

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC.,
Petitioner

v.

SOLENO THERAPEUTICS, INC.
Patent Owner

Post-Grant Review No. PGR2026-00034

U.S. Patent No. 12,419,895
Issue Date: September 23, 2025
Title: Methods for Treating Subjects with Prader-Willi Syndrome

**DECLARATION OF ERIC M. HOLLANDER, M.D. DFAPA, FACNP,
IN SUPPORT OF PETITION FOR POST GRANT REVIEW OF
U.S. PATENT NO. 12,419,895**

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1. I, Eric M. Hollander, M.D. DFAPA, FACNP, have been retained as an expert witness on behalf of Apotex Inc. (“Apotex” or “Petitioner”) in connection with the above-captioned request for Post Grant Review (“PGR”). I am being compensated for my time in connection with this PGR at my standard rate, which is \$1100 per hour.

2. I understand from counsel that Apotex is petitioning for Post Grant review of U.S. Patent No. 12,419,895 (“the ’895 patent”, EX1001), which is assigned to Soleno Therapeutics, Inc., (“Solen” or “Patent Owner”) and Apotex is requesting that the United States Patent and Trademark Office cancel Claims 1-26 (“challenged claims”) of the ’895 patent as unpatentable.

3. The following discussion and analysis provides my opinions as to why Claims 1-26 would have been obvious to a person of ordinary skill in the art (“POSA”).

I. BACKGROUND AND QUALIFICATIONS

4. In my work and career, I have primarily specialized in the field of psychiatric medicine, neurodevelopmental disorders, and psychopharmacology.

5. I am a psychiatrist licensed to practice medicine in the state of New York. I was board certified in 1987 by the American Board of Psychiatry and Neurology. I am a Professor of Psychiatry and Behavioral Sciences, and the Director of the Autism and Obsessive-Compulsive Spectrum Program, at the

Psychiatry Research Institute of Montefiore-Einstein at Albert Einstein College of Medicine (AECOM) and Montefiore Medicine, in the Bronx, New York. I am a fellow of the American College of Neuropsychopharmacology (ACNP) and a Distinguished Lifetime Fellow of the American Psychiatric Association (APA). I am the past president of the International Society of Research in Impulsivity (ISRI).

6. I have an extensive background in psychopharmacology and neuropsychopharmacology. I completed a Fellowship in Psychopharmacology at Columbia University and was the Principal Investigator for the National Institute of Mental Health (NIMH) Psychopharmacology Training Program.

7. Prior to 2009, I was an Esther and Joseph Klingenstein Professor of Psychiatry and Chairman of Psychiatry at Mount Sinai School of Medicine. I was also an attending psychiatrist at Mount Sinai Hospital from 1993 to 2008. From 1986 to 1993, I was faculty at Columbia University College of Physicians and Surgeons and the New York State Psychiatric Institute, and Associate Professor of Clinical Psychiatry.

8. I received my Medical Degree in 1982 from the State University of New York, Downstate Medical College, Brooklyn, New York. I served my Internship in Internal Medicine at Mount Sinai Hospital in New York, New York, from 1982 to 1983. I was a Resident in Psychiatry at Mount Sinai from 1983 to

1986, serving as Chief Resident – Psychiatry Research from 1985 to 1986. From 1986 to 1988, I was a NIMH Psychiatry Research Fellow at Columbia University College of Physicians and Surgeons. I was a Dana Foundation Fellow at Columbia from 1988 to 1989 and practiced as a NIMH Research Scientist Development Award recipient there from 1988 to 1993.

9. I have received numerous awards and honors throughout my career, including Best Doctors in New York and Best Doctors in the United States from 2007 until present, and a National Alliance for Research on Schizophrenia & Depression (NARSAD) distinguished investigator award in 2009. I am an inventor on several patents related to, among other things, oxytocin or memantine in autism and other disorders.

10. I have published more than 500 peer-reviewed scientific papers in professional literature sources. I have edited 20 books, including the Textbook of Autism Spectrum Disorders, 2nd edition (American Psychiatric Publishing, 2022), Textbook of Autism Spectrum Disorders, 1st edition (American Psychiatric Publishing, 2011), three editions of the Textbook of Anxiety, Trauma, and OCD Related Disorders (American Psychiatric Publishing, 2002, 2009, 2020), and the Clinical Manual of Impulse Control Disorders (2006).

11. I am the Chair of the Board of Directors of the International College of Obsessive Compulsive Spectrum Disorders (ICOCS). The ICOCS is primarily

aimed at advancing, promoting and facilitating research into the causes and consequences of obsessive compulsive disorder (OCD) and obsessive compulsive spectrum disorders. The organization intends to aid and stimulate mental health professionals and others to develop research projects in the field, and to help coordinate research efforts amongst members. The organization's website¹ is dedicated to news, research findings, funding opportunities and new developments in the study of OCD and OC spectrum disorders. The organization holds scientific meetings annually for ICOCS members and other interested clinicians and researchers. The ICOCS also increases public health awareness of OCD and OC spectrum disorders with the hope of improving diagnosis and encouraging better deployment of resources for assessment and treatment. Its members offer advice to legislative bodies and government agencies and cooperate on national and international treatment guidelines.

12. From 2002 to 2007, I served the APA as the Chair of the Diagnostic and Statistical Manual of Mental Disorders ("DSM") 5 Research Planning Agenda for Obsessive Compulsive Behavior Spectrum Disorders, and then from 2007 to 2009 as a member of the DSM-5 Anxiety, Obsessive-Compulsive Spectrum, Post-Traumatic and Dissociative Disorders Workgroup, and the Behavioral and

¹ <http://www.icocs.org>.

Substance Addictions Workgroup. In 1998, I served as the Workgroup Chair for the Impulse Control Disorder Section of the DSM-IV-TR. From 1992 to 1994, I served as a member of the Obsessive-Compulsive Disorder Workgroup for the DSM-IV. In 2006, I edited the APA Publishing Clinical Manual for Impulse Control Disorders. I was also a member of the editorial board of the APA Treatment Manual for Obsessive Compulsive Disorders, and the 2023 CANMAT/ICOCS Practice Guidelines for Obsessive Compulsive and Related Disorders.

13. I have served as the principal investigator on a number of federal grant funded research projects. I have received orphan drug grants from the Food and Drug Administration to study new treatments for Prader-Willi Syndrome (“PWS”) (a neurodevelopmental disorder and syndromic form of Autism Spectrum Disorder (ASD)), body dysmorphic disorder, child/adolescent autism, and adult autism, and a grant from the National Institute of Drug Abuse for a study on the neurobiology of pathological gambling.

14. I have received several grants from NIMH and the National Institute of Neurological Disorders and Stroke to develop treatments for borderline personality disorder, adolescent body dysmorphic disorder, and autism. I was the principal investigator of the Autism Clinical Trials Network and Chair of the eight centers participating in the National Institutes of Health Studies to Advance

Autism Research and Treatment (NIH STAART) Autism Steering Committee. I am involved in research funded by federal institutes, not-for-profit foundations, and by industry on the neuropharmacology, neuropsychiatry, functional imaging, and treatment of multiple disorders including, but not limited to, autism spectrum disorder, obsessive-compulsive disorder, impulsive/aggressive personality disorders, and obsessive-compulsive-related disorders, such as body dysmorphic disorder, attention deficit hyperactivity disorders, impulse control disorders, problematic use of the internet, and pathological gambling. I have served as Principal Investigator for numerous federal grants in Autism Spectrum Disorders, including active grants with NIH STAART studies, DOD CDMRP Autism Research Program, Foundation for Prader Willi Research, Roche Pharmaceuticals, and FDA Orphan Products Division grants. I have previously served as Principal Investigator for federal grants including the NIH Greater New York Autism Center of Excellence, the NIMH Research Training Grant in Psychopharmacology and Outcomes Research, and the Autism Clinical Trials Network. I have received funding from the Department of Defense for the study of cannabidiol (CBDV) in ASD, and from the Orphan Products Division of the FDA for the study of intranasal oxytocin in Prader-Willi Syndrome.

15. I have over 30 years of clinical and translational research experience. I currently serve as the Director of Spectrum Neuroscience and Treatment Institute

(SNTI). SNTI offers state of the art, interdisciplinary and personalized integrated treatments for obsessive-compulsive disorders (OCD), anxiety disorders, autism spectrum disorders, and attention-deficit/hyperactivity disorders. I have used my clinical experience and training to treat people with ASD, ADHD, OCD and related conditions, in addition to Prader-Willi Syndrome, depression, body dysmorphic disorder, anxiety disorders (including Generalized Anxiety Disorder, Social Anxiety and Panic Disorder), depersonalization disorder, cataplexy, trichotillomania, sleep disorders and pain disorders. In my research and clinical work, I routinely make assessments of potential causal associations between a substance and particular pharmacological effect. As a practitioner who specializes in neuropsychopharmacology, I have undertaken these types of assessments for more than two decades. As a clinician and researcher, my work involves diagnosing neurodevelopmental disorders, including ASD and ADHD, as well as understanding and examining the underlying causes and mechanisms of those disorders.

16. I have treated patients Prader-Willi Syndrome that have exhibited hyperphagia and am familiar with and have prescribed VYKAT™ XR for some of my patients. Prior to my involving with this matter, I have reviewed the prescribing information for VYKAT™ XR (EX1004); VYKAT™ XR is one of the treatment options that I use for my patients with Prader-Willi Syndrome

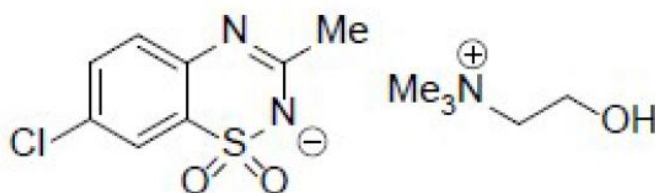
(“PWS”) with hyperphagia, however, it is one option available in a range of treatment options I utilize and at my disposal. I note that while VYKAT™ XR works for some patients, it does not work for every patient. Accordingly, I often utilize other treatment options for treatment in this patient population when the patient is not responding to VYKAT™ XR or, in my professional judgement the patient would be better suited to another course of treatment.

17. As general background on the drug, I provide a general description of VYKAT™ XR. As explained on its label, VYKAT™ XR is an extended release tablet for oral use containing diazoxide choline. VYKAT™ XR is indicated for the treatment of hyperphagia in adults and pediatric patients four years and older with Prader-Willi syndrome (PWS). EX1004, 1.

18. The label further provides the following “Description” of the diazoxide choline: “VYKAT XR contains diazoxide choline. Diazoxide choline is very slightly soluble to soluble in solvents dichloromethane, tetrahydrofuran, acetonitrile, and methanol and practically insoluble in solvents methyl *tert*-butyl ether. The pKa is 8.44 ± 0.01 .” *Id.* at 11.

19. As the label explains, diazoxide choline has the chemical formula 7-Chloro-3-methyl-1λ6, 2,4-benzothiadiazin-2-ide 1,1-dioxide 2-hydroxyethyl(trimethyl)azanium. The empirical formula is $C_8H_6ClN_2O_2S \cdot C_5H_{14}NO$ and the molecular weight is 333.83 g/mole. The

structural formula is:



Id. at 11.

20. VYKAT™ XR is for oral administration and is available as extended-release tablets in the following strengths: a tablet containing 25 mg diazoxide choline, equivalent to 17.2 mg diazoxide; a tablet containing 75 mg diazoxide choline, equivalent to 51.6 mg diazoxide; and a tablet containing 150 mg diazoxide choline, equivalent to 103.2 mg diazoxide.

21. My education, training, and decades of experience in this field qualifies me to render the opinions included in this Declaration. My Curriculum Vitae is included as EX1006.

II. MATERIAL CONSIDERED

22. In formulating my opinions, I have considered the materials referenced in this Declaration and the Exhibit List below. I have also reviewed the '895 patent (EX1001) and its prosecution history, as well as each of the documents cited herein, in light of the general knowledge in the state of the art

as of November 14, 2014.²

No.	Exhibit Description
EX1001	U.S. Patent No. 12,419,895 to Cowen
EX1002	U.S. Food & Drug Admin., <i>Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book): Vykat™ XR</i> , https://www.accessdata.fda.gov/scripts/cder/ob (last visited Feb. 9, 2026)
EX1003	Excerpts from Organic Chemistry 3 rd Ed. by L.G. Wade Jr. (1995)
EX1004	<i>Vykat™ XR</i> (diazoxide choline) [package insert]. Soleno Therapeutics; 2025.
EX1005	Declaration of Dr. Hollander
EX1006	Curriculum Vitae of Dr. Hollander
EX1007	Suzanne B. Cassidy & Daniel J. Driscoll, <i>Prader-Willi Syndrome</i> , 17 Eur. J. Hum. Genet. 3-13 (2009)
EX1008	International Patent Pub. No. WO 2014/197753 to Cotter
EX1009	International Patent Pub. No. WO 2009/006483 to Cowen <i>et al.</i>
EX1010	Frances M. Ashcroft, <i>ATP-Sensitive Potassium Channelopathies: Focus on Insulin Secretion</i> , 115 J. Clinical Investigation 2047 (2005)
EX1011	U.S. Food & Drug Admin., <i>Drugs@FDA: NDA 016996 (Hyperstat (diazoxide))</i> , https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=016996
EX1012	U.S. Food & Drug Admin., <i>Drugs@FDA: NDA 017453 (Proglycem (diazoxide))</i> , https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=017453
EX1013	<i>Remington: Essentials of Pharmaceutics</i> 53 (Linda A. Felton ed., 21st ed., Pharm. Press 2013)

² This Declaration was prepared with the assistance of Ms. Casara Ferreti, who worked at my direction, when instructed, for assistance with routine tasks such as confirmatory analysis, reviewing the cited art, and cite checking. The opinions and statements expressed in this Declaration are my own opinions.

No.	Exhibit Description
EX1014	U.S. Food & Drug Administration, <i>Guidance for Industry: Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications</i> (2003)
EX1015	U.S. Patent No. 12,419,895 File History
EX1016	U.S. Patent Pub. No. 2014/0364367 to Cotter
EX1017	Miller <i>et al.</i> , <i>Nutritional Phases in Prader-Willi Syndrome</i> , 155 Am. J. Med. Genet A. 1040, 1040-49 (2011)
EX1018	Excerpts from Physicians' Desk Reference (2008) entry for Proglycem® at pp. 1191-1192

III. SUMMARY OF OPINIONS/IDENTIFICATION OF GROUNDS

23. In my opinion, as explained in this Declaration, the challenged claims are invalid as being obvious for under the following bases:

Ground	Challenged Claims	Basis
1	1-26	Claims 1-26 are obvious over Cowen
2	1-26	Claims 1-26 are obvious over Cowen and Cotter
3	1-26	Claims 1-26 are obvious over Cowen and Miller

IV. LEGAL PRINCIPLES

24. Although I am not a lawyer, I have been informed by counsel about some general principles of patent invalidity. I provide my general understanding of the law of obviousness below. I used these principles in conducting my analysis and drawing any conclusions.

A. Person of Ordinary Skill in the Art

25. I understand that obviousness is evaluated from the perspective of a person of ordinary skill in the art (“POSA”) to which the patent pertains at the time of the invention. I have been advised that the relevant time for my analysis

of the patent is the earliest claimed priority date for the '895 patent, which is **November 14, 2014.**

26. I understand that the priority date may also be referred to as the “time of the invention.” In offering my opinions in this Declaration, I do so from the perspective of a POSA at this priority date, though my opinions would not change if a different priority date were used.

27. I understand that in determining the level of skill of a POSA, the following factors may be considered: (1) the educational level of the named inventor(s); (2) the type of problems encountered in the art; (3) the prior art solutions to those problems; (4) the rapidity with which innovations are made; and (5) the sophistication of the technology and educational level of active workers in the field. I have considered each of these factors in view of my experience in this field. I have also been informed that a POSA is a hypothetical person who is presumed to be aware of all pertinent art, thinks along conventional wisdom in the art, and is a person of ordinary creativity.

28. In my opinion, as of the relevant priority date, a POSA in the relevant field would have had an advanced professional degree, specifically an M.D. or equivalent, in fields relevant to the treatment of neurobehavioral disorders, which would include experience with Prader-Willi Syndrome, hyperphagia, and eating disorders. This could include primary care physicians,

pediatricians, psychiatrists, endocrinologists, geneticists, and the like. The POSA would have been aware of treatment options for neurobehavioral disorders, including Prader-Willi Syndrome (including PWS patients exhibiting hyperphagia) and other eating disorders. The POSA also would have practical experience, as of the priority date (November 14, 2014), with the administration, dosing, dose titration, starting doses, dose escalation, loading and maintenance dose, and efficacy of drugs for treating eating disorders and neurodevelopmental disorders such as PWS and characteristics associated therewith, including hyperphagia and food-related problems.

29. The POSA would review literature about pharmaceutical updates, individualized patient considerations, and treatment guidelines, and use library resources to find out more information about areas being researched. Furthermore, because the treatment of neurobehavioral disorders (including eating disorders) like PWS involves a multidisciplinary approach, the POSA may interface or consult with individuals having specialized expertise.

