide choline is in an amount from 50 mg to 275 mg.

35. (Previously Presented): The method of claim 29, wherein the once-daily administration of diazoxide choline is in an amount from 300 mg to 500 mg.
36. (Previously Presented): The method of claim 29, wherein the once-daily administration of diazoxide choline is in an amount from 500 mg to 2000 mg.
37. (Previously Presented): The method of claim 29, wherein the once-daily administration of diazoxide choline is in an amount from 25 mg to 500 mg.
38. (Previously Presented): The method of claim 31, wherein the once-daily administration of diazoxide choline is in an amount from 25 mg to 100 mg.
39. (Previously Presented): The method of claim 31, wherein the once-daily administration of diazoxide choline is in an amount from 50 mg to 180 mg.
40. (Previously Presented): The method of claim 31, wherein the once-daily administration of diazoxide choline is in an amount from 50 mg to 275 mg.
41. (Previously Presented): The method of claim 31, wherein the once-daily administration of diazoxide choline is in an amount from 300 mg to 500 mg.
42. (Previously Presented): The method of claim 31, wherein the once-daily administration of diazoxide choline is in an amount from 500 mg to 2000 mg.
43. (Previously Presented): The method of claim 31, wherein the once-daily administration of diazoxide choline is in an amount from 25 mg to 500 mg.

44. (Previously Presented): The method of claim 29, wherein the administration of diazoxide choline is initiated at a starting dose of diazoxide choline and then titrated every two weeks to reach a maintenance dose of diazoxide choline.
45. (Previously Presented): The method of claim 44, wherein the starting dose of diazoxide choline is between 25-100 mg of diazoxide choline.
46. (Previously Presented): The method of claim 44, wherein the starting dose of diazoxide choline is between 50-180 mg of diazoxide choline.
47. (Previously Presented): The method of claim 45, wherein the maintenance dose of diazoxide choline is between 100-200 mg of diazoxide choline.
48. (Previously Presented): The method of claim 46, wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline.
49. (Previously Presented): The method of claim 46, wherein the maintenance dose of diazoxide choline is between 300-500 mg of diazoxide choline.
50. (Previously Presented): The method of claim 46, wherein the maintenance dose of diazoxide choline is between 500-2000 mg of diazoxide choline.
51. (Previously Presented): The method of claim 46, wherein the maintenance dose of diazoxide choline is between 100-500 mg of diazoxide choline.
52. (Previously Presented): The method of claim 45, wherein the maintenance dose of diazoxide choline is between 25-250 mg of diazoxide choline.

53. (Previously Presented): The method of claim 45, wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline.

54. (Canceled)

55. (Currently Amended): The method of claim ~~[[54]]~~29, wherein the pharmaceutical formulation is administered orally.

REMARKS

Claims 29-55 were pending in the present application. Upon entry of these amendments claims 29-53 and 55 will be under consideration. Claims 1-28 were previously canceled, without prejudice or disclaimer. In this response, claim 55 is amended and claim 54 is canceled without prejudice or disclaimer. No claims are added. Support for the claim amendments can be found throughout the application as originally filed, including the claims. Claim 55 is amended to update the claim dependency in light of the cancellation of claim 54, on which claim 55 previously depended. No new matter is added.

The claims as presently presented total fewer than 30 claims and four independent claims. The claims as amended are therefore compliant with Track One examination requirements.

Amendment and cancellation of certain claims is not to be construed as a dedication to the public of any of the subject matter of the claims as previously presented. Applicant expressly reserves the right to pursue the presently unclaimed subject matter disclosed in the present application in one or more divisional and/or continuation applications or in an application claiming benefit of the present application.

Entry and consideration of the amendments is respectfully requested.

Amendment to the Specification

The “Cross Reference to Related Applications” section of the specification has been amended to reflect the patented status of the parent application. No new matter is added.

