

[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 improves insulin sensitivity 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 an anti-inflammatory 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 lowers circulating triglycerides to an overweight, obesity prone or obese individual to induce weight loss and treat obesity associated comorbidities.

[00371] 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.

[00372] 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.

[00373] 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.

[00374] 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.

[00375] 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.

[00376] 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.

[00377] 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.

[00378] 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.

[00379] 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.

[00380] 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.

[00381] 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.

[00382] 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.

[00383] 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.

[00384] 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.

[00385] 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.

[00386] 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.

[00387] 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.

[00388] 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.

[00389] 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.

[00390] 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.

[00391] 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

[00392] 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.

[00393] 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

[00394] 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

[00395] 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

[00396] 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.

[00397] 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*

[00398] 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.

[00399] 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.

[00400] 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.).

[00401] 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.

[00402] 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.

[00403] 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

[00404] 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

[00405] 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*

[00406] 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.

[00407] 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.

[00408] 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.

[00409] 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.

[00410] 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*

[00411] 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.

[00412] 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.

[00413] 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*

[00414] 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.

[00415] 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

[00416] 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.

[00417] 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/m^2)) 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

[00418] 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

[00419] 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.

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

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

[00420] 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.

[00421] 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.

[00422] 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

[00423] 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.

[00424] 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 tn*	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

[00425] 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

[00426] 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.

[00427] 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

[00428] 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.

[00429] 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.

[00430] 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.

[00431] 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.

[00432] 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

[00433] 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

[00434] 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

[00435] 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.

[00436] 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.

[00437] 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.

[00438] 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.

[00439] Figure 1 shows the change in hyperphagia from Baseline through Day 69.

Changes in Lipids

[00440] 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%

[00441] 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

[00442] 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

[00443] 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.

[00444] While ghrelin may or may not contribute substantially to hyperphagia in PWS, reductions in ghrelin are beneficial in PWS patients.

Behavioral Changes

[00445] 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%	

[00446] The impact on aggressive, threatening and destructive behaviors was independent of an impact on hyperphagia.

Changes in Resting Energy Expenditure and Respiratory quotient

[00447] 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

[00448] 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

[00449] 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.

[00450] 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.

[00451] 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.

[00452] 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.

[00453] 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.

[00454] 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.

[00455] 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.

[00456] 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.

[00457] Definitions provided herein are not intended to be limiting from the meaning commonly understood by one of skill in the art unless indicated otherwise.

[00458] 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.

[00459] 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.

[00460] 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.

THAT WHICH 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 K_{ATP} channel opener.
2. The method of claim 1 wherein said K_{ATP} 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 K_{ATP} 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 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.
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 K_{ATP} channel opener.

23. A kit comprising:
a unit dose of a K_{ATP} 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 K_{ATP} 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 K_{ATP} 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.

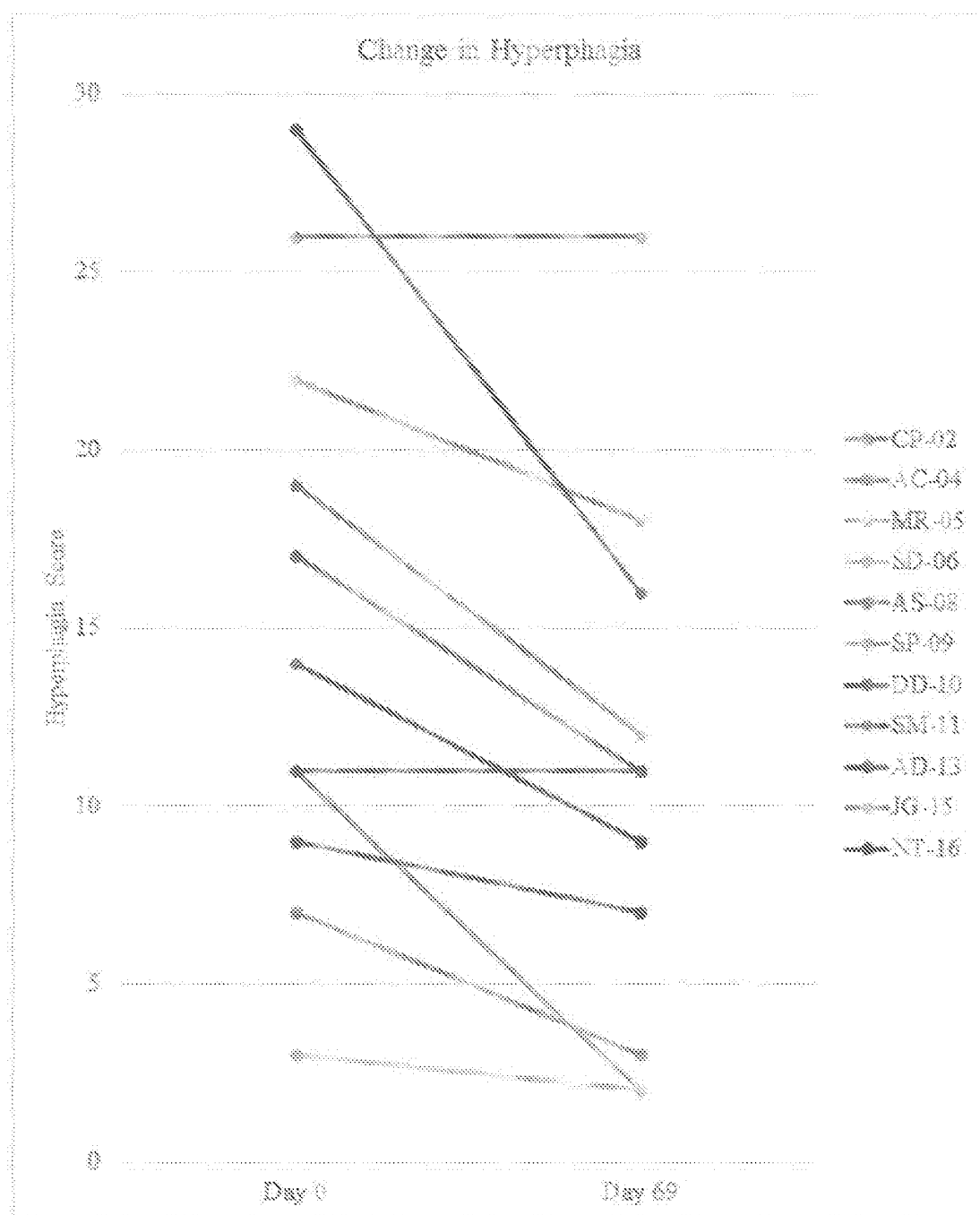


Figure 1

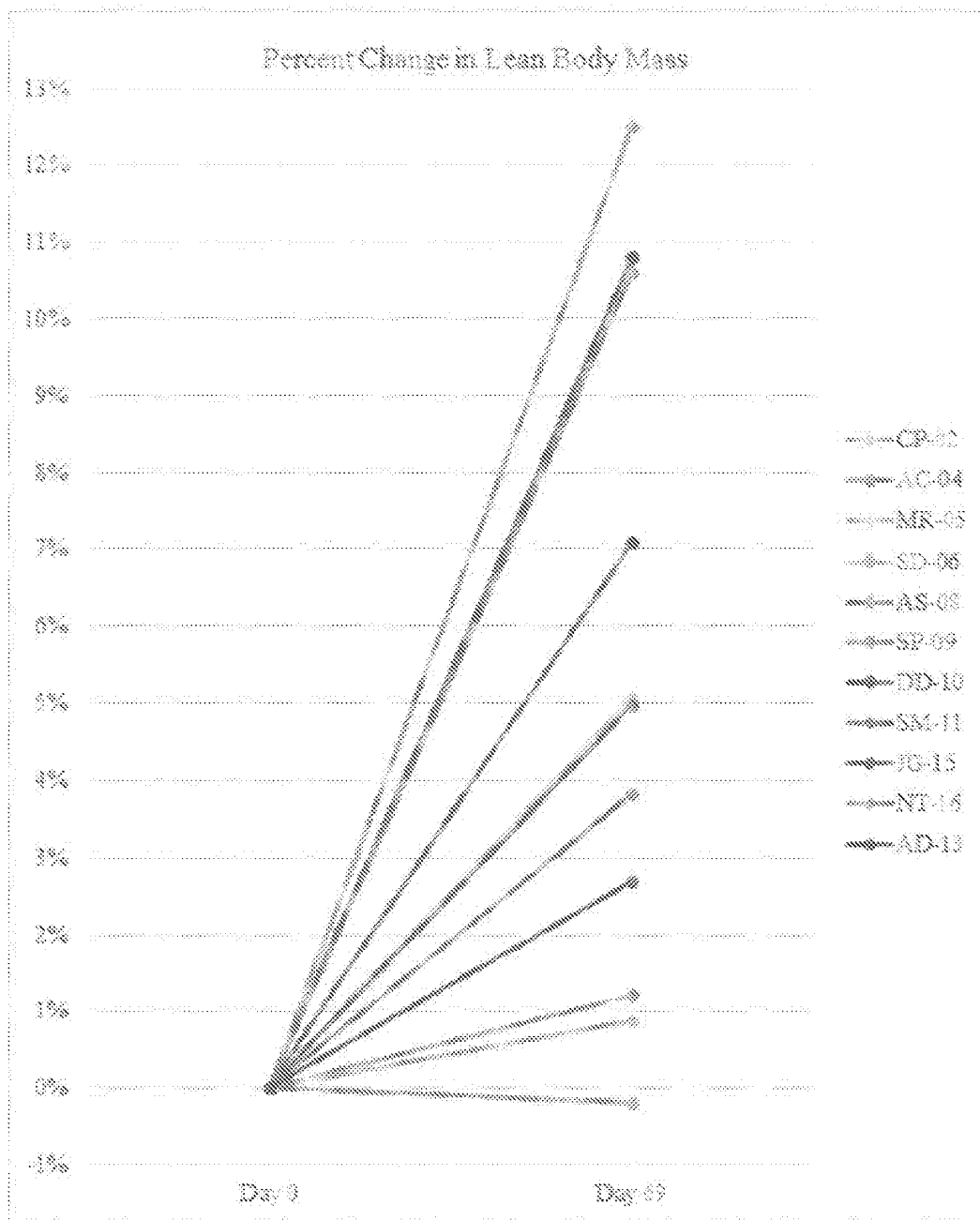


Figure 2

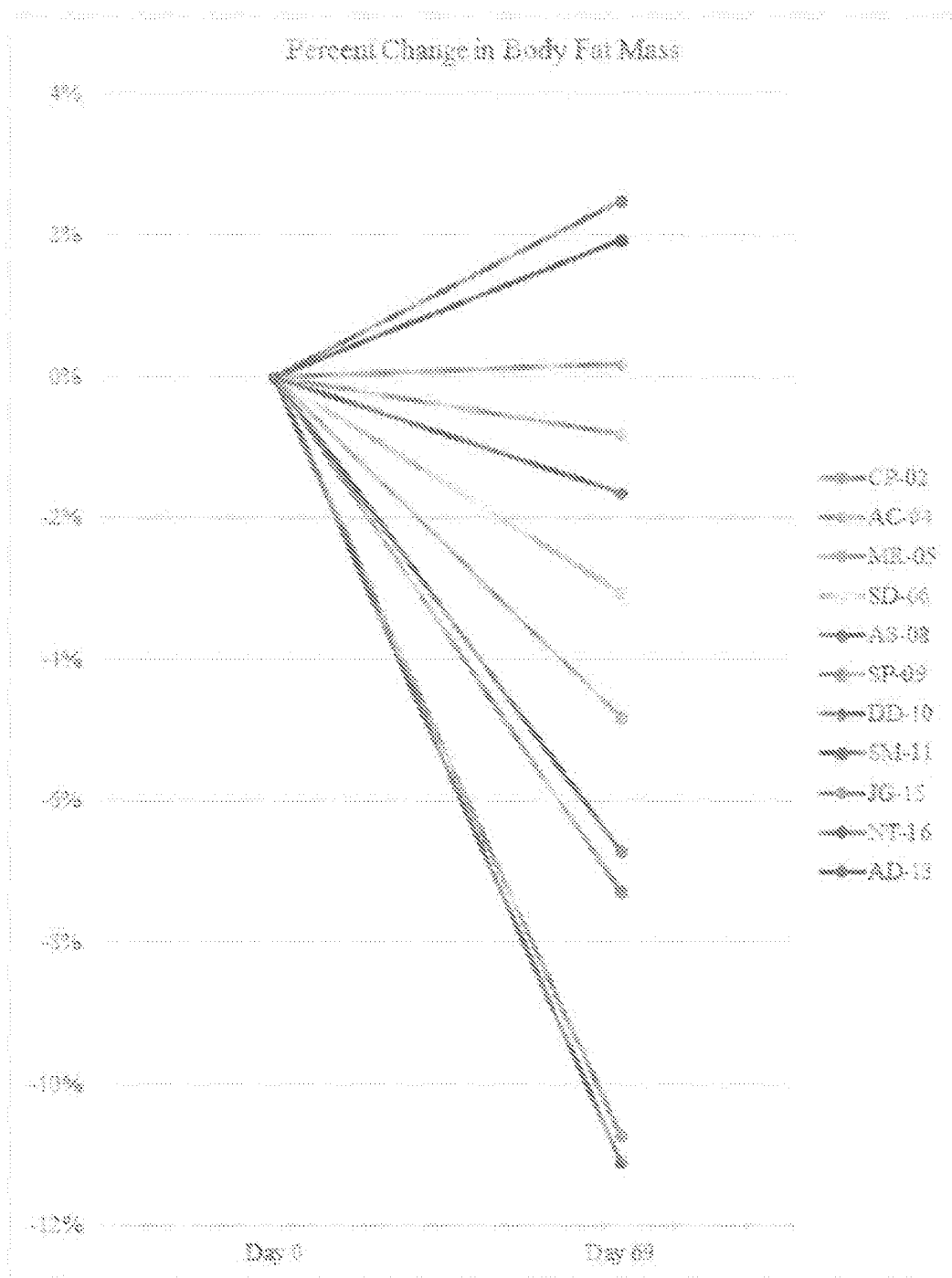


Figure 3

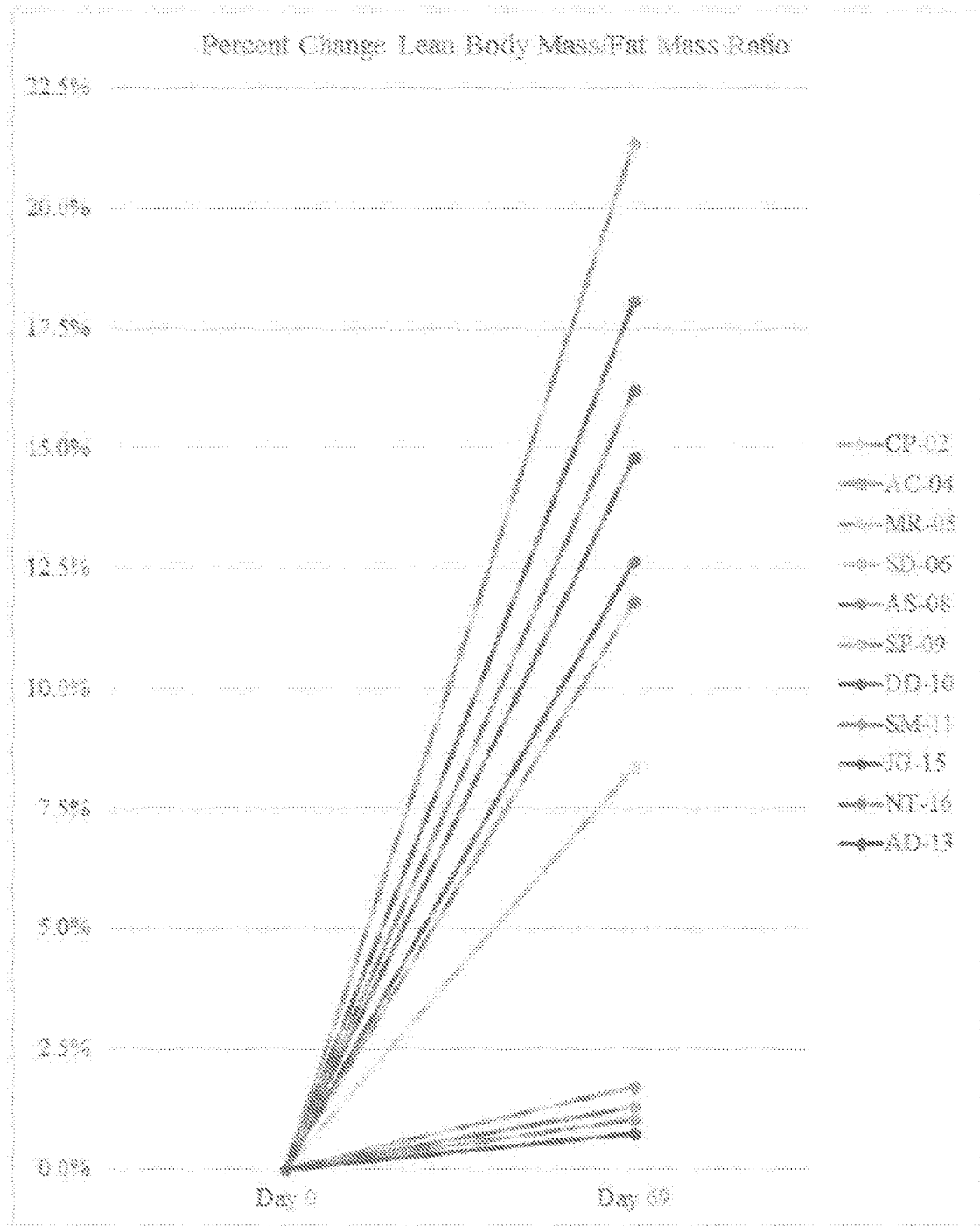


Figure 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US15/60455

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A61K 9/22, 31/54, 31/549; C07D 285/22 (2015.01) CPC - A61K 9/28, 31/54, 31/549; C07D 285/22 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC (8) - A61K 9/22, 31/54, 31/549; C07D 285/18, 285/22 (2015.01); CPC - A61K 9/28, 9/2853, 31/54, 31/549; C07D 285/18, 285/22, USPC - 424/474; 514/223.2, 223.5; 544/12 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, Other Countries (INFADOC), RU, AT, CH, IH, BR, PH), EBSCO, Google/Google Scholar, IP.com, pubmed, Prader-Willi Syndrome, PWS, Smith-Magenis Syndrome, SMS, KATP channel opener, potassium channel opener, diazoxide, choline, pharmaceutical formulation, human growth hormone, lean body mass, hyperphagia, IGF-1, kit, aggressive behaviors, hyperphrefinemia.		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y --- A	(CLINICALTRIALS.GOV) Clinical Study of Diazoxide Choline Controlled-Release Tablet (DCCR) in Patients With Prader-Willi Syndrome NCT02034071. 10 January 2014. [Retrieved on 18 December 2015]. Retrieved from the internet. URL: <https://clinicaltrials.gov/archive/NCT02034071/2014_01_10>; page 1, brief title, brief summary	1-4 --- 5-10, 15-19, 27-28 --- 11-14, 24-26
Y --- A	US 2009/0146525 A1 (COWEN, NM) 11 June 2009; paragraphs [0096], [0237]-[0238], [0240], [0246], [0264]	5-7, 27-28 --- 22
Y --- A	(EIHOLZER, U et al.) Treatment With Human Growth Hormone in Patients With Prader-Willi Syndrome Reduces Body Fat And Increases Muscle Mass And Physical Performance. European Journal of Pediatrics. 1998, vol. 157, no. 5; page 368, second column, third paragraph; page 374, sixth-seventh paragraphs; page 375, first column, fourth paragraph; page 375, second column, fourth paragraph	8-9, 19-21, 23
Y --- A	US 2012/0053172 A1 (DE BOER, JMM) 1 March 2012; paragraphs [0034], [0036], [0086], [0099], [0100], [0102], [0105]	10, 16-18 --- 11-14, 22, 24-26
Y --- A	US 2009/0062264 A1 (COWEN, NM et al.) 5 March 2009; paragraphs [0112], [0134], [0147], [0174], [0266], [0461], [0493]-[0494]; table 1	15, 20-21, 23 --- 11-14, 22, 24-26
☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle of theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "G" document member of the same patent family		
Date of the actual completion of the international search 19 December 2015 (19.12.2015)		Date of mailing of the international search report 02 FEB 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300		Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT ISP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US16/00455

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	(BAY, HE et al.) Diazoxide Choline Controlled Release in Hyperglycemic Subjects: Lipid and Other Metabolic Effects. Journal of the American College of Cardiology. 2010. vol 55, no. 10a. [Retrieved on 16 December 2015]. Retrieved from the internet; URL: < https://clinicaltrials.gov/archive/NCT02034071/2014_01_10 >; abstract	11-14, 24-26
A	(EINSPIELER, C) Early Behavioural Manifestation of Smith-Magenis Syndrome (Del 17p11.2) in a 4-Month-Old Boy. Developmental Neuropsychology. 2012. vol. 15, no. 4, page 313, first column, first paragraph	22

Form PCT/ISA/210 (continuation of second sheet) (January 2015)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 0955616	FOR FURTHER ACTION see Form PCT/ISA/229 as well as, where applicable, item 5 below.	
International application No. PCT/US15/60455	International filing date (day/month/year) 12 November 2015 (12.11.2015)	(Earliest) Priority Date (day/month/year) 14 November 2014 (14.11.2014)
Applicant ESSENTIALIS, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed.
☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ Certain claims were found unsearchable (see Box No. II).

3. ☐ Unity of invention is lacking (see Box No. III).

