

Filed on behalf of: Soleno Therapeutics, Inc.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC.,
Petitioner,

v.

SOLENO THERAPEUTICS, INC.,
Patent Owner.

PGR2026-00034
Patent 12,419,895

**DECLARATION OF LYNNE M. BIRD, M.D.
IN SUPPORT OF
PATENT OWNER'S PRELIMINARY RESPONSE**

Table of Contents

I.	Introduction	1
II.	Summary of Opinions	1
III.	Qualifications	1
IV.	Summary of Materials Reviewed and Considered	6
V.	Legal Standards	10
VI.	A Person of Ordinary Skill in the Art	13
VII.	Scientific Background and State of the Art	15
A.	Prader-Willi Syndrome (PWS) and Hyperphagia	15
B.	PWS Fundamentally Differs from Obesity and Diabetes	22
1.	PWS Versus Obesity	23
2.	PWS Versus Diabetes.....	29
C.	The '895 Patent (Ex.1001) and Vykate XR	31
D.	The Challenged Claims.....	33
E.	Dosing of PWS Population.....	35
VIII.	Asserted Prior Art	42
A.	Cowen (Ex.1009).....	42
B.	Cotter (Ex.1008)	45
C.	Miller (Ex.1017)	46
IX.	Ground 1: Cowen Does Not Render Claims 2-3 and 16-25 Obvious	47
A.	Claims 2-3 (Treatment Duration Claims).....	47
1.	One of Skill in the Art Would Have Recognized that Cowen Does Not Teach or Render Obvious Treating PWS Patients for at Least 10 Weeks or Up to 12 Months	48
2.	One of Skill in the Art Would Not Have Had Any Reason to Modify Cowen's Disclosures Nor A Reasonable Expectation of Success in Doing So	50
B.	Claim 16 (Dosing Titration Claim)	52

1.	One of Skill in the Art Would Have Recognized that Cowen Does Not Teach a Two-Week Titration Interval and One of Skill in the Art Would Not Have Had Reason to Adopt One	53
2.	One of Skill in the Art Would Have Recognized that Cowen's Dose-Escalation Disclosures Are Directed to Non-PWS Populations and Could Not Be Extrapolated to PWS Patients	54
3.	One of Skill in the Art Would Have Recognized that the Claimed Two-Week Interval Was the Result of a Specific Clinical Insight Tailored to the PWS Population.....	57
C.	Claims 17-18 (Starting Dose Claims).....	60
1.	One of Skill in the Art Would Have Recognized that Cowen's Claimed Range Is Directed to Different Subjects, Conditions, and Purpose	60
2.	One of Skill in the Art Would Not Have Been Motivated to Use the Claimed Ranges or Had a Reasonable Expectation of Success in Doing So	61
D.	Claims 19-25 (Maintenance Dose Claims).....	62
1.	One of Skill in the Art Would Not Have Had Any Reason to Combine the Various Paragraphs in Cowen That Dr. Hollander Combines	63
2.	One of Skill in the Art Would Have Recognized That the Claimed Ranges Are Not Disclosed in Cowen	64
3.	One of Skill in the Art Would Not Have Had Reason to Use the Claimed Ranges or a Reasonable Expectation of Success in Doing So.....	64
X.	Ground 2: Cowen and Cotter Do Not Render Claims 2-3 and 16-25 Obvious	65
A.	Cowen and Cotter Do Not Render Obvious Claims 2-3	66
1.	One of Skill in the Art Would Have Recognized that Cotter Does Not Teach Administering Diazoxide for 56 Weeks	66
2.	One of Skill in the Art Would Have Recognized that Cotter's Example 1 Is Directed to a Fundamentally Different Clinical Condition and Provides No Teaching Regarding Durational Treatment of Hyperphagia.....	67

3.	One of Skill in the Art Would Not Have Had Any Reason to Combine Cowen and Cotter with Respect to the Durational Limitations of Claims 2-3 or a Reasonable Expectation of Success	70
B.	Cowen and Cotter Do Not Render Obvious Claim 16	71
C.	Cowen and Cotter Do Not Render Obvious Claims 17-18 ...	73
D.	Cowen and Cotter Do Not Render Obvious Claims 19-25 ...	73
XI.	Ground 3: Cowen and Miller Do Not Render Claims 2-3 and 16-25 Obvious	75
A.	Cowen and Miller Do Not Render Obvious Claims 2-3	75
B.	Cowen and Miller Do Not Render Obvious Claim 16	75
C.	Cowen and Miller Do Not Render Obvious Claims 17-18 ...	75
D.	Cowen and Miller Do Not Render Obvious Claims 19-25 ...	75
XII.	Conclusion.....	76

I. Introduction

1. I have been retained by Soleno Therapeutics, Inc. (“Soleno” or “Patent Owner”) to provide my opinions concerning the validity of U.S. Patent No. 12,419,895 (“’895 patent”), which has been challenged by Apotex Inc. (“Apotex” or “Petitioner”). The ’895 patent recites a method of treating hyperphagia in a subject with Prader-Willi Syndrome (“PWS”) by administering diazoxide choline.

II. Summary of Opinions

2. Based on materials cited in this Declaration and my two decades of clinical expertise treating patients suffering from PWS, I conclude that Dr. Hollander (and Apotex) have not established that any of the Claims 2-3 and 16-25 of the ’895 patent is more likely than not unpatentable.

III. Qualifications

3. I am a Professor of Clinical Pediatrics at the University of California, San Diego (“UCSD”), a position I have held since September 2009. I also serve as the Medical Director of the PWS Multidisciplinary Clinic at Rady Children’s Hospital San Diego, a position I have held since 2005.

4. I earned my Bachelor of Science in Biology from Bucknell University in 1983 and my M.D. from Duke University School of Medicine in 1987. I completed my pediatric internship, residency, and chief residency at UCSD from 1987 to 1991, and my genetics fellowship through the UCSD Genetics Training Program at Children’s Hospital and Health Center in San Diego from 1992 to 1994.

I am board certified by both the American Board of Pediatrics and the American Board of Medical Genetics and Genomics.

5. My practice includes treating PWS patients as well as conducting clinical trials investigating the safety and efficacy of potential new therapies for PWS patients. Through the PWS Multidisciplinary Clinic, I oversee the care of approximately 40-50 PWS patients per year at variable frequency, and the multidisciplinary team includes a geneticist (myself), endocrinologist, dietician, and social worker. I have several PWS patients currently on diazoxide choline, marketed as VYKAT[®] XR, and routinely prescribe it in my clinical practice.

6. I am a Fellow of the American Academy of Pediatrics and a member of the Council on Genetics. I am also a member of the American College of Medical Genetics and Genomics, the PWS Clinical Investigator Consortium, the Prader-Willi California Foundation, and the Foundation for Prader-Willi Research.

7. Through the PWS Multidisciplinary Clinic and my clinical research activities, I have been involved in numerous clinical trials focused on finding treatments for hyperphagia and other symptoms of PWS. Among others, I have served as the Principal Investigator at the San Diego site on the following PWS-related clinical trials:

- Randomized, Double-Blind, Placebo Controlled, Phase 3 Trial of ZGN-440 (Subcutaneous Beloranib in Suspension) in Obese Subjects with Prader-

Willi Syndrome to Evaluate Total Body Weight, Food-related Behavior, and Safety Over 6 Months, sponsored by Zafgen, Inc. (July 2014 – November 2016);

- A Phase 2 Study to Evaluate Efficacy, Safety, and Pharmacokinetics of GLWL-01 in the Treatment of Patients with PWS, sponsored by GLWL Research, Inc. (September 2017 – October 2019);
- A Randomized, Double-Blind, Placebo-Controlled Study of Diazoxide Choline Controlled-Release Tablet (“DCCR”) in patients with PWS, sponsored by Soleno (March 2018 – June 2021);
- A Randomized Double-Blind, Placebo-Controlled, Phase 2 Study to Assess the Efficacy, Safety and Tolerability of Cannabidiol Oral Solution for The Treatment of Subjects with PWS, sponsored by Insys Therapeutics, Inc. (March 2018 – June 2019);
- Phase 3, Randomized, Double-Blind, Placebo-Controlled, 8-week Clinical Study to Assess the Efficacy, Safety, and Tolerability, of Intranasal Carbetocin (LV-101) in PWS with Long Term Follow-Up: CARE-PWS, sponsored by Levo Therapeutics, Inc. (October 2018 – August 2022);
- An open-label long-term safety evaluation of Diazoxide Choline Controlled-Release Tablet in patients with PWS, sponsored by Soleno (October 2018 – present);

- A Phase 2b/3 study to evaluate the safety, tolerability, and effects of Livoletide (AZP-531), an unacylated ghrelin analog, on food-related behaviors in patients with PWS, sponsored by Millendo Therapeutics, Inc. (October 2018 – July 2020);
- A Phase 2b, Double-blind, Randomized, Placebo-controlled, Multi-center, 16-week Dose-finding, Safety and Efficacy Study with Open-label Extension Period of Tesomet in Adult and Adolescent Subjects with PWS, sponsored by Saniona (August 2021 – April 2022);
- A Phase 2/3, Randomized, Double-Blind, Placebo-Controlled Study of RAD011 (Cannabidiol Oral Solution) for the Treatment of Patients with PWS, sponsored by Radius Health, Inc. (January 2022 – January 2023);
- A Randomized, Double-blind, Placebo-controlled, Multi-center, 2-part, Phase 2 Study to Evaluate Efficacy, Safety, and Tolerability of RGH-706 in PWS, sponsored by Gedeon Richter (September 2022 – July 2024);
- An Open-Label Study of Diazoxide Choline Extended-Release Tablets in Patients with PWS, sponsored by Soleno (February 2023 – present);
- An Open-Label Study of the Safety, Tolerability, and Pharmacokinetics of Oral NNZ-2591 in PWS, sponsored by Neuren Pharmaceuticals (June 2023 – September 2024);
- A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group

Study of Carbetocin Nasal Spray for the Treatment of Hyperphagia in PWS, sponsored by Acadia Pharmaceuticals (June 2023 – present);

- A Phase 3, Randomized, Double-Blind, Dose-Ranging, Evaluation of Transcutaneous Vagus Nerve Stimulation (“tVNS”) to Reduce Temper Outbursts in People with PWS, sponsored by the Foundation for Prader-Willi Research (July 2023 – present);
- A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Pitolisant Followed by an Open-Label Extension in Patients with PWS, sponsored by Harmony Biosciences (April 2024 – present);
- A Phase 3, Randomized, Double-blind, Placebo-controlled Study of ARD-101 for the Treatment of Hyperphagia in Patients with PWS, sponsored by Aardvark Therapeutics Inc. (“Aardvark”) (November 2024 – present); and
- A Phase 3, Multicenter, Open-Label Extension Study to Assess the Safety and Efficacy of ARD-101 in Patients with PWS, sponsored by Aardvark (August 2025 – present).

8. I have co-authored numerous peer-reviewed publications and conference presentations relating to PWS, including publications on the efficacy, safety, and pharmacology of DCCR in patients with PWS.

9. In total, I have over 20 years of experience treating patients with PWS, prescribing and dosing medications for patients with PWS, and consulting on the

development of treatments for PWS. I am familiar with the various clinical endpoints used to evaluate efficacy and safety of therapies for PWS. 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 Ex.2036.

10. I am receiving compensation at my standard consulting rate of \$700 per hour, plus reimbursement for reasonable expenses. My fee is not dependent on my opinions or on the outcome of this matter.