Double Patenting

A. Claims 29-53 stand rejected on the ground of statutory double patenting (35 U.S.C. §101) as allegedly claiming the same invention as claims 1-25 of U.S. Patent No. 12,343,348. Applicant respectfully disagrees.

As an initial matter, Applicant notes that at page 6 of the Office Action dated July 9, 2025, the Examiner indicates pending claim 29 to be as shown below:

Similarly, the current claims 29 and 54-55 do disclose the following method as shown below:

29. (New): A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising orally administering to said subject once per day a pharmaceutical formulation comprising an effective amount of diazoxide choline, wherein administration reduces hyperphagia and ~~one or more aggressive behaviors in the subject.~~

54. (New): The method of claim 29, wherein the one or more food related behaviors is an aggressive behavior.

55. (New): The method of claim 54, wherein the pharmaceutical formulation is administered orally.

(Office Action, page 6, Emphasis Added)

However, the claim indicated on page 6 of the Office Action is not presently pending claim 29. Claim 29 of the present application instead recites (emphasis added):

29. (Previously Presented): A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising administering to said subject once per day a pharmaceutical formulation comprising an effective amount of diazoxide choline, wherein administration reduces hyperphagia and **one or more food related behaviors** in the subject.

The claim presented as claim 29 by the Examiner is, in fact, claim 1 of U.S. Patent No. 12,343,348. During prosecution of the parent application USSN 18/988,636, which granted as U.S. Patent No. 12,343,348, issued claim 1 was also numbered as claim 29 (*i.e.*, the claim appearing on page 6 of the Office Action and shown above).

Thus, it appears that the Examiner's statutory double patenting rejection may have been based on a comparison of claim 29 presented on page 6 of the Office Action with issued claim 1 of U.S. Patent No. 12,343,348. These two claims are indeed the same claim (pending vs. issued).

In the interest of compact prosecution, Applicant additionally notes that pending claim 29 of the present application recites that "administration reduces hyperphagia and **one or more food related behaviors**" whereas issued claim 1 of U.S. Patent No. 12,343,348 recites that "administration reduces hyperphagia and **one or more aggressive behaviors**," and that PWS subjects may exhibit aggressive behaviors that are food related behaviors or not food related behaviors. Thus, the scope of "one or more food related behaviors" and "one or more aggressive behaviors" are not identical within the meaning of 35 U.S.C. §101.

For at least the reasons discussed above, Applicant respectfully requests that the statutory double patenting rejection of claim 29, and claims 30-53, which ultimately depend from claim 29, be withdrawn.

B. Claims 29 and 54-55 stand rejected on the ground of non-statutory double patenting as allegedly being unpatentable over claims 1, 3, 6-7, 12-13, and 16-24 of U.S. Patent No. 12,178,823.

As noted above, claim 54 is canceled, thereby rendering this rejection moot with respect to claim 54.

Without conceding to the propriety of the rejection and solely in the interest of expediting prosecution, Applicant submits herewith an electronic Terminal Disclaimer over U.S. Patent Nos. 12,343,348 and 12,178,823. The electronic Terminal Disclaimer is also over U.S. Patent No. 9,757,384.

For at least this reason, Applicant respectfully requests that the non-statutory double patenting rejection of claims 29 and 55 be withdrawn. As noted above, claim 54 is canceled rendering the rejection moot.

Regarding the Information Disclosure Statement (IDS)

Applicant thanks the Examiner for reviewing the IDS filed June 3, 2025 and return of the initialed SB/08.