4. With regard to the title,

- ☒ the text is approved as submitted by the applicant.
☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

- ☒ the text is approved as submitted by the applicant.
☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. 1
☐ as suggested by the applicant.
☒ as selected by this Authority, because the applicant failed to suggest a figure.
☐ as selected by this Authority, because this figure better characterizes the invention.
- b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US15/060455

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A61K 9/22, 31/54, 31/549; C07D 285/22 (2015.01) CPC - A61K 9/28, 31/54, 31/549; C07D 285/22 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC (8) - A61K 9/22, 31/54, 31/549; C07D 285/18, 285/22 (2015.01) CPC - A61K 9/28, 9/2054, 9/2853, 31/54, 31/549; C07D 285/18, 285/22, USPC - 424/474; 514/223.2, 223.5; 544/12 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PatSear (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, Other Countries (INPADOC), RU, AT, CH, IH, BR, PH), EBSCO, Google/Google Scholar, IP.com, pubmed; Prader-Willi Syndrome, PWS, Smith-Magenis Syndrome, SMS, KATP channel opener, potassium channel opener, diazoxide, choline, pharmaceutical formulation, human growth hormone, lean body mass, hyperphagia, IGF-1, fit, aggressive behaviors, hyperghrelinemia.		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y --- A	(CLINICALTRIALS.GOV) Clinical Study of Diazoxide Choline Controlled-Release Tablet (DCCR) in Patients With Prader-Willi Syndrome NCT02034071. 10 January 2014. [Retrieved on 16 December 2015]. Retrieved from the internet URL: <https://clinicaltrials.gov/archive/NCT02034071/2014_01_10>; page 1, brief title, brief summary	1-4 --- 5-10, 15-19, 27-28 --- 11-14, 24-26
Y --- A	US 2009/0148525 A1 (COWEN, NM) 11 June 2009; paragraphs [0086], [0237]-[0238], [0240], [0246], [0264]	5-7, 27-28 --- 22
Y --- A	(EIJOLZER, U et al.) Treatment With Human Growth Hormone in Patients With Prader-Willi Syndrome Reduces Body Fat And Increases Muscle Mass And Physical Performance. European Journal of Pediatrics. 1998, vol. 157, no. 5; page 368, second column, third paragraph; page 374, sixth-seventh paragraphs; page 375, first column, fourth paragraph; page 375, second column, fourth paragraph	8-8, 19-21, 23
Y --- A	US 2012/0053172 A1 (DE BOER, JMM) 1 March 2012; paragraphs [0024], [0026], [0085], [0099], [0100], [0102], [0105]	10, 16-18 --- 11-14, 22, 24-26
Y --- A	US 2009/0262264 A1 (COWEN, NM et al.) 5 March 2009; paragraphs [0112], [0134], [0147], [0174], [0268], [0461], [0493]-[0494]; table 1	15, 20-21, 23 --- 11-14, 22, 24-26
☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "Z" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
19 December 2015 (19.12.2015)		02 FEB 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1480, Alexandria, Virginia 22313-1450 Facsimile No.: 571-273-8300		Authorized officer: Shene Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US15/60455

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	(BAY, HE et al.) Diazoxide Choline Controlled Release in Hyperglycemic Subjects: Lipid and Other Metabolic Effects. <i>Journal of the American College of Cardiology</i> . 2010. vol 55, no. 10a. [Retrieved on 16 December 2015]. Retrieved from the internet: URL: < https://clinicaltrials.gov/archive/NCT02034071/2014_01_10 >; abstract	11-14, 24-26
A	(EJNSPIELER, C.) Early Behavioural Manifestation of Smith-Magenis Syndrome (Del 17p11.2) in a 4-Month-Old Boy. <i>Developmental Neurorehabilitation</i> . 2012. vol. 15, no. 4; page 313, first column, first paragraph	22

Form PCT/ISA/210 (continuation of second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/30481

A. CLASSIFICATION OF SUBJECT MATTER IPC: A61K 9/52(2006.01),9/22(2006.01) USPC: 424/457,468 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 424/457, 468 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EAST		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2003/0185873 A1 (CHASIN et al.) 02 October 2003 (02.10.2003), pages 1-14	1-23 ----- 24-49
X --- Y	US 6197765 B1 (VARDI et al.) 06 March 2001 (06.03.2001), cols. 1-8	1-42, 44-49 ----- 1-49
☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.		
* Special categories of cited documents:		
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	
"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	
"Q" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family	
"P" document published prior to the international filing date but later than the priority date claimed		
Date of the actual completion of the international search 13 February 2006 (13.02.2006)	Date of mailing of the international search report 16 JUN 2006	
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Authorized officer <i>Valerie Bell-Harris</i> Pili A. Hawes Telephone No. 571-272-1600	

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 05/42711

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A61K 31/54 (2007.10) USPC - 514/223.2 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) USPC -- 514/223.2 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC -- 514/217.05, 514/222.8, 514/223.8, 514/362, 514/363 (see search terms below) Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) WEST -- PGPB,USPT,USOC,EPAB,JPAB; Dialog Classic Files 351, 155, 6, 35, 65; Google Patents; USPTO Web Page Search terms -- KATP channel opener, salt, diazoxide, sodium, oral, dosage, chloride, ammonium, maleate, gastric transit, solid, pharmaceutical formulation, choline, polymer, coating, pH-sensitive, diabetes		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 6,225,310 B1 (MIELSEN et al.) 01 May 2001 (01.05.2001) col 2, in 14-20; col 2, in 55-67; col 3, in 4-11; col 4, in 1-34; col 4, in 42-51; col 12, in 7-18; col 12, in 51-56; col 18, in 11-16; col 18, in 21-25; col 18, in 31-33; col 18, in 49-52; col 29, in 27-31	1-5, 7-29 ----- 6, 30-31, 71-76
Y	US 2004/0228603 A1 (STEPHENSON et al.) 18 November 2004 (18.11.2004) para [0072], [0400], [0414]	6
Y	US 2004/0266822 A1 (WANG et al.) 30 December 2004 (30.12.2004) para [0001], [0007], [0214]	30-31, 71-76
Y	US 2005/0203072 A1 (RUDOLPH et al.) 15 November 2005 (15.11.2005) para [0154], [0237]	30-31, 77
☐ Further documents are listed in the continuation of Box C. ☐		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "G" document member of the same patent family		
Date of the actual completion of the international search 31 October 2007 (31.10.2007)		Date of mailing of the international search report 06 DEC 2007
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201		Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 06/48711

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 32-70
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Group I: claims 1-31 and 71-78, directed to salts and related formulations, comprising anions of a KATP channel opener selected from the group consisting of Formula I, II, III and IV an anion or cation of a KATP channel opener selected from the group consisting of Formula V, VI, VII and VIII, etc.

Group II: claims 79-116, directed to polymorphs of a salt of diazoxide and related method and processes, etc.

Group III: claims 117-124, directed to methods of treating obesity or obesity-related morbidity, etc.

Group IV: claims 125-129, directed to methods of treatment of a subject suffering from or at risk for Alzheimer's disease, etc.

It will be readily understood that the claims of groups I and II are each directed to subject matter that is distinct, i.e. the polymorph salts of the claims of group II are not limited by any of Formula I-VIII. It will also be readily understood that the methods of treating obesity, etc. of the claims of group III are distinct from the methods of treatment of a subject suffering from or at risk for Alzheimer's disease, etc., as the two diseases/conditions are physiologically distinct and unrelated. Finally, it will be understood that the salts, and related formulations, of the claims of group I and the polymorph salts, and related processes, of the claims of group II are not limited to any specific therapeutic use and are thus distinct from the claims of groups III and IV, directed to specific therapeutic uses, as well.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-31 and 71-78

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 08/68938

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/54 (2008.04)

USPC - 514/223.2

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

USPC: 514/223.2

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

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

Electronic Databases Searched: USPTO WEST (PGPUB, EPAB, JPAB, USPT), Google Patent, Google Scholar. Search Terms Used: benzothiadiazine, thyroid, pancreatitis or metab\$, alkali metal, diazoxide choline, pharmac\$ salt, channel opener

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/026489 A2 (Cowan et al.) 09 March 2006 (09.03.2006)	1-9, 12-14, 18, 20-28, 30-38, 40 and 42-75
-	entire document especially abstract; para [0021]-[0039]; [0074]; [0099]; [0140]; [0149]; [0224]; [0226]; [0256]-[0257]; [0274]; [0279]; [0388]	
Y		15-17, 19, 39 and 41
Y	US 6,140,343 A (DeNinno et al.) 31 October 2000 (31.10.2000) especially col 21, ln 23-33	15-16
Y	US 7,091,225 B2 (Sierra) 15 August 2006 ((15.08.2006) especially col 4, ln 06-15; col 7, ln 55-67	17, 19, 39 and 41

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principles or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"Z" document member of the same patent family

Date of the actual completion of the international search

24 September 2008 (24.09.2008)

Date of mailing of the international search report

30 SEP 2008

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpline: 571-272-4300

PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 08/68936

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 10-11 and 29
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims: it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (April 2007)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 169559-WO-1	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2013/027676	International filing date (day/month/year) 25 February 2013 (25.02.2013)	(Earliest) Priority Date (day/month/year) 27 February 2012 (27.02.2012)
Applicant ESSENTIALIS, INC. et al		

This International search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (See Box No. II)

3. ☐ **Unity of invention is lacking** (See Box No. III)

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant.
☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant.
☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. 1
☒ as suggested by the applicant.
☐ as selected by this Authority, because the applicant failed to suggest a figure.
☐ as selected by this Authority, because this figure better characterizes the invention.
 b. ☐ none of the figure is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/027676**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-34, 45-52
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 1-34 and 45-52 are directed to a treatment method of the human body by therapy and thus relate to a subject matter which this International Searching Authority is not required to search under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT.
2. ☒ Claims Nos.: 7, 18, 24, 30, 31, 33, 34, 39
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims 7, 18, 24, 30, 31, 33, 34, and 39 are unclear, since they either directly or indirectly refer to one of claims which are not drafted in accordance with PCT Rule 6.4(a) (PCT Article 6).
3. ☒ Claims Nos.: 6, 8-11, 15-17, 19-23, 25-29, 32, 38, 40-43, 49-52
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/549(2006.01); A61K 31/38(2006.01); A61P 3/00(2006.01); A61P 9/00(2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K 31/549; C12N 3/00; A61K 31/498; A61K 31/517; C12Q 1/68; A61P 3/04

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

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

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

eKOMPASS(KIPO internal) & Keywords: potassium channel opener, fibrate, blister card, kit, titration dosage

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2009-0062264 A1 (COWEN et al.) 05 March 2009 See paragraphs [0121] and [0301]; and claims 13 and 16.	35-37, 44
A	YOKOYAMA et al. 'Effects of KRN4684, a novel pyridinecarboxamide type K(ATP) channel opener, on serum triglyceride levels in rats'. British Journal of Pharmacology, 1997, Vol. 120, pp. 1471-1476. See abstract; pages 1474 and 1475; and figure 3.	35-37, 44
A	US 2004-0072216 A1 (JOHNSON et al.) 15 April 2004 See abstract; and paragraphs [0219], [0220], [0229], and [0234].	35-37, 44
A	US 2009-0149451 A1 (COWEN, S. M.) 11 June 2009 See abstract and claim 40.	35-37, 44
A	US 2009-0149043 A1 (HAMANARA et al.) 07 August 2009 See paragraphs [0734] and [0735]; and claims 165 and 166.	35-37, 44

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

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

21 June 2013 (21.06.2013)

Date of mailing of the international search report

21 June 2013 (21.06.2013)

Name and mailing address of the ISA/KR

Korean Intellectual Property Office
189 Cheongsa-ro, Seo-gu, Daejeon Metropolitan City,
302-701, Republic of Korea

Facsimile No. 82-42-472-7140

Authorized officer

CHOI, Sung Hee

Telephone No. 82-42-481-8740



INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2013/027676

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		CN 101795691 A	04.08.2010
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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: Stephen E. Reiter
Kilpatrick Townsend & Stockton LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111
United States of America

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year)

02 FEB 2016

Applicant's or agent's file reference
0955616

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US15/60455

International filing date (day/month/year)

12 November 2015 (12.11.2015)

Priority date (day/month/year)

14 November 2014 (14.11.2014)

International Patent Classification (IPC) or both national classification and IPC

IPC(8) - A61K 9/22, 31/54, 31/549; C07D 285/22 (2015.01)

CPC - A61K 9/28, 31/54, 31/549; C07D 285/22

Applicant
ESSENTIALIS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P. O. Box 14953, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-8300

Date of completion of this opinion

19 December 2015 (19.12.2015)

Authorized officer

Shane Thomas

PCT Helpdesk: 571-272-4500
PCT-DSB: 571-273-7774

Form PCT/ISA/237 (cover sheet) (January 2015)

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US15/60455

Box No. 1 Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:
- ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a)).
3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
- a. ☐ forming part of the international application as filed:
 - ☐ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US15/060455

Box No. V	Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement		
1. Statement			
Novelty (N)	Claims	5-28	YES
	Claims	1-4	NO
Inventive step (IS)	Claims	11-14, 22, 24-26	YES
	Claims	1-10, 15-21, 23, 27-28	NO
Industrial applicability (IA)	Claims	1-28	YES
	Claims	NONE	NO
2. Citations and explanations:			
Claims 1-4 lack novelty under PCT Article 33(2) as being anticipated by the publication "Clinical Study of Diazoxide Choline Controlled-Release Tablet (DCCR) in Patients with Prader-Willi Syndrome" in ClinicalTrials.gov NCT02034071 (hereinafter "Clinical"). As per claim 1, Clinical discloses a method of treating a subject having Prader-Willi Syndrome (PWS) (method of treating a subject having Prader-Willi Syndrome; page 1, brief title, brief summary) or Smith-Magenis syndrome (SMS), said method comprising administering to said subject for at least 10 weeks a pharmaceutical formulation (administering to subject for 83 days; page 1, brief summary) comprising an effective amount of a KATP channel opener (comprising effective dose of diazoxide; page 1, brief summary). As per claim 2, Clinical discloses the method of claim 1, and Clinical further discloses wherein said KATP channel opener is diazoxide or a pharmaceutically acceptable salt thereof (KATP channel opener is diazoxide choline; page 1, brief title). As per claim 3, Clinical discloses the method of claim 2, and Clinical further discloses wherein the pharmaceutically acceptable salt is diazoxide choline (diazoxide choline; page 1, brief title). As per claim 4, Clinical discloses the method of claim 2, and Clinical further discloses wherein said diazoxide or a pharmaceutically acceptable salt thereof is administered orally (diazoxide choline is administered as a tablet; page 1, brief title). Claims 5-7, and 27-28 lack an inventive step under PCT Article 33(3) as being obvious over Clinical in view of US 2009/0148525 A1 (COWEN '525). As per claim 5, Clinical discloses the method of claim 2, but Clinical does not disclose wherein the pharmaceutical formulation includes at least one excipient which affects the rate of release of diazoxide or a pharmaceutically acceptable salt thereof. However, Cowen '525 discloses wherein the pharmaceutical formulation includes at least one excipient which affects the rate of release of diazoxide or a pharmaceutically acceptable salt thereof (pharmaceutical formulation comprises at least one excipient that affects the rate of release of diazoxide or pharmaceutical salt; paragraph [0237]-[0238], [0240]). It would have been obvious to one skilled in the art at the time of the invention to have modified the method, as disclosed by Clinical, to provide the method wherein the pharmaceutical formulation includes at least one excipient which affects the rate of release of diazoxide or a pharmaceutically acceptable salt thereof, as disclosed by Cowen '525, as delaying the release of diazoxide to pass through the stomach can reduce the incidence of gastrointestinal adverse side effects (Cowen '525; paragraph [0246]). As per claim 6, Clinical and Cowen '525, in combination, disclose the method of claim 5, but Clinical does not disclose wherein the pharmaceutical formulation includes at least one excipient that delays release of diazoxide or a pharmaceutically acceptable salt thereof. However, Cowen '525 discloses wherein the pharmaceutical formulation includes at least one excipient that delays release of diazoxide or a pharmaceutically acceptable salt thereof (pharmaceutical formulation comprises at least one excipient that delays the rate of release of diazoxide or pharmaceutical salt; paragraph [0237]-[0238], [0242]). It would have been obvious to one skilled in the art at the time of the invention to have modified the method, as disclosed by Clinical, to provide the method wherein the pharmaceutical formulation includes at least one excipient that delays release of diazoxide or a pharmaceutically acceptable salt thereof, as disclosed by Cowen '525, as delaying the release of diazoxide to pass through the stomach can reduce the incidence of gastrointestinal adverse side effects (Cowen '525; paragraph [0246]). As per claim 7, Clinical discloses the method of claim 1, but Clinical does not disclose wherein the formulation further comprises at least one other active ingredient. However, Cowen '525 discloses wherein the formulation further comprises at least one other active ingredient (formulation contains at an additional ingredient; paragraph [0264]). It would have been obvious to one skilled in the art at the time of the invention to have modified the method, as disclosed by Clinical, to provide the method wherein the formulation further comprises at least one other active ingredient, as disclosed by Cowen '525, as to treat conditions with obesity, PWS, can be treated with co-formulations of a KATP channel opener and an obesity treating second agent (Cowen '525; paragraph [0264]). ***Continued Within the Next Supplemental Box***			

Form PCT/ISA/237 (Box No. V) (January 2015)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US15/060455

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Continued from Box V: Citations and Explanations.

As per claim 27, Clinical discloses the method of claim 1, but Clinical does not disclose wherein the pharmaceutical formulation is administered twice per day. However, Cowen '525 discloses wherein the pharmaceutical formulation is administered twice per day (pharmaceutical formulation is administered twice daily; paragraph [0238]). It would have been obvious to one skilled in the art at the time of the invention to have modified the method, as disclosed by Clinical, to provide the method wherein the pharmaceutical formulation is administered twice per day, as disclosed by Cowen '525, as administration of sustained release diazoxide is administered once or twice a day (Cowen '525; paragraphs [0237]-[0238]).

As per claim 28, Clinical discloses the method of claim 1, but Clinical does not disclose wherein the pharmaceutical formulation is administered once per day. However, Cowen '525 discloses wherein the pharmaceutical formulation is administered once per day (pharmaceutical formulation is administered once per day; paragraph [0238]). It would have been obvious to one skilled in the art at the time of the invention to have modified the method, as disclosed by Clinical, to provide the method wherein the pharmaceutical formulation is administered once per day, as disclosed by Cowen '525, as administration of sustained release diazoxide is administered once or twice a day (Cowen '525; paragraphs [0237]-[0238]).

Claims 8-9 and 19 lack an inventive step under PCT Article 33(3) as being obvious over Clinical in view of the publication "Treatment With Human Growth Hormone in Patients With Prader-Willi Syndrome Reduces Body Fat And Increases Muscle Mass And Physical Performance" by Eiholzer, et al. (hereinafter "Eiholzer").

As per claim 8, Clinical discloses the method of claim 1, but Clinical does not disclose further comprising administering human growth hormone to the subject. However, Eiholzer discloses further comprising administering human growth hormone to the subject (administration of human growth hormone to a subject; page 374, sixth paragraph). It would have been obvious to one skilled in the art at the time of the invention to have modified the method, as disclosed by Clinical, to provide the method further comprising administering human growth hormone to the subject, as disclosed by Eiholzer, as human growth hormone is useful in treating Prader-Willi Syndrome (Eiholzer; page 374, sixth-seventh paragraphs).

As per claim 9, Clinical and Eiholzer, in combination, disclose the method of claim 8, but Clinical does not disclose wherein said human growth hormone is administered by injection. However, Eiholzer discloses wherein said human growth hormone is administered by injection (human growth hormone is administered by injection; page 369, second column, third paragraph). It would have been obvious to one skilled in the art at the time of the invention to have modified the method, as disclosed by Clinical, to provide the method wherein said human growth hormone is administered by injection, as disclosed by Eiholzer, as human growth hormone administered by subcutaneous injection is used to treat PWS (Eiholzer; page 374, sixth-seventh paragraphs).

As per claim 19, Clinical discloses the method of claim 1, but Clinical does not disclose wherein the circulating concentration of IGF-1 is not increased. However, Eiholzer discloses wherein the circulating concentration of IGF-1 is not increased (IGF-1 levels is moderately reduced; page 375, second column, fourth paragraph). It would have been obvious to one skilled in the art at the time of the invention to have modified the method, as disclosed by Clinical, to provide the method wherein the circulating concentration of IGF-1 is not increased, as disclosed by Eiholzer, as decreasing food intake in patients with PWS is associated with moderate reduction in IGF-1 levels (Eiholzer; page 375, second column, fourth paragraph).

Claims 10 and 16-18 lack an inventive step under PCT Article 33(3) as being obvious over Clinical in view of US 2012/0053172 A1 ("DE BOER").

As per claim 10, Clinical discloses the method of claim 1, but Clinical does not disclose wherein the lean body mass or the lean body mass/fat mass ratio of said subject is increased by at least 1 percent. However, De Boer discloses wherein the lean body mass wherein the lean body mass or the lean body mass/fat mass ratio of said subject is increased by at least 1 percent (total fat mass decreased by 23.4 percent while lean body mass remained the same, 100/77, 1.3 percent; paragraph [0105]). It would have been obvious to one skilled in the art at the time of the invention to have modified the method, as disclosed by Clinical, by the method wherein the lean body mass or the lean body mass/fat mass ratio of said subject is increased by at least 1 percent, as disclosed by De Boer, as potassium channel activators including diazoxide administration is used to treat obesity related disorders in subject (De Boer; paragraphs [0055], [0059]).

As per claim 16, Clinical discloses the method of claim 1, but Clinical does not disclose wherein hyperphagia of said subject is reduced by at least 10 percent. However, De Boer discloses wherein hyperphagia of said subject is reduced by at least 10 percent (reduction in food intake is 31.3 percent; paragraph [0102]). It would have been obvious to one skilled in the art at the time of the invention to have modified the method, as disclosed by Clinical, to provide the method wherein hyperphagia of said subject is reduced by at least 10 percent, as disclosed by De Boer, as diazoxide administration to obese subjects for six months decreased food intake by 31.3 percent (De Boer; paragraphs [0100], [0102]).

As per claim 17, Clinical discloses the method of claim 1, but Clinical does not disclose wherein hyperphagia of said subject is reduced by at least 20 percent. However, De Boer discloses wherein hyperphagia of said subject is reduced by at least 20 percent (reduction in food intake is 31.3 percent; paragraph [0102]). It would have been obvious to one skilled in the art at the time of the invention to have modified the method, as disclosed by Clinical, to provide the method wherein hyperphagia of said subject is reduced by at least 20 percent, as disclosed by De Boer, as diazoxide administration to obese subjects for six months decreased food intake by 31.3 percent (De Boer; paragraphs [0100], [0102]).

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US15/60455

Supplemental Box

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As per claim 18, Clinical discloses the method of claim 1, but Clinical does not disclose wherein hyperphagia of said subject is reduced by at least 30 percent. However, De Boer discloses wherein hyperphagia of said subject is reduced by at least 30 percent (reduction in food intake is 31.3 percent; paragraph [0102]). It would have been obvious to one skilled in the art at the time of the invention to have modified the method, as disclosed by Clinical, to provide the method wherein hyperphagia of said subject is reduced by at least 30 percent, as disclosed by De Boer, as diazoxide administration to obese subjects for six months decreased food intake by 31.3 percent (De Boer; paragraphs [0100], [0102]).