IV. Summary of Materials Reviewed and Considered

11. All of the opinions contained in this Declaration are based on the documents I reviewed and my knowledge and professional judgment. In forming the opinions expressed in this Declaration, while drawing on my experience in treating PWS, I reviewed the following documents:

Ex.	Description
1001	U.S. Patent No. 12,419,895
1004	Vykat™ XR (diazoxide choline) [package insert]. Soleno Therapeutics; 2025
1005	Declaration of Dr. Hollander (Apotex's expert)
1008	International Patent Pub. No. WO 2014/197753 to Cotter
1009	International Patent Pub. No. WO 2009/006483 to Cowen et al.
1012	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

Ex.	Description
1017	Miller et al., <i>Nutritional Phases in Prader-Willi Syndrome</i> , 155 AM. J. MED. GENET A. 1040, 1040-49 (2011)
1018	Proglycem [®] prescribing information
2017	FDA, <i>Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations</i> , https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=216665&Appl_type=N (last visited June 10, 2026)
2037	Merel Gunay-Aygun et al., <i>The Changing Purpose of Prader-Willi Syndrome Clinical Diagnostic Criteria and Proposed Revised Criteria</i> , 108 PEDIATRICS 1–5 (2001)
2038	Phentermine Hydrochloride – phentermine hydrochloride capsule, Epic Pharma, LLC, Prescribing Information (Revised Nov. 2019)
2039	Charlotte Höybye et al., <i>Metabolic Profile and Body Composition in Adults with Prader-Willi Syndrome and Severe Obesity</i> , 87 J. CLINICAL ENDOCRINOLOGY METABOLISM 3590 (2002)
2040	M. Tracy Bekx et al., <i>Decreased Energy Expenditure is Caused by Abnormal Body Composition in Infants With Prader-Willi Syndrome</i> , 143 J. PEDIATRICS 372 (2003)
2041	Fortu Benarroch et al., <i>Prader-Willi Syndrome: Medical Prevention and Behavioral Challenges</i> , 16 CHILD ADOLESCENT PSYCHIATRIC CLINICS N. AM. 695 (2007)
2042	Paolo Brambilla et al., <i>Peculiar Body Composition in Patients With Prader-Labhart-Willi Syndrome</i> , 65 AM. J. CLINICAL NUTRITION 1369 (1997)
2043	P. Brambilla et al., <i>Metabolic Syndrome in Children With Prader-Willi Syndrome: The Effect of Obesity</i> , 21 NUTRITION METABOLISM CARDIOVASCULAR DISEASES 269 (2011)
2044	Merlin G. Butler et al., <i>Genetic Variants of the Human Obesity (OB) Gene in Subjects With and Without Prader-Willi Syndrome: Comparison With Body Mass Index and Weight</i> , 54 CLINICAL GENETICS 385 (1998)

Ex.	Description
2045	MANAGEMENT OF PRADER-WILLI SYNDROME (Merlin G. Butler et al. eds., 3rd ed. 2006) (EXCERPTS)
2046	Suzanne B. Cassidy et al., <i>Prader-Willi Syndrome</i> , 14 GENETICS MED. 10 (2012)
2047	Cheri L. Deal et al., <i>Growth Hormone Research Society Workshop Summary: Consensus Guidelines for Recombinant Human Growth Hormone Therapy in Prader-Willi Syndrome</i> , 98 J. CLINICAL ENDOCRINOLOGY METABOLISM E1072 (2013)
2048	Francis J. DiMario, Jr. et al., <i>Respiratory Sinus Arrhythmia in Patients With Prader-Willi Syndrome</i> , 11 J. CHILD NEUROLOGY 121 (1996)
2049	A. Dimitropoulos et al., <i>Appetitive Behavior, Compulsivity, and Neurochemistry in Prader-Willi Syndrome</i> , 6 MENTAL RETARDATION DEVELOPMENTAL DISABILITIES RSCH. REVS. 125 (2000)
2052	Anthony P. Goldstone et al., <i>Visceral Adipose Tissue and Metabolic Complication of Obesity Are Reduced in Prader-Willi Syndrome Female Adults: Evidence for Novel Influences on Body Fat Distribution</i> , 86 J. CLINICAL ENDOCRINOLOGY METABOLISM 4330 (2001)
2054	A.P. Goldstone et al., <i>Recommendations for the Diagnosis and Management of Prader-Willi Syndrome</i> , 93 J. CLINICAL ENDOCRINOLOGY METABOLISM 4183 (2008)
2055	A.M. Haqq et al., <i>Autonomic Nervous System Dysfunction in Obesity and Prader-Willi Syndrome Current Evidence and Implications for Future Obesity Therapies</i> , 1 CLINICAL OBESITY 175 (2012)
2056	Charlotte Höybye et al., <i>Peptides Associated for Hyperphagia in Adults With Prader-Willi Syndrome Before and During GH Treatment</i> , 13 GROWTH HORMONE IGF RSCH. 322 (2003)
2057	Charlotte Höybye, <i>Endocrine and Metabolic Aspects of Adult Prader Willi Syndrome With Special Emphasis on the Effect of Growth Hormone Treatment</i> (Ph.D. thesis, Karolinska Institutet (2003))
2059	Bianca K. Itariu et al., <i>Autoimmune Aspects of Type 2 Diabetes Mellitus – A Mini-Review</i> , 60 GERONTOLOGY 189 (2014)

Ex.	Description
2060	Paolo Marzullo et al., <i>The Impact of GH/IGF-I Axis and Nocturnal Breathing Disorders on Cardiovascular Features and Adult Patients With Prader-Willi Syndrome</i> , 90 J. CLINICAL ENDOCRINOLOGY METABOLISM 1–30 (2005)
2061	James S. McTaggart et al., <i>The Role of the K_{ATP} Channel in Glucose Homeostasis in Health and Disease: More than Meets the Islet</i> , 588.17 J. PHYSIOLOGY 3201 (2010)
2062	Jennifer L. Miller et al., <i>Enhanced Activation of Reward Mediating Prefrontal Regions in Response to Food Stimuli in Prader-Willi Syndrome</i> , 78 J. NEUROLOGY NEUROSURGICAL PSYCHIATRY 615 (2007)
2063	Jennifer L. Miller, <i>Approach to the Child With Prader-Willi Syndrome</i> , 97 J. CLINICAL ENDOCRINOLOGY METABOLISM 3837 (2012)
2064	Jennifer L. Miller et al., <i>Effects of Metformin in Children and Adolescents with Prader-Willi Syndrome and Early-Onset Morbid Obesity: A Pilot Study</i> , 1 J. PEDIATRIC ENDOCRINOLOGY METABOLISM 1–12 (2014)
2065	Abdulfatai B. Olokoba et al., <i>Type 2 Diabetes Mellitus: A Review of Current Trends</i> , 27 OMAN MED. J. 269 (2012)
2066	R.B. Paisey et al., <i>Successful Treatment of Obesity and Diabetes With Incretin Analogue Over Four Year in an Adult With Prader-Willi Syndrome</i> , 28 PRAC. DIABETES 306 (2011)
2067	Nathan A. Shapira et al., <i>Effects of Topiramate in Adults With Prader-Willi Syndrome</i> , 109 AM. J. MENTAL RETARDATION 301 (2004)
2068	Margje Sinnema et al., <i>The Use of Medical Care and the Prevalence of Serious Illness in an Adult Prader-Willi Syndrome Cohort</i> , 56 EUR. J. MED. GENETICS 397 (2013)
2069	Z. Talebizadeh & M.G. Butler, <i>Insulin Resistance and Obesity-Related Factors in Prader-Willi Syndrome: Comparison With Obese Subjects</i> , 67 CLINICAL GENETICS 1–17 (2005)
2070	Mariana F. Theodoro et al., <i>Body Composition and Fatness Patterns in Prader-Willi Syndrome: Comparison With Simple Obesity</i> , 14 OBESITY 1685 (2006)

Ex.	Description
2071	Kathleen De Waele et al., <i>Long-Acting Octreotide Treatment Causes a Sustained Decrease in Ghrelin Concentrations But Does Not Affect Weight, Behaviour and Appetite in Subjects With Prader-Willi Syndrome</i> , 159 EUR. J. ENDOCRINOLOGY 381 (2008)
2072	JACKIE WATERS, PRADER-WILLI SYNDROME - A PRACTICAL GUIDE (2014) (EXCERPT)
2073	William B. Zipf, <i>Prader-Willi Syndrome: The Care and Treatment of Infants, Children, and Adults</i> , in ADVANCES IN PEDIATRICS 409 (Michael S. Kappy et al. eds., Vol. 51 2004) (EXCERPT)
2091	Merlin G. Butler & Travis Thompson, <i>Prader-Willi Syndrome: Clinical and Genetic Findings</i> , 10 ENDOCRINOLOGIST 1–25 (2000)
2093	USPTO, Disclaimer in a Patent Under 37 C.F.R. § 1.321(a), Soleno Therapeutics, Inc., U.S. Patent No. 12,419,895, Methods For Treating Subjects With Prader-Willi Syndrome, Dkt. No. 46696-0264009 (July 22, 2026)

12. My opinions are additionally guided by my appreciation of how a person of ordinary skill in the art (“POSA”) would have understood the claims of the ’895 Patent at the time of the alleged invention, which I have been asked to assume is November 14, 2014. I refer to this date as the “priority date” below.

V. Legal Standards

13. I am not a lawyer. In forming my opinions, I have applied the legal standards that counsel provided to me, which are set forth below.

14. I understand that a patent is not invalid for obviousness unless the differences between the patent and the prior art are such that the subject matter as a whole would have been obvious as of the priority date of the patent to one skilled

in the art. I have been further informed that an analysis of whether a claim would have been obvious depends on (1) the scope and content of the prior art, (2) the differences between the claimed invention and the prior art, (3) the level of ordinary skill in the art, and (4) any objective indicia of nonobviousness.

15. I understand that, in addition to showing that a combination of prior art references discloses every element of a claim, Apotex must also prove that one of skill in the art would have had a motivation to combine those references and that one of skill in the art would have had a reasonable expectation of success in doing so.

16. I have been informed that the use of hindsight must be avoided in the obviousness analysis, and one must be cautious to avoid reading into the prior art the teachings of the claimed invention at issue. In other words, obviousness cannot be established by starting from the claimed invention and working backward to identify each limitation in the prior art. I have also been informed that obviousness must be assessed based on the prior art as a whole and that it is improper to pick and choose from any reference only so much as will support a given position, to the exclusion of other parts necessary for the full appreciation of what the reference suggests to one of skill in the art.

17. I have been informed that, when evaluating claims for obviousness, it is well settled that a petitioner cannot pick and choose teachings from any one

reference to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of skill in the art. I have also been informed that when a party challenging a patent relies on multiple prior art disclosures to demonstrate that an invention would have been obvious to one of skill in the art, the challenger must prove not only that the prior art taught or suggested the elements of the invention, but also that one of skill in the art would have had a reason to combine the teachings of the prior art disclosures to achieve the claimed invention as a whole as of the priority date. In other words, there needs to be a motivation to combine the known elements in the way claimed by the patent at issue. I have been informed that whether one of skill in the art would have had a motivation to make a combination includes whether he or she would select a particular reference or references from the available prior art in order to combine the elements. I have also been informed that the reason to combine analysis must account for “reasons not to combine.” For example, a motivation to combine may not exist where the combination would be inoperable, would have undesirable properties, or would be unlikely to be productive of the result sought by the inventor.

18. I have been informed that, in addition to having a motivation to combine the teachings of the prior art, one of skill in the art must have had a reasonable expectation of success in doing so as of the priority date. I have been

informed that to have a reasonable expectation of success, one must be motivated to do more than merely vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. Even where the prior art would have motivated one of skill in the art to perform experiments that would ultimately have resulted in the claimed invention, the invention would not have been obvious if one of skill in the art would not have had a reasonable expectation that such experiments would succeed in yielding the claimed properties.

VI. A Person of Ordinary Skill in the Art

19. For purposes of this Declaration, I have been informed by counsel that the undisputed priority date for the '895 patent is November 14, 2014. Therefore, for the purposes of this Declaration, I have considered the validity of the claims of the '895 patent, including the state of the art, as of November 14, 2014.

20. I have been informed by counsel that a POSA is a hypothetical person who is presumed to be familiar with the relevant scientific field and its literature at the time of the inventions. This hypothetical person is also a person of ordinary creativity capable of understanding the scientific principles applicable to the pertinent field. I understand one of skill in the art is presumed to be one who thinks

along the lines of conventional wisdom in the art and is not one who undertakes to innovate.

21. Dr. Hollander's proposed POSA definition is the following (Ex.1005 ¶¶ 28-29):

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.

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.

22. For purposes of my Declaration in support of Soleno's Preliminary Response only, I do not contest Dr. Hollander's proposed POSA definition (Ex.1005 ¶¶ 28-29).

23. As of November 14, 2014, I had at least the background and qualifications of one of skill in the art in relation to the '895 patent under Dr. Hollander's POSA definition.

24. For purposes of my analysis of the validity of the '895 patent, I rely on this POSA definition.

VII. Scientific Background and State of the Art

25. In this section, I explain the technical background relevant to the '895 patent claims and my analysis.

A. Prader-Willi Syndrome (PWS) and Hyperphagia

26. PWS is a complex and rare genetic disorder. PWS is caused by the loss of function of genes on chromosome 15q11-q13, which is typically through paternal deletion, maternal uniparental disomy, or imprinting defects. Ex.2046 (Cassidy 2012) at 1. This genetic abnormality disrupts hypothalamic development and function, which in turn produces the various clinical features that define PWS, including an impaired ability to regulate appetite, chronic and severe hunger, hyperphagia, food-seeking behavior, and behavioral and metabolic complications. '895 patent, 19:29-20:25; Ex.2054 (Goldstone 2008) at 1; Ex.2049 (Dimitropoulos 2000) at 1; Ex.2057 (Hoybye 2003 Thesis) at 11.

27. From a neuroendocrine perspective, the hypothalamic dysfunction in PWS results in dysregulated signaling of key appetite-modulating hormones and

neuropeptides, including ghrelin (hunger hormone), leptin (satiety hormone), and oxytocin. Ex.2057 (Hoybye 2003 Thesis) at 9, 24, 26. PWS patients characteristically exhibit elevated levels of acylated ghrelin—the orexigenic (appetite-stimulating) hormone—which may be a contributor to the persistent drive to eat. Ex.2071 (Waele 2008) at 1, 6; Ex.2046 (Cassidy 2012) at 3. Simultaneously, despite often elevated leptin levels (which in a normally functioning hypothalamus would signal satiety), PWS patients exhibit functional leptin resistance, meaning their brains fail to appropriately register satiety signals. Ex.2056 (Hoybye 2003 Paper) at 5. While the mechanism of how hypothalamic dysregulation results in unrelenting hunger is not completely understood, this experience seems to be distinct from the hunger experienced by typical individuals. Ex.2045 (Butler 2006) at 210.

