PTO/AIA/15 (10-17)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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.

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	SLNO-034/07US 333072-2052
First Named Inventor	Neil M. COWEN
Title	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMI
Priority Mail Express® Label No.	

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. [ ] **Fee Transmittal Form** (PTO/SB/17 or equivalent)
2. [ ] **Applicant asserts small entity status.** See 37 CFR 1.27
3. [ ] **Applicant certifies micro entity status.** See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.
4. [✓] **Specification** [*Total Pages* 109] Both the claims and abstract must start on a new page. *(See MPEP § 608.01(a) for information on the preferred arrangement)*
5. [✓] **Drawing(s)** (35 U.S.C. 113) [*Total Sheets* 5]
6. **Inventor's Oath or Declaration** [*Total Pages* 1] *(including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e))*
   a. [ ] Newly executed (original or copy)
   b. [✓] A copy from a prior application (37 CFR 1.63(d))
7. [✓] **Application Data Sheet** ** See note below.* See 37 CFR 1.76 (PTO/AIA/14 or equivalent)
8. **CD-ROM or CD-R** in duplicate, large table, or Computer Program (*Appendix*)
   [ ] Landscape Table on CD
9. **Nucleotide and/or Amino Acid Sequence Submission** (*if applicable, items a. – c. are required*)
   a. [ ] Computer Readable Form (CRF)
   b. [ ] Specification Sequence Listing on:
      i. [ ] CD-ROM or CD-R (2 copies); or
      ii. [ ] Paper
   c. [ ] Statements verifying identity of above copies

ADDRESS TO:

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ACCOMPANYING APPLICATION PAPERS

10. [ ] **Assignment Papers** (cover sheet & document(s))
    Name of Assignee _____
11. [ ] **37 CFR 3.73(c) Statement** (*when there is an assignee*) [✓] **Power of Attorney**
12. [ ] **English Translation Document** (*if applicable*)
13. [ ] **Information Disclosure Statement** (PTO/SB/08 or PTO-1449)
    [ ] Copies of citations attached
14. [ ] **Preliminary Amendment**
15. [ ] **Return Receipt Postcard** (*MPEP § 503*) (*Should be specifically itemized*)
16. [ ] **Certified Copy of Priority Document(s)** (*if foreign priority is claimed*)
17. [ ] **Nonpublication Request** Under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
18. [ ] **Other:** _____

Note*: (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 **must be included in an Application Data Sheet (ADS).
(2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).

19. CORRESPONDENCE ADDRESS

[✓] The address associated with Customer Number: 58249 **OR** [ ] Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone		Email	

Signature	/Catherine O. Liang/	Date	September 17, 2019
Name (Print/Type)	Catherine O. Liang	Registration No. (Attorney/Agent)	61,778

This collection of information is required by 37 CFR 1.53(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	SLNO-034/07US 333072-2052
	Application Number	
Title of Invention	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

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

Inventor Information:

Inventor 1 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Neil	M.	COWEN	

Residence Information (Select One) ● US Residency Non US Residency Active US Military Service

City	Carlsbad	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	7915 Corte Cardo		
Address 2			
City	Carlsbad	State/Province	CA
Postal Code	92009	Country	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	58249		
Email Address	zIPPatentDocketingMailboxUS@cooley.com	Add Email	Remove Email

Application Information:

Title of the Invention	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME		
Attorney Docket Number	SLNO-034/07US 333072-2052	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	5	Suggested Figure for Publication (if any)	

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	SLNO-034/07US 333072-2052
	Application Number	
Title of Invention	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME	

Filing By Reference:

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

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

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

Publication Information:

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

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

Representative Information:

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

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

Domestic Benefit/National Stage Information:

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

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	16/041237	2018-07-20

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	SLNO-034/07US 333072-2052
	Application Number	
Title of Invention	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME	

Prior Application Status	Patented	Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
16/041237	Continuation of	15/671792	2017-08-08	10058557	2018-08-28

Prior Application Status	Patented	Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15/671792	Division of	14/940018	2015-11-12	9757384	2017-09-12

Prior Application Status	Expired	Remove

Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
14/940018	Claims benefit of provisional	62/221359	2015-09-21

Prior Application Status	Expired	Remove

Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
14/940018	Claims benefit of provisional	62/170035	2015-06-02

Prior Application Status	Expired	Remove

Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
14/940018	Claims benefit of provisional	62/138245	2015-03-25

Prior Application Status	Expired	Remove

Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
14/940018	Claims benefit of provisional	62/080150	2014-11-14

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

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

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	SLNO-034/07US 333072-2052
	Application Number	
Title of Invention	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME	

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

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

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	SLNO-034/07US 333072-2052
	Application Number	
Title of Invention	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME	

Authorization or Opt-Out of Authorization to Permit Access:

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

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

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

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

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

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

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

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

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

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

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

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	SLNO-034/07US 333072-2052
	Application Number	
Title of Invention	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME	

Applicant Information:

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

Applicant 1 — Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

● Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.	Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	Essentialis, Inc.		
Mailing Address Information For Applicant:			
Address 1	203 Redwood Shores Pkwy, Ste 500		
Address 2			
City	Redwood City	**State/Province**	CA
Country	US	Postal Code	94065
Phone Number		Fax Number	
Email Address			

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

Assignee Information including Non-Applicant Assignee Information:

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

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	SLNO-034/07US 333072-2052
	Application Number	
Title of Invention	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME	

Assignee 1

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

Remove

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

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

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

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

Signature:

Remove

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

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

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

Signature	/Catherine O. Liang/			Date (YYYY-MM-DD)	2019-09-17
First Name	Catherine O.	Last Name	Liang	Registration Number	61,778

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

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	SLNO-034/07US 333072-2052
	Application Number	
Title of Invention	METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME	

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

Privacy Act Statement

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

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

1 The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. Patent Application No. 16/041,237, filed July 20, 2018, which is a continuation of U.S. Patent Application No. 15/671,792, filed August 8, 2017, now U.S. Patent No. 10,058,557, which is a divisional of U.S. Patent Application No. 14/940,018, filed November 12, 2015, now U.S. Patent No. 9,757,384, which claims priority to U.S. Provisional Patent Application No. 62/080,150, filed November 14, 2014, U.S. Provisional Patent Application No. 62/138,245, filed March 25, 2015, U.S. Provisional Patent Application No. 62/170,035, filed June 2, 2015, and U.S. Provisional Patent Application No. 62/221,359, filed September 21, 2015, each of which is incorporated herein in its entirety.

FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

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

[0004] ATP-sensitive potassium (K_{ATP}) channels play important roles in a variety of tissues by coupling cellular metabolism to electrical activity. The K_{ATP} channel has been identified as an octameric complex of two unrelated proteins, which assemble in a 4:4 stoichiometry. The first is a pore forming subunit, Kir6.x, which forms an inwardly rectifying K^+ channel; the second is an ABC (ATP binding cassette) transporter, also known as the sulfonylurea receptor (SURx) (Babenko, et al., *Annu. Rev. Physiol.*, 60:667-687 (1998)). The Kir6.x pore forming subunit is common for many types of K_{ATP} channels, and has two putative transmembrane domains (identified as TM1 and TM2), which are linked by a pore loop (H5). The subunit that comprises the SUR receptor includes multiple membrane-spanning domains and two nucleotide-binding folds.

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

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

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

diazoxide acts to open potassium channels in vascular smooth muscle, stabilizing the membrane potential at the resting level, and preventing vascular smooth muscle contraction.

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

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

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

[0011] Current oral formulations of diazoxide in therapeutic use result in a range of adverse side effects including dyspepsia, nausea, diarrhea, fluid retention, edema, reduced rates of excretion of sodium, chloride, and uric acid, hyperglycemia, vomiting, abdominal pain, ileus, tachycardia, palpitations, and headache (see current packaging insert for the Proglycem). Oral treatment with diazoxide is used in individuals experiencing serious disease where failing to treat results in significant morbidity and mortality. The adverse side effects from oral administration are tolerated because the benefits of treatment are substantial. The adverse side effects profile of oral diazoxide limit the utility of the drug in treating obese patients at doses within the labeled range of 3 to 8 mg/kg per day.

[0012] The effect of diazoxide in animal models of diabetes and obesity (e.g. obese and lean Zucker rats) has been reported. See e.g. Alemzadeh et al. (*Endocrinology* 133:705-712 (1993), Alemzadeh et al. (*Metabolism* 45:334-341 (1996)), Alemzadeh et al. (*Endocrinology* 140:3197-

3202 (1999)), Stanridge et al. (FASEB J 14:455-460 (2000)), Alemzadeh et al. (Med Sci Monit 10(3): BR53-60 (2004)), Alemzadeh and Tushaus (*Endocrinology* 145(12):3476-3484 (2004)), Aizawa et al. (*J of Pharma Exp Ther* 275(1): 194-199 (1995)), and Surwit et al. (*Endocrinology* 141:3630-3637 (2000)).

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

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

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

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

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

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

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

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

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

SUMMARY OF THE INVENTION

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

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

at least 4 weeks an effective amount of a K_{ATP} channel opener (optionally in combination with growth hormone).

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

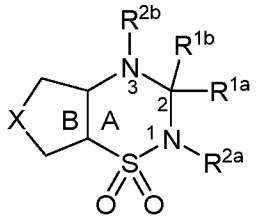
[0025] In addition to increasing the lean body mass of a subject, in some embodiments, invention methods also reduce the hyperphagia of a subject. In some embodiments, the hyperphagia of said subject is reduced by at least 10%. In some embodiments, the hyperphagia of said subject is reduced by at least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

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

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

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

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



Formula I

wherein:

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

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

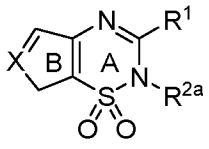
X is a 1, 2 or 3 atom chain, wherein each atom is independently selected from carbon, sulfur or nitrogen, and each atom is optionally substituted with halogen, hydroxyl, lower alkyl, substituted lower alkyl, lower alkoxy, cycloalkyl, substituted cycloalkyl, substituted lower alkoxy, amino, or substituted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

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

and all bioequivalents including salts, prodrugs and isomers thereof.

[0030] In particular embodiments, compounds of Formula I may include a double bond between either positions 1 and 2 or positions 2 and 3 of Ring A. When a double bond is present between positions 1 and 2 of Ring A, R^{2a} is absent and one of R^{1a} and R^{1b} are absent. When a double bond is present between positions 2 and 3 of Ring A, R^{2b} is absent and one of R^{1a} and R^{1b} are absent. In a preferred embodiment, R^{1a} and R^{1b} are not amino. In another preferred embodiment, Ring B does not include any heteroatoms.

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



Formula II

wherein:

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

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

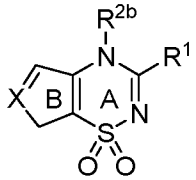
X is a 1, 2 or 3 atom chain, wherein each atom is independently selected from carbon, sulfur or nitrogen, and each atom is optionally substituted with halogen, hydroxyl, lower alkyl, substituted lower alkyl, lower alkoxy, cycloalkyl, substituted cycloalkyl, substituted lower alkoxy, amino, or substituted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

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

and all bioequivalents including salts, prodrugs and isomers thereof.

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

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



Formula III

wherein:

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

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

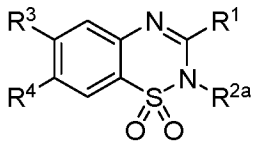
X is a 1, 2 or 3 atom chain, wherein each atom is independently selected from carbon, sulfur or nitrogen, and each atom is optionally substituted with halogen, hydroxyl, lower alkyl, substituted lower alkyl, lower alkoxy, cycloalkyl, substituted cycloalkyl, substituted lower alkoxy, amino, or substituted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

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

and all bioequivalents including salts, prodrugs and isomers thereof.

[0034] In particular embodiments of Formula III, X is $C(R^a)C(R^b)$, wherein R^a and R^b are independently selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, lower alkoxy, substituted lower alkoxy, amino, sulfonylamino, aminosulfonyl, sulfonyl, and the like. In further embodiments, R^a and R^b are independently selected from the group consisting of hydroxyl, substituted oxy, substituted thiol, alkylthio, substituted alkylthio, sulfinyl, sulfonyl, substituted sulfinyl, substituted sulfonyl, substituted sulfonylamino, substituted amino, substituted amine, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino, and the like. In a preferred embodiment, R^1 is not amino. In another preferred embodiment, Ring B does not include any heteroatoms.

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



Formula IV

wherein:

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

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

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

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

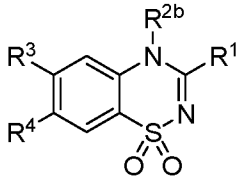
and all bioequivalents including salts, prodrugs and isomers thereof.

[0036] In particular embodiments of Formula IV, R^1 is a lower alkyl (preferably ethyl or methyl); R^{2a} is hydrogen; and R^3 and R^4 are each independently halogen.

[0037] In a preferred embodiment of Formula IV, R^1 is not amino.

[0038] In another embodiment of Formula IV, R^1 is methyl; R^{2a} is hydrogen; R^3 is selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, amino, substituted amino, cycloalkyl, and substituted cycloalkyl; and R^4 is chlorine.

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



Formula V

wherein:

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

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

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

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

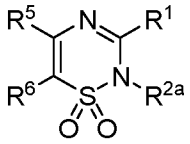
and all bioequivalents including salts, prodrugs and isomers thereof.

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

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

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

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



Formula VI

wherein:

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

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

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

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

wherein the ring formed by the cooperation of R^1 and R^5, or R^1 and R^6, or R^5 and R^6 is saturated, monounsaturated, polyunsaturated or aromatic;

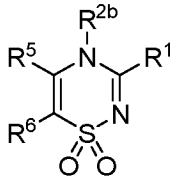
wherein the ring formed by the cooperation of R^1 and R^5, or R^1 and R^6, or R^5 and R^6 is optionally substituted with halogen, hydroxyl, lower alkyl, substituted lower alkyl, amino, substituted amino, sulfonyl, aminosulfonyl, or sulfonylamino;

and all bioequivalents including salts, prodrugs and isomers thereof.

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

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

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



Formula VII

wherein:

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

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

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

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

wherein the ring formed by the cooperation of R^1 and R^5, or R^1 and R^6, or R^5 and R^6 is saturated, monounsaturated, polyunsaturated or aromatic;

wherein the ring formed by the cooperation of R^1 and R^5, or R^1 and R^6, or R^5 and R^6 is optionally substituted with halogen, hydroxyl, lower alkyl, substituted lower alkyl, amino, substituted amino, sulfonyl, aminosulfonyl, or sulfonylamino;

and all bioequivalents including salts, prodrugs and isomers thereof.

[0047] In a preferred embodiment, R^1 is not an amino substituent.

[0048] In another embodiment of Formula VI, R^5 and R^6 combine to form a 6 membered ring. In another embodiment, R^5 and R^6 combine to form a 6 membered ring wherein at least one nitrogen is present. Preferably, the ring formed by R^5 and R^6 does not include any heteroatoms.

[0049] Unless otherwise indicated, reference in this application to K_{ATP} channel openers should be understood to refer to K_{ATP} channel opener(s) having one or more and preferably all three of the following properties: (1) opening SUR1/Kir6.2 potassium channels; (2) binding to the SUR1 subunit of K_{ATP} channels; and (3) inhibiting glucose induced release of insulin following administration of the compound *in vivo*. Such K_{ATP} channel openers preferably have the structure of any of the compounds of Formulae I-VII, or more preferably Formulae I-VII where R^1 is not amino and also where ring B or its equivalent does not include any heteroatoms, or more preferably, any of the compounds of Formulae II or III, or more preferably, any of the compounds of Formulae II or III where R^1 is not amino and also where ring B or its equivalent does not include any heteroatoms, or more preferably, the structure is diazoxide. Structural variants or bioequivalents of the compounds of any of Formulae I-VII such as derivatives, salts, prodrugs or isomers are also contemplated. Other K_{ATP} channel openers that are contemplated for use herein include BPDZ62, BPDZ 73, NN414, BPDZ 154.

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

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

[0052] Also provided herein are controlled release pharmaceutical formulations containing K_{ATP} channel openers obtained by at least one of the following: (a) particle size reduction involving comminution, spray drying, or other micronising techniques, (b) use of a pharmaceutical salt of the K_{ATP} channel opener, (c) use of an ion exchange resin, (d) use of inclusion complexes, for example cyclodextrin, (e) compaction of the K_{ATP} channel opener with a solubilizing agent including a low viscosity hypromellose, low viscosity metylcellulose or similarly functioning excipient or combinations thereof, (f) associating the K_{ATP} channel opener with a salt prior to formulation, (g) use of a solid dispersion of the K_{ATP} channel opener, (h) use of a self emulsifying system, (i) addition of one or more surfactants to the formulation, (j) use of nanoparticles, or (k) combinations of these approaches.