30. I consider myself to be at least a POSA having the requisite education and experience as outlined above, both at the time of the invention and

now.³

B. Legal Principles Related to Obviousness

31. It is my understanding that a patent claim is invalid if the claimed subject matter would have been obvious to a POSA at the time the alleged invention was made. I understand that a claimed invention may be considered obvious even if it is not identically disclosed in any single prior art reference. I understand a claim is considered obvious if the subject matter of the claimed invention as a whole would have been obvious at the time the invention was made to a POSA in which the claimed invention pertains. This analysis considers: (1) the scope and content of the prior art (“State of the Art”); (2) the differences between the claimed invention and the prior art; (3) the level of ordinary skill in the art; and (4) any secondary considerations (such as unexpected results, commercial success, long-felt but unsolved need, skepticism of experts, and failure of others). I have been informed by counsel that these four factors are sometimes referred to as the *Graham* factors.

32. I also have been advised that in considering obviousness, care must

³ I have more experience than a POSA, as defined. That said, the opinions provided in this Declaration are from the perspective of a POSA as I have defined it as of the priority date (November 14, 2014).

be taken to not employ a hindsight analysis. Thus, throughout this Declaration, I am careful to take into account only knowledge that was within the level of ordinary skill in the art (as defined above) at the time the claimed invention was made. I understand that in performing this analysis, I am not to use the claims of the patent in suit as a blueprint or roadmap for conducting my obviousness analysis.

33. However, this is not to say that I did not review the '895 patent in conducting my analysis (I did). For example, to determine the proper experience level of the POSA, several of the factors outlined above and in this Declaration make a review of the patent prudent. As another example, one of the obviousness factors is the difference or differences (if any) between the claimed subject matter and the prior art. This necessarily involves an understanding of the claimed invention. I also understand that a claim term should be accorded the full breadth of its plain and ordinary meaning as understood by a POSA when read in the context of the specification (including any definitions provided in the patent) and prosecution history. Again, to do this analysis, it means that a review of the patent is needed.

34. The assignment that I was given was, in view of the relevant prior art, what (if anything) would have been obvious to the POSA without using the patent as a roadmap to piece together the prior art or using hindsight. To do this

analysis, I imagined that I was the POSA at the time of the priority date (November 14, 2014). At that time, the POSA would not have had access to the '895 patent and would only have been aware of the relevant prior art. From that, I made an analysis of what the POSA would have known and reasonably expected (*i.e.*, what would have been obvious) based on the available prior art and knowledge of the POSA (as I discuss more fully throughout this Declaration). I understand from counsel that prior art includes information that existed prior to the date of the alleged invention or the date of filing of the patent application.

35. I have been informed that obviousness may be based on one reference, or more than one reference. In other words, I understand that obviousness does not require that every element of an invention be necessarily disclosed in a single reference. If the invention is found in a single reference as a whole, however, this is referred to as single-reference obviousness. Alternatively, the invention can be disclosed in the prior art as a whole (*i.e.*, more than one reference), including in multiple references or as part of the general knowledge in the art.

36. I understand that for a patent claim to be obvious, there must be some rationale (or motivation) to combine the teachings of the prior art to arrive at the claimed invention. The rationale for a POSA to combine the prior art in a particular way may be found in the references themselves, in the general

knowledge of one of ordinary skill in the art, or in the nature of the problem to be solved. A rationale to combine the teachings of the prior art need not be explicit in the prior art.

37. I further understand that to find whether the prior art renders an invention obvious, I must explain why a POSA would have had a reasonable expectation of success in arriving at the claimed subject matter. My understanding is that a reasonable expectation of success does not require an absolute certainty of success. I understand there can be a reasonable probability of success even if there is some degree of unpredictability or uncertainty.

38. Furthermore, an invention may not be obvious if the prior art teaches away from the invention. It is my understanding that a reference teaches away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference or would be led in a direction divergent from the path that was taken. However, I have been informed that a reference that merely expresses a general preference for an alternative invention, but does not criticize, discredit, or otherwise discourage investigation into the claimed invention, does not teach away. The mere disclosure of alternative designs does not teach away. Indeed, my understanding is that even if better alternatives exist in the prior art, under the law, it does not mean that an inferior combination is inapt for obviousness purposes.

39. It is my understanding that a POSA is also a person of ordinary creativity. When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a POSA has a good reason to pursue the known options within his or her grasp. If this leads to the claimed subject matter, it is likely the product of ordinary skill and common sense and not of innovation.

40. Furthermore, to determine obviousness, it is proper to look at the interrelated teachings of multiple pieces of prior art, the effects of demands known to the design community or present in the marketplace, and the background knowledge possessed by a person having ordinary skill in the art. The determination should be based upon whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. The analysis of obviousness need not seek out precise teachings directed to the specific subject matter of the challenged claim, but the analysis can consider inferences and creative steps that a person of skill in the art would employ.

41. I have also been informed by counsel that inherency may supply a missing claim limitation in an obviousness analysis. Indeed, in the context of obviousness, the mere recitation of a newly discovered function or property, inherently possessed by things in the prior art does not distinguish a claim drawn to those things from the prior art. A composition suggested by the prior

art is not simply patentable because it also possesses an inherent property, which the patentee claims to have discovered. Mere recitation of a newly discovered function or property inherently possessed by things in the prior art does not distinguish a claim drawn to those things from the prior art. I understand that an obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the result.

42. Furthermore, a claimed invention would have been “obvious to try” where there is a design need or market pressure to solve a problem, and there are a finite number of identified, predictable solutions a person of ordinary skill has good reason to pursue the known options within his or her technical grasp with a reasonable expectation of success.

43. Although I will not address them in this Declaration in any detail (but reserve the right to do so later), I also understand that in determining the obviousness of the claimed subject matter of an alleged invention, so-called “secondary considerations of non-obviousness” such as, *inter alia*, unexpected results, commercial success, long-felt but unsolved needs, failure of others, etc., to the extent they exist, should be considered. I reserve the right to address any of these “secondary considerations” issues should the Patent Owner or their expert(s) assert one or more of them as evidence of non-obviousness.

44. I have been informed by counsel that patent invalidity (including

obviousness) in a District Court proceeding is assessed under the clear and convincing evidence standard. I understand that this standard represents an intermediate burden of proof—more demanding than the “preponderance of the evidence” standard (which requires only that something is more likely than not), but less stringent than the “beyond a reasonable doubt” standard used in criminal proceedings. To satisfy the clear and convincing evidence standard, a challenger must produce evidence that is highly probable and leaves the fact finder with a firm belief or conviction that the patent is invalid.

45. That said, I have been informed this proceeding is not before a District Court but is a Post Grant Review proceeding before the Patent Trial and Appeal Board (“PTAB”). I have been informed by counsel that in a Post Grant Review proceeding, the PTAB applies a lower threshold, requiring only that it is “more likely than not” that the challenged claims are unpatentable. I have been informed by counsel that the “more likely than not” standard is less demanding than the clear and convincing evidence standard.

46. In any event, a protracted discussion of the differences in evidentiary standards is unnecessary for purposes of my discussion. Based on the prior art discussion and analysis presented in this Declaration, it is highly probable that the challenged claims are invalid, and I am left with a firm belief and conviction that the challenged claims are invalid for the reasons explained herein.

47. I recognize that the standard of invalidity I am referencing in the preceding paragraph is that of the clear and convincing evidence standard. In other words, if this were the standard of invalidity used in the Post Grant Review, I believe the challenged claims would be found invalid under that standard. It, therefore, stands to reason that under the lesser “more likely than not” standard applicable to this PGR proceeding, the invalidity determination would likewise be satisfied. Accordingly, based on the prior art discussion and analysis presented in this Declaration, it is more likely than not that the challenged claims are invalid for the reasons explained herein.

V. THE '895 PATENT

48. The '895 patent is entitled “Methods for Treating Subjects with Prader-Willi syndrome” and issued on September 23, 2025. It is part of the bigger family that has other issued patents as seen under “Related U.S. Application Data” on the face of the patent. Ultimately, the '895 patent claims priority to U.S. Provisional Applications 62/221,359 (filed Sep. 21, 2015), 62/170,035 (filed Jun. 2, 2015), and 62/080,150 (filed Nov. 14, 2014). The '895 patent names Niel M. Cowen as the sole inventor and is assigned to Essentialis, Inc. EX1001.

49. I have reviewed and considered the '895 patent (and its file history) in view of the general knowledge in the relevant field measured from the relevant priority date for the '895 patent from the perspective of a POSA as defined above.

I provide further discussion of the '895 patent, its claims, specification and file history throughout this Declaration.

A. The Specification of the '895 Patent

50. The '895 patent 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) and Smith-Magenis syndrome (SMS). EX1001, Abstract.

51. The '895 patent discloses K_{ATP} channel openers, with diazoxide being disclosed as an exemplary compound. *Id.*, 27:41-43, 67:59-61, Claim 1. Disclosed formulations included once-daily administration. *Id.*, 28:21-27, 29:65-66, Table 1. These formulations may contain between 25 and 500 mg of the K_{ATP} channel opener. *Id.*, 29:66-67, Table 1. Examples of the characteristics and properties of the disclosed formulations are provided in Table 1, as illustrated below:

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
	500-2000 mg
C. Dosing	Once daily (24 hours)
	Twice daily (24 hours)
D. Release time:	2-4 hrs
	4-8 hrs
	8-24 hours

Id., 30:26-41.

52. The '895 patent further provides that the disclosed formulations may be administered for the treatment of PWS, with the '895 patent specifically disclosing the administration of diazoxide choline for PWS. *Id.*, 4:20-24, Example 3. The diazoxide choline formulations could be administered at an initial dose and titrated up every 14 days until a maintenance dose is achieved. *Id.*, Example 3.

53. Administration of the disclosed formulation comprising diazoxide choline is disclosed as being associated with the reduction of hyperphagia, waist circumference, weight, and temper outbursts and aggressive behavior. *Id.*, Table 5, Table 16.

B. The Challenged Claims of the '895 Patent

54. Below I have reproduced the Challenged Claims:

1. A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising administering to said subject once per day a pharmaceutical formulation comprising an effective amount of diazoxide choline, wherein administration reduces hyperphagia and one or more food related behaviors in the subject.
2. The method of claim 1, wherein the diazoxide choline is administered for at least 10 weeks.
3. The method of claim 1, wherein the diazoxide choline is administered for one or more years.
4. The method of claim 1, wherein the once-daily administration of diazoxide choline is in an amount from 25 mg to 100 mg.
5. The method of claim 1, wherein the once-daily administration of diazoxide choline is in an amount from 50 mg to 180 mg.
6. The method of claim 1, wherein the once-daily administration of diazoxide choline is in an amount from 50 mg to 275 mg.

7. The method of claim 1, wherein the once-daily administration of diazoxide choline is in an amount from 300 mg to 500 mg.

8. The method of claim 1, wherein the once-daily administration of diazoxide choline is in an amount from 500 mg to 2000 mg.

9. The method of claim 1, wherein the once-daily administration of diazoxide choline is in an amount from 25 mg to 500 mg.

10. The method of claim 3, wherein the once-daily administration of diazoxide choline is in an amount from 25 mg to 100 mg.

11. The method of claim 3, wherein the once-daily administration of diazoxide choline is in an amount from 50 mg to 180 mg.

12. The method of claim 3, wherein the once-daily administration of diazoxide choline is in an amount from 50 mg to 275 mg.

13. The method of claim 3, wherein the once-daily administration of diazoxide choline is in an amount from 300 mg to 500 mg.

14. The method of claim 3, wherein the once-daily administration of diazoxide choline is in an amount from 500 mg to 2000 mg.

15. The method of claim 3, wherein the once-daily administration of diazoxide choline is in an amount from 25 mg to 500 mg.

16. The method of claim 1, wherein the administration of diazoxide choline is initiated at a starting dose of diazoxide choline and then titrated every two weeks to reach a maintenance dose of diazoxide choline.

17. The method of claim 16, wherein the starting dose of diazoxide choline is between 25-100 mg of diazoxide choline.

18. The method of claim 16, wherein the starting dose of diazoxide choline is between 50-180 mg of diazoxide choline.

19. The method of claim 17, wherein the maintenance dose of diazoxide choline is between 100-200 mg of diazoxide choline.

20. The method of claim 18, wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline.

21. The method of claim 18, wherein the maintenance dose of diazoxide choline is between 300-500 mg of diazoxide choline.

22. The method of claim 18, wherein the maintenance dose of diazoxide choline is between 500-2000 mg of diazoxide choline.

23. The method of claim 18, wherein the maintenance dose of diazoxide choline is between 100-500 mg of diazoxide choline.

24. The method of claim 17, wherein the maintenance dose of diazoxide choline is between 25-250 mg of diazoxide choline.

25. The method of claim 17, wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline.

26. The method of claim 1, wherein the pharmaceutical formulation is administered orally.

C. Prosecution History

55. The application that led to the '895 patent was filed on May 30, 2025. EX1015, 4, 131-133. On June 3, 2025, a Preliminary Amendment was filed in which the original claims were canceled, and new Claims 29-55 were presented. *Id.*, 187-194.

56. The text of independent Claim 29 is presented below:

29. (New) A method of hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising administering to said subject once per day a pharmaceutical formulation comprising an effective amount of diazoxide choline, wherein administration reduces hyperphagia and one or more food related behaviors in the subject.

Id.

57. On July 9, 2025, the Examiner issued a Non-Final Office Action rejecting pending Claims 29-53 for statutory double patenting over Claims 1-25 of the '348 patent and pending Claims 29 and 54-55 for non-statutory double patenting over Claims 1, 3, 6-7, 12-13, and 16-24 of U.S. Patent No. 12,178,823 ("the '823 patent"). *Id.*, 225-233.

58. In response, Applicant filed an Amendment and Response to Office Action in which they pointed out that the Examiner had erroneously reviewed the canceled original claims and not the pending claims, as recited in the Preliminary

Amendment. *Id.*, 243-253. Applicant further filed a Terminal Disclaimer ⁴ over the '823 patent. *Id.*, 237.

59. The Examiner issued a Notice of Allowance on February 13, 2025, providing the following “Reasons for Allowance”:

The rejection of Claims 29-53 under 35 U.S.C. 101 as claiming the same invention as that of claims 1-25 of prior U.S. Patent No.12,343,348 B2 is withdrawn due to applicant’s convincing arguments.

The rejection of Claims 29 and 54-55 on the ground of nonstatutory double patenting as being unpatentable over claims 1,3, 6-7, 12-13, 16-24 of U.S. Patent No. 12,178,823 B1 is withdrawn due to filing the Terminal Disclaimer on 8/07/25.

Id., 257-263. The application issued as U.S. Patent No. 12,419,895 on September 23, 2025. *Id.*, 280-281.

VI. CLAIM CONSTRUCTION

60. I have not been made aware of any prior claim construction

⁴ I have been informed by counsel that at a high level, a terminal disclaimer is a legal document filed with the USPTO where an applicant shortens the term of a patent to match the expiration date of another patent.

determination concerning the '895 patent in a civil action or a proceeding before the International Trade Commission.

61. To the extent the '895 patent specification defines any term, I used those definitions in my analysis, including if those definitions are claim terms. *See, e.g.*, EX1001, 15:32-23:13, 25:31-26:62.

62. As to all other claim terms, after reviewing the claims and the specification of the '895 patent, along with its associated file history, in my opinion, no other claim term needs to be specifically construed, and I do not believe any further specific construction is necessary for my analysis of the challenged claims. In other words, for any term that is not defined in the specification, I afforded that term the meaning in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent as of the time of the invention, *i.e.*, November 14, 2014.

VII. TECHNICAL BACKGROUND/STATE OF THE ART/SUMMARY OF THE PRIOR ART

A. Prader-Willi Syndrome and Hyperphagia

63. As explained above I treat patients with PWS, PWS patients who exhibit hyperphagia, other eating disorders, and neurodevelopmental disorders. PWS is a complex genetic disorder with a recognizable progression in the disease state. EX1007, 3. PWS first presents as prenatal hypotonia and neonatal feeding

difficulty, evolving to early childhood hyperphagia and obesity. *Id.*

64. PWS has an estimated prevalence of approximately 1 in 15,000 to 1 in 30,000. *Id.* PWS is caused by absent expression of paternally expressed genes in the chromosome 15q11.2-q13 region due to paternal deletion, maternal uniparental disomy (UPD), or an imprinting defect. *Id.*, 3, 6-7.

65. Major characteristics of PWS include infantile lethargy and hypotonia causing poor feeding and failure to thrive, developmental and intellectual disability, hypogonadism, hyperphagia leading to morbid obesity if uncontrolled, short stature, characteristic facial appearance and body habitus, and a typical behavioral phenotype that includes temper tantrums and compulsive traits. *Id.*

66. Hyperphagia is hypothalamic in origin and is characterized by an abnormal desire for food or excessive eating. *Id.*; EX1008, [0067]. Food seeking is common, including hoarding, foraging for food, eating unappealing food items, and stealing food or money to buy food.

