

Filed on behalf of: Soleno Therapeutics, Inc.

Entered: July 22, 2026

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

PATENT OWNER'S PRELIMINARY RESPONSE

TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	BACKGROUND	4
A.	Prader-Willi Syndrome (PWS) and Hyperphagia	4
1.	PWS Versus Obesity	7
2.	PWS Versus Diabetes	9
B.	The '895 Patent (Ex.1001) and VYKAT XR.....	11
C.	The Challenged Claims	13
D.	Dosing of PWS Population	14
III.	ASSERTED PRIOR ART	16
A.	Cowen (Ex.1009).....	16
B.	Cotter (Ex.1008).....	18
C.	Miller (Ex.1017).....	20
IV.	PROSECUTION HISTORY	20
V.	GROUND 1: APOTEX FAILS TO ESTABLISH THAT COWEN RENDERS CLAIMS 2-3 AND 16-25 OBVIOUS.....	21
A.	Claims 2-3 (Treatment Duration Claims) Are Not Obvious	23
1.	Cowen Does Not Teach or Render Obvious Treating PWS Patients for at Least 10 Weeks or Up to 12 Months.....	23
2.	Apotex Has Failed To Demonstrate Either Motivation To Modify Or Reasonable Expectation of Success.....	26
B.	Claim 16 (Dosing Titration Claim) Is Not Obvious	29
1.	Cowen Does Not Teach, and Apotex Fails To Show A POSA Would Have Been Motivated to Adopt, A Two- Week Titration Interval.....	31

2.	Cowen's Dose-Escalation Disclosures Are Directed to Non-PWS Populations and Cannot Be Extrapolated to PWS Patients	32
3.	The Claimed Two-Week Interval Reflects a Specific Clinical Insight Tailored to the PWS Population	37
a.	Pharmacokinetic and Clinical Rationale for the Two-Week Interval.....	38
b.	<i>In re Aller</i> Does Not Apply	39
c.	<i>Janssen</i> Confirms That Specific Dosing Choices Reflecting Clinical Insight Are Non-Obvious.....	41
4.	The Petition's Analysis Is Infected by Impermissible Hindsight.....	42
5.	Dr. Hollander's Declaration Provides No Independent Support for Obviousness.....	43
6.	Apotex Cannot Rely on a POSA's Knowledge to Supply the Two-Week Limitation.....	45
C.	Claims 17-18 (Starting Dose Claims) Are Not Obvious.....	46
1.	The Overlapping Range Presumption Does Not Apply	47
2.	Even If the Presumption Applied, It Is Rebutted.....	50
a.	A POSA Would Have Had No Motivation to Apply Cowen's Obesity/Diabetes Starting Doses to PWS Patients	50
b.	A POSA Would Have Had No Reasonable Expectation of Success	52
3.	Apotex's Expert Evidence Is Insufficient.....	53
D.	Claims 19-25 (Maintenance Dose Claims) Are Not Obvious	55
1.	Apotex Impermissibly Cobbles Together Disparate Cowen Embodiments to Reverse-Engineer the Claimed Maintenance Doses	56
2.	The Overlapping Range Presumption Does Not Apply	59

3.	Even If the Presumption Applied, It Is Rebutted.....	61
a.	No Motivation to Apply Cowen's Obesity/Diabetes Protocol to PWS.....	61
b.	No Reasonable Expectation of Success—including Pharmacokinetic Unpredictability	62
c.	Apotex's Expert Declaration Is Conclusory and Insufficient.....	64
VI.	GROUND 2: APOTEX FAILS TO ESTABLISH THAT COWEN AND COTTER RENDER CLAIMS 2-3 AND 16-25 OBVIOUS	65
A.	Cowen and Cotter Do Not Render Obvious Claims 2-3	65
1.	Cotter Does Not Teach Administering Diazoxide for 56 Weeks.....	66
2.	Cotter's Example 1 Is Directed to a Fundamentally Different Clinical Condition and Provides No Teaching Regarding Durational Treatment of Hyperphagia	67
3.	The Petition Fails to Establish a Motivation to Combine Cowen and Cotter with Respect to the Durational Limitations of Claims 2-3	69
4.	A POSA Would Not Have Had a Reasonable Expectation of Success.....	70
5.	Apotex's Expert Declaration Is Conclusory and Entitled to No Weight.....	71
6.	The Petition's Failure to Provide Particularized Evidence Is Independently Dispositive.....	72
B.	Cowen and Cotter Do Not Render Obvious Claim 16.....	73
C.	Cowen and Cotter Do Not Render Obvious Claims 17-18.....	76
D.	Cowen and Cotter Do Not Render Obvious Claims 19-25	76
VII.	GROUND 3: APOTEX FAILS TO ESTABLISH THAT COWEN AND MILLER RENDER CLAIMS 2-3 AND 16-25 OBVIOUS	78

A.	Cowen and Miller Do Not Render Obvious Claims 2-3	78
B.	Cowen and Miller Do Not Render Obvious Claim 16.....	78
C.	Cowen and Miller Do Not Render Obvious Claims 17-18.....	79
D.	Cowen and Miller Do Not Render Obvious Claims 19-25.....	79
VIII.	OBJECTIVE INDICIA CONFIRM NON-OBVIOUSNESS	79
IX.	CONCLUSION.....	86

TABLE OF AUTHORITIES**Page(s)****CASES**

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<i>Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.</i> , 776 F.2d 281 (Fed. Cir. 1985)	54, 59
<i>Crocs, Inc. v. Int'l Trade Comm'n</i> , 598 F.3d 1294 (Fed. Cir. 2010)	84
<i>Eli Lilly & Co. v. Teva Pharms. Int'l GmbH</i> , 8 F.4th 1331 (Fed. Cir. 2021)	21
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<i>Google LLC v. AGIS Dev. LLC</i> , IPR2018-01086, Paper 10 (Dec. 4, 2018).....	22, 58
<i>Graham v. John Deere Co.</i> , 383 U.S. 1 (1966).....	42
<i>Hewlett Packard Enter. Co. v. Intellectual Ventures II LLC</i> , IPR2022-00115, Paper 9 (Mar. 29, 2022)	22, 58, 78
<i>In re 318 Pat. Infringement Litig.</i> , 578 F. Supp. 2d 711 (D. Del. 2008).....	83
<i>In re Aller</i> , 220 F.2d 454 (CCPA 1955)	37, 47, 59
<i>In re Antonie</i> , 559 F.2d 618 (CCPA 1977)	39, 40
<i>In re Applied Materials, Inc.</i> , 692 F.3d 1289 (Fed. Cir. 2012)	47
<i>In re Hedges</i> , 783 F.2d 1038 (Fed. Cir. 1986)	22

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<i>InTouch Techs., Inc. v. VGO Commc'ns, Inc.</i> , 751 F.3d 1327 (Fed. Cir. 2015)	3, 29, 72
<i>Janssen Pharmaceuticals, Inc. v. Teva Pharmaceuticals USA, Inc.</i> , 141 F.4th 1367 (Fed. Cir. 2025)	41, 42
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<i>KSR Int'l Co. v. Teleflex Inc.</i> , 550 U.S. 398 (2007).....	31
<i>Merck Sharp & Dohme Corp. v. Genentech, Inc.</i> , PGR2021-00039, Paper 10 (July 24, 2021).....	82
<i>Mintz v. Dietz & Watson, Inc.</i> , 679 F.3d 1372 (Fed. Cir. 2012)	79
<i>ModernaTx, Inc. v. Arbutus Biopharma Corp.</i> , 18 F.4th 1364 (Fed. Cir. 2021)	40, 59, 60
<i>Mylan Pharms., Inc. v. AstraZeneca AB</i> , IPR2015-01340, Paper 79 (Aug. 18, 2017).....	80
<i>OSI Pharms., LLC v. Apotex Inc.</i> , 939 F.3d 1375 (Fed. Cir. 2019)	passim
<i>Pharmacyclics LLC v. Alvogen Pine Brook LLC</i> , 556 F. Supp. 3d 377 (D. Del. 2021), <i>aff'd</i> , 2022 WL 16943006 (Fed. Cir. Nov. 15, 2022).....	80

<i>Pharmacyclics LLC v. Alvogen, Inc.</i> , No. 2021-2270, 2022 WL 16943006 (Fed. Cir. Nov. 15, 2022).....	passim
<i>Quanergy Sys, Inc. v. Velodyne Lidar, Inc.</i> , IPR2018-00255, Paper 59 (May 23, 2019).....	83
<i>Tiktok Inc. v. Ntech Props., Inc.</i> , IPR2024-01339, Paper 9 (Feb. 25, 2025).....	3, 25
<i>Tris Pharma, Inc. v. Actavis Lab 'ys FL, Inc.</i> , No. 2021-1495, 2022 WL 2525318 (Fed. Cir. July 7, 2022)	69
<i>WBIP, LLC v. Kohler Co.</i> , 829 F.3d 1317 (Fed. Cir. 2016)	83
<i>Xactware Sols., Inc. v. Eagle View Techs., Inc.</i> , IPR2016-00590, Paper 41 (Aug. 14, 2017).....	85
<i>Xerox Corp. v. Bytemark, Inc.</i> , IPR2022-00624, Paper 9 (Aug. 24, 2022).....	3, 25, 72

STATUTES

21 U.S.C. § 360aa, Notes, Congressional Findings.....	83
35 U.S.C. § 312(a)(3).....	72, 75, 78

REGULATIONS

37 C.F.R. § 42.104(b)(4).....	45, 46, 73, 75, 78
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Exhibit List

Exhibit	Description
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Exhibit	Description
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I. INTRODUCTION

Patent Owner Soleno Therapeutics, Inc. (“Soleno” or “Patent Owner”) respectfully requests that the Director deny institution of the Petition for post-grant review filed by Petitioner Apotex Inc. (“Apotex” or “Petitioner”) challenging U.S. Patent No. 12,419,895 (“’895 patent”, Ex.1001). Because Apotex has not established that any of claims 2-3 and 16-25 is more likely than not unpatentable, the Director should deny institution.¹

Soleno invested years of research, millions of dollars, and considerable commercial risk to develop a groundbreaking treatment for Prader-Willi Syndrome (“PWS”), a rare, life-threatening genetic disorder. That investment culminated in VYKAT[®] XR, a diazoxide choline extended-release oral tablet (“DCCR”) that provides sustained drug exposure with once-daily dosing. VYKAT XR was the first and only FDA-approved treatment for hyperphagia in PWS patients, and the FDA granted VYKAT XR both Breakthrough Therapy designation and Orphan Drug status and exclusivity. The ’895 patent protects a specific diazoxide choline dosing regimen for treating hyperphagia in PWS patients.

Apotex now asks the Board to find that this novel treatment regimen was obvious all along. Its three Grounds are repetitive and invoke three references—

¹ Soleno has disclaimed claims 1, 4-15, and 26. Ex.2093.

Cowen, Cotter, and Miller—all of which were before the Examiner during prosecution. The Examiner issued the claims over these (and other) references because none discloses the claimed diazoxide choline dosing regimen to treat hyperphagia in PWS. Faced with that fatal omission, Apotex cherry-picks and combines disparate components from each reference without explaining why a POSA would do so, relying extensively on *ipse dixit* expert testimony to bridge critical gaps. The Petition suffers from three fundamental flaws, each independently sufficient to deny institution.

First, Apotex fails to articulate any motivation to modify and combine the cited references' disparate teachings. Apotex plucks disclosures related to obesity and diabetes from Cowen and grafts them onto the treatment of hyperphagia in PWS, but provides no reason why a POSA would have been motivated to do so. PWS is a complex genetic disorder with a distinct etiology, disease progression, characteristic symptomatology, and unique metabolic and drug metabolism profile that renders it fundamentally different from obesity or diabetes. Apotex fails to show that a POSA would have simply assumed that dosing regimens studied in obese or diabetic populations could be applied to PWS patients or would have been motivated to modify and/or combine them to arrive at the claimed methods.

Second, even if a POSA had been so motivated, Apotex fails to prove a reasonable expectation of success. Developing an effective dosing regimen for

hyperphagia in PWS was a highly unpredictable undertaking that no skilled artisan had previously accomplished. The prior art contains no efficacy, safety, or pharmacokinetic data for diazoxide choline in PWS patients, and its scattered references to diazoxide in the context of obesity and diabetes offered no basis from which a POSA could have reasonably predicted whether—let alone at what dose and regimen—diazoxide choline would effectively treat hyperphagia in PWS.

Third, Apotex's Petition depends on impermissible expert gap-filling to substitute for disclosures absent from the prior art. None of the cited references discloses the specific diazoxide choline dosing regimen claimed in the '895 patent for treating hyperphagia in PWS. Apotex attempts to paper over this deficiency with unsupported testimony from its expert, Dr. Hollander, who merely parrots the Petition's assertions without independent reasoning or evidence. The Federal Circuit and the Board have repeatedly held that such testimony is legally insufficient to establish obviousness. *See, e.g., InTouch Techs., Inc. v. VGO Commc'ns, Inc.*, 751 F.3d 1327, 1352 (Fed. Cir. 2015); *Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Paper 9, 15 (Aug. 24, 2022) (precedential); *Tiktok Inc. v. Ntech Props., Inc.*, IPR2024-01339, Paper 9, 16 (Feb. 25, 2025).

Compounding these flaws, multiple objective indicia of non-obviousness independently confirm that the Director should deny institution:

- *Failure of others and long-felt unmet need*: Others have tried and failed to

develop treatments for hyperphagia in PWS; Soleno's treatment regimen is the only treatment to receive FDA approval, satisfying a longstanding unmet need. The FDA granted Soleno's treatment a "Breakthrough Therapy" designation and Orphan Drug status and exclusivity.

- *Industry praise:* Soleno's treatment regimen has received extensive praise from both clinicians and caregivers of PWS patients.
- *Commercial success:* Soleno's treatment regimen has achieved significant commercial success. Since entering the market in April 2025 through the end of 2025, VYKAT XR generated \$190.4 million in revenue, with Soleno reporting its first profitable quarter. The treatment regimen even contributed to Neurocrine Biosciences, Inc.'s ("Neurocrine's") decision to acquire Soleno for \$2.9 billion.
- *Unexpected results:* Soleno's treatment regimen is unprecedented, serving as the first treatment to demonstrate a therapeutic benefit that safely and effectively treats hyperphagia in PWS patients.

Because Apotex has not demonstrated that any challenged claim is more likely than not unpatentable, the Board should deny institution.

II. BACKGROUND

A. Prader-Willi Syndrome (PWS) and Hyperphagia

PWS is a rare and complex genetic disorder caused by the loss of function of

genes on chromosome 15q11-q13, typically through paternal deletion, maternal uniparental disomy, or imprinting defects. Ex.2046 (Cassidy 2012), 1; Ex.2035 (Bird Decl. (“Bird”)) ¶26.² This genetic abnormality disrupts hypothalamic development and function, producing the physical, cognitive, and behavioral features that define PWS, including impaired appetite regulation, chronic and severe hunger, hyperphagia, food-seeking behavior, and behavioral and metabolic complications. ’895 patent, 19:29-20:25; Ex.2054 (Goldstone 2008), 1; Ex.2049 (Dimitropoulos 2000), 1; Ex.2057 (Hoybye 2003 Thesis), 11; Bird ¶26. As Apotex recognizes, hyperphagia—the hallmark of later-stage PWS—“is hypothalamic in origin and is characterized by an abnormal desire for food or excessive eating.” Pet. 9. PWS patients feel they are starving even when they are not; they may eat any food in sight, get up at night to eat, dig through trash for food, steal food, consume frozen, spoiled, or pet food, and even consume non-food items; and they may become angry or throw tantrums if denied food. ’895 patent, 20:14-25; Ex.2045 (Butler 2006), 212; Ex.2062 (Miller 2007), 1; Bird ¶¶27-28. PWS is also associated with short stature, intellectual disabilities, incomplete sexual development, severe hypotonia (low muscle tone), and distinctive behavioral challenges such as temper outbursts, stubbornness, and compulsive tendencies. Ex.2045 (Butler 2006), 20, 25-

² All internal quotation marks and citations are omitted unless otherwise noted.