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

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

[0055] Also provided herein are controlled release pharmaceutical formulations of K_{ATP} channel openers, wherein the formulation includes at least one component that contributes to sustained release of a K_{ATP} channel opener over a period of 2-4 hours following administration, or over a period of 4-8 hours following administration, or over a period of more than 8-24 hours following administration. These formulations are characterized in having one of the following components: (a) a pH sensitive polymeric coating, (b) a hydrogel coating, (c) a film coating that controls the rate of diffusion of the drug from a coated matrix, (d) an erodable matrix that controls rate of drug release, (e) polymer coated pellets, granules or microparticles of drug which

can be further encapsulated or compressed into a tablet, (f) an osmotic pump system containing the drug, (g) a compression coated tablet form of the drug, or (h) combinations of these approaches.

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

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

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

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

[0060] Still further provided is a controlled release pharmaceutical formulation of a K_{ATP} channel opener which upon administration to an obese, overweight or obesity prone individual results in at least one of the following: (a) inhibition of fasting insulin secretion (b) inhibition of glucose stimulated insulin secretion, (c) elevation of energy expenditure, (d) elevation of beta

oxidation of fat, (e) inhibition of hyperphagia for about 24 hours, or (f) increase in lean body mass.

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

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

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

[0064] Yet further provided herein is a method of achieving weight loss in an obese overweight, or obesity prone individual, the method comprising administering a therapeutically effective amount of a solid oral dosage form of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours. The daily dosage administered is preferably between 50 and 180 mg. In certain embodiments, the obese individual has a body mass index greater than 30 kg/m^2, or greater than 35 kg/m^2, or greater than 40 kg/m^2, or greater than 50 kg/m^2, or greater than 60 kg/m^2 at the time the method commences.

[0065] Also provided is a method of maintaining a weight loss in an obese overweight, or obesity prone individual, the method comprising administering a therapeutically effective

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

[0066] Further provided is a method of elevating energy expenditure in an overweight, obese or obesity prone individual, the method comprising administering an effective amount of a solid oral dosage form of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours. In certain embodiments, the individual has a body mass index greater than 20 kg/m^2, or greater than 25 kg/m^2, or greater than 30 kg/m^2, or greater than 35 kg/m^2, or greater than 40 kg/m^2, or greater than 50 kg/m^2, or greater than 60 kg/m^2 at the time the method commences.

[0067] Additionally provided is a method of elevating beta oxidation of fat in an overweight, obese or obesity prone individual, the method comprising administering an effective amount of a solid oral dosage form of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours. In certain embodiments, the individual has a body mass index greater than 20 kg/m^2, or greater than 25 kg/m^2, or greater than 30 kg/m^2, or greater than 35 kg/m^2, or greater than 40 kg/m^2, or greater than 50 kg/m^2, or greater than 60 kg/m^2 at the time the method commences.

[0068] Yet further provided is a method of reducing visceral fat in an overweight, obese or obesity prone individual, the method comprising administering an effective amount of a solid oral dosage form of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

[0069] Still further provided is a method of delaying or preventing the transition to diabetes of a prediabetic individual comprising administering an effective amount of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in

combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

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

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

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

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

[0074] Further provided is a method to increase lean body mass in a Prader-Willi Syndrome patient, in a Smith–Magenis syndrome patient, in a Froelich's Syndrome patient, in a Cohen Syndrome patient, in a Summit Syndrome patient, in an Alstrom Syndrome patient, in a Borjeson Syndrome patient or in a Bardet-Biedl Syndrome patient comprising the administration of an effective amount of a K_{ATP} channel opener (optionally in combination with growth hormone) or a

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

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

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

[0077] Further provided is a method of preventing weight gain, dyslipidemia or impaired glucose tolerance in a subject treated with an anti-psychotic drug, the method comprising administering a pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone.

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

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

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

[0081] The formulations containing K_{ATP} channel openers described herein provide for improved compliance, efficacy and safety, and for co-formulations with other agents. Included are co-formulations of K_{ATP} channel openers with one or more additional pharmaceutically active agents that have complementary or similar activities or targets. Other pharmaceutical active agents that can be combined with K_{ATP} channel openers to treat obesity or to maintain weight loss in an obesity prone individual include, but are not limited to: sibutramine, orlistat, phentermine, rimonabant, a diuretic, an antiepileptic, or other pharmaceutical active whose therapeutic utility includes weight loss. It is preferable to maintain weight in an obese individual once some weight loss has occurred when the alternative is to regain weight. Other pharmaceutically active agents that may be combined with K_{ATP} channel openers to treat type II diabetes, or prediabetes include acarbose, miglitol, metformin, repaglinide, nateglinide, rosiglitizone, proglitizone, ramipril, metaglidasen, or any other pharmaceutical active that improves insulin sensitivity or glucose utilization or glycemic control where the mode of action is not enhanced insulin secretion. Other pharmaceutical active agents that can be combined with K_{ATP} channel openers to treat obesity associated co-morbidities include a drug active used to lower cholesterol, a drug active used to lower blood pressure, an anti-inflammatory drug that is not a cox-2 inhibitor, a drug that is an antidepressant, a drug used to treat urinary incontinence, or other drug routinely used to treat disease conditions the incidence of which is elevated in

overweight or obese patients as compared to normal weight individuals including, but not limited to, drugs to treat atherosclerosis, osteoarthritis, disc herniation, degeneration of knees and hips, breast, endometrium, cervical, colon, leukemia and prostate cancers, hyperlipidemia, asthma/reactive airway disease, gallstones, GERD, obstructive sleep apnea, obesity hypoventilation syndrome, recurrent ventral hernias, menstrual irregularity, infertility, and the like.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[00133] Obesity: An increase in body weight beyond the limitation of skeletal and physical requirement, as the result of an excessive accumulation of fat in the body. Formally defined as having a body mass index greater than 30 kg/m^2.

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

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

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

[00137] Overweight: an individual whose weight is above that which is ideal for their height but who fails to meet the criteria for classification as obese. In humans using Body Mass Index (kg/m^2) an overweight individual has a BMI between 25 and 30.

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

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

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

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

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

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

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

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

[00146] The accumulation of excess body fat may begin about age 2 and can continue into adulthood (Miller 2011, supra). The vast majority of body fat in PWS is subcutaneous (Brambilla 1997, supra; Sode-Carlson, Growth hormone and IGF research 20:179-184 (2010), Bedogni J Endocrinol Invest DOI 10.1007/s40618-015-0266-y (2015)). Obesity is not universal in PWS, unlike the universality of low lean body mass and hypotonia. For example, Sode-Carlson et al. (2010), supra, evaluated 46 adult PWS patients, 25 women and 21 men. The average BMI in these adult PWS patients was 27.2 kg/m^2. Thus, on average, these patients were

overweight rather than obese, suggesting that more than half are not, in fact, obese by the best metric. Similarly, Brambilla et al. Nutr Metab Cardiovasc Dis 21(4):269-276 (2011) studied a population of 109 children with PWS. They found that 54% were not classified as obese by the best metric. Thus, both in adults and in children with PWS, obesity is not only not universal, but may, in fact, occur in less than half of the population. Subcutaneous fat makes up a greater percentage of total fat in PWS than it does in obese controls at all ages (Sode-Carlson 2010, supra).

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

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

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

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

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

[00152] Preadipocyte: A progenitor cell to adipocytes.

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

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

[00155] Prolonged Administration (prolonged basis): Administration of a pharmaceutically acceptable formulation of a drug for 7 or more days. Typically, prolonged administration is for at least two weeks, preferably at least one month, and even more preferably at least two months (i.e. at least 8 weeks).

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

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

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

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

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

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

[00162] Smith–Magenis syndrome is characterized by a clinically recognizable phenotype that includes physical, developmental, neurological, and behavioral features. Short stature (<5th percentile) was observed in ~67% of young patients. Short stature resolves over time with most individuals reaching the 10–25th percentile by adulthood (see, for example, Burns et al. supra). A majority of children with SMS also have significant early-onset obesity (see, for example, European Journal of Human Genetics (2008) 16, 412–421). Obesity in teens and adults is common, typically with broad chests and truncal obesity. RAI1 haploinsufficiency represents a

single-gene model of obesity with hyperphagia, abnormal fat distribution and altered hypothalamic gene expression associated with satiety, food intake, behavior and obesity.

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

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

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

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

[00167] Behavioral issues are one of the unique characteristic features of SMS. Maladaptive behaviors are a cause of major concern and include frequent outbursts/temper tantrums, attention seeking, aggression, disobedience, distraction, and self-injurious behaviors. Self-injurious behaviors include head banging, skin picking, wrist biting, onychotillomania and polyembolokoilamania. The behavioral phenotype of SMS escalates with age, typically with the onset of puberty. Age, degree of developmental delay, severity of any associated systemic

disorder, and degree of sleep disturbance have a strong influence on maladaptive behaviors. Individuals also have a lack of respect for personal space during a conversation and are emotionally volatile.

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

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

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

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

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

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

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

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

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

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

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

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

BRIEF DESCRIPTION OF THE FIGURES

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

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

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

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

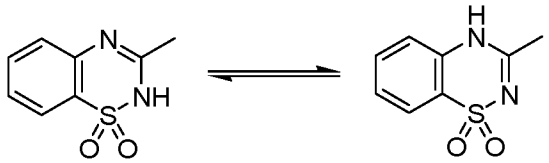
[00184] Figure 5 summarizes the clinical study treatment schedule for pediatric and adult patients who have PWS and are obese.

DETAILED DESCRIPTION OF THE INVENTION

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

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

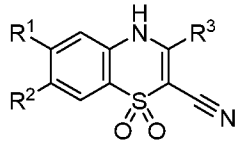
[00187] Compounds of formulas II and III, formulas IV and V, and formulas VI and VII, such as for example, diazoxide (shown below) can be proton tautomers. Proton tautomers are isomers that differ from each other only in the location of a hydrogen atom and a double bond. The hydrogen atom and double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



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

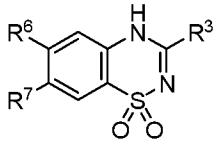
[00189] Analogs of diazoxide include 3-isopropylamino-7-methoxy-4H-1,2,4,-benzothiadiazine 1,1-dioxide, which is a selective Kir6.2/SUR1 channel opener (see Dabrowski, et al., *Diabetes*, 51, 1896-1906 (2002)). 2-alkyl substituted diazoxides are included (see, for example, Ouedraogo, et al., *Biol. Chem.*,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

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



R^1, R^2 and R^3 are:
a) H, Cl, $NHCH(CH_3)_2$
b) CF_3, H, $NHCH(CH_3)_2$
c) H, Cl, $NHCH_2CH_2CH(CH_3)_2$
d) H, Cl, NH-cyclobutyl

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



R^3, R^6 and R^7 are:
a) H, H, CH_3
b) H, H, Cl
c) CH_3, Cl, H
d) CH_2Cl, H, Cl
e) NH_2, H, H
f) CH_2CH_2Cl, H, Cl
g) nC_4H_9, H, Cl
h) nC_5H_{11}, H, Cl
i) nC_7H_{15}, H, Cl
j) nC_3H_7, Cl, H
k) nC_4H_9, Cl, H
l) nC_5H_{11}, Cl, H
m) nC_7H_{15}, Cl, H
n) nC_3H_7, Cl, Cl
o) nC_4H_9, Cl, Cl
p) nC_5H_{11}, Cl, Cl
q) nC_7H_{15}, Cl, Cl
r) H, Cl, H

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

[00193] Measurement of the inhibition of glucose-stimulated insulin release from βTC6 cells is described in Schou, et al., *Bioorg. Med. Chem.*, 13, 141-155 (2005). The ability of particular K_{ATP} channel openers to inhibit release of insulin from incubated rat pancreatic islets can be performed as described by Ouedraogo, et al., *Biol. Chem.*, 383, 1759-1768 (2002).

[00194] Activation of recombinant K_{ATP} channels by K_{ATP} channel openers can be examined by monitoring macroscopic currents of inside-out membrane patches from *Xenopus* oocytes coexpressing Kir6.2 and either SUR1, SUR2A or SUR2B. SUR expressing membranes can be

prepared by known methods. See, for example, Dabrowski, et al., *Diabetes*, 51, 1896-1906 (2002).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[00212] “Sulfonyl” denotes the group $-S(O)_2-$.

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

[00214] "Substituted sulfonyl" denotes the group -$S(O)_2$-R, where R is lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, cycloalkylalkyl, substituted cycloalkylalkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted hetereocyclylalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heteroaralkyl, substituted heteroaralkyl, aralkyl or substituted aralkyl.

[00215] "Sulfonylamino" denotes the group -$NRS(O)_2$- where R is hydrogen or lower alkyl.

[00216] "Substituted sulfonylamino" denotes the group -$NR^aS(O)_2$-R^b, where R^a is hydrogen or lower alkyl and R^b is lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heteroaralkyl, substituted heteroaralkyl, aralkyl or substituted aralkyl.

[00217] "Amino" or "amine" denotes the group –NH_2. A "divalent amine" denotes the group –NH-. A "substituted divalent amine" denotes the group –NR- wherein R is lower alkyl, substituted lower alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, acyl, substituted acyl, sulfonyl or substituted sulfonyl.

[00218] "Substituted amino" or "substituted amine" denotes the group -NR^iR^j, wherein R^i and R^j are independently hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, acyl, substituted acyl, sulfonyl, substituted sulfonyl, or cycloalkyl provided, however, that at least one of R^i and R^j is not hydrogen. R^iR^j in combination with the nitrogen may form an optionally substituted heterocyclic or heteroaryl ring.

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

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

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

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

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

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

citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, cyclohexylsulfamic acid, fumaric acid, and quinic acid.

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

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

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

[00228] Salts of K_{ATP} channel openers, and particular salts of diazoxide, may include, but are not limited to acetate, acetonide, acetyl, adipate, aspartate, besylate, biacetate, bitartrate, bromide, butoxide, butyrate, calcium, camsylate, caproate, carbonate, citrate, cyprionate, decaroate, diacetate, dimegulumine, dinitrate, dipotassium, dipropionate, disodium, disulfide, edisylate, enanthate, estolate, etabonate, ethylsuccinate, fumarate, furoate, gluceptate,gluconate, hexacetonide, hippurate, hyclate, hydrobromide, hydrochloride, isethionate, lactobionate, malate, maleate, meglumine, methylbromide, methylsulfate, metrizoate, nafate, napsylate, nitrate, oleate, palmitate, pamoate, phenpropionate, phosphate, pivalate, polistirex, polygalacturonate, probutate, propionate, saccharate, sodium glycinate, sodium phosphate, podium succinate, state, succinate, sulfate, sulfonate, sulfosalicylate, tartrate, tebutate, terephalate, terephthalate, tosylate, triflutate, trihydrate, trisilicate, tromethamine, valerate, xinafolate, or the like.

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

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

[00231] The formulations disclosed herein exhibit improved solubility and absorption of the K_{ATP} channel opener compared to previous formulations of these drugs. These advantageous properties are achieved by any one or more of the following approaches: (1) reducing particle size of the formulation by comminution, spray drying, or other micronising techniques, (2) using a pharmaceutical salt of the K_{ATP} channel opener, (3) using an ion exchange resin in the formulation, (4) using inclusion complexes, for example using a cyclodextrin, (5) compaction of the K_{ATP} channel opener with a solubilizing agent including low viscosity hypromellose, low viscosity metylcellulose or similarly functioning excipient and combinations thereof, (6) associating the K_{ATP} channel opener with a salt prior to formulation, (7) using a solid dispersion of the K_{ATP} channel opener, (8) using a self emulsifying system, (9) adding one or more surfactants to the formulation, (10) using nanoparticles in the formulation, or (11) combinations of these approaches. Preferably, when the K_{ATP} channel opener is a salt of diazoxide, the salt is not a sodium salt.

[00232] Release of K_{ATP} channel opener over a sustained period of time (2-24 hours) is achieved by the use of one or more approaches including, but not limited to: (1) the use of pH

sensitive polymeric coatings, (2) the use of a hydrogel, (3) the use of a film coating that controls the rate of diffusion of the drug from a coated matrix, (4) the use of an erodable matrix that controls rate of drug release, (5) the use of polymer coated pellets, granules, or microparticles which can be further encapsulated or compressed into a tablet, (6) the use of an osmotic pump system, or (7) the use of a compression coated tablet, or (8) combinations of these approaches.

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

[00234] Polymers that delay release can be applied to a tablet either by spray coating (as a thin film) or by compression coating. If a capsule is used, then the polymer(s) may be applied over the surface of the capsule or applied to microparticles of the drug, which may then be encapsulated such as in a capsule or gel. If the capsule is coated, then it will resist disintegration until after gastric transit. If microparticles are coated, then the capsule may disintegrate in the stomach but little to no drug will be released until after the free microparticles complete gastric transit. Finally, an osmotic pump system that uses e.g., a swellable hydrogel can be used to delay drug release in the stomach. The swellable hydrogel takes up moisture after administration. Swelling of the gel results in displacement of the drug from the system for absorption. The timing and rate of release of the drug depend on the gel used, and the rate at which moisture reaches the gel, which can be controlled by the size of the opening in the system through which fluid enters. See Drug Delivery Technologies online article Dong et al. "L-OROS® SOFTCAP™ for Controlled Release of Non-Aqueous Liquid Formulations."