Request for Examiner Teleconference

In light of the amendments and remarks presented herein, along with the filing of the above-referenced Terminal Disclaimer, Applicant has endeavored to address each of the Examiner's rejections and objections. However, if the Examiner identifies any further issues, he is urgent to contact the undersigned at the number below or Dr. Kimberly Bolin (Reg. No. 44,546) at (650) 843-5387.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejections of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

Any remarks in support of patentability of one claim should not be imputed to any other claim, even if similar terminology is used. Additionally, any remarks referring to only a portion of a claim should not be understood to base patentability on that portion; rather, patentability must rest on each claim taken as a whole. Applicant respectfully traverses each of the Examiner's rejections and each of the Examiner's assertions regarding what the prior art shows or teaches, even if not expressly discussed herein. Although amendments have been made, no acquiescence or estoppel is or should be implied thereby. Rather, the amendments are made only to expedite prosecution of the present application, and without prejudice to presentation or assertion, in the future, of claims on the subject matter affected thereby.

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child, or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Director to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 50-1283 referencing Docket No. SLNO-034/12US 333072-2199. However, the Director is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: August 7, 2025

Respectfully submitted,
COOLEY LLP

USPTO CUSTOMER No. 58249

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By: /John Kozlowski/
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UNITED STATES
PATENT AND TRADEMARK OFFICEP.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov**ELECTRONIC ACKNOWLEDGEMENT RECEIPT**APPLICATION #
19/224,580RECEIPT DATE / TIME
08/07/2025 02:58:26 PM Z ETATTORNEY DOCKET #
SLNO-034/12US 333072-2199**Title of Invention**

METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1503	FILED BY	Diana Sciamanna
PATENT CENTER #	71742535	FILING DATE	05/30/2025
CUSTOMER #	58249	FIRST NAMED INVENTOR	Neil M. COWEN
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	John Kozlowski

Documents**TOTAL DOCUMENTS: 4**

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
Response.pdf		12	-	328 KB
Response-A....pdf	(1-1)	1	Amendment/Request for Reconsideration-After Non- Final Rejection	123 KB
Response-SPEC.pdf	(2-2)	1	Specification	131 KB
Response-CLM.pdf	(3-6)	4	Claims	134 KB
Response-REM.pdf	(7-12)	6	Applicant Arguments/Remarks Made in an Amendment	318 KB

Digest**DOCUMENT****MESSAGE DIGEST(SHA-512)**

APOTEX_EX1015_PGR2026-00034_Page 255

Response.pdf	664D70D7204AC744717F4D0CCE8012F7E4520D7D944E22BD D2D9037B93AC7AB3B3AD673F605A91FCB19CD524E7F845F0 8DA44AB1098C84C1FCC1967CC64185E8
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Response-REM.pdf	3DAD791FCFE86E53D3FE930C01AEC3223DE2CECDCDA0704 6261558CD441756231588A1998CEEAC0BB02216A4F16D635F 4391B1DD0ACC81D7657B46CDD9CFFC6B

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If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

58249 7590 08/22/2025
COOLEY LLP
ATTN: IP Docketing Department
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

EXAMINER	
OH, TAYLOR V	
ART UNIT	PAPER NUMBER

1625

DATE MAILED: 08/22/2025

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
19/224,580	05/30/2025	Neil M. COWEN	SLNO-034/12US 333072-2199	1503

TITLE OF INVENTION: METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1290	\$0.00	\$0.00	\$1290	11/24/2025

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

58249 7590 08/22/2025

COOLEY LLP
ATTN: IP Docketing Department
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
19/224,580	05/30/2025	Neil M. COWEN	SLNO-034/12US 333072-2199	1503

TITLE OF INVENTION: METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1290	\$0.00	\$0.00	\$1290	11/24/2025

EXAMINER	ART UNIT	CLASS-SUBCLASS
OH, TAYLOR V	1625	514-005100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

1 _____

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☐ Issue Fee ☐ Publication Fee (if required)

4b. Method of Payment: (Please first reapply any previously paid fee shown above)

☐ Electronic Payment via the USPTO patent electronic filing system ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. Change in Entity Status (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____

Date _____

Typed or printed name _____

Registration No. _____



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
19/224,580	05/30/2025	Neil M. COWEN	SLNO-034/12US 333072-2199	1503
58249	7590	08/22/2025	EXAMINER OH, TAYLOR V	
COOLEY LLP ATTN: IP Docketing Department 1299 Pennsylvania Avenue, NW Suite 700 Washington, DC 20004			ART UNIT 1625	PAPER NUMBER
DATE MAILED: 08/22/2025				

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).