Claim 19 lacks an inventive step under PCT Article 33(3) as being obvious over Clinical in view of US 2009/0062264 A1 to Cowan, et al. (hereinafter 'Cowan '264').

As per claim 19, Clinical discloses the method of claim 1, but Clinical does not disclose wherein said administering is carried out for 1 one or more years. However, Cowan '264 discloses wherein said administering is carried out for 1 one or more years (administration is for at least 2 months and continuously; paragraphs [0301], [0493]). It would have been obvious to one skilled in the art at the time of the invention to have modified the method, as disclosed by Clinical, provide the method wherein said administering is carried out for 1 one or more years, as disclosed by Cowan '264, as to treat conditions with obesity, PWS, can be treated continuously with KCAT channel opener (Cowan '264; paragraph [0264], [0493]).

Claims 20-21 lack an inventive step under PCT Article 33(3) as being obvious over Eiholzer in view of Cowan '264).

As per claim 20, Eiholzer discloses a method of increasing the lean body mass of a subject having Prader-Willi Syndrome (method of increasing lean body mass in subject with PWS; page 374, first column, sixth paragraph; page 375, first column, fourth paragraph), wherein said subject is already being treated by administration thereto of growth hormone (subject with PWS is administered growth hormone; page 374, first column, sixth paragraph), but Eiholzer does not disclose said method comprising co-administering to said subject an effective amount of a KATP channel opener in addition to said growth hormone. However, Cowan '264 discloses said method comprising co-administering to said subject an effective amount of a KATP channel opener in addition to said growth hormone (co-administration to a subject a KATP channel opener and growth hormone, as part of a list; paragraph [0147]). It would have been obvious to one skilled in the art at the time of the invention to have modified the method, as disclosed by Eiholzer, to provide the method said method comprising co-administering to said subject an effective amount of a KATP channel opener in addition to said growth hormone, as disclosed by Cowan '264, as treatment of obesity related disorders including PWS includes KATP channel openers and growth hormones (Cowan '264; paragraphs [0147], [0494]).

As per claim 21, Eiholzer discloses a method of increasing the lean body mass of a subject having Prader-Willi Syndrome (method of increasing lean body mass in subject with PWS; page 374, first column, sixth paragraph; page 375, first column, fourth paragraph), wherein said subject is already being treated by administration thereto of an effective amount of growth hormone (subject with PWS is administered growth hormone; page 374, first column, sixth paragraph), but Eiholzer does not disclose 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 said growth hormone in addition to said KATP channel opener. However, Cowan '264 discloses wherein said subject is already being treated by administration thereto of an effective amount of a KATP channel opener (subject is being treated with an effective amount of KATP channel opener that can be combined with other agents; paragraph [0147]), said method comprising co-administering to said subject an effective amount of growth hormone in addition to said KATP channel opener (co-administration of effective amount of growth hormone to subject, as part of a list, and KATP channel opener; paragraph [0147]). It would have been obvious to one skilled in the art at the time of the invention to have modified the method, as disclosed by Eiholzer, to provide the method wherein said subject is already being treated by administration thereto of an effective amount of a KATP channel opener, said method comprising co-administering in said subject an effective amount of growth hormone in addition to said KATP channel opener, as disclosed by Cowan '264, as growth hormone is used to increase lean body mass in subjects with PWS (Cowan '264; page 374, first column, sixth paragraph; page 375, first column, fourth paragraph).

Claim 23 lacks an inventive step under PCT Article 33(3) as being obvious over Cowan '264 in view of Eiholzer.

As per claim 23, Cowan '264 discloses a kit (kit; paragraph [0268]) comprising: a unit dose of a KATP channel opener (unit dose of KATP channel opener; paragraph [0461]; table 1), and a unit dose of growth hormone (growth hormone as part of a list; paragraph [0147]), but Cowan '264 does not disclose and a unit dose of growth hormone within a single concise embodiment. However, Eiholzer discloses a unit dose of growth hormone (unit dose of growth hormone; page 369, second column, third paragraph). It would have been obvious to one skilled in the art at the time of the invention to have modified the method, as disclosed by Cowan '264, to provide the method comprising a unit dose of growth hormone, as disclosed by Eiholzer, as a unit dose of 14 $\mu\text{m}^2/\text{week}$ of human growth hormone is used to treat patients with PWS (Eiholzer; page 369, second column, third paragraph; page 374, sixth paragraph).

Claims 11-14, 22, and 24-26 meet the criteria set out in PCT Article 33(2)-(3).

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US15/60455

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

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Claim 11 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest 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 percent.

Clinical discloses the method of claim 1, but Clinical does not disclose wherein the lean body mass or the lean body mass/fat mass ratio of said subject is increased by at least 2 percent.

De Boer discloses wherein the lean body mass wherein the lean body mass or the lean body mass/fat mass ratio of said subject is increased by at least 1 percent (total fat mass decreased by 23.4 percent while lean body mass remained the same, 100/77, 1.3 percent; paragraph [0105]), but De Boer does not disclose wherein the lean body mass or the lean body mass/fat mass ratio of said subject is increased by at least 2 percent.

Cowen '264 discloses pharmaceutical formulation of KATP channel openers for administration to treat obesity and hyperphagia in a Prader-Willi Syndrome patient (paragraphs [0112], [0134]), but Cowen '264 does not disclose wherein the lean body mass or the lean body mass/fat mass ratio of said subject is increased by at least 2 percent.

The publication "Diazoxide Choline Controlled Release in Hyperglycemic Subjects: Lipid and Other Metabolic Effects" by Bay, et al. (hereinafter "Bay") discloses a PATP channel opener diazoxide for treating metabolic disorders (abstract), but Bay does not disclose wherein the lean body mass or the lean body mass/fat mass ratio of said subject is increased by at least 2 percent.

The prior art does not disclose PATP channel openers wherein the lean body mass or the lean body mass/fat mass ratio of said subject is increased by at least 2 percent.

Claim 12 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest 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 percent.

Clinical discloses the method of claim 1, but Clinical does not disclose wherein the lean body mass or the lean body mass/fat mass ratio of said subject is increased by at least 3 percent.

De Boer discloses wherein the lean body mass wherein the lean body mass or the lean body mass/fat mass ratio of said subject is increased by at least 1 percent (total fat mass decreased by 23.4 percent while lean body mass remained the same, 100/77, 1.3 percent; paragraph [0105]), but De Boer does not disclose wherein the lean body mass or the lean body mass/fat mass ratio of said subject is increased by at least 3 percent.

Cowen '264 discloses pharmaceutical formulation of KATP channel openers for administration to treat obesity and hyperphagia in a Prader-Willi Syndrome patient (paragraphs [0112], [0134]), but Cowen '264 does not disclose wherein the lean body mass or the lean body mass/fat mass ratio of said subject is increased by at least 3 percent.

Bay discloses a PATP channel opener diazoxide for treating metabolic disorders (abstract), but Bay does not disclose wherein the lean body mass or the lean body mass/fat mass ratio of said subject is increased by at least 3 percent.

The prior art does not disclose PATP channel openers wherein the lean body mass or the lean body mass/fat mass ratio of said subject is increased by at least 3 percent.

Claim 13 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest 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 percent.

Clinical discloses the method of claim 1, but Clinical does not disclose wherein the lean body mass or the lean body mass/fat mass ratio of said subject is increased by at least 4 percent.

De Boer discloses wherein the lean body mass wherein the lean body mass or the lean body mass/fat mass ratio of said subject is increased by at least 1 percent (total fat mass decreased by 23.4 percent while lean body mass remained the same, 100/77, 1.3 percent; paragraph [0105]), but De Boer does not disclose wherein the lean body mass or the lean body mass/fat mass ratio of said subject is increased by at least 4 percent.

Cowen '264 discloses pharmaceutical formulation of KATP channel openers for administration to treat obesity and hyperphagia in a Prader-Willi Syndrome patient (paragraphs [0112], [0134]), but Cowen '264 does not disclose wherein the lean body mass or the lean body mass/fat mass ratio of said subject is increased by at least 4 percent.

Bay discloses a PATP channel opener diazoxide for treating metabolic disorders (abstract), but Bay does not disclose wherein the lean body mass or the lean body mass/fat mass ratio of said subject is increased by at least 4 percent.

The prior art does not disclose PATP channel openers wherein the lean body mass or the lean body mass/fat mass ratio of said subject is increased by at least 4 percent.

Claim 14 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest 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 percent.

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Form PCT/ISA/237 (Supplemental Box) (January 2015)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US15/60455

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

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Continued from Previous Supplemental Box.

Clinical discloses the method of claim 1, but Clinical does not disclose wherein the lean body mass or the lean body mass/fat mass ratio of said subject is increased by at least 5 percent.

De Boer discloses wherein the lean body mass wherein the lean body mass or the lean body mass/fat mass ratio of said subject is increased by at least 1 percent (total fat mass decreased by 23.4 percent while lean body mass remained the same, 100/77, 1.3 percent; paragraph [0105]), but De Boer does not disclose wherein the lean body mass or the lean body mass/fat mass ratio of said subject is increased by at least 5 percent.

Cowen '264 discloses pharmaceutical formulation of KATP channel openers for administration to treat obesity and hyperphagia in a Prader-Willi Syndrome patient (paragraphs [0112], [0134]), but Cowen '264 does not disclose wherein the lean body mass or the lean body mass/fat mass ratio of said subject is increased by at least 5 percent.

Bay discloses a PATP channel opener diazoxide for treating metabolic disorders (abstract), but Bay does not disclose wherein the lean body mass or the lean body mass/fat mass ratio of said subject is increased by at least 5 percent.

The prior art does not disclose PATP channel openers wherein the lean body mass or the lean body mass/fat mass ratio of said subject is increased by at least 5 percent.

Claim 23 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest 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.

Cowen '264 discloses comprising administering to said subject an effective amount of a KATP channel opener (administration to a subject an effective amount of a KATP channel opener; paragraph [0147]), but Cowen '264 does not disclose a method of increasing lower limb muscle mass of a subject having Smith-Magenis syndrome (SMS).

De Boer discloses comprising administering to said subject an effective amount of a KATP channel opener (administration of effective amount of potassium channel activity; paragraph [0024]), but De Boer does not disclose a method of increasing lower limb muscle mass of a subject having Smith-Magenis syndrome (SMS).

Cowen '525 discloses comprising administering to said subject an effective amount of a KATP channel opener (administration to a subject an effective amount of a KATP channel opener; paragraph [0096]), but Cowen '525 does not disclose a method of increasing lower limb muscle mass of a subject having Smith-Magenis syndrome (SMS).

The publication "Early Behavioural Manifestation of Smith-Magenis Syndrome (Del 17p11.2) in a 4-Month-Old Boy" by Einspieler, et al. (hereinafter "Einspieler") discloses Smith-Magenis syndrome (page 313, first column, first paragraph), but Einspieler does not disclose said method comprising administering to said subject an effective amount of a KATP channel opener.

The prior art of Cowen '264, De Boer, Cowen '525, and Einspieler does not suggest or motivate 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.

Claim 24 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest 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.

Clinical discloses a method of treating a subject with Prader-Willi syndrome (PWS) (method of treating; page 1, brief summary) the method comprising administering to said subject for at least 10 weeks an effective amount of a KATP channel opener (effective amount of KATP channel opener is administered for at least 10 weeks; page 1, brief summary), but Clinical does not disclose a method of reducing one or more aggressive behaviors in a subject having Prader-Willi syndrome (PWS) or Smith-Magenis syndrome (SMS), wherein administration reduces one or more aggressive behaviors in the subject.

Cowen '264 discloses a method of treating a subject with Prader-Willi syndrome, as part of a list (paragraph [0495]), the method comprising administering to said subject an effective amount of KATP channel opener (paragraph [0147]), but Cowen '264 does not disclose 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.

Continued Within the Next Supplemental Box.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US15/060455

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Continued from Previous Supplemental Box

De Boer discloses a method of treating a subject with obesity with potassium channel activator (paragraph [0026]), but De Boer does not disclose 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.

Bay discloses a PAMP channel opener diazoxide for treating metabolic disorders (abstract), but Bay does not disclose 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.

The prior art does not disclose combining Clinical, Cowen '264, De Boer, and/or Bay to provide 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.

Claim 25 meets the criteria set out in PCT Article 33(2)-(3), based on its dependency on positive claim 24.

Claim 26 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest a method of reducing hyperphrefinemia 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.

Clinical discloses a method of treating a subject with Prader-Willi syndrome (PWS) (method of treating: page 1, brief summary) the method comprising administering to said subject for at least 10 weeks an effective amount of a KATP channel opener (effective amount of KATP channel opener is administered for at least 10 weeks; page 1, brief summary), but Clinical does not disclose a method of reducing hyperphrefinemia in a subject having Prader-Willi syndrome (PWS) or Smith-Magenis syndrome (SMS), wherein administration reduces one or more aggressive behaviors in the subject.

Cowen '264 discloses a method of treating a subject with Prader-Willi syndrome, as part of a list (paragraph [0495]), the method comprising administering to said subject an effective amount of KATP channel opener (paragraph [0147]), but Cowen '426 does not disclose a method of reducing hyperphrefinemia 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.

De Boer discloses a method of treating a subject with obesity with potassium channel activator (paragraph [0026]), but De Boer does not disclose a method of reducing hyperphrefinemia 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.

Bay discloses a PAMP channel opener diazoxide for treating metabolic disorders (abstract), but Bay does not disclose a method of reducing hyperphrefinemia 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.

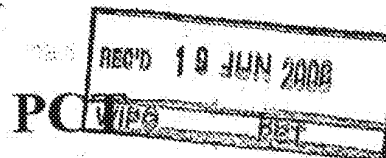
The prior art does not disclose combining Clinical, Cowen '264, De Boer, and/or Bay to provide a method of reducing hyperphrefinemia in a subject having Prader-Willi syndrome (PWS) or Smith-Magenis syndrome (SMS), the method comprising administering to said subject for at least 10 weeks an effective amount of a KATP channel opener, wherein administration reduces one or more aggressive behaviors in the subject.

Claims 1-28 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
RICHARD J. WARBURG
FOLEY & LARDNER LLP
P.O. BOX 80278
SAN DIEGO, CA 92138-0278



WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing (day/month/year) 16 JUN 2006	
Applicant's or agent's file reference 059599-0203	
FOR FURTHER ACTION See paragraph 2 below	
International application No. PCT/US05/30481	International filing date (day/month/year) 25 August 2005 (25.08.2005)
Priority date (day/month/year) 25 August 2004 (25.08.2004)	
International Patent Classification (IPC) or both national classification and IPC IPC: A61K 9/52(2006.01), 9/22(2006.01) USPC: 424/457, 468	
Applicant ESSENTIALS INC	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 56.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Date of completion of this opinion 13 February 2006 (13.02.2006)	Authorized officer <i>Valerie Bell-Hawes</i> Ph A. Hawes Telephone No. (571) 272-1600
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Form PCT/ISA/237 (cover sheet) (April 2005)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US05/30481

Box No. 1 Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

- ☐ a sequence listing
☐ table(s) related to the sequence listing

b. format of material

- ☐ on paper
☐ in electronic form

c. time of filing/furnishing

- ☐ contained in the international application as filed.
☐ filed together with the international application in electronic form.
☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US05/30481

Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-49	YES
	Claims NONE	NO
Inventive step (IS)	Claims NONE	YES
	Claims 1-49	NO
Industrial applicability (IA)	Claims 1-49	YES
	Claims NONE	NO

2. Citations and explanations:

Claims 1-42, 44-49 lack an inventive step under PCT Article 33(3) as being obvious over VARDI. VARDI teaches the treatment of obesity, hypertension, hyperlipidemia, hyperinsulinemia, impaired glucose tolerance, and Syndrome X. The composition comprises diazoxide. The reference teaches administering about 5 mg/kg of the composition. Thus a 125 kg person would be administered 650 mg per day.

The reference does not disclose that the oral dosage is controlled release however one of ordinary skill in the art would know how to adapt the dosage form disclosed by VARDI into a controlled release dosage form because it is a process well known in the art. It would be obvious to one of ordinary skill in the art to vary the dosage amount since the reference teaches that the dosage amount is dependent upon the weight of the patient to whom the composition is administered.

Claims 1-23 an inventive step under PCT Article 33(3) as being obvious over CHASIN. CHASIN teaches a biodegradable controlled release formulation for providing local anesthetics. One preferred embodiment of the invention comprises diazoxide. The composition also comprises vasoconstrictors. The formulation can be in the form of microspheres.

The reference does not teach the exact dosage amounts of the instant invention. However it would have been obvious to one of ordinary skill in the art to vary the dosage amount based on the patients, age, gender, and weight. The reference does not teach the administration times as claimed. However it would be obvious to one of ordinary skill in the art that a composition that affords controlled release of the active ingredients to be administered with less frequency than a composition that has a more immediate release profile.

Claims 1-49 lack an inventive step under PCT Article 33(3) as being obvious over CHASIN in view of VARDI. CHASIN and VARDI have been discussed above. One of ordinary skill in the art would be motivated to use the controlled release dosage form of CHASIN in the method of treating obesity taught by VARDI because VARDI teaches that diazoxides are used for treating obesity.

Claims 1-49 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: Richard J Warburg
Foley & Lardner LLP
PO Box 80278
San Diego CA 92137-0278

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year)

06 DEC 2007

Applicant's or agent's file reference
059599-0304

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US 06/48711

International filing date (day/month/year)

20 December 2006 (20.12.2006)

Priority date (day/month/year)

05 January 2006 (05.01.2006)

International Patent Classification (IPC) or both national classification and IPC

IPC(8) - A61K 31/54 (2007.10)

USPC - 514/223.2

Applicant: Essentialis Inc

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-3201

Date of completion of this opinion

31 October 2007 (31.10.2007)

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7714

Form PCT/ISA/237 (cover sheet) (April 2007)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 06/48711

Box No. 1 Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. ☐ This opinion has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a)).
3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established on the basis of:
 - a. type of material
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing
 - ☐ contained in the international application as filed
 - ☐ filed together with the international application in electronic form
 - ☐ furnished subsequently to this Authority for the purposes of search
4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 06/48711

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 32-70

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 32-70 are so unclear that no meaningful opinion could be formed (*specify*):

Claims 32-70 are improper multiple dependent claims because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 8.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☒ no international search report has been established for said claims Nos. 32-70

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 06/48711

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
- ☐ paid additional fees
- ☐ paid additional fees under protest and, where applicable, the protest fee
- ☐ paid additional fees under protest but the applicable protest fee was not paid
- ☒ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

☐ complied with

☒ not complied with for the following reasons:

Group I: claims 1-31 and 71-78, directed to salts and related formulations, comprising anions of a KATP channel opener selected from the group consisting of Formula I, II, III and IV an anion or cation of a KATP channel opener selected from the group consisting of Formula V, VI, VII and VIII, etc.

Group II: claims 79-118, directed to polymorphs of a salt of diazoxide and related method and processes, etc.

Group III: claims 117-124, directed to methods of treating obesity or obesity-related morbidity, etc.

Group IV: claims 125-129, directed to methods of treatment of a subject suffering from or at risk for Alzheimer's disease, etc.

It will be readily understood that the claims of groups I and II are each directed to subject matter that is distinct, i.e. the polymorph salts of the claims of group II are not limited by any of Formula I-VIII. It will also be readily understood that the methods of treating obesity, etc. of the claims of group III are distinct from the methods of treatment of a subject suffering from or at risk for Alzheimer's disease, etc., as the two diseases/conditions are physiologically distinct and unrelated. Finally, it will be understood that the salts, and related formulations, of the claims of group I and the polymorph salts, and related processes, of the claims of group II are not limited to any specific therapeutic use and are thus distinct from the claims of groups III and IV, directed to specific therapeutic uses, as well. Thus, the claims of groups I, II, III and IV do not share any underlying, common unknown technical feature and thus lack unity of invention as required under Rule 13.1.

4. Consequently, this opinion has been established in respect of the following parts of the international application:

☐ all parts

☒ the parts relating to claims Nos. 1-31 and 71-78.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US 06/48711

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-9, 30-31, 71-76	YES
	Claims	10-29	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-31, 71-78	NO
Industrial applicability (IA)	Claims	1-31, 71-78	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 10-29 lack novelty under PCT Article 33(2) as being anticipated by US 6,225,310 B1 to Nielsen et al. (hereinafter "Nielsen").

Regarding claim 10, directed to a salt comprising an anion of a KATP channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII, Nielsen teaches the compounds illustrated by the formula (col 2, in 45-55) corresponding to at least Formula VIII. Nielsen teaches that the compounds may contain an SO₂ ring substituent at the position corresponding to that in the structure of Formula VIII (col 2, in 64) and further having R₃ and R₄ substituents of the Formula VIII structure corresponding to the "A" ring as defined (col 4, in 1-34). Nielsen teaches that the A ring may have one or more amino substituents (col 4, in 7). Nielsen teaches that substituents corresponding to R₂b may be hydrogen (col 3, in 4-10) and R₁ may be a substituted amino group (col 3, in 4-11; col 3, in 12-20). Nielsen also teaches that the compounds function as openers of KATP channels (col 12, in 7-18) and that the compounds may be in the form of salts (col 4, in 33-35).

Regarding claim 11, directed to the salt according to claim 10 wherein at least one substituent comprises an amino group, Nielsen as above teaches that the compounds may be in the form of salts (col 4, in 33-35). Nielsen as above teaches that the A ring may have one or more amino substituents (col 4, in 7).

Regarding claim 12, directed to the salt according to claim 10 wherein R₁ comprises an amino group, Nielsen as above teaches that R₁ may be a substituted amino group (col 3, in 4-11; col 3, in 12-20).

Regarding claim 13, directed to the salt according to claim 10 wherein said anion is an anion of Formula VII, Nielsen teaches compounds corresponding to the structure of Formula VII (col 2, in 45-55). Nielsen as above teaches that the compounds may contain an SO₂ ring substituent at the position corresponding to that in the structure of Formula VII (col 2, in 64) and further having R₃ and R₄ substituents of the Formula VII structure corresponding to the "A" ring as defined (col 4, in 1-34). Nielsen as above teaches that the A ring may have one or more amino substituents (col 4, in 7). Nielsen as above teaches that substituents corresponding to R₂b may be hydrogen (col 3, in 4-10) and R₁ may be a substituted amino group (col 3, in 4-11; col 3, in 12-20). Nielsen as above teaches that the compounds may be in the form of salts (col 4, in 33-35).

