

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NEUROCRINE BIOSCIENCES, INC.
Petitioner

v.

SPRUCE BIOSCIENCES, INC.
Patent Owner

U.S. Patent 12,576,084 B2

DECLARATION OF MAYA LODISH, M.D.

IN SUPPORT OF PETITION FOR POST GRANT REVIEW OF U.S.
PATENT NO. 12,576,084 B2

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I, Maya Lodish, M.D., of San Francisco, California, declare that:

I. QUALIFICATIONS AND BACKGROUND INFORMATION

1. My curriculum vitae is attached hereto as Appendix A.

2. I earned a B.A. degree in Biochemistry and Molecular Biology at Dartmouth College in 1998. I then earned an M.D. from Yale University School of Medicine in 2003. I also hold a Masters in Health Science from Duke University, which I earned in 2013. After receiving my M.D., I completed my internship and residency in pediatrics at Johns Hopkins Hospital in Baltimore, Maryland from 2003 to 2006. I then completed a fellowship in pediatric endocrinology at the National Institutes of Health in Bethesda, Maryland from 2006 to 2009.

3. I am currently a Professor of Clinical Pediatrics and hold the Selma Kaplan Distinguished Professorship in Pediatric Endocrinology/Diabetes at the University of California, San Francisco (UCSF), a position I have held since 2018. Since 2019, I have also served as the Chief of the Division of Pediatric Endocrinology at UCSF. Prior to these positions, I served as a Deputy Program Director, Staff Clinician, Program Director, and Associate Research Physician at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), positions I held from 2009 to 2018.

4. As part of my position at UCSF, I teach medical students, residents, and fellows in formal courses, including foundational courses/lectures on the

thyroid; lectures on disorders of the adrenal glands, pituitary glands, and hypothalamus; lectures on diabetes; as well as lead small groups of students on a variety of topics. I lecture to students, residents, nursing students, and pediatric endocrinology fellows, as well adult endocrinology and reproductive endocrinology fellows. I also helped to draft the curriculum content guidelines for the American Board of Pediatrics subspecialty content in Pediatric Endocrinology. I have had the privilege of serving as a mentor to over 50 students, fellows in training, and junior faculty members, many of whom have had first author publications and gone on to successful academic careers.

5. I am and have been certified by the American Board of Pediatrics since 2006, as well as the American Board of Pediatrics Sub-board of Pediatric Endocrinology since 2009. I am currently licensed to practice medicine in California. I have also held licenses to practice medicine in Maryland and Virginia.

6. In addition to teaching, I attend in the pediatric endocrinology clinic and on the inpatient pediatric endocrinology consult service (with medical students, residents, and fellows). I collaborate with the UCSF hereditary cancer clinic for management of children with a predisposition to endocrine tumors. I also collaborate with the division of pediatric oncology, to provide endocrine care to survivors of childhood cancer and to neuro-oncology patients.

7. In my career, I have been invited by numerous universities and institutions around the world to present lectures on pediatric endocrinology. I have authored or co-authored over 140 scientific articles, 8 book chapters, and 3 books.

8. At UCSF, I am the principal clinical investigator for studies of novel therapeutics in pediatric endocrinology, including four active protocols. These include a Phase II study of the use of osilodrostat in children with Cushing's disease, a Phase III study of a once-yearly GnRH agonist in children with precocious puberty, a Phase IV study of long-acting growth hormone in children with short stature, and a randomized comparative study between liquid and tablet formulations of levothyroxine in neonates and infants with congenital hypothyroidism. I previously served as a co-investigator on an efficacy and safety study of palovarotene for the treatment of fibrodysplasia ossificans progressive.

9. During my time at the NIH, I was the primary investigator of a study evaluating mifepristone in children with refractory Cushing's disease, as well as primary investigator of a study evaluating the safety and efficacy of pegvisomant in children with growth hormone excess. I was also a co-investigator on a clinical trial studying the use of vandetanib to treat children and adolescents with medullary thyroid cancer.