28. In my experience, PWS patients feel that they are starving even when they are not. This subjective experience of starvation is not merely psychological but reflects a genuine neurobiological signal: the hypothalamus in PWS patients fails to generate appropriate post-prandial (after a meal) satiety signals, and the patient's brain continues to signal caloric deficit even after adequate or excessive caloric intake. Ex.2045 (Butler 2006) at 212; Ex.2062 (Miller 2007) at 1. As a result, PWS patients may eat any food in sight, steal and hoard food, consume unappetizing food-related items (e.g., frozen food, pet food, or spoiled food, and

food-flavored items like shampoo). '895 patent, 20:14-25; Ex.2045 (Butler 2006) at 210; Ex.2062 (Miller 2007) at 1. They may also become angry or throw tantrums if denied food. Ex.1017 (Miller 2011) at 14. Left unmanaged, this unrelenting hyperphagia poses life-threatening risks, including gastric rupture, choking, and morbid obesity with associated cardiopulmonary complications. Ex.2045 (Butler 2006) at 35, 262; Ex.2054 (Goldstone 2008) at 5.

29. PWS is further associated with short stature, intellectual disabilities, incomplete sexual development, and severe hypotonia (low muscle tone). Ex.2045 (Butler 2006) at 20, 25-26, 41, 76; Ex.2054 (Goldstone 2008) at 3, 5, 7. Moreover, PWS is associated with distinctive behavioral challenges—for example, temper outbursts, stubbornness, and compulsive tendencies. Ex.2045 (Butler 2006) at 18, 22, 24; Ex.2054 (Goldstone 2008) at 8.

30. PWS first presents with prenatal reduced movement and neonatal hypotonia and feeding difficulty, evolving to early childhood hyperphagia. Ex.2046 (Cassidy 2012) at 1; Ex.2045 (Butler 2006) at 22. This progression, which spans from failure to thrive (during infancy) to hyperphagia (in childhood onward), demonstrates the evolving impact of hypothalamic dysfunction across development. Ex.2046 (Cassidy 2012) at 2; Ex.2054 (Goldstone 2008) at 4. PWS's clinical course is characterized by a series of distinct nutritional phases, which I describe in detail below. Ex.2046 (Cassidy 2012) at 2, Tbl. 1; Ex.1017

(Miller 2011) at 1 (identifying “a total of seven different nutritional phases, with five main phases and sub-phases in phases 1 and 2”).

31. **Phase 0 (Prenatal).** Phase 0 occurs in utero and is characterized by decreased fetal movement and lower birth weight compared to unaffected siblings. This phase reflects the early neuromuscular impact of the genetic abnormality, with hypotonia already present before birth. Ex.2046 (Cassidy 2012) at 2, Tbl. 1; Ex.2073 (Zipf 2004) at 23; Ex.2045 (Butler 2006) at 62.

32. **Phase 1 (Infancy).** Phase 1 is subdivided into phases 1a and 1b. Ex.2046 (Cassidy 2012) at 2. Phase 1a typically spans from birth through approximately nine months of age and is defined by hypotonia and difficulty feeding. Ex.2046 (Cassidy 2012) at 2, Tbl. 1; Ex.2073 (Zipf 2004) at 23. Neonates in phase 1a often have apparently reduced drive to eat, a weak or absent suck reflex, requiring assisted feeding techniques such as specialized nipples, nasogastric tubes, or gavage feeding to achieve adequate caloric intake. Ex.2046 (Cassidy 2012) at 2, Tbl. 1; Ex.2073 (Zipf 2004) at 23. During this sub-phase, infants with PWS are frequently diagnosed with “failure to thrive” because they are unable to consume sufficient calories to support normal growth. Ex.2046 (Cassidy 2012) at 2; Ex.2054 (Goldstone 2008) at 4. This presentation is clinically significant because it is the *opposite* of the hyperphagia that will later dominate the disease course, and it reflects the severity of the underlying hypothalamic and

neuromuscular dysfunction. Ex.2046 (Cassidy 2012) at 1; Ex.2091 (Butler 2000) at 5.

33. Phase 1b typically begins around nine months of age and extends to approximately 25 months. Ex.2046 (Cassidy 2012) at 2, Tbl. 1. During phase 1b, feeding and growth improve, and the infant begins to grow along a normal trajectory. Ex.2046 (Cassidy 2012) at 2; Ex.2054 (Goldstone 2008) at 4. Both the desire to eat and the sense of satiety are apparently normal in this phase, so the infant can be allowed to self-regulate. Although appetite is not yet excessive, subtle changes in body composition—including a relative increase in fat mass—may already be detectable during this sub-phase. Ex.2040 (Bekx 2003) at 1; Ex.2070 (Theodoro 2006) at 1. Phase 1b represents a window in which the most dangerous features of PWS have not yet emerged, but the underlying metabolic and endocrine abnormalities are already developing.

34. **Phase 2 (Transition to Weight Gain).** Phase 2 is also subdivided. Phase 2a typically begins around age two and is characterized by weight gain without a corresponding increase in appetite or caloric intake, reflecting that metabolism has slowed to an abnormally low resting energy expenditure characteristic of PWS. Ex.2046 (Cassidy 2012) at 2, Tbl. 2; Ex.2054 (Goldstone 2008) at 4. Phase 2b follows, typically beginning around age four to five, and is marked by an increase in interest in food and caloric intake, though appetite is not

yet at the insatiable levels seen in later phases. Ex.2046 (Cassidy 2012) at 2, Tbl. 2; Ex.2054 (Goldstone 2008) at 4. During phase 2b, caregivers may begin to notice food-seeking behaviors and an increasing preoccupation with food. Ex.1017 (Miller 2011) at 5.

35. **Phase 3 (Hyperphagia).** Phase 3 is the most clinically consequential nutritional phase, wherein hyperphagia is the defining feature. PWS patients enter phase 3 and experience hyperphagia and associated problematic food-related behaviors most often between four and eight years of age. Ex.2046 (Cassidy 2012) at 2, Tbl. 1; '895 patent, 20:14-15. Phase 3 is characterized by insatiable appetite, aggressive food-seeking, and a complete or near-complete lack of satiety. Ex.2054 (Goldstone 2008) at 4. Patients in phase 3 exhibit a relentless drive to consume food that is qualitatively different from overeating in non-PWS populations: the hunger is not responsive to caloric intake, meal size, or nutritional status, and it does not abate after eating. Ex.2054 (Goldstone 2008) at 4. The neurobiological basis for this insatiable hunger lies in the hypothalamic dysfunction described above—specifically, the failure of post-prandial satiety signaling, elevated ghrelin, and functional leptin resistance—which converge to create a state of perceived perpetual starvation. Ex.2046 (Cassidy 2012) at 3, Tbl. 2; Ex.2054 (Goldstone 2008) at 4; Ex.2071 (Waele 2008) at 1, 6; Ex.2056 (Hoybye 2003 Paper) at 5.

36. Phase 3 hyperphagia is also accompanied by significant behavioral manifestations, including food stealing and hoarding, foraging through garbage, nocturnal food-seeking, consumption of non-food items (pica), and severe behavioral outbursts when food is restricted. Ex.2046 (Cassidy 2012) at 3; *see also* Ex.2045 (Butler 2006) at 210; Ex.2049 (Dimitropoulos 2000) at 4; Ex.2062 (Miller 2007) at 1; Ex.1017 (Miller 2011) at 14. These behaviors impose enormous burdens on caregivers and require constant environmental controls, such as locking refrigerators and pantries, to prevent life-threatening overconsumption. Ex.2046 (Cassidy 2012) at 12; Ex.2073 (Zipf 2004) at 23; *see also* Ex.2045 (Butler 2006) at 49. Without pharmacological intervention, there is no effective means of controlling the hyperphagia itself; environmental and behavioral management can limit access to food but do not address the underlying neurobiological drive. Ex.2064 (Miller 2014) at 6; Ex.2041 (Benarroch 2007) at 9.

37. **Phase 4 (Adulthood).** Some PWS patients transition to phase 4, which may be characterized by a modest reduction in appetite compared to phase 3. Ex.2046 (Cassidy 2012) at 2; Ex.2054 (Goldstone 2008) at 4. However, phase 4 is not universally observed, and many patients remain in phase 3 throughout adulthood. Ex.2046 (Cassidy 2012) at 2; Ex.2054 (Goldstone 2008) at 4. Even in patients who reach phase 4, appetite remains significantly elevated compared to

the general population, and ongoing food intake management remains essential. Ex.2054 (Goldstone 2008) at 4.

38. Importantly, the transition between nutritional phases is not always predictable and can vary significantly among patients, which adds complexity to both clinical management and the design of treatment regimens. Ex.2054 (Goldstone 2008) at 4. The age of onset, duration, and severity of each phase can vary. Ex.2045 (Butler 2006) at 46; Ex.2054 (Goldstone 2008) at 4; Ex.2046 (Cassidy 2012) at 8. This variability underscores the need for PWS-specific clinical data to inform dosing and treatment decisions, as therapeutic approaches developed in other populations may not apply to PWS. Ex.2041 (Benarroch 2007) at 3; Ex.2047 (Deal 2013) at 1; Ex.2037 (Aygün 2001) at 4.

B. PWS Fundamentally Differs from Obesity and Diabetes

39. As I have explained above, PWS is a rare genetic disorder with a distinct etiology, disease progression, and metabolic profile. *Supra* ¶¶ 26-38. In my expert opinion, the PWS population is fundamentally different from both the non-PWS obese population and the non-PWS diabetic population. These differences have direct implications for dosing, titration, and treatment design, and they preclude the straightforward application of protocols developed for obesity or diabetes to PWS patients without independent clinical investigation.

1. PWS Versus Obesity

40. In my expert opinion, the PWS population is fundamentally different from the non-PWS obese population. PWS is a genetic disorder with PWS patients having metabolic, endocrine, behavioral, and safety profiles that differ fundamentally from that of typical obese patients. Ex.2042 (Brambilla 1997) at 1; Ex.2043 (Brambilla 2011) at 1; Ex.2044 (Butler 1998) at 6-7; Ex.2070 (Theodoro 2006) at 4; Ex.2066 (Paisey 2011) at 1.

41. At the most basic level, common obesity is a multifactorial condition driven primarily by energy imbalance—excess caloric intake relative to expenditure—whereas PWS-related weight gain is driven by hypothalamic dysfunction that produces uncontrollable hyperphagia coupled with low energy expenditure. Ex.2069 (Talebizadeh 2005) at 2; Ex.2070 (Theodoro 2006) at 5. PWS patients have distinct body compositions (substantially reduced lean muscle mass with increased fat mass even at comparable body mass index (BMI)), along with central hypotonia (low muscle tone), which lower resting and total energy expenditure and alter caloric needs, weight-based dosing assumptions, and distribution volume in various ways that an obesity protocol would not contemplate. Ex.2042 (Brambilla 1997) at 1; Ex.2070 (Theodoro 2006) at 4; Ex.2040 (Bekx 2003) at 5; Ex.2045 (Butler 2006) at 286. This altered body composition means that pharmacokinetic parameters such as volume of

distribution, which is heavily influenced by the ratio of lean-to-fat tissue, cannot be reliably extrapolated from obese non-PWS populations to PWS patients. Ex.2045 (Butler 2006) at 256, 286. For example, a drug that distributes primarily into lean tissue will achieve higher plasma concentrations in a PWS patient compared to a non-PWS patient of comparable weight, while a lipophilic drug may have an extended duration of action due to increased fat stores. *Id.*

42. Because of these differences, in my opinion the same drug or dosing regimen could be less effective, require recalibration, or pose materially greater safety risks in a PWS patient than in a typical obesity patient. Ex.2041 (Benarroch 2007) at 3. A clinician treating PWS would therefore need to adapt monitoring, dosing, and endpoints to the PWS patient's unique pathophysiology rather than applying an obesity protocol wholesale.

43. There is a critical distinction between acknowledging that PWS has obesity as one of its symptoms and concluding that dosing protocols designed for common obesity are appropriate for, or transferable to, the treatment of PWS. Obesity is a consequence of hyperphagia if hyperphagia is not well-managed in PWS patients, but it is hyperphagia (not obesity) that is the condition being treated in PWS patients. Ex.2054 (Goldstone 2008) at 4, 10.

44. While PWS patients universally have low lean body mass and hypotonia (low muscle tone), obesity is not universal in PWS. Ex.2063 (Miller

2012) at 2; Ex.2072 (Waters 2014) at 14; Ex.2043 (Brambilla 2011) at 1. This is because managing weight in PWS patients can be accomplished through implementing strict and constant supervision, along with environmental control measures (for example, supervising meals closely, and locking refrigerators, pantries, and trash cans). The '895 patent reports that PWS patients are on average, overweight rather than obese—in other words, the '895 patent reports that more than half of PWS patients are not, in fact, obese. '895 patent, 20:3-8 (reporting a study of 109 children with PWS and finding “54% were not classified as obese by the best metric”), 20:9-11 (“both in adults and in children with PWS, obesity is not only not universal, but may, in fact, occur in less than half of the population”). In PWS patients, subcutaneous fat comprises a greater percentage of total fat when compared to obese controls at all ages. '895 patent, 20:11-13; Ex.2052 (Goldstone 2001) at 2, Tbl. 1. Moreover, PWS patients are more sedentary and expend less energy than either the general population or obese controls. '895 patent, 20:35-37; Ex.2040 (Bekx 2003) at 1; Ex.2045 (Butler 2006) at 31, 132.