Regarding claim 14, directed to the salt according to claim 10 wherein said anion is an anion of Formula VIII, Nielsen teaches compounds corresponding to the structure of Formula VIII (col 2, in 45-55). Nielsen as above teaches that the compounds may contain an SO₂ ring substituent at the position corresponding to that in the structure of Formula VII (col 2, in 64) and further having R₃ and R₄ substituents of the Formula VIII structure corresponding to the "A" ring as defined (col 4, in 1-34). Nielsen as above teaches that the A ring may have one or more amino substituents (col 4, in 7). Nielsen as above teaches that substituents corresponding to R₂b may be hydrogen (col 3, in 4-10) and R₁ may be a substituted amino group (col 3, in 4-11; col 3, in 12-20). Nielsen as above teaches that the compounds may be in the form of salts (col 4, in 33-35).

Regarding claim 15, directed to the salt according to claim 10 wherein said salt comprises a cation of an alkali metal, Nielsen as above teaches that the compounds may be in the form of salts (col 4, in 33-35). Nielsen teaches sodium and potassium cations (col 4, in 42-51).

Regarding claim 16, directed to a pharmaceutical formulation comprising the salt according to claim 10, Nielsen further teaches that the compounds may be a pharmaceutical formulation (col 18, in 31-33).

Regarding claim 17, directed to a salt comprising a cation of a KATP channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII, wherein at least one substituent comprises an amino group, Nielsen as above teaches compounds corresponding to the structure of Formula VIII (col 2, in 45-55). Nielsen as above teaches that the compounds may contain an SO₂ ring substituent at the position corresponding to that in the structure of Formula VII (col 2, in 64) and further having R₃ and R₄ substituents of the Formula VIII structure corresponding to the "A" ring as defined (col 4, in 1-34). Nielsen as above teaches that the A ring may have one or more amino substituents (col 4, in 7). Nielsen as above teaches that substituents corresponding to R₂b may be hydrogen (col 3, in 4-10) and R₁ may be a substituted amino group (col 3, in 4-11; col 3, in 12-20). Nielsen as above teaches that the compounds may be in the form of salts (col 4, in 33-35).

Regarding claim 18, see the discussion set forth for claim 12.

-----continued in Supplemental Box-----

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 06/48711

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:
Box V 2. Citations and explanations

Regarding claim 19, Nielsen as above teaches compounds corresponding to the structure of Formula VII (col 2, in 45-55). Nielsen as above teaches that the compounds may be in the form of salts (col 4, in 33-35). Nielsen as above teaches sodium and potassium cations (col 4, in 42-51).

Regarding claim 20, directed to the salt according to claim 17 wherein said cation is a cation of Formula VIII, Nielsen as above teaches compounds corresponding to the structure of Formula VIII (col 2, in 45-55). Nielsen as above teaches that the compounds may be in the form of salts (col 4, in 33-35). Nielsen as above teaches sodium and potassium cations (col 4, in 42-51).

Regarding claim 21, directed to the salt according to claim 17 wherein said salt comprises an anion selected from the group consisting of sulfate, chloride, hydrochloride, fumarate, maleate, phosphate, sulfamate, acetate, citrate, lactate, tartrate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluene sulfonate, cyclohexylsulfamate and quinate ions, Nielsen further teaches that the anion of the salt may be maleate or hydrochloride, among others (col 4, in 42-46).

Regarding claim 22, directed to the salt according to claim 17 wherein said salt comprises an anion selected from a halogen, Nielsen further teaches that the anion may be hydrochloride (col 4, in 42-46).

Regarding claim 23, see the discussion set forth for claim 16.

Regarding claim 24, directed to the formulation according to any one of claims 9, 16 and 23 for a single administration that contains between 10 and 100 mg of the salt, Nielsen as above teaches that the compounds may be in the form of salts (col 4, in 33-35). Nielsen further teaches a dosage of between 0.5mg to 1000 mg per day (col 18, in 11-18).

Regarding claims 25-28, see the discussion set forth for claim 24.

Regarding claim 29, directed to the formulation according to any one of claims 9, 16 and 23 that is suitable for oral administration, Nielsen further teaches a preferred oral administration route (col 18, in 21-25).

Claims 1-5 and 7-9 lack an inventive step under PCT Article 33(3) as being obvious over Nielsen.

Regarding claim 1, directed to a salt comprising: an anion of a KATP channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV; and a cation selected from the group consisting of an alkali metal and a compound comprising a tertiary amine or ammonium group, wherein when said salt comprises diazoxide as the anion and sodium as the cation, said salt is not in a form suitable for intravenous use, Nielsen as above teaches compounds corresponding to the structure of Formula III (col 2, in 45-55). Nielsen as above teaches that the compounds may contain an SO₂ ring substituent at the position corresponding to that in the structure of Formula III (col 2, in 64) and further having R3 and R4 substituents of the Formula III structure corresponding to the "A" ring as defined (col 4, in 1-34). Nielsen as above teaches that the A ring may have one or more amino substituents (col 4, in 7). Nielsen as above teaches that substituents corresponding to R2b may be hydrogen (col 3, in 4-10). Nielsen also teaches that R1, which position corresponds to the combination of "B", R4 and R5 taught by Nielsen, and described as where R4 together with R5 represent one of the bonds in a double bond between the atoms 2 and 3 of the illustrated formula or R1 together with R4, represents one of the bonds in a double bond between the atoms 3 and 4 of the illustrated formula (col 2, in 57-64; col 3, in 6-10). Nielsen as above teaches that the compounds function as openers of KATP channels (col 12, in 7-18) and that the compounds may be in the form of salts (col 4, in 33-35). Nielsen as above teaches sodium and potassium cations (col 4, in 42-51). Nielsen also teaches diazoxide and derivatives (col 2, in 14-20). Nielsen does not explicitly teach that the compounds may not be used intravenously, but does teach a preference for oral administration (col 18, in 21-25). It would have been obvious to one of skill in the art to conduct tests on safety and pharmacology of delivery by various modes of administration before use as a pharmaceutical agent, wherein results of such testing may preclude intravenous administration. It would have been obvious to one of skill in the art that the substituted amino substituent at position R1 could be readily deaminated by techniques known in the art at the time the invention was made. Also, and alternatively, it would have been obvious to one of skill in the art to utilize a derivative of diazoxide as taught by Nielsen since the ring structure of diazoxide is not amino-substituted at the 3 position of the ring.

Regarding claim 2, directed to the salt according to claim 1 wherein when said salt comprises diazoxide as the anion and sodium as the cation, said salt is not in a liquid form, Nielsen as above teaches sodium and potassium cations (col 4, in 42-51). Nielsen as above teaches diazoxide and derivatives (col 2, in 14-20). Nielsen also teaches that the exemplary salts are solids (col 28, in 27-31).

Regarding claim 3, directed to the salt according to claim 1 wherein said anion is an anion of Formula III, Nielsen as above teaches compounds corresponding to the structure of Formula III (col 2, in 45-55). Nielsen as above teaches that the compounds may contain an SO₂ ring substituent at the position corresponding to that in the structure of Formula III (col 2, in 64) and further having R3 and R4 substituents of the Formula III structure corresponding to the "A" ring as defined (col 4, in 1-34). Nielsen as above teaches that the A ring may have one or more amino substituents (col 4, in 7). Nielsen as above teaches that substituents corresponding to R2b may be hydrogen (col 3, in 4-10). Nielsen as above teaches that R1, which position corresponds to the combination of "B", R4 and R5 taught by Nielsen, and described as where R4 together with R5 represent one of the bonds in a double bond between the atoms 2 and 3 of the illustrated formula or R1 together with R4, represents one of the bonds in a double bond between the atoms 3 and 4 of the illustrated formula (col 2, in 57-64; col 3, in 6-10). It would have been obvious to one of skill in the art that the substituted amino substituent at position R1 could be readily deaminated by techniques known in the art. Alternatively, it would have been obvious to one of skill in the art to utilize a derivative of diazoxide as taught by Nielsen since the ring structure of diazoxide is not amino-substituted at the 3 position of the ring.

-----continued in next Supplemental Box-----

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 05/48711

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:
Prior Supplemental Box

Regarding claim 4, directed to the salt according to claim 1 wherein said anion is an anion of Formula IV, Nielsen teaches compounds corresponding to the structure of Formula IV (col 2, in 45-55). Nielsen as above teaches that the compounds may contain an SO₂ ring substituent at the position corresponding to that in the structure of Formula IV (col 2, in 64) and further having R3 and R4 substituents of the Formula IV structure corresponding to the "A" ring as defined (col 4, in 1-34). Nielsen as above teaches that the A ring may have one or more amino substituents (col 4, in 7). Nielsen as above teaches that substituents corresponding to R2b may be hydrogen (col 3, in 4-10). Nielsen as above teaches that R1, which position corresponds to the combination of "B", R4 and R5 taught by Nielsen, and described as where R4 together with R5 represent one of the bonds in a double bond between the atoms 2 and 3 of the illustrated formula or R1 together with R4, represents one of the bonds in a double bond between the atoms 3 and 4 of the illustrated formula (col 2, in 57-64, col 3, in 6-10). It would have been obvious to one of skill in the art that the substituted amino substituent at position R1 could be readily deaminated by techniques known in the art. Alternatively, it would have been obvious to one of skill in the art to utilize a derivative of diazoxide as taught by Nielsen since the ring structure of diazoxide is not amino-substituted at the 3 position of the ring.

Regarding claim 5, directed to the salt according to claim 1 wherein said anion is an anion of diazoxide, Nielsen as above teaches diazoxide and derivatives (col 2, in 14-20).

Regarding claim 7, directed to the salt according to claim 1 wherein said alkali metal cation is selected from a sodium cation or a potassium cation, Nielsen as above teaches sodium and potassium cations (col 4, in 42-51).

Regarding claim 8, directed to the salt according to claim 1 wherein said salt is selected from a sodium, potassium, choline, or hexamethyl hexamethylene diammonium salt of Formula III or Formula IV, Nielsen as above teaches sodium and potassium cations (col 4, in 42-51).

Regarding claim 9, directed to a pharmaceutical formulation comprising the salt according to claim 1, Nielsen further teaches that the compounds may be a pharmaceutical formulation (col 18, in 31-33).

Claim 6 lacks an inventive step under PCT Article 33(3) as being obvious over Nielsen in view of US 2004/0229803 A1 to Stephenson et al. (hereinafter "Stephenson").

Regarding claim 6, directed to the salt according to claim 1 wherein said compound comprising a tertiary amine or ammonium group is selected from choline or hexamethyl hexamethylene diammonium, Nielsen as above teaches that the compounds may be in the form of salts (col 4, in 33-35). Nielsen also teaches ammonium cations (col 4, in 42-51). Nielsen does not explicitly teach choline or hexamethyl hexamethylene diammonium. Stephenson further teaches potassium ion channel modulators (para [0414]) which utilize choline as a cationic species (para [0072], [0400]). It would have been obvious to one of skill in the art to combine the teachings of Nielsen and Stephenson to use choline as a cationic species for a salt of the compounds of Formulas I-IV, because both references teach compounds active in the modulation of potassium channels and choline would have been expected to act as a suitable pharmaceutical cation with the anion of formulas I-IV.

Claims 71-76 and 78 lack an inventive step under PCT Article 33(3) as being obvious over Nielsen in view of US 2004/0266822 A1 to Wang et al. (hereinafter "Wang").

Regarding claim 71, directed to the formulation according to any one of claims 9, 16 and 23 further comprising another pharmaceutically active agent, Nielsen as above teaches that the compounds may be a pharmaceutical formulation (col 18, in 31-33). Nielsen does not explicitly teach the formulation in combination with another pharmaceutically active agent. Wang further teaches amine derivatives which can be antagonized by sulfonylureas that inhibit the KATP channel (para [0005], [0007]). Wang also teaches that the amine derivatives could be combined with other agents that influence the activity of potassium ion channels (para [0007]). It would have been obvious to one of skill in the art to combine the teachings of Nielsen and Wang to combine the pharmaceutical agent taught by Wang with the compounds of Nielsen, because of the direct suggestion to combine agents for affecting KATP channel activity for therapeutic use.

Regarding claim 72, directed to the formulation according to claims 71 wherein 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, obesity associated co-morbidities, ischemic and reperfusion injury, epilepsy, cognitive impairment, schizophrenia, mania, and other psychotic condition, Wang further teaches an agent useful for treatment of diabetes (para [0001]).

Regarding claim 73, directed to the pharmaceutical formulation according to any one of claims 9, 16 and 23 further comprising a pharmaceutically active agent other than the KATP channel opener, Wang as above teaches amine derivatives which can be antagonized by sulfonylureas that inhibit the KATP channel (para [0005], [0007]).

Regarding claim 74, see the discussion set forth for claim 72.

Regarding claim 75, directed to the formulation according to claim 9 wherein said cation of the salt is selected from the sodium, potassium, choline and hexamethyl hexamethylene diammonium hydroxide of diazoxide, Nielsen as above teaches sodium and potassium cations (col 4, in 42-51).

Regarding claim 76, directed to the formulation according to claim 75 for a single administration that contains between 10 and 2000 mg of the salt, Nielsen as above teaches a dosage of between 0.5mg to 1000 mg per day (col 18, in 11-16).

-----continued in next Supplemental Box-----

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 06/48711

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:
Prior Supplemental Box

Regarding claim 78, directed to the formulation according to claim 75 further comprising a component that contributes to the sustained release of the KATP channel opener over a period of 2-24 hours, Nielsen further teaches sustained release formulations (col 18, ln 49-52). Although neither Nielsen nor Wang specify the duration of sustained release, it would have been obvious to one of skill in the art to combine the teaching of Nielsen and Wang to determine the period of composition release and to infer that a sustained release formulation would be active at least two hours.

Claims 30-31 and 77 lack an inventive step under PCT Article 33(3) as being obvious over Nielsen in view of Wang and further in view of US 2005/0203072 A1 to Rudolph et al. (hereinafter 'Rudolph')

Regarding claim 30, directed to the formulation according to claim 29 further comprising at least one component that substantially inhibits release of the KATP channel opener from the formulation until after gastric transit, Wang further teaches antagonists to inhibit KATP channel activity (para [0214]). Neither Nielsen nor Wang specifically teach components inhibiting the release of a KATP channel opener. Rudolph further teaches pH-sensitive dose release formulations (para [0237]) of benzothiadiazine compounds (para [0154]). It would have been obvious to one of skill in the art to combine the teachings of Nielsen, Wang and Rudolph to add a component that substantially inhibits release of the KATP channel opener from the formulation until after gastric transit, because benzothiadiazines are chemically and pharmaceutically related to the KATP channel openers and would have been expected to be prevented from release and activity until after gastric transit due to the pH-sensitivity of the coating.

Regarding claim 31, directed to the formulation according to claim 30 wherein the component is 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 copolymer 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, and (h) combinations of these approaches, wherein the pH sensitive polymer or co-polymer is resistant to degradation under acid conditions, Rudolph, as above, teaches a pH-sensitive dose release formulations (para [0237]) of benzothiadiazine compounds (para [0154]). Rudolph also teaches polymer compression coatings of tablets (para [0234], [0237]).

Regarding claim 77, directed to the formulation according to claim 75 wherein said formulation is a controlled release formulation further comprising at least one component that substantially inhibits release of the KATP channel opener from the formulation until after gastric transit, Nielsen teaches delayed release formulations (col 18, ln 49-52). Wang, as above, teaches antagonists to inhibit KATP channel activity (para [0214]). Rudolph further teaches pH-sensitive dose release formulations (para [0237]) of benzothiadiazine compounds (para [0154]). It would have been obvious to one of skill in the art to combine the teachings of Nielsen, Wang and Rudolph to provide a controlled release formulation further comprising at least one component that substantially inhibits release of the KATP channel opener from the formulation until after gastric transit, because benzothiadiazines are chemically and pharmaceutically related to the KATP channel openers and would have been expected to be prevented from release and activity until after gastric transit due to the pH-sensitivity of the coating, especially in view of delayed release teaching of Nielsen.

Claims 1-31 and 71-78 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
RICHARD J. WARBURG
FOLEY & LARDNER LLP
P.O. BOX 80278
SAN DIEGO, CA 92138-0278

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year)

30 SEP 2008

Applicant's or agent's file reference
059599-0406

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US 08/68936

International filing date (day/month/year)

01 July 2008 (01.07.2008)

Priority date (day/month/year)

02 July 2007 (02.07.2007)

International Patent Classification (IPC) or both national classification and IPC

IPC(8) - A61K 31/54 (2008.04)

USPC - 514/223.2

Applicant ESSENTIALIS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-3201

Date of completion of this opinion

24 September 2008 (24.09.2008)

Authorized officer:

Lss W. Young

PCT Helpdesk: 571-272-4302
PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (April 2007)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 08/68936

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 10-11 and 29

because: improper multiple dependent claims

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____ are so unclear that no meaningful opinion could be formed (*specify*):

Claims 10-11 and 29 are improper multiple dependent claims because they are dependent claims and are not drafted in accordance with the first and second sentences of Rule 6.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☒ no international search report has been established for said claims Nos. 10-11 and 29

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details.

Form PCT/ISA/237 (Box No. III) (April 2007)

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US 08/68936

Box No. V	Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement							
1.	Statement							
	Novelty (N)	<table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 30%;">Claims</td> <td style="width: 40%;">15-18, 17, 19, 39 and 41</td> <td style="width: 30%; text-align: right;">YES</td> </tr> <tr> <td>Claims</td> <td>1-9, 12-14, 18, 20-28, 30-38, 40 and 42-75</td> <td style="text-align: right;">NO</td> </tr> </table>	Claims	15-18, 17, 19, 39 and 41	YES	Claims	1-9, 12-14, 18, 20-28, 30-38, 40 and 42-75	NO
Claims	15-18, 17, 19, 39 and 41	YES						
Claims	1-9, 12-14, 18, 20-28, 30-38, 40 and 42-75	NO						
	Inventive step (IS)	<table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 30%;">Claims</td> <td style="width: 40%;">NONE</td> <td style="width: 30%; text-align: right;">YES</td> </tr> <tr> <td>Claims</td> <td>1-9, 12-28 and 30-75</td> <td style="text-align: right;">NO</td> </tr> </table>	Claims	NONE	YES	Claims	1-9, 12-28 and 30-75	NO
Claims	NONE	YES						
Claims	1-9, 12-28 and 30-75	NO						
	Industrial applicability (IA)	<table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 30%;">Claims</td> <td style="width: 40%;">1-9, 12-28 and 30-75</td> <td style="width: 30%; text-align: right;">YES</td> </tr> <tr> <td>Claims</td> <td>NONE</td> <td style="text-align: right;">NO</td> </tr> </table>	Claims	1-9, 12-28 and 30-75	YES	Claims	NONE	NO
Claims	1-9, 12-28 and 30-75	YES						
Claims	NONE	NO						
2.	Citations and explanations: Claims 1-9, 12-14, 18, 20-28, 30-38, 40 and 42-75 lack novelty under PCT Article 33 (2) as being anticipated by WO 2006/026469 A2 to Cowen et al. (hereafter "Cowen"). Regarding claim 1, Cowen teaches the method of treating a dyslipidemia (abstract; para [0066]) by (a) reducing an abnormally high total cholesterol level in a subject's blood (para [0226]), (b) reducing an abnormally high LDL cholesterol level in a subject's blood (para [0274]; [0279]), (c) reducing an abnormally high VLDL cholesterol level in a subject's blood (para [0274]; [0398]), (d) reducing an abnormally high non-HDL cholesterol level in a subject's blood (para [0274]; [0279]) (e) reducing an abnormally high triglyceride level in a subject's blood (para [0398]) and/or (b) raising an abnormally low HDL cholesterol level in a subject's blood, comprising administering to said subject a therapeutically effective amount of a formulation selected from (para [0021]; [0256]-[0257]; [0279]): i) a formulation comprising a K ATP channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, Formula V, Formula VI, Formula VII, and Formula VIII (see para [0021]-[0039]); Regarding claim 2, Cowen teaches the method of claim 1 wherein said subject suffers from nonalcoholic steatohepatitis (para [0130]; [0149]). Regarding claim 3, Cowen teaches the method of claim 1 wherein said subject is at risk for pancreatitis (para [0240]; [0269]). Regarding claim 4, Cowen teaches the method of claim 1 wherein said subject suffers or is at risk for metabolic syndrome (para [0398]). Regarding claim 5, Cowen teaches the method of claim 1 wherein said subject is obese (para [0052]). Regarding claim 6, Cowen teaches the method of claim 1 wherein the total cholesterol level in said subject's blood is reduced (para [0074]). Regarding claim 7, Cowen teaches the method of claim 1 wherein said formulation is administered once per 24 hours (para [0099]). Regarding claim 8, Cowen teaches the method of claim 1 wherein said formulation is administered twice per 24 hours (para [0099]). Regarding claim 9, Cowen teaches the method of anyone of claims 1-8 wherein said KATP channel opener is diazoxide choline (para [0197]). Regarding claim 12, Cowen teaches the method of reducing the level of circulating triglycerides in a subject with an elevated level of circulating triglycerides, comprising administering to said subject a therapeutically effective amount of a formulation (para [0021]; [0120]; [0226]; [0274]) selected from a formulation comprising a KATP channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, Formula V, Formula VI, Formula VII, and Formula VIII (see para [0021]-[0039]). Regarding claims 13-14, The method of claim 11 wherein the formulation further comprises a HMGCoA reductase inhibitor statin (para [0226]). Regarding claim 18, Cowen teaches the method of claim 12 wherein the formulation further comprises a thyroid receptor activator (para [0224]). Regarding claim 20, Cowen teaches the method of claim 12 wherein the formulation further comprises a squalene synthase inhibitor (para [0266]). Regarding claim 21, Cowen teaches the method of anyone of claims 12-20 wherein the KATP channel opener is diazoxide choline (para [0197]). Regarding claim 22, Cowen teaches the method of anyone of claims 12-20 wherein said subject is diagnosed with conditions selected from the group consisting of hypercholesterolemia, combined hyperlipidemia, endogenous hyperlipidemia, and hypertriglyceridemia (para [0273]). (please see continuation in supplemental box)							

Form PCT/ISA/237 (Box No. V) (April 2007)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 08/68936

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Box V.2 (Citations and Explanations):

Regarding claim 23, Cowen teaches the method of anyone of claims 12-20 wherein said subject has elevated circulating total cholesterol (para [0334]; [0337]).