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

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

[00237] The formulations provided herein exhibit improved safety of the administered drug product. This improvement in safety occurs by at least two mechanisms. First, delay of release of active drug until gastric transit is complete can reduce the incidence of a range of gastrointestinal adverse side effects including nausea, vomiting, dyspepsia, abdominal pain, diarrhea and ileus. Second, by sustaining release of the active drug over 2 or more hours to as long as 24 hours, peak drug levels are reduced relative to the peak drug levels observed for the same administered dose using any oral formulation that does not have sustained or controlled release. This reduction in peak drug levels can contribute to reductions in adverse effects that are partially or completely determined by peak drug levels. These adverse effects include: fluid retention with the associated reduced rates of excretion of sodium, chloride and uric acid, edema, hyperglycemia and the associated potential for progression to ketoacidosis, cataracts and non-ketotic hyperosmolar coma, headaches, tachycardia and palpitations.

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

Table 1: Controlled Release Formulation Characteristics and Properties

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

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

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

[00241] The controlled release formulations provided herein comprise the active compound (e.g., K_{ATP} channel opener, optionally in combination with growth hormone) and a matrix which comprises a gelling agent that swells upon contact with aqueous fluid. The active compound(s) entrapped within the gel is(are) slowly released into the body upon dissolution of the gel. The active compound(s) can be evenly dispersed within the matrix or can be present as pockets of drug in the matrix. For example, the drug can be formulated into small granules which are

dispersed within the matrix. In addition, the granules of drug also can include a matrix, thus, providing a primary and a secondary matrix as described in U.S. Pat. No. 4,880,830 to Rhodes.

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

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

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

[00245] The matrix of the controlled release composition can further include a hydrophobic material which slows the hydration of the gelling agent without disrupting the hydrophilic nature of the matrix, as described in U.S. Pat. No. 5,399,359. The hydrophobic polymer can include, for example, alkylcellulose such as ethylcellulose, other hydrophobic cellulosic materials, polymers or co-polymers derived from acrylic or methacrylic acid esters, co-polymers of acrylic and methacrylic acid esters, zein, waxes, shellac, hydrogenated vegetable oils, waxes and waxy

substances such as carnauba wax, spermaceti wax, candellila wax, cocoa butter, cetosteryl alcohol, beeswax, ceresin, paraffin, myristyl alcohol, stearyl alcohol, cetylalcohol and stearic acid. and any other pharmaceutically acceptable hydrophobic material known to those skilled in the art.

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

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

[00248] The controlled release composition also can be coated to retard access of liquids to the active compound and/or retard release of the active compound through the film-coating. The film-coating can provide characteristics of gastroresistance and enterosolubility by resisting rapid dissolution of the composition in the digestive tract. The film-coating generally represents about 5-15% by weight of the controlled release composition. Preferably, the core by weight represents about 90% of the composition with the remaining 10% provided by the coating. Such coating can be a film-coating as is well known in the art and include gels, waxes, fats, emulsifiers, combination of fats and emulsifiers, polymers, starch, and the like.

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

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

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

[00252] A plasticizing agent may be included in the coating to improve the elasticity and the stability of the polymer film and to prevent changes in the polymer permeability over prolonged storage. Such changes may affect the drug release rate. Suitable conventional plasticizing agents include, for example, diethyl phthalate, glycerol triacetate, acetylated monoglycerides, acetyltributylcitrate, acetyltriethyl citrate, castor oil, citric acid esters, dibutyl phthalate, dibutyl sebacate, diethyloxalate, diethyl malate, diethylfumarate, diethylphthalate, diethylsuccinate, diethylmalonate, diethyltartarate, dimethylphthalate, glycerin, glycerol, glyceryl triacetate, glyceryltributyrate, mineral oil and lanolin alcohols, petrolatum and lanolin alcohols, phthalic acid esters, polyethylene glycols, propylene glycol, rape oil, sesame oil, triacetin, tributyl citrate,

triethyl citrate, and triethyl acetyl citrate, or a mixture of any two or more of the foregoing. Plasticizers which can be used for aqueous coatings include, for example, propylene glycol, polyethylene glycol (PEG 400), triacetin, polysorbate 80, triethyl citrate, and diethyl d-tartrate.

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

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

[00255] The specified tablet or capsule formulations of Table 1 may include co-formulation with an obesity treating drug (in addition to the K_{ATP} channel opener). Obesity treating drugs that may be used include, but are not limited to, sibutramine hydrochloride (5-30 mg/unit), orlistat (50-360 mg/unit), phentermine hydrochloride or resin complex (15 to 40 mg/unit), zonisamide (100 to 600 mg/unit) topiramate (64 to 400 mg/unit), naltrexone hydrochloride (50 to 600 mg/unit), rimonabant (5 to 20 mg/unit), ADP356 (5 to 25 mg/unit), ATL962 (20 to 400 mg/unit), or AOD9604 (1 to 10 mg/unit). These formulations are preferably used once daily. For a twice daily dosing, the amount of K_{ATP} channel opener is one half the amount included in the once daily formulation and the coformulated obesity treating drug is half of the amount

specified. Alternative obesity treating drugs may include: selective serotonin 2c receptor agonists, dopamine antagonists, cannabinoid-1 receptor antagonists, leptin analogues, leptin transport and/or leptin receptor promoters, neuropeptide Y and agouti-related peptide antagonists, proopiomelanocortin and cocaine and amphetamine regulated transcript promoters, melanocyte-stimulating hormone analogues, melanocortin-4 receptor agonists, and agents that affect insulin metabolism/activity, which include protein-tyrosine phosphatase-1B inhibitors, peroxisome proliferator activated receptor- receptor antagonists, short-acting bromocriptine (ergoset), somatostatin agonists (octreotide), and adiponectin, gastrointestinal-neural pathway agents, including those that increase cholecystokinin activity, increase glucagon-like peptide-1 activity (extendin 4, liraglutide, dipeptidyl peptidase IV inhibitors), and increase protein YY3-36 activity and those that decrease ghrelin activity, as well as amylin analogues, agents that may increase resting metabolic rate ("selective" β-3 stimulators/agonist, uncoupling protein homologues, and thyroid receptor agonists), melanin concentrating hormone antagonists, phytostanol analogues, amylase inhibitors, growth hormone fragments, synthetic analogues of dehydroepiandrosterone sulfate, antagonists of adipocyte 11Bhydroxysteroid dehydrogenase type 1 activity, corticotropin releasing hormone agonists, inhibitors of fatty acid synthesis, carboxypeptidase inhibitors, indanones/indanols, aminosterols, and other gastrointestinal lipase inhibitors.

[00256] The specified tablet or capsule formulations of Table 1 may include co-formulation with a diabetes treating drug (in addition to the K_{ATP} channel opener). Diabetes treating drugs that may be used include, but are not limited to acarbose (50 to 300 mg/unit), miglitol (25 to 300 mg/unit), metformin hydrochloride (300 to 2000 mg/unit), repaglinide (1-16 mg/unit), nateglinide (200 to 400 mg/unit), rosiglitizone (5 to 50 mg/unit), metaglidasen (100 to 400 mg/unit) or any drug that improves insulin sensitivity, or improves glucose utilization and uptake. These formulations are preferably used once daily. For a twice daily dosing, the amount of the the K_{ATP} channel opener is half the amount included in the once daily formulation and the co-formulated diabetes treating drug is half of the amount specified.

[00257] The specified tablet or capsule formulations of Table 1 may include co-formulation with a cholesterol lowering drug. Cholesterol lowering drugs that may be used include, but are not limited to pravastatin or simvastatin or atorvastatin or fluvastatin or rosuvastatin or lovastatin

(all at 10 to 80 mg/unit). These formulations are preferably used once daily. For a twice daily dosing, the amount of K_{ATP} channel opener is preferably 25 to 200 mg/unit and the coformulated cholesterol lowering drug is half of the amount specified.

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

[00259] The specified tablet or capsule formulations of Table 1 may include co-formulation with a hypertension treating drug. Hypertension treating drugs that may be used include, but are not limited to enalapril maleate (2.5 to 40 mg/unit), captopril (2.5 to 150 mg/unit), lisinopril (10 to 40 mg/unit), benzaepril hydrochloride (10 to 80 mg/unit), quinapril hydrochloride (10 to 80 mg/unit), peridopril erbumine (4 to 8 mg/unit), ramipril (1.25 to 20 mg/unit), trandolapril (1 to 8 mg/unit), fosinopril sodium (10 to 80 mg/unit), moexipril hydrochloride (5 to 20 mg/unit), losartan potassium (25 to 200 mg/unit), irbesartan (75 to 600 mg/unit), valsartan (40 to 600 mg/unit), candesartan cilexetil (4 to 64 mg/unit), olmesartan medoxamil (5 to 80 mg/unit), telmisartan (20 to 160 mg/unit), eprosartan mesylate (75 to 600 mg/unit), atenolol (25 to 200 mg/unit), propranolol hydrochloride (10 to 180 mg/unit), metoprolol tartrate, succinate or fumarate (all at 25 to 400 mg/unit), nadolol (20 to 160 mg/unit), betaxolol hydrochloride (10 to 40 mg/unit), acebutolol hydrochloride (200 to 800 mg/unit), pindolol (5 to 20 mg/unit), bisoprolol fumarate (5 to 20 mg/unit), nifedipine (15 to 100 mg/unit), felodipine (2.5 to 20 mg/unit), amlodipine besylate (2.5 to 20 mg/unit), nicardipine (10 to 40 mg/unit), nisoldipine (10 to 80 mg/unit), terazosin hydrochloride (1 to 20 mg/unit), doxasoxin mesylate (4 to 16 mg/unit),

prazosin hydrochloride (2.5 to 10 mg/unit), or alfuzosin hydrochloride (10 to 20 mg/unit). These formulations are preferably used once daily. For a twice daily dosing, the amount of K_{ATP} channel opener is preferably half the amount included in the once daily formulation and the coformulated hypertension treating drug is half of the amount specified.

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

[00261] The specified tablet or capsule formulations of Table 1 may include co-formulation with a drug to treat inflammation or pain. Drugs for treating inflammation or pain that may be used include, but are not limited to aspirin (100 to 1000 mg/unit), tramadol hydrochloride (25 to 150 mg/unit), gabapentin (100 to 800 mg/unit), acetominophen (100 to 1000 mg/unit), carbamazepine (100 to 400 mg/unit), ibuprofen (100 to 1600 mg/unit), ketoprofen (12 to 200 mg/unit), fenprofen sodium (100 to 600 mg/unit), flurbiprofen sodium or flurbiprofen (both at 50 to 200 mg/unit), or combinations of any of these with a steroid or aspirin. These formulations are preferably used once daily. For a twice daily dosing, the amount of K_{ATP} channel opener is preferably half the amount included in the once daily formulation and the coformulated diuretic is half of the amount specified.

[00262] The specified tablet or capsule formulations of Table 1 may include co-formulation with a drug to treat obesity associated comorbidities include those specified above for treating diabetes, cholesterol, depression, hypertension and edema, or drugs to treat atherosclerosis, osteoarthritis, disc herniation, degeneration of knees and hips, breast, endometrial, cervical,

colon, leukemia and prostate cancers, hyperlipidemia, asthma/reactive airway disease, gallstones, GERD, obstructive sleep apnea, obesity hypoventilation syndrome, recurrent ventral hernias, menstrual irregularity and infertility.

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

[00264] The specified tablet or capsule formulations of Table 1 may include co-formulation with a drug to treat or prevent ischemic or reperfusion injury. Drugs for treating or preventing ischemic or reperfusion injury that may be used include, but are not limited to: low molecular weight heparins (dalteparin, enoxaparin, nadroparin, tinzaparin or danaparoid), ancrd, pentoxifylline, nimodipine, flunarizine, ebselen, tirilazad, clomethiazole, an AMPA agonist (GYKI 52466, NBQX, YM90K, zonampanel, orMPQX), SYM 2081, selfotel, Cerestat, CP-101,606, dextrophan, dextromethorphan, MK-801, NPS 1502, remacemide, ACEA 1021, GV150526, eliprodil ifenprodil, lubeluzole, naloxone, nalfemene citicoline, acetyl-l-carnitine, nifedipine, resveratrol, a nitrone derivative, clopidogrel, dabigatram, prasugrel, troxoprodil, AGY-94806, or KAI-9803.

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

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

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

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

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

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

[00271] The various pharmaceutical K_{ATP} channel opener formulations have a variety of applications, including, but not limited to: (1) treatment of obesity; (2) prevention of weight gain in individuals who are predisposed to obesity; (3) treatment of hyperinsulemia or hyperinsulinism; (4) treatment of hypoglycemia; (5) treatment of hyperlipidemia, (6) treatment of type II diabetes, (7) preservation of pancreatic function in type I diabetics; (8) treatment of metabolic syndrome (or syndrome X); (9) prevention of the transition from prediabetes to diabetes, (10) correction of the defects in insulin secretion and insulin sensitivity contributing to prediabetes and type II diabetes, (11) treatment of polycystic ovary syndrome, (12) prevention of ischemic or reperfusion injury, (13) treat weight gain, dyslipidemia, or impairment of glucose

tolerance in subjects treated with antipsychotics drugs, (14) prevent weight gain, dyslipidemia, or impairment of glucose tolerance in subjects treated with antipsychotics drugs and (15) treatment of any disease where hyperlipidemia, hyperinsulemia, hyperinsulinism, hyperlipidemia, hyperphagia or obesity are contributing factors to the severity or progression of the disease, including but not limited to, Prader-Willi Syndrome, Smith–Magenis syndrome, Froelich's syndrome, Cohen syndrome, Summit Syndrome, Alstrom, Syndrome, Borjesen Syndrome, Bardet-Biedl Syndrome, hyperlipoproteinemia type I, II, III, and IV, and the like.

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

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

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

diabetic, (d) is not a type II diabetic, (e) does not have metabolic syndrome, or (f) is not experiencing chronic, recurrent or drug-induced hypoglycemia.

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

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

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

[00278] In another embodiment, a K_{ATP} channel opener is administered to an overweight or obese individual as a solid oral dosage form administered from one, two, three or four times per 24 hours, optionally in combination with growth hormone, to induce weight loss at a daily dose of 50 to 275 mg. In a further embodiment, the overweight or obese individual individual (a) is not type I diabetic, (b) is not type II diabetic, (c) is not suffering chronic, recurrent or drug-induced hypoglycemia, or (d) does not have metabolic syndrome.

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

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

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

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

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

[00284] In additional embodiments, a solid oral dosage of a K_{ATP} channel opener is administered on a prolonged basis one, two or three times per 24 hours at daily doses of 50 to 275 mg to an individual, optionally in combination with growth hormone, to (a) induce the loss of 25%, 50% or 75% of initial body fat, (b) induce the preferential loss of body fat, or (c) induce the preferential loss of visceral fat.

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

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

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

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

[00289] In another embodiment, a solid oral dosage of a K_{ATP} channel opener is co-administered with growth hormone and optionally one or more of a drug that lowers blood pressure, a drug that lowers cholesterol, a drug that raises HDL, an anti-inflammatory that is not a Cox-2 inhibitor, a drug that lowers circulating triglycerides, to maintain weight and/or treat obesity associated comorbidities in an overweight, obese, or obesity prone individual, as it is preferable to maintain weight in an obese individual once some weight loss has occurred when the alternative is to regain weight. In further embodiments, the overweight, obese, or obesity prone individual (a) is not a type I diabetic, (b) is not a type II diabetic, (c) is not suffering from chronic, recurrent or drug-induced hypoglycemia, or (d) does not have metabolic syndrome.

[00290] In additional embodiments, a tablet formulation of a K_{ATP} channel opener is used to administer a therapeutically effective dose of a K_{ATP} channel opener to an obese, overweight or

obesity prone individual in need thereof to treat obesity, to (a) provide beta cell rest, (b) treat type I or type II diabetes, or (c) prevent the occurrence of diabetes.

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

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

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

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

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

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

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

[00298] Upon administration of the formulations provided herein to humans or animals, some or all of the following effects are observed: (1) the production of lipoprotein lipase by adipocytes is reduced; (2) enhanced lipolysis by adipocytes; (3) expression of fatty acid synthase by adipocytes is reduced; (4) glyceraldehydes phosphate dehydrogenase activity of adipocytes is reduced; (5) little or no new triglycerides are synthesized and stored by adipocytes; (6) enhanced expression of $ß_3$ Adrenergic Receptor ($ß_3$AR) an improvement in the adrenergic function in adipocytes; (7) reduced glucose stimulated secretion of insulin by pancreatic B-cells; (8) decreased insulinemia; (9) enhanced blood glucose levels; (10) increased expression of Uncoupling Protein 1 in adipocytes; (11) enhanced thermogenesis in white and brown adipose tissue; (12) reduction of plasma triglyceride concentration; (13) decrease in circulating leptin concentrations; (14) up-regulation of insulin receptors; (15) enhanced glucose uptake; (16) reduced adipocyte hyperplasia; (17) reduced adipocyte hypertrophy; (18) reduced rates of conversion of preadipocytes to adipocytes; (19) reduced rates of hyperphagia, (20) increased protection of CNS, cardiac and other tissues from ischemic or reperfusion injury, (21) improved insulin sensitivity, (22) elevated CSF insulin concentrations, (23) elevated circulating adiponectin concentrations, (25) reduced circulating triglyceride concentrations, (26) enhancement of beta-cell rest, and/or (27) increase in lean body mass.