<https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf>

Routine uses of the information in this record may include disclosure to:

- 1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;
- 2) a federal, state, local, or international agency, in response to its request;
- 3) a contractor of the USPTO having need for the information in order to perform a contract;
- 4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;
- 5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;
- 6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
- 7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;
- 8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c));
- 9) the Office of Personnel Management (OPM) for personnel research purposes; and
- 10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

Notice of Allowability	Application No. 19/224,580	Applicant(s) COWEN, Neil M.	
	Examiner TAYLOR V OH	Art Unit 1625	AIA (First Inventor to File) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to 8/7/25.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are 29-53 and 55 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information , please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

- a) ☐ All b) ☐ Some* c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
 3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.

THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .
Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

- | | |
|---|--|
| 1. ☐ Notice of References Cited (PTO-892) | 5. ☐ Examiner's Amendment/Comment |
| 2. ☐ Information Disclosure Statements (PTO/SB/08),
Paper No./Mail Date _____. | 6. ☒ Examiner's Statement of Reasons for Allowance |
| 3. ☐ Examiner's Comment Regarding Requirement for Deposit
of Biological Material _____. | 7. ☐ Other _____. |
| 4. ☐ Interview Summary (PTO-413),
Paper No./Mail Date _____. | |

/TAYLOR V OH/
Primary Examiner, Art Unit 1625

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Reasons of Allowance

The Status of Claims:

Claims 29-53, and 55 are pending.

Claims 29-53, and 55 are allowed.

I. The following is an examiner's statement of reasons for allowance:

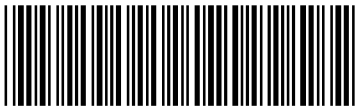
- The rejection of Claims 29-53 under 35 U.S.C. 101 as claiming the same invention as that of claims 1-25 of prior U.S. Patent No.12,343,348 B2 is withdrawn due to applicant's convincing arguments .
- The rejection of Claims 29 and 54-55 on the ground of nonstatutory double patenting as being unpatentable over claims 1,3, 6-7, 12-13, 16-24 of U.S. Patent No. 12,178,823 B1 is withdrawn due to filing the Terminal Disclaimer on 8/07/25.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning the communication after allowance such as sending all post-allowance correspondence should be directed to “ Box Issue Fee” or faxed directly to PUBS at 703-305-8755. This will expedite the process of these papers.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/TAYLOR V OH/
Primary Examiner, Art Unit 1625
8/14/2025

Issue Classification 	Application/Control No. 19/224,580	Applicant(s)/Patent Under Reexamination COWEN, Neil M.	
	Examiner TAYLOR V OH	Art Unit 1625	

CPC						
Symbol					Type	Version
A61K	/	31	/	549	F	2013-01-01
A61K	/	9	/	2054	I	2013-01-01
A61K	/	9	/	5047	I	2013-01-01
C07D	/	285	/	18	I	2013-01-01
C07D	/	285	/	22	I	2013-01-01
A61K	/	38	/	27	I	2013-01-01
A61K	/	45	/	06	I	2013-01-01
A61K	/	31	/	137	I	2013-01-01
A61K	/	31	/	155	I	2013-01-01
A61K	/	31	/	551	I	2013-01-01
A61K	/	9	/	00	I	2013-01-01
A61K	/	9	/	5026	I	2013-01-01
A61K	/	9	/	5042	I	2013-01-01
A61K	/	9	/	0004	I	2013-01-01
A61K	/	2300	/	00	A	2013-01-01