26, 41, 76; Ex.2054 (Goldstone 2008), 3, 5, 7; Bird ¶29.

PWS initially presents with prenatal reduced movement and neonatal hypotonia and feeding difficulty, leading to failure to thrive, eventually evolving to early childhood reduced metabolic rate and intense hyperphagia requiring lifelong, strict dietary management. Ex.2046 (Cassidy 2012), 1; Ex.2045 (Butler 2006), 22; Bird ¶30. This progression—from failure to thrive in infancy to hyperphagia in childhood onward—reflects the evolving impact of hypothalamic dysfunction across development. Ex.2046 (Cassidy 2012), 2; Ex.2054 (Goldstone 2008), 4; Bird ¶30. The clinical course is characterized by distinct nutritional phases: phase 0 (prenatal), phase 1 (infancy), phase 2 (increased appetite and transition to hyperphagia), phase 3 (hyperphagia), and phase 4 (insatiable appetite diminishes in some adults). Ex.2046 (Cassidy 2012), 2, Tbl. 1; Ex.1017 (Miller 2011), 1; Bird ¶¶30-37. 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), 2, Tbl. 1; '895 patent, 20:14-15; Bird ¶¶35-36. Hyperphagia is the defining feature of nutritional phase 3, characterized by insatiable appetite, food-seeking, and lack of satiety. Bird ¶¶35-36; Ex.2054 (Goldstone 2008), 4. The transition between nutritional phases is not always predictable and can vary significantly among patients, adding complexity to clinical management and treatment regimen design. Ex.2054 (Goldstone 2008), 4; Bird ¶38.

1. PWS Versus Obesity

Most PWS patients are not obese, as implementation of strict, constant supervision and environmental control measures (e.g., closely supervised meals; locked refrigerators, pantries, and trash cans) is a cornerstone of management. Bird ¶¶40-44; Ex.2063 (Miller 2012), 6; Ex.2072 (Waters 2014), 14; Ex.2043 (Brambilla 2011), 2-3, 7-8. The '895 patent reports that PWS patients are on average, overweight rather than obese, meaning that more than half 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"). However, all PWS patients have low lean body mass and hypotonia. '895 patent, 19:65-67; Ex.2063 (Miller 2012), 1-2, 5; Ex.2072 (Waters 2014), 14; Bird ¶¶41, 44, 68. Subcutaneous fat comprises a greater percentage of total fat in PWS patients than in obese controls at all ages. '895 patent, 20:11-13; Ex.2052 (Goldstone 2001), 2, Tbl. 1; Bird ¶44. And PWS patients "expend less energy and are more sedentary than either the general population, obese controls or patients with similar intellectual disabilities." '895 patent, 20:35-37; Ex.2040 (Bekx 2003), 1; Ex.2045 (Butler 2006), 31, 132; Bird ¶44.

Even PWS patients who are obese differ fundamentally from the non-PWS obese population. Bird ¶45. PWS is a genetic disorder whose metabolic, endocrine,

behavioral, and safety profile differs fundamentally from that of a typical obese patient. Ex.2042 (Brambilla 1997), 1; Ex.2044 (Butler 1998), 6-7; Ex.2070 (Theodoro 2006), 4; Ex.2066 (Paisey 2011), 1; Bird ¶40. PWS patients have distinct body compositions—substantially reduced lean muscle mass with increased fat mass even at comparable BMI—together with central hypotonia, which lowers resting and total energy expenditure and alters caloric needs, weight-based dosing assumptions, and volume of distribution in ways that an obesity protocol does not contemplate. Ex.2042 (Brambilla 1997), 1; Ex.2070 (Theodoro 2006), 4; Ex.2040 (Bekx 2003), 5; Ex.2045 (Butler 2006), 286; Bird ¶¶41, 47.

PWS patients also experience comorbidities not associated with common obesity—growth hormone deficiency, hypogonadism, central adrenal insufficiency, hypothyroidism, and behavioral disturbance, each of which might complicate a treatment protocol designed for typical obese patients. Ex.2045 (Butler 2006), 286; Ex.2054 (Goldstone 2008), 5, 9; Ex.2063 (Miller 2012), 4; Ex.2060 (Marzullo 2005), 3; Bird ¶46. Furthermore, PWS patients may have a blunted emesis (vomiting) response and a high pain threshold that can mask gastrointestinal adverse events, elevated risk of respiratory and cardiac adverse events from sleep-disordered breathing, temperature dysregulation that can mask infection, and heightened susceptibility to behavioral and psychiatric adverse events. Ex.2041 (Benarroch 2007), 3, 9; Ex.2068 (Sinnema 2013), 2; Bird ¶46.

The fundamental differences between PWS and common obesity are further underscored by the well-documented history of obesity treatments failing in PWS patients. Bird ¶¶39, 48-50. Pharmacological agents and bariatric surgeries effective 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), 5; Ex.2054 (Goldstone 2008), 4; Ex.2063 (Miller 2012), 5; Ex.2047 (Deal 2013), 9-10; Ex.2073 (Zipf 2004), 33; Bird ¶¶48-50. For example, as of November 2014, topiramate, which has shown efficacy for weight loss in non-PWS obese patients, had not demonstrated meaningful benefits for hyperphagia or weight management in PWS patients. Ex.2067 (Shapira 2004), 4-5; Bird ¶49. And as of November 2014, metformin, widely used in obese patients to improve insulin sensitivity and promote modest weight loss, did not consistently address the hypothalamic-driven hyperphagia central to PWS. Ex.2064 (Miller 2014), 3; Bird ¶49.

2. PWS Versus Diabetes

Not all PWS patients are diabetic. While PWS patients are at increased risk of developing type 2 diabetes due to obesity and metabolic dysfunction, 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. Bird ¶¶39, 54.

The PWS condition state is likewise fundamentally different from the non-PWS type 1 and type 2 condition states. Bird ¶51. Type 1 diabetes is an autoimmune condition in which the immune system destroys pancreatic beta cells, leading to absolute insulin deficiency; type 2 diabetes is characterized by progressive insulin resistance and relative insulin deficiency. Ex.2059 (Itariu 2014), 1; Ex.2065 (Olokoba 2012), 1; Ex.2046 (Cassidy 2012), 1; Ex.2045 (Butler 2006), 133-134; Bird ¶51. In both conditions, pharmacodynamic effects can be monitored through well-established metabolic markers such as fasting glucose, fasting insulin, HOMA-IR, and glycosylated hemoglobin. Ex.2069 (Talebizadeh 2005), 4; Ex.2045 (Butler 2006), 135; Bird ¶51.

By contrast, PWS is a neurodevelopmental/genetic disorder in which the primary therapeutic target—hyperphagia—arises from hypothalamic dysfunction and dysregulated appetite signaling, not from insulin resistance or beta-cell failure. Ex.2064 (Miller 2014), 2; Ex.2045 (Butler 2006), 129; Bird ¶52. Moreover, PWS patients frequently have intellectual disability, limited expressive language, and impaired interoception, making self-reporting unreliable and requiring caregivers and clinicians to observe to detect safety signals following treatment. Ex.2045 (Butler 2006), 278; Ex.2068 (Sinnema 2013), 5; Ex.2073 (Zipf 2004), 35; Bird ¶53.

As another distinction, 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. Bird ¶55. 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. Bird ¶55; Ex.1012, 1, 2, 6.

B. The '895 Patent (Ex.1001) and VYKAT XR

The '895 patent, entitled "Methods for Treating Subjects with Prader-Willi Syndrome," discloses methods of treating hyperphagia in a subject with PWS. '895 patent, cl. 1, 17:43-44.

The '895 patent and three other patents in its continuity chain are listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") for VYKAT XR, 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 DCCR that provides sustained drug exposure with once-daily dosing.

The '895 patent discloses a specific novel treatment regimen for PWS: administering 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 (Example 3), Figs. 1-5, 23:15-28 (description of figures); Bird ¶¶56-60. This novel regimen was ultimately included in the FDA-approved prescribing information for VYKAT XR. Ex.1004 (VYKAT XR package insert), 1.

The '895 patent's treatment regimen—including once-daily dosing and particular ranges of administration—is supported by efficacy data disclosed in the '895 patent. '895 patent, 59:9-67:17 (Example 3), Figs. 1-5, 23:15-28 (description of figures); *see also id.* 10:10-34 (ranges of administration), 14:2-3 (once-daily dosing); Bird ¶¶56-60. Example 3 reports 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. Patients were initiated on a DCCR dose of about 1.5 mg/kg per day (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 (maximum dose of 507.5 mg/day) per day. *Id.* 59:14-20. Patients were up-titrated at each visit at the investigator's discretion. *Id.* 59:21-22.

Example 3's efficacy endpoints included hyperphagia (measured using parent/caregiver responses on a modified Dykens hyperphagia questionnaire, converted to a numeric score between 0 and 34); weight; body fat (measured by Dual-Energy X-ray Absorptiometry ("DEXA")); lean body mass (measured by DEXA); resting energy expenditure (measured by indirect calorimetry); respiratory quotient (measured by indirect calorimetry); waist circumference; body mass index ("BMI"); ghrelin; leptin; triglycerides; total cholesterol; HDL cholesterol; non-HDL cholesterol and LDL cholesterol. *Id.* 60:5-13. Additional information was collected via a behavioral questionnaire. *Id.* 60:14-16.

Based on 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, and in those who continued on DCCR through the double-blind phase from Baseline through Day 97. '895 patent, 64:55-59; *see also id.* Tbls. 2-3, 10-12, 65:18-20; Bird ¶¶56-60. At the end of the double-blind phase, DCCR-treated patients showed more than twice the improvement in hyperphagia compared to those randomized to placebo. '895 patent, 64:64-67; Bird ¶¶56-60. In addition to reduction in hyperphagia, Example 3 reports that leptin levels decreased more than 20% from Baseline and food-related behaviors were reduced. '895 patent, 66:14-32, 65:3-14; Bird ¶¶56-60.

C. The Challenged Claims

Solenio claimed its data-backed novel PWS treatment regimen in the '895 patent. Bird ¶¶61-65. Independent claim 1—now disclaimed, but from which all challenged claims depend—recites a method of treating hyperphagia in a PWS patient by administering diazoxide choline once-daily, whereby such administration reduces hyperphagia and one or more food related behaviors. '895 patent, cl. 1.

Dependent claims 2-3 depend from claim 1 and cover durations of the administration of diazoxide choline. *Id.*, cls. 2-3. Claim 2 recites administration for “at least 10 weeks,” and claim 3 recites administration for “one or more years.” *Id.*

Dependent claim 16 depends from claim 1 and covers a titration schedule,

requiring administration of diazoxide choline to be “initiated at a starting dose” and “then titrated every two weeks to reach a maintenance dose.” *Id.*, cl. 16.

Dependent claims 17-25 recite doses for titrating diazoxide choline. Claims 17-18 depend from Claim 16 and recite “starting dose[s] of diazoxide choline.” *Id.*, cls. 17-18. Claim 17 recites a starting dose “between 25-100 mg” and claim 18 recites a starting dose “between 50-180 mg.” *Id.* Claims 19-25 recite “maintenance dose[s] of diazoxide choline.” *Id.*, cls. 19-25. Claim 19 depends from claim 17 and recites a maintenance dose “between 100-200 mg.” *Id.*, cl. 19. Claims 20-23 depend from 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.*, cls. 20-23. And claims 24-25 depend from claim 17 and recite maintenance doses, respectively, “between 25-250 mg” (claim 24) and “between 200-300 mg” (claim 25). *Id.*, cls. 24-25.

D. Dosing of PWS Population

Due to comorbidities common to PWS, dosing of orally-administered medications presents unique difficulties. Ex.2047 (Deal 2013), 1, 6; Ex.2068 (Sinnema 2013), 6; Ex.2073 (Zipf 2004), 27; Bird ¶¶66-76. Several of diazoxide's 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), 267; Ex.2068 (Sinnema 2013), 6; Bird ¶67. PWS patients also universally have low lean body mass and hypotonia. Ex.2045 (Butler 2006), 150; Ex.2070 (Theodoro 2006), 3; Ex.2042 (Brambilla 1997), 1; Bird ¶68. Critically, PWS patients exhibit nervous system irregularities, including abnormal heart rate variability and blunted cardiovascular reflexes, rendering cardiovascular pharmacodynamic markers such as supine heart rate normalization unreliable in this population. Ex.2045 (Butler 2006), 95; Ex.2060 (Marzullo 2005), 13, 18; Ex.2055 (Haqq 2012), 6; Ex.2048 (DiMario 1996), 1, 3; Bird ¶70. Because of these conditions, dosing for all medications must be approached differently in PWS patients compared to other populations. Bird ¶71; Ex.2045 (Butler 2006), 189, 286.

Moreover, as of the priority date, a POSA would have recognized that PWS patients have extremely different pharmacokinetics as compared to other patient populations. Ex.2045 (Butler 2006), 138, 256, 286; Ex.2041 (Benarroch 2007), 3, 9; Bird ¶¶72-74. But 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 for the PWS population. Bird ¶¶72-74. Such altered pharmacokinetics is an additional reason why dosing protocols developed in non-PWS populations cannot be directly applied to PWS populations without substantial adaptation. Ex.2045 (Butler 2006), 256, 286; Ex.2047 (Deal 2013), 1, 5;

Bird ¶¶72-74.

For similar reasons, as of November 2014, a POSA would have understood that titrating dosing in PWS likewise involves distinct challenges. Ex.2045 (Butler 2006), 189, 286; Bird ¶75. POSAs would have understood that dose escalations need to occur more slowly in PWS patients in order to reliably identify drug-related adverse events and distinguish them from the patient's underlying condition. Ex.2067 (Shapira 2004), 3; Ex.2047 (Deal 2013), 4; Ex.2045 (Butler 2006), 256; Ex.2054 (Goldstone 2008), 9; Bird ¶¶75-76. A too-short titration interval risks stacking dose increases before adverse effects have fully manifested, potentially leading to serious and avoidable harm. *Id.*

III. ASSERTED PRIOR ART

Apotex cumulatively invokes three references across its three grounds: Cowen (Grounds 1-3), Cotter (Ground 2), and Miller (Ground 3). Apotex admits that each of these references was before the Examiner during prosecution. Pet. 16, 18, 20.