[00299] Threshold concentrations of the current invention include those circulating concentrations of K_{ATP} channel openers, optionally in combination with growth hormone, resulting from the administration of the drug as an i.v. formulation, an immediate release oral formulation, a controlled release formulation, a transdermal formulation, or an intranasal

formulation to an overweight or obese individual which results in (1) measurable suppression of fasting insulin levels, (2) suppression of fasting insulin levels by at least 20% from the baseline measurement in the same individual prior to treatment with a K_{ATP} channel openers, (3) suppression of fasting insulin levels by at least 30% from the baseline measurement in the same individual prior to treatment with K_{ATP} channel openers, (4) suppression of fasting insulin levels by at least 40% from the baseline measurement in the same individual prior to treatment with a K_{ATP} channel openers, (5) suppression of fasting insulin levels by at least 50% from the baseline measurement in the same individual prior to treatment with K_{ATP} channel openers, (6) suppression of fasting insulin levels by at least 60% from the baseline measurement in the same individual prior to treatment with K_{ATP} channel openers, (7) suppression of fasting insulin levels by at least 70% from the baseline measurement in the same individual prior to treatment with K_{ATP} channel openers, (8) suppression of fasting insulin levels by at least 80% from the baseline measurement in the same individual prior to treatment with K_{ATP} channel openers, (9) loss of weight, (10) elevation of resting energy expenditure, or (11) elevation of the oxidation of fat or fatty acids.

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

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

[00302] Threshold effects of the current invention include those circulating concentrations of K_{ATP} channel openers resulting from the administration of an i.v. formulation of the drug, or an immediate release oral formulation of the drug, or a controlled release formulation of the drug, or

a sustained release formulation, or a transdermal formulation, or an intranasal formulation of the drug to a individual with type 1 diabetes which result in beta cell rest.

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

[00304] Prolonged administration of pharmaceutical formulations of K_{ATP} channel openers to overweight or obese humans or animals, optionally in combination with growth hormone, results in substantial and sustained weight loss including some or all of the following effects: (1) preferential loss of body fat; (2) loss of greater than 25% of initial body fat mass; (3) loss of greater than 50% of initial body fat mass; (4) loss of greater than 75% of initial body fat mass; (5) significant increase in resting energy expenditure; (6) increase in the oxidation of fat and fatty acids; (7) reduction in blood pressure; (8) production of lipoprotein lipase by adipocytes is reduced; (9) enhanced lipolysis by adipocytes; (10) expression of fatty acid synthase by adipocytes is reduced; (11) glyceraldehydes phosphate dehydrogenase activity of adipocytes is reduced; (12) little or no new triglycerides are synthesized and stored by adipocytes; (13) enhanced expression of $ß_3$ Adrenergic Receptor ($ß_3$AR) and an improvement in the adrenergic function in adipocytes; (14) reduced glucose stimulated secretion of insulin by pancreatic B-cells; (15) decreased insulinemia; (16) enhanced blood glucose levels; (17) increased expression of Uncoupling Protein 1 in adipocytes; (18) enhanced thermogenesis in white and brown adipose tissue; (19) reduction of plasma triglyceride concentration; (20) decrease in circulating leptin concentrations; (21) up-regulation of insulin receptors; (22) enhanced glucose uptake; (23) reduced adipocyte hyperplasia; (24) reduced adipocyte hypertrophy; (25) reduced rates of conversion of preadipocytes to adipocytes; (26) reduced rates of hyperphagia; (27) the sequential loss first of the metabolically most active adipose tissue (visceral), followed by the loss of less

metabolically active adipose tissue, (28) elevation of circulating adiponectin concentrations, (29) elevation of cerebrospinal fluid insulin levels, (30) enhanced islet insulin mRNA and insulin content, (31) enhanced metabolic efficiency of insulin, or (32) increase in lean body mass.

[00305] Prolonged administration of formulations of K_{ATP} channel openers, optionally in combination with growth hormone, to obesity prone humans or animals, including individuals who have undergone various types of bariatric surgery, results in sustained maintenance of weight including some or all of the following effects: (1) increased resting energy expenditure; (2) increase in the oxidation of fat and fatty acids; (3) reduction in blood pressure; (4) production of lipoprotein lipase by adipocytes is reduced; (5) enhanced lipolysis by adipocytes; (6) expression of fatty acid synthase by adipocytes is reduced; (7) glyceraldehyde phosphate dehydrogenase activity of adipocytes is reduced; (8) little or no new triglycerides are synthesized and stored by adipocytes; (9) enhanced expression of $ß_3$ Adrenergic Receptor ($ß_3$AR) and improvement in the adrenergic function in adipocytes; (10) reduced glucose stimulated secretion of insulin by pancreatic B-cells; (11) decreased insulinemia; (12) enhanced blood glucose levels; (13) increased expression of Uncoupling Protein 1 in adipocytes; (14) enhanced thermogenesis in white and brown adipose tissue; (15) reduction of plasma triglyceride concentration; (16) decreased circulating leptin concentration; (17) up-regulation of insulin receptors; (18) enhanced glucose uptake; (19) reduced adipocyte hyperplasia; (20) reduced adipocyte hypertrophy; (21) reduced rates of conversion of preadipocytes to adipocytes; and (22) reduced rates of hyperphagia, (23) elevated circulating adiponectin concentration, (24) elevated cerebrospinal fluid insulin levels, (25) enhanced islet insulin mRNA and insulin content, or (26) enhanced metabolic efficiency of insulin.

[00306] Immediate or prolonged administration of formulations of K_{ATP} channel openers, optionally in combination with growth hormone, to prediabetic or type I diabetic humans or animals results in the prevention of beta cell failure, improved glycemic control, and prevention of the transition from prediabetes to diabetes including some or all of the following effects: (1) increase in resting energy expenditure; (2) increase in the oxidation of fat and fatty acids; (3) reduction in blood pressure; (4) production of lipoprotein lipase by adipocytes is reduced; (5) enhanced lipolysis by adipocytes; (6) expression of fatty acid synthase by adipocytes is reduced; (7) glyceraldehyde phosphate dehydrogenase activity of adipocytes is reduced; (8) little or no

new triglycerides are synthesized and stored by adipocytes; (9) enhanced expression of $ß_3$ Adrenergic Receptor ($ß_3$AR) and an improvement in the adrenergic function in adipocytes; (10) reduced glucose stimulated secretion of insulin by pancreatic B-cells; (11) decreased insulinemia; (12) enhanced blood glucose levels; (13) increased expression of Uncoupling Protein 1 in adipocytes; (14) enhanced thermogenesis in white and brown adipose tissue; (15) reduction of plasma triglyceride concentration; (16) decreased circulating leptin concentrations; (17) up-regulation of insulin receptors; (18) enhanced glucose uptake; (19) reduced adipocyte hyperplasia; (20) reduced adipocyte hypertrophy; (21) reduced rates of conversion of preadipocytes to adipocytes; (22) reduced rates of hyperphagia, (23) elevated circulating adiponectin concentrations, (24) elevated cerebrospinal fluid insulin levels, (25) enhanced islet insulin mRNA and insulin content, or (26) enhanced metabolic efficiency of insulin.

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

[00308] Pharmaceutical formulations as provided herein are designed to be used in the treatment of obesity, hyperlipidemia, hypertension, weight maintenance, type I diabetes, prediabetes, type II diabetes, or any condition where weight loss, reduction in circulating triglycerides or beta cell rest contributes to therapeutic outcomes provide for a range of critical changes in pharmacodynamic and pharmacokinetic responses to administered doses of K_{ATP} channel openers, optionally in combination with growth hormone, which changes include one or more of the following: (1) extending the pharmacodynamic effect of an administered dose to greater than 24 hours as measured by the suppression of insulin secretion, (2) providing for substantial uptake of the active pharmaceutical ingredient in the small intestine, (3) providing for substantial uptake of the active pharmaceutical ingredient in the large intestine, (4) result in lowered Cmax versus current oral suspension or capsule products for the same administered dose of active pharmaceutical ingredient, (5) provide for circulating concentrations of unbound active pharmaceutical ingredient above threshold concentrations for 24 or more hours from a single

administered dose, and (6) provide for more consistent drug absorption by treated individuals as compared to existing capsule formulations.

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

[00310] Treatment of humans or animals of the current invention using pharmaceutical formulations of K_{ATP} channel openers, optionally in combination with growth hormone, result in reduced incidence of adverse side effects including but not limited to edema, fluid retention, reduced rates of excretion of sodium, chloride, and uric acid, hyperglycemia, ketoacidosis, nausea, vomiting, dyspepsia, ileus and headaches. These reductions in frequency of adverse side effects are achieved by: (1) initiating dosing of individuals at subtherapeutic doses and in a step wise manner increasing the dose daily until the therapeutic dose is achieved where the number of days over which the step up in dose is effected is 2 to 10, (2) use of the lowest effective dose to achieve the desired therapeutic effect, (3) use of a pharmaceutical formulation that delays release of active until gastric transit is complete, (4) use of a pharmaceutical formulation that delays release of active until gastric transit is complete, (5) use of a pharmaceutical formulation that results in lower circulating peak drug levels as compared to an immediate release oral suspension or capsule formulation for the same administered dose, and (6) optimizing the timing of administration of dose within the day and relative to meals.

[00311] Treatment of patients suffering from Prader-Willi Syndrome, Smith–Magenis syndrome, Froelich's syndrome, Cohen syndrome, Summit Syndrome, Alstrom, Syndrome, Borjesen Syndrome, Bardet-Biedl Syndrome, and hyperlipoproteinemia type I, II, III, and IV with the current invention using pharmaceutical formulations of K_{ATP} channel openers,

optionally in combination with growth hormone, result in some or all of the following therapeutic outcomes: (1) weight loss, (2) reduced rates of weight gain, (3) inhibition of hyperphagia, (4) reduced incidence of impaired glucose tolerance, prediabetes or diabetes, (5) reduced incidence of congestive heart failure, (6) reduced hypertension, and (7) reduced rates of all cause mortality.

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

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

[00314] Co-administration of drugs with formulations of K_{ATP} channel openers in the treatment of diseases of overweight, obese or obesity prone human and animal subjects involves the co-administration of a pharmaceutically acceptable formulation of K_{ATP} channel openers with an acceptable formulation of growth hormone and optionally one or more of: (1) Sibutramine, (2) orlistat, (3) Rimonabant, (4) a drug that is an appetite suppressant, (5) any drug used to induce weight loss in an obese or overweight individual, (6) a non-thiazide diuretic, (7) a drug that lowers cholesterol, (8) a drug that raises HDL cholesterol, (9) a drug that lowers LDL cholesterol, (10) a drug that lowers blood pressure, (11) a drug that is an anti-depressant, (12) a drug that improves insulin sensitivity, (13) a drug that improves glucose utilization and uptake (14) a drug that is an anti-epileptic, (15) a drug that is an anti-inflammatory, or (16) a drug that lowers circulating triglycerides.

[00315] Co-administration of drugs with formulations of K_{ATP} channel openers in the treatment or prevention of weight gain, dyslipidemia, or impaired glucose tolerance in subjects treated with antipsychotics drugs involve the co-administration of a pharmaceutically acceptable

formulation of K_{ATP} channel openers with growth hormone and optionally one or more of an acceptable formulation of: lithium, carbamazepine, valproic acid and divalproex, and lamotrigine, antidepressants generally classified as monoamine oxidase inhibitors including isocarboxazid, phenelzine sulfate and tranylcypromine sulfate, tricyclic antidepressants including doxepin, clomipramine, amitriptyline, maproiline, desipromine, nortryptyline, desipramine, doxepin, trimipramine, imipramine and protryptyline, tetracyclic antidepressants including mianserin, mirtazapine, maprotiline, oxaprotline, delequamine, levoprotline, triflucarbine, setiptiline, lortalaline, azipramine, aptazapine maleate and pirlindole, and major tranquilizers and atypical antipsychotics including paloproxidol, perphenazine, thioridazine, risperidone, clozapine, olanzapine and chlorpromazine.

[00316] In one embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an overweight or obese individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation to reach and maintain the threshold concentration required to measurably reduce fasting insulin levels for a prolonged period. Preferably the K_{ATP} channel opener formulation reduces fasting insulin levels by at least 20%, more preferably by at least 30%, more preferably by at least by 40%, more preferably by at least 50%, more preferably by at least by 60% more preferably by at least by 70%, and more preferably by at least 80%. Fasting insulin levels are commonly measured using the glucose tolerance test (OGTT). After an overnight fast, a patient ingests a known amount of glucose. Initial glucose levels are determined by measuring pre-test glucose levels in blood and urine. Blood insulin levels are measured by a blood is draw every hour after the glucose is consumed for up to three hours. In a fasting glucose assay individuals with plasma glucose values greater than 200 mg/dl at 2 hours post-glucose load indicate an impaired glucose tolerance.

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

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

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

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

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

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

[00323] In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an overweight or obese individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal

formulation or an intranasal formulation for a prolonged period of time to reduce body fat by more than 25%, more preferably by at least 50%, and more preferably by at least 75%.

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

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

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

[00327] In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to a prediabetic individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation to reach and maintain a drug concentration above the threshold concentration required to prevent the transition to diabetes for a prolonged period.

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

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

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

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

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

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

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

[00335] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is administered over a prolonged basis

to an individual in need thereof no more than once per 24 hours that results in circulating concentration of active drug sufficient to induce weight loss on a continuous basis.

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

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

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

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

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

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

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

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

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

[00345] In another embodiment, the adverse effects of frequent treatment with a K_{ATP} channel opener, optionally in combination with growth hormone, is reduced using a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, that is administered to an overweight or obese individual in need thereof

on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached, the active ingredient is not released from the formulation until gastric transit is complete, in which the maximum circulating concentration of active ingredient is lower than what would be realized by the administration of the same dose using an oral suspension or capsule formulation, and in which the maximum dose is less than 2.5 mg/kg/day.

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

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

[00348] In another embodiment, the treatment of an overweight or obese individual is optimized for weight loss by administration of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, once per 24 hours in which the release of the active ingredient from the formulation has been modified to provide near zero order release for at least 18 hours.

[00349] In another embodiment, the treatment of an overweight or obese individual is optimized for weight loss by administration of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, once per 24 hours in

which the release of the active ingredient from the formulation has been modified to provide a rising drug concentration in circulation for at least 12 hours.

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

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

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

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

using an oral suspension or capsule formulation, and in which the maximum dose is less than 1.75 mg/kg/day.

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

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

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

[00357] In another embodiment, the treatment of an obesity prone individual is optimized for weight maintenance by administration of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, once per 24 hours in which the release of the active ingredient from the formulation has been modified to provide a rising drug concentration in circulation for at least 18 hours.

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

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

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

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

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

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

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

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

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

[00367] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with a drug that

lowers blood pressure to an overweight, obesity prone or obese individual to induce weight loss and treat obesity associated comorbidities.

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

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

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

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

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

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

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

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

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

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

[00378] In another embodiment, K_{ATP} channel openers, optionally in combination with growth hormone, are co-formulated with an anti-cholesteremic active in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese individual to induce weight loss and treat obesity-associated co-morbidities.

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

[00380] In another embodiment, K_{ATP} channel openers, optionally in combination with growth hormone, are co-formulated with an insulin sensitizing active in a pharmaceutically acceptable

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

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

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

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

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

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

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

[00387] A solid oral dosage form of K_{ATP} channel opener can be used to administer a therapeutically effective dose of K_{ATP} channel opener to an overweight or obesity prone

individual in need thereof to maintain weight, as it is preferable to maintain weight in an obese individual once some weight loss has occurred when the alternative is to regain weight.

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

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

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

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

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

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

EXAMPLES

Example 1: Potassium ATP channel activator containing formulations

1. *Compressed Tablet Formulations*

[00394] Diazoxide or a derivative thereof at about 15-30% by weight is mixed with hydroxypropyl methylcellulose at about 55-80% by weight, ethylcellulose at about 3-10 wt/vol % and magnesium stearate (as lubricant) and talc (as glidant) each at less than 3% by weight.

The mixture is used to produce a compressed tablet as described in Reddy et al., *AAPS Pharm Sci Tech* 4(4):1-9 (2003). The tablet may be coated with a thin film as discussed below for microparticles.