45. Even obese PWS patients and non-PWS obese population differ fundamentally, as obese PWS patients have body compositions that are markedly distinct from obese non-PWS patients: they typically carry a higher proportion of body fat relative to lean mass, and their adipose tissue distribution differs

substantially from that seen in simple obesity. Ex.2042 (Brambilla 1997) at 1; Ex.2045 (Butler 2006) at 134; Ex.2052 (Goldstone 2001) at 2, Tbl. 1.

46. Additionally, PWS patients experience comorbidities not associated with common obesity, such as growth hormone deficiency, hypogonadism, central adrenal insufficiency, hypothyroidism, and behavioral disturbance, each of which might complicate a treatment protocol designed for a typical obese patient. Ex.2045 (Butler 2006) at 286; Ex.2054 (Goldstone 2008) at 5, 9; Ex.2063 (Miller 2012) at 4; Ex.2060 (Marzullo 2005) at 3. Moreover, PWS patients may have a blunted emesis (vomiting) response and a high pain threshold—these can mask the usual warning signs of gastrointestinal adverse events, elevated risk of respiratory and cardiac adverse events from sleep-disordered breathing and abnormal ventilatory responses, temperature dysregulation (which can mask infection), and heightened susceptibility to behavioral and psychiatric adverse events. Ex.2041 (Benarroch 2007) at 3, 9; Ex.2068 (Sinnema 2013) at 2. These altered safety signals are particularly relevant in the titration context: in a population where adverse effects present atypically and may be indistinguishable from baseline symptoms, a clinician cannot safely escalate doses at the same pace as for non-PWS patients (e.g., obese adults who can reliably manifest and self-report adverse effects). Ex.2045 (Butler 2006) at 278; Ex.2067 (Shapira 2004) at 3.

47. Moreover, PWS patients frequently have intellectual disability, limited expressive language, and impaired interoception, making self-reporting of adverse effects unreliable and requiring caregivers and clinicians to observe the patient over a longer period to detect safety signals following each dose change. Ex.2046 (Cassidy 2012) at 2; Ex.2045 (Butler 2006) at 278. This impaired self-reporting capacity has direct implications for titration: in an obese patient, a clinician can typically escalate doses with confidence that the patient will promptly report symptoms, whereas in a PWS patient, the clinician must rely on external observation (including caregiver reports) over an extended period. Ex.2045 (Butler 2006) at 278; Ex.2068 (Sinnema 2013) at 5; Ex.2073 (Zipf 2004) at 35.

48. There is also a well-documented history of obesity treatments failing to produce comparable results in PWS patients, which further supports the fundamental differences between PWS and common obesity. In my clinical experience, pharmacological agents and bariatric surgeries that have demonstrated efficacy for weight loss or appetite suppression in non-PWS obese populations have consistently failed to achieve similar outcomes in PWS patients. Ex.2091 (Butler 2000) at 5; Ex.2054 (Goldstone 2008) at 4; Ex.2063 (Miller 2012) at 5; Ex.2047 (Deal 2013) at 9-10; Ex.2073 (Zipf 2004) at 33.

49. As one example, as of the November 2014 priority date, topiramate—which has shown efficacy for weight loss in non-PWS obese patients—has failed

to demonstrate meaningful or consistent benefits for hyperphagia or weight management in PWS patients. Ex.2067 (Shapira 2004) at 4-5. As another example, as of the November 2014 priority date, metformin—which has been widely used in obese patients to improve insulin sensitivity and promote modest weight loss—likewise fails to consistently address the hypothalamic-driven hyperphagia that is the central clinical challenge in PWS. Ex.2064 (Miller 2014) at 3. These failures are not surprising given the distinct pathophysiology of PWS: the hyperphagia in PWS arises from hypothalamic dysfunction and dysregulated appetite signaling—a fundamentally different mechanism from the energy imbalance that drives common obesity—and drugs targeting the peripheral metabolic pathways involved in obesity do not address the central neurobiological defect in PWS. Ex.2045 (Butler 2006) at 212; Ex.2069 (Talebizadeh 2005) at 2.

50. Indeed, as of the November 2014 priority date, there was no pharmacological treatment for hyperphagia in PWS—none had been approved by the FDA, and none had demonstrated sufficient efficacy in clinical trials to support approval. Ex.2064 (Miller 2014) at 1, 6. The complete absence of any approved or clinically validated pharmacological treatment for hyperphagia in PWS as of the priority date reflects both the difficulty of the problem and the fundamental inadequacy of extrapolating from obesity treatments. One of skill in the art as of the November 2014 priority date would have been acutely aware of the numerous

failed attempts to repurpose an obesity drug for hyperphagia in PWS. This track record of failure would have further diminished any motivation to apply an obesity-derived dosing protocol to PWS patients, and would have further undermined any reasonable expectation of success in doing so.

2. PWS Versus Diabetes

51. In my expert opinion, the PWS population is fundamentally different from the non-PWS type 1 diabetes and type 2 diabetes populations. While Type 1 diabetes is an autoimmune condition wherein the immune system destroys pancreatic beta cells, which leads to absolute insulin deficiency, type 2 diabetes is characterized by progressive insulin resistance and relative insulin deficiency, which is driven by metabolic dysfunction. Ex.2059 (Itariu 2014) at 1; Ex.2065 (Olokoba 2012) at 1; Ex.2046 (Cassidy 2012) at 1; Ex.2045 (Butler 2006) at 133-134. For both type 1 and type 2 diabetes, one can monitor pharmacodynamic effects via well-established metabolic markers: fasting glucose, fasting insulin, homeostasis model assessment insulin resistance (HOMA-IR), and glycosylated hemoglobin. Ex.2069 (Talebizadeh 2005) at 4; Ex.2045 (Butler 2006) at 135.

52. In comparison to type 1 and type 2 diabetes, PWS is a neurodevelopmental/genetic disorder, wherein the main therapeutic target (hyperphagia) arises from hypothalamic dysfunction and dysregulated appetite signaling, rather than from insulin resistance or beta-cell failure. Ex.2064 (Miller

2014) at 2; Ex.2045 (Butler 2006) at 129. Although diazoxide acts on K_{ATP} channels in both diabetic and PWS contexts, its therapeutic purpose differs fundamentally between these populations. Ex.1009 (Cowen) at [0765]; Ex.1008 (Cotter) at [0057].

53. Moreover, PWS patients often face issues such as intellectual disabilities, limited expressive language, and impaired interoception, and these issues frequently make self-reporting unreliable. Accordingly, clinicians must rely on external observation (including caregiver reports). Ex.2045 (Butler 2006) at 278; Ex.2068 (Sinnema 2013) at 5; Ex.2073 (Zipf 2004) at 35.

54. Additionally, not all PWS patients are diabetics. Indeed, diabetes is not a universal feature of PWS and a significant proportion of PWS patients do not meet diagnostic criteria for either type 1 or type 2 diabetes, despite PWS patients being at an increased risk of developing type 2 diabetes due to obesity and metabolic dysfunction. Ex.2063 (Miller 2012) at 4-5; Ex.2039 (Hoybye 2002) at 5-6.

55. In my opinion, diazoxide would not be used as a treatment for diabetes because its mechanism of action—inhibiting insulin release from the pancreas—tends to worsen rather than improve hyperglycemia. Indeed, the Proglycem[®] (diazoxide) label contraindicates its use for functional hypoglycemia and identifies

hyperglycemia, including diabetic ketoacidosis, as a known adverse effect that would require monitoring and dose modification. Ex.1012 at 1, 2, 6.

C. The '895 Patent (Ex.1001) and Vykat XR

56. I have reviewed the '895 patent, titled "Methods for Treating Subjects with Prader-Willi Syndrome," which discloses methods of treating hyperphagia in a subject with PWS by administering diazoxide choline. '895 patent at cl. 1, 17:43-44.

57. It is my understanding that the '895 patent is listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book") for Vykat XR. Vykat XR is the first and only FDA-approved treatment for hyperphagia in adults and pediatric patients four (4) years of age and older with PWS. Ex.2017. Vykat XR is a diazoxide choline extended-release oral tablet ("DCCR"), which provides sustained drug exposure with once-daily dosing.

58. The '895 patent discloses a specific novel treatment regimen for PWS. In particular, the '895 patent discloses the administration of diazoxide choline at a particular starting dose and then titrating every two weeks to reach a target maintenance dose. '895 patent, 59:9-67:17 ('895 patent's Example 3), Figs. 1-5, 23:15-28 ('895 patent's description of figures). Soleno's novel regimen disclosed in the '895 patent was included in Vykat XR's prescribing information. Ex.1004 at 1. In my opinion, the '895 patent's efficacy data supports the disclosed treatment

regimen in detail. '895 patent at 59:9-67:17 ('895 patent's Example 3), Figs. 1-5, 23:15-28 ('895 patent's description of figures), 10:10-34 ('895 patent's ranges of administration), 14:2-3 ('895 patent's once-daily dosing).

59. The '895 patent's Example 3 discloses results from a single-center, open-label, single-arm clinical study (PC025) with a double-blind, placebo-controlled, randomized withdrawal extension. '895 patent, 59:9-14. Twelve PWS patients were enrolled; patients were initiated on a DCCR dose of about 1.5 mg/kg per day (with a maximum starting dose of 145 mg/day) and titrated every 2 weeks to about 2.4 mg/kg, 3.3 mg/kg, and 4.2 mg/kg (with a maximum dose of 507.5 mg/day) per day; and at each visit, patients were up-titrated at the investigator's discretion. *Id.* at 59:14-20, 59:21-22, 59:35-36. Efficacy endpoints included the following: hyperphagia, which was measured on a modified Dykens hyperphagia questionnaire using parent and caregiver responses, converted to a score between 0 and 34; weight; body fat, which was measured by Dual-Energy X-ray Absorptiometry ("DEXA"); lean body mass, which was measured by DEXA; resting energy expenditure, which was measured by indirect calorimetry; respiratory quotient, which was measured by indirect calorimetry; waist circumference; BMI; ghrelin; leptin; triglycerides; total cholesterol; HDL cholesterol; non-HDL cholesterol; and LDL cholesterol. *Id.* at 60:5-13.

Furthermore, a behavioral questionnaire collected additional information. *Id.* at 60:14-16.

60. Based on my review of Example 3, the '895 patent reports that there was a statistically significant reduction in hyperphagia in subjects randomized to DCCR compared to placebo in the double-blind phase from Baseline through Day 69, which continued for those randomized to remain on DCCR through the double-blind phase through Day 97. *Id.* at 64:55-59; *see also id.* at Tbls. 2-3, 10-12, 65:18-20. The '895 patent reports that the DCCR-treated patients showed more than twice the improvement in hyperphagia compared to those randomized to placebo, leptin levels decreased more than 20% from Baseline, and food-related behaviors were reduced. *Id.* at 64:64-67, 66:14-32, 65:3-14.

D. The Challenged Claims¹

61. It is my understanding that the '895 patent contains claims covering Soleno's novel PWS treatment regimen, which is supported by data disclosed in the '895 patent. I understand that independent claim 1 has been disclaimed, but recited a method of treating hyperphagia in a PWS patient by administering diazoxide choline once daily, such that administration reduces hyperphagia and one or more food-related behaviors. '895 patent at cl. 1.

¹ I have been informed that Soleno has disclaimed claims 1, 4-15, and 26. Ex.2093.

62. Dependent claims 2 and 3 depend from claim 1—which means that they incorporate and include all the limitations of claim 1—and cover administration duration of diazoxide choline. *Id.* at cls. 2-3. While Claim 2 recites administration for “at least 10 weeks,” claim 3 recites administration for “one or more years.” *Id.* at cls. 2-3.

63. Dependent claim 16 depends from claim 1—which means that it incorporates and includes all the limitations of claim 1—and requires administration of diazoxide choline to be “initiated at a starting dose” and “then titrated every two weeks to reach a maintenance dose.” *Id.* at cl. 16.

64. Dependent claims 17 through 25 recite doses for titrating diazoxide choline. Claims 17 and 18 depend from claim 16—which means that they incorporate and include all the limitations of claim 16—and recite “starting dose[s] of diazoxide choline.” *Id.* at cls. 17-18. While claim 17 recites a starting dose “between 25-100 mg,” claim 18 recites a starting dose “between 50-180 mg.” *Id.* at cls. 17-18.

65. Claims 19 through 25 recite “maintenance dose[s] of diazoxide choline.” *Id.* at cls. 19-25. Claims 19 and 24-25 depend from claim 17—which means that they incorporate and include all the limitations of claim 17—and recite maintenance doses, respectively, “between 100-200 mg” (claim 19), “between 25-250 mg” (claim 24) and “between 200-300 mg” (claim 25). *Id.* at cls. 19, 24-25.

Claims 20-23 depend from claim 18—which means that they incorporate and include all the limitations of claim 18—and recite maintenance doses, respectively, “between 200-300 mg” (claim 20), “between 300-500 mg” (claim 21), “between 500-2000 mg” (claim 22), and “between 100-500 mg” (claim 23). *Id.* at cls. 20-23.