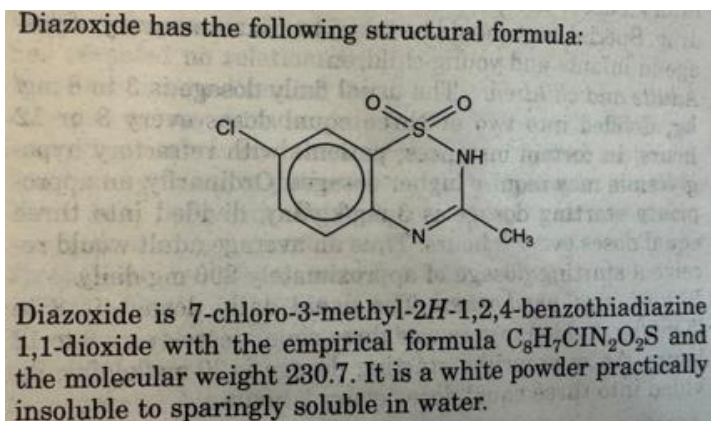
67. Once hyperphagia begins, the feeling of hunger is typically never completely relieved, even after a large meal. Thus, if food intake is not controlled externally, central obesity may result from these behaviors. EX1007, 4; *see also* EX1008, [0067].

B. Treatment of PWS and Inhibition of Hyperphagia Using Diazoxide Choline Was Well Known As of the Priority Date

68. Diazoxide is a potassium ATP (hereafter also referred to as “K_{ATP}” or “KATP”) channel opener, stimulating K_{ATP} channels, for example, in pancreatic β -cells. EX1009, [0006]. These channels, also known as potassium channel openers (PCOs or KCOs), are found in pancreatic β -cells, vascular smooth muscle, and various regions of the brain, including the hippocampus, substantia nigra, and hypothalamus. The opening of K_{ATP} channels by diazoxide increases potassium efflux, leading to cell membrane hyperpolarization and reduced electrical activity. *See generally id.*; EX1010, 2047.

69. Due to its known effects on pancreatic β -cells and vascular smooth muscle, diazoxide formulations were also recognized in the prior art as treatments for hypertensive emergency (HYPERSTAT®, diazoxide intravenous injection) and hyperinsulinemic hypoglycemic conditions (PROGLYCEM®, diazoxide oral solution). EX1011; EX1012; EX1018, 1191-1192 (PDR entry for Proglycem); EX1009, [0007] (discussing Hyperstat).

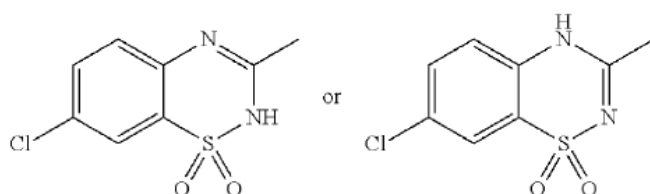
70. The structure of diazoxide was known to the POSA. As the Physicians’ Desk Reference (2008) entry for PROGLYCEM® states:



EX1018, 1191.

71. Diazoxide has an empirical formula of $C_8H_7ClN_2O_2S$ and (as discussed in the prior paragraph) was commercialized as of the priority date of the '895 patent. EX1008, [0135]; *see generally* EX1011; EX1012. As shown in Cowen, diazoxide has the following chemical structure:

[0135] The KATP channel opener may also have the formula 7-chloro-3-methyl-2-H-1,2,4-benzothiadiazine 1,1 dioxide (shown below with its tautomer) with the empirical formula $C_8H_7ClN_2O_2S$ and a molecular weight of 230.7.



[0136] The KATP channel opener may also be a salt of one of the compounds described by Formulae I-VIII and may have at least one, of the following properties: (1) opening $SURx/Kir6.y$ potassium channels, in which $x=1, 2A$ or $2B$ and $y=1$ or 2 ; (2) binding to the $SURx$ subunit of KATP channels; and (3) inhibiting glucose induced release of insulin following administration of the compound in vivo.

EX1008, [0135]-[0136]. Diazoxide salts, including diazoxide choline, were also known as of the priority date. EX1009, [00750]. In Cowen paragraph [0135], the structure of diazoxide (free base) is shown on the left, with its tautomer structure

shown on the right. EX1008, [0135]; EX1018, 1191 (prior art PDR providing the same structure (though inverted), name, molecular weight and empirical formula as Cowen at paragraph [0135]).

72. Furthermore, Cowen (EX1008, [0135]) refers to the two structures as tautomers. When two compounds are referred to as tautomers, they are isomers of one another due to migration of the proton and movement of the double bond. EX1003, 1043 (“This type of isomerization, occurring by the migration of a proton and the movement of a double bond, is called tautomerism, and the isomers that interconvert are called tautomers. Tautomers are true isomers, and (under the right circumstances), with no catalyst present) either individual tautomeric form may be isolated”). That said, the POSA would understand that diazoxide (free base) is the structure shown on the left. EX1018, 1191.

73. The prior art would have also taught the POSA that diazoxide choline was a treatment for PWS due to its therapeutic efficacy in inhibiting hyperphagia. EX1009, [0093] (providing a method of treating diseases characterized by obesity, hyperphagia, dyslipidemia, or decreased energy expenditure, “including (a) Prader-Willi Syndrome”), [00442] (reduced rates of hyperphagia), [00449] (teaching treatment of PWS patients with K_{ATP} channel openers resulting in inhibition of hyperphagia).

74. Furthermore, the effect of diazoxide on obesity and diabetes in

humans was also known, with diazoxide treatment resulting in weight loss in obese and obese hyperinsulinemic patients. EX1009, [0007]-[0008], [0017].

C. Dose Titration in Clinical Practice Was Well Known as of the Priority Date

75. Dose titration is a well-established clinical practice in which the administered amount of a drug is adjusted to achieve the desired therapeutic effect. In clinical practice, physicians frequently begin treatment at a relatively low starting dose (sometimes called an initiation or starting dose) and then gradually increase the dose over time until the patient reaches a target or maintenance dose that provides the desired therapeutic effect. Often, this method of dose titration (sometimes referred to as dose escalation) is used to minimize the occurrence of adverse effects in patients. EX1013, 52.

76. As is the typical case, a physician's decision to titrate a medication upward over time is guided by what is known about the medication, the patient's tolerability, the presence or absence of adverse effects, and the patient's therapeutic response. When a medication is first initiated at a low starting dose, the prescriber will monitor the patient over a period of time to assess how well the drug is tolerated. If the patient experiences minimal or manageable side effects and the therapeutic effect is not yet sufficient, the physician may increase the dose incrementally at subsequent visits or after a defined interval.

77. Physicians commonly increase the dose every one to two weeks.

EX1009, [0077], [00478], [00448]. Indeed, in clinical practice, many marketed drugs are titrated over a two-week interval such that it is common for physicians to utilize two weeks as a standard titration interval when titration is needed.

78. Waiting this period helps the prescriber evaluate both tolerability and early therapeutic response before increasing the dose again. Dosing adjustments are typically spaced to allow the physician to observe the patient's response and adverse-effect profile before further escalation. *Id.*; *see also id.*, [0089].

79. If the patient develops adverse effects during dose titration—examples could include gastrointestinal symptoms, dizziness, or other dose-related reactions/complications—the physician may elect to delay further dose escalation and maintain the current dose until adverse effects subside. *Id.* In this way, dose titration allows the prescriber to balance efficacy and safety on an individualized basis based on their professional judgement and patient response.

80. This patient-centered approach to dose adjustment has long been a routine aspect of clinical pharmacology and prescribing practice, as reflected in standard practice references such as Remington Essentials of Pharmaceutics, which describes dose titration as an effort “to attain and maintain a blood level that exceeds the minimum effective level required for response but does not exceed the minimum toxic (side-effect) level.” EX1013, 52; *see* EX1014, 5, 12,

26.

D. International Patent Publication No. WO 2009/006483 to Cowen *et al.* (“Cowen”)

81. International Patent Publication No. WO 2009/006483 to Cowen *et al.* (“Cowen” or EX1009), titled “Salts of Potassium ATP Channel Openers and Uses Thereof,” published on January 8, 2009, which is more than one year prior to the earliest priority date of the ’895 patent.

82. Cowen was disclosed to the Examiner during prosecution of the application that led to the ’895 patent. That said, even though it was disclosed to the Examiner, for the reasons provided in this Declaration, the teachings of Cowen render the challenged claims obvious.

83. Cowen discloses methods of preparation and use of pharmaceutical formulations that include K_{ATP} channel openers such as diazoxide and diazoxide salts. EX1009, Abstract, Title.

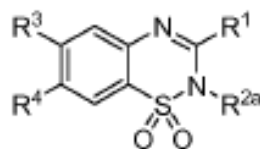
84. More specifically, Cowen discloses K_{ATP} channel openers including at least one tertiary amine or at least one quaternary ammonium ion (*e.g.*, diethylamine ethanol, triethylamine, hydroxyethylpyrrolidine, **choline** and hexamethylhexamethylenediammonium, and the like). *Id.*, [0058]. Cowen further discloses diazoxide choline as a preferred K_{ATP} channel opener with multiple exemplary formulations comprising diazoxide choline. *Id.*, [0072], [00143], [00596], Claim 71.

85. In highlighting the favorable characteristics of diazoxide choline over the diazoxide free base, Cowen teaches diazoxide choline as “significantly greater aqueous solubility over diazoxide free base, [and] rapid conversion to diazoxide base on exposure to an aqueous environment.” *Id.*, [00750]. The pharmaceutical formulations of Cowen may be administered once daily (*i.e.*, once per 24 hours). *Id.*, [00143]. These formulations may contain between 25 and 500 mg of the disclosed K_{ATP} channel openers. *Id.*, [0061], [00380].

86. To reduce incidence of adverse side effects known to occur with diazoxide, patients may be initiated at subtherapeutic doses and titrated up in a stepwise manner, until a therapeutic dose is achieved. *Id.*, [0089], [00478]. The starting dose is preferably between 10 and 200 mg of diazoxide and given to the patient daily for days or a few weeks. *Id.*, [0077]. The increment in dose during dose titration is preferably 25 to 150 mg of diazoxide. *Id.* Further rounds of dose escalation may continue until the therapeutically effective dose is reached. *Id.*

87. As I explain later in this Declaration, the use of diazoxide choline would have been obvious, and the structure of diazoxide was known. *Supra* at ¶¶ 70-72 (discussing POSA knowledge of diazoxide). The POSA would have understood diazoxide (free base) falls with generic Formula III of Cowen:

[0040] K_{ATP} channel openers defined by Formula III are as follows:



Formula III

EX1009, [0040].

88. Cowen provides information about the nature of the substituents in paragraph [0040].

89. The known structure of diazoxide (free base) (*supra*, ¶¶ 70-72) falls within the generic structure of Formula III in Cowen by setting the substituents in paragraph [0040] as follows: R¹ = “lower alkyl” (which would include methyl)⁵, R^{2a} = “hydrogen”, R³ = “hydrogen”, R⁴ = “halogen” (which would include chlorine); *see also* EX1009, [0042] (“In another embodiment of Formula III, R¹ is **methyl**; R^{2a} is **hydrogen**; R³ is selected from the group consisting of **hydrogen**, halogen, lower alkyl, substituted lower alkyl, cycloalkyl, and substituted cycloalkyl; and R⁴ is **chlorine**.”)

E. International Patent Publication No. WO 2014/197753 to Cotter (“Cotter”)

⁵ EX1009, 00311 (Cowen): “‘Lower alkyl’ refers to an alkyl group having 1-6 carbon atoms.”

90. International Patent Publication No. WO 2014/197753 to Cotter (“Cotter” or EX1008), titled “Method of Treating Prader Willi Syndrome and Conditions Associated with Low Basal Metabolic Rate or Hyperphagia,” published on December 11, 2014. Cotter claims priority from U.S. Provisional Patent Application No. 61/832,779, filed on June 8, 2013. The date of the Provisional Application is before the earliest priority date of the ’895 patent.

91. Cotter does not share an inventor with the ’895 patent, nor does it share common ownership (*e.g.*, common assignee).

92. The U.S. equivalent of Cotter, U.S. Patent Publication No. 2014/0364367 (EX1016), was disclosed to the Examiner during prosecution of the application that led to the ’895 patent. That said, even though it was disclosed to the Examiner, for the reasons provided in this Declaration, the teachings of Cotter (in combination with Cowen) render the challenged claims obvious.

93. Cotter discloses a method for treating PWS comprising administering a K_{ATP} channel opener, such as diazoxide, to a patient in need thereof. EX1008, [0008], [0150], Claim 14.

94. Cotter further discloses the K_{ATP} channel opener may be administered in combination with other therapies used to treat PWS, allowing 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. *Id.*, [0010].

95. The patient may be in PWS nutritional phase 0, 1a, 1b, 2a, 2b, 3, or 4. *Id.*, [0007]. The patient's PWS nutritional phase may be prevented from progressing to a later phase or may be "shifted back" to an earlier PWS nutritional phase. *Id.*

96. Cotter discloses that Phase 2-3 is characterized by an increase in appetite, excessive calories, or hyperphagia, as displayed below:

Phase 2a: Weight increasing without an increase in appetite or excessive calories (2.1–4.5 years)	Infant starts crossing growth curve centile lines
	No increase in appetite
	Appetite appropriate for age
	Will become obese if given the recommended daily allowance (RDA) for calories or if eating a "typical" toddler diet of 70% carbohydrates
	Typically needs to be restricted to 60–80% of RDA to prevent obesity
Phase 2b: Weight increasing with an increase in appetite (4.5–8 years)	Increased interest in food. Frequently asking "food related" questions
	Preoccupied with food. Very concerned about the next meal/snack (e.g., "Did you remember to pack my lunch?")
	Increased appetite
	Will eat more food than a typical child if allowed
	Will eat food within their line of sight if unattended
	Will become obese if allowed to eat what they want
	Can be fairly easily redirected about food
	Can feel full
Phase 3: Hyperphagic, rarely feels full (8 years to adulthood)	Will stop eating voluntarily
	Constantly thinking about food
	While eating one meal they are already thinking about the next meal
	Will awaken from sleep early thinking about food
	Will continue eating if portion size is not limited
	Rarely (truly) feels full
	Will steal food or money to pay for food
	Can eat food from garbage and other unsavory/inedible sources (e.g., dog food, frozen food, crayons, etc.)
	Typically are not truthful about what they have eaten (i.e. amount and types of food)
	Will gain considerable amount of weight over a short period of time if not supervised (e.g., some individuals are known to have gained up to 20 pounds in one weekend)
	Food typically needs to be locked up. Frequently the child will ask the parent to lock the food if the parent has forgotten
	Will break into neighbors' houses for food
	Temper tantrums and "meltdowns" frequently related to food
	Needs to be placed on a diet that is approximately 50–70% of the RDA to maintain a healthy weight

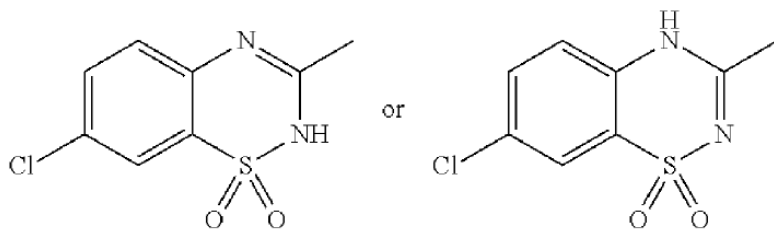
Id., [0067].

97. The dose of the K_{ATP} channel opener may be at least 1, 5, 10, 15, 20, 30, 40, 50, 100, 200, 300, 400, 500, 1,000, or 2,000 mg. *Id.*, [0065]. The dose may also be less than 1, 5, 10, 15, 20, 30, 40, 50, 100, 200, 300, 400, 500, 1,000, or 2,000 mg. *Id.*

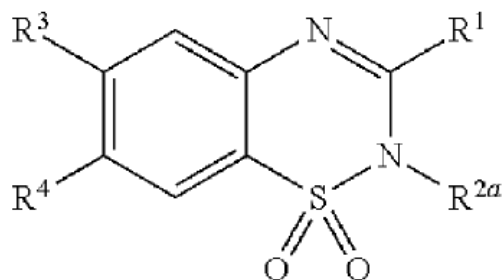
98. Administration of the composition using the method described in Cotter may be orally, parenterally, sublingually, transdermally, rectally, transmucosally, topically, via inhalation, via buccal administration, or combinations thereof. *Id.*, [0141]. The composition may be administered 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 times per day. *Id.*, [0141].