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

2. *Encapsulated Coated Microparticle Formulation of Diazoxide*

[00396] Diazoxide or a derivative thereof is encapsulated into microparticles in accordance with well known methods (see, e.g. U.S. Patent No. 6,022,562). Microparticles of between 100 and 500 microns in diameter containing diazoxide or derivative, alone or in combination with one or more suitable excipient, is formed with the assistance of a granulator and then sieved to separate microparticles having the appropriate size. Micriparticles are coated with a thin film by spray drying using commercial instrumentation (e.g. Uniglatt Spray Coating Machine). The thin film comprises ethylcellulose, cellulose acetate, polyvinylpyrrolidone and/or polyacrylamide. The coating solution for the thin film may include a plasticizer which may be castor oil, diethyl phthalate, triethyl citrate and salicylic acid. The coating solution may also include a lubricating agent which may be magnesium stearate, sodium oleate, or polyoxyethylenated sorbitan laurate. The coating solution may further include an excipient such as talc, colloidal silica or of a mixture of the two added at 1.5 to 3% by weight to prevent caking of the film coated particles.

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

[00397] Prior to mixing, both the active ingredient and hydroxypropyl methylcellulose (Dow Methocel K4M P) are passed through an ASTM 80 mesh sieve. A mixture is formed from 1 part diazoxide or a derivative thereof to 4 parts hydroxypropyl methylcellulose. After thorough mixing, a sufficient volume of an ethanolic solution of ethylcellulose as a granulating agent is added slowly. The quantity of ethylcellulose per tablet in the final formulation is about 1/10th part. The mass resulting from mixing the granulating agent is sieved through 22/44 mesh.

Resulting granules are dried at 40° C for 12 hours and thereafter kept in a desiccator for 12 hours at room temperature. Once dry the granules retained on 44 mesh are mixed with 15% fines (granules that passed through 44 mesh). Talc and magnesium stearate are added as glidant and lubricant at 2% of weight each. A colorant is also added. The tablets are compressed using a single punch tablet compression machine.

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

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

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

[00399] The core tablet is formulated by mixing either 100 mg of diazoxide or a derivative thereof with 10 mg of ethylcellulose (Dow Ethocel 10FP), or by mixing 75 mg of diazoxide or a derivative thereof with 25 mg lactose and 10 mg of ethylcellulose (Dow Ethocel 10FP), or by mixing 50 mg of diazoxide or a derivative thereof with 50 mg of lactose and 10 mg of ethylcellulose (Dow Ethocel 10FP). The core tablets are formed on an automated press with concave tooling. The compression coating consisting of 400 mg of ethylene oxide (Union Carbide POLYOX WSR Coagulant) is applied and compressed to 3000 psi (Dasbach, et al., Poster at AAPS Annual Meeting Oct 26-30 (2003)).

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

[00400] Diazoxide or a derivative thereof is formulated as an osmotically regulated release system. In general, two components, and expandable hydrogel that drives release of the active

drug is assembled with diazoxide or a derivative thereof into a semipermeable bilaminate shell. Upon assembly a hole is drilled in the shell to facilitate release of active upon hydration of the hydrogel.

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

[00402] A hydrogel composition is prepared as follows: first, 69% weight of polyethylene oxide weight, 25% weight of sodium chloride and 1% weight ferric oxide separately are screened through a 40 mesh screen. Then, all the screened ingredients are mixed with 5% weight of hydroxypropyl methylcellulose to produce a homogeneous blend. Next, a volume of denatured anhydrous alcohol equal to 50% of the dry mass is added slowly to the blend with continuous mixing for 5 minutes. The freshly prepared wet granulation is passed through a 20 mesh screen, allowed to dry at room temperature for 16 hours, and again passed through a 20 mesh screen. The screened granulation is mixed with 0.5% weight of magnesium stearate 5 minutes (see U.S. Patent No. 6,361,795 by Kuczynski, et al.).

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

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

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

7. *Preparation of a salt of diazoxide*

[00406] A hydrochloride salt of diazoxide is prepared by dissolving one mole of diazoxide (230.7 g) in 500 ml of Et_2O. 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 Et_2O.

Example 2: *In vivo* Obesity Testing

1. *Obesity animal model*

[00407] Formulations of diazoxide or derivatives prepared as described herein can be tested for efficacy in an animal model of obesity as described by Surwit et al. (*Endocrinology* 141:3630-3637 (2000)). Briefly, 4-week-old B6 male mice are housed 5/cage in a temperature-controlled (22°C) room with a 12-h light, 12-h dark cycle. The high fat (HF) and low fat (LF) experimental diets contain 58% and 11% of calories from fat, respectively. A group of mice are fed the HF diet for the first 4 weeks of the study; the remaining 15 mice are fed the LF diet. The mice assigned to the LF diet are maintained on this diet throughout the study as a reference group of lean control mice. At week 4, all HF-fed mice a reassigned to 2 groups of mice. The first group remains on the HF diet throughout the study as the obese control group. The remaining 3 groups of mice are fed the HF diet and administered the controlled release formulation of diazoxide or derivative at about 150 mg of active per kg per day as a single dose administered by oral gavage. Animals are weighed weekly, and food consumption is measured per cage twice weekly until the diets are changed at week 4, whereupon body weight and food intake are determined daily. The feed efficiency (grams of body weight gained per Cal consumed) is calculated on a per cage basis. Samples for analysis of insulin, glucose, and leptin are collected on day 24 (4 days before the diets are changed), on day 32 (4 days after the change), and biweekly thereafter. In all cases food is removed 8 h before samples are collected. Glucose is analyzed by the glucose oxidase method. Insulin and leptin concentrations are

determined by double antibody RIA. The insulin assay is based on a rat standard, and the leptin assay uses a mouse standard. At the termination of the study, a postprandial plasma sample is collected and analyzed for triglyceride and nonesterified fatty acid concentrations. After 4 weeks of drug treatment, a subset of 10 animals from each group is killed. The epididymal white adipose tissue (EWAT), retroperitoneal (RP) fat, interscapular brown adipose tissue (IBAT) fat pads, and gastrocnemius muscle are removed, trimmed, and weighed. The percent body fat is estimated from the weight of the epididymal fat pad. A subset of five animals from each group is injected ip with 0.5 g/kg glucose. At 30 min postinjection, a plasma sample is collected and analyzed for glucose content by the glucose oxidase method.

2. *Treatment of obesity in humans*

[00408] Formulations of diazoxide or derivatives prepared as described herein can be tested for efficacy in obese humans. The study is conducted as described by Alemzadeh (Alemzadeh, et al., *J Clin Endocr Metab* 83:1911-1915 (1998)). Subjects consist of moderate-to-morbidly obese adults with a body mass index (BMI) greater than or equal to 30 kg/m^2. Each subject undergoes a complete physical examination at the initial evaluation, body weight being measured on a standard electronic scale and body composition by DEXA.

[00409] Before the initiation of the study, all subjects are placed on a hypocaloric diet for a lead-in period of 1 week. This is designed to exclude individuals who are unlikely to be compliant and to ensure stable body weight before treatment. Up to 50 patients are tested at each dosage of drug. Daily dosage is set at 100, 200, and 300 mg/day. The daily dose is divided into 2 doses for administration. The dose is administered as either one, two or three 50 mg capsules or tablets at each time of administration. Individual patients are dosed daily for up to 12 months. Patients are reviewed weekly, weighed, and asked about any side effects or concurrent illnesses.

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

[00411] Before commencing, and after completion of the study, the following laboratory tests are obtained: blood pressure fasting plasma glucose, insulin, cholesterol, triglycerides, free fatty acids (FFA), and glycohemoglobin and measures of rate of appearance and oxidation of plasma

derived fatty acids. Additionally, routine chemistry profiles and fasting plasma glucose are obtained weekly to identify those subjects with evidence of glucose intolerance and/or electrolyte abnormalities. Glucose is analyzed in plasma, by the glucose oxidase method.

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

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

[00413] Evaluation of a prolonged co-administration of solid oral dosage form of diazoxide or a derivative thereof and phentermine in obese humans with a moderate-to-morbidly and a body mass index (BMI) greater than or equal to 30 kg/m^2. Each subject undergoes a complete physical examination at the initial evaluation, body weight being measured on a standard electronic scale and body composition by DEXA.

[00414] Before the initiation of the study, all subjects are placed on a hypocaloric diet for a lead-in period of 1 week. This is designed to exclude individuals who are unlikely to be compliant and to ensure stable body weight before treatment. Up to 100 patients are tested. Daily dosage of diazoxide is set at 200 mg. The daily dose is divided into 2 doses for administration. The dose is administered as either a 100 mg capsule or a 100 mg tablet at each

time of administration. Individual patients are dosed daily for up to 12 months. Phentermine is administered as a single daily dose of 15 mg. Patients are reviewed every two weeks, weighed, and asked about any side effects or concurrent illnesses.

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

4. *Prevention of diabetes in prediabetic humans*

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

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

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

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

[00419] Type II diabetic patients are treated with the oral dosage form by administration of two tablets once per day or one tablet every 12 hours. Treatment of the patient with the drug is continued until one of two therapeutic endpoints is reached, or for so long as the patient derives therapeutic benefit from administration. The two therapeutic endpoints that would serve as the basis for the decision to cease treatment include the patient reaching a Body Mass Index (BMI (kg/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*

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

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

[00421] A single-center, open-label, single-arm clinical study (PC025) with a double-blind, placebo-controlled, randomized withdrawal extension has been carried out. Patients were initiated on a DCCR dose of about 1.5 mg/kg (maximum starting dose of 145 mg) and were titrated every 14 days to about 2.4 mg/kg, 3.3 mg/kg, and 4.2 mg/kg (maximum dose of 507.5 mg). These DCCR doses are equivalent to diazoxide doses of 1.03, 1.66, 2.28, and 2.9 mg/kg, respectively. Patients were up-titrated at each visit at the discretion of the investigator. Any patient who showed an increase in resting energy expenditure and/or a reduction in hyperphagia from Baseline through Day 27 or Day 55 was designated a Responder and eligible to be randomized in the double-blind phase. Everyone who completed the open-label phase was a Responder and was randomized in and completed the double-blind phase. During the double-blind, placebo-controlled, randomized withdrawal phase, Responders were randomized in a 1:1 ratio either to continue on active treatment at the dose they were treated with on Day 55 or to the placebo equivalent of that dose for an additional 4 weeks (29 days). Non-responders continued open label treatment with DCCR at the dose they were treated with on Day 55 for an additional 29 days. A total of 12 patients were enrolled in the study.

Inclusion Criteria: Basic requirements

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

General demographic characteristics

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

- Generally healthy as documented by the medical history, physical examination, vital sign assessments, 12-lead electrocardiogram (ECG), and clinical laboratory assessments

Specific laboratory test results

- fasting glucose ≤ 126 mg/dL
- HbA1c ≤ 6.5 %

Endpoints and Statistical Analysis

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

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

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

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

Parameter	Screening	Baseline	Visit 3	Visit 4	Visit 5	Visit 6	End of Open label treatment
Hyperphagia	+	+	+	+	+	+	+
Body fat	Either at screening or baseline						+
Lean body mass							+
Weight	+	+	+	+	+	+	+

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

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

Parameter	Screening	Baseline	Day 69 End of Open label treatment	Day 97 End of double blind treatment
Hyperphagia	+	+	+	+
Body fat	Either at screening or baseline		+	
Lean body mass			+	
Weight	+	+	+	+
REE & RQ		+	+	+
Waist circumference	+	+	+	+
Ghrelin, leptin		+	+	
Lipids		+	+	+
Behavioral questionnaire		+	+	

Patients in the Study

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

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

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

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

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

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

Dosing

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

Changes in Body Composition, Waist Circumference and Weight

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

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

Table 6.

Changes in body composition by DEXA from Baseline through Day 69

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Changes in Hyperphagia

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

Table 10. Changes in hyperphagia from Baseline through Day 69

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

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

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

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

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

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

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

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

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

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

Changes in Lipids

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

Table 13. Changes in Lipids from Baseline through Day 69

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

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

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

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

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

Changes in Leptin and Ghrelin

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

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

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

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

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

Behavioral Changes

[00447] A questionnaire, adapted from the PWS natural history study, was used to document the presence or absence of 23 PWS-associated behaviors at Baseline and again on Day 69. These behaviors generally fell into 4 categories:

(1) aggressive, threatening and destructive behaviors;

(2) self-injurious behaviors;

(3) compulsive behaviors; and

(4) other behaviors.

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

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

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

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

Changes in Resting Energy Expenditure and Respiratory quotient

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

Changes in Insulin Sensitivity

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

Example 4: Clinical Studies with Smith–Magenis syndrome Patients

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CLAIMS

What is claimed is:

1. A method of treating a subject having Prader-Willi Syndrome (PWS) or Smith-Magenis syndrome (SMS), said method comprising administering to said subject for at least 10 weeks a pharmaceutical formulation comprising an effective amount of a KATP channel opener.

2. The method of claim 1 wherein said KATP channel opener is diazoxide or a pharmaceutically acceptable salt thereof.

3. The method of claim 2 wherein the pharmaceutically acceptable salt is diazoxide choline.

4. The method of claim 2 wherein said diazoxide or a pharmaceutically acceptable salt thereof is administered orally.

5. The method of claim 2 wherein the pharmaceutical fo1mulation 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 J 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 l %.

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 l wherein hyperphagia of said subject is reduced by at least 30%.

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

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

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

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

23. A kit comprising:

a unit dose of a KATP channel opener, and

a unit dose of growth hormone.

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

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

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

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

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

ABSTRACT OF THE INVENTION

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

Electronic Acknowledgement Receipt

EFS ID:	37193927
Application Number:	16573965
International Application Number:	
Confirmation Number:	9170
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:	Catherine O. Liang/Diana Sciamanna
Filer Authorized By:	Catherine O. Liang
Attorney Docket Number:	SLNO-034/07US 333072-2052
Receipt Date:	17-SEP-2019
Filing Date:	
Time Stamp:	20:24:05
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal of New Application	Transmittal.pdf	198498 1f95f80eb8e57ffccf44a9adbabf1d7e54612743	no	1

Warnings:

Information:					
2	Power of Attorney	POA.pdf	118908 67a029f18d363878eda1b1ad617feb4fbd7bf726	no	1
Warnings:					
Information:					
3	Application Data Sheet	ADS.PDF	1256204 5e626d06a0a0179a24b7897b304a254b16acdccc	no	9
Warnings:					
Information:					
4	Oath or Declaration filed	Declaration.pdf	113697 7d4f9d8ac79c5c74999beff05d1f17a57f2c608d	no	1
Warnings:					
Information:					
5		Application.pdf	531269 3c4c8d9962a4d4ce52130115000f81768e3e444d	yes	109

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	105
Claims	106	108
Abstract	109	109

Warnings:					
Information:					
6	Drawings-only black and white line drawings	Drawings.PDF	206272 b9ade5f3c2fde048f721168e0f6e1142e59b7fde	no	5
Warnings:					
Information:					
			Total Files Size (in bytes):	2424848	

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 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.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings of claims in the application:

Claims 1-28. (Canceled)

Claim 29 (New): A method of increasing lower limb muscle mass of a subject having Smith-Magenis syndrome (SMS), said method comprising administering to the subject a pharmaceutical formulation comprising an effective amount of a K_{ATP} channel opener, or a pharmaceutically acceptable salt thereof.

Claim 30 (New): The method of claim 29, wherein the K_{ATP} channel opener is diazoxide.

Claim 31 (New): The method of claim 29, wherein the pharmaceutically acceptable salt is diazoxide choline.

Claim 32 (New): The method of claim 29, wherein the pharmaceutical formulation further comprises at least one other active ingredient.

Claim 33 (New): The method of claim 29, wherein the pharmaceutical formulation comprises at least one excipient that affects the rate of release of the K_{ATP} channel opener or the pharmaceutically acceptable salt thereof.

Claim 34 (New): The method of claim 29, wherein the pharmaceutical formulation comprises at least one excipient that delays release of the K_{ATP} channel opener or the pharmaceutically acceptable salt thereof.

Claim 35 (New): The method of claim 29, wherein the pharmaceutical formulation is administered once per day.

Claim 36 (New): The method of claim 29, wherein the pharmaceutical formulation is administered twice per day.

Claim 37 (New): The method of claim 29, wherein the pharmaceutical formulation is administered for 1 or more years.

Claim 38 (New): The method of claim 29, wherein the diazoxide or a pharmaceutically acceptable salt thereof is administered orally.

Claim 39 (New): The method of claim 29, wherein the subject is an adult.

Claim 40 (New): The method of claim 29, wherein the subject is over the age of 16.

REMARKS

Claims 1-28 were pending in the present application. By way of this Preliminary Amendment, claims 1-28 are canceled, and new claims 29-40 are added. Support for the new claims can be found in the original claims and specification as filed. After entry of this amendment, claims 29-40 will be under consideration.

No new matter is believed to be added by way of this amendment.

Amendment or cancelation of certain claims is not to be construed as a dedication to the public of any of the subject matter of the claims as previously presented. Applicant expressly reserves the right to pursue prosecution of any presently unclaimed subject matter in one or more future continuation and/or divisional application(s) claiming priority benefit of the present application.

Regarding the Information Disclosure Statement

An Information Disclosure Statement is submitted herewith. Applicant thanks the Examiner in advance for review of the cited references and return of the initialed form SB/08. Should any of the references be unavailable to the Examiner, the Examiner is requested to contact the undersigned prior to issuance of the first action on the merits and additional copies will be provided.