10. I have been a Principal Investigator in numerous clinical trials. I helped to design the Phase III clinical trial design of crinecerfont in pediatric CAH

patients and went on to serve as a Principal Investigator. I am an author of the New England Journal of Medicine article reporting the result of that study. *See* EX1053. I continue to serve as primary investigator in the open label extension of this trial.

11. During my time at the National Institutes of Health, I served as a member of the Institutional Review Board (IRB) of the National Institute of Dental and Craniofacial Research (NIDCR) for approximately six years (2009-2014). An IRB is an independent committee established to review and oversee research involving human subjects. Before any clinical study involving human participants may proceed, the study protocol, informed consent documents, and related materials must be reviewed and approved by an IRB to ensure that the rights, safety, and welfare of the research subjects are adequately protected. As part of my service on the IRB, I reviewed proposed clinical study designs, evaluated the scientific merit and ethical considerations of research protocols, and assessed whether the potential risks to participants were justified by the anticipated benefits of the research.

12. I currently serve as a reviewer for various medical journals including the Journal of the American Medical Association, Lancet, Thyroid, Endocrine, Endocrinology, Diabetes and Metabolism Case Reports, the Journal of Pediatrics, Molecular and Cellular Endocrinology, and others. I have previously served on the editorial board of the Journal of Clinical Endocrinology & Metabolism.

13. I am a member of the Endocrine Society and the Pediatric Endocrine Society, where I have served on various committees and subcommittees.

II. COMPENSATION

14. I am being compensated at my customary rate of \$600 per hour for my work in this matter. My compensation is in no way based on the outcome of this matter and has not influenced my views in this matter.

III. MATERIALS CONSIDERED

15. In writing this Declaration, I have relied on my background, education, and experience as a physician, both in treating patients with endocrine disorders, including CAH, and studying the treatment of such disorders in clinical trials. I have also considered, in whole or in part, the following documents in forming my opinion in this matter.

Exhibit No.	Exhibit Description
1001	U.S. Patent No. 12,576,084 to Howerton et al. (“the ‘084 Patent”)
1002	Excerpts from the Prosecution History of the ‘084 Patent (“the Prosecution History”)
1004	PCT Publication WO/2015/112642 to Grigoriadis et al. (“Grigoriadis PCT”).
1005	Final Written Decision, Paper 64, <i>Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc.</i> , No. PGR2021-00088 (PTAB Nov. 27, 2024).
1006	U.S. Patent Application Publication No. 2017/0020877 to Grigoriadis et al. (“Grigoriadis”).

Exhibit No.	Exhibit Description
1007	Final Written Decision, Paper 62, <i>Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc.</i> , No. PGR2022-00025 (PTAB Nov. 26, 2024).
1008	Turcu et al., “Single-Dose Study of a Corticotropin-Releasing Factor Receptor-1 Antagonist in Women With 21-Hydroxylase Deficiency,” <i>J. Clin. Endocrinol. Metab.</i> , 101(3):1174-80 (March 2016) (“Turcu 2016”).
1010	CRENESSITY® (crinecerfont) Prescribing Label, U.S. Food and Drug Administration (Dec. 13, 2024).
1012	PCT Publication WO 2007/105113 to Richard (“Richard”)
1013	Speiser et al., “Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline,” <i>J. Clin. Endocrinol. Metab.</i> , 95(9):4133-60 (2010) (“Speiser 2010”).
1014	Turcu A.F. & Auchus R.J., “The Next 150 Years of Congenital Adrenal Hyperplasia,” <i>J. Steroid. Biochem. Mol. Biol.</i> , 153:63-71 (Sept. 2015) (“Turcu & Auchus 2015”).
1015	El Maouche et al., “Congenital Adrenal Hyperplasia,” <i>Lancet</i> 390:2194-10 (2017) (“El Maouche 2017”).
1016	Merke D.P. & Bornstein S.R., “Congenital Adrenal Hyperplasia,” <i>Lancet</i> , 365:2125-36 (2005) (“Merke & Bornstein 2005”).
1017	Speiser et al., “Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline,” <i>J. Clin. Endocrinol. Metab.</i> , 103(11):4043-88 (2018) (“Speiser 2018”).
1018	Fahmy et al., “Structure and Function of Small Non-Peptide CRF Antagonists and their Potential Clinical Use,” <i>Curr. Mol. Pharmacol.</i> , 10(4): 270-281 (2017) (“Fahmy 2017”).