99. As I explain later in this Declaration the use of diazoxide choline would have been obvious and the structure of diazoxide was known. *Supra* at ¶¶ 70-72 (discussing POSA knowledge of diazoxide and tautomerism). As Cotter states, “[t]he KATP channel opener may have the structure of one of Formula I-VIII.” EX1008, [0074]. Furthermore, Cotter shows diazoxide (free base) at paragraph [0135] with its “tautomer” (*supra* ¶72 (discussing tautomerism); EX1003, 1043 (same)):

[0135] The KATP channel opener may also have the formula 7-chloro-3-methyl-2-H-1,2,4-benzothiadiazine 1,1 dioxide (shown below with its tautomer) with the empirical formula C₈H₇ClN₂O₂S and a molecular weight of 230.7.



100. The POSA would have understood diazoxide (free base) depicted at Cotter [0135] falls with generic Formula III of Cotter:



Formula III

Id., [0089]

101. Cotter provides information about the nature of the substituents in paragraphs [0090]-[0093]. The known structure of diazoxide (free base) (*supra* at ¶¶70-72) falls within the generic structure of Formula III in Cotter by setting the substituents in paragraphs [0090]-[0093] as follows: R¹ = “lower alkyl” (i.e.,

methyl),⁶ R^{2a} = “hydrogen”, R³ = “hydrogen”, R⁴ = “halogen” (i.e., chlorine).

F. Miller et al., Nutritional Phases in Prader-Willi Syndrome, 155 Am. J. Med. Genet A. 1040, 1040-49 (2011) (“Miller”)

102. Miller *et al.*, *Nutritional Phases in Prader-Willi Syndrome*, 155 AM. J. MED. GENET A. 1040, 1040-49 (2011) (“Miller” or EX1017) published in May 2011, which is more than one year prior to the earliest priority date of the ’895 patent.

103. Miller was disclosed to the Examiner during prosecution of the ’895 patent. That said, even though it was disclosed to the Examiner, for the reasons provided in this Declaration, the teachings of Miller (in combination with Cowen) render the challenged claims obvious.

104. Miller is a review discussing PWS. EX1017, 1. In contrast to the long-held view that there are only two stages of PWS, Miller explains there are five major nutritional phases, highlighting the nutritional phases and transitions in individuals with PWS. *Id.*, 5.

105. Miller provides an overview of each of the five phases of PWS. *Id.*, 13-14.

⁶ EX1008, 00019 (Cotter): “‘Lower alkyl’ means an alkyl group having 1-6 carbon atoms.”

VIII. GROUND 1: CLAIMS 1-26 OF THE '895 PATENT ARE OBVIOUS OVER COWEN

106. In my opinion, Claims 1-26 of the '895 patent would have been obvious in light of the teachings of Cowen. The reasons for my conclusion and my analysis are presented below.

A. Claim 1

107. Claim 1 provides as follows:

1. A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising administering to said subject once per day a pharmaceutical formulation comprising an effective amount of diazoxide choline, wherein administration reduces hyperphagia and one or more food related behaviors in the subject.

i. *“A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising”*

108. Cowen teaches “a method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS)”:

Claim	Exemplary Citations
1. A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising administering	EX1009, [0087] (“Further provided is a method to treat obesity, or hyperphagia in a Prader-Willi Syndrome patient ”); <i>see also id.</i> , [0093] (“Prader-Willi Syndrome”); <i>id.</i> , [00413] (same); <i>id.</i> , [00449] (same); <i>id.</i> , [0069] (“inhibition of hyperphagia”); <i>id.</i> , [0070] (same); <i>id.</i> , [0071] (same); <i>id.</i> , [0087]

	(“hyperphagia”); <i>id.</i> , [0093] (same); <i>id.</i> , [0093] (same).
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- ii. ***“administering to said subject once per day a pharmaceutical formulation comprising an effective amount of diazoxide choline,”***

1) The use of diazoxide choline would have been obvious

109. In my opinion, the use of diazoxide choline would have been obvious to a POSA in light of Cowen.

110. The '895 patent explains that diazoxide is “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.” EX1001, 17:1-3, 2:30-33. As explained above, the structure of the diazoxide was known to the POSA. EX1018; *supra* at ¶¶70-72.

111. Cowen discloses the same compound and also identifies it as diazoxide. EX1009, [0007] (“Diazoxide, [has] the formula 7-chloro-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (empirical formula $C_8H_7ClN_2O_2S$)”).

112. As explained above, diazoxide falls within the generic structure of Formula III of Cowen (*supra* at Section VII(D)), and Cowen teaches that diazoxide and other salts are used for the treatment of hyperphagia in a Prader-Willi Syndrome patient. EX1009, [0087] (“Further provided is a method to treat obesity, or hyperphagia in a Prader-Willi Syndrome patient, a . . . comprising the administration of an effective amount of a KATP channel opener selected from

the salts of the compounds of Formulae I – VIII.”).

113. While it is true that Cowen may teach diazoxide (free base) and a limited number of its salts (*id.*, [00137]-[00138], [00348]), the POSA would readily recognize diazoxide choline as the preferred compound over diazoxide (free base) and the other salts, making its selection obvious. For example, Cowen only specifically claims “diazoxide choline” immediately drawing the POSA’s attention to this specific compound. *Id.*, Claims 9, 21, 32, 48, 53, 57, 62, 63, & 70.

114. Furthermore, Cowen specifically highlights the favorable properties of diazoxide choline over its free base, stating for oral administration, it has “significantly greater aqueous solubility over diazoxide free base, rapid conversion to diazoxide base on exposure to an aqueous environment.” *Id.*, [00750].

115. Cowen then solidifies the selection of diazoxide choline by providing numerous detailed examples and formulations that prominently feature this compound. For instance, Cowen includes extensive pharmaceutical formulation information using diazoxide choline (*id.*, [0596]-[00603]), details on dissolution studies (*id.*, [00604]-[00607]), excipient compatibility and stability studies (*id.*, [00608]-[00615]), and methods for its preparation (*id.*, [00623]-[000634]). Moreover, Cowen discusses polymorphic forms (*id.*, [00680]-

[00690]) and crystallization of diazoxide choline (*id.*, [00689]-[00706]). Cowen also provides clinical information for various human disorders using diazoxide choline (*id.*, [00749]-[00760], [00764], [00766], [00770], [00772], [00778], [00783]-[0084]) and pharmacokinetic data (*id.*, [00763], [00769]). These teachings highlight diazoxide choline within Cowen over diazoxide (free base) and any other salt form.

116. For these reasons, a POSA would have been motivated to make a pharmaceutical formulation using diazoxide choline for treating hyperphagia in PWS patients with a reasonable expectation of success from Cowen.

iii. ***“administering to said subject once per day a pharmaceutical formulation comprising an effective amount of diazoxide choline,”***

117. Cowen discloses pharmaceutical formulations comprising diazoxide choline. *Id.*, [0596]-[00603] (providing extensive pharmaceutical formulation information using diazoxide choline). As a general matter, once-daily administration is always preferable since it increases patient compliance.

118. In any event, Cowen discloses and claims once-daily administration, so it would have been an obvious choice for the POSA. *Id.*, [0087] (treating “hyperphagia in a Prader-Willi Syndrome patient, comprising the administration of an effective amount of a K_{ATP} channel opener . . . In a preferred embodiment, administration is no more than two times per 24 hours, **or once per 24 hours.**”),

[00766] (“A controlled clinical study was conducted to evaluate the potential for **Diazoxide Choline** Controlled-Release Tablets administered **once daily**”), [00411] (formulations of K_{ATP} channel openers selected from a salt of a compound of Formulae I – VIII administered as a **single dose**); Claims 31 (“the formulation is **administered once per 24 hours**.”), 52, 59, 62 & 65.

119. Finally, Claim 1 also recites use of “an effective amount” of the diazoxide choline pharmaceutical composition. The ’895 patent provides a definition of an “effective amount.” EX1001, 15:32-36. Cowen discloses an “effective amount” within the meaning of Claim 1 of the ’895 patent. EX1009, [00087] (treating “hyperphagia in a Prader-Willi Syndrome patient, comprising the administration of an effective amount of a K_{ATP} channel opener.”).

iv. “wherein administration reduces hyperphagia”

120. The final recitation of Claim 1 is “wherein administration reduces hyperphagia and one or more food related behaviors in the subject.” Focusing first on the reduction of hyperphagia portion.

121. Cowen explicitly discloses that a pharmaceutical formulation comprising diazoxide choline (a K_{ATP} channel opener) effectively reduces or inhibits hyperphagia. Specifically, Cowen repeatedly references “**reduced rates of hyperphagia**.” *Id.*, [00439], [00442]-[00444]. As if that were not enough, Cowen explains its formulations result in an “**inhibition of hyperphagia**” for

about 18 hours and 24 hours. *Id.*, [0070]-[0071]. Cowen also provides a method to treat “hyperphagia in a Prader-Willi Syndrome patient” (*id.*, [0087]) and diseases “characterized by . . . hyperphagia” (*id.*, [0093]).

122. Additionally, Cowen describes formulations 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.” *Id.*, [00411]. These disclosures undeniably teach a reduction/inhibition in hyperphagia.

v. ***“wherein administration reduces . . . one or more food related behaviors in the subject.”***

123. Next, turning to the recitation “reduces . . . one or more food related behaviors in the subject”: it is important to give some context to the meaning of “food related behaviors” within the meaning of the ’895 patent.

124. I have been informed by counsel that the specification of a patent is highly relevant to understanding and giving proper context to the meaning of the claims and claim terms. As the ’895 patent explains:

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.

EX1001, 20:14-22. I am guided by this description in the '895 patent, though I note that this is consistent with the understanding of the POSA even outside the context of the '895 patent.

125. At the outset, in my opinion, a reduction in “one or more food related behaviors in the subject” upon administration of diazoxide choline would have inherently occurred. I reach this conclusion for the following reasons.

126. First, the administration of diazoxide choline would necessarily result in a reduction in “one or more food related behaviors in the subject” because that is precisely what the chemical does when administered to PWS patients experiencing hyperphagia. In the body, an active pharmaceutical will act as it does. Specifically, Cowen expressly teaches administering diazoxide choline to the specific patient population that has PWS, which then inhibits or reduces hyperphagia. Because hyperphagia and the associated problematic food-related behaviors are linked in these patients, reducing one necessarily reduces the other.

127. As the '895 patent itself acknowledges (citing to prior art Miller (EX1017)), hyperphagia is associated with problematic **food-related behaviors** in PWS patients. EX1001, 20:14-22. Here, the patent specification describes

these behaviors as manifestations of hyperphagia, not independent phenomena. *Id.* I discussed Miller (EX1017) above (*supra* at Section VII(F)) and also discuss further in Ground 3. *Infra* at Section X.

128. Thus, following the teachings of Cowen, when diazoxide choline is administered to a PWS patient experiencing hyperphagia and thereby reducing hyperphagia, it would have necessarily led to a corresponding reduction in the problematic food-related behaviors.

129. I have been informed by counsel that to support inherency I may also rely on post-priority date evidence including extrinsic evidence and the work of the inventor and patentee. Following Cowen's express teaching—that administering diazoxide choline to a PWS patient with hyperphagia inhibits or reduces hyperphagia—would then also inherently reduce the problematic food-related behaviors in the patient because this is precisely the outcome that the '895 patent claims would occur.

130. In any event, I do not just have to rely on inherency in view of the teachings of Cowen. Cowen explains that hyperphagia means “[i]ngestion of a greater than optimal quantity of food.” EX1009, [00192]. And since Cowen teaches that diazoxide choline **inhibits or reduces** hyperphagia, the POSA would understand this to mean that the patient would reduce its consumption of “a greater than optimal quantity of food”; rather, the patient would consume a

reduced or normal amount of food due to the administration of the diazoxide choline. In other words, reducing or inhibiting hyperphagia using diazoxide choline means that the patient will eat a reduced or normal quantity of food.

131. The POSA's understanding that the (problematic) food-related behaviors in PWS patients are reduced in Cowen is solidified by its other teachings. Specifically, Cowen teaches that diazoxide choline "induce[s] weight loss" and can even be the "sole treatment to induce weight loss". *Id.*, [00407], [00415], [00416]. The POSA would understand that for diazoxide choline to induce weight loss, especially as a "sole treatment," it must necessarily reduce the (problematic) food-related behaviors described in the '895 patent (*e.g.*, "PWS patients will eat any food in the line of sight, get up at night to eat."). Furthermore, given the teachings of Cowen, the POSA would have had a reasonable expectation of success of achieving these outcomes.

132. Therefore, a reduction in hyperphagia and one or more food-related behaviors would have been obvious to the POSA.

B. Claims 2-3

133. Claims 2 and 3 depend from Claim 1 and recite "wherein the diazoxide choline is administered for at least 10 weeks" (Claim 2) and "wherein the diazoxide choline is administered for one or more years." (Claim 3). These administration periods are taught by Cowen.

134. For example, Cowen teaches “prolonged administration” (EX1009, Abstract) with specific administration periods ranging from at least 7 days to 12 months:

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)**.

Id., [00234], [00735]-[00736] (“Formulations of salts of any of the compounds of Formulae I - IV⁷ prepared as described herein can be tested for efficacy in obese humans . . . [s]ubjects are dosed daily for **up to 12 months**.”); *id.*, [00741] (“up to 12 months”). “[U]p to 12 months” is a year.

135. Even if paragraphs [00735]-[00736] may refer to a study dealing with the “[t]reatment of obesity in humans,” as Cowen makes clear, this would include patients suffering from Prader-Willi Syndrome. *Id.*, [0093] (“treating diseases characterized by obesity . . . including (a) Prader-Willi Syndrome”).

136. The teachings of Cowen necessarily include administering treatment

⁷ The generic Formula III in Cowen includes diazoxide. *Supra* at Section VII(D). As I have explained in this Declaration, use of the choline salt would have been obvious to the POSA.

for least 10 weeks and more than a year (*i.e.*, 52 weeks). Thus, based on Cowen, administration “for at least 10 weeks” (Claim 2) or “for one or more years” would have overlapped with the administration periods of Cowen.

137. I have been informed that when the claimed ranges overlap or lie inside ranges disclosed by the prior art, a case of obviousness exists. Accordingly, the methods of Claims 2-3 would have been obvious.

C. Claims 4-15

138. Claims 4-15 depend from Claim 1. As explained above, Claim 1 would have been obvious.

139. As to the specific recitations of Claims 4-9, they recite various ranges of the obvious “once-daily administration of diazoxide choline,” *i.e.*, 25 to 100 mg (Claim 4), 50 mg to 180 mg (Claim 5), 50 mg to 275 mg (Claim 6), 300 mg to 500 mg (Claim 7), 500 mg to 2000 mg (Claim 8); and 25 mg to 500 mg (Claim 9).

140. Turning to Claims 10-15, these claims depend from Claim 3. As explained above, Claim 3 would have been obvious. As to the specific recitations of Claims 10-15, they recite various ranges of the obvious “once-daily administration of diazoxide choline,” *i.e.*, 25 to 100 mg (Claim 10), 50 mg to 180 mg (Claim 11), 50 mg to 275 mg (Claim 12), 300 mg to 500 mg (Claim 13), 500 mg to 2000 mg (Claim 14); and 25 mg to 500 mg (Claim 15).

141. As explained above, the “once-daily administration of diazoxide choline” would have been obvious. Furthermore, Cowen teaches “the salt can be formulated for controlled release following 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 salt of the K_{ATP} channel openers provided in Formulae I - VIII.” EX1009, [0061], [00380].⁸

142. Thus, Cowen discloses the once-daily administration of diazoxide choline in an amount of 1 mg to 2,000 mg, which overlaps with the claimed ranges of 25 to 100 mg (Claims 4 and 10), 50 mg to 180 mg (Claims 5 and 11), 50 mg to 275 mg (Claims 6 and 12), 300 mg to 500 mg (Claims 7 and 13), 500 mg to 2,000 mg (Claims 8 and 14); and 25 mg to 500 mg (Claims 9 and 15).

143. Accordingly, the methods of Claims 4-15 would have been obvious.

D. Claim 16

144. The text of Claim 16 is provided as follows:

16. The method of claim 1, wherein the administration of diazoxide choline is initiated at a starting dose of

⁸ The generic Formula III in Cowen includes diazoxide. *Supra* at Section VII(D). As explained in this Declaration, use of the diazoxide choline salt would have been obvious to the POSA.

diazoxide choline and then titrated every two weeks to reach a maintenance dose of diazoxide choline.

145. At a high level, Claim 16 covers the well-known method of dose titration using a starting dose (to address adverse patient side effects) followed by dose titration every two weeks to reach another level referred to as a maintenance dose. *Supra* at Section VII(C) (“Dose Titration in Clinical Practice Was Well Known as of the Priority Date”). Indeed, using such dose titration to arrive at a maintenance (therapeutic) dose is common practice.

146. In any event, Cowen repeatedly teaches, for various disease states, that in order to reduce the adverse side effects known to occur with diazoxide, patients can be initiated at subtherapeutic doses and titrated up in a stepwise manner until a therapeutic dose is achieved:

In another embodiment, the frequency of adverse effects caused by treatment with a KATP channel opener selected from a salt of a compound of Formulae I - VIII⁹ is reduced using a pharmaceutically acceptable formulation of diazoxide or its derivatives that is administered to an subject in need thereof on a daily basis in which the first

⁹ The generic Formula III in Cowen includes diazoxide. *Supra* at Section VII(D). As explained in this Declaration, use of the diazoxide choline salt would have been obvious to the POSA.

dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached.