Regarding claim 24, Cowen teaches the method of anyone of claims 12-20 wherein said subject has elevated circulating LDL-cholesterol (para [0337]; [0358]).

Regarding claim 25, Cowen teaches the method of anyone of claims 12-20 wherein said subject has normal circulating total cholesterol (para [0337]; [0350]).

Regarding claim 26, Cowen teaches the method of anyone of claims 12-20 wherein said subject has normal circulating LDL-cholesterol (para [0337]; [0350]).

Regarding claim 27, Cowen teaches the method of claim 12 wherein the patient has low circulating HDL-cholesterol (para [0254]; [0256]).

Regarding claim 28, Cowen teaches the method of claim 12 wherein the patient has normal circulating HDL-cholesterol (para [0254]; [0256]).

Regarding claim 30, Cowen teaches the method of (a) reducing insulin dosing (para [0235]), (b) increasing glycemic control (para [0271]) comprising administering to said subject a therapeutically effective amount of a formulation (para [0270]) selected from the formulation comprising a salt, said salt comprising an amon of a KATP channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII (see para [0021]-[0039]).

Regarding claim 31, Cowen teaches the method of claim 30 wherein the formulation is administered once per 24 hours (para [0099]).

Regarding claim 32, Cowen teaches the method of claims 30 or 31 wherein the KATP channel opener is diazoxide choline (para [0197]).

Regarding claim 33, Cowen teaches the method of treating a subject suffering from type II diabetes, comprising co-administering to said subject a therapeutically effective amount of a formulation a (para [0273]) and an anti-diabetic drug that stimulates insulin secretion or is a short-acting antidiabetic drug (para [0396]), wherein the formulation is selected from a formulation comprising a KATP channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, Formula V, Formula VI, Formula VII, and Formula VIII (see para [0021]-[0039]).

Regarding claim 34, Cowen teaches the method of claim 33 wherein the formulation is administered once per 24 hours (para [0099]).

Regarding claim 35, Cowen teaches the method of claim 33 wherein the formulation and the short-acting antidiabetic drug are co-administered separately, sequentially or simultaneously (para [0396]).

Regarding claim 36, Cowen teaches the method of claim 33 wherein the anti-diabetic drug is one or more agents selected from the group consisting of a DPP-IV inhibitor, a PPAR agonist or partial agonist, a GLP-1 analog or mimetic, a thiazolidinedione, a disaccharidase inhibitor, a fructose-1, 6-bisphosphatase inhibitor, and a sulfonylurea receptor antagonist (para [0079]).

Regarding claim 37, Cowen teaches the method of claim 36 wherein the sulfonylurea receptor antagonist is a meglitinide (para [0194]; [0225]).

Regarding claim 38, Cowen teaches the method of claim 37 wherein the meglitinide is one or more agents selected from the group consisting of repaglinide, nateglinide, mitiglinide and pharmaceutically acceptable salts thereof (para [0225]).

Regarding claim 40, Cowen teaches the method of claim 36 wherein the GLP-1 analog or mimetic is one or more agents selected from the group consisting of exenatide, liraglutide, albugan, exendin-4 analogs and conjugates, and pharmaceutically acceptable salts and conjugates thereof (para [0225]).

Regarding claim 42, Cowen teaches the method of claim 36 wherein the disaccharidase inhibitor is one or more agents selected from the group consisting of acarbose, AO-128, and pharmaceutically acceptable salts thereof (para [0074]).

Regarding claim 43, Cowen teaches the method of claim 36 wherein the fructose-1,6-bisphosphatase inhibitor is one or more agents selected from the group consisting of phenyl phosphonates, benzimidazoles, CS-917, emlinquinazones, benzoxazole benzenesulfonamides, and pharmaceutically acceptable salts thereof. (para [0193]).

(please see continuation in supplemental box)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/68936

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:
Box V.2 (Citations and Explanations):

Regarding claim 44, Cowen teaches the method of claim 36 wherein the formulation comprises 50 to 450 mg of diazoxide choline and is administered once per 24 hours as a controlled release oral formulation, and the anti-diabetic is a pharmaceutical composition comprising 5 to 10 ug exenatide and is administered twice per 24 hours, before meals (para [0205]).

Regarding claim 45, Cowen teaches the method of claim 44 wherein the controlled release oral formulation is a tablet and the exenatide is administered by subcutaneous injection (para [0241]; [0245]).

Regarding claim 46, Cowen teaches the method of claim 36 wherein the formulation comprises 50 to 500 mg of diazoxide choline and is administered once per 24 hours as a controlled release oral formulation, and the short-acting anti-diabetic is a pharmaceutical composition comprising the meglitinide and is administered three times per 24 hours, before meals (para [0205]; [0396]).

Regarding claim 47, Cowen teaches the method of claim 36 wherein the anti-diabetic is exenatide, nateglinide, mitglinide, repaglinide, and pharmaceutically acceptable salts or conjugates thereof. (para [0225]).

Regarding claim 48, Cowen teaches the method of anyone of claims 33-47 wherein the K ATP channel opener is diazoxide choline (para [0197]).

Regarding claim 49, Cowen teaches the method of anyone of claims 33-47 wherein the K ATP channel opener is administered at bedtime (para [0205]; [0069]).

Regarding claims 50 and 54, Cowen teaches the method of treating poly-cystic ovarian syndrome, comprising administering to said subject a therapeutically effective amount of a formulation (para [0240]) selected from a formulation comprising a salt, said salt comprising an anion of a K ATP channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and a cation selected from the group consisting of an alkali metal and a compound comprising a tertiary amine or ammonium group (para [0194]; [0021]-[0039]).

Regarding claim 51, Cowen teaches the method of claim 50 wherein said treatment reduces circulating androgen levels or reestablishes normal ovulation cycles (para [0205]).

Regarding claims 52 and 55, Cowen teaches the method of claim 50 wherein the formulation is administered once per 24 hours (para [0099]).

Regarding claims 53 and 57, Cowen teaches the method of claims 50-52 wherein the K ATP channel opener is diazoxide choline (para [0197]).

Regarding claim 56, Cowen teaches the method of claim 54 wherein the formulation and the androgen inhibitor, selective estrogen receptor modulator (SERM), or ovulation inducing agent are co-administered separately, sequentially or simultaneously (para [0396]).

Regarding claim 58, Cowen teaches the method of treating a subject suffering from poly-cystic ovarian syndrome comprising administering to said subject a therapeutically effective amount of a formulation selected from a formulation comprising a salt, said salt comprising an anion of a K ATP channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and a cation selected from the group consisting of an alkali metal and a compound comprising a tertiary amine or ammonium group (para [0240]; [0021]-[0039]).

Regarding claim 59, Cowen teaches the method of claim 58 wherein the formulation is administered once per 24 hours (para [0099]).

Regarding claim 60, Cowen teaches the method of anyone of claims 58-59 wherein the K ATP channel opener is diazoxide choline (para [0197]).

Regarding claim 61, Cowen teaches the method of treating a subject suffering from hypertension consisting essentially of administering to said subject a therapeutically effective amount of a single oral agent (para [0228]; [0241]) wherein the oral agent is a formulation comprising a salt, said salt comprising an anion of a K ATP channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and a cation selected from the group consisting of an alkali metal and a compound comprising a tertiary amine or ammonium group (para [0194]; [0021]-[0039]).

Regarding claim 62, Cowen teaches the method of claim 61 wherein the formulation is administered once per 24 hours (para [0099]).

Regarding claim 63, Cowen teaches the method of claims 61 or 62 wherein the K ATP channel opener is diazoxide choline (para [0197]).

(please see continuation in supplemental box)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/68936

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:
Box V.2 (Citations and Explanations):

Regarding claim 64, Cowen teaches the method of treating a subject suffering from hypoglycemia-associated autonomic failure (para [0241]) comprising administering to said subject a therapeutically effective amount of a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and a cation selected from the group consisting of an alkali metal and a compound comprising a tertiary amine or ammonium group (para [0194]; [0021]-[0039]).

Regarding claim 65, Cowen teaches the method of claim 61 wherein the formulation is administered once per 24 hours (para [0099]).

Regarding claim 66, Cowen teaches the method of claim 64 wherein the formulation is administered two times per 24 hours (para [0099]).

Regarding claim 67, Cowen teaches the method of claim 64 wherein the subject is suffering from type I Diabetes (para [0151]).

Regarding claim 68, Cowen teaches the method of claim 64 wherein the subject is suffering from type II diabetes (para [0239]).

Regarding claim 69, Cowen teaches the method of claim 64 wherein the formulation is an oral or an intranasal formulation (para [0267]).

Regarding claim 70, Cowen teaches the method of anyone of claims 64-69 wherein the KATP channel opener is diazoxide choline (para [0197]).

Regarding claim 71, Cowen teaches the formulation comprising diazoxide choline and about 1% to about 55% by weight of a polymer selected from the group consisting of polyethylene oxide and Cellulose (para [0360]).

Regarding claim 72, Cowen teaches the formulation of claim 71 wherein the cellulose is selected from hydroxypropylmethyl cellulose, hydroxypropylcellulose, ethylcellulose, methylcellulose, carboxymethylcellulose, and a mixture of any two or more thereof (para [0360]).

Regarding claim 73, Cowen teaches the formulation of claim 71 wherein the polyethylene oxide is selected from PEO N750, PEO 303 or a mixture thereof. (para [0373]).

Regarding claim 74, Cowen teaches the method of reducing the incidence of adverse effects resulting from orally administering a salt of a KATP channel opener comprising causing to be orally injected a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and a cation selected from the group consisting of an alkali metal and a compound comprising a tertiary amine or ammonium group (para [0055]; [0069]; [0194]; [0021]-[0039]).

Regarding claim 75, Cowen teaches the method of claim 74 wherein the formulation and the meal are taken within 15 minutes or less of each other (para [0069]; [0099]).

Claims 15 and 16 lack inventive step under PCT Article 33 (3) as being obvious over Cowen in view of US 6,140,343 A to DeNinno et al. (hereafter, DeNinno.).

Regarding claim 15, DeNinno teaches the method of claim 12 wherein the formulation further comprises a fibrate (col 21, in 23-33). It would have been obvious to one of skill in the art to incorporate fibrate as taught by DeNinno in to the method of treating dyslipidemia as taught by Cowen in order to provide a more effective treatment.

Regarding claim 16, DeNinno teaches the method of claim 12 wherein the formulation further comprises niacin (col 21, in 23-33).

Claims 17, 19, 39 and 41 lack inventive step under PCT Article 33 (3) as being obvious over Cowen in view of US 7,091,225 B2 (Sierra).

Regarding claim 17, Sierra teaches the method of claim 12 wherein the formulation further comprises a PPAR delta agonist or modulator (col 4, in 06-15). It would have been obvious to one of skill in the art to incorporate PPAR delta agonist as taught by Sierra in to the method of treating dyslipidemia as taught by Cowen in order to provide a more effective treatment.

Regarding claim 19, Sierra teaches the method of claim 12 wherein the formulation further comprises a MTP inhibitor (col 7, in 55-60).

Regarding claim 39, Sierra teaches the method of claim 36 wherein the DPP-IV inhibitor is one or more agents selected from the group consisting of sitagliptin, saxagliptin, vildagliptin, and pharmaceutically acceptable salts thereof (col 7, in 55-67).

Regarding claim 41, Sierra teaches the method of claim 36 wherein the thiazolidinedione or PPAR agonist or partial agonist is one or more agents selected from pioglitazone, rosiglitazone, troglitazone, tesaglitazar, muraglitazar, netoglitazar, LY518674, ragaglitazar, sipoglitazar, and pharmaceutically acceptable salts thereof. (col 7, in 55-67).

Claims 1-75 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

ANTHONY KUHLMANN

SHEPPARD MULLIN RICHTER & HAMPTON LLP 12275
EL CAMINO REAL, SUITE 200 SAN DIEGO CA 92130
USA

PCT

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

(PCT Rule 43bis.1)

Date of mailing
(day/month/year) **21 June 2013 (21.06.2013)**

Applicant's or agent's file reference
169559-WO-1

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US2013/027676

International filing date (day/month/year)

25 February 2013 (25.02.2013)

Priority date (day/month/year)

27 February 2012 (27.02.2012)

International Patent Classification (IPC) or both national classification and IPC

A61K 31/549(2006.01)I, A61K 31/38(2006.01)I, A61P 3/00(2006.01)I, A61P 9/00(2006.01)I

Applicant

ESSENTIALIS, INC. et al

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/KR
Korean Intellectual Property Office
189 Cheongsu-ro, Seo-gu, Daejeon
Metropolitan City, 302-701, Republic of
Korea
Facsimile No. 82-42-472-7140

Date of completion of this opinion

21 June 2013 (21.06.2013)

Authorized officer

CHOI, Sung Hee

Telephone No. 82-42-481-8740



WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US2013/027676

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of :

- ☒ the international application in the language in which it was filed
- ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

2. ☐ This opinion has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

a. a sequence listing filed or furnished

- ☐ on paper
- ☐ in electronic form

b. time of filing or furnishing

- ☐ contained in the international application as filed.
- ☐ filed together with the international application in electronic form.
- ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 1-34, 38-43, 45-52

because:

☒ the said international application, or the said claims Nos. 1-34, 45-52

relate to the following subject matter which does not require an international search (*specify*):

The subject matter of claims 1-34 and 45-52 is directed to a method for treatment of the human body by therapy (PCT Rule 43 bis.1(b), Rule 67.1(iv)).

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 7, 18, 24, 30, 31, 33, 34, 39 are so unclear that no meaningful opinion could be formed (*specify*):

Claims 7, 18, 24, 30, 31, 33, 34, and 39 are unclear, since they either directly or indirectly refer to one of claims which are not drafted in accordance with PCT Rule 6.4(a) (PCT Article 6).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☒ no international search report has been established for said claims Nos. 1-34, 38-43, 45-52

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).

☐ See Supplemental Box for further details.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2013/027676

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	35-37,44	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	35-37,44	NO
Industrial applicability (IA)	Claims	35-37,44	YES
	Claims	NONE	NO

2. Citations and explanations :

Reference is made to the following document:

D1: US 2009-0062264 A1 (COWEN et al) 05 March 2009

1. Novelty and Inventive Step

1.1. Independent Claim 35

The subject matter of claim 35 relates to a kit comprising: a pharmaceutical treatment blister card with a plurality of blister cavities; seven to twenty eight daily dosages of a K_{ATP} channel opener; and seven to twenty eight daily dosages of a fibrate or a salt thereof, wherein the daily dosages of said K_{ATP} channel opener and said fibrate are suboptimal titration dosages.

D1, which is considered to be the closest prior art to the subject matter of claim 35, discloses a formulation comprising a K_{ATP} channel opener and fibrate (See claims 13 and 16 in D1.) and administration of said formulation for 7 or more days (See paragraph [0301] in D1.), wherein the administration of the formulation may include escalating dose from a starting dose (See paragraph [0121] in D1).

Claim 35 differs from D1 in a kit comprising a pharmaceutical treatment blister card with a plurality of blister cavities. However, said feature is merely a matter of design option when the general knowledge in relevant field of the art is used.

Continued on Supplemental Box

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2013/027676

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

Claims 6, 8-11, 15-17, 19-23, 25-29, 32, 38, 40-43, and 49-52 do not comply with PCT Rule 6.4(a), because multiple dependent claims should not serve as a basis for any other multiple dependent claim.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of : Box No. V

Therefore, claim 35 is novel under PCT Article 33(2), but lacks an inventive step under PCT Article 33(3).

1.2. Dependent Claims 36, 37, and 44

Claims 36, 37, and 44, ultimately dependent on claim 35, define contents of said plurality of blister cavities (claims 36 and 37); and a type of said fibrate or a salt thereof (claim 44). D1 does not explicitly disclose the additional features of claims 36, 37, and 44. However, said features are merely one of several straightforward possibilities from which a skilled person in the art would select in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed. Therefore, claims 36, 37, and 44 are novel under PCT Article 33(2), but lack an inventive step under PCT Article 33(3).

2. Industrial Applicability

Claims 35-37 and 44 are industrially applicable under PCT Article 33(4).

Substitute for form 1449A/PTO

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT***(Use as many sheets as necessary)***Complete if Known**

Sheet	1	of	4	Application Number	14/940,018
				Filing Date	November 12, 2015
				First Named Inventor	Neil M. Cowen
				Art Unit	1625
				Examiner Name	Taylor V. Oh
				Attorney Docket Number	CAPN-034/04US 328512-2375

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-2003/0068366-A1	04-10-2003	Chungi et al.	
	2.	US-2003/0211123-A1	11-13-2003	Shukla et al.	
	3.	US-2004/0143213-A1	07-22-2004	Hunter et al.	
	4.	US-2006/0051418-A1	03-09-2006	Cowen et al.	
	5.	US-2006/0128673-A1	06-15-2006	Firnges et al.	
	6.	US-2009/0062264-A1	03-05-2009	Cowen et al.	
	7.	US-2009/0148525-A1	06-11-2009	Cowen	
	8.	US-2009/0149451-A1	06-11-2009	Cowen	
	9.	US-2010/0028429-A1	02-04-2010	Cowen et al.	
	10.	US-2010/0256360-A1	10-07-2010	Cowen et al.	
	11.	US-2012/0053172-A1	03-01-2012	De Boer	
	12.	US-2012/0238554-A1	09-20-2012	Cowen	
	13.	US-2013/0040942-A1	02-14-2013	Cowen et al.	
	14.	US-2013/0309301-A1	11-21-2013	Cowen et al.	
	15.	US-2014/0350001-A1	11-27-2014	Cowen	
	16.	US-2014/0364425-A1	12-11-2014	Cowen et al.	
	17.	US-7,572,789-B2	08-11-2009	Cowen et al.	
	18.	US-7,799,777-B2	09-21-2010	Cowen et al.	
	19.	US-9,381,202-B2	07-05-2016	Cowen et al.	

Examiner Signature		Date Considered	
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Substitute for form 1449A/PTO

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT***(Use as many sheets as necessary)***Complete if Known**

Application Number	14/940,018
Filing Date	November 12, 2015
First Named Inventor	Neil M. Cowen
Art Unit	1625
Examiner Name	Taylor V. Oh
Attorney Docket Number	CAPN-034/04US 328512-2375

Sheet

2

of

4

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 ² "Number" "Kind Code" ³ (if known)				
	20.	WO-2006/026469-A2,A3	03-09-2006	Essentialis, Inc.		
	21.	WO-2007/081521-A2,A3	07-19-2007	Essentialis, Inc.		
	22.	WO-2009/006483-A1	01-08-2009	Essentialis, Inc.		
	23.	WO-2013/130411-A1	09-06-2013	Essentialis, Inc.		
	24.	WO-2016/077629-A1	05-19-2016	Essentialis, Inc.		

Examiner Signature		Date Considered	
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Substitute for form 1449B/PTO

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT***(Use as many sheets as necessary)***Complete if Known**

Application Number	14/940,018
Filing Date	November 12, 2015
First Named Inventor	Neil M. Cowen
Art Unit	1625
Examiner Name	Taylor V. Oh
Attorney Docket Number	CAPN-034/04US 328512-2375

Sheet 3 of 4

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
	25.	Advisory Action mailed on December 30, 2015, for U.S. Patent Application Number 14/458,032, filed on August 12, 2014, 3 pages.	
	26.	Ashcroft, F.M. et al. (1999). "ATP-sensitive K ⁺ channels and insulin secretion: their role in health and disease," <i>Diabetologia</i> . 42:903-919.	
	27.	Ashcroft, F.M. et al. (2000). "New windows on the mechanism of action of K(ATP) channel openers," <i>Trends Pharmacol. Sci.</i> 21:439-445.	
	28.	Bay, H.E. et al. (2010). "Diazoxide choline controlled release in hyperglyceridemic subjects: Lipid and other metabolic effects," <i>J. American College of Cardiology</i> 55(10a), 1 total page.	
	29.	Clinical Trials.Gov (2014). "Clinical study of diazoxide choline controlled-release tablet (DCCR) in patients with Prader-Willi syndrome," Clinical trials identifier NCT02034071, updated January 10, 2014, Retrieved from https://clinicaltrials.gov/archive/nct02034071/2014_01_10 , 4 total pages.	
	30.	Eiholzer, U. et al. (1998). "Treatment with human growth hormone in patients with Prader-Labhart-Willi syndrome reduces body fat and increases muscle mass and physical performance," <i>Eur. J. Pediatr.</i> 157:368-377.	
	31.	Einspieler, C. et al. (2012). "Early behavioural manifestation of Smith-Magenis syndrome (del 17p11.2) in a 4-month-old boy" <i>Dev. Neurorehab.</i> 15(4):313-316.	
	32.	Final Office Action mailed on March 24, 2010, for U.S. Patent Application Number 11/212,130, filed on August 25, 2005, 15 pages.	
	33.	Final Office Action mailed on June 9, 2010, for U.S. Patent Application Number 12/368,215, filed on February 9, 2009, 9 pages.	
	34.	Final Office Action mailed on October 17, 2014, for U.S. Patent Application Number 12/370,456, filed on February 12, 2009, 14 pages.	
	35.	Final Office Action mailed on March 8, 2012, for U.S. Patent Application Number 12/370,456, filed on February 12, 2009, 13 pages.	
	36.	Final Office Action mailed on January 13, 2017, for U.S. Patent Application Number 14/458,032, filed on August 12, 2014, 14 pages.	
	37.	Final Office Action mailed on November 2, 2015, for U.S. Patent Application Number 14/458,032, filed on August 12, 2014, 13 pages.	
	38.	International Search Report mailed on February 2, 2016, for PCT Application Number PCT/US2015/60455, filed on November 12, 2015, 3 pages.	
	39.	International Search Report mailed on June 16, 2006, for PCT Application Number PCT/US2005/30481, filed on August 25, 2005, 1 page.	
	40.	International Search Report mailed on December 6, 2007, for PCT Application Number PCT/US2006/48711, filed on December 20, 2006, 2 pages.	