Exhibit No.	Exhibit Description
1019	Griebel et al., “4-(2-Chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]5-methyl-N-(2-propynyl)-1,3-thiazol-2-amine Hydrochloride (SSR125543A), a Potent and Selective Corticotrophin-Releasing Factor1 Receptor Antagonist. II. Characterization in Rodent Models of Stress-Related Disorders,” <i>J. Pharmacol. Exp. Ther.</i> , 301(1):333-45 (2002) (“Griebel 2002”).
1020	Gully et al., “4-(2-Chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]5-methyl-N-(2-propynyl)-1,3-thiazol-2-amine Hydrochloride (SSR125543A): A Potent and Selective Corticotrophin-Releasing Factor1 Receptor Antagonist. I. Biochemical and Pharmacological Characterization,” <i>J. Pharmacol. Exp. Ther.</i> , 301(1):322-32 (2002) (“Gully 2002”).
1024	Merke D.P. & Auchus R.J., “Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency,” <i>N. Engl. J. Med.</i> 383(13):1248-61 (2020) (“Merke & Auchus 2020”).
1025	Turcu A.F. & Auchus R.J., “Novel Treatment Strategies in Congenital Adrenal Hyperplasia,” <i>Curr. Opin. Endocrinol. Diabetes Obes.</i> , 23(3):225-32 (June 2016) (“Turcu & Auchus 2016”).
1026	Webb E.A. & Krone N., “Current and Novel Approaches to Children and Young People with Congenital Adrenal Hyperplasia and Adrenal Insufficiency,” <i>Best Pract. Res. Clin. Endocrinol. Metab.</i> , 29:449-68 (2015) (“Webb & Krone 2015”).
1027	“Neurocrine Biosciences to Present New Data Analyses for Crinecerfont in Adults with Classical Congenital Adrenal Hyperplasia at ENDO 2021,” Neurocrine Biosciences (March 20, 2021) (“Neurocrine March 20, 2021, Press Release”).
1029	Williams, “Corticotropin-Releasing Factor 1 Receptor Antagonists: A Patent Review,” <i>Expert Opin. Ther. Pat.</i> , 23(8):1057-68 (2013) (“Williams 2013”).
1030	Zorrilla E.P. & Koob G.F., “Progress in Corticotropin-Releasing Factor-1 Antagonist Development,” <i>Drug Discovery Today</i> , 15(9/10):371-83 (2010) (“Zorrilla & Koob 2010”).

Exhibit No.	Exhibit Description
1033	National Center for Biotechnology Information, PubChem Compound Summary for CID 5282340, Crinicerfont (2026).
1038	Zaarour et al., “Bilateral Ovary Adrenal Rest Tumor in a Congenital Adrenal Hyperplasia Following Adrenalectomy,” <i>Endo. Prac.</i> , 20:4 (Apr. 2014).
1039	Sarafoglou et al., “Interpretation of Steroid Biomarkers in 21-Hydroxylase Deficiency and Their Use in Disease Management,” <i>J. Clin. Endocrinol. Metabol.</i> 108:2154-75 (March 2023) (“Sarafoglou 2023”).
1040	Chen et al., “Ovarian Adrenal Rest Tumors Undetected by Imaging Studies and Identified at Surgery in Three Females with Congenital Adrenal Hyperplasia Unresponsive to Increased Hormone Therapy Dosage,” <i>Endocr. Pathol.</i> , 28:146-151 (2017).
1041	Sarafoglou et al., “Tildacerfont in Adults With Classic Congenital Adrenal Hyperplasia: Results from Two Phase 2 Studies,” <i>J. Clin. Endocrinol. Metabol.</i> 106(11):e4666-79 (2021) (“Sarafoglou 2021”).
1043	“Spruce Biosciences Achieves Proof of Concept in Phase 2 Study of Tildacerfont in Congenital Adrenal Hyperplasia,” Spruce Biosciences (Mar. 25, 2019) (“Spruce Mar. 25, 2019, Press Release”).
1044	“Spruce Biosciences Announces Topline Results from CAHmelia-203 in Adult Classic CAH and CAHptain-205 in Pediatric Classic CAH,” Spruce Biosciences (March 13, 2024) (“Spruce March 13, 2024, Press Release”).
1045	“Spruce Biosciences Announces Topline Results from CAHmelia-204 in Adult CAH and CAHptain-205 in Adult and Pediatric CAH,” Spruce Biosciences (December 10, 2024) (“Spruce December 10, 2024, Press Release”).
1046	Turcu A.F. & Auchus R.J., “Adrenal Steroidogenesis and Congenital Adrenal Hyperplasia,” <i>Endocrinol. Metabol. Clin. N. Am.</i> , 44:275-96 (2015) (“Turcu & Auchus 2015a”).