EX1009, [00478], [00448] (providing examples of adverse effects that can be reduced using titration to therapeutic dose), [0089], [00481], [00482], [00483], [00489], [00490].

147. Cowen clearly explains that the adverse effects of diazoxide are addressed by using an initiation or starting dose and then increasing the dose to a maintenance (therapeutic) dose. *Id.*, [0089] (“method of reducing the incidence of adverse effects from administration of a KATP channel opener . . . 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”), [00448] (“These reductions in frequency of adverse side effects are achieved by: (1) initiating dosing of subjects at subtherapeutic doses and in a step wise manner increasing the dose daily until the therapeutic dose is achieved”), [00478].

148. In providing a more specific example in the context of obesity or type 1 or type 2 diabetes with a salt of K_{ATP} channel opener to achieve a therapeutic dose (*i.e.*, maintenance dose), Cowen teaches:

In accordance with this method, the initial dose is chosen to provide for elevations in supine heart rate that on average are not greater than 5 beats per minute, followed by tolerization and a return to baseline heart rate by the time steady state circulating KATP channel opener levels are reached. This starting dose is preferably between 10 and 200 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide. Preferably, the KATP channel opener is diazoxide. The starting dose is given to the patient daily for days or a few weeks. In further embodiments, the method includes escalating the dose which is administered when after supine heart rates return to baseline. An initial escalating dose is established using the same criteria as the initial dose. The initial escalating dose is given to the patient daily for days or a few weeks. The increment in dose is preferentially 25 to 150 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide. Further rounds of this dose escalation would continue until the therapeutically effective dose is reached.

Id., [0077].

149. Thus, as Cowen teaches, the starting dose “preferably between 10 and 200 mg” of diazoxide, may be given to the patient daily “for days or a few weeks,” then escalated thereafter. *Id.* The “initial escalating dose” may thereafter be given

“for days or a few weeks.” *Id.* The rounds of dose escalation may continue until the therapeutically effective dose is reached. *Id.* Furthermore, Cowen would have taught the POSA that “the number of steps is 2 to 10 to reduce the incidence of adverse side effects.” *Id.*, [0089].

i. ***“wherein the administration of diazoxide choline is initiated at a starting dose of diazoxide choline”***

150. Turning to the limitations of Claim 16: as explained above with respect to my discussion of Claim 1 and Cowen, administration of diazoxide choline would have been obvious to the POSA.

151. It would have been obvious to the POSA to “initiate[] at a starting dose of diazoxide choline” based on the teachings of Cowen. For example, Cowen teaches a “starting dose is preferably between 10 and 200 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide. Preferably, the KATP channel opener is diazoxide. The starting dose is given to the patient daily for days or a few weeks.” EX1009, [0077], [00478] (“in which the first dose is known to be **subtherapeutic**”).

ii. ***“and then titrated every two weeks to reach a maintenance dose of diazoxide choline”***

152. As to “then titrat[ing] every two weeks to reach a maintenance dose of diazoxide choline,” this is also taught by Cowen.

153. This recitation has three parts, all of which are taught by Cowen: (1)

a titration (escalation) of the medication; (2) this titration occurs every two weeks and continues until (3) maintenance dose is reached.

154. As to the first part, i.e., the titration, this is taught in Cowen. Once the starting dose (*id.*, [0077]), which is subtherapeutic (*id.*, [00478]), is given to the patient:

[T]he method includes escalating the dose which is administered when after supine heart rates return to baseline. An initial escalating dose is established using the same criteria as the initial dose. The initial escalating dose is given to the patient daily for days or a few weeks. The increment in dose is preferentially 25 to 150 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide. Further rounds of this dose escalation would continue until the therapeutically effective dose is reached.

Id., [0077].

155. Thus, the POSA would understand that Cowen “initial escalating dose” is the dose that is titrated up. *See also id.*, [00478] (“daily dose is subsequently **increased** stepwise until the therapeutic dose is reached.”).

156. Turning the second part of this recitation: Claim 16 of the ’895 patent recites the titration (dose escalation) occurs “every two weeks to reach a maintenance dose,” whereas Cowen *teaches* titration “for days or a few weeks.”

The claimed titration escalation of “two weeks” falls within the range disclosed in Cowen, *i.e.*, “for days or a few weeks,” and therefore would have been obvious because it is nothing more than routine optimization of a parameter identified in the prior art. Moreover, as I explained above, it is common for physicians to utilize two weeks as a standard titration interval when titration is needed. *Supra* at ¶ 77.

157. Furthermore, the teachings of Cowen are not limited to a single step increase at the two-week mark; rather Cowen teaches the claimed “every two weeks to reach a maintenance dose.” As Cowen teaches, “[f]urther rounds of this dose escalation would continue until the therapeutically effective dose is reached.” *Id.*, [0077]. Elsewhere, Cowen would have taught the POSA that “the number of steps is 2 to 10 to reduce the incidence of adverse side effects.” EX1009, [0089]. In other words, Cowen teaches 2 to 10 rounds of increases. Therefore, titration “every two weeks” until a maintenance dose is reached would have been obvious and nothing more than an exercise in routine experimentation for the POSA to arrive at the maintenance dose.

158. The third part of this recitation *requires* a maintenance dose. This is taught in Cowen: “Further rounds of this dose escalation would continue **until the therapeutically effective dose is reached.**” EX1009, [0077], [00478] (“diazoxide or its derivatives that is administered to a subject 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.**”).

159. Any suggestion that Cowen paragraph [0077] is directed only to the use of diazoxide for treating *obesity* or type 1 or type 2 diabetes, and not PWS and/or hyperphagia, and so a POSA would not consider it misplaced. Cowen *expressly* associates obesity, with “Prader-Willi Syndrome.” *Id.*, [0093]. And elsewhere, Cowen makes clear that the use of dose titration to reduce diazoxide’s adverse effects is not confined to the treatment of obesity or type 1 or type 2 diabetes, or for that matter any particular disease state. *Id.*, [00478], [00448], [0089], [00481], [00482], [00483], [00489], [00490].

160. The POSA would conclude from the teachings of Cowen that the dose escalation method successfully used for obesity or type 1 or type 2 diabetes is safe and effective. Thus, a POSA would logically apply this same dose escalation method to any disease state taught in Cowen, including PWS and/or hyperphagia, as referenced at [0087] with a reasonable expectation of success.

161. Thus, not only does Cowen disclose to a POSA a multidose regime with a lower starting dose, followed by dose titration until a maintenance dose is reached, *it does so with diazoxide choline*. *Id.*, [0077], [00478]. And as explained above, use of diazoxide choline would have been obvious in light of the teachings of Cowen.

162. For all the above reasons, Claim 16 would have been obvious to a POSA.

E. Claims 17-18 (Starting Dose Claims)

163. Claims 17-18 depend from Claim 16. Claim 16 has been addressed above. Claims 17-18 recite “that the starting dose of diazoxide choline is between 25-100 mg” (Claim 17) and “the starting dose of diazoxide choline is between 50-180 mg” (Claim 18).

164. Cowen teaches in the context of its multidose regimen: “This **starting dose is preferably between 10 and 200 mg of KATP channel opener** or the equivalent based on relative bioavailability and potency compared to diazoxide. Preferably, the KATP channel opener is **diazoxide**.” EX1009, [0077]. And as explained above, use of diazoxide choline would have been obvious in light of the teachings of Cowen. The starting doses taught by Cowen overlap with the claimed starting doses of Claims 17 and 18.

F. Claims 19-25 (Maintenance Dose Claims)

165. Claims 19 and 24-25 depend from Claim 17 (which has been addressed above).

166. Claims 19 and 24-25 are then directed to the subsequent maintenance dose from Claim 17’s starting doses, and, importantly, in each case Claims 19 and 24-25 include a range of diazoxide choline that is ***higher*** than

Claim 17's starting dose of **25-100 mg**:

Claim 19	"wherein the maintenance dose of diazoxide choline is between 100-200 mg of diazoxide choline"
Claim 24	"wherein the maintenance dose of diazoxide choline is between 25-250 mg of diazoxide choline"
Claim 25	"wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline."

Claims 20-23 depend from Claim 18 (which has been addressed above). Claims 20-23 are then directed to the subsequent maintenance dose from Claim 18's starting doses, and, importantly, in each case Claims 20-23 include a range of diazoxide choline that is *higher* than Claim 17's starting dose of **50-180 mg**:

Claim 20	"wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline"
Claim 21	"wherein the maintenance dose of diazoxide choline is between 300-500 mg of diazoxide choline"
Claim 22	"wherein the maintenance dose of diazoxide choline is between 500-2000 mg of diazoxide choline"; and
Claim 23	"wherein the maintenance dose of diazoxide choline is between 100-500 mg of diazoxide choline."

167. Cowen teaches a multidose regimen, and, like Claims 19-25, Cowen teaches the maintenance dose will be higher than the starting dose when using diazoxide choline. EX1009, [0077] ("The initial **escalating** dose is given to the patient daily for days or a few weeks. The increment in dose is preferentially 25 to 150 mg of KATP channel opener . . . Further rounds of this dose escalation would continue until the therapeutically effective dose is reached."), [00478] ("diazoxide or its derivatives that is administered to a subject 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”). And as explained above, use of diazoxide choline would have been obvious in light of the teachings of Cowen.

168. This only leaves the amounts recited in Claims 19-25 of the '895 patent. And in this regard, Cowen teaches the POSA some important points.

169. First, the dose may be escalated (titrated up) in increments of “preferentially 25 to 150 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide.” *Id.*, [0077].

170. Next, it is not limited to a single stepwise increase, but “[f]urther rounds of this dose escalation would continue until the therapeutically effective dose is reached.” *Id.* And along that same vein, Cowen teaching that the “rounds of this dose escalation would continue until the therapeutically effective dose is reached” expressly tell the POSA to use routine experimentation. *Id.* EX1013, 52 (“In the dose titration of any patient the objective is, in conceptual terms, to attain and maintain a blood level that exceeds the minimum effective level required for response but does not exceed the minimum toxic (side-effect) level.”). Elsewhere, Cowen would have taught the POSA that “the number of steps is 2 to 10 to reduce the incidence of adverse side effects.” EX1009, [0089]. In other words, Cowen teaches 2 to 10 rounds of increases.

171. The nature of routine experimentation would involve dose titration based on factors such as patient response, tolerability and the physician's professional judgement. As explained above, dose titration is a standard medical approach where a physician starts a patient on a low dose of a medication and gradually adjusts (usually increases) the dose over time to reach the optimal therapeutic effect while minimizing side effects. A physician typically begins therapy at a lower-than-therapeutic dose because it allows the patient's body to adapt to the medication, reduces early or dose dependent side effects and provides a safe baseline to evaluate tolerance. If the patient tolerates the medication, the physician then increases the dose incrementally until the maintenance dose is reached. The maintenance dose is the dose that: provides the desired therapeutic benefit and once the patient reaches this dose, upward titration stops and the patient remains at this stable dose. *Supra* at Section VII(C).

172. With this POSA's knowledge of routine dose titration beginning with Cowen's starting dose of "between 10 and 200 mg of KATP channel opener", and then using Cowen's stepwise increase of "2 to 10" rounds to arrive at a therapeutic (maintenance) dose, increasing the medication by two rounds in escalation increments of "25 to 150 mg of KATP channel opener", as taught by the prior art, would have resulted in the POSA arriving the claimed maintenance amounts:

Starting Dose	First Round	Second Round	Third Round
Lower value 10 mg	35 mg-160 mg	60 mg-310 mg	85-460 mg
Upper value 200 mg	225 mg-350 mg	250 mg-500 mg	275-650 mg

173. As the chart above shows, two rounds would have resulted in a range of 60 mg to 500 mg of diazoxide choline; three rounds would have resulted in the range of 85 mg to 650 mg, which are the claimed ranges recited in Claims 19-25.¹⁰ Determining the therapeutic (maintenance dose) is what a physician would do as part of their routine practice based on factors such patient response, tolerability and the physician's professional judgement.

174. Furthermore, the POSA would have known from the teaching of Cowen that these amounts would have been safe and effective for the patient providing the POSA a reasonable expectation of success: "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 salt of the K_{ATP} channel openers

¹⁰ Claim 19 (100-200 mg); Claim 20 (200-300 mg); Claim 21 (300-500 mg); Claim 22 (500-2000 mg); Claim 23 (100-500 mg); Claim 24 (25-250 mg); Claim 25 (200-300 mg).

provided in Formulae I - VIII.” EX1009, [0061], [00380].¹¹

175. Therefore, Claims 19-25 would have been obvious.

G. Claim 26

176. Claim 26 depends from Claim 1 and recites, “wherein the pharmaceutical formulation is administered orally.” Cowen discloses pharmaceutical formulations comprising diazoxide choline for oral administration. EX1009, [00369], [00380], [00596].

177. Accordingly, it would have been obvious for a POSA to administer the claimed pharmaceutical formulation orally, with a reasonable expectation of success.

IX. GROUND 2: CLAIMS 1-26 ARE OBVIOUS OVER COWEN AND COTTER

178. In my opinion, Claims 1-26 of the '895 patent would have been obvious in light of the teachings of Cowen and Cotter. The reasons for my conclusion and my analysis are presented below.

A. Claim 1

179. The text of independent Claim 1 is provided as follows:

¹¹ The generic Formula III in Cowen includes diazoxide. *Supra* at Section VII(D). As explained in this Declaration, use of the diazoxide choline salt would have been obvious to the POSA.

1. A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising administering to said subject once per day a pharmaceutical formulation comprising an effective amount of diazoxide choline, wherein administration reduces hyperphagia and one or more food related behaviors in the subject.

i. ***“A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising”***

180. As shown in the chart below, Cowen and Cotter teaches “a method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS)”:

Claim	Exemplary Citations
1. A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising administering	Cowen EX1009, [0087] (“Further provided is a method to treat obesity, or hyperphagia in a Prader-Willi Syndrome patient”); <i>see also id.</i>, [0093] (“Prader-Willi Syndrome”); <i>id.</i>, [00413] (same); <i>id.</i>, [00449] (same); <i>id.</i>, [0069] (“inhibition of hyperphagia”); <i>id.</i>, [0070] (same); <i>id.</i>, [0071] (same); <i>id.</i>, [0087] (“hyperphagia”); <i>id.</i>, [0093] (same); <i>id.</i>, [0093] (same). Cotter Title: “METHOD OF TREATING PRADER WILLI SYNDROME AND CONDITIONS ASSOCIATED WITH LOW BASAL METABOLIC RATE OR HYPERPHAGIA” Abstract: “The invention also relates to treating PWS based on the PWS nutritional phase of a patient, to prevent the patient’s PWS nutritional

	phase from progressing or shift the patient's PWS nutritional phase back to an earlier phase. The invention further relates to treating PWS, and conditions associated with low basal metabolic rate or hyperphagia.” EX1008, [0002] (“Clinical features of PWS include hypotonia and poor feeding in infancy which almost always requires some type of assisted feeding for a period of time, followed by hyperphagia as the child ages.”). <i>Id.</i>, [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.”). <i>Id.</i>, [0010] (“Surprisingly, the inventor has also discovered that PWS and conditions associated with low basal metabolic rate or hyperphagia can be treated by modulating the dose of KATP channel opener based on a patient's blood ketone level and/or diet.”). <i>Id.</i>, Claim 14 (“A method for treating a disease or condition selected from the group consisting of Prader-Willi Syndrome, a condition associated with low basal metabolic rate, and a condition associated with hyperphagia, comprising administering a K_{ATP} channel opener to a patient in need thereof.”). <i>See also id.</i>, [0057] (“inhibit hyperphagia”), [0073].
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181. A POSA would have been motivated to combine the teachings of Cowen with those of Cotter for several reasons. Cowen and Cotter operate

squarely within the same technical field: pharmaceutical compositions comprising KATP channel openers, specifically diazoxide and its salts (including diazoxide choline), for treating metabolic and neuroendocrine disorders. EX1008, [0001] (“This invention relates to treating Prader-Willi Syndrome (PWS) and conditions affecting basal metabolic rate using a KATP channel opener.”); EX1009, [0087] (“Further provided is a method to treat obesity, or hyperphagia in a Prader-Willi Syndrome patient”). A POSA working with diazoxide choline would consult both references, as they form part of the same body of prior art relating to KATP channel opener salts.

182. Both references also disclose the same similar mechanism of action by which diazoxide and its salts exert therapeutic effects. For example, Cowen teaches that a KATP channel openers “inhibit[] glucose induced release of insulin following administration of the compound *in vivo*.” EX1009, [00204]. Likewise, Cotter explains that KATP channel openers “(a) inhibit fasting insulin secretion, (b) inhibit stimulated insulin secretion” EX1008, [0058]. A POSA would understand that both references teach the same biological pathways motivating them to look to both for guidance on using diazoxide choline therapeutically.