Examiner Signature		Date Considered	
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Substitute for form 1449B/PTO

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT***(Use as many sheets as necessary)***Complete if Known**

Sheet	4	of	4	Application Number	14/940,018
				Filing Date	November 12, 2015
				First Named Inventor	Neil M. Cowen
				Art Unit	1625
				Examiner Name	Taylor V. Oh
				Attorney Docket Number	CAPN-034/04US 328512-2375

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
	41.	International Search Report mailed on September 30, 2008, for PCT Application Number PCT/US2008/68936, filed on July 1, 2008, 2 pages.	
	42.	International Search Report mailed on June 21, 2013, for PCT Application Number PCT/US2013/027676, filed on February 25, 2013, 4 pages.	
	43.	Lee, P.D. (2002). "Disease management of Prader-Willi syndrome," <i>Expert Opin. Pharmacother.</i> 3:1451-1459.	
	44.	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.	
	45.	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.	
	46.	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.	
	47.	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.	
	48.	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.	
	49.	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.	
	50.	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.	
	51.	Proglycem® (2003). Pharmaceutical Information, Diazoxide Hyperglycemic Agent, 5 total pages.	
	52.	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.	
	53.	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.	
	54.	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.	
	55.	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.	
	56.	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.	

Examiner Signature		Date Considered	
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Electronic Patent Application Fee Transmittal				
Application Number:		14940018		
Filing Date:		12-Nov-2015		
Title of Invention:		METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME		
First Named Inventor/Applicant Name:		Neil M. Cowen		
Filer:		Kimberly Anne Bolin/Patricia Ellison		
Attorney Docket Number:		CAPN-034/04US 328512-2375		
Filed as Small Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Miscellaneous:				
RCE- 1st Request	2801	1	600	600
Total in USD (\$)				600

Electronic Acknowledgement Receipt

EFS ID:	29024413
Application Number:	14940018
International Application Number:	
Confirmation Number:	6992
Title of Invention:	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME
First Named Inventor/Applicant Name:	Neil M. Cowen
Customer Number:	58249
Filer:	Kimberly Anne Bolin/Patricia Ellison
Filer Authorized By:	Kimberly Anne Bolin
Attorney Docket Number:	CAPN-034/04US 328512-2375
Receipt Date:	25-APR-2017
Filing Date:	12-NOV-2015
Time Stamp:	17:54:42
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	\$600
RAM confirmation Number	042617INTEFSW00009083501283
Deposit Account	501283
Authorized User	Patricia Ellison
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.16 (National application filing, search, and examination fees) 37 CFR 1.17 (Patent application and reexamination processing fees)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Continued Examination (RCE)	RCE.pdf	1349864	no	3
			5f20038b901a5026929d5691b29b26d85b00a672		

Warnings:**Information:**

2		Amendment_with_RCE.pdf	118195	yes	5
			c88c05f09269b55f818fcfb7f91286a9a00e271e		

Multipart Description/PDF files in .zip description

Document Description		Start	End
Amendment Submitted/Entered with Filing of CPA/RCE		1	1
Specification		2	2
Applicant Arguments/Remarks Made in an Amendment		3	5

Warnings:**Information:**

3	Transmittal Letter	SIDS_Cover_Letter.pdf	78991	no	2
			bebd66e41f83e4539c211853f87957fbc1153d6f		

Warnings:**Information:**

4	Foreign Reference	20_WO2006026469A2A3.pdf	17189074	no	86
			42b9ab90567f2f5a8f7cdeb46c2730c4fe3bc13		

Warnings:**Information:**

5	Foreign Reference	21_WO2007081521A2A3.pdf	17995879	no	248
			43233abef82a00f669202345ba8274de6b335682		

Warnings:					
Information:					
6	Foreign Reference	22A_WO2009006483A1.pdf	12441760	no	150
			1860076462a8bbbbe643d30bd3042e0eca6a3a5f		
Warnings:					
Information:					
7	Foreign Reference	22B_WO2009006483A1.pdf	17457421	no	145
			fa5ae9be93c68bfc6d7b5b6aaad7c86065033e34		
Warnings:					
Information:					
8	Foreign Reference	23A_WO2013130411A1.pdf	13021264	no	160
			541acddb8dbab6dc4e04e2c64c9a730074ae05c		
Warnings:					
Information:					
9	Foreign Reference	23B_WO2013130411A1.pdf	9913228	no	166
			535e29b1da21eae064e3be3c1422a2bddb05cb67		
Warnings:					
Information:					
10	Foreign Reference	24_WO2016077629A1.pdf	18539585	no	111
			66f62b20cb9737d0389717e51ab39f9882fee794		
Warnings:					
Information:					
11	Non Patent Literature	25_AA_12_30_2015.pdf	640106	no	3
			90423335138fa6dc1244a6a1bc714599ed3de3be		
Warnings:					
Information:					
12	Non Patent Literature	26_Ashcroft_1999_p903.pdf	6287445	no	17
			563e0720261cf8fd2426a057726fc705f134d707		
Warnings:					
Information:					

13	Non Patent Literature	27_Ashcroft_2000_p439.pdf	4589993	no	7
			77e1f0b97ab837fd35a0aaab62875d344a1e761f		
Warnings:					
Information:					
14	Non Patent Literature	28_Bay_2010_55_10a.pdf	43754	no	1
			e01a84a7ce139232edabeb882ff948d1a604a6af		
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Information:					
15	Non Patent Literature	29_Clinical_Trials_NCT_02034071_2014.pdf	117861	no	4
			2cf6fdcb9976f003096548738679a523be451ae		
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Information:					
16	Non Patent Literature	30_Eiholzer_1998_p368.pdf	2293255	no	10
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Information:					
17	Non Patent Literature	31_Einspieler_2012_p313.pdf	75553	no	4
			b52b71ee1dcd91ba4eccb0c2a3261fb37856cf84		
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18	Non Patent Literature	32_FOA_3_24_2010.pdf	2476620	no	15
			714ae5d2c9c77f0350f99fbd3f43651720351e81		
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19	Non Patent Literature	33_FOA_6_9_2010.pdf	1531397	no	9
			5457cf62b16c455efa13bb4ac01874ad6cb1cd3		
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Information:					

20	Non Patent Literature	34_FOA_10_17_2014.pdf	2261059	no	14
			b092e689ee627396acdde4b6e6e9ee0aa2e2d88d		
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Information:					
21	Non Patent Literature	35_FOA_3_8_2012.pdf	2171714	no	13
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22	Non Patent Literature	36_FOA_1_13_2017.pdf	2617797	no	15
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24	Non Patent Literature	38_ISR_2_2_2016.pdf	477606	no	3
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25	Non Patent Literature	39_ISR_6_16_2006.pdf	198746	no	1
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26	Non Patent Literature	40_ISR_12_6_2007.pdf	412455	no	2
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Information:					

27	Non Patent Literature	41_ISR_9_30_2008.pdf	327828	no	2
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28	Non Patent Literature	42_ISR_6_21_2013.pdf	695686	no	4
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29	Non Patent Literature	43_Lee_2002_p1451.pdf	2632627	no	9
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30	Non Patent Literature	44_OA_9_17_2009.pdf	2234905	no	14
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31	Non Patent Literature	45_OA_8_1_2013.pdf	2020571	no	12
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Warnings:					
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32	Non Patent Literature	46_OA_12_8_2009.pdf	1224177	no	8
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Information:					
33	Non Patent Literature	47_OA_5_28_2014.pdf	2876297	no	17
			560e1c5b83b297c7621601a2427a5442889dd0e0		
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34	Non Patent Literature	48_OA_9_8_2011.pdf	1654398	no	11
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35	Non Patent Literature	49_OA_6_30_2016.pdf	2024326	no	12
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36	Non Patent Literature	50_OA_7_31_2015.pdf	2652004	no	16
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37	Non Patent Literature	51_Proglycem_2003.pdf	737421	no	5
			92d49b5f76dfcd1ef0d43c4266085ac7530d318		
Warnings:					
Information:					
38	Non Patent Literature	52_Written_Opinion_2_2_2016.pdf	1913569	no	8
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39	Non Patent Literature	53_Written_Opinion_6_16_2006.pdf	520671	no	3
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40	Non Patent Literature	54_Written_Opinion_12_6_2007.pdf	1783838	no	8
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Warnings:					
Information:					

41	Non Patent Literature	55_Written_Opinion_9_30_2008.pdf	1368693 7942055c002231e6908f8d6e657dec16271a4b7b	no	7
Warnings:					
Information:					
42	Non Patent Literature	56_Written_Opinion_6_21_2013.pdf	748636 73fc74ba6789676e3d3ccc9df58639e829d2d5d1	no	6
Warnings:					
Information:					
43	Information Disclosure Statement (IDS) Form (SB08)	SB08_.pdf	161279 ab45c9a9a9788c07dfacd8ae0ede85940fb9daa6	no	4
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
44	Fee Worksheet (SB06)	fee-info.pdf	30903 868dacc3b92f8bfa4728a65feb5cf728d6898b91	no	2
Warnings:					
Information:					
Total Files Size (in bytes):			162062737		
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. <u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a 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. <u>National Stage of an International Application under 35 U.S.C. 371</u> 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. <u>New International Application Filed with the USPTO as a Receiving Office</u> 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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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 06/28/2017
COOLEY LLP
ATTN: Patent Group
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

EXAMINER

OH, TAYLOR V

ART UNIT

PAPER NUMBER

1625

DATE MAILED: 06/28/2017

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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14/940,018

11/12/2015

Neil M. Cowen

CAPN-034/04US

6992

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	SMALL	\$480	\$0	\$0	\$480	09/28/2017

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 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity 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 and an extra copy of the form should be submitted. 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: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: **Mail** **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (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 including the Patent, advance orders and notification of maintenance fees 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.

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

58249 7590 06/28/2017
COOLEY LLP
ATTN: Patent Group
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 facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/940,018	11/12/2015	Neil M. Cowen	CAPN-034/04US 328512-2375	6992

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	SMALL	\$480	\$0	\$0	\$480	09/28/2017

EXAMINER	ART UNIT	CLASS-SUBCLASS
OH, TAYLOR V	1625	514-223500

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/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form 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 _____
 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 has been filed for recordation as set forth in 37 CFR 3.11. 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. The following fee(s) are submitted:

- ☐ Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies _____

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

- ☐ A check is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☐ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

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. _____



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/940,018	11/12/2015	Neil M. Cowen	CAPN-034/04US 328512-2375	6992
58249 7590 06/28/2017 COOLEY LLP ATTN: Patent Group 1299 Pennsylvania Avenue, NW Suite 700 Washington, DC 20004			EXAMINER OH, TAYLOR V	
			ART UNIT 1625	PAPER NUMBER
DATE MAILED: 06/28/2017				

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 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, 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. 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 disclosure of these records is required by the Freedom of Information Act.
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 inspection 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.

Notice of Allowability	Application No. 14/940,018	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 4/25/17.
☐ 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 3-9, 15, 19, 24, 25 and 27-29. 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 <u>4/25/17</u> | 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 _____. | |

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The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/25/17 has been entered.

Reasons of Allowance

The Status of Claims

Claims 3-9,15,19,24-25,27-29 are pending.

Claims 3-9,15,19,24-25,27-29 are allowed.

I. The following is an examiner's statement of reasons for allowance:

- The IDS filed on 4/25/17 have been reviewed and considered; however, they are irrelevant to the claimed invention.
- The close prior art to the current invention is Cotter (US2014/0364367) which teaches the combinational use of various active ingredients of a K_{ATP} channel opener in general and other therapies for treating an aggressive behaviors in a subject having PWS. However, there is no

motivation or suggestion in the prior art to use the specific diazoxide alone for at least 10 weeks to treat an aggressive behaviors in a subject having PWS. Therefore, it would have been unobvious to the skilled artisan in the art to arrive at the claimed invention.

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

6/10/17

Application/Control Number: 14/940,018
Art Unit: 1625

Page 4

WEST Search History for Application 14940018

Creation Date: 2017061000:07

Interference Searches

Query	DB	Hits	Op.	Plur.	Thes.	Date
(aggressive or psychotic) and behavior \$ 1	PGPB, USPT	43791	ADJ	YES		06-10-2017
((aggressive or psychotic) and behavior \$ 1) and (prader \$ 1willi syndrome or pws or smith \$ 1imagenis syndrome or sms)	PGPB, USPT	4260	ADJ	YES		06-10-2017
((aggressive or psychotic) and behavior \$ 1 and (prader \$ 1willi syndrome or pws or smith \$ 1imagenis syndrome or sms)) and diazoxide	PGPB, USPT	396	ADJ	YES		06-10-2017
((aggressive or psychotic) and behavior \$ 1 and (prader \$ 1willi syndrome or pws or smith \$ 1imagenis syndrome or sms) and diazoxide) and katp channel opener	PGPB, USPT	8	ADJ	YES		06-10-2017
((aggressive or psychotic) and behavior \$ 1 and (prader \$ 1willi syndrome or pws or smith \$ 1imagenis syndrome or sms) and diazoxide) and (514/ \$.ccls. or (a61k31/ \$ or a61k9/ \$ or a61k45/ \$ or a61k38/ \$ or a61k2300/ \$.cpc.)	PGPB, USPT	305	ADJ	YES		06-10-2017
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((aggressive or psychotic) and behavior \$ 1 and (prader \$ 1willi syndrome or pws or smith \$ 1imagenis syndrome or sms) and diazoxide and (514/ \$.ccls. or (a61k31/ \$ or a61k9/ \$ or a61k45/ \$ or a61k38/ \$ or a61k2300/ \$.cpc.) and (human growth hormone or igf \$ 1)) and katp channel opener	PGPB, USPT	2	ADJ	YES		06-10-2017
((aggressive or psychotic) and behavior \$ 1 and (prader \$ 1willi syndrome or pws or smith \$ 1imagenis syndrome or sms) and diazoxide and (514/ \$.ccls. or (a61k31/ \$ or a61k9/ \$ or a61k45/ \$ or a61k38/ \$ or a61k2300/ \$.cpc.) and (human growth hormone or igf \$ 1)) and choline	PGPB, USPT	286	ADJ	YES		06-10-2017

Prior Art Searches

Query	DB	Hits	Op.	Plur.	Thes.	Date
(aggressive or psychotic) and behavior\$1	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	45229	ADJ	YES		06-09-2017
((aggressive or psychotic) and behavior\$1) and (prader \$1willi syndrome or pws or smith\$1magenis syndrome or sms)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	4669	ADJ	YES		06-09-2017
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((aggressive or psychotic) and behavior\$1 and (prader \$1willi syndrome or pws or smith\$1magenis syndrome or sms) and diazoxide) and katp channel opener	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	10	ADJ	YES		06-09-2017
((aggressive or psychotic) and behavior\$1 and (prader \$1willi syndrome or pws or smith\$1magenis syndrome or sms) and diazoxide and katp channel opener) and (human growth hormone or igf\$1)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	4	ADJ	YES		06-09-2017
((aggressive or psychotic) and behavior\$1 and (prader \$1willi syndrome or pws or smith\$1magenis syndrome or sms) and	PGPB, USPT, USOC,	3	ADJ	YES		06-09-2017

diazoxide and katp channel opener and (human growth hormone or igf\$1)) and choline	EPAB, JPAB, DWPI, TDBD, FPRS					
((aggressive or psychotic) and behavior\$1 and (prader \$1willi syndrome or pws or smith\$1magenis syndrome or sms)) and diazoxide and (514/\$.ccls. or (a61k31/\$ or a61k9/\$ or a61k45/\$ or a61k38/\$ or a61k2300/\$).cpc.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	308	ADJ	YES		06-10-2017
((aggressive or psychotic) and behavior\$1 and (prader \$1willi syndrome or pws or smith\$1magenis syndrome or sms) and diazoxide and (514/\$.ccls. or (a61k31/\$ or a61k9/\$ or a61k45/\$ or a61k38/\$ or a61k2300/\$).cpc.)) and katp channel opener	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	10	ADJ	YES		06-10-2017
((aggressive or psychotic) and behavior\$1 and (prader \$1willi syndrome or pws or smith\$1magenis syndrome or sms) and diazoxide and (514/\$.ccls. or (a61k31/\$ or a61k9/\$ or a61k45/\$ or a61k38/\$ or a61k2300/\$).cpc.) and katp channel opener) and choline	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	9	ADJ	YES		06-10-2017

Substitute for form 1449A/PTO

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT***(Use as many sheets as necessary)***Complete if Known**

Sheet	1	of	4	Application Number	14/940,018
				Filing Date	November 12, 2015
				First Named Inventor	Neil M. Cowen
				Art Unit	1625
				Examiner Name	Taylor V. Oh
				Attorney Docket Number	CAPN-034/04US 328512-2375

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)			
/T.V.O/	1.	US-2003/0068366-A1	04-10-2003	Chungi et al.	
/T.V.O/	2.	US-2003/0211123-A1	11-13-2003	Shukla et al.	
/T.V.O/	3.	US-2004/0143213-A1	07-22-2004	Hunter et al.	
/T.V.O/	4.	US-2006/0051418-A1	03-09-2006	Cowen et al.	
/T.V.O/	5.	US-2006/0128673-A1	06-15-2006	Firnges et al.	
/T.V.O/	6.	US-2009/0062264-A1	03-05-2009	Cowen et al.	
/T.V.O/	7.	US-2009/0148525-A1	06-11-2009	Cowen	
/T.V.O/	8.	US-2009/0149451-A1	06-11-2009	Cowen	
/T.V.O/	9.	US-2010/0028429-A1	02-04-2010	Cowen et al.	
/T.V.O/	10.	US-2010/0256360-A1	10-07-2010	Cowen et al.	
/T.V.O/	11.	US-2012/0053172-A1	03-01-2012	De Boer	
/T.V.O/	12.	US-2012/0238554-A1	09-20-2012	Cowen	
/T.V.O/	13.	US-2013/0040942-A1	02-14-2013	Cowen et al.	
/T.V.O/	14.	US-2013/0309301-A1	11-21-2013	Cowen et al.	
/T.V.O/	15.	US-2014/0350001-A1	11-27-2014	Cowen	
/T.V.O/	16.	US-2014/0364425-A1	12-11-2014	Cowen et al.	
/T.V.O/	17.	US-7,572,789-B2	08-11-2009	Cowen et al.	
/T.V.O/	18.	US-7,799,777-B2	09-21-2010	Cowen et al.	
/T.V.O/	19.	US-9,381,202-B2	07-05-2016	Cowen et al.	

Examiner Signature	/TAYLOR V OH/	Date Considered	06/09/2017
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Substitute for form 1449A/PTO

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT***(Use as many sheets as necessary)***Complete if Known**

Application Number	14/940,018
Filing Date	November 12, 2015
First Named Inventor	Neil M. Cowen
Art Unit	1625
Examiner Name	Taylor V. Oh
Attorney Docket Number	CAPN-034/04US 328512-2375

Sheet

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of

4

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* "Number" "Kind Code" (if known)				
/T.V.O/	20.	WO-2006/026469-A2,A3	03-09-2006	Essentialis, Inc.		
/T.V.O/	21.	WO-2007/081521-A2,A3	07-19-2007	Essentialis, Inc.		
/T.V.O/	22.	WO-2009/006483-A1	01-08-2009	Essentialis, Inc.		
/T.V.O/	23.	WO-2013/130411-A1	09-06-2013	Essentialis, Inc.		
/T.V.O/	24.	WO-2016/077629-A1	05-19-2016	Essentialis, Inc.		

Examiner Signature	/TAYLOR V OH/	Date Considered	06/09/2017
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Substitute for form 1449B/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	14/940,018
				Filing Date	November 12, 2015
				First Named Inventor	Neil M. Cowen
				Art Unit	1625
				Examiner Name	Taylor V. Oh
Sheet	3	of	4	Attorney Docket Number	CAPN-034/04US 328512-2375

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	
/T.V.O/	25.	Advisory Action mailed on December 30, 2015, for U.S. Patent Application Number 14/458,032, filed on August 12, 2014, 3 pages.		
/T.V.O/	26.	Ashcroft, F.M. et al. (1999). "ATP-sensitive K ⁺ channels and insulin secretion: their role in health and disease," <i>Diabetologia</i> . 42:903-919.		
/T.V.O/	27.	Ashcroft, F.M. et al. (2000). "New windows on the mechanism of action of K(ATP) channel openers," <i>Trends Pharmacol. Sci.</i> 21:439-445.		
/T.V.O/	28.	Bay, H.E. et al. (2010). "Diazoxide choline controlled release in hyperglyceridemic subjects: Lipid and other metabolic effects," <i>J. American College of Cardiology</i> 55(10a), 1 total page.		
/T.V.O/	29.	Clinical Trials.Gov (2014). "Clinical study of diazoxide choline controlled-release tablet (DCCR) in patients with Prader-Willi syndrome," Clinical trials identifier NCT02034071, updated January 10, 2014, Retrieved from https://clinicaltrials.gov/archive/nct02034071/2014_01_10 , 4 total pages.		
/T.V.O/	30.	Eiholzer, U. et al. (1998). "Treatment with human growth hormone in patients with Prader-Labhart-Willi syndrome reduces body fat and increases muscle mass and physical performance," <i>Eur. J. Pediatr.</i> 157:368-377.		
/T.V.O/	31.	Einspieler, C. et al. (2012). "Early behavioural manifestation of Smith-Magenis syndrome (del 17p11.2) in a 4-month-old boy" <i>Dev. Neurorehab.</i> 15(4):313-316.		
/T.V.O/	32.	Final Office Action mailed on March 24, 2010, for U.S. Patent Application Number 11/212,130, filed on August 25, 2005, 15 pages.		
/T.V.O/	33.	Final Office Action mailed on June 9, 2010, for U.S. Patent Application Number 12/368,215, filed on February 9, 2009, 9 pages.		
/T.V.O/	34.	Final Office Action mailed on October 17, 2014, for U.S. Patent Application Number 12/370,456, filed on February 12, 2009, 14 pages.		
/T.V.O/	35.	Final Office Action mailed on March 8, 2012, for U.S. Patent Application Number 12/370,456, filed on February 12, 2009, 13 pages.		
/T.V.O/	36.	Final Office Action mailed on January 13, 2017, for U.S. Patent Application Number 14/458,032, filed on August 12, 2014, 14 pages.		
/T.V.O/	37.	Final Office Action mailed on November 2, 2015, for U.S. Patent Application Number 14/458,032, filed on August 12, 2014, 13 pages.		
/T.V.O/	38.	International Search Report mailed on February 2, 2016, for PCT Application Number PCT/US2015/60455, filed on November 12, 2015, 3 pages.		
/T.V.O/	39.	International Search Report mailed on June 16, 2006, for PCT Application Number PCT/US2005/30481, filed on August 25, 2005, 1 page.		
/T.V.O/	40.	International Search Report mailed on December 6, 2007, for PCT Application Number PCT/US2006/48711, filed on December 20, 2006, 2 pages.		