Exhibit No.	Exhibit Description
1047	Mallappa A. & Merke D.P., “Management challenges and therapeutic advances in congenital adrenal hyperplasia,” <i>Nature Reviews Endocrinol.</i> , 18:337-52 (June 2022) (“Mallappa & Merke”).
1048	Auchus et al., “Crinecerfont Lowers Elevated Hormone Markers in Adults With 21-Hydroxylase Deficiency Congenital Adrenal Hyperplasia,” <i>J. Clin. Endocrinol. Metabol.</i> , 107(3):801-12 (2022) (“Auchus 2022”).
1049	Claahsen-van der Grinten et al., “Congenital Adrenal Hyperplasia—Current Insights in Pathophysiology, Diagnostics, and Management,” <i>Endocrine Reviews</i> , 43(1):91-159 (2022) (“Claahsen-van der Grinten”).
1051	International Application PCT/US2019/029486 to Spruce Biosciences, Inc. (“the PCT application”).
1052	Auchus et al., “Phase 3 Trial of Crinecerfont in Adult Congenital Adrenal Hyperplasia,” <i>N. Engl. J. Med.</i> , 391(6):504-14 (June 2024) (“Auchus 2024”).
1053	Sarafoglou et al., “Phase 3 Trial of Crinecerfont in Pediatric Congenital Adrenal Hyperplasia,” <i>N. Engl. J. Med.</i> , 391(6):493-503 (June 2024) (“Sarafoglou et al. 2024”).
1055	U.S. Provisional App. No. 62/663,951 (the “951 provisional”).
1056	U.S. Provisional App. No. 62/822,815 (the “815 provisional”).
1058	“Neurocrine Biosciences Announces FDA Approval of CRENESSITY® (crinecerfont), a First-in-Class Treatment for Children and Adults With Classic Congenital Adrenal Hyperplasia,” Neurocrine Biosciences (Dec. 13, 2024) (“Dec. 13, 2024, Neurocrine Press Release”).
1059	National Center for Biotechnology Information, PubChem Compound Summary for CID 134694266, Tildacerfont (2026).
1060	U.S. Pat. No. 6,586,456 to Fontaine, et al. (the “456 patent”).
1061	U.S. Patent Appl. No. 17/081,694, Office Action Response with Declaration of Chris N. Barnes (Dec. 13, 2021).