A. Cowen (Ex.1009)

Cowen (WO 2009/006483A1) is a published patent application filed by Essentialis, Inc., a predecessor to Soleno, entitled "Salts of Potassium ATP Channel Openers and Uses Thereof." Cowen relates to salts of potassium ATP ("K_{ATP}") channel openers (including diazoxide choline), methods of preparing such salts, and methods of using such salts to treat various diseases and conditions, including type

1 and type 2 diabetes (“T1D” and “T2D”), hypertension, dyslipidemia, nonalcoholic steatohepatitis, pulmonary hypertension, myocardial infarction and arrhythmias following myocardial infarction, and polycystic ovarian syndrome. Cowen, [0002].

Cowen discloses the use of diazoxide salts, but its dosing duration, ranges, and titration with starting and maintenance dosages are directed to treating obesity or T1D or T2D—not PWS. *Id.* [0735]-[0736] (duration of “up to 12 months”), [0077] (dosing ranges and titration); Bird ¶¶77-83. Cowen does not disclose dosing specific to PWS or dose titration with starting and maintenance dosages for any particular disease or condition or any particular K_{ATP} channel opener. Cowen, [0061] (dosing ranges), [0478] (dosing titration); Bird ¶¶77-83.

Cowen provides no clinical data in PWS patients. Instead, any such data involves healthy volunteers or patients with different conditions, primarily obesity, as referenced below:

- Example 7: A clinical study in obese subjects that compared safety, tolerability, and bioavailability/pharmacokinetics (“PK”) of single-dose of diazoxide free base (Proglycem[®]) with DCCR under fasting conditions. Cowen, [00749]; *see also id.* [00750]-[00764].
- Example 8: A clinical study in obese subjects that evaluated potential of once-daily DCCR to improve insulin sensitivity and provide beta-cell rest as evidenced by reductions in homeostasis model assessment-insulin resistance

(“HOMA-IR”) and reductions in fasting insulin. *Id.* [00766].

- Example 9: A clinical study in overweight or obese subjects that evaluated the relationship between PK parameters and weight and BMI. *Id.* [00767]-[00769].
- Example 10: A clinical study in obese subjects that evaluated diazoxide treatment for dyslipidemia. *Id.* [00770]-[00771].
- Example 11: A clinical study in subjects with elevated fasting triglycerides, with or without elevated total cholesterol or LDL-cholesterol, that evaluated diazoxide treatment for hypertriglyceridemia. *Id.* [00772]-[00776].
- Example 12: A clinical study in healthy volunteers that evaluated lipid parameters and blood pressure. *Id.* [00777]-[00779].
- Example 13: A clinical study in hypertriglyceridemic patients that evaluated diazoxide treatment. *Id.* [00780]-[00782].
- Example 14: A clinical study in fasted subjects that evaluated diazoxide choline administration with food to reduce incidence of adverse events. *Id.* [00783]-[00784].

B. Cotter (Ex.1008)

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

treating PWS and conditions affecting basal metabolic rate by 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, [0001].

Cotter does not disclose dosages of a specific K_{ATP} channel opener for any particular indication. *Id.* [0138]; Bird ¶¶84-87. Cotter provides only a single example of treating a PWS patient—who did not have hyperphagia—and in combination with other treatments. Cotter, [0148]-[0150] (Example 1); Bird ¶¶84-87. Diazoxide was administered to an infant with PWS (nutritional phase 1a transitioning to phase 1b) experiencing hypoglycemic episodes. Cotter, [0149]. The infant was started at 0.5 mg/kg BID (twice per day) of diazoxide at eight months of age, increasing to 1 mg/kg BID. *Id.* The infant did not progress to PWS nutritional phase 2a after 56 weeks, “perhaps as a result of the administration of diazoxide,” which Cotter states “supports the utility of diazoxide in the treatment of PWS.” *Id.* at [0149], [0150]. Notably, 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. Bird ¶86.

C. Miller (Ex.1017)

Miller is a 2011 publication authored by Jennifer L. Miller et al., titled “Nutritional Phases in Prader-Willi Syndrome,” published in The American Journal of Medical Genetics. *See* Ex.1017. Miller reports a study characterizing the growth, metabolic, and laboratory changes associated with the various nutritional phases of PWS. Ex.1017, 1 (identifying “a total of seven different nutritional phases, with five main phases and sub-phases in phases 1 and 2”). Miller does not address administration of diazoxide choline or any specific pharmacological therapy for hyperphagia in PWS. Bird ¶¶88-90.

IV. PROSECUTION HISTORY

The '895 patent is part of a continuity chain dating back to an initial 2015 application in which Soleno disclosed methods, dosing regimens, and pharmaceutical formulations for administration of K_{ATP} channel openers to treat diseases or conditions involving K_{ATP} channels, including PWS. Ex.2003 ('895 patent family tree). That application matured into U.S. Patent No. 9,757,384 (“’384 patent”), which issued on September 12, 2017. *Id*; Ex.2001 ('384 patent). The '895 patent is terminally disclaimed against the '384 patent and expires—along with two other patents in the same family—on November 12, 2035.

The Examiner allowed the '895 and '384 patent claims after considering the same or cumulative prior art to that Apotex now asserts against dependent claims 2-

3 and 16-25. Apotex argues that various combinations of Cowen and Cotter render claims 2-3 and 16-25 unpatentable.³ However, the Examiner previously considered—and rejected—the same or similar arguments during prosecution.

V. GROUND 1: APOTEX FAILS TO ESTABLISH THAT COWEN RENDERS CLAIMS 2-3 AND 16-25 OBVIOUS⁴

Apotex, as Petitioner, bears the burden of proving “a proposition of unpatentability by a preponderance of the evidence.” *Eli Lilly & Co. v. Teva Pharms. Int’l GmbH*, 8 F.4th 1331, 1348 (Fed. Cir. 2021). “An obviousness determination requires finding that a [POSA] would have been motivated to combine or modify the teachings in the prior art and would have had a reasonable expectation of success in doing so.” *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1382 (Fed. Cir. 2019).

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

³ Although Apotex relies on Miller for Ground 3, Apotex does not rely on Miller for any teaching for dependent claims 2-3 and 16-25. *See* Pet. 73-86.

⁴ For purposes of this Preliminary Response only, Soleno does not contest Apotex’s proposed POSA definition. Pet. 7-8.

to one of ordinary skill in the art.” *Google LLC v. AGIS Dev. LLC*, IPR2018-01086, Paper 10, 20-22 (Dec. 4, 2018) (denying IPR institution) (quoting *In re Hedges*, 783 F.2d 1038, 1041 (Fed. Cir. 1986)) (cleaned up); *see also In re Stepan Co.*, 868 F.3d 1342, 1346 n.1 (Fed. Cir. 2017) (explaining that motivation is required to combine embodiments from a single reference); *Hewlett Packard Enter. Co. v. Intellectual Ventures II LLC*, IPR2022-00115, Paper 9, 16-17 (Mar. 29, 2022) (denying IPR institution where petitioner’s “combination of select features from [a prior art reference’s] different embodiments to arrive at the invention of [the] claim [wa]s fraught with hindsight bias”); *ABiomed, Inc. v. Maquet Cardiovascular, LLC*, IPR2017-01204, Paper 9, 8-11 (Oct. 23, 2017) (same).

As set forth below, Apotex’s Ground 1 fails because: (A) Cowen does not teach or render obvious treating PWS patients with diazoxide choline for the claimed durations, and Apotex has demonstrated neither motivation to apply Cowen’s obesity protocol to PWS nor a reasonable expectation of success in doing so (Claims 2-3); (B) Cowen does not teach a fixed two-week titration interval, its dose-escalation disclosures are directed to non-PWS populations, and the claimed interval reflects a specific clinical insight rather than routine optimization (Claim 16); (C) the overlapping range presumption does not apply to Cowen’s starting doses—and even if it did, it is rebutted (Claims 17-18); and (D) Apotex impermissibly cobbles together disparate Cowen embodiments to reverse-engineer the claimed

maintenance doses (Claims 19-25). Throughout, Dr. Hollander's conclusory declaration provides no independent support because it merely parrots the Petition's assertions.

A. Claims 2-3 (Treatment Duration Claims) Are Not Obvious

Claims 2-3 depend from Claim 1 and require that diazoxide choline be administered for "at least 10 weeks" (Claim 2) and for "one or more years" (Claim 3). '895 patent, cls. 2-3.

Apotex argues that Cowen teaches "prolonged administration"—wherein a patient is "dosed daily for up to 12 months"—of formulations containing salts including diazoxide choline, and that this disclosure satisfies the treatment-duration limitations of Claims 2-3. Pet. 29-31 (citing Cowen, Abstract, [0234], [0735]-[0736], [0741]). These arguments fail for two independent reasons. Bird ¶92. First, Cowen does not teach or render obvious treating PWS patients with diazoxide choline for at least 10 weeks or up to 12 months. Second, Apotex has not shown that a POSA would have been motivated to apply Cowen's obesity-study protocol to PWS patients or would have had a reasonable expectation of success in doing so.

1. Cowen Does Not Teach or Render Obvious Treating PWS Patients for at Least 10 Weeks or Up to 12 Months

The portions of Cowen cited by Apotex are directed exclusively to treating obese adults, a fundamentally different patient population than the population of PWS patients, many of whom are children, and many of whom are not obese. Bird

¶¶93-97; *supra* §II.A.1. Specifically, paragraphs [0735]-[0736], cited at Pet. 30, disclose dosing “moderate-to-morbidly obese adults with a body mass index (BMI) greater than or equal to 30 kg/m²” with “[f]ormulations of salts of any of the compounds of Formulae I – IV ... for up to 12 months.” Paragraph [0741], also cited at Pet. 30, discloses “co-administration of solid oral dosage form of salts of any of the compounds of Formulae I – IV thereof in combination with phentermine ... in humans with moderate-to-morbidly [obese] and a body mass index (BMI) greater than or equal to 30 kg/m² ... for up to 12 months.” Cowen, [0740]-[0741]. Both of these disclosures are expressly directed to obese adults, not to PWS patients. *Supra* §II.A.1.

Recognizing that the cited portions of Cowen refer to “[t]reatment of obesity in humans” rather than treating PWS patients, Apotex attempts to bridge this gap by asserting that “Cowen makes clear” that the obesity study would also apply to “patients suffering from [PWS].” Pet. 30 (citing Cowen, [0093]). That assertion is both unsupported and incorrect. Paragraph [0093] does not teach that an obesity treatment protocol is applicable to PWS. It merely lists PWS as one of eight diseases characterized by *any one* of four conditions—obesity, hyperphagia, dyslipidemia, or decreased energy expenditure. Cowen, [0093] (“Also provided is a method of treating diseases characterized by *obesity, hyperphagia, dyslipidemia, or decreased energy expenditure* including (a) Prader-Willi Syndrome, (b) Froelich’s syndrome,

(c) Cohen syndrome, (d) Summit Syndrome, (e) Alstrom Syndrome, (f) Borjesen Syndrome, (g) Bardet-Biedl Syndrome, or (h) hyperlipoproteinemia type I, II, III, and IV”) (emphasis added).⁵ PWS is a disease characterized at times by hyperphagia and decreased energy expenditure, but not necessarily by obesity, and nothing in Cowen suggests differently. *Supra* §II.A.1; Bird ¶¶96-97. Critically, there is a fundamental distinction between acknowledging that PWS patients may become obese and affirmatively teaching that a dosing protocol designed for treating adult obesity is appropriate for, or transferable to, treating PWS. Bird ¶¶96-97.

Apotex relies on the declaration of its expert, Dr. Hollander, to support its position, but Dr. Hollander's testimony adds nothing beyond what the Petition itself already states. It merely repeats—almost verbatim—the Petition's incorrect and conclusory assertions. *Compare* Pet. 30 with Ex.1005 ¶135; *see also* Ex.2031, 25, 48 (side-by-side comparison of Apotex's Petition and Expert Declaration). An expert declaration that parrots the petition verbatim “is conclusory and unsupported, adds little to the conclusory assertion for which it is offered to support, and is entitled to little weight.” *Xerox*, IPR2022-00624, Paper 9, 15; *see also Tiktok*, IPR2024-01339, Paper 9, 16 (according “little or no weight” to testimony that “repeats, almost

⁵ The use of the disjunctive term “or” means that the listed diseases need only be characterized by one of the listed conditions.

verbatim, the language in the Petition without any further explanation or supporting reasoning or evidence”).

Further, the disclosure in paragraphs [0740]-[0741] is expressly limited to co-administration with phentermine—a short-term, metabolic drug prescribed to obese patients for weight loss that does not address the neurobiological appetite dysregulation underlying hyperphagia in PWS. Bird ¶102. Phentermine is also contraindicated in pediatric populations, which comprise a significant portion of PWS patients, further confirming that a POSA would have recognized that Cowen's co-administration protocol is neither relevant to nor adaptable for treating hyperphagia in PWS. Bird ¶¶101-102. Apotex wholly fails to consider the impact of Cowen's disclosure of co-administration with phentermine, and likewise fails to explain why a POSA would have reliably extrapolated treatment duration data from a co-administration regimen to monotherapy with diazoxide choline alone.

2. Apotex Has Failed To Demonstrate Either Motivation To Modify Or Reasonable Expectation of Success

Beyond the fatal deficiencies in Cowen's disclosure, Apotex has not demonstrated that a POSA would have applied a treatment protocol designed for adult obese patients to the distinct PWS population. Nor can it; a POSA would have lacked both the requisite motivation and reasonable expectation of success. PWS is a genetic disorder whose metabolic, endocrine, behavioral, and safety profiles differ fundamentally from those of a typical obese patient. *Supra* §II.A.1; Bird ¶¶98-99.

PWS patients have profoundly different body compositions—substantially reduced lean muscle mass with increased fat mass even at comparable BMI—together with central hypotonia, which lowers resting and total energy expenditure and alters caloric needs, weight-based dosing assumptions, and volume of distribution in ways that an obesity dosing protocol does not contemplate. Bird ¶¶99.

PWS patients also experience significant comorbidities not associated with obesity—growth hormone deficiency, hypogonadism, central adrenal insufficiency, hypothyroidism, intellectual disability, and behavioral disturbance—each of which can interact unpredictably with an obesity treatment protocol. Bird ¶¶46-47. Furthermore, PWS patients may have a blunted emesis response and a high pain threshold that can mask gastrointestinal adverse events, elevated risk of respiratory and cardiac adverse events from sleep-disordered breathing, temperature dysregulation that can mask infection, and heightened susceptibility to behavioral and psychiatric adverse events. Bird ¶¶46-47.

Because PWS is typically diagnosed in infancy or early childhood, and patients with PWS experience early mortality with a median age of death in the early 20s, pediatric patients comprise a significant portion of the PWS population. Bird ¶101. Cowen's obesity protocol was designed for and studied in adults. Cowen, [0735]-[0736], [0740]-[0741]. A POSA would have understood that pediatric patients have pharmacokinetic and pharmacodynamic differences (e.g., in drug

metabolism, body composition, dosing requirements) that preclude straightforward application of an adult obesity protocol to a PWS population that includes a substantial number of children. Bird ¶101. Cowen itself recognizes that “oral formulations of diazoxide in therapeutic use result in a range of adverse side effects including dyspepsia, nausea, diarrhea, fluid retention, edema, reduced rates of excretion of sodium, chloride, and uric acid, hyperglycemia, vomiting, abdominal pain, ileus, tachycardia, palpitations, and headache.” Cowen, [0015]. The PWS population is especially susceptible to several of these adverse effects. Bird ¶¶67-69. A POSA would have been aware of these heightened risks and would not have been motivated to treat PWS patients on a prolonged basis absent safety and efficacy data specific to that population. Bird ¶¶98-103.