Examiner Signature	/TAYLOR V OH/	Date Considered	06/09/2017
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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	14/940,018
				Filing Date	November 12, 2015
				First Named Inventor	Neil M. Cowen
				Art Unit	1625
				Examiner Name	Taylor V. Oh
Sheet	4	of	4	Attorney Docket Number	CAPN-034/04US 328512-2375

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
/T.V.O/	41.	International Search Report mailed on September 30, 2008, for PCT Application Number PCT/US2008/68936, filed on July 1, 2008, 2 pages.	
/T.V.O/	42.	International Search Report mailed on June 21, 2013, for PCT Application Number PCT/US2013/027676, filed on February 25, 2013, 4 pages.	
/T.V.O/	43.	Lee, P.D. (2002). "Disease management of Prader-Willi syndrome," <i>Expert Opin. Pharmacother.</i> 3:1451-1459.	
/T.V.O/	44.	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.	
/T.V.O/	45.	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.	
/T.V.O/	46.	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.	
/T.V.O/	47.	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.	
/T.V.O/	48.	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.	
/T.V.O/	49.	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.	
/T.V.O/	50.	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.	
/T.V.O/	51.	Proglycem® (2003). Pharmaceutical Information, Diazoxide Hyperglycemic Agent, 5 total pages.	
/T.V.O/	52.	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.	
/T.V.O/	53.	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.	
/T.V.O/	54.	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.	
/T.V.O/	55.	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.	
/T.V.O/	56.	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.	

Examiner Signature	/TAYLOR V OH/	Date Considered	06/09/2017
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Dispatch and Receive

Inventor Information for 14/940018

Inventor Name	City
COWEN, NEIL M.	CARLSBAD
Appln Info	Contents
Petition Info	Atty/Agent Info
Continuity Data	Foreign Data
Inventors	Applicant

Search Another: Application # or Patent # or International Registration #
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Attorney Docket #
Bar Code #

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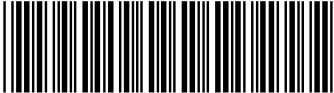
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6/10/17

Issue Classification 	Application/Control No. 14940018	Applicant(s)/Patent Under Reexamination COWEN, NEIL M.	
	Examiner T. VICTOR OH	Art Unit 1625	

CPC					
Symbol				Type	Version
A61K	31	/	549	F	2013-01-01
A61K	38	/	27	A	2013-01-01
A61K	45	/	06	I	2013-01-01
A61K	9	/	00	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	/	0004	I	2013-01-01
A61K	9	/	2054	I	2013-01-01
A61K	9	/	5026	I	2013-01-01
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A61K	9	/	5047	I	2013-01-01
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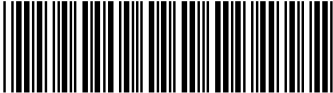
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A61K		38		/	27	A	5	1	2013-01-01
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NONE		Total Claims Allowed:	
		14	
(Assistant Examiner) /T. VICTOR OH/ Primary Examiner.Art Unit 1625	(Date) 6/09/17	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	24	1

Issue Classification 	Application/Control No. 14940018	Applicant(s)/Patent Under Reexamination COWEN, NEIL M.
	Examiner T. VICTOR OH	Art Unit 1625

US ORIGINAL CLASSIFICATION						INTERNATIONAL CLASSIFICATION									
CLASS		SUBCLASS				CLAIMED						NON-CLAIMED			
514		223.5				A	6	1	K	31 / 54 (2006.01.01)					
CROSS REFERENCE(S)															
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)														
514	5.1	11.4	223.2												

NONE		Total Claims Allowed:	
		14	
(Assistant Examiner) /T. VICTOR OH/ Primary Examiner.Art Unit 1625	(Date) 6/09/17	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	24	1

Issue Classification 	Application/Control No. 14940018	Applicant(s)/Patent Under Reexamination COWEN, NEIL M.
	Examiner T. VICTOR OH	Art Unit 1625

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47															
Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
2	3														
3	4														
4	5														
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13	28														
14	29														

NONE (Assistant Examiner) _____ (Date) _____		Total Claims Allowed: 14	
/T. VICTOR OH/ Primary Examiner.Art Unit 1625 (Primary Examiner) _____ (Date) _____		O.G. Print Claim(s) 24	O.G. Print Figure 1

Search Notes 	Application/Control No. 14940018	Applicant(s)/Patent Under Reexamination COWEN, NEIL M.
	Examiner T.VICTOR OH	Art Unit 1625

CPC- SEARCHED		
Symbol	Date	Examiner
A61K31/549,155,137,551;A61K9/5026,2054,0004,5042,5047,00;A61K45/06	6/10/17	t.o.
A61K38/27	6/10/17	t.o.

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner
A61K31/549; A61K31/155; A61K31/551;A61K61/137;A61K38/27	6/10/17	t.o.
A61K2300/00; A61K2300/00; A61K2300/00; A61K2300/00;A61K2300/00	6/10/17	t.o.

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
514	5.1,11.4,223.2,223.5	6/10/17	t.o.

SEARCH NOTES		
Search Notes	Date	Examiner
west search updated .p.3	6/10/17	t.o.
inventor's name search updated .p.1	6/10/17	t.o.

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
A61K	31/549,155,137,551;9/5026,2054,0004,5042,5047,00;4 5/06	6/10/17	t.o.
514/A61K	5.1/38/27	6/10/17	t.o.
514/A61K	223.2/31/54	6/10/17	t.o.

	/T.O./ Primary Examiner.Art Unit 1625
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PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: **Mail** Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (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 including the Patent, advance orders and notification of maintenance fees 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.

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

58249 2590 06/28/2017
COOLEY LLP
ATTN: Patent Group
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 facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/940,018	11/12/2015	Neil M. Cowen	CAPN-034/04US 328512-3175	6992

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

APPL. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEES DUE	DATE DUE
nonprovisional	~~SMALL~~ LARGE	~~\$430~~ \$960	\$0	\$0	~~\$430~~ \$960	09/28/2017

EXAMINER	ART UNIT	CLASS-SUBCLASS
OH, TAYLOR V	1625	514-223500

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/SB/122) attached.
☐ "Fee Address" indication (or "Fee Address" Indication form 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 has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE (CITY and STATE OR COUNTRY)

Essentialis, Inc.

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. The following fee(s) are submitted:

- ☒ Issue Fee
☒ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies _____

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

- ☐ A check is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☒ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number **50-1283** (enclose an extra copy of this form).

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 /Katherine J. Mackenzie/

Date August 8, 2017

Typed or printed name Katherine J. Mackenzie

Registration No. 74,563

Electronic Patent Application Fee Transmittal				
Application Number:		14940018		
Filing Date:		12-Nov-2015		
Title of Invention:		METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME		
First Named Inventor/Applicant Name:		Neil M. Cowen		
Filer:		Katherine Jean Mackenzie/Patricia Ellison		
Attorney Docket Number:		CAPN-034/04US 328512-2375		
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
UTILITY APPL ISSUE FEE	1501	1	960	960
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				960

Electronic Acknowledgement Receipt

EFS ID:	30014042
Application Number:	14940018
International Application Number:	
Confirmation Number:	6992
Title of Invention:	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME
First Named Inventor/Applicant Name:	Neil M. Cowen
Customer Number:	58249
Filer:	Katherine Jean Mackenzie/Patricia Ellison
Filer Authorized By:	Katherine Jean Mackenzie
Attorney Docket Number:	CAPN-034/04US 328512-2375
Receipt Date:	08-AUG-2017
Filing Date:	12-NOV-2015
Time Stamp:	15:08:11
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	\$ 960
RAM confirmation Number	080917INTEFSW00001659501283
Deposit Account	501283
Authorized User	Patricia Ellison
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.16 (National application filing, search, and examination fees) 37 CFR 1.17 (Patent application and reexamination processing fees)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	Issue_Fee.pdf	501192	no	1
			a353d8746291e34ef1b24a81243dae6b74303d20		

Warnings:**Information:**

2	Fee Worksheet (SB06)	fee-info.pdf	32599	no	2
			3c39b19275d7852e47b7782793fe6fe192301e00		

Warnings:**Information:**

Total Files Size (in bytes):			533791
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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 a 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

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/940,018	09/12/2017	9757384	CAPN-034/04US 328512-2375	6992

58249 7590 08/23/2017
COOLEY LLP
ATTN: Patent Group
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

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 Application Information Retrieval (PAIR) WEB site (<http://pair.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 Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site <http://pair.uspto.gov> for additional applicants):

Neil M. Cowen, Carlsbad, CA;
Essentialis, Inc., Carlsbad, CA;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.



ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
14/940,018	05/14/2025 02:06:21 PM Z ET	SLNO-034/04US 333072-2375

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 #	9757384
CONFIRMATION #	6992	FILED BY	Diana Sciamanna
PATENT CENTER #	70417788	AUTHORIZED BY	Kimberly Bolin
CUSTOMER #	58249	FILING DATE	11/12/2015
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Neil M. Cowen

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 501283	E20255DE07115241	Diana Sciamanna

FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
1457	APPLICATION FOR EXTENSION OF TERM OF PATENT (SEE 37 CFR 1.740)	2500.00	1	2500.00
TOTAL AMOUNT:				\$2,500.00

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.



ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
14/940,018	05/14/2025 02:06:21 PM Z ET	SLNO-034/04US 333072-2375

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 #	9757384
CONFIRMATION #	6992	FILED BY	Diana Sciamanna
PATENT CENTER #	70417788	FILING DATE	11/12/2015
CUSTOMER #	58249	FIRST NAMED INVENTOR	Neil M. Cowen
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Kimberly Bolin

Documents

TOTAL DOCUMENTS: 18

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
SLNO-034_04US_Exhibit_1.pdf	43	Exhibits or attachments to a PTE application.	4786 KB
SLNO-034_04US_Exhibit_2.pdf	4	Exhibits or attachments to a PTE application.	400 KB
SLNO-034_04US_Exhibit_3.pdf	6	Exhibits or attachments to a PTE application.	542 KB
SLNO-034_04US_Exhibit_4.pdf	3	Exhibits or attachments to a PTE application.	359 KB
SLNO-034_04US_Exhibit_5.pdf	3	Exhibits or attachments to a PTE application.	183 KB
SLNO-034_04US_Exhibit_6.pdf	5	Exhibits or attachments to a PTE application.	756 KB

SLNO-034_04US_Exhibit_7.pdf	32	Exhibits or attachments to a PTE application.	11824 KB
SLNO-034_04US_Exhibit_8.pdf	3	Exhibits or attachments to a PTE application.	170 KB
SLNO-034_04US_Exhibit_9.pdf	3	Exhibits or attachments to a PTE application.	160 KB
SLNO-034_04US_Exhibit_10.pdf	3	Exhibits or attachments to a PTE application.	200 KB
SLNO-034_04US_Exhibit_11.pdf	19	Exhibits or attachments to a PTE application.	354 KB
SLNO-034_04US_Exhibit_12.pdf	2	Exhibits or attachments to a PTE application.	135 KB
SLNO-034_04US_Exhibit_13.pdf	2	Exhibits or attachments to a PTE application.	135 KB
SLNO-034_04US_Exhibit_14.pdf	4	Exhibits or attachments to a PTE application.	165 KB
SLNO-034_04US_Exhibit_15.pdf	5	Exhibits or attachments to a PTE application.	111 KB
SLNO-034_04US_Exhibit_16.pdf	26	Exhibits or attachments to a PTE application.	186 KB
SLNO-034_04US_Exhibit_17.pdf	16	Exhibits or attachments to a PTE application.	168 KB
SLNO-034_04US_PTE_Application.pdf	24	Patent Term Extension Application Under 35 USC 156	242 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
SLNO-034_04US_Exhibit_1.pdf	524A68BD4FFD024767E135A70A31A2CC26CE2CFA1517877B D352D8978F9BCCFEE1C080A7CBC008DB13C394F81868EF6B 41A0FA599878E7903F24EB7477948DDE
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SLNO-034_04US_Exhibit_8.pdf	58D7639509809DD145AFBEE90D07D82703E496937C8430FA3 9893A472E2F8BAB865736BD8AEA83000083A0D027FA5D05F4 0E6C8C222C9AF624C00BBE5BEEE3E9
SLNO-034_04US_Exhibit_9.pdf	C2B1D4B6DF9B222C953C3F1FE4EAF24C21E504706550DFC3 64FC54F35A3EAE4CC8C818E0F55C893F291A670BC4D5A51D E2CE8ED41735C18B0AC8B4AC6DD3F92D
SLNO-034_04US_Exhibit_10.pdf	E5664C8F4D0AD9BDF6603D1512F8FA19BB7435918307F08A1 A43B80C17D3E0C3FCC174E7EAF3E752AE672E15330584062 113C053333694BE84E1860A7399778
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SLNO-034_04US_Exhibit_14.pdf	BDB918B6B41C99B3308826B385F1A2437C7083E1D6B9F6D45 8E3E04BB99FF75C3AD2F1C87EAD7A7B7F41BFCBF406D3F45 75BB086838BC8FFEE86543A2F5EE53B
SLNO-034_04US_Exhibit_15.pdf	DF2558BC18693D3FE4DECC9A36E3F208BC5A7F04FCE942D6 8CA951BCB09E5E74905E80B7439CBFD99C83F14CC931197E F6429C8560A83181C7B24EEDF57105C0
SLNO-034_04US_Exhibit_16.pdf	7592ED02DEB2837A5595596E7199EBC535B8B3684D65DE9EE 53072F89B2A20084E8DE74CB9C1904DB28993BB0495AE9D91 5ACADEFE78EC2B6F53974AA6D091F5
SLNO-034_04US_Exhibit_17.pdf	349EBE1A5E4D477B126BAB6B9E98E0BDCAF53A70D6D68722 F1F245C9EDA694133107B2628FD1AB4A57DF0373E30A39B05

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SLNO-

034_04US_PTE_Application.pdf

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A04408EF45B5DFCA41E90CB778DBC4A22B7541F19BE6EB7C

1522836BF19D169BABBCAB0F121C7A47D4ACA61D5A676303

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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

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Docket No.: SLNO-034/04US 333072-2375
PTE Application for U.S. Pat. No. 9,757,384
VYKAT™ XR
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor: Neil M. COWEN Assignee: Essentialis, Inc.

Confirmation No.: 6992

Patent No.: 9,757,384 Unit: Office of Patent Legal
Administration

Issue Date: September 12, 2017 Examiner: Taylor V. OH

Application No.: 14/940,018

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

Commissioner of Patents and Trademarks
P.O. Box 1450
Mail Stop: Hatch-Waxman Patent Term Extension
Alexandria, VA 22313-1450

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Dear Sir/Madam:

INTRODUCTORY COMMENTS

Applicant, Essentialis, Inc. (“Essentialis”), hereby submits this application for extension of the term of United States Letters Patent No. 9,757,384 (the ’384 patent) under 35 U.S.C. § 156 based upon the regulatory review period that ended with the Food and Drug Administration’s (“FDA”) approval of New Drug Application (“NDA”) number 216665 for VYKAT™ XR (diazoxide choline) extended-release tablets, for oral use. Information in accordance with the requirements specified in 37 C.F.R. § 1.740 is provided herein.

The '384 patent contains method of treatment claims directed to the approved use of the active ingredient in VYKAT™ XR (diazoxide choline), extended-release tablets for oral use (*see Exhibit 1*). On March 26, 2025, an NDA for VYKAT™ XR (diazoxide choline), extended-release tablets for oral use was approved for commercial marketing or use under Section § 505(b)(2) of the Food, Drug and Cosmetic Act. NDA number 216665 relates to the use of VYKAT™ XR (diazoxide choline) for the treatment of hyperphagia in adults and pediatric patients 4 years of age and older with Prader-Willi syndrome (PWS).

This application for patent term extension of the '384 patent is based upon the regulatory review period that ended with the approval of NDA number 216665 on March 26, 2025. Applicant is concurrently submitting applications for extension of the term of U.S. Patent No. 7,799,777 (the '777 patent), U.S. Patent No. 7,572,789 (the '789 patent), and U.S. Patent No. 12,178,823 (the '823 patent) under 35 U.S.C. § 156 in connection with the same regulatory review period. The '777 patent and the '789 patent contain claims to the approved product. The '823 patent contains claims directed to the approved use of the product.

Applicant understands that multiple applications for extension of term under 35 U.S.C. § 156(d)(1) may be filed in connection with any particular regulatory review period, but that only one such application may be granted per regulatory approval. Accordingly, Applicant intends to withdraw all but one application for extension of term filed under 35 U.S.C. § 156(d)(1) in connection with NDA number 216665 prior to the grant of any extension of term of any patent under 35 U.S.C. § 156(d)(1). *See also* Section 13 of this application.

Applicant represents that Essentialis is the assignee of the entire right, title and interest in and to the '384 patent granted to Essentialis on September 12, 2017, by virtue of assignment of U.S. Application No. 14/940,018 by the inventor, Neil M. COWEN on November 13, 2015 and recorded for the Patent with the Office on November 13, 2015 at reel/frame 037039/0755.

A copy of the assignment is included as **Exhibit 2**.

Patent owner Essentialis is a wholly owned subsidiary of Soleno Therapeutics, Inc. (“Soleno”). Soleno is the current marketing applicant for NDA 216665 for VYKAT™ XR.

The acquisition of Essentialis by Capnia, Inc. (“Capnia”) was completed on March 7, 2017. At that time, Essentialis merged with a wholly owned Capnia subsidiary – Company E Merger Sub, Inc. – with the surviving corporation after the merger being Essentialis. *See Exhibit 3.* Capnia underwent a name change to Soleno Therapeutics, Inc. on May 12, 2017. *See Exhibit 4.*

PTE Applicant and patent owner, Essentialis, is authorized to rely upon the activities of Soleno and its affiliates before the Food and Drug Administration during the regulatory review period for VYKAT™ XR in its request for extension of patent term for the purposes of this application for patent term extension of the ’384 patent. *See Exhibit 5.*

As noted above, Soleno is the Marketing Applicant (*see Exhibits 6 and 7*) and conducted certain studies leading to approval by the FDA of NDA 216665 for VYKAT™ XR and will commercialize the approved product. Essentialis was the original sponsor of IND 73,179 and IND 132,498, which were later transferred to Soleno. Data generated under these INDs were included in NDA 216665. Sponsorship of IND 73,179 was transferred to Soleno on July 12, 2017. *See Exhibit 8.* Sponsorship of IND 132,498 was transferred to Capnia on or about March 10, 2017 (*see Exhibit 9*), after which the name of the sponsor was changed to Soleno (*see Exhibit 4*), and the FDA was notified of the change on May 22, 2017 (*see Exhibit 10*).

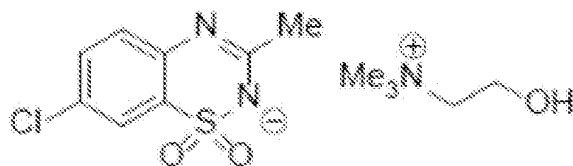
Pursuant to the provisions of 37 C.F.R. § 1.730, Applicant hereby applies for an extension of the term of U.S. Patent No. 9,757,384 under 35 U.S.C. § 156 of 1230 days based on the materials set forth herein and in the accompanying submissions.

In the materials which follow, numbered paragraphs (1) through (15) correspond to paragraphs (1) through (15) of 37 C.F.R. § 1.740(a).

1. Identification of the Approved Product [37 C.F.R. § 1.740(a)(1)]

The approved product is “VYKAT™ XR (diazoxide choline) extended-release tablets, for oral use.” VYKAT™ XR is indicated for the treatment of hyperphagia in adults and pediatric patients 4 years of age and older with Prader-Willi syndrome (PWS).

The chemical name for diazoxide choline is 7-Chloro-3-methyl-1λ6, 2,4-benzothiadiazin-2-ide 1,1-dioxide 2-hydroxyethyl(trimethyl)azanium. Diazoxide choline is also referred to as a “K_{ATP} channel opener”. The molecular weight is 333.83 g/mole, and the molecular formula is C₈H₆ClN₂O₂S•C₅H₁₄NO. The structural formula is:



VYKAT™ XR is provided as extended-release tablets for oral administration. VYKAT™ XR is provided in three strengths:

Each VYKAT™ XR, 25mg tablet contains diazoxide choline 25 mg.

Each VYKAT™ XR, 75mg tablet contains diazoxide choline 75 mg

Each VYKAT™ XR, 150mg tablet contains diazoxide choline 150 mg

A complete description of the product is set forth in Section 11 of the VYKAT™ XR Prescribing Information (“PI”), provided as **Exhibit 11**.

**2. Federal Statute Governing Regulatory Approval of the Approved Product
[37 C.F.R. § 1.740(a)(2)]**

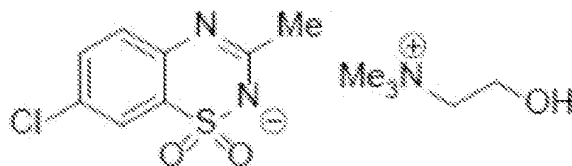
The approved product was subject to regulatory review under § 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (“FDCA”) (21 U.S.C. § 355 *et seq.*).

3. Date of Approval for Commercial Marketing [37 C.F.R. § 1.740(a)(3)]

NDA number 216665 for VYKAT™ XR (diazoxide choline), extended-release tablets for oral use was approved for commercial marketing or use under § 505(b)(2) of the FDCA on March 26, 2025. A copy of the approval letter from the FDA is provided as **Exhibit 7**.

4. Identification of Active Ingredient and Certifications Related to Commercial Marketing of Approved Product [37 C.F.R. § 1.740(a)(4)]

- (a) The active ingredient in VYKAT™ XR (diazoxide choline), extended-release tablets for oral use is diazoxide choline. The chemical name for diazoxide choline is 7-Chloro-3-methyl-1λ6, 2,4-benzothiadiazin-2-ide 1,1-dioxide 2-hydroxyethyl(trimethyl)azanium. The molecular weight is 333.83 g/mole, and the molecular formula is C₈H₆ClN₂O₂S•C₅H₁₄NO. The structural formula is:



An alternative name for diazoxide choline is: 7-chloro-3-methyl-2H-1,2,4-benzothiadiazine dioxide:2-hydroxy-N,N,N-trimethyl ethanaminium (1:1) salt.

- (b) On information and belief, Applicant certifies that diazoxide choline, the active ingredient in VYKAT™ XR, had not been approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act prior to the approval granted on March 26, 2025.
- (c) NDA number 216665 was approved on March 26, 2025. A copy of the approval letter from the FDA is provided as **Exhibit 7**.