CPC Combination Sets				
Symbol	Type	Set	Ranking	Version
/				

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	26	
/TAYLOR V OH/ Primary Examiner, Art Unit 1625	14 August 2025	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	29	1

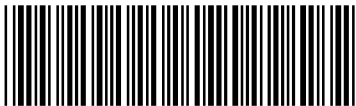
<i>Issue Classification</i> 	Application/Control No. 19/224,580	Applicant(s)/Patent Under Reexamination COWEN, Neil M.
	Examiner TAYLOR V OH	Art Unit 1625

INTERNATIONAL CLASSIFICATION			
CLAIMED			
A61K	/	31	/ 549
NON-CLAIMED			
/		/	

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS
514	5.1

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	26	
/TAYLOR V OH/ Primary Examiner, Art Unit 1625	14 August 2025	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	29	1

Issue Classification 	Application/Control No. 19/224,580	Applicant(s)/Patent Under Reexamination COWEN, Neil M.
	Examiner TAYLOR V OH	Art Unit 1625

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47															
CLAIMS															
Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	29	10	38	19	47										
2	30	11	39	20	48										
3	31	12	40	21	49										
4	32	13	41	22	50										
5	33	14	42	23	51										
6	34	15	43	24	52										
7	35	16	44	25	53										
8	36	17	45	26	55										
9	37	18	46												

NONE (Assistant Examiner) _____ (Date) _____		Total Claims Allowed: 26	
/TAYLOR V OH/ Primary Examiner, Art Unit 1625 (Primary Examiner) _____ (Date) 14 August 2025		O.G. Print Claim(s) 29	O.G. Print Figure 1

Search Notes 	Application/Control No. 19/224,580	Applicant(s)/Patent Under Reexamination COWEN, Neil M.
	Examiner TAYLOR V OH	Art Unit 1625

CPC - Searched*		
Symbol	Date	Examiner
C07D285/18 , C07D285/22 , A61K2300/00	08/14/2025	t.o.
A61K9/5026 , A61K9/5042 , A61K9/5047 , A61K31/137	08/14/2025	t.o.
A61K31/155 , A61K31/551 , A61K38/27 , A61K45/06	08/14/2025	t.o.
(A61K31/549 , A61K9/00 , A61K9/0004 , A61K9/2054	08/14/2025	t.o.

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
514	5.100	08/14/2025	t.o.

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
PE2E search including cpc classes/subclasses limited by the text search updated p.4	08/14/2025	t.o.
STNext search updated .p.1	08/14/2025	t.o.

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
514/A61K	5.100/31/549	08/14/2025	t.o.

/TAYLOR V OH/ Primary Examiner, Art Unit 1625	
--	--

Bibliographic Data

Application No: 19/224,580

Foreign Priority claimed: ☐ Yes ☒ No

35 USC 119 (a-d) conditions met: ☐ Yes ☒ No ☐ Met After Allowance

Verified and Acknowledged:

/TAYLOR V OH/

Examiner's Signature

Initials

Title:

METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
05/30/2025	514	1625	SLNO-034/12US 333072-2199
RULE			