Exhibit No.	Exhibit Description
1064	Delfino et al., “Testicular Adrenal Rest Tumors in Patients With Congenital Adrenal Hyperplasia: Prevalence and Sonographic, Hormonal, and Seminal Characteristics,” <i>J. Ultrasound Med.</i> , 31:383-88 (2012).
1067	Yu et al., “Clinical manifestations of testicular adrenal rest tumor in males with congenital adrenal hyperplasia,” <i>Ann. Ped. Endocrinol. Metab.</i> , 20:155-161 (2015).
1068	Aycan et al., “Prevalence and long-term follow-up outcomes of testicular adrenal rest tumours in children and adolescent males with congenital adrenal hyperplasia,” <i>Clin. Endocrinol.</i> , 78, 667-72 (2013).
1069	Claahsen-van der Grinten et al., “Gonadal dysfunction in congenital adrenal hyperplasia,” <i>Eur. J. Endocrinol.</i> , 184(3):R85-R97 (2021).
1070	Reisch et al., “Testicular Adrenal Rest Tumors Develop Independently of Long-Term Disease Control: A Longitudinal Analysis of 50 Adult Men With Congenital Adrenal Hyperplasia due to Classic 21-Hydroxylase Deficiency,” <i>J. Clin. Endocrinol. Metab.</i> , 98(11):E1820-E1826 (Nov. 2013).
1071	Mendes-dos-Santos et al., “Prevalence of Testicular Adrenal Rest Tumor and Factors Associated with Its Development in Congenital Adrenal Hyperplasia,” <i>Horm. Res. Paed.</i> , 90:161-168 (2018).
1072	Spruce Biosciences Clinical Study Report, SPR001-202 Protocol, https://cdn.clinicaltrials.gov/large-docs/42/NCT03687242/Prot_000.pdf (2025).
1074	International Publication No. WO 2016/065177 A1 to Howerton et al. (“Howerton”).
1077	U.S. Pat. App. No. 17/081,694 (“the ’694 Application”), Notice of Allowance and Reasons for Allowance (Feb. 1, 2022).
1078	Smeets et al., “Molecular Characterization of Testicular Adrenal Rest Tumors in Congenital Adrenal Hyperplasia: Lesions With Both Adrenocortical and Leydig Cell Features,” <i>J. Clin. Endocrinol. Metab.</i> , 100(3):E524-E530 (Mar. 2015).
1088	Deussing & Chen, “The Corticotropin-Releasing Factor Family: Physiology of the Stress Response,” <i>Physiol. Rev.</i> , 98:2225-2286 (2018).

Exhibit No.	Exhibit Description
1089	FDA News Release, “FDA Approves New Treatment for Congenital Adrenal Hyperplasia” (December 13, 2024)
1090	National Center for Biotechnology Information, PubChem Compound Summary for CID 11596613, Verucerfont (2026).
1091	National Center for Biotechnology Information, PubChem Compound Summary for CID 24758885, 3-[4-Bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-a]pyrimidine] (2026).
1092	National Center for Biotechnology Information, PubChem Compound Summary for CID 24898976, 3-(4-Bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (2026).
1093	National Center for Biotechnology Information, PubChem Compound Summary for CID 9821250, NBI-30775 (2026).
1094	National Center for Biotechnology Information, PubChem Compound Summary for CID 9888194, NBI-34041 (2026).
1095	National Center for Biotechnology Information, PubChem Compound Summary for CID 9884878, DMP-904 (2026).
1096	National Center for Biotechnology Information, PubChem Compound Summary for CID 177990, Antalarmin (2026).
1104	Sacks et al., “Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus,” <i>Diabetes Care</i> 46(10):e151-e199 (2023)
1105	Fujimoto, “The importance of insulin resistance in the pathogenesis of type 2 diabetes mellitus,” <i>Am J Med.</i> 108(6a):9S-14S (2000)
1106	Abdul-Ghani et al., “Contributions of beta-cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose,” <i>Diabetes Care</i> 29(5):1130-9 (2006).
1107	Merkatz, “Inclusion of Women in Clinical Trials: A Historical Overview of Scientific, Ethical, and Legal Issues,” <i>JOGNN Clinical Issues</i> , 27(1):78-84 (1997)
1108	Moller DE, Flier JS. Insulin Resistance — Mechanisms, Syndromes, and Implications. <i>N Engl J Med.</i> 1991;325(13):938-948P