The absence of any motivation to apply obesity treatments to PWS patients is confirmed by the track record of failed obesity treatments in PWS. As of the priority date, topiramate and metformin—both effective for weight loss or metabolic improvement in obese patients—failed to demonstrate meaningful benefits for hyperphagia in PWS, and restrictive bariatric surgeries likewise failed. Bird ¶100. And also as of the priority date, there was no FDA-approved or clinically validated treatment for hyperphagia in PWS, and the only successful method for managing hyperphagia remained constant supervision and strict environmental controls to limit food access. Bird ¶¶49-50. A POSA would have been aware of this track record of

failure, which would have further diminished any motivation to apply an obesity-derived dosing protocol to PWS patients and undermined any reasonable expectation of success. Bird ¶¶49-50.

Because of these differences, a POSA would have understood that the same drug or dosing regimen could be less effective—if effective at all—or pose materially greater safety risks in a PWS patient than in a typical obesity patient. Bird ¶¶42-43. Moreover, Cowen's disclosure describes a study protocol—how a drug could be tested and a window of observation for gathering data—not a recommended treatment duration. Bird ¶103. A POSA reading Cowen would have understood paragraphs [0735]-[0741] as disclosing hypothetical experimental designs, not as clinical directives applicable to any patient population, let alone for a disease as medically complex as PWS. Such disclosures would not have motivated a POSA to arrive at the claimed inventions. *See InTouch Techs.*, 751 F.3d at 1352 (obviousness is not established by finding that a POSA could have made the invention, but rather requires that the POSA would have been motivated to do so).

Accordingly, Apotex has not established obviousness of Claims 2-3 over Cowen alone.

B. Claim 16 (Dosing Titration Claim) Is Not Obvious

Claim 16 recites a method wherein “the administration of diazoxide choline is initiated at a starting dose of diazoxide choline and then titrated every two weeks

to reach a maintenance dose of diazoxide choline.” ’895 patent, cl. 16. The Petition fails to establish that Claim 16 would have been obvious. Pet. 32-40. Apotex did not identify any prior art reference that discloses, teaches, or suggests a fixed two-week titration interval for diazoxide choline in PWS patients—because none exists. Instead, the Petition resorts to impermissible hindsight reconstruction, cobbling together disparate teachings from Cowen directed to different patient populations, different therapeutic endpoints, and fundamentally different dose-escalation paradigms.

The claimed two-week titration interval is not an arbitrary time period that a POSA would have arrived at through routine experimentation. It reflects a specific clinical insight tailored to the unique pharmacokinetic profile and behavioral assessment challenges of the PWS population. As Dr. Bird explains, the dramatically prolonged half-life of diazoxide choline in PWS patients (approximately 106 hours, compared to 28.7-32.4 hours in healthy subjects), combined with the need to assess tolerability for adverse events such as hyperglycemia, fluid retention, and edema—which require extended observation in cognitively impaired patients—dictated the selection of a two-week interval that no prior art reference teaches or suggests. Bird ¶¶113-115.

Apotex’s obviousness case for Claim 16 fails for at least six independent reasons, each addressed below. Bird ¶104.

1. Cowen Does Not Teach, and Apotex Fails To Show A POSA Would Have Been Motivated to Adopt, A Two-Week Titration Interval

The Petition's obviousness theory fails at the outset because Cowen does not teach or suggest a fixed, calendar-based titration interval of any duration—let alone two weeks. Pet. 35-38 (citing Cowen, [0077]). Cowen's express teaching is an *event-driven* dose-escalation paradigm tied to physiological biomarkers. Paragraph [0077] teaches that the dose is escalated "after supine heart rates return to baseline." A POSA reading Cowen would therefore have understood that the trigger for dose escalation is the patient's individualized physiological response—not the passage of a predetermined number of days or weeks. Bird ¶¶105-106.

The Petition identifies no reason why a POSA would have abandoned Cowen's expressly taught event-driven approach in favor of a fixed two-week calendar interval. Under *KSR*, an obviousness finding requires "some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)). A POSA faithfully following Cowen's teachings would have monitored the patient's heart rate and escalated the dose when—and only when—the patient's heart rate returned to baseline. The Petition offers no explanation for why a POSA would have disregarded this express teaching and substituted a fixed temporal interval. This omission is fatal. Bird ¶¶105-106.

Cowen's remaining dose-escalation disclosures further undermine the Petition's theory. Paragraphs [0089] and [00448] expressly teach "increasing dose daily" with "2 to 10" dose escalation steps. Cowen, [0089], [00448]. These passages describe *daily* dose increments—the antithesis of the claimed two-week titration interval. A POSA reading these passages would have understood that Cowen contemplates rapid, daily dose adjustments—not the prolonged, 14-day intervals required by Claim 16. Bird ¶106.

The Petition attempts to derive a two-week interval from Cowen's statement that the starting dose is given "daily for days or a few weeks." Pet. 35 (citing Cowen, [0077]). But this language does not disclose a titration *interval*. It describes the *duration* over which a given dose is administered before the physiological trigger (heart rate normalization) may signal readiness for escalation. Bird ¶106. The phrase "days or a few weeks" is not a range of titration intervals from which a POSA would have selected; it describes the variable time required for heart rates to normalize—reinforcing the event-driven nature of Cowen's teaching and distinguishing it from the claimed titration protocol. Bird ¶106.

2. Cowen's Dose-Escalation Disclosures Are Directed to Non-PWS Populations and Cannot Be Extrapolated to PWS Patients

Even if Cowen's teachings could somehow be read to disclose a fixed two-week titration interval—which they cannot—those teachings are directed to patient

populations fundamentally different from the claimed PWS population. Bird ¶107. A POSA would have had no reason to extrapolate dose-escalation protocols designed for obese or diabetic adults to the unique clinical context of PWS. In fact, a POSA would have expected such protocols to be ineffective in treating PWS patients.

A paragraph-by-paragraph examination of the Petition's cited passages confirms that each and every dose-escalation disclosure in Cowen is either expressly anchored in non-PWS therapeutic contexts or not specifically directed to PWS patients:

- **Paragraph [0077]** (the Petition's primary citation) discloses dose escalation explicitly in the context of "obesity or type 1 or type 2 diabetes"—not PWS. The dose-escalation trigger (supine heart rate return to baseline) is a cardiovascular biomarker relevant to a metabolic syndrome, not a behavioral endpoint relevant to hyperphagia in PWS. A POSA would have recognized that the use of supine heart rate as a dose-escalation trigger would be an unreliable marker for PWS due to the existing autonomic dysfunction, including abnormal heart rate variability and blunted cardiovascular reflexes, that is characteristic of the PWS population. Bird ¶108.
- **Paragraphs [0089] and [00448]** teach "increasing dose daily" with "2 to 10" escalation steps. A POSA would have understood these daily-increment

protocols to be designed for patients who can reliably self-report adverse effects and whose therapeutic endpoints can be measured through routine laboratory values. Bird ¶109. In obese patients, weight loss can be tracked through daily weigh-ins; in diabetic patients, glycemic control can be monitored through daily blood glucose readings—straightforward metrics justifying a rapid, daily-increment titration regimen. *Id.* PWS patients, by contrast, may be unable to reliably communicate adverse effects due to cognitive impairment, high pain thresholds, and blunted physiological warning signs. And the treatment of hyperphagia cannot be assessed through standard laboratory measures. *Id.*

- **Paragraphs [00478], [00481]-[00484], and [00489]-[00490]** are not directed to and do not mention PWS. Several are expressly directed to an “overweight or obese subject” or an “obesity prone subject.” Cowen, [00482]-[00484], [00489]-[00490]. Critically, paragraphs [00481]-[00482] reference Proglycem® (commercial diazoxide), which is approved for the treatment of hyperinsulinemic hypoglycemia—not hyperphagia or PWS. Ex.1018 (Proglycem prescribing information). This confirms that the disclosed titration teachings are for an entirely different therapeutic context targeting a different pharmacological mechanism (reducing insulin secretion rather than appetite regulation). While paragraphs [00478] and [00481] are directed to

“a subject in need thereof,” neither mentions PWS. Bird ¶110.

- **Paragraph [0093]**—the only paragraph in Cowen that mentions PWS—merely lists it as one of eight diseases “characterized by obesity, hyperphagia, dyslipidemia, *or* decreased energy expenditure.” (emphasis added). This passing reference to PWS in a laundry list of metabolic conditions does not constitute a teaching of how to titrate diazoxide choline specifically for PWS patients. Critically, paragraph [0093] contains no dose-escalation disclosure whatsoever, nor does it in any way suggest that dosing for obese patients may be applied to PWS patients. Bird ¶111.

The distinction between PWS and the populations addressed in Cowen’s titration teachings is clinically dispositive. PWS patients present a unique constellation of challenges that render dose-escalation protocols designed for other patient populations, like obese or diabetic adults, inapplicable:

First, a POSA would have understood that PWS patients have dramatically different pharmacokinetics and would not have expected dosing for other populations to work in PWS patients. Bird ¶¶112-114; Ex.2045 (Butler 2006), 286 (unique body composition of PWS patients creates “[p]harmacokinetic variations” affecting drug metabolism and bioavailability); *see also* Ex.2041 (Benarroch 2007), 9 (“The therapeutic and side effects of medications in patients who have PWS often can be greater than expected, even in severely obese patients who receive low

dosages when considering their body weight.”); Ex.2045 (Butler 2006), 256 (“[D]ue to an altered body composition and metabolism, persons with [PWS] often have extremely idiosyncratic, frequently unpredictable, and often negative responses to medications. ... [S]ide effects may be different, more intense, and longer lasting than in other populations.”). Clinical research confirmed the extreme difference: the terminal half-life of diazoxide choline in PWS patients was approximately 106 hours, more than three times longer than the 28.7-32.4-hour half-life observed in healthy subjects. Ex.1004 (VYKAT XR package insert). This means steady-state concentrations take substantially longer to achieve in PWS patients, and dose-escalation intervals calibrated for non-PWS populations would be dangerously short. Bird ¶114.

Second, PWS patients frequently have intellectual disabilities and limited expressive language capabilities, making self-reporting of adverse effects unreliable. Ex.1007 (Cassidy & Driscoll). Unlike obese or diabetic adults who can typically articulate side effects to their physicians, a POSA would have understood that PWS patients require extended observation periods to detect adverse reactions. Bird ¶115.

Third, the therapeutic endpoint in PWS—reduction of hyperphagia—is a behavioral outcome that requires assessment through validated questionnaires and observation of behavior over time. This stands in stark contrast to the simple metabolic markers (blood glucose, lipid panels, heart rate) that serve as endpoints in

Cowen's obesity and diabetes contexts. A POSA would have understood that assessment of behavioral endpoints in patients with communication difficulties requires longer intervals between dose adjustments. Bird ¶115.

For all these reasons, a POSA would have had no reason to take Cowen's dose-escalation teachings—developed for different patient populations with normal pharmacokinetics, normal cognitive function, and readily measurable metabolic endpoints—and apply them to the PWS population. Bird ¶¶105-115. The Petition's failure to address these fundamental differences is an independent basis for denying institution.

3. The Claimed Two-Week Interval Reflects a Specific Clinical Insight Tailored to the PWS Population

The Petition's fallback argument—that the two-week titration interval is the product of “routine optimization”—fails because it mischaracterizes both the nature of the claimed interval and the applicable legal standard. Pet. 38 (citing *In re Aller*, 220 F.2d 454, 456 (CCPA 1955)). The claimed two-week titration interval is not an arbitrary selection from a recognized range of a result-effective variable; it is the product of specific clinical insight into the pharmacokinetics and behavioral assessment requirements unique to PWS patients.

a. Pharmacokinetic and Clinical Rationale for the Two-Week Interval

The claimed two-week titration interval integrates multiple pharmacokinetic and clinical considerations specific to the PWS population that no prior art reference discloses or suggests:

Time to steady state. As of November 2014, it was known that PWS patients have dramatically different pharmacokinetics as compared to other patients. However, it was unknown how fast PWS patients could metabolize drugs (let alone the claimed diazoxide choline)—making the time to reach steady state a black box. Bird ¶¶113-114. Accordingly, a POSA would not have known whether a PWS patient could reach steady state in the “days” contemplated by Cowen’s daily-escalation protocols. *Id.*

Soleno’s VYKAT XR clinical data revealed the extreme difference in steady state between PWS patients and non-PWS patients. Soleno discovered that diazoxide choline has a terminal half-life of approximately 106 hours in PWS patients. Ex.1004 (VYKAT XR package insert). Under standard pharmacokinetic principles, steady-state plasma concentrations are not achieved until approximately five half-lives have elapsed—which, for PWS patients, equates to approximately 22 days. Bird ¶114. The package insert for VYKAT XR acknowledges that steady state is reached after only approximately 7 days in healthy volunteers with the shorter half-life of 28.7-32.4 hours. Ex.1004.

Safety monitoring in a vulnerable population. Many PWS patients cannot reliably self-report adverse effects due to cognitive impairment, impaired interoception (the ability to perceive internal bodily signals), or a combination of both. Ex.1007. A titration interval must therefore account for the time needed for caregivers and/or clinicians to observe and identify adverse reactions that the patient themselves cannot articulate. This necessitates a longer interval than would be typically required for cognitively intact adult patients. Bird ¶115.

The claimed two-week interval represents an integration of these considerations. It is not mere “routine optimization” of a known variable—it is the product of clinical investigation into a previously uncharacterized therapeutic context. Bird ¶¶112, 116.

b. *In re Aller* Does Not Apply

The Petition's reliance on *In re Aller* is misplaced because the legal prerequisites for applying the routine optimization doctrine are not satisfied. *In re Aller* applies only where: (1) the prior art recognizes the variable at issue as “result-effective”—i.e., a variable that achieves a recognized result; and (2) the claimed range falls within or overlaps with the prior art range. *In re Antonie*, 559 F.2d 618, 620 (CCPA 1977); *In re Peterson*, 315 F.3d 1325, 1329-32 (Fed. Cir. 2003). Neither condition is met here.

First, the titration interval is not recognized as a result-effective variable in Cowen. Cowen does not disclose that varying the titration interval affects therapeutic outcomes. To the contrary, Cowen's event-driven paradigm treats the interval as an *output* of the patient's physiological response (how long it takes heart rate to return to baseline), not as an *input* variable that the clinician adjusts to optimize results. A variable that the prior art does not recognize as result-effective cannot support a routine optimization theory. *See In re Antonie*, 559 F.2d at 620 (finding no basis for routine optimization where the prior art neither disclosed the claimed ratio nor recognized that one of the ratio's variables affected the desired property). Bird ¶¶112, 116.

Second, there is no prior art range encompassing two weeks. The Petition characterizes "days or a few weeks" as a range that encompasses two weeks. Pet. 38. But as discussed above, this phrase describes the duration of drug administration before a physiological trigger—not a range of titration intervals from which a POSA would select. Bird ¶¶105, 108. There is no disclosed range of titration intervals that includes, let alone optimizes around, a two-week period. Bird ¶116. *In re Aller* does not apply when the range was not disclosed in the prior art. *See ModernaTx, Inc. v. Arbutus Biopharma Corp.*, 18 F.4th 1364, 1373 (Fed. Cir. 2021) ("The Board correctly recognized that we have never before applied the presumption of

obviousness for overlapping ranges in a case in which the prior art does not contain an express disclosure of a range.”).