E. Dosing of PWS Population

66. Based on my training and experience, the particular comorbidities of the PWS population mean that dosing of orally-administered medications in PWS patients brings on unique difficulties. Ex.2047 (Deal 2013) at 1, 6; Ex.2068 (Sinnema 2013) at 6; Ex.2073 (Zipf 2004) at 27.

67. Known adverse effects of diazoxide include: dyspepsia, nausea, diarrhea, fluid retention, edema, reduced rates of excretion of sodium, chloride, and uric acid, hyperglycemia, vomiting, abdominal pain, ileus, tachycardia, palpitations, hypertrichosis, and headache. Ex.1009 (Cowen) at [0227], [0228], Tbl. 50; Ex.1008 (Cotter) at [0073]. Several of these adverse effects—including fluid retention, edema (swelling caused by excess fluid), hyperglycemia (high blood sugar), and gastrointestinal events such as nausea, vomiting, abdominal pain, and ileus (stoppage of normal intestinal movement) are particularly relevant to the PWS population. Ex.2045 (Butler 2006) at 267; Ex.2068 (Sinnema 2013) at 6.

68. PWS patients universally have low lean body mass and hypotonia (low muscle tone). Ex.2045 (Butler 2006) at 150; Ex.2070 (Theodoro 2006) at 3; Ex.2042 (Brambilla 1997) at 1. The reduced lean body mass in PWS has pharmacokinetic implications: because drug distribution, metabolism, and clearance are influenced by body composition, a standard weight-based dose may result in higher effective drug concentrations in a PWS patient than in a non-PWS patient of similar total body weight, increasing the risk of dose-dependent adverse events. Ex.2041 (Benarroch 2007) at 3; Ex.2045 (Butler 2006) at 256.

69. Moreover, PWS patients may have a blunted emesis (vomiting) response and a high pain threshold that can mask the usual warning signs of gastrointestinal adverse events. Ex.2068 (Sinnema 2013) at 2, 5. They also face elevated risk of respiratory and cardiac adverse events from sleep-disordered breathing and abnormal ventilatory responses, temperature dysregulation that can mask infection, and heightened susceptibility to behavioral and psychiatric adverse events. Ex.2045 (Butler 2006) at 88, 92; Ex.2068 (Sinnema 2013) at 2, 6.

70. PWS patients also exhibit autonomic dysfunction, including abnormal heart rate variability and blunted cardiovascular reflexes. Ex.2045 (Butler 2006) at 95; Ex.2060 (Marzullo 2005) at 13, 18. This autonomic dysfunction means that cardiovascular pharmacodynamic markers, such as supine heart rate normalization, are unreliable in the PWS population. Ex.2045 (Butler 2006) at 95; Ex.2055 (Haqq

2012) at 6; Ex.2048 (DiMario 1996) at 1, 3. A dose-escalation protocol that relies on supine heart rate returning to baseline presupposes normal cardiovascular reflexes that may not be present in PWS patients, and would therefore be inappropriate and potentially dangerous if applied to this population. Ex.2055 (Haqq 2012) at 6. In my clinical experience, when titrating medications for PWS patients, one of skill in the art would focus on hyperglycemia (measured using blood glucose or A1C tests) and fluid retention or edema (measured using physical examination), not cardiovascular markers like supine heart rate, which is neither applicable to nor practical for the PWS population. Ex.2045 (Butler 2006) at 134-135, 267; Ex.2055 (Haqq 2012) at 6; Ex.2048 (DiMario 1996) at 1, 3.

71. Because of these conditions, it is my opinion that dosing for all medications must be approached differently in PWS patients when compared to other patient populations. Ex.2045 (Butler 2006) at 189, 286.

72. As of the November 2014 priority date, one skilled in the art would have recognized that PWS patients have an altered body composition which contributes to dramatically different pharmacokinetics as compared to other patient populations. Ex.2045 (Butler 2006) at 138, 256, 286; Ex.2041 (Benarroch 2007) at 3, 9. However, as of November 2014, it was not known how rapidly PWS patients could metabolize drugs, making the time required to reach steady-state plasma concentrations unknown. This altered pharmacokinetics is yet another

reason why dosing protocols developed in non-PWS populations cannot be directly applied to PWS patients without substantial adaptation. Ex.2045 (Butler 2006) at 256, 286; Ex.2047 (Deal 2013) at 1, 5. Indeed, one of skill in the art would not have known when a PWS patient could reach steady state compared to other patient populations.

73. In particular, diazoxide acts directly on K_{ATP} channels of pancreatic beta cells, thereby suppressing insulin secretion. Ex.2061 (McTaggart 2010) at 2. Because the mechanism of action is intimately tied to insulin regulation, a patient's response to diazoxide is highly dependent on the patient's underlying insulin sensitivity and secretion profile. Ex.2061 (McTaggart 2010) at 2. PWS patients have fundamentally different metabolic and physiological profiles compared to non-PWS obese or diabetic patients. As I have explained above, even obese PWS patients have body compositions that are markedly distinct from obese non-PWS patients: they typically carry a higher proportion of body fat relative to lean mass, and their adipose tissue distribution differs substantially from that seen in simple obesity or Type 2 diabetes. Ex.2042 (Brambilla 1997) at 1; Ex.2045 (Butler 2006) at 134; Ex.2052 (Goldstone 2001) at 2, Tbl. 1. These differences in body composition directly influence insulin dynamics and metabolic abnormalities. Ex.2052 (Goldstone 2001) at 5; Ex.2069 (Talebizadeh 2005) at 8. The unique interplay between the altered fat profile, atypical insulin sensitivity, and the

insulin-suppressive mechanism of diazoxide choline in PWS patients would have led one of skill in the art to recognize that dose-response relationships observed in metabolically distinct populations could not be reliably extrapolated to the PWS population without independent clinical investigation. Ex.2042 (Brambilla 1997) at 1; Ex.2045 (Butler 2006) at 134; Ex.2052 (Goldstone 2001) at 2, 5, Tbl. 1; Ex.2069 (Talebizadeh 2005) at 8.

74. Subsequent clinical data developed by Soleno revealed just how extreme the difference in steady-state kinetics is between PWS patients and non-PWS patients. As reflected in the Vykat XR Package Insert, Soleno discovered that diazoxide choline has a terminal half-life of approximately 106 hours in PWS patients. Ex.1004 (Vykat XR Package Insert). Applying standard pharmacokinetic principles, steady-state plasma concentrations are not achieved until approximately five half-lives have elapsed, which equates to approximately 22 days for PWS patients taking diazoxide choline. By comparison, steady state is reached after approximately 7 days in healthy volunteers, who exhibit a substantially shorter half-life of 28.7 to 32.4 hours. *Id.* This large difference confirms that the rapid, daily-increment titration protocols disclosed in Cowen—which were designed for non-PWS populations with fundamentally different pharmacokinetic profiles—would have been wholly inappropriate for PWS patients, as each successive daily dose increase would occur long before the prior dose had reached steady state,

creating a risk of dangerous drug accumulation. A two-week (14-day) interval between dose escalations allows meaningful drug accumulation at each dose level, providing clinicians a window in which to observe the patient's response and assess tolerability before increasing the dose.

75. For similar reasons, in my opinion, one of skill in the art at the time of the invention would have recognized that titrating dosing in the PWS population involved distinct challenges. Ex.2045 (Butler 2006) at 189, 286. Unlike treatment duration—which concerns how long a patient remains on a stable dose—the titration interval determines how rapidly the dose is escalated and, consequently, how much time the clinician has to detect emerging adverse effects before the next dose increase compounds them. Ex.2067 (Shapira 2004) at 3; Ex.2047 (Deal 2013) at 4; Ex.2045 (Butler 2006) at 256; Ex.2054 (Goldstone 2008) at 9. One of skill in the art would have understood that dose escalations need to occur more slowly in the PWS population to reliably identify drug-related adverse events and distinguish them from the patient's underlying condition. *Id.* This is particularly important because many PWS-associated comorbidities—such as edema, gastrointestinal dysmotility, and glucose dysregulation—overlap with known side effects of diazoxide, making it clinically difficult to attribute a new symptom to the drug versus the underlying disease without adequate observation time. Ex.1009

(Cowen) at [0227], [0228], Tbl. 50; Ex.1008 (Cotter) at [0073]; Ex.2045 (Butler 2006) at 267; Ex.2068 (Sinnema 2013) at 6.

76. Furthermore, a too-short titration interval in the PWS population risks stacking dose increases before adverse effects have fully manifested, potentially leading to serious and avoidable harm. Ex.2067 (Shapira 2004) at 3; Ex.2047 (Deal 2013) at 4; Ex.2045 (Butler 2006) at 256; Ex.2054 (Goldstone 2008) at 9. In pharmacological terms, as explained above, in people with normal drug metabolism, diazoxide has a relatively long half-life of approximately 24-36 hours, and steady-state plasma concentrations are not achieved until approximately 4-5 half-lives after a dose change—meaning it may take several days for the full pharmacological effect of a new dose level to be realized. Ex.1009 (Cowen) at [0764]; Ex.1008 (Cotter) at [0766]. If a clinician escalates the dose before steady state is reached, the cumulative drug exposure may exceed what was intended, amplifying the risk of hyperglycemia, fluid retention, and other dose-dependent toxicities. Ex.1009 (Cowen) at [0764]; Ex.1008 (Cotter) at [0766]. This concern is heightened in PWS patients because of their blunted emesis response and elevated pain thresholds, which can cause dose-dependent adverse effects to have an insidious onset that takes longer to fully declare itself than in non-PWS populations. Ex.2068 (Sinnema 2013) at 2; Ex.2042 (Brambilla 1997) at 2.

VIII. Asserted Prior Art

77. I have reviewed each of the three prior art references that Dr. Hollander (and Apotex) asserts across the three grounds: Cowen (Grounds 1-3), Cotter (Ground 2), and Miller (Ground 3). As I explain below, none of these references discloses the specific diazoxide choline dosing regimen claimed in the '895 patent for treating hyperphagia in PWS. Each reference's clinical data, dosing disclosures, and treatment parameters are directed to fundamentally different patient populations, therapeutic endpoints, and/or clinical conditions.

A. Cowen (Ex.1009)

78. Cowen (WO 2009/006483A1), titled "Salts of Potassium ATP Channel Openers and Uses Thereof," is a published patent application by Essentialis, Inc. I am told that Essentialis is a predecessor to Soleno.

79. Based on my review, Cowen describes salts of K_{ATP} channel openers, methods of preparing such salts, and methods of using such salts to treat a litany of diseases and conditions, including type 1 and type 2 diabetes, hypertension, dyslipidemia, nonalcoholic steatohepatitis, pulmonary hypertension, myocardial infarction and arrhythmias following myocardial infarction, and polycystic ovarian syndrome. Cowen at [0002].

80. In my opinion, the breadth of conditions listed in Cowen reflects a general disclosure of K_{ATP} channel opener utility without the kind of disease-

specific clinical validation necessary to guide treatment in any one of those conditions, let alone in the complex and vulnerable patient population associated with PWS.

81. Notably, Cowen discloses the use of diazoxide salts, but its disclosures of any dosing duration, dosing ranges, and titration with starting and maintenance dosages are not directed to treating PWS; rather, they are directed to obesity or type 1 and type 2 diabetes. *See, e.g.*, Cowen at [0735]-[0736], [0740]-[0741]. Cowen also discloses general dosages of K_{ATP} channel openers and general dosing titration with starting and maintenance dosages that are untethered to any particular disease or condition or any particular K_{ATP} channel opener. *Id.* at [0061] (dosing ranges), [0478] (dosing titration).

82. Based on my review, Cowen provides limited clinical data, only in non-PWS subjects, and primarily in obese patients. Not a single clinical example involves a PWS patient or addresses hyperphagia. Notably, Example 11—the only example using dose titration—titrated hypertriglyceridemic patients at 7-day intervals, not two-week intervals. *Id.* at [00772]-[00776].

83. Cowen's clinical examples are as follows:

- Example 7: clinical study in obese subjects comparing safety, tolerability, and bioavailability/pharmacokinetics of single-dose of diazoxide free base (Proglycem[®]) with DCCR under fasting conditions. *Id.* at [00749]; *see also*

id. at [00750]-[00764].

- Example 8: clinical study in obese subjects evaluating the potential of once-daily DCCR to improve insulin sensitivity and provide beta-cell rest as evidenced by reductions in HOMA-IR and fasting insulin. *Id.* at [00766].
- Example 9: clinical study in overweight or obese subjects evaluating the relationship between pharmacokinetic parameters and weight and BMI. *Id.* at [00767]-[00769].
- Example 10: clinical study in obese subjects evaluating diazoxide for treatment of dyslipidemia. *Id.* at [00770]-[00771].
- Example 11: clinical study in subjects with elevated fasting triglycerides, with or without elevated total cholesterol or LDL-cholesterol, evaluating diazoxide for treatment of hypertriglyceridemia. *Id.* at [00772]-[00776].
- Example 12: clinical study in healthy volunteers evaluating lipid parameters and blood pressure. *Id.* at [00777]-[00779].
- Example 13: clinical study in hypertriglyceridemic patients evaluating diazoxide treatment. *Id.* at [00780]-[00782].
- Example 14: clinical study in fasted subjects evaluating diazoxide choline administration with food to reduce the incidence of adverse events. *Id.* at [00783]-[00784].