183. Finally, as discussed below (*infra* ¶185), Cowen provides detailed formulation and synthesis information about diazoxide choline including its synthesis, salt characterization, polymorphic forms, controlled release tablet

formulations, excipient compatibility, dissolution profiles, stability data, and human clinical pharmacokinetic and safety data. Cotter does not provide this same information. Therefore, a POSA would have naturally consulted a reference like Cowen that provides formulation and synthetic information for a pharmaceutical active of interest in conjunction with Cotter.

184. For all the above reasons, given the closely aligned teachings of Cowen and Cotter, with the references building on the other, the POSA would have had a motivation to combine the references. Furthermore, these same complementary teachings would have given the POSA a reasonable expectation of success of combining the references.

ii. ***“administering to said subject once per day a pharmaceutical formulation comprising an effective amount of diazoxide choline,”***

1) The use of diazoxide choline would have been obvious

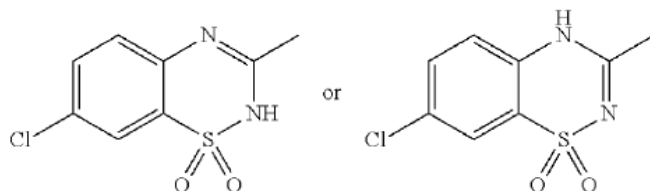
185. As explained in Ground 1, diazoxide choline would have stood out to the POSA from the teachings of Cowen. For example, Cowen expressly discusses the favorable properties of diazoxide choline over the free base. EX1009, [00750]. Cowen then provides numerous examples and formulations highlighting the use of diazoxide choline including: (1) extensive pharmaceutical formulation information using diazoxide choline (*id.*, at [0596]-[00603]); (2) dissolution studies (*id.*, [00604]-[00607]); (3) excipient compatibility studies and stability studies (*id.*,

[00608]-[00615]); (4) its preparation, synthesis and characterization (*id.*, [00623]-[00634], [00680]-[00706]); (5) clinical information for the treatment of different human disorders (*id.*, [00749]-[00760], [00764], [00766], [00770], [00772], [00778], [00783]-[0084]); and (6) pharmacokinetic data (*id.*, [00763], [00769]). And importantly, Cowen only specifically claims “diazoxide choline” immediately drawing the POSA’s attention to this specific compound. EX1009, Claims 9, 21, 32, 48, 53, 57, 62, 63, & 70. Simply put, diazoxide choline is the most highlighted active pharmaceutical agent in Cowen.

186. The POSA would also have been aware of the teachings of Cotter which (like Cowen) teaches the use of diazoxide and other salts for the treatment of hyperphagia in a Prader-Willi Syndrome patient. In other words, both references teach using the same API for treating the same disease states. *Supra* at Sections VII(D) and VII(E).

187. Cotter teaches generic Formulas I - VIII for the KATP channel opener (EX1008, [0074]), i.e., the active pharmaceutical ingredient, but significantly, when depicting an actual chemical species, it only depicts diazoxide (free base) which would have immediately drawn the attention of the POSA:

[0135] The KATP channel opener may also have the formula 7-chloro-3-methyl-2-H-1,2,4-benzothiadiazine 1,1 dioxide (shown below with its tautomer) with the empirical formula C₈H₇ClN₂O₂S and a molecular weight of 230.7.



[0136] The KATP channel opener may also be a salt of one of the compounds described by Formulae I-VIII and may have at least one, of the following properties: (1) opening SURx/Kir6.y potassium channels, in which x=1, 2A or 2B and y=1 or 2; (2) binding to the SURx subunit of KATP channels; and (3) inhibiting glucose induced release of insulin following administration of the compound in vivo.

EX1008, [0135]-[0136]. As explained above, the POSA would have been aware of the structure of diazoxide. EX1018; *supra* at ¶¶ 70-72, 99-101.

188. As shown in Cotter at [0135], the empirical formula of the depicted compound is “C₈H₇ClN₂O₂S”. *See also* EX1009, [0007] (“Diazoxide, [has] the formula 7-chloro-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (empirical formula C₈H₇ClN₂O₂S)”). As explained in Ground 1, the ’895 patent explains diazoxide (free base) [] and it has the same empirical chemical formula. EX1001, 2:30-33, 17:1-3; see also EX1018; *supra* at ¶¶ 70-72, 99-101.

189. Cotter also teaches diazoxide choline. EX1008, [00137] (“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**.”). As explained above, Formula III of Cotter includes diazoxide. *Supra* at Section VII(D). Furthermore, as Cotter explains, Formula III can be the choline salt:

The KATP channel opener may also be a structural variant or bioequivalent of a compound defined by **Formulae I-VIII**, such as a derivative, **salt**, prodrug or isomer thereof . . . 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.

EX1008, [0137], [0136] (“The KATP channel opener may also be a **salt** of one of the compounds described by Formulae I-VIII.”).

190. Therefore, Cotter teaches diazoxide (free base) and a limited number of its corresponding salts: sodium, potassium, **choline** or hexamethyl hexamethylene diammonium. And as I provided above, from the teachings of the prior art (including Cowen) diazoxide choline would have stood out to the POSA.

191. As such, in view of the teachings of Cowen and Cotter, a POSA would have been motivated to select a pharmaceutical formulation comprising diazoxide choline with a reasonable expectation of success.

iii. “administering to said subject once per day a pharmaceutical formulation comprising an effective amount”

192. Both Cowen and Cotter disclose the claimed pharmaceutical formulations. EX1008, [0142]-[0147] (disclosing pharmaceutical compositions); EX1009, [00380], [00596]-[00603] (providing extensive pharmaceutical formulation information using diazoxide choline).

193. Furthermore, once-daily administration is always preferable since it increases patient compliance, and this is taught in Cowen and Cotter. EX1009 (Cowen), [0087] (treating “hyperphagia in a Prader-Willi Syndrome patient, comprising the administration of an effective amount of a KATP channel opener . . . In a preferred embodiment, administration is no more than two times per 24 hours, **or once per 24 hours.**”), [00766] (“A controlled clinical study was conducted to evaluate the potential for **Diazoxide Choline** Controlled-Release Tablets administered **once daily**”), [00411] (formulations of KATP channel openers selected from a salt of a compound of Formulae I - VIII¹² administered as a **single dose**); Claims 31 (“the formulation is administered once per 24 hours.”), 52, 59, 62 & 65; EX1008 (Cotter), [0138] (teaching “single administration”), [0141] (“The composition may be administered **1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12** times per day.”)

194. Finally, the limitation also recites “an effective amount” of the diazoxide choline pharmaceutical composition. The ’895 patent provides a definition of an “effective amount” (EX1001, 15:32-36). Cowen and Cotter teach

¹² The generic Formula III in Cowen and Cotter includes diazoxide. *Supra* at Section VII(D) & (E). As explained in this Declaration, use of the diazoxide choline salt would have been obvious to the POSA.

the same thing. EX1008, [0140] (“This invention also relates to a method of treatment comprising administering a composition comprising a K_{ATP} channel opener, which may be a **therapeutically effective amount.**”); EX1009, [00087] (treating “hyperphagia in a Prader-Willi Syndrome patient, comprising the administration of an effective amount of a KATP channel opener”).

iv. *“wherein administration reduces hyperphagia and one or more food related behaviors in the subject.”*

195. The remaining limitation of Claim 1 is “wherein administration reduces hyperphagia and one or more food related behaviors in the subject.”

196. Both Cowen and Cotter disclose that administering a pharmaceutical formulation diazoxide choline (*i.e.*, the K_{ATP} channel opener) reduces hyperphagia. EX1008, [0001] (“The K_{ATP} channel opener dosage for treating PWS or conditions associated with low basal metabolic rate or hyperphagia, such as obesity, may be modulated according to a patient’s blood ketone level or diet.”), [0057] (“The K_{ATP} channel opener may . . . inhibit hyperphagia”); EX1009, [0070] (“pharmaceutical formulation of a KATP channel opener selected from the salts of the compounds of Formulae I – VIII¹³ wherein

¹³ The generic Formula III in Cowen and Cotter includes diazoxide. *Supra* at Section VII(D) & (E). As explained in this Declaration, use of the diazoxide choline salt would have been obvious to the POSA.

administration to an obese, overweight or obesity prone subject results in at **least inhibition of hyperphagia** for about 18 hours.”), [0071] (“inhibition of hyperphagia for about 24 hours”), [0087] (“[f]urther provided is a method to treat obesity, or hyperphagia in a Prader-Willi Syndrome patient,”), [0093] (“method of treating diseases characterized by . . . hyperphagia”), [00411] (“formulations of KATP channel openers selected from a salt of a compound of Formulae I - VIII 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.”), [00439] (“(19) **reduced rates of hyperphagia**”), [00442] (“(26) reduced rates of hyperphagia”), [00443] (“(22) reduced rates of hyperphagia”), [00444] (“(22) reduced rates of hyperphagia”).

197. Turning to the limitation of “*reduces . . . one or more food related behaviors in the subject*”: as explained in Ground 1, the ’895 patent explains what it means by “food related behaviors.” EX1001, 20:14-22.

198. As explained above in Ground 1, Cowen teaches this limitation either inherently or expressly (*supra* at Section VIII(A)(v)) but to the extent there is any disagreement over this point, then as explained above the POSA would have been aware of Cotter and given it is in the same field as Cowen using the same API for the treatment of the same disorders, the POSA would have been motivated to combine the references with a reasonable expectation of success.

199. Turning to the teaching of Cotter: Cotter teaches that “the patient may be in PWS nutritional phase 0, 1a, 1b, 2a, 2b, 3, or 4.” EX1008, [0007].

Cotter explains that Phase 3 begins at “8 years”¹⁴ and is hyperphagia:

Phase 3: Hyperphagic, rarely feels full (8 years to adulthood)	Constantly thinking about food
	While eating one meal they are already thinking about the next meal
	Will awaken from sleep early thinking about food
	Will continue eating if portion size is not limited
	Rarely (truly) feels full
	Will steal food or money to pay for food
	Can eat food from garbage and other unsavory/inedible sources (e.g., dog food, frozen food, crayons, etc.)
	Typically are not truthful about what they have eaten (i.e. amount and types of food)
	Will gain considerable amount of weight over a short period of time if not supervised (e.g., some individuals are known to have gained up to 20 pounds in one weekend)
	Food typically needs to be locked up. Frequently the child will ask the parent to lock the food if the parent has forgotten
	Will break into neighbors’ houses for food
	Temper tantrums and “meltdowns” frequently related to food
	Needs to be placed on a diet that is approximately 50–70% of the RDA to maintain a healthy weight

200. As the Cotter table above shows, hyperphagia (Phase 3) is characterized by related food behaviors in the subject such as: constantly thinking about food, thinking about the next meal while eating, waking from sleep early thinking about food, stealing food or money to pay for food, eating food from the garbage, and the like. *Id.* These are the same “food related behaviors” discussed in the ’895 patent. EX1001, 20:14-22.

¹⁴ The ’895 patent also explains that hyperphagia begins at 8 years old. EX1001, 20:14-22.

201. Claim 1 of the '895 patent specifically requires that administration of diazoxide choline “**reduces** . . . [the] one or more food related behaviors in the subject.” This is taught by Cotter because Cotter taught that the patient “**shifted back**” to a pre-hyperphagic phase:

Further provided herein is a method for treating Prader-Willi Syndrome which may comprise administering a K_{ATP} channel opener to a patient in need thereof. The patient may be in PWS nutritional phase 0, 1a, 1b, 2a, 2b, 3, or 4. The patient's PWS nutritional phase may be prevented from progressing to a later phase. . . The patient's PWS nutritional phase may be shifted back to an earlier PWS nutritional phase. **The patient may be in PWS nutritional phase 3 or 4, and the patient's PWS nutritional phase may be shifted back to phase 1a, 1b, 2a, or 2b.**

EX1008, [0007].

202. In other words, according to Cotter, if the PWS patient is hyperphagic (*i.e.*, in Phase 3), administration of K_{ATP} channel opener (which would include a pharmaceutical formulation of diazoxide choline) results in the PWS patient being “**shifted back**” to an earlier phase, *i.e.*, “phase 1a, 1b, 2a, or 2b,” *i.e.*, before hyperphagia (Phase 3).

203. Therefore, it would have been obvious to a POSA, in view of the teachings of Cowen and Cotter, that administration of a pharmaceutical

formulation comprising diazoxide choline results in the reduction of hyperphagia and one or more food-related behaviors in the subject.

B. Claims 2-3

204. Claims 2 and 3 depend from Claim 1 and recite “wherein the diazoxide choline is administered for at least 10 weeks” (Claim 2) and “wherein the diazoxide choline is administered for one or more years.” (Claim 3). These administration periods are taught by Cowen and Cotter.

205. For example, Cowen, as explained in Ground 1, teaches “prolonged administration” (EX1009, Abstract) with specific administration periods ranging from at least 7 days to 12 months:

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)**.

EX1009, [00234], [00735]-[00736] (“Formulations of salts of any of the compounds of Formulae I - IV¹⁵ prepared as described herein can be tested for efficacy in obese

¹⁵ In both Cowen and Cotter, generic Formula III includes diazoxide. *Supra* at Section VII(D). For the reasons explained in this Declaration, use of the choline salt would have been obvious to the POSA.

humans . . . [s]ubjects are dosed daily for **up to 12 months.**”), [00741] (“up to 12 months”). Even if paragraphs [00735]-[00736] refer to a study dealing with the “[t]reatment of obesity in humans,” as Cowen makes clear, this would include patients suffering from Prader-Willi Syndrome. *Id.*, [0093] (“treating diseases characterized by obesity . . . including (a) Prader-Willi Syndrome”). Thus, the teachings of Cowen necessarily include administering for least 10 weeks and more than a year, *i.e.*, 52 weeks.

206. Next, turning to Cotter: Cotter discloses the administration of a pharmaceutical formulation comprising diazoxide being administered to a PWS patient “for a period of 56 weeks.” EX1008, [0150]. That necessarily means that the formulation was administered for least 10 weeks and more than a year, *i.e.*, 52 weeks.

207. Thus, based on the teachings of Cowen and Cotter, use of diazoxide choline would have been obvious, and administration “for at least 10 weeks” (Claim 2) or “for one or more years” would have overlapped with the administration periods taught in Cowen and Cotter.

208. Accordingly, the methods of Claims 2-3 would have been obvious.

C. Claims 4-15

209. Claims 4-15 depend from Claim 1. As explained above, Claim 1 would have been obvious. As to the specific recitations of Claims 4-15, they

recite various ranges of the obvious “once-daily administration of diazoxide choline,” *i.e.*, 25 to 100 mg (Claim 4), 50 mg to 180 mg (Claim 5), 50 mg to 275 mg (Claim 6), 300 mg to 500 mg (Claim 7), 500 mg to 2,000 mg (Claim 8); and 25 mg to 500 mg (Claim 9).

210. Turning to Claims 10-15, these claims depend from Claim 3. As explained above, Claim 3 would have been obvious. As to the specific recitations of Claims 10-15, they recite various ranges of the obvious “once-daily administration of diazoxide choline,” *i.e.*, 25 to 100 mg (Claim 10), 50 mg to 180 mg (Claim 11), 50 mg to 275 mg (Claim 12), 300 mg to 500 mg (Claim 13), 500 mg to 2,000 mg (Claim 14); and 25 mg to 500 mg (Claim 15).

211. As explained above, the claimed “once-daily administration of diazoxide choline” would have been obvious, as would have recited ranges in view of Cowen and/or Cotter. Cowen teaches, “the salt can be formulated for controlled release following 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 salt of the KATP channel openers provided in

Formulae I - VIII.”¹⁶ EX1009, [0061], [00380].

212. Likewise, Cotter teaches “[t]he dose of the K_{ATP} channel opener may be at least 1, 5, 10, 15, 20, 30, 40, 50, 100, 200, 300, 400, 500, 1000, or 2000 mg.” EX1008, [0138].

213. Thus, Cowen and Cotter would have rendered obvious a once-daily administration of diazoxide choline in amounts that overlaps with the claimed ranges of 25 to 100 mg (Claims 4 and 10), 50 mg to 180 mg (Claims 5 and 11), 50 mg to 275 mg (Claims 6 and 12), 300 mg to 500 mg (Claims 7 and 13), 500 mg to 2,000 mg (Claims 8 and 14); and 25 mg to 500 mg (Claims 9 and 15).

214. Accordingly, the methods of Claims 4-15 would have been obvious.

D. Claim 16

215. The text of Claim 16 is provided as follows:

16. The method of claim 1, wherein the administration of diazoxide choline is initiated at a starting dose of diazoxide choline and then titrated every two weeks to reach a maintenance dose of diazoxide choline.

216. At a high level, Claim 16 covers the well-known method and

¹⁶ Generic Formula III in Cowen and Cotter includes diazoxide. *Supra* at Section VII(D) & (E). As explained in this Declaration, use of the diazoxide choline salt would have been obvious to the POSA.

common practice method of dose titration of using a starting dose (to address adverse patient side effects) followed by dose titration every two weeks to reach another level referred to as a maintenance dose. *Supra* at Section VII(C).