IV. TECHNOLOGY BACKGROUND

A. Congenital Adrenal Hyperplasia

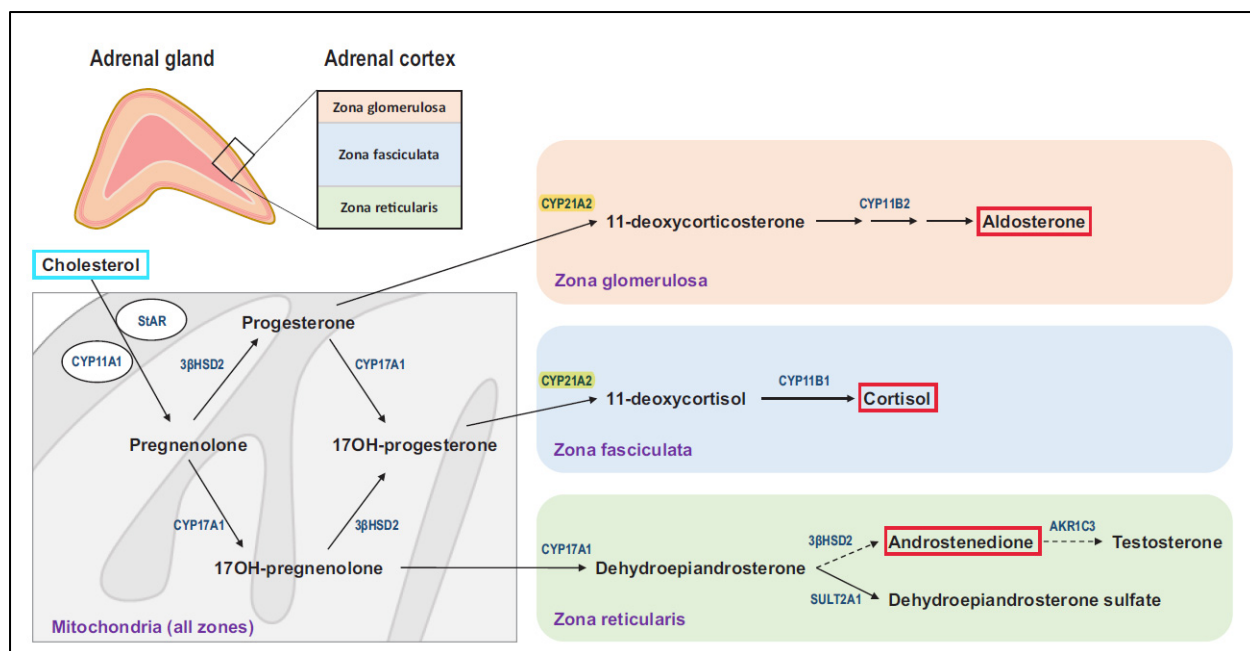
16. Congenital adrenal hyperplasia (CAH) refers to a group of inherited autosomal recessive disorders affecting cortisol biosynthesis. EX1049, 93; EX1053, 2155. Reduced cortisol production disrupts the dynamic equilibrium of the negative feedback inhibition of both hypothalamic corticotropin-releasing factor (CRF) and adrenocorticotropin (ACTH), which results in hyperplasia of the adrenal cortex. EX1046, 278; EX1053, 494. Approximately 90% to 99% of all CAH cases are caused by 21-hydroxylase deficiency (21OHD) due to mutations to the *CYP21A2* gene. EX1049, 93. CAH and 21OHD are often used interchangeably. EX1049, 93. CAH is conventionally separated into “classic” and “non-classic” forms, based on the severity of enzyme deficiency. EX1049, 93-94; EX1048, 802. However, current thinking views the different allelic variants of *CYP21A2* and their clinical manifestations as a continuum rather than two separate entities. EX1049, 93-94; EX1006, ¶ [0004].

17. CAH is a rare genetic disorder. Classic CAH occurs in roughly 1-in-10,000 to 1-in-20,000 persons. EX1024, 1248. Non-classic CAH occurs in roughly 1-in-200 to 1-in-1,000 persons. *Id.* The underlying mechanism for the classic and non-classic forms of 21OHD are the same. Less common forms of CAH include a mutation of the 11 β -hydroxylase gene *CYP11B1*. EX1006, ¶

[0004]; EX1015, 2195; EX1046, 279. Diagnosis of CAH, either as an adult or an infant, requires lifelong treatment to manage symptoms of CAH – there is no cure.