Request for Examiner Teleconference

Should the Examiner identify any issues that can be addressed in a teleconference, the Examiner is urged to contact the undersigned at the number listed below.

CONCLUSION

Entry and consideration of the foregoing amendments is respectfully requested. The above-noted amendments are supported by the application as originally-filed and do not introduce any new matter.

Although amendments have been made, no acquiescence or estoppel is or should be implied thereby. Rather, the amendments are made only to expedite prosecution of the present application, and without prejudice to presentation or assertion, in the future, of claims on the subject matter affected thereby.

Although the present communication may include alterations to the application or claims, Applicant is not conceding in this application that previously pending claims are not patentable. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child, or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to **Deposit Account No. 50-1283** referencing docket no. SLNO-034/07US 333072-2052. However the Director is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: February 3, 2020

Respectfully submitted,
COOLEY LLP

COOLEY LLP
ATTN: IP Docketing Department
1299 Pennsylvania Avenue NW, Suite 700
Washington, DC 20004

Tel: (650) 843-5875
Fax: (202) 842-7899

Electronic signature: /Catherine O. Liang/
Catherine O. Liang
Reg. No. 61,778

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.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/573,965	09/17/2019	Neil M. COWEN	SLNO-034/07US 333072-2052	9170

58249 7590 02/19/2020

COOLEY LLP
ATTN: IP Docketing Department
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

EXAMINER	
OH, TAYLOR V	

ART UNIT	PAPER NUMBER
1625	

NOTIFICATION DATE	DELIVERY MODE
02/19/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

zIPPatentDocketingMailboxUS@cooley.com

Office Action Summary	Application No. 16/573,965	Applicant(s) COWEN, Neil M.	
	Examiner TAYLOR V OH	Art Unit 1625	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 2/03/2020.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 29-40 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 29-40 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on 9/17/2019 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 2/03/20.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

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

Non-Final Rejection

The Status of Claims:

Claims 29-40 are pending.

Claims 29-40 are rejected.

DETAILED ACTION

1. Claims 29-40 are under consideration in this Office Action.

Priority

2. It is noted that this application is a continuation of 16/041,237 (07/20/2018)(US 10456408, which is a continuation of 15/671,792 (08/08/2017)(US 10058557), which is a division of 14/940,018(11/12/2015)(US 9,757,384), which claims benefit of 62/080,150(11/14/2014) and claims benefit of 62/138,245(03/25/2015) and claims benefit of 62/170,035(06/02/2015) and claims benefit of 62/221,359(09/21/2015).

Drawings

3. The drawings filed on 9/17/2019 are accepted by the examiner.

IDS

4. The IDS filed on 2/03/2020 is reviewed by the examiner.

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102 of this title, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. Claims 29-40 are rejected under 35 U.S.C. 103 as being unpatentable over Cotter (US2014/0364367) which has a provisional application No. 61/832,779 filed on Jun. 8, 2013 in view of Eiholzer et al (Eur. J. Pediatr. , 1998, 157, p. 368-37& and Crain (UT GSBS Dissertations and theses(open access, 39, 2010, p. 1-117).

Cotter discloses a method of treating Prader Willi Syndrome and a method of improving a lean body mass and decrease body fat associated with Prader Willi Syndrome in the followings:

> **[0008]** Also provided herein is a method for treating a disease or condition selected from Prader-Willi Syndrome, a condition associated with low basal metabolic rate, and a condition associated with hyperphagia. The method may comprise administering a K_{ATP} channel opener to a patient in need thereof, and the patient's blood ketone level may be less than a target level selected from 3.0, 2.5, 2.0, 1.5, 1.0, 0.6, 0.5, 0.4, 0.3, 0.2, and 0.1 mmol/mL. The method may further comprise the step of administering a subsequent dose of the K_{ATP} channel opener to the patient. The subsequent dose may be higher than the previous dose if the patient's blood ketone level is less than or equal to the target level after administration of the previous dose, and the subsequent dose may be equal to or less than the previous dose if the patient's blood

(see page 1 , a paragraph#0008)

> **[0010]** The inventor has made the surprising discovery that administering a K_{ATP} channel opener (e.g., diazoxide) in combination with other therapies used to treat Prader-Willi Syndrome (PWS) allows the dosages of these other therapies to be reduced relative to the dosages that would ordinarily be administered in the absence of the K_{ATP} channel opener, or to be entirely eliminated from a PWS treatment regimen. For example, various symptoms of PWS can be treated with human growth hormone, wakefulness promoting agents (e.g.,

(see page 2 , apargraph#0010)

[0057] Provided herein are methods of treating PWS by administering a K_{ATP} channel opener to a patient. The K_{ATP} channel opener may be used to treat obesity, prediabetes, diabetes, hypertension, depression, elevated cholesterol, other obesity associated co-morbidities, ischemic and reperfusion injury, epilepsy, cognitive impairment, schizophrenia, mania, other psychotic diseases, and the like. The K_{ATP} channel opener may (a) inhibit fasting insulin secretion, (b) inhibit stimulated insulin secretion, (c) elevate energy expenditure, (d) elevate beta oxidation of fat, or (e) inhibit hyperphagia.

[0058] a. Combined Treatment with Reduced Dosage of Growth Hormone

[0059] The K_{ATP} channel opener may be coadministered with a human growth hormone (GH) to treat PWS. The combination therapy may be used to improve body composition abnormalities and improve linear growth of an infant or child with PWS, or to improve body composition abnormalities in an adult with PWS. The combination therapy may also be used to improve lean body mass, decrease body fat, modulate bone mineral density, or normalize adult height. The therapy may also be used to improve cognition, tone, endurance, stamina, strength, agility, or motor development, or to positively affect nitrogen balance or increase energy expenditure.

[0060] The GH dose may be 0.18-0.3 mg/kg/week, and may be administered as a daily subcutaneous injection. The baseline GH dose may also be at least 0.01, 0.05, 0.1, 0.15,

0.2, 0.3, 0.4, 0.5, 1.0, 1.5, or 2.0 mg/kg/week. The baseline GH dose may also be less than 0.01, 0.05, 0.1, 0.15, 0.2, 0.3, 0.4, 0.5, 1.0, 1.5, or 2.0 mg/kg/week. The GH dose may be adjusted based on the weight of the patient. The dose may also be adjusted based on the patient's lean mass or on insulin growth factor (IGF-1) levels, such that the IGF-1 levels do not exceed 3 standard deviations above the upper limit of normal. The upper limit of normal for IGF-1 levels may be 25-1000 ng/mL, and may be in a range as described in Table 1.

(see page 4, paragraphs#0057-0060)

3. METHOD OF TREATING PRADER-WILLI SYNDROME AND CONDITIONS ASSOCIATED WITH LOW BASAL METABOLIC RATE OR HYPERPHAGIA BASED ON BLOOD KETONE LEVELS

[0079] Provided herein is a method of treating PWS or conditions associated with low basal metabolic rate or hyperphagia by administering the K_{ATP} channel to a patient. The condition may be obesity. The K_{ATP} channel opener may be

administered according to a PWS patient's blood ketone level. The patient's blood ketone level may be less than or equal to a target level of 3.0, 2.5, 2.0, 1.5, 1.0, 0.6, 0.5, 0.4, 0.3, 0.2, or 0.1 mmol/L. The patient's target level may also be 0.6-1.5 mmol/L, 1.6-3.0 mmol/L, less than or equal to 1.4, 1.5 or 1.6 mmol/L, or greater than or equal to 1.5 mmol/L or 3.0 mmol/L. The dose of the K_{ATP} channel opener may be increased for the patient in comparison to the patient's previous dose until the patient's blood ketone level is at least at

the target level. The dose of the K_{ATP} channel opener being administered to the patient may be maintained if the patient's blood ketone level is at the target level. The dose of the K_{ATP} administered to the patient may be decreased in comparison to the patient's previous dose until the patient's blood ketone level is less than or equal to the target level. The dose of the K_{ATP} channel opener may also be decreased in the event that the patient experiences an undesirable side effect, such as hyperglycemia.

(see page 7 , a paragraph#0079)

If the anion is diazoxide in a solution suitable for intravenous use, then the cation may not be sodium. In solutions suitable

for intravenous use, if the cation is sodium, then the anion may not be an anion of diazoxide. If the salt includes an anion of diazoxide and a sodium cation, then the salt may not be in liquid form. The KATP channel opener may be a salt of a compound of one of Formulae I-VIII in which the cation is sodium, potassium, choline or hexamethyl hexamethylene diammonium. The KATP channel opener may also be BPDZ

(see apge 10, a paragraph#0142)

[0148] c. Administration

[0149] Administration of the composition using the method described herein may be orally, parenterally, sublingually, transdermally, rectally, transmucosally, topically, via inhalation, via buccal administration, or combinations thereof. Parenteral administration includes, but is not limited to, intravenous, intraarterial, intraperitoneal, subcutaneous, intramuscular, intrathecal, and intraarticular. The compositions may be administered to a human patient, cat, dog, large animal, or an avian. The composition may be administered 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 times per day.

(see page 10 , paragraphs#00148-0149)

[0150] d. Formulation

[0151] The compositions provided herein may be in the form of capsules, sprinkle formulation, tablets or lozenges formulated in a conventional manner. For example, tablets and capsules for oral administration may contain conventional excipients including, but not limited to, binding agents, fillers, lubricants, disintegrants and wetting agents. Binding agents include, but are not limited to, syrup, accacia, gelatin, sorbitol, tragacanth, mucilage of starch and polyvinylpyrroli-

(see page 10 , apargraph#0150-0151)

> **[0159]** With respect to safety, no side effects have been reported for a period of 56 weeks. The infant's blood sugar levels were monitored and were in the normal range. Minimal or no excess lanugo hair growth had been noted. Taken together, this case supports the utility of diazoxide in the treatment of PWS.

(see page 11 , a paragraph#0159)

The instant invention, however, differs from the prior art in that increasing the lower limb muscle mass of a subject having Smith-Magenis syndrome (SMS) and administering an effective amount of a K_{ATP} channel opener for a year or more and the use of an excipient delaying release of diazoxide are unspecified in the prior art.

Eiholzer et al teaches a treatment with human growth hormone in patients with Prader-Labhart-Willi syndrome, which can increase muscle mass in the following:

> **Abstract** Twelve children with documented Prader-Labhart-Willi syndrome were treated with human growth hormone (24 U/m^2/week) during 1 year. The children were divided into three groups: group 1: overweight and prepubertal (n = 6, age 3.8–7.0 years); group 2: underweight and prepubertal (n = 3, age 0.6–4.1 years); group 3: pubertal (n = 3, age 9.2–14.6 years). In group 1, height increased from −1.7 SD to −0.6 SD, while weight decreased from 1.1 SD to 0.4 SD, with a dramatic drop in weight for height from 3.8 SD to 1.2 SD. Hand length increased from −1.5 SD to −0.4 SD and foot length from −2.5 SD to −1.4 SD. Body fat, measured by dual X-ray energy absorptiometry, dropped by a third, whereas muscle mass increased by a fourth. Physical capability (Wingate test) improved considerably. The children were reported to be much more active and capable. In group 2, similar changes were seen, but weight for height increased, probably because muscle mass increase exceeded fat mass decrease. Changes in group 3 were similar as in group 1, even though far less distinct.
>
> **Conclusion** Growth hormone treatment in Prader-Labhart-Willi syndrome led to dramatic changes: distinct increase in growth velocity, height and muscle mass, as well as an improvement in physical performance. Fat mass and weight for height decreased in the initially overweight children, and weight for height increased in underweight children.

(see page 368, abstract)

Crain discloses an assessment of obesity and hyperphagia in individuals with Smith-Magenis syndrome in the followings::

> SMS shares common features with those seen in Prader-Willi syndrome (PWS; OMIM 176270) and before much was known about SMS, some individuals with SMS were misdiagnosed as having PWS (Dykens & Smith, 1998). As first published by Greenberg et al., the overlapping features of PWS and SMS include the following: infantile hypotonia, short stature, skin picking, sleep disturbances and behavioral abnormalities. Greenberg et al., 1996 also noted that individuals with SMS also have hyperphagia (Greenberg et al., 1996b). Although there continues to be overlap of the PWS and SMS phenotypes, there are certain features now know to be unique to each of these syndromes (Dykens & Smith, 1998). In a study comparing the neurobehavioral abnormalities of PWS and SMS, individuals with PWS were found to have higher levels of obsessive food related thoughts (Dykens & Smith, 1998). SMS individuals were also found to show obsessive thinking but

(see page 8, the 2nd paragraph)

Regarding the use of an excipient affecting the rate of release or delaying release of diazoxide, the prior art is silent about it. Even so, the prior art does offer some guidance as to what kinds of excipients are available for delaying release of diazoxide; for example, it describes gelatin, mucilage of starch , polyvinylpyrrolidone as the binding agents. So, it would have been obvious to the skilled artisan in the art before the effective filing date of the claimed invention to be motivated to use one of the binding agents in the composition in order to control the rate of release or develop the

delay-release of a formulation containing diazoxide. This is because the skilled artisan in the art would expect such a manipulation to be successful and feasible as guidance shown in the prior art.

Regarding the lack of teaching administering the an effective amount of a K_{ATP} channel opener for a year or more, the prior art is silent about it, However, the prior art does teach generally that the combination therapy containing the K_{ATP} channel opener with GH to treat PWS can be used to improve lean body mass. Furthermore, with respect to the duration of administering the an effective amount of a K_{ATP} channel opener, the prior art does mention generally that there were no side effects for using diazoxide in the treatment of PWS for 56 weeks (see page 11, a paragraph#0159). From the above information, it seems reasonable for the skilled artisan in the art to assume that improving lean body mass can be observable steadily without any side-effects as long as the combination therapy consisted of the K_{ATP} channel opener and GH may last for 56 weeks or even longer than that period.

Cotter expressly discloses the method of improving a lean body mass and decrease body fat associated with Prader Willi Syndromel by means of the K_{ATP} channel opener such as diazoxide choline in combination with GH ; similarly, Eiholzer does teach the human growth hormone-treatment for the patients having Prader-Labhart-Willi syndrome, which can increase muscle mass. Furthermore, Crain does describe that the individuals with SMS may display profound neurodevelopmental behavioral deficiencies and exhibit food-related behaviors equivalent to Prader-Willi syndrome (PWS).

Both prior art of Cotter and Eiholzer are very closely related to each other with respect to either improving the lean body mass or increasing the muscle mass in the patient; furthermore, Crain advocates that SMS and Prader-Willi syndrome may display and share the very similar food-related behaviors, thereby implying the application of a similar treatment method for them.. In addition, Eiholzer does offer guidance that growth hormone treatment can be led to a dramatic increase in muscle mass in the children (see page 376, the left col. the second paragraph)

So, it would have been obvious to the skilled artisan in the art before the effective filing date of the claimed invention to be motivated to incorporate Crain's teaching of the treatment of SMS equivalent to that of PWS for in combination with Eiholzer's teaching of the human growth hormone-treatment for increasing the patient's muscle mass into the Cotter method in order to treat and improve the overall SMS subject's lean body mass. This is because the skilled artisan in the art would expect such a combined prior art to be successful and feasible as guidance shown in the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TAYLOR V OH whose telephone number is (571)272-0689. The examiner can normally be reached on 8:00-5:00.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Kosar can be reached on 571-272-0913. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

1. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000

/TAYLOR V OH/
Primary Examiner, Art Unit 1625
2/14/2020

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 12

Complete if Known	
Application Number	16/573,965
Filing Date	September 17, 2019
First Named Inventor	Neil M. COWEN
Art Unit	1629
Examiner Name	Not Yet Assigned
Attorney Docket Number	SLNO-034/07US 333072-2052

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
/T.V.O/	1.	US-2002/0035106-A1	03-21-2002	Hansen et al.	
/T.V.O/	2.	US-2003/0035106-A1	02-20-2003	Yeh et al.	
/T.V.O/	3.	US-2003/0068366-A1	04-10-2003	Chungi et al.	
/T.V.O/	4.	US-2003/0211123-A1	11-13-2003	Shukla et al.	
/T.V.O/	5.	US-2004/0143213-A1	07-22-2004	Hunter et al.	
/T.V.O/	6.	US-2004/0204472-A1	10-14-2004	Briggs et al.	
/T.V.O/	7.	US-2006/0051418-A1	03-09-2006	Cowen et al.	
/T.V.O/	8.	US-2006/0128673-A1	06-15-2006	Firnges et al.	
/T.V.O/	9.	US-2009/0062264-A1	03-05-2009	Cowen et al.	
/T.V.O/	10.	US-2009/0148525-A1	06-11-2009	Cowen	
/T.V.O/	11.	US-2009/0149451-A1	06-11-2009	Cowen	
/T.V.O/	12.	US-2010/0028429-A1	02-04-2010	Cowen et al.	
/T.V.O/	13.	US-2010/0256360-A1	10-07-2010	Cowen et al.	
/T.V.O/	14.	US-2012/0053172-A1	03-01-2012	De Boer	
/T.V.O/	15.	US-2012/0238554-A1	09-20-2012	Cowen	
/T.V.O/	16.	US-2013/0040942-A1	02-14-2013	Cowen et al.	
/T.V.O/	17.	US-2013/0309301-A1	11-21-2013	Cowen et al.	
/T.V.O/	18.	US-2014/0364367-A1	12-11-2014	Cotter	
/T.V.O/	19.	US-2018/0280405-A1	10-04-2018	Cowen	
/T.V.O/	20.	US-2019/0117665-A1	04-25-2019	Cowen et al.	
/T.V.O/	21.	US-2,986,573	05-30-1961	Topliss et al.	
/T.V.O/	22.	US-4,880,830	11-14-1989	Rhodes	
/T.V.O/	23.	US-5,284,845-A	02-08-1994	Paulsen	
/T.V.O/	24.	US-5,399,359-A	03-21-1995	Baichwal	
/T.V.O/	25.	US-5,415,871-A	05-16-1995	Pankhania et al.	
/T.V.O/	26.	US-5,629,045-A	05-13-1997	Veech et al.	
/T.V.O/	27.	US-6,022,562-A	02-08-2000	Autant et al.	
/T.V.O/	28.	US-6,197,765-B1	03-06-2001	Vardi et al.	