217. As explained above in Ground 1, Cowen repeatedly teaches, for various disease states, that in order to reduce the adverse side effects known to occur with diazoxide, patients can be initiated at subtherapeutic doses and titrated up in a stepwise manner, until a therapeutic dose is achieved. EX1009, [0089], [00448] (providing examples of adverse effects that can be reduced using titration to therapeutic dose), [00478], [00481]-[00483], [00489]-[00490]. To a POSA, Cowen clearly explains that the adverse effects of diazoxide are addressed by using initiation or starting dose and then increasing the dose to a maintenance (therapeutic) dose. *Id.*

218. Similarly, a POSA would recognize that Cotter also teaches the use of a lower starting dose followed by titration up to a maintenance dose. EX1008, [0149] (“The infant was in PWS nutritional phase 1a transitioning to phase 1b was started at 0.5 mg/kg BID of diazoxide at eight months of age, increasing to 1 mg/kg BID”). These teachings clearly demonstrate the routine nature of dose titration in the prior art.

219. Moreover, Cowen teaches more specific examples in the context of obesity or type 1 or type 2 diabetes with a salt of K_{ATP} channel opener to achieve

a therapeutic dose (*i.e.*, maintenance dose. EX1009, [0077]). Thus, as Cowen teaches, the starting dose “preferably between 10 and 200 mg” of diazoxide may be given to the patient daily “for days or a few weeks,” then escalated thereafter. *Id.* The “initial escalating dose” may thereafter be given “for days or a few weeks.” *Id.* The rounds of dose escalation may continue until the therapeutically effective dose is reached. *Id.*

i. “wherein the administration of diazoxide choline is initiated at a starting dose of diazoxide choline”

220. Turning to the limitations of Claim 16: as explained above with respect to my analysis of Claim 1, the administration of diazoxide choline would have been obvious to the POSA.

221. It would have been obvious to the POSA to “initiate[] at a starting dose of diazoxide choline” based on the teachings of Cowen. For example, Cowen teaches a “starting dose is preferably between 10 and 200 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide. Preferably, the KATP channel opener is diazoxide. The starting dose is given to the patient daily for days or a few weeks.” EX1009, [0077], [00478] (“in which the first dose is known to be **subtherapeutic**”).

ii. “and then titrated every two weeks to reach a maintenance dose of diazoxide choline”

222. As explained above, use of diazoxide choline would have been

obvious. As to “then titrat[ing] every two weeks to reach a maintenance dose of diazoxide choline,” this is also taught by Cowen. This recitation has three parts, all of which are taught by Cowen: (1) a titration (escalation) of the medication; (2) this titration occurs every two weeks and continues until (3) maintenance dose is reached.

223. As to the first part, *i.e.*, the titration, this is taught in Cowen. Once the starting dose (*id.*, [0077]), which is “subtherapeutic” (*id.*, [00478]), is given to the patient:

[T]he method includes escalating the dose which is administered when after supine heart rates return to baseline. An initial escalating dose is established using the same criteria as the initial dose. The initial escalating dose is given to the patient daily for days or a few weeks. The increment in dose is preferentially 25 to 150 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide. Further rounds of this dose escalation would continue until the therapeutically effective dose is reached.

Id., [0077].

224. Thus, the POSA would understand that Cowen “initial escalating dose” is the dose that is titrated up. *See also id.*, [00478] (“daily dose is subsequently increased stepwise until the therapeutic dose is reached.”).

225. Turning the second part of this recitation: Claim 16 of the '895 patent recites the titration (dose escalation) occurs “every two weeks to reach a maintenance dose,” whereas Cowen teaches titration “for days or a few weeks.” The claimed titration escalation of “two weeks” falls within the range disclosed in Cowen, *i.e.*, “for days or a few weeks” and therefore would have been obvious because it is nothing more than routine optimization of a parameter identified in the prior art. Moreover, as I explained above, it is common for physicians to utilize two weeks as a standard titration interval when titration is needed. *Supra* at ¶ 77.

226. Furthermore, the teachings of Cowen are not limited to a single step increase at the two-week mark, rather Cowen teaches the claimed “every two weeks to reach a maintenance dose.” As Cowen teaches “[f]urther rounds of this dose escalation would continue until the therapeutically effective dose is reached.” EX1009, [0077]. Elsewhere, Cowen would have taught the POSA that “the number of steps is 2 to 10 to reduce the incidence of adverse side effects.” *Id.*, [0089]. In other words, Cowen teaches 2 to 10 rounds of increases. Therefore, titration “every two weeks” until a maintenance dose is reached would have been obvious and nothing more than an exercise in routine experimentation for the POSA to arrive at the maintenance dose.

227. The third part of this recitation requires a maintenance dose. This is

taught in Cowen: “Further rounds of this dose escalation would continue **until the therapeutically effective dose is reached.**” EX1009, [0077], [00478] (“diazoxide or its derivatives that is administered to a subject 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.**”).

228. As explained in Ground 1, I previously addressed why any position suggested that Cowen paragraph [0077] is directed only to the use of diazoxide for treating obesity or type 1 or type 2 diabetes, and not PWS and/or hyperphagia, is misplaced. *Supra* at ¶¶ 159-61.

229. Given it would have been obvious to a POSA to use diazoxide choline, for all the above reasons, Claim 16 would have been obvious to a POSA.

E. Claims 17-18 (Starting Dose Claims)

230. Claims 17-18 depend from Claim 16. Claim 16 has been addressed above. Claims 17-18 recite “that the starting dose of diazoxide choline is between 25-100 mg” (Claim 17) and “the starting dose of diazoxide choline is between 50-180 mg” (Claim 18).

231. As explained above, use of diazoxide choline would have been obvious. Cowen teaches in the context of its multidose regimen: “This **starting dose is preferably between 10 and 200 mg of KATP channel opener** or the equivalent based on relative bioavailability and potency compared to diazoxide.

Preferably, the KATP channel opener is **diazoxide**.” EX1009, [0077]. The starting doses taught by Cowen overlap with the claimed starting doses of Claims 17 and 18.

232. Therefore, Claims 17 and 18 would have been obvious.

F. Claims 19-25 (Maintenance Dose Claims)

233. Claims 19 and 24-25 depend from Claim 17 (which has been addressed above).

234. Claims 19 and 24-25 are then directed to the subsequent maintenance dose from Claim 17’s starting doses, and, importantly, in each case Claims 19 and 24-25 include a range of diazoxide choline that is *higher* than Claim 17’s starting dose of **25-100 mg**:

Claim 19	“wherein the maintenance dose of diazoxide choline is between 100-200 mg of diazoxide choline”
Claim 24	“wherein the maintenance dose of diazoxide choline is between 25-250 mg of diazoxide choline”
Claim 25	“wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline.”

235. Claims 20-23 depend from Claim 18 (which has been addressed above). Claims 20-23 are then directed to the subsequent maintenance dose from Claim 18’s starting doses, and, importantly, in each case Claims 20-23 include a range of diazoxide choline that is *higher* than Claim 17’s starting dose of **50-180 mg**:

Claim 20	“wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline”
Claim 21	“wherein the maintenance dose of diazoxide choline is between 300-500 mg of diazoxide choline”
Claim 22	“wherein the maintenance dose of diazoxide choline is between 500-2000 mg of diazoxide choline”; and
Claim 23	“wherein the maintenance dose of diazoxide choline is between 100-500 mg of diazoxide choline.”

236. As explained above, use of diazoxide choline would have been obvious. Cowen teaches a multidose regimen, and like Claims 19-25, Cowen teaches the maintenance dose will be higher than the starting dose when using diazoxide choline. EX1009, [0077] (“The initial **escalating** dose is given to the patient daily for days or a few weeks. The increment in dose is preferentially 25 to 150 mg of KATP channel opener . . . Further rounds of this dose escalation would continue until the therapeutically effective dose is reached.”), [00478] (“diazoxide or its derivatives that is administered to a subject 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”).

237. This only leaves the amounts recited in Claims 19-25 of the '895 patent. And in this regard, Cowen teaches the POSA some important points.

238. First, the dose may be escalated (titrated up) in increments of “preferentially 25 to 150 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide.” *Id.*, [0077].

239. Next, it is not limited to single stepwise increase but “[f]urther

rounds of this dose escalation would continue until the therapeutically effective dose is reached.” *Id.* And along that same vein, Cowen teaching that the “rounds of this dose escalation would continue until the therapeutically effective dose is reached” expressly tell the POSA to use routine experimentation. *Id.* Elsewhere, Cowen would have taught the POSA that “the number of steps is 2 to 10 to reduce the incidence of adverse side effects.” *Id.*, [0089]. In other words, Cowen teaches 2 to 10 rounds of increases.

240. With the POSA’s knowledge of routine dose titration, beginning with Cowen’s starting dose of “between 10 and 200 mg of KATP channel opener”, and then using Cowen’s stepwise increases of “2 to 10” rounds to arrive at a therapeutic (maintenance) dose, increasing the medication by two rounds in escalation increments of “25 to 150 mg of KATP channel opener” as taught by the prior art would have resulted in the POSA arriving at the claimed maintenance amounts:

Starting Dose	First Round	Second Round	Third Round
Lower value 10 mg	35 mg-160 mg	60 mg-310 mg	85-460 mg
Upper value 200 mg	225 mg-350 mg	250 mg-500 mg	275-650 mg

241. As the chart above shows, two rounds would have resulted in a range of 60 mg to 500 mg of diazoxide choline; three rounds would have resulted in the range of 85 mg to 650 mg, which are the claimed ranges recited in Claims 19-25. Determining the therapeutic (maintenance dose) is what a physician would do as

part of their routine practice based on factors such patient response, tolerability and the physician's professional judgement.

242. Furthermore, the POSA would have known from the teaching of Cowen or Cotter that these amounts would have been safe and effective for the patient, providing the POSA a reasonable expectation of success: "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 2,000 mg of the salt of the K_{ATP} channel openers provided in Formulae I - VIII." EX1009, [0061], [00380]¹⁷; EX1008, [0138] ("[t]he dose of the K_{ATP} channel opener may be at least 1, 5, 10, 15, 20, 30, 40, 50, 100, 200, 300, 400, 500, 1000, or 2000 mg.").

243. Therefore, Claims 19-25 would have been obvious.

G. Claim 26

244. Claim 26 depends from Claim 1 and recites, "wherein the pharmaceutical formulation is administered orally." Cowen and Cotter disclose pharmaceutical formulations comprising diazoxide choline for oral

¹⁷ Generic Formula III in Cowen includes diazoxide. *Supra* at Section VII(D). As explained in this Declaration, use of the diazoxide choline salt would have been obvious to the POSA.

administration. EX1008, [0141]-[0142]; EX1009, [00369], [00380], [00596].

245. Accordingly, it would have been obvious for a POSA to administer the claimed pharmaceutical formulation orally, with a reasonable expectation of success.

X. GROUND 3: CLAIMS 1-26 ARE OBVIOUS OVER COWEN IN VIEW OF MILLER

246. In my opinion, Claims 1-26 of the '895 patent would have been obvious in light of the teachings of Cowen and Miller. The reasons for my conclusion and my analysis are presented below.

A. Claim 1

247. The text of independent Claim 1 is provided as follows:

1. A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising administering to said subject once per day a pharmaceutical formulation comprising an effective amount of diazoxide choline, wherein administration reduces hyperphagia and one or more food related behaviors in the subject.

i. *“A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising”*

248. As explained in Ground 1, Cowen teaches “a method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS)”:

Claim	Exemplary Citations
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1. A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising administering	EX1009, [0087] (“Further provided is a method to treat obesity, or hyperphagia in a Prader-Willi Syndrome patient ”); <i>see also id.</i> , [0093] (“Prader-Willi Syndrome”); <i>id.</i> , [00413] (same); <i>id.</i> , [00449] (same); <i>id.</i> , [0069] (“inhibition of hyperphagia”); <i>id.</i> , [0070] (same); <i>id.</i> , [0071] (same); <i>id.</i> , [0087] (“hyperphagia”); <i>id.</i> , [0093] (same); <i>id.</i> , [0093] (same).
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ii. *“administering to said subject once per day a pharmaceutical formulation comprising an effective amount of diazoxide choline,”*

1) **The use of diazoxide choline would have been obvious**

249. The '895 patent explains that diazoxide is “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.” EX1001, 17:1-3, 2:30-33. Cowen discloses the same compound also identified as diazoxide. EX1009, [0007]. Furthermore, the structure of diazoxide was well known to the POSA. EX1018; *supra* at ¶¶ 70-72. Cowen also teaches the use of diazoxide and other salts for the treatment of hyperphagia in a Prader-Willi Syndrome patient. EX1009, [0087].

250. From Cowen, the POSA would have readily recognized diazoxide choline as a preferred compound over diazoxide and other corresponding salts. Cowen only specifically claims “diazoxide choline,” immediately drawing the POSA’s attention to this specific compound. EX1009, Claims 9, 21, 32, 48, 53, 57, 62, 63, & 70. Cowen also specifically highlights the favorable properties of

diazoxide choline over the free base. *Id.*, [00750]. Cowen then solidifies the selection of diazoxide choline by providing numerous detailed examples and formulations that prominently feature this compound. For instance, Cowen includes numerous examples and formulations highlighting the use of diazoxide choline including: (1) extensive pharmaceutical formulation information using diazoxide choline (*id.*, [0596]-[00603]); (2) dissolution studies (*id.*, [00604]-[00607]); (3) excipient compatibility studies and stability studies (*id.*, [00608]-[00615]); (4) its preparation, synthesis and characterization (*id.*, [00623]-[000634], [00680]-[00706]); (5) clinical information for the treatment of different human disorders (*id.*, [00749]-[00760], [00764], [00766], [00770], [00772], [00778], [00783]-[0084]); and (6) pharmacokinetic data (*id.*, [00763], [00769]).

251. Therefore, a POSA would have been motivated to select a pharmaceutical formulation comprising diazoxide choline, with a reasonable expectation of success for treating hyperphagia in PWS patients.

iii. “administering to said subject once per day a pharmaceutical formulation comprising an effective amount of diazoxide choline,”

252. Cowen discloses pharmaceutical formulations comprising diazoxide choline. *Id.*, [0596]-[00603] (providing extensive pharmaceutical formulation information using diazoxide choline).

253. Once-daily administration is always preferable since it increases

patient compliance, and it is disclosed and claimed in Cowen. *Id.*, [0087] (treating “hyperphagia in a Prader-Willi Syndrome patient, comprising the administration of an effective amount of a K_{ATP} channel opener . . . In a preferred embodiment, administration is no more than two times per 24 hours, **or once per 24 hours.**”), [00411] (formulations of KATP channel openers selected from a salt of a compound of Formulae I - VIII¹⁸ administered as a **single dose**), [00766] (“A controlled clinical study was conducted to evaluate the potential for **Diazoxide Choline** Controlled-Release Tablets administered **once daily**”); Claims 31 (“the formulation is **administered once per 24 hours.**”), 52, 59, 62 & 65.

254. Finally, Claim 1 also recites use of “an effective amount” of the diazoxide choline pharmaceutical composition. The ’895 patent provides a definition of an “effective amount.” EX1001, 15:32-36. Cowen discloses an “effective amount” within the meaning of Claim 1 of the ’895 patent. EX1009, [00087] (treating “hyperphagia in a Prader-Willi Syndrome patient, comprising the administration of an **effective amount** of a KATP channel opener.”).

iv. “wherein administration reduces hyperphagia and one or more food related behaviors in the subject.”

¹⁸ Generic Formula III in Cowen includes diazoxide. *Supra* at Section VII(D). As explained in this Declaration, use of the diazoxide choline salt would have been obvious to the POSA.

255. The remaining limitation of Claim 1 is “wherein administration reduces hyperphagia and one or more food related behaviors in the subject.”

256. Cowen explicitly discloses that a pharmaceutical formulation comprising diazoxide choline (*i.e.*, a K_{ATP} channel opener) reduces hyperphagia. For instance, Cowen teaches methods to treat obesity or hyperphagia in a Prader-Willi Syndrome patient through administration of a K_{ATP} channel opener. *Id.*, [0087].

257. Furthermore, Cowen provides that such formulations result in inhibition of hyperphagia for about 18 or 24 hours. *Id.*, [0068], [0070]-[0071], [00411]. This reduction in hyperphagia is a consistent therapeutic outcome highlighted by Cowen. *Id.*, [00439] (“(19) reduced rates of hyperphagia”), [00442] (“(26) reduced rates of hyperphagia”), [00443] (“(22) reduced rates of hyperphagia”), [00444] (“(22) reduced rates of hyperphagia”).

258. Turning to the limitation of “reduces . . . one or more food related behaviors in the subject”: as explained in Ground 1, the ’895 patent explains what is meant by “food related behaviors.” EX1001, 20:14-22. As explained above in Ground 1, Cowen teaches this limitation either inherently or expressly (*supra* at Section VII(A)(v)) but to the extent there is disagreement on this point, a POSA would have been aware of the teachings of Miller which would have rendered the limitation obvious.