18. In normal adrenocortical steroid production, all steroids produced in the adrenal cortex are derived from cholesterol. EX1039, 2155. There, cholesterol is enzymatically converted into various adrenocortical steroids, including aldosterone, cortisol, and androstenedione. EX1015, 2196-97. Aldosterone is the main mineralocorticoid steroid hormone produced by the adrenal gland, and it plays a central role in the homeostatic regulation of blood pressure, plasma sodium (Na^+) and potassium (K^+) levels. Cortisol is a glucocorticoid steroid hormone, which plays an important role in regulating blood sugar, immune responses, bone formation, and in the metabolism of fat, protein, and carbohydrates. Androstenedione is a common precursor in the biosynthesis of androgen and estrogen sex hormones.

19. The diagram below, taken from Sarafoglou (2023), depicts a simplified pathway of normal adrenocortical steroid production. In individuals without CAH, this pathway produces the appropriate amount of androgens, mineralocorticoids, and glucocorticoids necessary for normal growth and function. Further, in individuals without CAH, intermediates in this pathway do not significantly accumulate and the production of theoretical side products is minimal. EX1039, 2155.

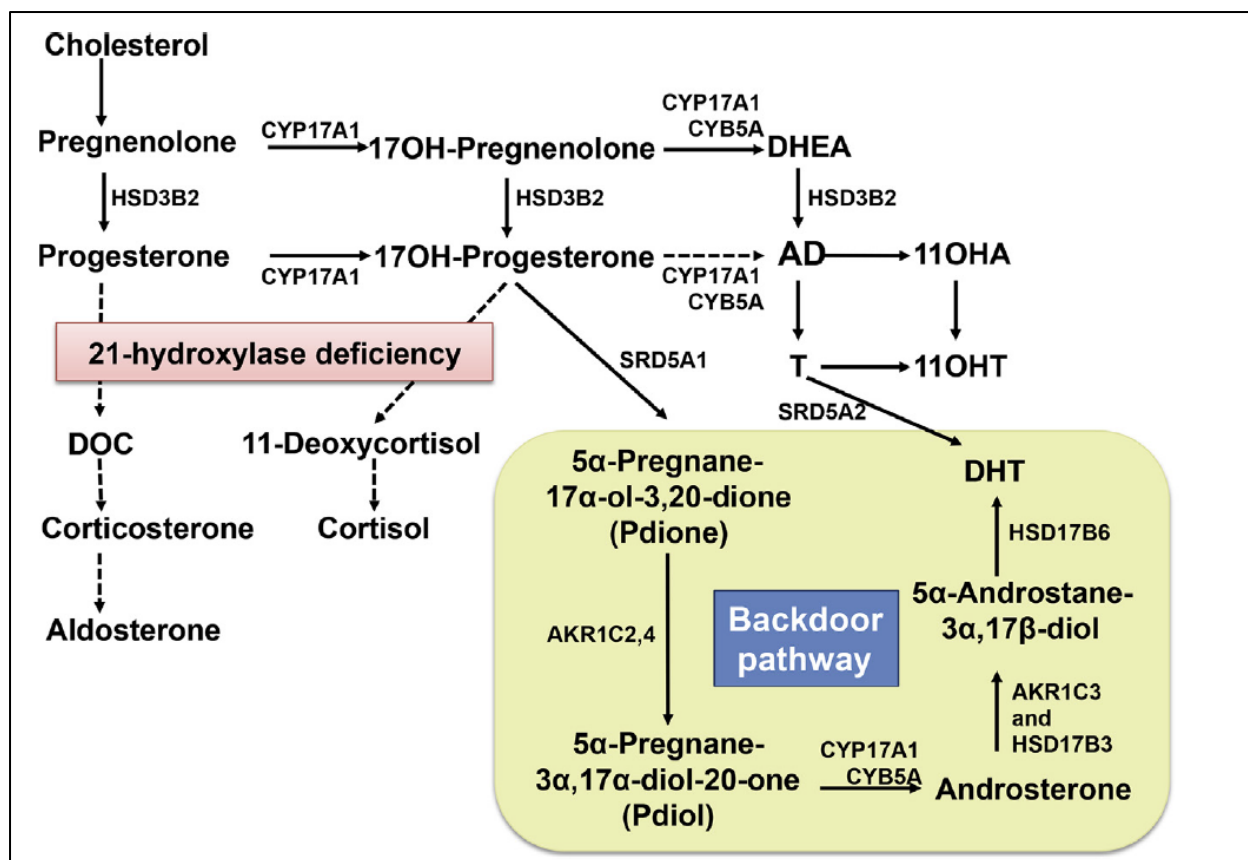


Adapted from EX1039, 2157, Fig. 3. Cholesterol (blue box) is enzymatically converted into various steroids, including aldosterone, cortisol, and androstenedione (red boxes). The protein encoded by the *CYP21A2* gene (yellow highlighting) is involved in the conversion of progesterone into aldosterone and 17-OHP to cortisol.

20. In persons with the most common type of CAH due to 21-hydroxylase deficiency, the protein encoded by *CYP21A2* cannot properly function and fails to convert progesterone into the precursor molecule for aldosterone and likewise fails to convert 17-OH-progesterone (17-OHP) into the precursor molecule for cortisol. EX1046, 280. As a result, insufficient amounts of cortisol are produced along this pathway and 17-OHP begins to accumulate both from overproduction due to ACTH signaling, as well as its inability to be broken down further due to enzymatic deficiency. EX1039, 2155. The reduction of cortisol in turn reduces the negative feedback on the hypothalamic-pituitary-adrenal axis and leads to excess adrenal androgen production, especially 17-OHP. EX1049, 94. The