Examiner Signature	/TAYLOR V OH/	Date Considered	02/13/2020

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. 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 2 hours 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, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS.

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 12

Complete if Known	
Application Number	16/573,965
Filing Date	September 17, 2019
First Named Inventor	Neil M. COWEN
Art Unit	1629
Examiner Name	Not Yet Assigned
Attorney Docket Number	SLNO-034/07US 333072-2052

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
/T.V.O/	29.	US-7,572,789-B2	08-11-2009	Cowen et al.	
/T.V.O/	30.	US-7,799,777-B2	09-21-2010	Cowen et al.	
/T.V.O/	31.	US-9,381,202-B2	07-05-2016	Cowen et al.	
/T.V.O/	32.	US-9,757,384-B2	09-12-2017	Cowen	
/T.V.O/	33.	US-9,765,043-B2	09-19-2017	Cowen et al.	
/T.V.O/	34.	US-9,782,416-B2	10-10-2017	Cowen	
/T.V.O/	35.	US-10,058,557-B2	08-28-2018	Cowen	
/T.V.O/	36.	US-10,085,998-B2	10-02-2018	Cowen et al.	
/T.V.O/	37.	US-10,456,408-B2	10-29-2019	Cowen	

Examiner Signature	/TAYLOR V OH/	Date Considered	02/13/2020

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 3 of 12

Complete if Known	
Application Number	16/573,965
Filing Date	September 17, 2019
First Named Inventor	Neil M. COWEN
Art Unit	1629
Examiner Name	Not Yet Assigned
Attorney Docket Number	SLNO-034/07US 333072-2052

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] "Number[4] "Kind Code[5] (if known)	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]
/T.V.O/	38.	CN-101043879-A	09-26-2007	Essentialis, Inc.		
/T.V.O/	39.	JP-2010-532383-A	10-07-2010	Essentialis, Inc.		
/T.V.O/	40.	JP-2014-74004-A	04-24-2014	Niijima Shinichi	Full English Translation	√
/T.V.O/	41.	WO-98/10786-A2,A3	03-19-1998	Cohen		
/T.V.O/	42.	WO-2006/026469-A2,A3	03-09-2006	Essentialis, Inc.		
/T.V.O/	43.	WO-2007/081521-A2,A3	07-19-2007	Essentialis, Inc.		
/T.V.O/	44.	WO-2009/006483-A1	01-08-2009	Essentialis, Inc.		
/T.V.O/	45.	WO-2013/130411-A1	09-06-2013	Essentialis, Inc.		
/T.V.O/	46.	WO-2016/077629-A1	05-19-2016	Essentialis, Inc.		

Examiner Signature	/TAYLOR V OH/	Date Considered	02/13/2020

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. 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 2 hours 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, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Substitute for form 1449B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 4 of 12

Complete if Known	
Application Number	16/573,965
Filing Date	September 17, 2019
First Named Inventor	Neil M. COWEN
Art Unit	1629
Examiner Name	Not Yet Assigned
Attorney Docket Number	SLNO-034/07US 333072-2052

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/	47.	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/	48.	Aguilar-Bryan, L. et al. (1998). "Toward understanding the assembly and structure of KATP channels," *Physiological Review* 78(1), 227-245.	
/T.V.O/	49.	Aizawa, T. et al. (1995). "Prophylaxis of genetically determined diabetes by diazoxide: a study in a rat model of naturally occurring obese diabetes," *J. of Pharma Exp. Ther.* 275(1):194-199.	
/T.V.O/	50.	Alaimo, J.T. et al. (2015). "Individuals with Smith-Magenis syndrome display profound neurodevelopmental behavioral deficiencies and exhibit food-related behaviors equivalent to Prader-Willi syndrome," *Res. Dev. Disabil.* 47:27-38.	
/T.V.O/	51.	Alemzadeh, R. et al. (1998). "Beneficial effect of diazoxide in obese hyperinsulinemic adults," *J Clin Endocr Metab* 83:1911-1915.	
/T.V.O/	52.	Alemzadeh, R. et al. (2004). "Diazoxide enhances adipose tissue protein kinase B activation and glucose transporter-4 expression in obese Zucker rats," Med Sci Monit 10(3):BR53-60.	
/T.V.O/	53.	Alemzadeh, R. et al. (1999). "Effect of diazoxide on brain capillary insulin receptor binding and food intake in hyperphagic obese Zucker rats," *Endocrinology* 140:3197-3202.	
/T.V.O/	54.	Alemzadeh, R. et al. (2004). "Modulation of adipoinsular axis in prediabetic zucker diabetic fatty rats by diazoxide," *Endocrinology* 145(12):5476-5484.	

Examiner Signature	/TAYLOR V OH/	Date Considered	02/13/2020

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.98. 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 2 hours 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, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Substitute for form 1449B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 5 of 12

Complete if Known	
Application Number	16/573,965
Filing Date	September 17, 2019
First Named Inventor	Neil M. COWEN
Art Unit	1629
Examiner Name	Not Yet Assigned
Attorney Docket Number	SLNO-034/07US 333072-2052

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/	55.	Alemzadeh, R. et al. (1993). "Modification of insulin resistance by diazoxide in obese Zucker rats," *Endocrinology* 133:705-712.	
/T.V.O/	56.	Ashcroft, F.M. et al. (1999). "ATP-sensitive K+ channels and insulin secretion: their role in health and disease," *Diabetologia*. 42:903-919.	
/T.V.O/	57.	Ashcroft, F.M. et al. (2000). "New windows on the mechanism of action of K(ATP) channel openers," *Trends Pharmacol. Sci.* 21:439-445.	
/T.V.O/	58.	Babenko, A.P. et al. (2000). "Pharmaco-topology of sulfonylurea receptors. Separate domains of the regulatory subunits of K(ATP) channel isoforms are required for selective interaction with K(+) channel openers," *J. Biol. Chem.* 275(2):717-720.	
/T.V.O/	59.	Bay, H.E. et al. (2010). "Diazoxide choline controlled release in hyperglyceridemic subjects: Lipid and other metabolic effects," *J. American College of Cardiology* 55(10a), 1 total page.	
/T.V.O/	60.	Bertolino, M. et al. (1993). "Modulation of AMPA/kainate receptors by analogues of diazoxide and cyclothiazide in thin slices of rat hippocampus," Receptors and Channels 1:267-278.	
/T.V.O/	61.	Bjork, E. et al. (1998). "Induction of beta-cell rest in type 1 diabetes. Studies on the effects of octreotide and diazoxide," *Diabetes Care* 21(3):427-430.	
/T.V.O/	62.	Björklund, A. et al. (2000). "Glucose-induced [Ca2+]i abnormalities in human pancreatic islets: important role of overstimulation," *Diabetes* 49:1840-1848.	
/T.V.O/	63.	Butler, M.G. et al. (2007). "Energy expenditure and physical activity in Prader-Willi syndrome: comparison with obese subjects," AM J. Med Gent A. 143A(5):449-459.	
/T.V.O/	64.	Calesnick, B. et al. (1965). "Importance of dissolution rates in producing effective diazoxide blood levels in man," *J. Pharm. Sci.* 54:1277-1280.	

Examiner Signature	/TAYLOR V OH/	Date Considered	02/13/2020

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.98. 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 2 hours 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, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Substitute for form 1449B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 6 of 12

Complete if Known	
Application Number	16/573,965
Filing Date	September 17, 2019
First Named Inventor	Neil M. COWEN
Art Unit	1629
Examiner Name	Not Yet Assigned
Attorney Docket Number	SLNO-034/07US 333072-2052

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/	65.	Carrel, A.L. et al. (2010). "Long-term growth hormone therapy changes the natural history of body composition and motor function in children with Prader-Willi Syndrome," *J. Clin. Endocrinol. Metab.* 95:1131-1136.	
/T.V.O/	66.	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/	67.	Corrected Notice of Allowability mailed on February 23, 2017, for U.S. Patent Application Number 14/940,018, filed on November 12, 2015, 5 pages.	
/T.V.O/	68.	Cosgrove, K.E. et al. (2002). "BPDZ 154 activates adenosine 5'-triphosphate-sensitive potassium channels: in vitro studies using rodent insulin-secreting cells and islets isolated from patients with hyperinsulinism," *J. Clin. Endocrinol. Metab.* 87:4860-4868.	
/T.V.O/	69.	Dabrowski, M. et al. (2002). "The novel diazoxide analog 3-isopropylamino-7-methoxy-4H-1,2,4-benzothiadiazine 1,1-dioxide is a selective Kir6.2/SUR1 channel opener," *Diabetes* 51:1896-1906.	
/T.V.O/	70.	de Lind van Wijngaarden, R.F. et al. (2010). "Cardiovascular and metabolic risk profile and acylation-stimulating protein levels in children with Prader-Willi syndrome and effects of growth hormone treatment," J Clin Endocrinol Metab 95(4):1758-1766.	
/T.V.O/	71.	de Tullio, P. et al. (2003). "Toward tissue-selective pancreatic B-cells KATP channel openers belonging to 3-alkylamino-7-halo-4H-1,2,4-benzothiadiazine 1,1-dioxides," *J. Med. Chem.* 46:3342-3353.	
/T.V.O/	72.	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," *Eur. J. Pediatr.* 157:368-377.	
/T.V.O/	73.	Einspieler, C. et al. (2012). "Early behavioural manifestation of Smith-Magenis syndrome (del 17p11.2) in a 4-month-old boy" *Dev. Neurorehab.* 15(4):313-316.	
/T.V.O/	74.	Extended European Search Report mailed on June 4, 2018, for EP Application No. 15 859 169.3, filed on November 12, 2015, 8 pages.	

Examiner Signature	/TAYLOR V OH/	Date Considered	02/13/2020

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.98. 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 2 hours 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, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Substitute for form 1449B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 7 of 12

Complete if Known	
Application Number	16/573,965
Filing Date	September 17, 2019
First Named Inventor	Neil M. COWEN
Art Unit	1629
Examiner Name	Not Yet Assigned
Attorney Docket Number	SLNO-034/07US 333072-2052

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/	75.	Feigerlova, E. et al. (2008). "Hyperghrelinemia Precedes Obesity in Prader-Willi Syndrome," J. Clin. Endocrinol. Metab. 93:2800-2805.	
/T.V.O/	76.	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/	77.	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/	78.	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/	79.	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/	80.	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/	81.	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/	82.	Guldstrand, M. et al. (2002). "Improved beta cell function after short-term treatment with diazoxide in obese subjects with type 2 diabetes," *Diabetes and Metabolism* 28:448-456.	
/T.V.O/	83.	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/	84.	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/	85.	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	02/13/2020

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.98. 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 2 hours 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, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Substitute for form 1449B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 8 of 12

Complete if Known	
Application Number	16/573,965
Filing Date	September 17, 2019
First Named Inventor	Neil M. COWEN
Art Unit	1629
Examiner Name	Not Yet Assigned
Attorney Docket Number	SLNO-034/07US 333072-2052

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/	86.	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/	87.	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/	88.	Lang, Y. (2005). "World Drug News (77th)," Tianjin Pharmacy, No. 5, Vol. 17, pp. 73-75 (with English Translation), 10 total pages.	√
/T.V.O/	89.	Lee, P.D. (2002). "Disease management of Prader-Willi syndrome," *Expert Opin. Pharmacother.* 3:1451-1459.	
/T.V.O/	90.	Marugo, M. et al. (1977). "Diazoxide in the treatment of obesity," *Boll Spec It Biol Sper* 53:1860-1866.	
/T.V.O/	91.	Non-Final Office Action mailed on November 16, 2016, for U.S. Patent Application Number 14/940,018, filed on November 12, 2015, 13 pages.	
/T.V.O/	92.	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/	93.	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.	

Examiner Signature	/TAYLOR V OH/	Date Considered	02/13/2020

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.98. 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 2 hours 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, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Substitute for form 1449B/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/573,965
				Filing Date	September 17, 2019
				First Named Inventor	Neil M. COWEN
(Use as many sheets as necessary)				Art Unit	1629
				Examiner Name	Not Yet Assigned
Sheet	9	of	12	Attorney Docket Number	SLNO-034/07US 333072-2052

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/	94.	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/	95.	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/	96.	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/	97.	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/	98.	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/	99.	Non-Final Office Action mailed on February 22, 2018, for U.S. Patent Application Number 15/671,792, filed on August 8, 2017, 13 pages.	
/T.V.O/	100.	Non-Final Office Action mailed on January 8, 2019, for U.S. Patent Application Number 16/041,237, filed on July 20, 2018, 15 pages.	
/T.V.O/	101.	Notice of Allowance mailed on February 1, 2017, for U.S. Patent Application Number 14/940,018, filed on November 12, 2015, 8 pages.	
/T.V.O/	102.	Notice of Allowance mailed on June 28, 2017, for U.S. Patent Application Number 14/940,018, filed on November 12, 2015, 8 pages.	
/T.V.O/	103.	Notice of Allowance mailed on June 26, 2018, for U.S. Patent Application Number 15/671,792, filed on August 8, 2017, 7 pages.	

Examiner Signature	/TAYLOR V OH/	Date Considered	02/13/2020

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.98. 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 2 hours 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, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Substitute for form 1449B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 10 of 12

Complete if Known	
Application Number	16/573,965
Filing Date	September 17, 2019
First Named Inventor	Neil M. COWEN
Art Unit	1629
Examiner Name	Not Yet Assigned
Attorney Docket Number	SLNO-034/07US 333072-2052

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/	104.	Notice of Allowance mailed on June 19, 2019, for U.S. Patent Application Number 16/041,237, filed on July 20, 2018, 7 pages.	
/T.V.O/	105.	Ortqvist, E. et al. (2004). "Temporary preservation of beta-cell function by diazoxide treatment in childhood type 1 diabetes," *Diabetes Care* 27(9):2191-2197.	
/T.V.O/	106.	Ouedraogo, R. et al. (2002). "2-alkyl-3-Alkylamino-2H-Benzo- and pyridothiadiazine 1,1-dioxides: from K+ATP channel openers to Ca++ channel blockers?" *Biol. Chem.* 383:1759-1768.	
/T.V.O/	107.	Qvigstad, E. et al. (2004). "Nine weeks of bedtime diazoxide is well tolerated and improves beta-cell function in subjects with Type 2 diabetes," *Diabetic Medicine* 21:73-76.	
/T.V.O/	108.	Partial Supplementary European Search Report mailed on March 28, 2018, for EP Application Number 15 859 169.3, filed on November 12, 2015, 8 pages.	
/T.V.O/	109.	Proglycem® (2003). Pharmaceutical Information, Diazoxide Hyperglycemic Agent, 5 total pages.	
/T.V.O/	110.	Ratzmann, K.P. et al. (1983). "Effect of pharmacological suppression of insulin secretion on tissue sensitivity to insulin in subjects with moderate obesity," *Int J Obesity* 7(5):453-458.	
/T.V.O/	111.	Reddy, K.R. et al. (2003). "Once-daily sustained-release matrix tablets of nicorandil: formulation and in vitro evaluation," *AAPS Pharm Sci Tech* 4(4):E61, 9 total pages.	
/T.V.O/	112.	Schou, S.C. et al. (2005). "Synthesis and pharmacological evaluation of 4H-1,4-benzothiazine-2-carbonitrile 1,1-dioxide and N-(2-cyanomethylsulfonylphenyl)acylamide derivatives as potential activators of ATP sensitive potassium channels," *Bioorg. Med. Chem.* 13:141-155.	
/T.V.O/	113.	Schwanstecher, M. et al. (1998). "Potassium channel openers require ATP to bind to and act through sulfonylurea receptors," *EMBO J.* 17:5529-5535.	
/T.V.O/	114.	Stanridge, M. et al. (2000). "Diazoxide down-regulates leptin and lipid metabolizing enzymes in adipose tissue of Zucker rats," FASEB J 14:455-460.	