Moreover, even if *In re Aller* could apply in principle, it does not apply where—as here—the claimed parameter reflects a critical insight distinguishable because of the unique characteristics of the claimed patient population. *See Pharmacyclics LLC v. Alvogen, Inc.*, No. 2021-2270, 2022 WL 16943006, at *6 (Fed. Cir. Nov. 15, 2022) (rejecting routine optimization theory where the claimed dosing reflected specific clinical insight). The two-week interval is not a routine selection from a known range—it is a clinically significant choice driven by the PWS population’s unique pharmacokinetics and assessment requirements.

c. *Janssen* Confirms That Specific Dosing Choices Reflecting Clinical Insight Are Non-Obvious

The Federal Circuit’s decision in *Janssen Pharmaceuticals, Inc. v. Teva Pharmaceuticals USA, Inc.*, 141 F.4th 1367 (Fed. Cir. 2025), confirms that specific dosing parameters reflecting clinical insight into a particular patient population are patentable and non-obvious. In *Janssen*, the Court upheld the non-obviousness of specific dosing regimens for paliperidone palmitate, rejecting the argument that the claimed doses were merely “routine optimization” of known dosing ranges. *Id.* 1377-80.

The *Janssen* Court emphasized that where a dosing parameter is selected based on clinical investigation into a specific patient population’s pharmacokinetic

characteristics—rather than mere arithmetic interpolation within a known range—the resulting claim is non-obvious. *Id.* The same principle applies here. The two-week titration interval was not derived by selecting a midpoint from Cowen's teachings; it was determined through clinical investigation (the PC025 study) designed specifically for PWS patients, accounting for their unique drug metabolism (resulting in a prolonged half-life), behavioral endpoints, and assessment challenges. Bird ¶¶112-116.

As in *Janssen*, the prior art here would not have led a POSA inevitably to the claimed interval. Cowen's teachings, if anything, lead away from a two-week interval—toward daily escalation or event-driven titration. The claimed two-week interval represents the kind of specific, population-tailored dosing insight that *Janssen* confirms is patentable.

4. The Petition's Analysis Is Infected by Impermissible Hindsight

The Petition's obviousness theory is a textbook example of impermissible hindsight reconstruction. *See Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966) (cautioning against "slipping into use of hindsight"). Knowing that the '895 patent claims a two-week titration interval, the Petition works backward from the claim language to locate any passage in Cowen that could arguably encompass "two weeks"—and lands on the phrase "days or a few weeks" in paragraph [0077].

But this post hoc rationalization ignores the totality of Cowen's teachings. A POSA reading Cowen prospectively—without knowledge of the '895 patent—would have understood paragraph [0077] to teach an event-driven protocol in which the clinician monitors heart rate and escalates when physiological normalization occurs. Bird ¶¶105-106, 108. A POSA would not have read this passage as an invitation to select a fixed two-week calendar interval. The Petition's contrary reading is available only through improper hindsight.

The hindsight problem is compounded by the Petition's selective citation of Cowen. The Petition highlights paragraph [0077]'s "days or a few weeks" language while ignoring: (a) that this same paragraph teaches event-driven escalation tied to heart rate and (b) that paragraphs [0089] and [00448] teach *daily* dose escalation. A fair reading of Cowen in its entirety would lead a POSA *away from*—not toward—a two-week interval. Bird ¶¶105-106.

5. Dr. Hollander's Declaration Provides No Independent Support for Obviousness

The Petition relies on Dr. Hollander's declaration to assert that "it is common for physicians to utilize two weeks as a standard titration interval when titration is needed." Ex.1005 ¶77. This conclusory assertion fails to supply the evidentiary support the Petition otherwise lacks, for several reasons.

First, Dr. Hollander's statement is an *ipse dixit* generalization that does not identify any specific prior art reference, clinical study, prescribing guideline, or peer-

reviewed publication that teaches a two-week titration interval for diazoxide or any K_{ATP} channel opener in any context—let alone for PWS patients. It merely repeats the Petition's conclusions nearly verbatim without independent evidentiary support. *Supra* §V.A.1.

Second, even accepting Dr. Hollander's generalization at face value, the fact that "two weeks" is a "common" titration interval in *general medical practice* does not establish that a POSA would have applied that interval to diazoxide choline in PWS patients *specifically*. General assertions about common medical practice cannot substitute for a prior art teaching directed to the claimed subject matter. A POSA's (alleged) general awareness that two-week intervals exist in medicine does not provide motivation to adopt that interval for a specific drug (with a 106-hour half-life in the target population) for a specific condition (PWS) whose behavioral endpoints require specialized assessment protocols. Bird ¶¶112-116.

Third, Dr. Hollander does not address the fundamental disconnect between Cowen's event-driven escalation paradigm and the fixed calendar-based interval of Claim 16. His declaration does not explain why a POSA would have abandoned Cowen's expressly taught heart-rate-based trigger in favor of a fixed two-week schedule. This gap in Dr. Hollander's reasoning mirrors the gap in the Petition itself. Bird ¶¶105-106.

Fourth, Dr. Hollander does not account for the dramatically different pharmacokinetics of diazoxide choline in PWS patients, the unique challenges of assessing behavioral endpoints in this population, or the inapplicability of titration conventions developed for cognitively intact adult patients to the PWS context, where many patients have intellectual disabilities. His declaration thus fails to grapple with the very factors that make the claimed two-week interval a non-obvious clinical insight rather than the result of routine optimization. Bird ¶¶113-115.

6. Apotex Cannot Rely on a POSA's Knowledge to Supply the Two-Week Limitation

The Petition's reliance on general POSA knowledge to supply the two-week titration interval is independently foreclosed by 37 C.F.R. § 42.104(b)(4) and the USPTO's July 2025 Memorandum interpreting that rule. EX.2094 (July 2025 Memorandum). Under the USPTO's guidance, "expert testimony, common sense, and other evidence that is not 'prior art consisting of patents or printed publications' (collectively, 'general knowledge') may not be used to supply a missing claim limitation." *Id.*, 1. The prior art must itself teach or suggest the claimed limitation; a POSA's knowledge cannot fill gaps in the evidentiary record.

Here, the two-week titration interval is not found in any prior art reference cited by the Petition. As addressed above, Cowen does not disclose a two-week interval. And none of the Petition's other cited references disclose a two-week titration interval for diazoxide choline in PWS patients. The Petition's theory rests

entirely on the proposition that a POSA would have *known* to use a two-week interval—but under Rule 104(b)(4), such background knowledge is insufficient.

Dr. Hollander's statement that two weeks is a "common" interval (Ex.1005 ¶77) is precisely the type of POSA-knowledge gap-filling that Rule 104(b)(4) prohibits. If the two-week interval were truly taught by the prior art, the Petition would not need to rely on Dr. Hollander's assertion about clinical customs. The very need for this testimony confirms that the claimed limitation is absent from the prior art record and cannot support institution.

C. Claims 17-18 (Starting Dose Claims) Are Not Obvious

Claims 17-18 depend from Claim 16 and further specify the dose of diazoxide choline used to initiate treatment in PWS patients. Claim 17 recites that "the starting dose of diazoxide choline is between 25-100 mg of diazoxide choline." Claim 18 recites that "the starting dose of diazoxide choline is between 50-180 mg of diazoxide choline." Both claims incorporate every limitation of Claim 16, including administration of diazoxide choline to PWS patients, initiation at a starting dose, and titration every two weeks to reach a maintenance dose.

Apotex's entire obviousness theory for these claims rests on a single observation: Cowen's paragraph [0077] discloses a starting dose range of 10-200 mg that numerically overlaps with the claimed ranges. Pet. 40-41. From this overlap alone, Apotex asserts a *prima facie* case. But this superficial numerical comparison

ignores that Cowen's 10-200 mg range is expressly calibrated for a fundamentally different patient population (obese and diabetic adults), a different therapeutic mechanism (cardiovascular-response-based dose selection), and a different pharmacokinetic profile (terminal half-life of approximately 30 hours versus approximately 106 hours in PWS patients). As set forth below, the overlapping range presumption does not apply; even if it did, it would be rebutted; and Apotex's expert provides no independent analysis to bridge these gaps. Bird ¶117.

1. The Overlapping Range Presumption Does Not Apply

The overlapping range doctrine established in *Aller*, 220 F.2d at 456, and its progeny creates a presumption of obviousness only where the prior art discloses the “general conditions” of the claim and the claimed range falls within or overlaps with the prior art range. *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012); *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003). This presumption arises only when the prior art and the claims share the same operative context—that is, the same subject, the same conditions, and the same purpose for the claimed range. Where there are “additional differences” between the prior art context and the claimed invention beyond the numerical value of the range, the presumption does not attach. *See Pharmacyclics*, 2022 WL 16943006, at *5-6.

Here, the “general conditions” of Claims 17-18 are nowhere disclosed in Cowen. Claims 17-18 require a starting dose of diazoxide choline administered to

PWS patients, initiated as part of an every-two-week titration protocol to reach a maintenance dose for the treatment of hyperphagia. Cowen's 10-200 mg range, by contrast, is expressly directed to patients with "obesity, type 1 or type 2 diabetes." Cowen at [0077]. The starting dose is calibrated to produce "elevations in supine heart rate that on average are not greater than 5 beats per minute"—a cardiovascular biomarker that has no relevance to the treatment of hyperphagia in PWS. *Id.*; *supra* § II.D. And Cowen's dosing protocol contemplates event-driven dose escalation (when heart rate returns to baseline), not the fixed two-week titration interval required by Claim 16 and incorporated into Claims 17-18. *Supra* § V.B.

The differences between Cowen's disclosure and the claimed inventions are not merely contextual—they are pharmacokinetically fundamental. Cowen's 10-200 mg starting dose range was developed assuming the pharmacokinetic profile of diazoxide in obese and diabetic patients, who exhibit a terminal half-life of approximately 28.7-32.4 hours. Ex.1004. But as of November 2014, it was known that PWS patients have dramatically different pharmacokinetics. Bird ¶122. The actual half-life and steady-state time periods were unknown. *Id.* Post-priority evidence confirms the extreme difference: diazoxide choline exhibits a terminal half-life of approximately 106 hours in PWS patients—more than three times longer than in the obesity/diabetes population. Ex.1004. A given milligram dose thus produces dramatically different systemic drug exposures in PWS patients. At a 106-hour half-

life, drug accumulation at any given dose is far greater than predicted by a 30-hour half-life model; steady-state concentrations are reached more slowly; and the pharmacological effects of each dose are more pronounced and prolonged. Bird ¶122.

Because the same numerical dose produces a fundamentally different pharmacological reality in PWS patients, the numerical “overlap” between Cowen’s 10-200 mg range and the claimed 25-100 mg and 50-180 mg ranges is illusory. A dose of 100 mg in a patient with a 30-hour half-life is not pharmacokinetically equivalent to 100 mg in a patient with a 106-hour half-life. The exposure, accumulation, and safety profile differ drastically. The *Aller* presumption presupposes that the overlapping numbers represent comparable therapeutic propositions—but here they do not. The presumption therefore does not arise.

Moreover, as the Federal Circuit recognized in *Pharmacyclics*, where the claimed invention operates in a materially different context from the prior art’s numerical disclosure—different patient population, different pharmacokinetic profile, different therapeutic endpoints—the mere fact that numerical ranges overlap does not give rise to a presumption of obviousness. 2022 WL 16943006, at *6. That principle controls here.

2. Even If the Presumption Applied, It Is Rebutted

Even assuming arguendo that the overlapping range presumption applies, it is overcome by evidence demonstrating that a POSA would have had no motivation to apply Cowen's obesity/diabetes starting doses to PWS patients, and no reasonable expectation of success in doing so.

a. A POSA Would Have Had No Motivation to Apply Cowen's Obesity/Diabetes Starting Doses to PWS Patients

Cowen's 10-200 mg starting dose was not selected arbitrarily. It was specifically calibrated using a cardiovascular biomarker: the dose is chosen to produce "elevations in supine heart rate that on average are not greater than 5 beats per minute." Cowen, [0077]. This cardiovascular-response-based selection criterion reflects the therapeutic context in which Cowen operates—treatment of obesity and type 2 diabetes in adults whose cardiovascular parameters serve as reliable proxies for drug activity. Bird ¶¶121-123.

A POSA would have recognized that this dose-selection rationale could not be transposed onto PWS patients. PWS patients exhibit autonomic nervous system dysfunction that renders heart rate an unreliable marker of drug activity. Ex.1007 (Cassidy & Driscoll). A dose-selection strategy premised on heart rate elevations of "not greater than 5 beats per minute" is meaningless in a population whose autonomic responses are dysregulated. A POSA would therefore have had no

basis—and no motivation—to assume that the milligram ranges selected by Cowen on the basis of cardiovascular criteria would be appropriate starting doses for PWS patients treated for hyperphagia. Bird ¶¶118-120.

The pharmacokinetic disconnect further eliminates any motivation to adopt Cowen's starting doses. Cowen's 10-200 mg range presupposes a terminal half-life of approximately 30 hours. A POSA working from Cowen would have assumed that a given starting dose would reach steady state in approximately 5-7 days and produce a predictable level of drug exposure. But in PWS patients, the approximate half-life and steady-state concentration was unknown as of November 2014. Bird ¶122. However, it was known that PWS patients have dramatically different pharmacokinetics. *Id.* A 100 mg starting dose producing acceptable exposure in a patient with a 30-hour half-life may produce dangerously elevated exposure in a patient with vastly different pharmacokinetics (and this was indeed proven true in Soleno's clinical studies). *Id.* A POSA aware of these differences would not simply transplant Cowen's range into the PWS context. *Id.*

Moreover, the therapeutic endpoint differs entirely. Cowen's starting dose is titrated toward metabolic endpoints (weight loss, glycemic control) using cardiovascular biomarkers as safety guardrails. In PWS, the therapeutic target is reduction of hyperphagia—a behavioral endpoint assessed through caregiver observation and validated questionnaires over extended periods. Bird ¶123. The

starting dose for a behavioral endpoint in a cognitively impaired population with unpredictable pharmacokinetics cannot be derived from a cardiovascular-biomarker-based protocol developed for adults with normal drug metabolism. Bird ¶¶119-123.

b. A POSA Would Have Had No Reasonable Expectation of Success

An obviousness determination requires not only motivation to arrive at the claimed invention, but also a reasonable expectation of success. *OSI Pharms.*, 939 F.3d at 1384-85. Here, a POSA would have lacked any reasonable expectation that Cowen's starting doses would be safe or effective in PWS patients.

No prior art reference cited by the Petition reports clinical data on the use of diazoxide choline—at any dose—in PWS patients. The prior art is devoid of efficacy data, safety data, or pharmacokinetic data for diazoxide choline in this population. As the Federal Circuit has held, the absence of efficacy data in the target population undermines any reasonable expectation of success. *OSI Pharms.*, 939 F.3d at 1385 (finding no reasonable expectation of success where the prior art lacked efficacy data in the claimed patient population); *see also Janssen Pharms., Inc. v. Teva Pharms. USA, Inc.*, 760 F. Supp. 3d 184, 207 (D.N.J. 2024) (“no efficacy data” impacts the reasonable expectation of success), *aff'd*, 141 F.4th 1367 (Fed. Cir. 2025).