B. Cotter (Ex.1008)

84. Cotter (WO 2014/197753A1), titled “Method of Treating Prader Willi Syndrome and Conditions Associated with Low Basal Metabolic Rate or Hyperphagia,” is a published patent application by Sedogen, LLC.

85. Based on my review, Cotter describes treating PWS and conditions that would affect basal metabolic rate by, in general, co-administering a K_{ATP} channel opener with “other therapies used to treat PWS, such as human growth hormone, a wakefulness promoting agent, or a psychiatric/mood stabilizing medication, which may allow the dose of these other therapies to be reduced relative to the dose that would otherwise be given to a patient with PWS in the absence of the K_{ATP} channel opener (e.g., baseline dose).” Cotter at [0001].

86. Notably, Cotter only provides a single example of treating a PWS patient, an infant who did not have hyperphagia. *Id.* at [0148]-[0150] (Example 1). Diazoxide was administered to an 8-month-old infant with PWS (nutritional phase 1a transitioning to phase 1b) who was experiencing hypoglycemic episodes. *Id.* at [0149]. The infant was started at 0.5 mg/kg BID (twice daily) diazoxide and eventually increased to 1 mg/kg BID. *Id.* The infant did not progress to nutritional phase 2a after a period of 56 weeks, “perhaps as a result of the administration of diazoxide,” which “supports the utility of diazoxide in the treatment of PWS.” *Id.* at [0149], [0150]. I note that after 56 weeks, the 8-month-old infant would have

been about 21 months old and would likely not have progressed to phase 2a anyway because the median age of onset for phase 2a is 25 months. *Supra* ¶¶ 33-34.

87. In my opinion, one of skill in the art would not have extrapolated from Example 1's single case report involving the use of diazoxide in an infant to treat hypoglycemia (likely due to hyperinsulinism) to conclude that diazoxide could safely and effectively treat hyperphagia in older PWS patients, given the entirely different pathophysiology, patient population, and clinical endpoints involved. *Infra* § X. Moreover, in my experience, hypoglycemia is not a typical problem experienced by patients with PWS, which further undermines any extrapolation.

C. Miller (Ex.1017)

88. "Nutritional Phases in Prader-Willi Syndrome" (Miller) is a 2011 publication by Jennifer L. Miller and others that was published in The American Journal of Medical Genetics.

89. Based on my review, Miller reports a study describing the various nutritional phases of PWS. *See* Miller at 1 (identifying "a total of seven different nutritional phases, with five main phases and sub-phases in phases 1 and 2"). Importantly, Miller does not address pharmacological therapy, let alone administration of diazoxide choline, for treatment of hyperphagia in PWS. Thus, while Miller provides a valuable clinical characterization of the PWS nutritional phases, it is a descriptive, observational study that offers no pharmacological

guidance whatsoever—no dosing, no titration, no drug selection, and no treatment outcomes.

90. In my opinion, Miller's contribution is limited to disease characterization, and it does not, standing alone or in combination with other references, teach or suggest a specific pharmacological treatment regimen for hyperphagia in PWS.

IX. Ground 1: Cowen Does Not Render Claims 2-3 and 16-25 Obvious

91. I have been asked whether, in my expert opinion, Cowen alone renders obvious Claims 2-3 and 16-25 of the '895 patent. For the reasons set forth below, it is my opinion that it does not. Cowen's dosing disclosures are directed to fundamentally different patient populations (obese and diabetic adults), and there would have been no scientific basis for one of skill in the art to apply those disclosures to PWS patients with any reasonable expectation of success.

A. Claims 2-3 (Treatment Duration Claims)

92. Apotex's expert, Dr. Hollander, opines that Cowen's references to K_{ATP} channel opener salts being "dosed daily for up to 12 months" satisfy the durational requirements in Claims 2 ("at least 10 weeks") and 3 ("one or more years"). Ex.1005 ¶¶ 133-137 (citing Cowen at Abstract, [0234], [0735]-[0736], [0741]). I disagree for two independent reasons. First, one of skill in the art would have recognized that Cowen's cited passages do not actually teach or suggest

treating PWS patients with diazoxide choline over these time frames. Second, even setting that aside, one of skill in the art would not have had any reason to apply Cowen's obesity-focused study design to the PWS population or have any expectation that doing so would be successful.

1. One of Skill in the Art Would Have Recognized that Cowen Does Not Teach or Render Obvious Treating PWS Patients for at Least 10 Weeks or Up to 12 Months

93. Based on my review of Cowen, every disclosure cited by Apotex and Dr. Hollander for treatment duration is limited to obese adults—a patient population that fundamentally differs from PWS patients in several critical respects, including age demographics, body composition, and disease etiology. *Supra* § VII.B.1 (explaining fundamental differences between PWS and common obesity).

94. Cowen paragraphs [0735]-[0736] specifically reference dosing “moderate-to-morbidly obese adults” with a BMI of 30 or above for up to 12 months. Paragraph [0741] also describes co-administration with phentermine in the same adult obesity context for the same duration. Neither disclosure addresses PWS.

95. Paragraph [0093] does not change that. Instead, it just lists PWS as one of eight conditions characterized by obesity, hyperphagia, dyslipidemia, or reduced energy expenditure. Pet. 30 (citing Cowen at [0093]). In my opinion, one

of skill in the art would not have considered this listing a teaching that an obesity protocol would be applicable to treating hyperphagia in PWS. *Supra* ¶¶ 40-50.

96. In my opinion, one of skill in the art would have recognized a fundamental distinction between acknowledgment that PWS patients may develop obesity as a clinical feature of the syndrome and the affirmative teaching that a dosing protocol specifically designed and optimized for the treatment of adult obesity would be appropriate for, or readily transferable to, the treatment of hyperphagia in PWS. The fact that obesity can be a downstream consequence of PWS does not, alone, suggest to one of skill in the art that a therapeutic regimen developed for a different patient population—adults with common obesity—would be suitable for PWS patients, who present with a distinct and complex pathophysiology involving hypothalamic dysfunction, hormonal dysregulation, hyperphagia, and altered body composition. *Supra* ¶¶ 40-47.

97. Indeed, one of skill in the art would have understood that PWS is not simply another form of obesity but rather a genetic disorder in which obesity, when it occurs, arises through mechanisms that differ materially from those underlying typical adult obesity. *Supra* § VII.E (explaining unique dosing and titration challenges in PWS patients). Accordingly, even where a reference discusses the prevalence of obesity among PWS patients, one of skill in the art would not have understood such references as teaching or suggesting that dosing regimens

validated in common obesity could be applied to PWS patients without independent investigation into the safety, efficacy, and pharmacokinetic considerations unique to this vulnerable population.

2. One of Skill in the Art Would Not Have Had Any Reason to Modify Cowen's Disclosures Nor A Reasonable Expectation of Success in Doing So

98. One of skill in the art would not have applied an obesity protocol to treat hyperphagia in PWS patients and would not have had a reasonable expectation of success in doing so.

99. First, as I explained above, PWS differs fundamentally from common obesity in its etiology, body composition, metabolic profile, comorbidity burden, and patient demographics. *Supra* ¶¶ 40-47. These differences directly affect drug safety and efficacy. The therapeutic target in PWS is hyperphagia—a behavioral endpoint driven by hypothalamic dysfunction—not the metabolic endpoints (e.g., weight loss, insulin sensitivity, lipid profiles) that inform treatment duration decisions in obesity studies. *Supra* ¶¶ 26-28, 40-50. Duration for an obesity protocol is selected based on expectations about metabolic adaptation, weight-loss plateaus, and cardiovascular risk reduction timelines; none of which applies to treating hyperphagia in PWS. *Supra* ¶¶ 43, 73-74.

100. Second, the track record of obesity treatments failing in PWS would have significantly diminished any motivation to borrow treatment parameters from

obesity protocols. As of the priority date, topiramate, metformin, and bariatric surgery—all effective in common obesity—have failed to provide meaningful benefit for hyperphagia in PWS. *Supra* ¶¶ 49-50. This well-documented pattern of failure demonstrates that obesity and PWS respond differently to the same interventions, and it would have discouraged one of skill in the art from assuming transferability of treatment parameters.

101. Third, one of skill in the art would have recognized that pediatric patients constitute a meaningful share of the PWS population because PWS is typically diagnosed in infancy or early childhood. Ex.2054 (Goldstone 2008) at 2. Moreover, PWS patients experience early mortality with an average age of death in their early 20s. In my clinical experience, a substantial number of my PWS patients are children. This demographic reality is significant because Cowen's obesity protocols were developed in and for adults. Cowen at [0735]-[0736], [0740]-[0741]. One of skill in the art would have understood that pediatric patients present distinct pharmacokinetic and pharmacodynamic considerations—including differences in drug metabolism, body composition, and dosing requirements—that prevent the straightforward application of an adult obesity protocol to a population that includes many pediatric patients.

102. Fourth, paragraphs [0740]-[0741] describe co-administration with phentermine, a metabolic, weight-management drug used specifically for weight

loss in obese patients. Ex.2038 (phentermine prescribing information) at 1. It is not used to treat hyperphagia and I am not aware of it being used to treat PWS. Moreover, phentermine is not recommended for use in pediatric patients. *Id.* at 4, 7. Given the prevalence of pediatric patients in the PWS population, *supra* ¶ 101, one of skill in the art would have had even greater reason not to look to Cowen's co-administration disclosure as relevant to the treatment of hyperphagia in PWS.

103. Fifth, one of skill in the art would have understood Cowen's disclosures as describing hypothetical study protocols—frameworks for how a drug might be tested and a window of observation for gathering data—rather than as clinically-validated teachings that recommend a particular treatment duration for any patient population, let alone for a condition as complex as PWS. Cowen's disclosures outline how a study could be structured in obese adults, not how a clinician should treat a PWS patient.

B. Claim 16 (Dosing Titration Claim)

104. Apotex's expert, Dr. Hollander, opines that Cowen's dose-escalation disclosures render obvious Claim 16's titration regimen of administering diazoxide choline at a starting dose and then titrating every two weeks until a maintenance dose is reached. Ex.1005 ¶¶ 77-80, 144-162 (citing Cowen at [0077], [0089], [00448], [00478], [00481]-[00483], [00489]-[00490]). I disagree for the reasons listed below.

1. One of Skill in the Art Would Have Recognized that Cowen Does Not Teach a Two-Week Titration Interval and One of Skill in the Art Would Not Have Had Reason to Adopt One

105. Paragraph [0077] teaches dose escalation “after supine heart rates return to baseline.” This is an event-driven titration regimen—the trigger for dose escalation is a specific physiological event (return of heart rate to baseline) that is unique to each individual patient, not the passage of a fixed period of time. From a pharmacological standpoint, these are two fundamentally different approaches to titration. An event-driven approach escalates the dose whenever a cardiovascular biomarker indicates that the body has adapted to the current dose, regardless of how many days have passed. A fixed two-week interval, by contrast, is a calendar-based titration regimen that reflects independent clinical considerations about how long to observe patients for adverse effects before increasing the dose. One of skill in the art would have recognized this difference and would not have had any reason to change Cowen’s disclosure of an event-driven dose escalation approach into a fixed two-week interval, as claimed.

106. In addition, one of skill in the art would have seen that Cowen’s disclosure of “daily for days or a few weeks” in paragraph [0077] describes the time period over which each dose level is maintained before the physiological event (return of heart rate to baseline) may occur to signal that the patient is ready for the next dose escalation, not a titration interval. Cowen separately teaches, in

paragraphs [0089] and [00448], “increasing dose daily” with “2 to 10 escalation steps”—a teaching of daily dose escalation that is directly inconsistent with a two-week titration interval. In my opinion, one of skill in the art reading Cowen as a whole would not have arrived at a fixed two-week titration schedule; if anything, Cowen teaches either daily escalation or event-driven escalation, both of which are far more aggressive than a two-week interval.

2. One of Skill in the Art Would Have Recognized that Cowen’s Dose-Escalation Disclosures Are Directed to Non-PWS Populations and Could Not Be Extrapolated to PWS Patients

107. Cowen’s guidance is rooted in patient populations with little to no clinical overlap with PWS. Cowen at [0077], [0089], [00448], [00478], [00481]-[00484], [00489]-[00490]. There would have been no reason for one of skill in the art to use dose-adjustment protocols for obese or diabetic adults to treat hyperphagia in PWS.

108. First, paragraph [0077] is expressly directed to treating “obesity, type 1 or type 2 diabetes.” Its dose escalation trigger (supine heart rate normalization) is a cardiovascular pharmacodynamic marker that is not relevant for PWS patients. As explained above, PWS patients exhibit autonomic nervous system irregularities, including abnormal heart rate variability and blunted cardiovascular reflexes, which render supine heart rate normalization unreliable as a dose-escalation trigger in this population. *Supra* ¶¶ 70-71. One of skill in the art would

have recognized that Cowen’s event-driven titration paradigm is scientifically inapplicable to PWS patients because the underlying physiological signal it depends upon is unreliable in that population. *Id.*

109. Second, paragraphs [0089] and [00448] teach “increasing dose daily” with “2 to 10” escalation steps—a rapid, daily-increment titration protocol. In my opinion, one of skill in the art would have understood these daily-increment protocols as designed for patient populations who can reliably self-report adverse effects and whose therapeutic endpoints can be measured through routine, objective laboratory values. For example, in obese patients, the relevant therapeutic endpoint—weight loss—can be tracked through daily weigh-ins, and in diabetic patients, glycemic control can be monitored through daily blood glucose readings. These are straightforward, readily quantifiable metrics that justify a rapid, daily-increment titration regimen because the treating physician receives near-real-time feedback on both safety and efficacy. PWS patients, by contrast, present fundamentally different challenges that render such a rapid titration approach inappropriate. *Supra* § VII.E (explaining the unique dosing and titration challenges in PWS). PWS patients may be unable to reliably communicate adverse effects due to cognitive impairment, characteristically high pain thresholds, and blunted physiological warning signs. *Supra* ¶¶ 45-47, 69, 76. One of skill in the

art would therefore not have looked at the daily-increment protocols of paragraphs [0089] and [00448] and applied them to PWS patients.