259. Miller, entitled “Nutritional Phases in Prader–Willi Syndrome,” provides a review of PWS. EX1017, 1. A POSA would have been motivated to combine the teachings of Cowen and Miller, with a reasonable expectation of success. Cowen discloses methods of inhibiting and reducing hyperphagia in a PWS patient using diazoxide choline preparations, and Miller provides additional details on the manifestations of hyperphagia in a PWS patient, thus informing a POSA what it means to inhibit or reduce hyperphagia using the diazoxide choline preparations taught in Cowen. EX1017, Table 1.

260. Miller teaches that “Phase 3 is characterized by hyperphagia, typically accompanied by food-seeking and lack of satiety (median age of onset: 8 years; quartiles 5–13 years).” *Id.*, Abstract, 5. Miller Table 1 provides various clinical manifestations of hyperphagia. *Id.*, Table 1. The table in Miller provides the same “food related behaviors” discussed in the ’895 patent. EX1001 at 20:14–22.

261. Accordingly, if a PWS patient is hyperphagic (*i.e.*, in Phase 3), administration of a K_{ATP} channel opener, such as a pharmaceutical formulation of diazoxide choline, results in the reduction or inhibition of hyperphagia. EX1009, [0087].

262. That inhibition or reduction of hyperphagia necessarily means that the food-related behaviors discussed in Miller will be reduced or inhibited. As

Miller explains, if a patient is introduced to an intervention method, Phase 3 tends to be less severe. EX1017, 8 (“As a result, when phase 3 begins it is often less severe in those families who have implemented early intervention measures versus what has been traditionally described in the literature”).

263. A POSA would consider Cowen’s diazoxide choline an intervention method and, based on the teachings of Cowen regarding a reduction/inhibition of hyperphagia, the POSA would reasonably expect a corresponding reduction in the food-related behaviors described in Miller.

264. Therefore, it would have been obvious to a POSA, in view of the teachings of Cowen and Miller, that administration of a pharmaceutical formulation comprising diazoxide choline results in the reduction of hyperphagia which, in turn, causes the reduction of one or more food-related behaviors in the subject. Accordingly, it would have been obvious to a POSA to achieve the method of treating hyperphagia in a patient having PWS as recited in Claim 1.

B. Claims 2-3

265. Claims 2 and 3 depend from Claim 1 and recite, “wherein the diazoxide choline is administered for at least 10 weeks” (Claim 2) and “wherein the diazoxide choline is administered for one or more years.” (Claim 3). These administration periods are taught by Cowen.

266. As explained above, use of diazoxide choline would have been

obvious in light of Cowen. Cowen teaches “prolonged administration” (EX1009, Abstract) with specific administration periods ranging from at least 7 days to 12 months:

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).

EX1009, [00234], [00736] (“Formulations of salts of any of the compounds of Formulae I - IV¹⁹ prepared as described herein can be tested for efficacy in obese humans . . . [s]ubjects are dosed daily for up to 12 months.”), [00741] (“up to 12 months”).

267. Based on the teachings of Cowen, use of diazoxide choline would have been obvious, and administration “for at least 10 weeks” (Claim 2) or “for one or more years” would have overlapped with the administration periods disclosed in Cowen. Accordingly, Claims 2-3 would have been obvious.

C. Claims 4-15

¹⁹ Generic Formula III in Cowen includes diazoxide. *Supra* at Section VII(D). As explained in this Declaration, use of the diazoxide choline salt would have been obvious to the POSA.

268. Claims 4-15 depend from Claim 1. As explained above, Claim 1 would have been obvious. As to the specific recitations of Claims 4-9, they recite various ranges of the obvious “once-daily administration of diazoxide choline,” *i.e.*, 25 to 100 mg (Claim 4), 50 mg to 180 mg (Claim 5), 50 mg to 275 mg (Claim 6), 300 mg to 500 mg (Claim 7), 500 mg to 2,000 mg (Claim 8); and 25 mg to 500 mg (Claim 9).

269. Turning to Claims 10-15, these claims depend from Claim 3. As explained above, Claim 3 would have been obvious. As to the specific recitations of Claims 10-15, they recite various ranges of the obvious “once-daily administration of diazoxide choline,” *i.e.*, 25 to 100 mg (Claim 10), 50 mg to 180 mg (Claim 11), 50 mg to 275 mg (Claim 12), 300 mg to 500 mg (Claim 13), 500 mg to 2,000 mg (Claim 14); and 25 mg to 500 mg (Claim 15).

270. As explained above, the “once-daily administration of diazoxide choline” would have been obvious, as would have recited ranges in view of Cowen. Cowen teaches that “the salt can be formulated for controlled release following 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 salt of the KATP channel openers provided in Formulae

I - VIII.”²⁰ EX1009, [0061], [00380].

271. Thus, Cowen discloses the once-daily administration of diazoxide choline in an amount of 1 mg to 2000 mg, which overlaps with the claimed ranges of 25 to 100 mg (Claims 4 and 10), 50 mg to 180 mg (Claims 5 and 11), 50 mg to 275 mg (Claims 6 and 12), 300 mg to 500 mg (Claims 7 and 13), 500 mg to 2,000 mg (Claims 8 and 14); and 25 mg to 500 mg (Claims 9 and 15).

272. Accordingly, Claims 4-15 would have been obvious.

D. Claim 16

273. The text of Claim 16 is provided as follows:

16. The method of claim 1, wherein the administration of diazoxide choline is initiated at a starting dose of diazoxide choline and then titrated every two weeks to reach a maintenance dose of diazoxide choline.

274. At a high level, Claim 16 covers the well-known method of dose titration using a starting dose (to address adverse patient side effects) followed by dose titration every two weeks to reach another level referred to as a maintenance dose. *Supra* at Section VII(C). (“Dose Titration in Clinical Practice

²⁰ Generic Formula III in Cowen includes diazoxide. *Supra* at Section VII(D). As explained in this Declaration, use of the diazoxide choline salt would have been obvious to the POSA.

Was Well Known as of the Priority Date”). Using such dose titration to arrive at a maintenance (therapeutic) dose is common practice.

275. As explained above in Ground 1, Cowen repeatedly teaches, for various disease states, that in order to reduce the adverse side effects known to occur with diazoxide, patients can be initiated at subtherapeutic doses and titrated up in a stepwise manner, until a therapeutic dose is achieved. EX1009, [00478], [00448] (providing examples of adverse effects that can be reduced using titration to therapeutic dose), [0089], [00481]-[00483], [00489]-[00490]. Cowen clearly explains that the adverse effects of diazoxide are addressed by using an initiation or starting dose and then increasing the dose to a maintenance (therapeutic) dose.

276. Moreover, Cowen teaches more specific examples in the context of obesity or type 1 or type 2 diabetes with a salt of K_{ATP} channel opener to achieve a therapeutic dose (*i.e.*, maintenance dose). *Id.*, [0077]. Thus, as Cowen teaches, the starting dose of “preferably between 10 and 200 mg” of diazoxide may be given to the patient daily “for days or a few weeks,” then escalated thereafter. *Id.* The “initial escalating dose” may thereafter be given “for days or a few weeks.” *Id.* The rounds of dose escalation may continue until the therapeutically effective dose is reached. *Id.*

i. “wherein the administration of diazoxide choline is initiated at a starting dose of diazoxide choline”

277. Turning to the limitations of Claim 16: as explained above with

respect to my analysis of Claim 1, the administration of diazoxide choline would have been obvious to the POSA.

278. It would have been obvious to the POSA to “initiate[] at a starting dose of diazoxide choline” based on the teachings of Cowen. For example, Cowen teaches a “starting dose is preferably between 10 and 200 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide. Preferably, the KATP channel opener is diazoxide. The starting dose is given to the patient daily for days or a few weeks.” EX1009, [0077], [00478] (“in which the first dose is known to be **subtherapeutic**”).

ii. ***“and then titrated every two weeks to reach a maintenance dose of diazoxide choline”***

279. As to “then titrat[ing] every two weeks to reach a maintenance dose of diazoxide choline,” this is also taught by Cowen. This recitation has three parts, all of which are taught by Cowen: (1) a titration of the medication; (2) this titration occurs every two weeks and continues until (3) maintenance dose is reached.

280. As to the first part, *i.e.*, the titration, this is taught in Cowen. Once the starting dose (*id.*, [0077]), which is “subtherapeutic” (*id.*, [00478]), is given to the patient:

[T]he method includes escalating the dose which is administered when after supine heart rates return to

baseline. An initial escalating dose is established using the same criteria as the initial dose. The initial escalating dose is given to the patient daily for days or a few weeks. The increment in dose is preferentially 25 to 150 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide. Further rounds of this dose escalation would continue until the therapeutically effective dose is reached.

Id., [0077].

281. Thus, the POSA would understand that Cowen’s “initial escalating dose” is the dose that is titrated up. *See also id.*, [00478] (“daily dose is subsequently increased stepwise until the therapeutic dose is reached.”).

282. Turning to the second part of this recitation: Claim 16 of the ’895 patent recites that the titration (dose escalation) occurs “every two weeks to reach a maintenance dose,” whereas Cowen teaches titration “for days or a few weeks.” The claimed titration escalation of “two weeks” falls within the range disclosed in Cowen, *i.e.*, “for days or a few weeks” and therefore would have been obvious because it is nothing more than routine optimization of a parameter identified in the prior art. Moreover, as I explained above, it is common for physicians to utilize two weeks as a standard titration interval when titration is needed. *Supra* at ¶ 77.

283. Furthermore, the teachings of Cowen are not limited to a single step

increase at the two-week mark, rather Cowen teaches the claimed “every two weeks to reach a maintenance dose.” As Cowen teaches “[f]urther rounds of this dose escalation would continue until the therapeutically effective dose is reached.” EX1009, [0077]. Elsewhere, Cowen would have taught the POSA that “the number of steps is 2 to 10 to reduce the incidence of adverse side effects.” *Id.*, [0089]. In other words, Cowen teaches 2 to 10 rounds of increases. Therefore, titration “every two weeks” until a maintenance dose is reached would have been obvious and nothing more than an exercise in routine experimentation for the POSA to arrive at the maintenance dose.

284. Finally, the third part of this recitation requires a maintenance dose. This is taught in Cowen: “Further rounds of this dose escalation would continue **until the therapeutically effective dose is reached.**” *Id.*; *see also id.*, [00478] (“diazoxide or its derivatives that is administered to a subject 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.**”).

285. As explained in Ground 1, I have already addressed why any position that Cowen paragraph [0077] is directed only to the use of diazoxide for treating obesity or type 1 or type 2 diabetes, and not PWS and/or hyperphagia, is misplaced. *Supra* at ¶¶159-61.

286. Given it would have been obvious to use diazoxide choline, for all

the above reasons, Claim 16 would have been obvious to a POSA.

E. Claims 17-18 (Starting Dose Claims)

287. Claims 17-18 depend from Claim 16. Claim 16 has been addressed above. Claims 17-18 recite “that the starting dose of diazoxide choline is between 25-100 mg” (Claim 17) and “the starting dose of diazoxide choline is between 50-180 mg” (Claim 18).

288. As explained above, use of diazoxide choline would have been obvious in light of the teachings of Cowen and Cowen teaches in the context of its multidose regimen: “This **starting dose is preferably between 10 and 200 mg of KATP channel opener** or the equivalent based on relative bioavailability and potency compared to diazoxide. Preferably, the KATP channel opener is **diazoxide.**” EX1009, [0077]. The starting doses taught by Cowen overlap with the claimed starting doses of Claims 17 and 18.

289. Therefore, Claims 17 and 18 would have been obvious.

F. Claims 19-25 (Maintenance Dose Claims)

1. Claims 19 and 24-25 depend from Claim 17 (which has been addressed above). Claims 19 and 24-25 are then directed to the subsequent maintenance dose from Claim 17’s starting doses, and, importantly, in each case Claims 19 and 24-25 include a range of diazoxide choline that is higher than Claim 17’s starting dose of **25-100 mg**:

Claim 19	“wherein the maintenance dose of diazoxide choline is between 100-200 mg of diazoxide choline”
Claim 24	“wherein the maintenance dose of diazoxide choline is between 25-250 mg of diazoxide choline”
Claim 25	“wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline.”

290. Claims 20-23 depend from Claim 18 (which has been addressed above). Claims 20-23 are then directed to the subsequent maintenance dose from Claim 18’s starting doses, and, importantly, in each case Claims 20-23 include a range of diazoxide choline that is *higher* than Claim 17’s starting dose of **50-180 mg**:

Claim 20	“wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline”
Claim 21	“wherein the maintenance dose of diazoxide choline is between 300-500 mg of diazoxide choline”
Claim 22	“wherein the maintenance dose of diazoxide choline is between 500-2000 mg of diazoxide choline”; and
Claim 23	“wherein the maintenance dose of diazoxide choline is between 100-500 mg of diazoxide choline.”

291. Cowen teaches a multidose regimen, and like Claims 19-25, Cowen teaches the maintenance dose will be higher than the starting dose when using diazoxide choline. EX1009, [0077] (“The initial **escalating** dose is given to the patient daily for days or a few weeks. The increment in dose is preferentially 25 to 150 mg of KATP channel opener . . . Further rounds of this dose escalation would continue until the therapeutically effective dose is reached.”), [00478] (“diazoxide or its derivatives that is administered to a subject 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”).

292. This only leaves the amounts recited in Claims 19-25 of the '895 patent. And in this regard, Cowen teaches the POSA some important points.

293. First, the dose may be escalated (titrated up) in increments of “preferentially 25 to 150 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide.” *Id.*, [0077].

294. Next, it is not limited to a single stepwise increase but “[f]urther rounds of this dose escalation would continue until the therapeutically effective dose is reached.” *Id.* And, along that same vein, Cowen teaching that the “rounds of this dose escalation would continue until the therapeutically effective dose is reached” expressly tell the POSA to use routine experimentation. *Id.* Elsewhere, Cowen would have taught the POSA that “the number of steps is 2 to 10 to reduce the incidence of adverse side effects.” *Id.*, [0089]. In other words, Cowen teaches 2 to 10 rounds of increases.

295. With the POSA’s knowledge of routine dose titration, beginning with Cowen’s starting dose of “between 10 and 200 mg of KATP channel opener”, and then using Cowen’s stepwise increases of “2 to 10” rounds to arrive at a therapeutic (maintenance) dose, increasing the medication by two rounds in escalation increments of “25 to 150 mg of KATP channel opener” as taught by

the prior art would have resulted in the POSA arriving the claimed maintenance amounts:

Starting Dose	First Round	Second Round	Third Round
Lower value 10 mg	35 mg-160 mg	60 mg-310 mg	85-460 mg
Upper value 200 mg	225 mg-350 mg	250 mg-500 mg	275-650 mg

296. As the chart above shows, two rounds would have resulted in a range of 60 mg to 500 mg of diazoxide choline; three rounds would have resulted in the range of 85 mg to 650 mg, which are the claimed ranges recited in Claims 19-25. Determining the therapeutic (maintenance dose) is what a physician would do as part of their routine practice based on factors such patient response, tolerability and the physician's professional judgement.

297. Furthermore, the POSA would have known from the teaching of Cowen that these amounts would have been safe and effective for the patient, providing the POSA a reasonable expectation of success: "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 salt of the K_{ATP} channel openers

provided in Formulae I - VIII.” EX1009, [0061], [00380].²¹ Therefore, Claims 19-25 would have been obvious.

G. Claim 26

298. Claim 26 depends from Claim 1 and recites “wherein the pharmaceutical formulation is administered orally.” Cowen discloses pharmaceutical formulations comprising diazoxide choline for oral administration. *Id.*, [00369], [00380], [00596].

299. Accordingly, it would have been obvious for a POSA to administer the claimed pharmaceutical formulation orally, with a reasonable expectation of success.

XI. SECONDARY CONSIDERATIONS DO NOT CHANGE THE CONCLUSION OF OBVIOUSNESS

300. I have reviewed the prosecution history of the '895 patent and I am aware of no objective indicia of non-obviousness presented (or discussed) during prosecution of the '895 patent.

301. At this time, I am not aware of any evidence of non-obviousness with regard to the claims of the '895 patent, including failure of others, copying,

²¹ As explained above, generic Formula III of Cowen includes diazoxide and for the reasons explained in this Declaration, use of the diazoxide choline salt would have been obvious to the POSA in light of the teachings of Cowen.

perception in the industry, commercial success, or long-felt but unmet need.

302. Should Patent Owner expand on these alleged secondary considerations, I may be called upon to respond in the future.

303. In summary, having considered the Graham factors, as explained above, a POSA would have found the challenged claims of the '895 patent to be obvious for the reasons discussed in this Declaration.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: April 20, 2026

A handwritten signature in black ink, reading "Eric Hollander MD", is positioned above a solid horizontal line.

Eric M. Hollander, M.D. DFAPA, FACNP