APPLICANTS

Essentialis, Inc., Redwood City, CA, UNITED STATES

INVENTORS

Neil M. COWEN, Carlsbad, CA, UNITED STATES

CONTINUING DATA

This application is a CON of 18988636 12/19/2024 PAT 12343348

18988636 is a CON of 18824811 09/04/2024 PAT 12178823

18824811 is a CON of 18421914 01/24/2024 PAT 12109216

18421914 is a CON of 17104433 11/25/2020ABN

17104433 is a CON of 16573965 09/17/2019 PAT 10874676

16573965 is a CON of 16041237 07/20/2018 PAT 10456408

16041237 is a CON of 15671792 08/08/2017 PAT 10058557

15671792 is a DIV of 14940018 11/12/2015 PAT 9757384

14940018 has PRO of 62221359 09/21/2015

14940018 has PRO of 62170035 06/02/2015

14940018 has PRO of 62138245 03/25/2015

14940018 has PRO of 62080150 11/14/2014

FOREIGN APPLICATIONS

IF REQUIRED, FOREIGN LICENSE GRANTED**

06/11/2025

STATE OR COUNTRY

UNITED STATES

ADDRESS

COOLEY LLP

ATTN: IP Docketing Department

1299 Pennsylvania Avenue, NW

Suite 700

Washington, DC 20004

UNITED STATES

FILING FEE RECEIVED

\$11,095

d his

(FILE 'HOME' ENTERED AT 19:16:25 ON 14 AUG 2025)

FILE 'REGISTRY' ENTERED AT 19:16:32 ON 14 AUG 2025

L1 1 S DIAZOXIDE/CN
L2 1 S CHOLINE/CN

FILE 'HCAPLUS' ENTERED AT 19:17:51 ON 14 AUG 2025

S DIAZOXIDE OR 364-98-7/REG#

FILE 'REGISTRY' ENTERED AT 19:18:51 ON 14 AUG 2025

L3 1 S 364-98-7/RN

FILE 'HCAPLUS' ENTERED AT 19:18:51 ON 14 AUG 2025

L4 2322 S L3
L5 3920 S DIAZOXIDE OR L4
S CHOLINE OR 62-49-7/REG#

FILE 'REGISTRY' ENTERED AT 19:19:40 ON 14 AUG 2025

L6 1 S 62-49-7/RN

FILE 'HCAPLUS' ENTERED AT 19:19:40 ON 14 AUG 2025

L7 32534 S L6
L8 110363 S CHOLINE OR L7
L9 32534 S L7 AND L8
L10 0 S L9 AND PY,2014
L11 0 S L9 AND (PWE OR PRADER WILLI SYNDROME)
L12 0 S L9 AND (PWS OR PRADER WILLI SYNDROME)

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	2076890	(A61K31/549 OR A61K9/00 OR A61K9/0004 OR A61K9/2054 OR A61K9/5026 OR A61K9/5042 OR A61K9/5047 OR A61K31/137 OR A61K31/155 OR A61K31/551 OR A61K38/27 OR A61K45/06 OR C07D285/18 OR C07D285/22 OR A61K2300/00).cpc. OR 514/\$.ccls.	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/08/14 07:26 PM
L2	7910834	Essentialis, Inc.as. OR Neil M. COWEN.in.	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/08/14 07:27 PM
L3	201872	L1 AND L2	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	AND	ON	ON	2025/08/14 07:27 PM
L4	351	L1 AND L2 AND TREATING SUBJECTS WITH PRADER-WILLI	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY,	AND	ON	ON	2025/08/14 07:28 PM

		SYNDROME OR SMITH-MAGENIS SYNDROME AND diazoxide AND choline AND hyperphagia	CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L5	1404	L1 AND TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME AND diazoxide AND choline AND aggressive behavior\$3 AND hyperphagia	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	AND	ON	ON	2025/08/14 07:29 PM
L6	46	L1 AND (TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME) AND diazoxide AND choline AND aggressive behavior\$3 AND hyperphagia	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	AND	ON	ON	2025/08/14 07:30 PM

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N1	501031	(A61K31/549 OR A61K9/00 OR A61K9/0004 OR A61K9/2054 OR A61K9/5026 OR A61K9/5042 OR	(US-PGPUB; USPAT)	OR	ON	ON	2025/08/14 07:30 PM