5. Statement Regarding Timeliness of Submission of Patent Term Extension Request [37 C.F.R. § 1.740(a)(5)]

This application for patent term extension is being timely submitted within the sixty (60) day period permitted for submission specified in 35 U.S.C. § 156(d)(1) and 37 C.F.R. § 1.720(f). The last date on which this application may be submitted is May 24, 2025 (*i.e.*, within 60 days of March 26, 2025, beginning on March 26, 2025).

6. Complete Identification of the Patent for Which Extension Is Being Sought [37 C.F.R. § 1.740(a)(6)]

The complete identification of the patent for which an extension is being sought is as follows:

- (a) Names of the inventors: Neil M. COWEN
- (b) Patent Number: 9,757,384
- (c) Entitled: METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME
- (d) Date of Issue: September 12, 2017
- (e) Date of Expiration: November 12, 2035

7. Copy of the Patent for Which an Extension Is Being Sought

[37 C.F.R. § 1.740(a)(7)]

A copy of U.S. Patent No. 9,757,384 is provided as **Exhibit 1**.

8. Copies of Disclaimers, Certificates of Correction, Receipt of Maintenance Fee Payment, or Reexamination Certificate [37 C.F.R. § 1.740(a)(8)]

- (a) No terminal disclaimers have been filed for U.S. Patent No. 9,757,384.
- (b) No Certificates of Correction have been filed for U.S. Patent No. 9,757,384.
- (c) The first maintenance fee window opened on September 12, 2020, and closed on September 13, 2021. The first maintenance fee was paid on February 24, 2021. A copy of the receipt for payment of the first maintenance fee is provided as **Exhibit 12**.
- (d) The second maintenance fee window opened on September 12, 2024, and closes on September 13, 2025. The second maintenance fee was paid on January 13, 2025. A copy of the receipt for payment of the first maintenance fee is provided as **Exhibit 13**.
- (e) The third maintenance fee window will open on September 12, 2028, and will close on September 12, 2029. Accordingly, the third maintenance fee window is not open yet.
- (f) U.S. Patent No. 9,757,384 has not been the subject of reexamination proceedings.

9. Statement Regarding Patent Claims Relative to Approved Product
[37 C.F.R. § 1.740(a)(9)]

The statements below are made solely to comply with the requirements of 37 C.F.R. § 1.740(a)(9). Applicant notes that, as the M.P.E.P. acknowledges, 37 C.F.R. § 1.740(a)(9) does not require an applicant to show whether or how the listed claims would be infringed, and that this question cannot be answered without specific knowledge concerning acts performed by third parties. As such, these comments are not an assertion or an admission of Applicant as to the scope of the listed claims, or whether or how any of the listed claims would be infringed, literally or under the doctrine of equivalents, by the manufacture, use, sale, offer for sale, or the importation of any product.

- (a) Claims 1-5, 9-10, and 13-14 of U.S. Patent No. 9,757,384 claims an approved method of use of the approved product.
- (b) Pursuant to M.P.E.P. § 2753 and 37 C.F.R. § 1.740(a)(9), the following table is provided to show how claim 1 of U.S. Patent No. 9,757,384 claims the method of use of the approved product.

Claim 1 of U.S. Patent 9,757,384 (Limitation by Limitation)	VYKAT™ XR (diazoxide choline) extended-release tablets for oral use
A method of reducing one or more aggressive behaviors in a subject having Prader-Willi syndrome (PWS) or Smith-Magenis syndrome (SMS),	VYKAT™ XR (diazoxide choline) extended-release tablets for oral use are indicated for the treatment of hyperphagia in adult and pediatric patients 4 years of age and older with Prader-Willi syndrome. <i>See, e.g., Prescribing Information, Highlights, Section 1, Section 3, Section 11, and Section 14 (Exhibit 11).</i> Hyperphagia manifests as a constant, insatiable hunger, accompanied by an intense, persistent preoccupation with food, an extreme drive to seek and consume food, food-related behavior problems, distress with temper

Claim 1 of U.S. Patent 9,757,384 (Limitation by Limitation)	VYKAT™ XR (diazoxide choline) extended-release tablets for oral use
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.	outbursts if denied food, and becoming aggressive to obtain food. In clinical trials, VYKAT™ XR (diazoxide choline) extended-release tablets were administered for at least 10 weeks. <i>See, e.g.</i>, Prescribing Information, Section 14 (Exhibit 11). Patients were administered a pharmaceutical formulation with an effective amount of diazoxide choline (based on the patient's weight, and in the form of VYKAT™ XR (diazoxide choline) extended-release tablets) for a mean duration of 3.3 years before participating in the random withdrawal period study presented in the Prescribing Information. <i>See, e.g.</i>, Prescribing Information, Sections 2.2 and 14 (Exhibit 11). In clinical trials, the primary efficacy endpoint of VYKAT™ XR was assessed using the HQ-CT (Hyperphagia Questionnaire for Clinical Trials), which assesses a range of hyperphagic and food-related behaviors (<i>e.g.</i>, including food-related aggressive behaviors). <i>See, e.g.</i>, Prescribing Information, Section 14 (Exhibit 11). The totality of the clinical trial data for VYKAT™ XR demonstrates a clinically meaningful and highly statistically significant difference in the HQ-CT Total Score between the VYKAT™ XR and placebo groups, a substantial long-term reduction in hyperphagia, and that VYKAT™ XR reduces one or more aggressive behaviors in Prader-Willi syndrome patients who have hyperphagia

**10. Relevant Dates Under 35 U.S.C. § 156 for Determination of Applicable
Regulatory Review Period [37 C.F.R. § 1.740(a)(10)]**

(a) Patent Issue Date

U.S. Patent No. 9,757,384 issued on September 12, 2017.

*(b) IND Effective Date [35 U.S.C. § 156(g)(1)(B)(i);
37 C.F.R. § 1.740(a)(10)(i)(A)]*

An Investigational New Drug Application (IND) for diazoxide choline was submitted August 22, 2006, under § 505(i) of the FDCA and the date of receipt confirmed as August 22, 2006 by FDA. IND number 73,179 was assigned and the effective date confirmed as 30 days after receipt of the IND, September 21, 2006. *See Exhibit 14.*

Applicant has used the date of September 21, 2006 as the “IND Effective Date” in its calculations below.

*(c) NDA Submission Date [35 U.S.C. § 156(g)(1)(B)(i);
37 C.F.R. § 1.740(a)(10)(i)(B)]*

A New Drug Application (NDA) was submitted on June 27, 2024. A copy of the letter from the FDA accepting NDA number 216665 for review and reflecting the June 27, 2024 submission date is provided as **Exhibit 6**. The NDA submission date is also identified as June 27, 2024 in the NDA approval letter (**Exhibit 7**).

Applicant has used the date of June 27, 2024 as the “NDA Submission Date” in its calculation below.

*(d) NDA Approval Date [35 U.S.C. § 156(g)(1)(B)(ii);
37 C.F.R. § 1.740(a)(10)(i)(C)]*

The FDA approved NDA number 216665 authorizing the marketing of
VYKAT™ XR (diazoxide choline) extended-release tablets for oral use on
March 26, 2025. A copy of the NDA approval letter from the FDA is provided as
Exhibit 7.

11. Summary of Significant Events During Regulatory Review Period
[37 C.F.R. § 1.740(a)(11)]

A brief description of the significant activities by the marketing applicant (Solenol¹) during the applicable regulatory review period with respect to the approved product and the dates applicable to these significant activities are set forth in a chronological listing of events in **Exhibits 15-17**.

Pursuant to 37 C.F.R. § 1.740(a)(11), 21 C.F.R. § 60.20(a), and M.P.E.P. § 2753, copies of all such communications are not provided in this application but can be obtained from records maintained by the FDA.

¹ Soleno is the Marketing Applicant for NDA number 216665 and current sponsor of IND numbers 73,179 and 132,498. However, as detailed in the Introductory Comments section of this application, Essentialis was the original sponsor of IND numbers 73,179 and 132,498. Sponsorship of these INDs was transferred to Soleno and Soleno is thereby authorized to rely on the activities undertaken by Essentialis of these INDs. Additionally, for the purposes of this PTE application, as confirmed by **Exhibit 5**, Essentialis, as patent owner, is authorized to rely on activities undertaken by NDA holder Soleno with respect to the regulatory review period associated with the approval of VYKAT™ XR (diazoxide choline) extended-release tablets for oral use.

The dates set forth in **Exhibit 1, 6, 7, and 14** and used in the calculations described herein are as summarized below.

Receipt of IND number 73,179	August 22, 2006
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Exemption under FDCA § 505(i) became effective (effective date of IND number 73,179)	September 21, 2006
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Exhibit 14

Patent was granted	September 12, 2017
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Exhibit 1

New Drug Application (NDA) number 216665 under FDCA § 505(b)(2) was submitted	June 27, 2024
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Exhibit 6

NDA number 216665 was approved	March 26, 2025
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Exhibit 7

**12. Statement Concerning Eligibility for and Duration of Extension Sought
Under 35 U.S.C. § 156 [37 C.F.R. § 1.740(a)(12)]**

A. In the opinion of the Applicant, U.S. Patent No. 9,757,384 is eligible for an extension under 35 U.S.C. § 156 and 37 C.F.R. § 1.720 because:

(i) 35 U.S.C. § 156(a) and 37 C.F.R. § 1.720(a)

U.S. Patent No. 9,757,384 claims a method of using the compound that is the active ingredient in VYKAT™ XR (diazoxide choline), extended-release tablets for oral use, the approved product, as the term “product” is defined in 35 U.S.C. § 156, as described in § 9(b) above.

(ii) 35 U.S.C. § 156(a)(1) and 37 C.F.R. § 1.720(g)

U.S. Patent No. 9,757,384 has not expired.

(iii) 35 U.S.C. § 156(a)(2) and 37 C.F.R. § 1.720(b)

The term of U.S. Patent No. 9,757,384 has not been previously extended on the basis of 35 U.S.C. § 156.

(iv) 35 U.S.C. § 156(a)(3) and 37 C.F.R. § 1.720(c)

The application for extension is submitted by an owner of record or an agent authorized to act on behalf of the owner of record in accordance with the requirements of paragraphs (1) through (4) of 35 U.S.C. § 156(d) and the rule of the Patent and Trademark Office (35 U.S.C. § 156(a)(3)). See **Exhibit 5**.

(v) 35 U.S.C. § 156(a)(4) and 37 C.F.R. § 1.720(d)

There is an eligible period of regulatory review by which the patent may be extended pursuant to 35 U.S.C. § 156.

(vi) 35 U.S.C. § 156(a)(5)(A) and 37 C.F.R. § 1.720(e)

The approved product, diazoxide choline, has received permission for commercial marketing or use, and the permission for the commercial marketing or use of the product is the first such permission received under 21 U.S.C. § 355(a) and Section 505(b)(2) of the FDCA, *codified at* 21 U.S.C. § 355(b)(2).

(vii) 35 U.S.C. § 156(c)(4) and 37 C.F.R. § 1.720(h)

No other patent has been extended pursuant to 35 U.S.C. § 156 on the basis of the regulatory review process associated with the approved product.²

(viii) 35 U.S.C. § 156(d)(1) and 37 C.F.R. § 1.720(f)

This application is submitted within the permitted sixty-day period beginning on the date the product first received permission for commercial marketing or use.

(ix) 35 U.S.C. § 156(d)(3)

The applicant for marketing approval exercised due diligence within the meaning of 35 U.S.C. § 156(d)(3) during the period of regulatory review.

(x) This application otherwise complies with all requirements of 35 U.S.C. § 156 and applicable rules and procedures.

B. Applicant believes that the extension should be for 1230 days so that the expiration date for U.S. Patent No. 9,757,384 will be March 26, 2039. The term of the extension is calculated as follows pursuant to 37 C.F.R. § 1.775 as shown in section C, below.

² See page 2 and section 13 of this application regarding three concurrently filed applications for Patent Term Extension based on the '777, '789, and '823 patents.

C. The requested period of extension of term for U.S. Patent No. 9,757,384 corresponds to the regulatory review period that is eligible for extension pursuant to 35 U.S.C. § 156, based on the facts and circumstances of the regulatory review associated with the approved product and the issuance of the U.S. Patent No. 9,757,384. The period was determined as follows.

- (i) The relevant dates for calculating the regulatory review period, based on the events discussed in the section above, are the following:

Exemption under FDCA § 505(i) became effective (effective date of IND number 73179)	September 21, 2006
--	--------------------

Patent was granted	September 12, 2017
--------------------	--------------------

New Drug Application (NDA) number 216665 under FDCA § 505(b)(2) was received	June 27, 2024
---	---------------

NDA number 216665 was approved	March 26, 2025
--------------------------------	----------------

- (ii) Regulatory review period – Testing Phase:

The regulatory review period from the IND number 73,179 effective date to the NDA receipt date is 6490 days (September 21, 2006 through June 27, 2024).

U.S. Patent No. 9,757,384 was granted after the start of the period specified in 35 U.S.C. § 156(g)(1)(B)(i) (i.e., the period from the date of the grant of the exemption under § 505(i) of the FDCA until the date of submission of the NDA). Pursuant to 35 U.S.C. § 156(b) and (c)(2), the calculated regulatory review period therefore includes a component of time between when the patent issued and when NDA number 216665 was received (September 12, 2017 to June 27, 2024). Accordingly, pursuant to 37 C.F.R. § 1.775(d)(1)(i), the regulatory review period

is reduced by the number of days in the period defined by 37 C.F.R. § 1.775(c)(1) and (c)(2) which occurred on and before the issuance of U.S. Patent No. 9,757,384 patent (September 12, 2017). Thus, the testing phase (6490 days) is reduced by 4010 days (days from September 21, 2006 up to and including September 12, 2017). *The adjusted testing period is therefore 2480 days (6490 days minus 4010 days).*

(iii) Regulatory Review Period – Approval Phase:

The patent was granted prior to the start of the period specified in 35 U.S.C. § 156(g)(1)(B)(ii) (i.e., the period from the date of submission of the NDA until the date of approval). The regulatory review period under 35 U.S.C. § 156(b) therefore includes a component of time between when the NDA was received and when the NDA was approved from June 27, 2024 to March 26, 2025. *The regulatory review period from the NDA receipt date to the NDA approval date is therefore 273 days (June 27, 2024 to March 26, 2025).*

(iv) Total Regulatory Review Period – as adjusted for patent issuance:

The total regulatory review period is 2753 days (2480 days in the testing phase and 273 days in the approval phase). *The adjusted regulatory review period, calculated as the sum of the days after patent issuance in the testing phase (“adjusted testing period” in (ii) above, 2480 days) plus the number of days in the approval phase (273 days) is 2753 days.*

(v) Initial Calculation of Term:

Pursuant to 37 C.F.R. § 1.775(d)(1)(iii), the term of extension is calculated by subtracting from the total regulatory review period (as adjusted under

37 C.F.R. § 1.775(d)(1)(i) for the date of patent issuance – 2753 days, as calculated in (iv), above) one-half of the days remaining in the period defined by 37 C.F.R. § 1.775(c)(1) (testing phase adjusted for date of patent issuance (as calculated in (ii), above) – 2480 days/2 is 1240 days). *Thus, the initial calculation of the term of extension is 2753 days – 1240 days, or 1513 days.*

- (vi) “Diligence” is described in 35 U.S.C. § 156(d)(3). Soleno and the prior sponsor, Essentialis, of IND numbers 73,179 and 132,498 were diligent as of at least September 12, 2017 as shown in **Exhibits 15-17**.
- (vii) Thus, period determined according to 35 U.S.C. § 156(b), (c)(2), and (g)(1) for the approved product is 1513 days.
- (viii) The original expiration date for U.S. Patent No. 9,757,384 is November 12, 2035, which is calculated as 20 years from the earliest-claimed non-provisional filing date (November 12, 2015 plus 20 years = November 12, 2035).
- (ix) The date of approval of the approved product is March 26, 2025.
- (x) The date that is provided by adding the number of days determined according to 35 U.S.C. § 156(b), (c)(2), and (g)(1) for the approved product (1513 days) to the expiration date of U.S. Patent No. 9,757,384 (November 12, 2035) is January 3, 2040.
- (xi) The date that is fourteen years from the date of approval of the approved product (March 26, 2039) is before the date that is determined by adding the number of days determined according to 35 U.S.C. § 156(b), (c)(2), and (g)(1) for the approved product (1513 days) to the expiration date (November 12, 2035) of U.S. Patent No. 9,757,358, which is January 3, 2040 (as noted in (x) above). Thus, the

period remaining in the term of the patent after approval of the approved product when added to the regulatory review period as revised under 35 U.S.C.

§ 156(c)(1) and (c)(2), exceeds fourteen years. As such, the period by which the patent may be extended is limited by 35 U.S.C. § 156(c)(3). Thus, the extension otherwise obtainable is limited to not more than fourteen years, i.e., March 26, 2039.

- (xii) The provisions of 37 C.F.R. § 1.775(d)(5) do not apply. The date that is five years from the expiration date of U.S. Patent No. 9,757,384 is November 12, 2040, which is after the date determined in (x), above (January 3, 2040). As such, the period by which the patent may be extended is not limited by 37 C.F.R. § 1.775(d)(5).
- (xiii) U.S. Patent No. 9,757,384 issued after the effective date of Public Law No. 98-417. As such the limit of 35 U.S.C. § 156(g)(6)(c) does not apply.
- (xiv) Taking into account the calculations and provisions detailed above, the earlier date of sections (x), (xi) and (xii) is March 26, 2039 (i.e., 1230 days). Applicant requests that the term of U.S. Patent No. 9,757,384 be extended by 1230 days, thus, until March 26, 2039.

13. Statement Pursuant to 37 C.F.R. § 1.740(a)(13)

Pursuant to 37 C.F.R. § 1.740(a)(13), Applicant acknowledges its duty to disclose to the Director of the PTO and to the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought, particularly as that duty is defined in 37 C.F.R. § 1.765.

In light of the duty to disclose, Applicant hereby notes the following on the co-pending PTE applications:

- VYKAT™ XR PTE application concurrently filed to extend U.S. Patent No. 7,799,777
- VYKAT™ XR PTE application concurrently filed to extend U.S. Patent No. 7,572,789
- VYKAT™ XR PTE application concurrently filed to extend U.S. Patent No. 12,178,823

Applicant understands that multiple applications for extension of term under 35 U.S.C. § 156(d)(1) may be filed in connection with any one particular regulatory approval, but that only one such application may be granted. Accordingly, Applicant intends to withdraw all but one application for extension of term filed under 35 U.S.C. § 156(d)(1) in connection with NDA number 216665 prior to the grant of any extension of term of any patent under 35 U.S.C. § 156(d)(1).

14. Applicable Fee [37 C.F.R. § 1.740(a)(14)]

Payment of the fee prescribed in 37 C.F.R. § 1.20(j)(1) for a patent term extension application under 35 U.S.C. § 156 is authorized to be charged against **Deposit Account No. 50-1283** referencing **docket no. SLNO-034/04US 333072-2375**. The undersigned also authorizes any additional required fees to be deducted from, or any overpayments to be credited to, **Deposit Account No. 50-1283**.

15. Name and Address for Correspondence [37 C.F.R. § 1.740(a)(15)]

Please direct all inquiries, questions, and communications regarding this application for term extension to:

Kimberly A. Bolin, D. Phil.
Registration No. 44,546
Cooley LLP
ATTN: Patent Group
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004
KBolin@Cooley.com
Telephone: (650) 843-5387
Fax: (202) 842-7899

In accordance with the Notice of March 2, 2023, requiring the initial filing of Applications for Extension of Patent Term under 35 U.S.C. § 156 via Patent Center, Applicant is submitting a single copy of this Application via Patent Center under document code TERM.REQ. As required by the Notice, contact information for the undersigned includes an email address.

Dated: May 14, 2025

Sincerely,

/Kimberly A. Bolin/

Kimberly A. Bolin, D. Phil
Registration No. 44,546

USPTO CUSTOMER NO. 58249

Cooley LLP
ATTN: IP Docketing Department
1299 Pennsylvania Avenue NW, Suite 700
Washington, DC 20004
KBolin@Cooley.com
Telephone: (650) 843-5387
Fax: (202) 842-7899

INDEX OF EXHIBITS

- Exhibit 1: U.S. Patent No. 9,757,384
- Exhibit 2: Copy of recordation and accompanying assignment from inventor to Essentialis, Inc. (recorded at reel/frame 037039/0755)
- Exhibit 3: Copy of Certificate of Merger of Company E Merger Sub, Inc. with and into Essentialis, Inc.
- Exhibit 4: Copy of Certificate of Amendment for Capnia, Inc. for name change to Soleno Therapeutics, Inc.
- Exhibit 5: Authorization from Soleno Therapeutics, Inc. for Essentialis, Inc. to rely upon marketing activities of Soleno Therapeutics, Inc. in request for Patent Term Extension under 35 U.S.C. § 156
- Exhibit 6: FDA acknowledgement letter dated July 8, 2024 for NDA number 216665
- Exhibit 7: FDA approval letter dated March 26, 2025 for NDA number 216665
- Exhibit 8: Letter dated July 12, 2017 from Essentialis, Inc. to FDA transferring sponsorship of IND 73,179 to Soleno Therapeutics, Inc.
- Exhibit 9: Letter dated March 10, 2017 from Essentialis, Inc. to FDA transferring sponsorship of IND 132,498 to Capnia, Inc.

- Exhibit 10: Letter dated May 22, 2017 from Soleno Therapeutics, Inc. to FDA for IND 132,498 alerting FDA of name change from Capnia, Inc. to Soleno Therapeutics, Inc.
- Exhibit 11: VYKAT™ XR (diazoxide choline), tablets for oral use Prescribing Information (PI)
- Exhibit 12: USPTO Patent Maintenance Fee Statement Confirming Payment of First Maintenance Fee for U.S. Patent No. 9,757,384
- Exhibit 13: USPTO Patent Maintenance Fee Statement Confirming Payment of Second Maintenance Fee for U.S. Patent No. 9,757,384
- Exhibit 14: IND acknowledgement letter from FDA for IND 73,179 dated August 31, 2006
- Exhibit 15: Description of significant activities undertaken by marketing applicant during the applicable regulatory review period relating to IND number 73,179
- Exhibit 16: Description of significant activities undertaken by marketing applicant during the applicable regulatory review period relating to IND number 132,498
- Exhibit 17: Description of significant activities undertaken by marketing applicant during the applicable regulatory review period relating NDA number 216665.

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EXHIBIT 1