The unpredictable pharmacokinetics of diazoxide choline in PWS patients further undermines any expectation of success. Cowen's teachings assume a

terminal half-life of 28.7-32.4 hours. But a POSA would have understood that the actual half-life in PWS patients was likely substantially different, and the actual half-life of approximately 106 hours was unknown and unpredictable from the prior art. Ex.1004. This more-than-threelfold increase fundamentally alters the dose-response relationship: it changes the time to steady state, the degree of drug accumulation, and the duration of any adverse effects. A POSA confronting this uncertainty would not have had a reasonable expectation that starting doses derived from a 30-hour half-life population would prove safe or effective in a 106-hour half-life population. Bird ¶122; *see also Janssen Pharms.*, 760 F. Supp. 3d at 208 (“Multi-dose regimens are unpredictable in ways that single-dose regimens are not. With multi-dose regimens ... a POSA must account for ‘accumulation’ of the drug in a patient’s body.”), *aff’d*, 141 F.4th 1367.

The combination of (1) zero clinical data for diazoxide choline in PWS, (2) an unpredictable and dramatically different pharmacokinetic profile, and (3) a dose-selection criterion (heart rate) that is unreliable in the target population renders any expectation of success unreasonable as a matter of law.

3. Apotex’s Expert Evidence Is Insufficient

The Petition relies on Dr. Hollander’s declaration (Ex.1005 ¶¶163-64, 231-32, 288-89) to support its overlapping-range theory. But Dr. Hollander’s testimony on Claims 17-18 consists entirely of restating the numerical overlap between

Cowen's 10-200 mg range and the claimed ranges—the same conclusory, single-sentence argument made in the Petition itself. Dr. Hollander provides no independent analysis of the pharmacokinetic, clinical, or population-specific factors that distinguish the claimed starting doses from Cowen's disclosure, and thus should be given no weight. *Supra* §V.A.1.

Specifically, Dr. Hollander does not address: (1) the dramatically different terminal half-life of diazoxide choline in PWS patients (106 hours versus ~30 hours) and its implications for starting dose selection; (2) the inapplicability of Cowen's cardiovascular-biomarker-based dose-selection criterion to PWS patients with autonomic dysfunction; (3) the absence of any clinical data supporting the use of Cowen's starting doses in PWS patients; or (4) the fundamental differences between the therapeutic endpoints, patient populations, and treatment paradigms at issue. An expert declaration that merely identifies a numerical overlap without engaging these material differences is conclusory and entitled to no weight. *See Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 294 (Fed. Cir. 1985).

Dr. Hollander's failure to grapple with the substance of the non-obviousness case confirms the weakness of Apotex's position. If the claimed starting doses were truly obvious, one would expect the Petition's expert to explain—with specificity and supporting evidence—why a POSA would have selected those doses for PWS patients notwithstanding the fundamental pharmacokinetic, physiological, and

clinical differences between the populations. Dr. Hollander offers no such explanation.

D. Claims 19-25 (Maintenance Dose Claims) Are Not Obvious

Claims 19-25 depend from Claims 17 or 18 (which in turn depend from Claim 16) and further specify the maintenance dose of diazoxide choline reached through the two-week titration protocol. Each claim recites a defined maintenance dose range: Claim 19 (100-200 mg); Claim 20 (200-300 mg); Claim 21 (300-500 mg); Claim 22 (500-2000 mg); Claim 23 (100-500 mg); Claim 24 (25-250 mg); and Claim 25 (200-300 mg). Through their dependency chain, each of these claims requires treating hyperphagia in a PWS patient with diazoxide choline, initiated at a starting dose, and titrated every two weeks to reach the specified maintenance dose.

The Petition's obviousness theory for these claims is different from—and even weaker than—its theory for Claims 16-18. Rather than pointing to a disclosed maintenance dose range, Apotex cobbles together three separate Cowen embodiments, each addressing a different therapeutic context, and performs arithmetic to calculate maintenance dose ranges overlapping with the claims. Pet. 41-45. Specifically, Apotex takes a starting dose from paragraph [0077] (obesity/diabetes), an escalation increment from paragraph [0077], a number of escalation steps from paragraph [0089] (a different embodiment), and formulation dose ranges from paragraphs [0061] and [00380] (yet another embodiment), then

combines them arithmetically to reverse-engineer the claimed maintenance doses. This is precisely the hindsight-driven reconstruction the law forbids.

The Petition's approach fails for four independent reasons, each addressed in turn: (1) it impermissibly combines disparate Cowen embodiments without motivation; (2) the overlapping range presumption does not apply to Apotex's calculated ranges; (3) even if the presumption applied, it is rebutted; and (4) Apotex's expert provides no independent analysis. Bird ¶¶124-125.

1. Apotex Impermissibly Cobbles Together Disparate Cowen Embodiments to Reverse-Engineer the Claimed Maintenance Doses

The foundation of Apotex's obviousness case for Claims 19-25 is a multi-step mathematical exercise that uses parameters from at least three distinct embodiments of Cowen, though none is part of a unified titration protocol, and none is directed to a PWS population. Examining the Petition's sources reveals the extent of this impermissible hindsight reconstruction:

- **Paragraph [0077].** Apotex relies on this disclosure for the starting dose of 10-200 mg and escalation increments of 25-150 mg. Pet. 43. Apotex ignores that this paragraph is expressly directed to "obesity, type 1 or type 2 diabetes." Both the starting dose and its escalation are calibrated based on cardiovascular criteria, specifically "elevations in supine heart rate that on average are not greater than 5 beats per minute." The dose-escalation trigger is physiological:

escalation occurs “when after supine heart rates return to baseline.” This is an event-driven protocol for metabolic disease, not a fixed-interval protocol for PWS. *Supra* §§V.B.1-2, V.C.1-2; Bird ¶¶105-108, 126-128.

- **Paragraph [0089].** Apotex combines the disclosure in paragraph [0077] with paragraph [0089]’s disclosure that the number of dose escalation steps is 2 to 10. Pet. 43. But paragraph [0089] describes “a method of reducing the incidence of adverse effects”—a different embodiment of Cowen that discloses “increasing dose daily.” Paragraph [0089] does not teach a maintenance dose; it teaches daily escalation steps as a safety strategy. And it explicitly contemplates daily dose increases—not the two-week titration intervals required by the claims nor the event-driven dose escalation disclosed in paragraph [0077]. Bird ¶¶106-109.
- **Paragraphs [0061] and [00380].** Finally, Apotex relies on paragraphs [0061] and [00380] to assert that the dosing ranges it calculated would have been “safe and effective for the patient.” Pet. 43-44. However, these paragraphs describe the composition of pharmaceutical formulations—the amount of active ingredient contained in a dosage form. They do not teach titration protocols, maintenance doses, or dose-escalation strategies. They describe what a pill or capsule contains, not what dose a patient should receive as part of a therapeutic regimen. Bird ¶¶127-128.

Apotex's theory thus requires a POSA to: (a) select a starting dose from a cardiovascular biomarker-based obesity/diabetes protocol (paragraph [0077]); (b) pair it with escalation steps from a separate embodiment contemplating daily dose increases (paragraph [0089]); (c) apply an escalation increment from paragraph [0077]; (d) compare the resulting range to formulation composition ranges from paragraphs [0061] and [00380]; and (e) alter the titration interval to two weeks to arrive at the claimed maintenance doses for PWS patients. The Petition identifies no disclosure in Cowen or elsewhere that teaches or suggests combining these parameters, no motivation, and no reasonable expectation of success. Bird ¶¶126, 129.

The Federal Circuit has recognized that even within a single prior art reference, a petitioner must identify a motivation to select and combine particular embodiments. *In re Stepan Co.*, 868 F.3d at 1346 n.1 (motivation required to combine embodiments from a single reference). The Board has denied institution where—as here—the petitioner cherry-picks parameters from disparate portions of a reference without explaining why a POSA would combine them. *See, e.g., Hewlett Packard*, IPR2022-00115, Paper 9 at 16-17 (denying institution where petitioner's “combination of select features from [a prior art reference's] different embodiments to arrive at the invention of [the] claim [wa]s fraught with hindsight bias”); *Google*,

IPR2018-01086, Paper 10 at 20-22 (same); *ABiomed*, IPR2017-01204, Paper 9 at 8-11 (same).

Apotex's failure to identify any motivation is not surprising—any such motivation exists only in hindsight. Using the '895 patent claims as a roadmap, Apotex worked backward through Cowen to identify any combination of parameters that could be made to overlap with the claimed maintenance doses. But “[i]t is impermissible to use the claimed invention as a guide to reconstructing the prior art.” *Ashland Oil*, 776 F.2d at 294. That is precisely what the Petition does here.

2. The Overlapping Range Presumption Does Not Apply

The overlapping range presumption under *In re Aller*, 220 F.2d 454, 456 (CCPA 1955), requires that the prior art *disclose* a range overlapping with the claimed range. The “ranges” on which Apotex relies are not disclosed in Cowen—they are *calculated by Apotex* through the multi-embodiment arithmetic described above. No paragraph in Cowen states: “the maintenance dose is between 100 and 500 mg” or anything comparable. Instead, Apotex takes a starting dose from one paragraph, multiplies an escalation increment by a number of steps from a different paragraph, adds the results, and declares the product a “disclosed range.” This is not how the overlapping range doctrine works.

The *Aller* presumption applies where the prior art itself discloses a range—not where the petitioner derives one through post hoc calculation. *See ModernaTx*,

18 F.4th at 1373 (rejecting presumption application where “Moderna’s theory [was] that a phospholipid range can be *derived or calculated* from the disclosures of the prior art” because “Moderna[] fail[ed] to show that the overlapping range is actually taught by the prior art”); *see also id.* at 1375 (“[T]he possibility of calculating multiple different ranges for the phospholipid cuts against Moderna’s argument that there is a clearly taught overlapping phospholipid range that compels the application of a presumption of obviousness.”). A range that exists only in the petitioner’s brief—constructed by combining parameters from disparate embodiments—is not a “disclosed” range entitled to the presumption of obviousness.

Moreover, even if the calculated ranges could qualify as “disclosed,” the “general conditions” of the claims are absent. Claims 19-25 require maintenance doses of diazoxide choline administered to PWS patients following an every-two-week titration protocol for the treatment of hyperphagia. Cowen discloses none of these conditions. *Supra* §V.D. The disparate Cowen paragraphs from which Apotex draws its arithmetic inputs are directed to: obesity/diabetes treatment (paragraph [0077]); adverse effect reduction through daily escalation (paragraph [0089]); and formulation composition (paragraphs [0061], [00380]). None is directed to PWS, none contemplates a two-week titration interval, and none targets hyperphagia. Where—as here—the prior art context is materially different from the claimed

invention, the overlapping range presumption does not arise. *See Pharmacyclics*, 2022 WL 16943006, at *5-6.

3. Even If the Presumption Applied, It Is Rebutted

Even assuming arguendo that Apotex's calculated ranges could give rise to a presumption of obviousness, that presumption is rebutted by the absence of any motivation to apply Cowen's protocol to PWS patients and the absence of any reasonable expectation of success in doing so.

a. No Motivation to Apply Cowen's Obesity/Diabetes Protocol to PWS

The arguments set forth above regarding the absence of motivation to apply Cowen's teachings to PWS patients apply with equal force to Claims 19-25. *Supra* §§V.A, V.B. Cowen's dose-escalation protocol is expressly designed for obesity and diabetes patients, utilizes cardiovascular biomarkers irrelevant to PWS, and assumes pharmacokinetic parameters that do not apply to the PWS population. A POSA would have had no motivation to take Cowen's obesity/diabetes parameters—starting doses calibrated to heart rate elevations, escalation increments designed for daily titration, and a number of escalation steps directed to reducing adverse effects in adults with normal drug metabolism—and combine them to derive maintenance doses for PWS patients titrated every two weeks. *Bird ¶¶126-131*.

The motivation deficit is compounded for Claims 19-25 because the Petition requires combining multiple Cowen embodiments to reach the claimed maintenance

doses. Even if a POSA had some reason to look to Cowen's paragraph [0077] for starting dose guidance (which Soleno disputes, *supra* §V.D.2), Apotex identifies no reason why a POSA would then turn to paragraph [0089]—a separate embodiment—to obtain the number of escalation steps. Absent motivation to combine these embodiments, Apotex's argument fails.

b. No Reasonable Expectation of Success—Including Pharmacokinetic Unpredictability

A POSA would also have lacked any reasonable expectation that maintenance doses derived from Cowen's obesity/diabetes protocol would be safe or effective in PWS patients. *OSI Pharms*, 939 F.3d at 1384-85; *Janssen*, 760 F. Supp. 3d at 207, *aff'd*, 141 F.4th 1367.

The pharmacokinetic unpredictability of diazoxide choline in PWS patients is particularly devastating to the Petition's maintenance dose theory. Apotex's own exhibit—the VYKAT XR package insert (Ex.1004)—establishes a terminal half-life of approximately 106 hours in PWS patients, compared to 28.7-32.4 hours in healthy subjects. Ex.1004, § 12.3. This more-than-threelfold increase was unexpected and reflects the unpredictability inherent in treating PWS patients. Bird ¶¶130-131.

This is not a minor difference. It fundamentally transforms the dose-response relationship for maintenance doses. Cowen's escalation increments of 25-150 mg were designed for patients with an approximately 30-hour half-life, in whom each dose increment reaches a new steady state within approximately 5-7 days. In PWS

patients with a 106-hour half-life, the same increments produce dramatically different results: steady state takes approximately 22 days to achieve; drug accumulation at steady state is far greater; and the resulting plasma concentrations are substantially higher than predicted from healthy-subject pharmacokinetics. Bird ¶¶130-131.

The practical consequence is that a maintenance dose derived by applying Apotex's arithmetic (starting dose + escalation increments $\times$ number of steps) to PWS patients would produce unpredictable—and potentially unsafe—drug exposures. Bird ¶¶130-131. A POSA would have had no basis to predict that the calculated doses of 60-650 mg (the Petition's own arithmetic) would be safe or effective in a population whose pharmacokinetics were unknown and dramatically different from the population for which those parameters were developed. This is the paradigmatic case in which no reasonable expectation of success exists. *Id.* A POSA would have appreciated the unpredictability in this field and would not have had a reasonable expectation of success in applying Apotex's calculated maintenance doses to the PWS context.

No prior art reference cited by the Petition reports any clinical data on diazoxide choline—at any dose, for any indication—in PWS patients. The complete absence of clinical data independently forecloses any reasonable expectation that Apotex's arithmetically derived maintenance doses would succeed in this

population. *Supra* §V.D.2; Bird ¶¶130-131; *Janssen*, 760 F. Supp. 3d at 207, *aff'd*, 141 F.4th 1367; *OSI Pharms.*, 939 F.3d at 1384-85 (similar).

c. Apotex's Expert Declaration Is Conclusory and Insufficient

Dr. Hollander's testimony on Claims 19-25 (Ex.1005 ¶¶165-75, 233-42, 287-97) consists of merely repeating the Petition's math exercise: he takes Apotex's selected parameters from disparate Cowen embodiments, performs the same addition and multiplication, and declares that the resulting ranges overlap with the claims. He provides no independent scientific reasoning to support the Petition's legal conclusion. This is not expert analysis—it is a cut and paste math exercise expressly aimed at matching the prior art to the claims.