		A61K9/5047 OR A61K31/137 OR A61K31/155 OR A61K31/551 OR A61K38/27 OR A61K45/06 OR C07D285/18 OR C07D285/22 OR A61K2300/00).cpc. OR 514/\$.ccls.					
N2	2897510	Essentialis, Inc.as. OR Neil M. COWEN.in.	(US-PGPUB; USPAT)	OR	ON	ON	2025/08/14 07:30 PM
N3	26	((A61K31/549 OR A61K9/00 OR A61K9/0004 OR A61K9/2054 OR A61K9/5026 OR A61K9/5042 OR A61K9/5047 OR A61K31/137 OR A61K31/155 OR A61K31/551 OR A61K38/27 OR A61K45/06 OR C07D285/18 OR C07D285/22 OR A61K2300/00).cpc. OR 514/\$.ccls.) AND (Essentialis, Inc.as. OR Neil M. COWEN.in.)	(US-PGPUB; USPAT)	AND	ON	ON	2025/08/14 07:31 PM
N4	24	((A61K31/549 OR A61K9/00 OR A61K9/0004 OR A61K9/2054 OR A61K9/5026 OR A61K9/5042 OR A61K9/5047 OR A61K31/137 OR A61K31/155 OR A61K31/551 OR A61K38/27 OR A61K45/06 OR C07D285/18 OR C07D285/22 OR A61K2300/00).cpc. OR 514/\$.ccls.) AND (Essentialis, Inc.as. OR Neil M. COWEN.in.) AND TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME AND diazoxide AND choline AND hyperphagia	(US-PGPUB; USPAT)	AND	ON	ON	2025/08/14 07:31 PM

N5	667	((A61K31/549 OR A61K9/00 OR A61K9/0004 OR A61K9/2054 OR A61K9/5026 OR A61K9/5042 OR A61K9/5047 OR A61K31/137 OR A61K31/155 OR A61K31/551 OR A61K38/27 OR A61K45/06 OR C07D285/18 OR C07D285/22 OR A61K2300/00).cpc. OR 514/\$.ccls.) AND TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME AND diazoxide AND choline AND aggressive behavior\$3 AND hyperphagia	(US-PGPUB; USPAT)	AND	ON	ON	2025/08/14 07:31 PM
N6	16	((A61K31/549 OR A61K9/00 OR A61K9/0004 OR A61K9/2054 OR A61K9/5026 OR A61K9/5042 OR A61K9/5047 OR A61K31/137 OR A61K31/155 OR A61K31/551 OR A61K38/27 OR A61K45/06 OR C07D285/18 OR C07D285/22 OR A61K2300/00).cpc. OR 514/\$.ccls.) AND (TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME) AND diazoxide AND choline AND aggressive behavior\$3 AND hyperphagia	(US-PGPUB; USPAT)	AND	ON	ON	2025/08/14 07:31 PM



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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/224,580	08/25/2025 05:56:05 PM Z ET	SLNO-034/12US 333072-2199

Title of Invention

METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1503	FILED BY	Diana Sciamanna
PATENT CENTER #	72007772	FILING DATE	05/30/2025
CUSTOMER #	58249	FIRST NAMED INVENTOR	Neil M. COWEN
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	John Kozlowski

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
Issue_Fee.pdf	1	Issue Fee Payment (PTO-85B)	168 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
Issue_Fee.pdf	2CF7A46477E8877940B87E3023F3849A6EDF191F286C37F17B A0FAFE7902B6582481001A0A2A8ADF24D1D0F044621B0C389 E0F57C91EA649F2386258E5F4F989

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

APOTEX_EX1015_PGR2026-00034_Page 275

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.



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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/224,580	08/25/2025 05:56:05 PM Z ET	SLNO-034/12US 333072-2199

Title of Invention

METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1503	FILED BY	Diana Sciamanna
PATENT CENTER #	72007772	AUTHORIZED BY	John Kozlowski
CUSTOMER #	58249	FILING DATE	05/30/2025
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Neil M. COWEN

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 501283	E20258OH56486627	Diana Sciamanna

FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
1501	UTILITY ISSUE FEE	1290.00	1	1290.00
TOTAL AMOUNT:				\$1,290.00

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

58249 7590 08/22/2025

COOLEY LLP

ATTN: IP Docketing Department
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
19/224,580	05/30/2025	Neil M. COWEN	SLNO-034/12US 333072-2199	1503

TITLE OF INVENTION: METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1290	\$0.00	\$0.00	\$1290	11/24/2025

EXAMINER	ART UNIT	CLASS-SUBCLASS
OH, TAYLOR V	1625	514-005100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Cooley LLP

2

3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

ESSENTIALIS, INC.