110. Third, paragraphs [00478], [00481]-[00484], and [00489]-[00490], do not even mention PWS. Several are expressly directed to an “overweight or obese subject” or an “obesity prone subject.” Cowen at [00482]-[00484], [00489]-[00490]. While paragraphs [00478] and [00481] refer to “a subject in need thereof,” neither mentions PWS, and one of skill in the art would not have read this generic language as encompassing the distinct PWS patient population without further direction. Paragraphs [00481]-[00482] reference Proglycem[®], the commercially available form of diazoxide that is FDA-approved for treating hyperinsulinemic hypoglycemia, not hyperphagia or PWS. Cowen at [00481]-[00482]; Ex.1018 (Proglycem[®] prescribing information). In my opinion, this confirms that the titration teachings in these passages are anchored to an entirely different therapeutic context, targeting a pancreatic mechanism of insulin suppression rather than the hypothalamic appetite regulation relevant to PWS. One of skill in the art would have recognized that dose-escalation guidance developed for hyperinsulinemic hypoglycemia cannot be extrapolated to the treatment of hyperphagia.

111. Fourth, and perhaps more tellingly, the only mention of PWS anywhere in Cowen appears in paragraph [0093], where it is listed as one of eight

conditions “characterized by obesity, hyperphagia, dyslipidemia, or decreased energy expenditure.” But that paragraph says nothing about titration or dose escalation, and it certainly does not suggest that obesity dosing parameters can be imported wholesale into the PWS context. One of skill in the art would not have seen that mention of PWS as a potential indication as providing any basis for determining how to titrate doses for PWS patients to accommodate their specific needs. *Supra* §§ VII.E (explaining the unique dosing and titration challenges in PWS), VII.B (distinguishing PWS from obesity and diabetes populations). In my opinion, one of skill in the art would have understood that developing an appropriate titration schedule for PWS requires population-specific clinical investigation, not mechanical application of escalation parameters developed for metabolically distinct conditions.

3. One of Skill in the Art Would Have Recognized that the Claimed Two-Week Interval Was the Result of a Specific Clinical Insight Tailored to the PWS Population

112. In my opinion, the two-week titration interval claimed in Claim 16 reflects specific clinical insight into the pharmacokinetics and clinical management requirements of PWS patients.

113. The scientific rationale for a two-week interval is grounded in the dramatically prolonged half-life of diazoxide choline in PWS patients. As of the priority date, it was known that PWS patients have dramatically different

pharmacokinetics compared to other patient populations. *Supra* ¶¶ 72-74. However, it was not known how rapidly PWS patients could metabolize drugs—let alone the specific compound claimed here, diazoxide choline—making the time required to reach steady-state plasma concentrations unknown. *Id.* Accordingly, one of skill in the art would not have known whether a PWS patient could reach steady state in the timeframe of “days” contemplated by Cowen’s daily-escalation protocols, and would have had no basis to assume that daily dose increments would be safe or meaningful before the prior dose had reached its full pharmacological effect.

114. As explained above, subsequent clinical data developed by Soleno revealed just how extreme the difference in steady-state kinetics is between PWS patients and non-PWS patients. *Supra* ¶ 74. As reflected in the Vykat XR Package Insert, Soleno discovered that diazoxide choline has a terminal half-life of approximately 106 hours in PWS patients. Ex.1004 (Vykat XR Package Insert). Applying standard pharmacokinetic principles, steady-state plasma concentrations are not achieved until approximately five half-lives have elapsed, which equates to approximately 22 days for PWS patients taking diazoxide choline. By comparison, steady state is reached after approximately 7 days in healthy volunteers, who exhibit a substantially shorter half-life of 28.7 to 32.4 hours. *Id.* This large difference confirms that the rapid, daily-increment titration protocols disclosed in

Cowen—which were designed for non-PWS populations with fundamentally different pharmacokinetic profiles—would have been wholly inappropriate for PWS patients, as each successive daily dose increase would occur long before the prior dose had reached steady state, creating a risk of dangerous drug accumulation. A two-week (14-day) interval between dose escalations allows meaningful drug accumulation at each dose level, providing clinicians a window in which to observe the patient’s response and assess tolerability before increasing the dose.

115. This two-week interval also accounts for the clinical realities of managing cognitively impaired patients. Many PWS patients have intellectual disability, limited expressive language, and impaired ability to recognize and communicate internal states (interoception). *Supra* ¶¶ 47, 53. Unlike cognitively intact adult patients who can report symptoms of adverse effects promptly, PWS patients require external observation over an extended period for caregivers and clinicians to identify subtle signs of edema/fluid retention, metabolic disturbance, or behavioral change. *Supra* ¶ 75. A two-week interval provides that necessary observation window.

116. This two-week interval was not disclosed in Cowen or any of the references that I reviewed.

C. Claims 17-18 (Starting Dose Claims)

117. Apotex's expert, Dr. Hollander, opines these claims are obvious because Cowen's paragraph [0077] discloses a starting dose range of "10 to about 200 mg" that overlaps with the claimed ranges of "between 25-100 mg" (Claim 17) and "between 50-180 mg" (Claim 18). Ex.1005 ¶¶ 163-164. In my opinion, Dr. Hollander's arguments fail for the following reasons.

1. One of Skill in the Art Would Have Recognized that Cowen's Claimed Range Is Directed to Different Subjects, Conditions, and Purpose

118. Cowen's paragraph [0077] discloses a starting dose of "10 to about 200 mg" of diazoxide for treating "obesity, type 1 or type 2 diabetes" in non-PWS patients. These are not the same "general conditions" as administering diazoxide choline to treat hyperphagia in PWS patients.

119. The differences between these contexts are not merely semantic—they are scientifically distinct. The dose-selection rationale in Cowen is tied to a cardiovascular biomarker (supine heart rate) that is unreliable in PWS patients due to their autonomic dysfunction. *Supra* § VII.E. The starting dose in Cowen is calibrated for a population with different body composition, different pharmacokinetics, different comorbidities, and different therapeutic goals.

120. Cowen does not expressly disclose any starting dose for treating hyperphagia in PWS patients. Its disclosed starting dose range is for obesity and diabetes treatment.

2. One of Skill in the Art Would Not Have Been Motivated to Use the Claimed Ranges or Had a Reasonable Expectation of Success in Doing So

121. First, there was no motivation for one of skill in the art to select a starting dose within the claimed range for PWS patients. Cowen's dose selection is driven by heart-rate-based titration—a clinician starts at a dose and escalates when supine heart rates return to baseline. Cowen at [0077] (“the initial dose is chosen to provide for elevations in supine heart rate that on average are not greater than 5 beats per minute”). Again, as I have explained, PWS patients have autonomic dysfunction that renders this approach scientifically meaningless. *Supra* § VII.E. One of skill in the art would have had no rational basis for selecting any particular starting dose from Cowen's range for use in a PWS patient because the entire dose-selection paradigm depends on a physiological marker that is unreliable in this population.

122. Second, there would have been no reasonable expectation of success. Although it was recognized by the priority date that PWS patients exhibit markedly distinct pharmacokinetics, the metabolism rate for specific drugs such as diazoxide choline in this population was unknown—leaving one of skill in the art with no

reasonable basis to expect that Cowen's starting doses would be either safe or clinically effective in PWS patients. Clinical data later generated by Soleno underscores this point: in PWS patients, diazoxide choline has a terminal half-life of roughly 106 hours, requiring approximately 22 days to reach steady state, versus only about 7 days in healthy subjects (half-life of 28.7–32.4 hours). Ex. 1004 (Vykat XR Package Insert); *supra* ¶¶ 72-74, 113-114.

123. Third, the therapeutic endpoint is entirely different. Cowen's dose selection targets metabolic outcomes (insulin sensitivity, weight loss) measured through quantitative biomarkers. In contrast, the '895 patent's dose selection aims at reducing hyperphagia—a behavioral outcome measured through questionnaires and caregiver observation. There is no scientific basis for assuming that a starting dose selected to affect metabolic parameters in obese adults would also be the appropriate starting dose to affect behavioral parameters in PWS patients.

D. Claims 19-25 (Maintenance Dose Claims)

124. Claims 19-25 recite various maintenance dose ranges for diazoxide choline.

125. Apotex's expert, Dr. Hollander, opines that these claims are obvious based on a combination of disclosures drawn from multiple disparate sections of Cowen. Ex.1005 ¶¶ 165-175. In my opinion, Dr. Hollander is wrong for the following reasons.

1. One of Skill in the Art Would Not Have Had Any Reason to Combine the Various Paragraphs in Cowen That Dr. Hollander Combines

126. Dr. Hollander does not identify any single disclosure in Cowen that teaches the claimed maintenance dose ranges for PWS patients. Ex.1005 ¶¶ 165-175. Instead, he pieces together: (a) paragraph [0077]’s dose-escalation ranges for obesity/diabetes treatment; (b) paragraphs [0089] and [00448]’s daily-escalation protocol; and (c) paragraphs [0061] and [00380]’s formulation-composition ranges describing what a pill may contain. He then performs arithmetic calculations to derive maintenance dose values that fall within the claimed ranges.

127. From a scientific perspective, this approach is fundamentally flawed. Paragraphs [0061] and [00380] describe the composition of a pharmaceutical formulation—i.e., how much active ingredient a dosage form may contain—not a therapeutic dose. The amount of drug in a pill and the dose administered to a patient for a specific therapeutic purpose are different scientific concepts. A formulation may contain anywhere from a trace amount to a large quantity of active ingredient depending on manufacturing considerations, and one cannot properly infer a therapeutic maintenance dose from formulation-composition data.

128. Moreover, combining paragraph [0077]’s event-driven obesity titration with paragraph [0089]’s daily escalation and paragraph [0061]’s formulation compositions requires selecting and combining elements from entirely

different technical contexts within the same document. In my opinion, there would have been no reason for one of skill in the art to combine these particular disclosures in this particular way to arrive at a maintenance dose for treating hyperphagia in PWS patients—a population and indication not addressed in any of the cited paragraphs.

2. One of Skill in the Art Would Have Recognized That the Claimed Ranges Are Not Disclosed in Cowen

129. The “ranges” that Dr. Hollander identifies are not disclosed in Cowen as maintenance dose ranges for any patient population. Rather, they are the product of Dr. Hollander’s own calculations—multiplying formulation-composition data by dosing-frequency assumptions to derive a daily dose that happens to overlap with the claimed maintenance ranges.

3. One of Skill in the Art Would Not Have Had Reason to Use the Claimed Ranges or a Reasonable Expectation of Success in Doing So

130. The dramatically different pharmacokinetics of diazoxide choline in PWS patients means that maintenance doses producing acceptable steady-state plasma levels in non-PWS populations could produce vastly different—and potentially dangerous—levels in PWS patients. *Supra* § VII.E. As explained above, as of the priority date, it was known that PWS patients have markedly different pharmacokinetics, but it was not known how specific drugs were metabolized by PWS patients. *Supra* ¶¶ 72-74, 113-114, 122. Later clinical data

by Soleno confirmed that the ~106-hour half-life in PWS patients versus the ~30 hour half-life in healthy subjects could result in roughly 3-4 times higher steady-state concentrations in a PWS patient if a dosing protocol for non-PWS populations were followed.

131. There was no clinical data in the prior art to predict what steady-state plasma levels any particular maintenance dose would produce in PWS patients, whether those levels would be safe, or whether they would effectively reduce hyperphagia. The relationship between dose and therapeutic outcome for hyperphagia in PWS was entirely uncharacterized as of the priority date. One of skill in the art would not have had a reasonable expectation that any particular maintenance dose within or derived from Cowen's disclosures would safely and effectively treat hyperphagia in PWS patients.

X. Ground 2: Cowen and Cotter Do Not Render Claims 2-3 and 16-25 Obvious

132. I have been asked whether, in my expert opinion, the combination of Cowen and Cotter renders obvious Claims 2-3 and 16-25 of the '895 patent. For the reasons set forth below, it is my opinion that this combination does not render the challenged claims obvious. Adding Cotter to the analysis does not cure the fundamental deficiencies I identified in Ground 1, *supra* § IX, and Cotter's own disclosures do not support the obviousness arguments that Dr. Hollander advances.