Dr. Hollander does not address any of the substantive obstacles. He does not explain why a POSA would combine parameters from paragraphs [0077], [0089], [0061], and [00380]—embodiments directed to different therapeutic problems. He does not address the dramatically different pharmacokinetics of diazoxide choline in PWS patients or its implications for maintenance dose selection. He does not discuss the absence of clinical data for diazoxide in PWS patients. He does not explain how a POSA could have a reasonable expectation of success in applying escalation increments designed for a 30-hour half-life population to patients with a 106-hour half-life. And he does not address the differences between Cowen's cardiovascular-

biomarker-driven protocol and the behavioral-endpoint-driven treatment of hyperphagia in PWS.

An expert declaration that merely parrots the petition's arithmetic without independent scientific reasoning is conclusory and entitled to no weight. *Supra* §V.A.1. Without substantive expert testimony addressing the real-world obstacles to arriving at the claimed maintenance doses, the Petition cannot carry its burden.

VI. GROUND 2: APOTEX FAILS TO ESTABLISH THAT COWEN AND COTTER RENDER CLAIMS 2-3 AND 16-25 OBVIOUS

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

Claims 2-3 depend from Claim 1 and add durational limitations to the administration of diazoxide choline for the treatment of hyperphagia in PWS patients. Claim 2 requires that “the diazoxide choline is administered for at least 10 weeks” while claim 3 recites that “the diazoxide choline is administered for one or more years.” ’895 patent, cls. 2-3. The Petition asserts that the combination of Cowen and Cotter renders these claims obvious. As discussed above, Cowen does not disclose or render obvious either of these limitations. *Supra* §V.A. In Ground 2, Apotex relies on a single passage from Cotter's Example 1 describing an eight-month-old infant treated with diazoxide for hyperinsulinism-related symptoms. Pet. 57-58.

Apotex's reliance on Cotter's Example 1 to supply the durational limitations of Claims 2-3 fails for six independent reasons, each addressed in turn. Bird ¶¶132-133.

1. Cotter Does Not Teach Administering Diazoxide for 56 Weeks

As a threshold matter, Apotex mischaracterizes Cotter's disclosure, alleging that Cotter teaches dosing "for a period of 56 weeks." Pet. 58. But the paragraphs Apotex cites, paragraphs [0149]-[0150], indicate that "56 weeks" describes how long the infant was "observed" not to have progressed to a later nutritional phase, not how long diazoxide was continuously administered.

The relevant sentence reads: "This child has not progressed to PWS nutritional phase 2a for a period of 56 weeks, perhaps as a result of the administration of diazoxide." Cotter, [0149]. The 56-week timeframe grammatically modifies the duration of "non-progression"—a disease-status observation—not the duration of drug administration. Cotter does not state that the infant "was treated with diazoxide for 56 weeks" or that "diazoxide was administered for a period of 56 weeks." The sentence structure is observational: it tracks how long a clinical status (non-progression) has persisted and speculates ("perhaps") about causation. Bird ¶134.

Paragraph [0150] reinforces the observational character: "With respect to safety, no side effects have been reported for a period of 56 weeks. The infant's blood sugar levels were monitored and were in the normal range." Cotter, [0150].

This too is an observational report describing how long the infant was monitored and what was observed. It does not teach that diazoxide was administered during the 56-week monitoring window. A POSA reading this passage would have recognized it as clinical follow-up language, not a specification of treatment duration. Bird ¶¶135-136.

Indeed, while Cotter describes initiating diazoxide at 0.5 mg/kg BID and increasing to 1 mg/kg BID, it never states that the infant “remained on” or “continued to receive” diazoxide for 56 weeks. Cotter, [0149]. Because Cotter does not teach administering diazoxide for 56 weeks—or for any specified treatment duration—it cannot supply the durational limitations of Claims 2-3. The Petition’s theory fails at the threshold.

2. Cotter’s Example 1 Is Directed to a Fundamentally Different Clinical Condition and Provides No Teaching Regarding Durational Treatment of Hyperphagia

Even if Cotter’s 56-week observation could be read as disclosing continuous treatment—which it cannot—the disclosure is directed to a fundamentally different clinical condition and patient population from Claims 2-3. The Cotter infant was eight months old, in PWS nutritional phase 1a transitioning to phase 1b, and “had experienced hypoglycemic episodes.” Cotter, [0149]. Hypoglycemic episodes are the hallmark of hyperinsulinism—excessive insulin secretion producing dangerously low blood glucose—and the infant’s treatment with diazoxide is

consistent with a diagnosis of hyperinsulinism, given that diazoxide is commonly used to treat that condition by opening K_{ATP} channels on pancreatic beta cells to suppress insulin release, a well-characterized pancreatic mechanism. Bird ¶¶137-140; Ex.2061 (McTaggart 2010), 2-3; Ex.2062 (Miller 2007), 4; Ex.2063 (Miller 2012), 3, Tbl. 1.

Hyperphagia—the condition treated by the claimed invention—is a fundamentally different disorder. It involves dysregulated appetite signaling from hypothalamic dysfunction, producing insatiable hunger, food-seeking behavior, and lack of satiety. Bird ¶¶35-36; Ex.2054 (Goldstone 2008), 4. Hyperphagia typically emerges in PWS nutritional phase 3, at a median age of eight years. Ex.1007; Ex.2054 (Goldstone 2008), 4; Bird ¶¶35-36. The mechanism by which diazoxide choline treats hyperphagia is unknown—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; Bird ¶141.

The Cotter infant had not progressed even to phase 2a—the infant did not have hyperphagia and was not being treated for hyperphagia. Bird ¶137. The durational limitations of Claims 2-3 address the duration of *treatment for hyperphagia*—a condition the Cotter infant did not have and that Cotter's Example 1 does not treat. Nothing in an eight-month-old's hypoglycemia (likely due to hyperinsulinism) case

report teaches a POSA how long to administer diazoxide choline to manage hyperphagia in older children and adults. Bird ¶¶143-144. Regardless of the fundamentally different clinical conditions, a POSA would not have extrapolated dosing from the single infant in Example 1 to older children, adolescents, and adults with PWS who experience hyperphagia, because of substantial differences in body size, composition, and developmental physiology between infants and older patients that directly affect drug absorption, distribution, metabolism, and clearance. Bird ¶142.

3. The Petition Fails to Establish a Motivation to Combine Cowen and Cotter with Respect to the Durational Limitations of Claims 2-3

The Petition also fails because it never articulates a motivation to combine Cowen and Cotter to arrive at the durational limitations of Claims 2-3. The Petition's entire argument is that Cotter's 56-week observation period numerically satisfies "at least 10 weeks" and "one or more years." Pet. 57-58. But numerical sufficiency is not motivation. *See, e.g., Tris Pharma, Inc. v. Actavis Lab'ys FL, Inc.*, No. 2021-1495, 2022 WL 2525318, at *4-6 (Fed. Cir. July 7, 2022) (affirming no obviousness where the prior art disclosed various claimed features but failed to provide a reason why a POSA would have combined those features in the manner claimed). Apotex provides no reason a POSA would have looked to Cotter's infant hypoglycemia

(likely due to hyperinsulinism) case report and combined its disclosure with Cowen's teachings.

The Petition does not explain why treating hyperphagia—a chronic behavioral condition driven by hypothalamic dysfunction—would require a treatment duration informed by an infant's hypoglycemia observation. It does not explain why the 56-week period during which the Cotter infant did not progress to phase 2a bears on how long a phase 3 patient should receive treatment for active hyperphagia. And it does not explain why a POSA would have been motivated to combine Cowen's obesity/diabetes disclosures with Cotter's infant case report to arrive at a durational treatment protocol for hyperphagia. Bird ¶¶134-144.

This gap reflects the fundamental incoherence of the Petition's theory. Cowen addresses dose-escalation for obesity and diabetes; Cotter's Example 1 reports disease progression observations in an infant with hypoglycemia (likely due to hyperinsulinism). Neither reference, alone or in combination, addresses how long diazoxide choline should be administered to treat hyperphagia. Bird ¶¶143-144.

4. A POSA Would Not Have Had a Reasonable Expectation of Success

The Petition also fails to establish that a POSA would have had a reasonable expectation of success in treating hyperphagia for the claimed durations. *OSI Pharms.*, 939 F.3d at 1384-85. The gulf between Cotter's hypoglycemia observation and hyperphagia treatment precludes any reasonable expectation that a drug used in

an eight-month-old infant would translate to effective hyperphagia management over 10 weeks or one or more years in older patients. Bird ¶143.

Cotter's Example 1 does not report that the infant's treatment was effective for any condition over 56 weeks—it reports only that the infant did not progress to phase 2a during that period, with the equivocal notation “*perhaps* as a result of the administration of diazoxide.” Cotter, [0149] (emphasis added). This tentative, anecdotal observation about disease-progression delay in a single infant—hedged by the word “perhaps”—provides no basis to predict that treating hyperphagia would be safe and effective over the time periods claimed. Bird ¶144.

Indeed, no prior art reference in the record reports efficacy data for diazoxide choline in treating hyperphagia at any time point. Without data showing that diazoxide choline reduces hyperphagia at all—let alone over periods of 10 weeks or one year—no reasonable expectation of durational treatment success exists. *OSI Pharms.*, 939 F.3d at 1385 (finding no reasonable expectation of success where the prior art lacked efficacy data in the claimed patient population); *see also Janssen Pharms.*, 760 F. Supp. 3d at 207 (“no efficacy data” impacts the reasonable expectation of success), *aff'd*, 141 F.4th 1367.

5. Apotex's Expert Declaration Is Conclusory and Entitled to No Weight

Dr. Hollander's testimony on Claims 2-3 under Ground 2 consists of a single citation to Cotter. Ex.1005 ¶206 (citing Cotter, [0150]). He does not independently

analyze how Cotter's observation of an infant monitored for phase progression translates to a teaching about the duration of hyperphagia treatment. He simply cites the same Cotter paragraph that the Petition cites.

A side-by-side comparison of the Petition and Dr. Hollander's declaration confirms that the declaration parrots the Petition verbatim on this point. Ex.2031 at 49. An expert declaration that merely restates the petition's legal theory without providing independent reasoning or factual support is conclusory and entitled to no weight. *See Xerox*, IPR2022-00624, Paper 9 at 15; *InTouch Techs.*, 751 F.3d at 1352 (expert opinions lacking independent reasoning are "entitled to little or no weight").

The insufficiency of Dr. Hollander's testimony is particularly significant because the Petition's theory requires bridging a substantial gap—from an infant's hypoglycemia case observation to a durational treatment regimen for hyperphagia. That gap cannot be bridged by citation alone; it requires expert reasoning explaining why the connection is scientifically sound. Dr. Hollander provides none.

6. The Petition's Failure to Provide Particularized Evidence Is Independently Dispositive

The Petition's deficiency is independently fatal under 35 U.S.C. § 312(a)(3), which requires that a petition identify "with particularity" each claim challenged and "the evidence that supports the grounds for the challenge." The durational limitations of Claims 2-3—treatment of hyperphagia for "at least 10 weeks" and "one or more years"—are not taught by any prior art reference in the context of

hyperphagia treatment. The Petition provides no evidence or reasoning connecting Cotter's disclosure to the durational treatment of hyperphagia.

Moreover, under 37 C.F.R. § 42.104(b)(4) and the USPTO's July 2025 Memorandum (Ex.2094), a petitioner may not rely on the general knowledge of a POSA to supply a claim limitation not disclosed in any prior art patent or printed publication. The durational limitations of Claims 2-3—as applied to hyperphagia treatment—are not found in Cowen, Cotter, or any other reference of record. To the extent the Petition implicitly relies on POSA knowledge to bridge the gap between Cotter's hypoglycemia (likely due to hyperinsulinism) observation and hyperphagia treatment duration, that reliance is impermissible. Ex.2094, 1.

B. Cowen and Cotter Do Not Render Obvious Claim 16

Claim 16 recites that “the administration of diazoxide choline is initiated at a starting dose of diazoxide choline and then titrated every two weeks to reach a maintenance dose of diazoxide choline.” ’895 patent, cl. 16. The Petition asserts that combining Cowen and Cotter renders this claim obvious. Pet. 61-65. Adding Cotter does not cure any of the deficiencies that defeat the Petition's Ground 1 challenge to Claim 16. *Supra* §V.B.

Apotex relies on Cotter as allegedly teaching “the use of a lower starting dose followed by titration up to a maintenance dose.” Pet. 61. But Cotter's Example 1 does not teach a titration “every two weeks”—or any periodic titration schedule. It

discloses a single infant case report in which a starting dose was replaced by a higher dose at an undisclosed time—nothing more.

Cotter's Example 1 discloses that an eight-month-old infant "was started at 0.5 mg/kg BID of diazoxide at eight months of age, increasing to 1 mg/kg BID." Cotter, [0149]. That sentence provides a starting dose and an ending dose. It does not disclose whether the dose increase was accomplished in a single step or through multiple adjustments, the interval between adjustments, the criteria used to adjust the dose, or whether any structured titration protocol was followed. A POSA would understand it as a case narrative, not a dosing protocol. Bird ¶¶145-146.

Cotter's Example 1 is directed to a different patient population and clinical condition. As explained above, *supra* §VI.A.2, the Cotter infant was being treated for hypoglycemia (likely due to hyperinsulinism), which is mechanistically distinct from hyperphagia. That infant had not developed hyperphagia. Bird ¶¶147-148. A POSA would not extrapolate titration parameters from an infant's hypoglycemia case report to treating hyperphagia in older children and adults. Titration schedules are specifically tailored to the pharmacokinetic and pharmacodynamic characteristics of the target population—characteristics that differ profoundly between an eight-month-old infant and the hyperphagia patient population. Bird ¶142.

Further, Apotex fails to demonstrate any motivation to combine or reasonable expectation of success in combining Cotter's infant case report to arrive at the *specific two-week titration interval* of Claim 16. Pet. 61-65. Even accepting that Cotter teaches "the use of a lower starting dose followed by titration up to a maintenance dose" (Pet. 61), that does not explain why a POSA would have adopted a *two-week* interval for titrating diazoxide choline to treat hyperphagia. Bird ¶148. Apotex bears the burden to specify its grounds with particularity, and it has failed to do so. See 35 U.S.C. § 312(a)(3).

Dr. Hollander's testimony regarding Claim 16 under Ground 2 consists of a single paragraph citing Cotter, [0149] with no independent reasoning beyond the Petition. Ex.1005 ¶218. A side-by-side comparison confirms verbatim repetition—entitling the opinions to no weight. Ex.2031 at 54; *supra* §V.A.1.

Finally, the Petition's deficiency cannot be rescued by POSA knowledge. Under 37 C.F.R. § 42.104(b)(4) and the USPTO's July 2025 Memorandum, a petitioner may not rely on POSA knowledge to supply a claim limitation not disclosed in any prior art patent or printed publication. Ex.2094, 1. The two-week titration interval is not disclosed in Cotter (which teaches no titration interval) or in Cowen. *Supra* §§III.B, V.B.1. To the extent the Petition relies on POSA knowledge to supply this limitation, that reliance is impermissible under Rule 42.104(b)(4).

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

Apotex's Ground 2 arguments for Claims 17-18 are identical to its Ground 1 arguments. *Compare* Pet. 40-41 *with* Pet. 65. Apotex does not rely on Cotter for any independent teaching on these claims. *Id.* These arguments fail for the same reasons as Ground 1. *Supra* §V.C; Bird ¶149.