Examiner Signature	/TAYLOR V OH/	Date Considered	02/13/2020

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.98. 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 2 hours 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, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Substitute for form 1449B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 11 of 12

Complete if Known	
Application Number	16/573,965
Filing Date	September 17, 2019
First Named Inventor	Neil M. COWEN
Art Unit	1629
Examiner Name	Not Yet Assigned
Attorney Docket Number	SLNO-034/07US 333072-2052

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/	115.	Surwit, R.S. et al. (2000). "Diazoxide Restores β3-Adrenergic Receptor Function in Diet-Induced Obesity and Diabetes," *Endocrinology* 141:3630-3637.	
/T.V.O/	116.	Trube, G. et al. (1986). "Opposite effects of tolbutamide and diazoxide on the ATP-dependent K+ channel in mouse pancreatic beta-cells," *Pfluegers Arch.* 407:493-499.	
/T.V.O/	117.	van Boekel, G. et al. (2008). "Weight loss in obese men by caloric restriction and high-dose diazoxide-mediated insulin suppression," Diabetes Obes. Metab. 10:1195-1203.	
/T.V.O/	118.	van Mil, E.G. et al. (2000). "Activity related energy expenditure in children and adolescents with Prader-Willi syndrome," Int J Obes Relat Metab Disord 24(4):429-434.	
/T.V.O/	119.	Wigand, J.P. et al. (1979). "Downregulation of insulin receptors in obese man," *Diabetes* 28(4):287-291.	
/T.V.O/	120.	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/	121.	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/	122.	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/	123.	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/	124.	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.	
/T.V.O/	125.	U.S. Patent Application Number 16/573,965, filed on September 17, 2019, by Cowen (Copy not attached)	

Examiner Signature	/TAYLOR V OH/	Date Considered	02/13/2020

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.98. 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 2 hours 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, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Substitute for form 1449B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 12 of 12

Complete if Known	
Application Number	16/573,965
Filing Date	September 17, 2019
First Named Inventor	Neil M. COWEN
Art Unit	1629
Examiner Name	Not Yet Assigned
Attorney Docket Number	SLNO-034/07US 333072-2052

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/	126.	U.S. Patent Application Number 16/680,093, filed on November 11, 2019, by Cowen et al. (Copy not attached)	
/T.V.O/	127.	U.S. Patent Application Number 16/692,852, filed on November 22, 2019, by Cowen (Copy not attached)	

Examiner Signature	/TAYLOR V OH/	Date Considered	02/13/2020

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.98. 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 2 hours 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, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO:**

Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Docket No.: SLNO-034/07US 333072-2052
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor:	Neil M. COWEN	Confirmation No.:	9170
Application No.:	16/573,965	Group Art Unit:	1625
Filed:	September 17, 2019	Examiner:	Taylor V. Oh

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

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NON-FINAL OFFICE ACTION

This is in response to the Non-Final Office Action dated February 19, 2020, for which a response was due on May 19, 2020. Applicant hereby petitions for, and authorizes payment of, a two (2) month extension of time, thus extending the deadline for response up to and including July 19, 2020. Accordingly, this response is timely filed. Reconsideration and allowance of the pending claims, as amended, in light of the remarks presented herein are respectfully requested.

A Supplemental Information Disclosure Statement is submitted herewith.

Amendments to the Claims begin on page **2** of this paper.

Remarks/Arguments begin on page **4** of this paper.

223832174

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application:

Claims 1-28. (Canceled)

Claim 29 (Currently Amended): A method of increasing lower limb muscle mass of a subject having Smith-Magenis [[s]]Syndrome (SMS), said method comprising administering to the subject a pharmaceutical formulation comprising an effective amount of a K_{ATP} channel opener, or a pharmaceutically acceptable salt thereof, and
wherein the method does not comprise administering human growth hormone to the subject.

Claim 30 (Previously Presented): The method of claim 29, wherein the K_{ATP} channel opener is diazoxide.

Claim 31 (Previously Presented): The method of claim 29, wherein the pharmaceutically acceptable salt is diazoxide choline.

Claim 32 (Previously Presented): The method of claim 29, wherein the pharmaceutical formulation further comprises at least one other active ingredient.

Claim 33 (Previously Presented): The method of claim 29, wherein the pharmaceutical formulation comprises at least one excipient that affects the rate of release of the K_{ATP} channel opener or the pharmaceutically acceptable salt thereof.

Claim 34 (Previously Presented): The method of claim 29, wherein the pharmaceutical formulation comprises at least one excipient that delays release of the K_{ATP} channel opener or the pharmaceutically acceptable salt thereof.

Claim 35 (Previously Presented): The method of claim 29, wherein the pharmaceutical formulation is administered once per day.

Claim 36 (Previously Presented): The method of claim 29, wherein the pharmaceutical formulation is administered twice per day.

Claim 37 (Previously Presented): The method of claim 29, wherein the pharmaceutical formulation is administered for 1 or more years.

Claim 38 (Previously Presented): The method of claim 29, wherein the diazoxide or a pharmaceutically acceptable salt thereof is administered orally.

Claim 39 (Previously Presented): The method of claim 29, wherein the subject is an adult.

Claim 40 (Previously Presented): The method of claim 29, wherein the subject is over the age of 16.

REMARKS

Claims 29-40 are pending in the present application. By virtue of this response, claim 29 is amended. No claims are added or canceled. Accordingly, claims 29-40 are currently under consideration. No new matter is added. Amendment or cancellation of certain claims is not to be construed as a dedication to the public of any of the subject matter of the claims as previously presented.

Claim 29 is amended to recite a method that does not comprise administering human growth hormone to the subject. Support for the amendment may be found throughout the specification of the application as filed. For instance, support for administering K_{ATP} channel openers optionally in combination with growth hormone may be found in at least paragraphs [0022], [0074], and [00310]. This alternative element has basis in the original disclosure and may be explicitly excluded in the claims. MPEP 2173.05(i). No new matter is added.

Information Disclosure Statement

Applicant thanks the Examiner for return of the initialed SB/08 form filed on February 3, 2020.

Applicant submits a Supplemental Information Disclosure Statement herewith. Applicant requests consideration of the cited publications and return of the initialed SB/08 with the next Office Action. If the Examiner has any difficulty in accessing the publications, Applicant urges the Examiner to contact the undersigned prior to the next action. Applicant will provide further copies of the references.

Claim Rejections – 35 U.S.C. § 103

Claims 29-40 are rejected under 35 U.S.C. 103 as allegedly being unpatentable over Cotter (US 2014/0364367) ("Cotter"), which has a provisional application No. 61/832,779 filed on Jun. 8, 2013, in view of Eiholzer et al. (Eur. J. Pediatr. , 1998, 157, p. 368-377) ("Eiholzer")

and Crain (UT GSBS Dissertations and theses; open access, 39, 2010, p. 1-117) ("Crain"). Applicant disagrees with the rejection for at least the following reasons.

COTTER REQUIRES THE COMBINATION OF GROWTH HORMONE AND KATP CHANNEL OPENERS TO IMPROVE LEAN BODY MASS

Amended claim 1 recites a method of increasing lower limb muscle mass of a subject having Smith-Magenis Syndrome (SMS) comprising administering a K_{ATP} channel opener, or a pharmaceutically acceptable salt thereof, and does not permit administering human growth hormone to the subject.

The Examiner relies on Cotter as the primary reference as disclosing a method of improving lean body mass and decreasing body fat in subjects with Prader Willi Syndrome (PWS). Office Action, page 4. On page 5 of the Office Action, the Examiner refers to paragraph [0059] in Cotter, which states "the combination therapy may also be used to improve lean body mass, decrease body fat. . ." (Underline added.) Improving lean body mass is only disclosed in the context of combination therapy and only under the heading "Combined Treatment with Reduced Dosage of Growth Hormone" in paragraph [0058]. Thus, Cotter attributes improvement in lean body mass and decreased body fat to the use of the combination of a K_{ATP} channel opener and growth hormone. Cotter is silent regarding the use of a K_{ATP} channel opener alone in improving lean body mass, or in increasing lower limb muscle mass in a subject having SMS as recited in the claims.

The scope of the amended claims do not encompass the combination use of K_{ATP} channel openers and human growth hormone. A person having ordinary skill in the art reading Cotter's disclosure under the heading "Combined Treatment with Reduced Dosage of Growth Hormone" in paragraph [0058] would need to eliminate the administration of growth hormone treatment to arrive at the pending claimed methods. Cotter provides no suggestion, motivation, or expectation that administration of a K_{ATP} channel opener in the absence of growth hormone

treatment will be successful in increasing lower limb muscle mass in a subject having SMS as recited in the claims.

Eiholzer and Crain do not address the deficiency in Cotter. Eiholzer discloses an increase in muscle mass as the result of treatment with human growth hormone, and not K_{ATP} channel openers, in patients with PWS. Crain is entitled "An Assessment of obesity and hyperphagia in individuals with Smith-Magenis syndrome" and does not disclose or suggest any treatment methods for SMS, let alone the use of K_{ATP} channel openers for increasing lower limb muscle mass in SMS.

COTTER DOES NOT SUGGEST THAT K_{ATP} CHANNEL OPENERS WILL INCREASE LEAN BODY MASS IN SUBJECTS

Cotter discloses that administration of a K_{ATP} channel opener results in a dosage reduction of other therapies used to treat PWS. Cotter [0001], [0003]. Cotter lists human growth hormone, a wakefulness promoting agent, and a psychiatric/mood stabilizing medication as other therapies. Cotter [0001], [0003]. The decrease in dosage of other therapies as a result of administration with a K_{ATP} channel opener is described as a benefit because the undesirable side effects of the other therapies is reduced as a result of the lowered dose. Cotter Abstract, [003], [010]. For instance, Cotter discloses that the undesirable effect of insulin resistance is associated with a standard dose of growth hormone, and suggests that co-administration of a K_{ATP} channel opener may allow for a lower dose of growth hormone. Cotter [0010]. Such reduction in growth hormone may, reduce the adverse side effect of insulin resistance. Cotter [0010]. In sum, Cotter teaches that K_{ATP} channel openers may be used to reduce dosages of other therapies and does not disclose that use of a K_{ATP} channel opener alone results in the increase of lean body mass in subjects with PWS or SMS as recited in the present claims.

Furthermore, studies showing the increase of lean body mass of PWS subjects as the result of treatment with human growth hormone has been documented in scientific literature prior to the earliest priority date of the Cotter application. (Long-Term Growth Hormone Therapy Changes the Natural History of Body Composition and Motor Function in Children with

Prader-Willi Syndrome Carrel, A. L., et al. *J. Clin. Endocrinol. Metab*. 95(3) **2010**, p. 1131-1136; included in the SIDS submitted herewith.) As discussed in the previous section, Cotter discloses the increase of lean body mass in the context of co-administration of a K_{ATP} channel opener with growth hormone as a combination therapy. Cotter [0059]. Thus, a person having ordinary skill in the art reading Cotter would likely attribute lean body mass improvements to the administration of growth hormone rather than the K_{ATP} channel opener.

Cotter does not address nor provide any data relating to changes in lean body mass. The only clinical observations provided are in Example 1 where a K_{ATP} channel opener is administered to an infant (8 months old) with PWS who is undergoing growth hormone therapy. Cotter [0158]. The publication describes observations related to narcoleptic response, stamina, IGF and genotropin levels, blood sugar levels, and lanugo hair growth. Cotter [0158]. Cotter does not provide any discussion on changes in lean body mass in the infant.

There is no suggestion or disclosure in Cotter that administration of the K_{ATP} channel opener is responsible for an increase in lean body mass, nor that administration of a K_{ATP} channel opener to a subject having PWS or SMS will result in an increase in lean body mass by at least 2% as claimed. Although Cotter discloses that combination therapy with growth hormone may improve lean body mass as discussed above, a person having ordinary skill in the art is most likely to attribute the improvement to growth hormone therapy rather than the effect of a K_{ATP} channel opener. Thus, Cotter's data does not support nor suggest an increase of lean body mass as a result administration of a K_{ATP} channel opener in the absence of co-administration with human growth hormone.

Furthermore, the pending application provides data on the effect of a K_{ATP} channel opener on lean body mass. Administration of a K_{ATP} channel opener over 69 days resulted in a change in body composition both with and without co-administration of growth hormone. [00427]-[00432], specification as filed. Table 6 summarizes the results. Lean body mass increased by 5.50%, lean body mass/fat mass ratio increased by 9.37%, and body fat decreased by 3.31% in subjects treated with both growth hormone and K_{ATP} channel opener. In subjects that received only a K_{ATP} channel opener, lean body mass increased by 5.30%, lean body mass/fat mass ratio

increased by 10.36%, and body fat decreased by 4.34%. The changes in body composition are similar in magnitude in both groups. This is a surprising result because these results show that the K_{ATP} channel opener was as effective in improving the body composition in subjects who did not receive growth hormone as it was in those co-administered growth hormone.

In addition, the changes in body composition were dose dependent. Subjects receiving a higher dose of the K_{ATP} channel opener at 4.2 mg/kg experienced a greater increase in lean body mass compared to subjects receiving 1.5 mg/kg, 2.4 mg/kg, or 3.3 mg/kg. This further demonstrates that the K_{ATP} channel opener is responsible for the improvements in body composition.

For at least the foregoing reasons, the Applicant respectfully requests that the rejection of claims 29-48 under §103 over Cotter be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejections of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

Any remarks in support of patentability of one claim should not be imputed to any other claim, even if similar terminology is used. Additionally, any remarks referring to only a portion of a claim should not be understood to base patentability on that portion; rather, patentability must rest on each claim taken as a whole. Applicant respectfully traverses each of the Examiner's rejections and each of the Examiner's assertions regarding what the prior art shows or teaches, even if not expressly discussed herein. Although amendments have been made, no acquiescence or estoppel is or should be implied thereby. Rather, the amendments are made only to expedite prosecution of the present application, and without prejudice to presentation or assertion, in the future, of claims on the subject matter affected thereby.

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child, or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Director to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to **Deposit Account No. 50-1283** referencing Attorney Docket No. SLNO-034/07US 333072-2052. However, the Director is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: July 17, 2020

Respectfully submitted,
COOLEY LLP

COOLEY LLP
ATTN: IP Docketing Department
1299 Pennsylvania Avenue NW, Suite 700
Washington, DC 20004

Tel: (650) 843-5875
Fax: (202) 842-7899

Electronic signature: /Catherine O. Liang/
Catherine O. Liang
Reg. No. 61,778

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

58249 7590 08/31/2020

COOLEY LLP
ATTN: IP Docketing Department
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

EXAMINER	
OH, TAYLOR V	
ART UNIT	PAPER NUMBER
1625	

DATE MAILED: 08/31/2020

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/573,965	09/17/2019	Neil M. COWEN	SLNO-034/07US 333072-2052	9170

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

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	11/30/2020

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

APOTEX_EX1025_PGR2026-00034_Page 162

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

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

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

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence 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 08/31/2020

COOLEY LLP
ATTN: IP Docketing Department
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

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

Certificate of Mailing or Transmission

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

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/573,965	09/17/2019	Neil M. COWEN	SLNO-034/07US 333072-2052	9170

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

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	11/30/2020

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

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

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

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 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 must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

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

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

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

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

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

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

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

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

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

APOTEX EX1025 PGR2026-00034 Page 163

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.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/573,965	09/17/2019	Neil M. COWEN	SLNO-034/07US ~~333072-2052~~	9170

EXAMINER
OH, TAYLOR V

ART UNIT	PAPER NUMBER
1625	

58249 7590 08/31/2020

COOLEY LLP
ATTN: IP Docketing Department
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

DATE MAILED: 08/31/2020

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

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

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

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

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. 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. 16/573,965	Applicant(s) COWEN, Neil M.	
	Examiner TAYLOR V OH	Art Unit 1625	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to 7/17/2020.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 29-40 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 7/17/2020.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/TAYLOR V OH/
Primary Examiner, Art Unit 1625

Notice of Pre-AIA or AIA Status

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

Reasons of Allowance

The Status of Claims:

Claims 29-40 are pending.

Claims 29-40 are allowed.

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

- The rejection of Claims 29-40 under 35 U.S.C. 103 as being unpatentable over Cotter (US2014/0364367) which has a provisional application No. 61/832,779 filed on Jun. 8, 2013 in view of Eiholzer et al (Eur. J. Pediatr. , 1998, 157, p. 368-37& and Crain (UT GSBS Dissertations and theses(open access, 39, 2010, p. 1-117) is withdrawn due to the modification of the claims and applicant's convincing arguments about the difference between the prior art and the claimed invention (see pages 5-8, response).

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning the communication after allowance such as sending all post-allowance correspondence should be directed to " Box Issue Fee" or faxed directly to PUBS at 703-305-8755. This will expedite the process of these papers.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/TAYLOR V OH/
Primary Examiner, Art Unit 1625
8/25/2020

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.
16/573,965	12/29/2020	10874676	SLNO-034/07US 333072-2052	9170

58249 7590 12/09/2020

COOLEY LLP
ATTN: IP Docketing Department
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

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., Redwood City, 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.