A. Cowen and Cotter Do Not Render Obvious Claims 2-3

133. For Ground 2, Dr. Hollander relies on Cotter's Example 1 in which an eight-month-old infant with PWS in nutritional phase 1a/1b allegedly received diazoxide "for a period of 56 weeks"—to supply the treatment-duration limitations of Claims 2-3. Ex.1005 ¶¶ 204-208 (citing Cotter at [0150]). In my opinion, this reliance is scientifically unfounded for multiple reasons.

1. One of Skill in the Art Would Have Recognized that Cotter Does Not Teach Administering Diazoxide for 56 Weeks

134. Based on my reading of Cotter's Example 1, "56 weeks" does not represent a confirmed duration of drug administration. Cotter states that the infant "has not progressed to PWS nutritional phase 2a for a period of 56 weeks, perhaps as a result of the administration of diazoxide." Cotter at [0149]. Cotter also states that "[w]ith respect to safety, no side effects have been reported for a period of 56 weeks. The infant's blood sugar levels were monitored and were in the normal range." Cotter at [0150].

135. In my opinion, one of skill in the art would have recognized that these references to "56 weeks" describe an observation period—the length of time over which disease-progression status was monitored—not a confirmed treatment duration. Cotter does not state that diazoxide was continuously administered throughout the 56-week period, but rather that PWS progression was not observed over that timeframe. These are scientifically different claims.

136. Moreover, the qualified language “perhaps as a result” indicates that even the authors were uncertain whether the observed non-progression was causally attributable to diazoxide administration. This level of uncertainty is incompatible with the notion that Cotter “teaches” a 56-week treatment duration in any meaningful scientific sense. One of skill in the art would have recognized this as preliminary, observational data from which no firm conclusions about treatment duration could be drawn.

2. One of Skill in the Art Would Have Recognized that Cotter’s Example 1 Is Directed to a Fundamentally Different Clinical Condition and Provides No Teaching Regarding Durational Treatment of Hyperphagia

137. In my opinion, one of skill in the art would have recognized that Cotter’s Example 1 is directed to a clinical condition fundamentally different from the treatment of hyperphagia. As explained above, hyperphagia is associated only with PWS nutritional phase 3, which is characterized by insatiable appetite, food-seeking, and lack of satiety and typically does not emerge until childhood. *Supra* ¶ 35; Cotter at [0067]. Example 1, by contrast, discloses treatment of an infant in PWS nutritional phase 1a/1b, which is characterized by hypotonia, feeding difficulties, poor appetite, and failure to thrive. *Supra* ¶¶ 32-33. Because the infant described in Example 1 had not progressed even to PWS nutritional phase 2a (onset of weight gain without increase in appetite or excessive calories), let alone to phase 3, Cotter’s disclosed diazoxide regimen was necessarily directed to a clinical

condition fundamentally different from the treatment of hyperphagia. *Supra* ¶¶ 32-36. Moreover, the infant's non-progression to phase 2a is entirely expected given that the median age of onset for phase 2a is 25 months and the infant would have only been 21 months old after the 56-week period. *Supra* ¶¶ 33-34, 86.

138. In my opinion, one of skill in the art would have understood that treating an infant in phase 1, when the clinical challenge is poor feeding and failure to thrive, says nothing about the safety or efficacy of using diazoxide to treat the very different and far later-emerging hyperphagia of phase 3 in older PWS patients.

139. Moreover, Example 1 discloses that the infant "had experienced hypoglycemic episodes." Cotter at [0149]. That disclosure, combined with the use of diazoxide, would have suggested to one of skill in the art that the infant had hyperinsulinism, not hyperphagia. I also note that this infant's condition (hyperinsulinemic hypoglycemia), is very atypical of PWS and, as such, one of skill in the art would not have extrapolated PWS treatments from that example.

140. Hyperinsulinism and hyperphagia are mechanistically distinct conditions: hyperinsulinism involves excessive insulin secretion leading to dangerously low blood glucose, while hyperphagia involves dysregulated appetite signaling leading to insatiable hunger and compulsive food-seeking behavior. Ex.2061 (McTaggart 2010) at 3; Ex.2045 (Butler 2006) at 129; Ex.2049 (Dimitropoulos 2000) at 1. Diazoxide has a well-established mechanism of action

in hyperinsulinism—it opens K_{ATP} channels on pancreatic beta cells to suppress insulin release—but this mechanism provides no basis for predicting efficacy against the far more complex neuroendocrine appetite dysregulation underlying hyperphagia in PWS. Ex.2061 (McTaggart 2010) at 2; Ex.2062 (Miller 2007) at 4; Ex.2063 (Miller 2012) at 3, Tbl. 1.

141. I also note that the exact mechanism by which diazoxide choline treats hyperphagia remains unknown to this day. Even the approved Vykat XR label acknowledges that “[t]he exact mechanism of action of diazoxide choline in the treatment of hyperphagia in patients 4 years of age and older with Prader-Willi syndrome (PWS) is unknown.” Ex.1004. This uncertainty further underscores why one of skill in the art could not have predicted that a drug used for treating hyperinsulinism would be effective against hyperphagia in PWS, let alone at what dose or for how long.

142. Even setting aside the fact that Example 1 is directed to a treating a fundamentally different clinical condition, one of skill in the art would have recognized that the single patient in Example 1 is not equivalent to, or representative of, the PWS patients who suffer from hyperphagia. An infant has fundamental physiological differences that preclude extrapolation to older PWS patients. Ex.2063 (Miller 2012) at 3, Tbl. 1. To illustrate, an infant has different body size, body weight, lean body mass, muscle mass, and overall body

composition compared to the older children, adolescents, and adults who experience hyperphagia. Ex.2040 (Bekx 2003) at 1, Tbl. 1; Ex.2042 (Brambilla 1997) at 3, Tbl. 1. These differences have direct pharmacokinetic and pharmacodynamic implications: drug absorption, distribution, metabolism, and clearance all vary substantially with age and body composition. Ex.2045 (Butler 2006) at 189, 191, 286. One of skill in the art would have understood that dosing parameters established in an infant cannot be reliably extrapolated to treat older PWS patients.

3. One of Skill in the Art Would Not Have Had Any Reason to Combine Cowen and Cotter with Respect to the Durational Limitations of Claims 2-3 or a Reasonable Expectation of Success

143. In my opinion, one of skill in the art would not have been motivated to combine Cowen's obesity-treatment duration with Cotter's observational data from an infant with hypoglycemia (likely due to hyperinsulinism) to arrive at a treatment duration for hyperphagia in PWS patients. These references address different patient populations (obese adults vs. an infant in nutritional phase 1a/1b), different conditions (obesity vs. hypoglycemia/failure to thrive), different therapeutic endpoints (metabolic markers vs. behavioral assessment), and provide different types of information (a study-protocol duration vs. an observation period). *Supra* ¶¶ 40-50, 78-83, 137-142. There is no scientific thread connecting

these disclosures that would motivate their combination for the purpose of determining how long to treat hyperphagia.

144. Even if one of skill in the art had been motivated to combine these references, there would have been no reasonable expectation that administering diazoxide choline for the durations suggested by Cowen or Cotter would successfully treat hyperphagia in PWS patients. Cotter's Example 1 involves a single infant, the outcome is hedged with "perhaps," there is no dose-response data, no efficacy measurement for hyperphagia (which the infant did not have), and no pharmacokinetic data. Cowen provides no data in PWS patients whatsoever. *Supra* ¶¶ 81-83. One of skill in the art would have had no rational basis for expecting that any particular treatment duration derived from these references would produce a therapeutic benefit for hyperphagia.

B. Cowen and Cotter Do Not Render Obvious Claim 16

145. For Ground 2, Dr. Hollander opines that adding Cotter to Cowen cures the deficiencies identified in Ground 1 regarding Claim 16's fixed, two-week titration interval. Ex.1005 ¶¶ 215-229. In my expert opinion, Cotter adds nothing to the obviousness analysis for Claim 16.

146. Cotter's Example 1 describes an infant started at 0.5 mg/kg BID (twice per day) of diazoxide, whose dose was increased to 1 mg/kg BID. Cotter at [0149]. This single dose increase in an infant does not constitute a titration

schedule, let alone a two-week titration interval. Cotter provides no information about when or why the dose was increased, what observation period elapsed between doses, or what clinical criteria triggered the dose increase. There is simply no titration-interval teaching in Cotter. In my opinion, one of skill in the art reading Cotter's Example 1 would understand it as a case narrative, not a titration protocol.

147. Moreover, the fundamental deficiencies I identified in the context of Claims 2-3 remain: Cotter's Example 1 involves a fundamentally different clinical condition and patient population (infant with hypoglycemia likely due to hyperinsulinism) than the population addressed by Claim 16 (PWS patients with hyperphagia). *Supra* ¶¶ 137-142. One of skill in the art would not have been motivated to derive titration parameters from an observational study in an infant being treated for a mechanistically distinct condition, nor would there have been any reasonable expectation that such parameters would be relevant to treating hyperphagia.

148. The fundamental deficiencies I identified in Ground 1 also remain: Cowen teaches event-driven escalation for non-PWS populations, whereas Claim 16's two-week interval reflects PWS-specific pharmacokinetic and clinical insights not found in the prior art. *Supra* ¶¶ 105-116. Adding Cotter—which provides no titration information—does not cure any of these deficiencies.

C. Cowen and Cotter Do Not Render Obvious Claims 17-18

149. For Ground 2, Dr. Hollander does not identify any additional teaching in Cotter that would cure the deficiencies I identified in Ground 1 regarding Claims 17-18. *Supra* § IX.C. Cotter's Example 1 describes an infant started at 0.5 mg/kg BID of diazoxide (not diazoxide choline), whose dose was increased to 1 mg/kg BID. These are weight-based doses for an infant being treated for hypoglycemia (likely due to hyperinsulinism)—not fixed-milligram starting doses for treating hyperphagia in children, adolescents, or adults with PWS.

D. Cowen and Cotter Do Not Render Obvious Claims 19-25

150. For Ground 2, Dr. Hollander additionally relies on Cotter's paragraph [0138], which lists doses 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." Ex.1005 ¶¶ 233-243. In my opinion, this additional disclosure would have provided no meaningful dosing guidance for maintenance treatment of hyperphagia in PWS patients to one of skill in the art.

151. First, this list is not tied to any formulation, titration protocol, or therapeutic objective, and does not distinguish between starting and maintenance doses or indicate which doses are appropriate for diazoxide choline specifically.

152. Second, this list spans from 1 mg to 2000 mg, and thus covers any conceivable dose. In my opinion, such a broad enumeration does not provide any guidance for selecting the specific maintenance dose ranges of Claims 19-25.

153. Third, there is no efficacy or safety data associated with any dose on this list for treating hyperphagia in PWS patients. Cotter's Example 1 consists of its only clinical data, and this example involves an eight-month-old infant treated for hypoglycemia (likely due to hyperinsulinism) at 0.5-1 mg/kg BID, a condition and population mechanistically distinct from the claims. *Supra* § VIII.B. Therefore, one of skill in the art reading Cotter would not have a reasonable expectation of success that any particular maintenance dose would be safe and effective for treating hyperphagia in PWS patients.

154. Fourth, Dr. Hollander provides no reasoning in Cowen, Cotter, or the general knowledge of one of skill in the art, as to why one of skill in the art would have combined the obesity and diabetes dose-escalation arithmetic of Cowen with the bare list of dose values of Cotter in order to arrive at the specific maintenance dose ranges of Claims 19-25 for treating hyperphagia in PWS patients. Dr. Hollander is using hindsight, starting from the claimed maintenance dosing ranges and working backwards to find these ranges in the Cowen and Cotter combination.

XI. Ground 3: Cowen and Miller Do Not Render Claims 2-3 and 16-25 Obvious**A. Cowen and Miller Do Not Render Obvious Claims 2-3**

155. For Ground 3, Dr. Hollander does not identify any additional teaching in Miller that would cure the deficiencies I identified in Grounds 1 and 2 regarding Claims 2-3. *Supra* §§ IX.A, X.A. Accordingly, adding Miller does not cure any of these deficiencies.

B. Cowen and Miller Do Not Render Obvious Claim 16

156. For Ground 3, Dr. Hollander does not identify any additional teaching in Miller that would cure the deficiencies I identified in Grounds 1 and 2 regarding Claim 16. *Supra* §§ IX.B, X.B. Accordingly, adding Miller does not cure any of these deficiencies.

C. Cowen and Miller Do Not Render Obvious Claims 17-18

157. For Ground 3, Dr. Hollander does not identify any additional teaching in Miller that would cure the deficiencies I identified in Grounds 1 and 2 regarding Claims 17-18. *Supra* §§ IX.C, X.C. Accordingly, adding Miller does not cure any of these deficiencies.

D. Cowen and Miller Do Not Render Obvious Claims 19-25

158. For Ground 3, Dr. Hollander does not identify any additional teaching in Miller that would cure the deficiencies I identified in Grounds 1 and 2 regarding

Claims 19-25. *Supra* §§ IX.D, X.D. Accordingly, adding Miller does not cure any of these deficiencies.

XII. Conclusion

All statements made herein of my own knowledge are true, and all statements made on information and belief are believed to be true. Further, I am aware that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001. I declare under penalty of perjury that the foregoing is true and correct.

Executed on July 22, 2026 (date), in San Diego, CA (city, state).

A handwritten signature in cursive script that reads "Lynne M. Bird".

Lynne Bird, M.D.