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

Apotex's Ground 2 arguments for Claims 19-25 are nearly identical to its Ground 1 arguments. *Compare* Pet. 41-45 *with* Pet. 65-69. For Ground 2, Apotex relies on the same Cowen disclosures—which fail for the same reasons (*supra* §V.D)—but adds a single Cotter disclosure. *See* Pet. 68-69 (citing Cotter, [0138]). This fleeting reference to Cotter does not save the argument.

After repeating its Cowen-based arguments from Ground 1, Apotex argues that “the POSA would have known from the teaching of Cowen *or Cotter* that these [maintenance dose] amounts would have been safe and effective for the patient, providing the POSA a reasonable expectation of success.” Pet. 68-69. In support, Apotex points to Cotter's paragraph [0138]: “The dose of the K_{ATP} channel opener may be at least 1, 5, 10, 15, 20, 30, 40, 50, 100, 200, 300, 400, 500, 1000, or 2000 mg.” *Id.* This disclosure is a bare enumeration of potential dose values. It 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. Bird ¶¶150-154.

A POSA reviewing this list would have had no basis for selecting any particular value—or range of values—as the endpoint of a two-week titration regimen for treating hyperphagia in PWS patients. *Id.* The list spans from 1 mg to 2000 mg—so broad as to encompass virtually any conceivable dose. *Id.* Selecting the specific maintenance dose ranges of Claims 19-25 from this undifferentiated list requires precisely the roadmap that the claimed invention provides. *In re Stepan Co.*, 868 F.3d at 1346-48 (prior art disclosing broad range does not render specific selection obvious absent reason to select); Bird ¶¶150-154. Nor does Cotter's list establish a reasonable expectation that any particular maintenance dose would be safe and effective for treating hyperphagia in PWS patients. Bird ¶¶150-154. Cotter provides no efficacy or safety data for any dose in PWS patients with hyperphagia. Its only clinical data—Example 1—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* §VI.A.2.

The Petition identifies no rationale—in either Cowen, Cotter, or the general knowledge of a POSA—for combining Cowen's obesity and diabetes dose-escalation arithmetic with Cotter's bare list of dose values to arrive at the specific maintenance dose ranges of Claims 19-25 for treating hyperphagia. Pet. 65-69. The only apparent basis for the combination is the claimed invention itself—the classic

hallmark of impermissible hindsight reconstruction. *See Hewlett Packard*, IPR2022-00115, Paper 9 at 16-17 (combination of select features from reference “fraught with hindsight bias”); *In re Stepan Co.*, 868 F.3d at 1346 n.1.

Under 37 C.F.R. § 42.104(b)(4) and the USPTO's July 2025 Memorandum (Ex.2094), a petitioner may not rely on POSA knowledge to supply a claim limitation not disclosed in any prior art patent or printed publication. The specific maintenance dose ranges of Claims 19-25—as the endpoints of a two-week titration regimen for treating hyperphagia with diazoxide choline—are not found in Cowen, Cotter, or any other reference of record. To the extent the Petition relies on POSA knowledge to bridge the gap between Cotter's undifferentiated dose list and the specific claimed maintenance dose ranges in the context of hyperphagia treatment, that reliance is impermissible. Ex.2094, 1; 35 U.S.C. § 312(a)(3).

VII. GROUND 3: APOTEX FAILS TO ESTABLISH THAT COWEN AND MILLER RENDER CLAIMS 2-3 AND 16-25 OBVIOUS

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

Apotex's Ground 3 arguments for Claims 2-3 are identical to its Ground 1 arguments. *Compare* Pet. 29-31 *with* Pet. 75-76. Apotex does not rely on Miller for any independent teaching on these claims. *Id.* These arguments fail for the same reasons as Ground 1. *Supra* §V.A; Bird ¶155.

B. Cowen and Miller Do Not Render Obvious Claim 16

Apotex's Ground 3 arguments for Claim 16 are identical to its Ground 1

arguments. *Compare* Pet. 32-40 *with* Pet. 77-82. Apotex does not rely on Miller for any independent teaching on Claim 16. *Id.* These arguments fail for the same reasons as Ground 1. *Supra* §V.B; Bird ¶156.

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

Apotex's Ground 3 arguments for Claims 17-18 are identical to its Ground 1 arguments. *Compare* Pet. 40-41 *with* Pet. 82. Apotex does not rely on Miller for any independent teaching on these claims. *Id.* These arguments fail for the same reasons as Ground 1. *Supra* §V.C; Bird ¶157.

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

Apotex's Ground 3 arguments for Claims 19-25 are identical to its Ground 1 arguments. *Compare* Pet. 41-45 *with* Pet. 82-86. Apotex does not rely on Miller for any independent teaching on these claims. *Id.* These arguments fail for the same reasons as Ground 1. *Supra* §V.D; Bird ¶158.

VIII. OBJECTIVE INDICIA CONFIRM NON-OBVIOUSNESS

Objective indicia of non-obviousness constitute “independent evidence of nonobviousness” and “must be considered.” *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1378-79 (Fed. Cir. 2012). The objective evidence here establishes that Soleno's novel diazoxide choline dosing regimen (1) succeeded where others failed; (2) satisfied a long-felt, unmet need; (3) received extensive industry praise; (4) is a commercial success; and (5) achieved unexpected results.

Soleno is entitled to a presumption of nexus where, as here, there is evidence

of objective indicia, that evidence is tied to the FDA-approved product label, and the claims are coextensive with that label. *See Pharmacyclics LLC v. Alvogen Pine Brook LLC*, 556 F. Supp. 3d 377, 404-07 (D. Del. 2021), *aff'd*, 2022 WL 16943006 (Fed. Cir. Nov. 15, 2022). The challenged claims cover diazoxide choline, the active ingredient in VYKAT XR, and the claimed dosing regimen is coextensive with the VYKAT XR label. Ex.1004. Thus, there is a nexus between the objective indicia related to Soleno's FDA-approved product and associated dosing regimen, and the claimed invention, such that Soleno's objective evidence "also counsel[s] against a finding of obviousness." *Pharmacyclics*, 556 F. Supp. 3d at 404-07.

Failure of Others. Others' failures to develop an FDA-approved treatment for hyperphagia in PWS patients further establish non-obviousness. Failure to obtain FDA approval is an appropriate benchmark for failure of others. *E.g., Knoll Pharm. Co. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004); *Mylan Pharms., Inc. v. AstraZeneca AB*, IPR2015-01340, Paper 79 at 48-49 (Aug. 18, 2017). To this day—more than *11 years after the priority date* of the challenged patent—Solen's novel diazoxide choline treatment regimen is the *only FDA-approved treatment for hyperphagia* in PWS, despite numerous attempts by others. *See* Ex.2088, 6-7 ("Prior to the recent DCCR approval for the treatment of hyperphagia in adults and pediatric patients 4 years of age and older with PWS by the US Food and Drug Administration, no therapy has been approved, with failures

of several drugs in phase 2 or phase 3 trials.”).

For instance, Acadia Pharmaceuticals abandoned its efforts to investigate intranasal carbetocin (ACP-101) for hyperphagia treatment after its Phase 3 trial did not meet its primary endpoint. Ex.2080, 1 (Acadia's Head of R&D sharing that Acadia is “disappointed by these findings” and “do[es] not intend to investigate intranasal carbetocin any further”); Ex.2084. Likewise, Millendo Therapeutics discontinued its livoletide PWS program after its Phase 2b/3 trial evaluating livoletide did not result in a statistically significant improvement in hyperphagia and food-related behaviors. Ex.2081.

Long-Felt, Unmet Need. At the time of Soleno's invention, no treatment options existed for PWS targeting hyperphagia. Soleno's novel treatment regimen satisfied this void, targeting hyperphagia and thereby addressing “the highest priority unmet need in PWS.” Ex.2088, 6-7; *see* Ex.2086, 2 (Pediatric Endocrinology professor touting “the critical role that VYKAT XR can play in addressing hyperphagia, the most debilitating and distressing symptom of PWS, *where no other effective therapeutic options are currently available*”); Ex.2075, 1 (PWS Association CEO praising Soleno's treatment as a “monumental step forward in *addressing the longstanding unmet needs* of individuals living with PWS and their families”).

Indeed, the FDA recognized Soleno's treatment regimen as satisfying a long-

felt, unmet need, granting “Breakthrough Therapy” designation to diazoxide choline based on clinical data. Ex.2074. As was the case here, the FDA grants “Breakthrough Therapy” designations “to expedite the development and review of drugs that are intended to treat a serious condition” when “preliminary clinical evidence indicates that the drug may demonstrate ***substantial improvement over available therapy*** on a clinically significant endpoint(s).” Ex.2076, 1; *see also Gene Co. Pty. Ltd. v. Trs. of Colum. Univ. in the City of N.Y.*, IPR2024-00313, Paper 54, 64-67 (June 23, 2025) (finding FDA designation of treatment as “Breakthrough Therapy” probative of non-obviousness); *Merck Sharp & Dohme Corp. v. Genentech, Inc.*, PGR2021-00039, Paper 10, 38-39 (July 24, 2021) (similar and denying PGR institution).

Likewise, the FDA granted Soleno’s treatment Orphan Drug status and exclusivity, recognizing that VYKAT XR is the first diazoxide drug approved to treat PWS. Ex.2079. Orphan Drug status and exclusivity are granted to “new treatments for rare diseases [or] condition[s],” like Soleno’s, because development of such treatments “is in the public interest.” Ex.2078; Ex.2077; 21 U.S.C. § 360aa, Notes, Congressional Findings.

The long-felt, unmet need is only underscored by the fact that the compound (diazoxide) and condition (PWS) were discovered, respectively, at least as early as 54 years and 58 years before the 2014 priority date, and diazoxide was approved to

treat other conditions 41 years (hypertension in 1973) and 38 years (hypoglycemia in 1976) before the priority date. Ex.2092, 2 (reporting diazoxide discovery at least as early as 1960); Ex.2045, 14 (reporting PWS discovery at least as early as 1956); Ex.1011 (1973 FDA approval of diazoxide for hypertension); Ex.1012 (1976 FDA approval of diazoxide for hypoglycemia); Ex.1005 ¶69. Despite this long-standing knowledge, Soleno's treatment regimen was only discovered in November 2014 and diazoxide choline was only approved to treat PWS in March 2025—supporting non-obviousness. *See In re 318 Pat. Infringement Litig.*, 578 F. Supp. 2d 711, 716, 719-23, 730-32 (D. Del. 2008) (finding long-felt, unmet need existed as of 1986 priority date and supported non-obviousness of claimed method of treating Alzheimer's disease ("AD") using galanthamine, where condition (AD) was discovered 80 years prior in 1906, compound (galanthamine) was discovered 25 years prior in 1961, and galanthamine was known to treat conditions other than AD).

Industry Praise. Soleno's novel diazoxide choline treatment regimen has received extensive industry praise, "weigh[ing] in favor of nonobviousness." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1334-35 (Fed. Cir. 2016); *see also Quanergy Sys, Inc. v. Velodyne Lidar, Inc.*, IPR2018-00255, Paper 59, 34-36 (May 23, 2019) ("widespread praise and acceptance" from "numerous participants in the [field]" and in news publications "weigh[ed] distinctly in favor of non-obviousness"). In particular, Soleno's novel treatment regimen has received widespread industry

acclaim. *E.g.*, Ex.2083, 2 (“game-changer” treatment), 3 (“[f]amilies [of PWS patients] are really feeling hopeful for the first time in a long time”); Ex.2085, 2 (“incredible achievement for the entire PWS community”), *id.* (“major step forward in changing the future for individuals navigating hyperphagia associated with PWS”); Ex.2025, 1 (“*monumental* victory for individuals with PWS, our families, and the entire rare disease community” (emphasis in original)), 1 (“much-needed treatment [is now] a reality for our families and loved ones”), 3 (“groundbreaking approval”).

And notably, parents and caretakers of children suffering from PWS have touted Soleno's treatment. *E.g.*, Ex.2026, 2 (“[T]he PWS community has cause for far more hope! . . . [W]e can perhaps breathe a little deeper, release some of that tension in our shoulders, and revel in the sweet calm of victory. . . . That glow on the horizon just got a whole lot brighter.”); Ex.2027, 5 (“Before the drug, it just felt like a dead end. My child was miserable. Now, we have our son back.”); *see Gene Co.*, IPR2024-00313, Paper 54 at 64-67 (patient family praise supported non-obviousness).

Commercial Success. Soleno's novel diazoxide choline treatment regimen has also achieved significant commercial success, further contradicting Apotex's obviousness assertion. *See Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310-11 (Fed. Cir. 2010). Since entering the market in April 2025 through the end of

2025, VYKAT XR generated \$190.4 million in revenue, with Soleno reporting its first profitable quarter. Ex.2082, 1; Ex.2089, 1 (“Soleno Therapeutics marked a significant turning point in its corporate history by reporting its first profitable quarter, driven by robust sales of VYKAT XR, its groundbreaking therapy”); *Xactware Sols., Inc. v. Eagle View Techs., Inc.*, IPR2016-00590, Paper 41 at 14-17 (Aug. 14, 2017) (commercial success supported non-obviousness where patent owner offered evidence of “rapid growth of its business after introducing [patented] products”).

The commercial success of Soleno's novel treatment regimen is further evidenced by Neurocrine's acquisition of Soleno for \$2.9 billion. *See* Ex.2028; *Xactware*, IPR2016-00590, Paper 41 at 14-17 (commercial success supported non-obviousness where patent owner offered evidence of its company's “purchase price of \$650 million” due to, in part, its “significant intellectual property” and “position as a market leader”). Neurocrine acquired Soleno in part because “VYKAT XR is well positioned as the foundational first-line therapy for PWS and is supported by a strong intellectual property estate that is expected to extend into the mid-2040s, providing a durable platform for long-term value creation.” Ex.2028, 2.

Unexpected Results. The unprecedented safety and efficacy of Soleno's novel treatment regimen likewise support non-obviousness. Soleno's treatment “is the first to demonstrate a therapeutic benefit that safely and effectively improves

hyperphagia in people with PWS.” Ex.2088, 6-7; *see also id.*, 7 (Solenó’s treatment “was well tolerated” and “demonstrates significant and durable efficacy . . . for the treatment of hyperphagia in patients with PWS”), 7 (“[H]yperphagia worsens significantly when treatment with DCCR is withdrawn compared to continued DCCR administration.”); Ex.2087, 8-9 (Solenó’s treatment “was well tolerated” with “significant improvement in hyperphagia and other broad-ranging behavioral improvements”).

IX. CONCLUSION

For the reasons set forth above, Soleno respectfully requests that the Director deny the Petition for Post-Grant Review.

Respectfully submitted,

Dated: July 22, 2026

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CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. § 42.24

I hereby certify that this Patent Owner's Preliminary Response complies with the word count limitation of 37 C.F.R. § 42.24(b)(1) because the Patent Owner's Preliminary Response contains 18,570 words using Microsoft Word's counting feature, excluding the cover page, signature block, and the parts of the Patent Owner's Preliminary Response exempted by 37 C.F.R. § 42.24(b)(1).

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I certify that on this 22nd day of July, 2026, a true and correct copy of the foregoing **Patent Owner's Preliminary Response and all Exhibits** were served by electronic mail on Petitioner's lead and backup counsel at the following email addresses:

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