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

REDWOOD CITY, CALIFORNIA

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☒ Issue Fee ☐ Publication Fee (if required)

4b. Method of Payment: (Please first reapply any previously paid fee shown above)

☒ Electronic Payment via the USPTO patent electronic filing system ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. **50-1283**

5. Change in Entity Status (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /John Kozlowski/

Date August 25, 2025

Typed or printed name John Kozlowski

Registration No. 82,124



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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
19/224,580	09/23/2025	12419895	SLNO-034/12US 333072-2199	1503

58249 7590 09/10/2025
COOLEY LLP
ATTN: IP Docketing Department
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

ISSUE NOTIFICATION

The projected patent number and issue date are specified above. The patent will issue electronically. The electronically issued patent is the official patent grant pursuant to 35 U.S.C. § 153. The patent may be accessed on or after the issue date through Patent Center at <https://patentcenter.uspto.gov/>. The patent will be available in both the public and the private sides of Patent Center. Further assistance in electronically accessing the patent, or about Patent Center, is available by calling the Patent Electronic Business Center at 1-888-217-9197.

The USPTO is implementing electronic patent issuance with a transition period, during which period the USPTO will mail a ceremonial paper copy of the electronic patent grant to the correspondence address of record. Additional copies of the patent (i.e., certified and presentation copies) may be ordered for a fee from the USPTO's Certified Copy Center at <https://certifiedcopycenter.uspto.gov/index.html>. The Certified Copy Center may be reached at (800)972-6382.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Center (<https://patentcenter.uspto.gov>).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Patents Stakeholder Experience (OPSE), Stakeholder Support Division (SSD) at (571)-272-4200.

INVENTOR(s) (Please see PATENT CENTER site <https://patentcenter.uspto.gov> for additional inventors):

Neil M. COWEN, Carlsbad, CA;

APPLICANT(s) (Please see PATENT CENTER site <https://patentcenter.uspto.gov> for additional applicants):

Essentialis, Inc., Redwood City, CA;

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
19/224,580	05/30/2025	Neil M. COWEN	SLNO-034/12US 333072-2199

CONFIRMATION NO. 1503

58249
COOLEY LLP
ATTN: IP Docketing Department
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

PUBLICATION NOTICE



OC00000094680645

Date Mailed: 09/18/2025

Title:METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME

Publication No.US-2025-0288593-A1

Publication Date:09/18/2025

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be viewed using the USPTO's publicly available Searchable Databases via the Patent Public Search tool at www.uspto.gov. The direct link to access the Patent Public Search tool is currently <https://ppubs.uspto.gov/pubwebapp/static/pages/ppubsbasic.html>.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through Patent Center, the USPTO's electronic patent application filing and management system. The direct link to access this status information is currently <https://patentcenter.uspto.gov/>. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of Patent Center.

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Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
19/224,580	05/30/2025	Neil M. COWEN	SLNO-034/12US 333072-2199	1503
58249	7590	09/23/2025	EXAMINER	
COOLEY LLP			OH, TAYLOR V	
ATTN: IP Docketing Department			ART UNIT	
1299 Pennsylvania Avenue, NW			PAPER NUMBER	
Suite 700			1625	
Washington, DC 20004			NOTIFICATION DATE	
			DELIVERY MODE	
			09/23/2025	
			ELECTRONIC	

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

zIPPatentDocketingMailboxUS@cooley.com



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UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	ISSUE DATE	PATENT NO.
19/224,580	23-Sep-2025	12419895

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