accumulation of precursor steroids are then shifted to nonaffected androgen pathways or “backdoor pathway,” specifically through CYP17A1, resulting in the overproduction of androstenedione, which are then converted to the sex hormones testosterone and dihydroxytestosterone. EX1046, 280-81; EX1039, 2157.

21. The diagram below, adapted from Turcu & Auchus (2015a), shows the “backdoor pathway” in patients with 21OHD. The red box labeled “21-hydroxylase deficiency” disrupts the downstream conversion of 17-OHP and progesterone into cortisol and aldosterone, respectively. Instead, excess 17-OHP is converted downstream to androstenedione (“A4”, depicted as “AD” in the diagram below) and alternative paths (green box) leading to the overproduction of sex hormones.



Adapted from EX1046, 280, Fig. 2

22. Treatment of patients with classic CAH aims to reset the multiple hormonal imbalances by replacing deficient hormones (cortisol and aldosterone) and controlling adrenal androgen over-production triggered by the accumulation of precursor steroids and their metabolism by alternative androgenic pathways. EX1047, 338. Glucocorticoid replacement is the current standard of care for adults with CAH and has been the standard of care for many decades. EX1047, 338; EX1026, 456-59; EX1001, 11:27-31. But there is no single standard treatment regimen for all CAH patients—the steroid treatments used, and the dosing of those treatments, necessarily vary with a patient’s age, symptoms, severity of CAH, and

response to hormone replacement therapy. For example, hydrocortisone is the steroid predominately used in children with CAH given its short half-life and lessened growth suppression. EX1047, 338-39. For adult patients with CAH, either hydrocortisone or longer acting glucocorticoids are used. EX1047, 339; EX1017, 4056; EX1013, 4140, 4147. Mineralocorticoid replacement is also recommended in patients unable to maintain normal blood volume to maintain blood pressure and electrolyte balance. EX1047, 339; EX1001, 11:38-41; EX1017, 4056-57; EX1013, 4147-48.

23. Glucocorticoid treatment regimens must ensure that sufficient cortisol is available to support normal human physiology. However, the short to intermediate impact of glucocorticoid is often insufficient to reduce the early morning surge in ACTH, which is the principal driver of downstream androgen overproduction. EX1014, 8; EX1006, ¶ [0066]. Normally, the pituitary gland secretes ACTH in rhythmic (pulsatile) patterns throughout the day as part of hypothalamic-pituitary-adrenal axis regulation, including circadian regulation and cortisol-mediated negative feedback. The release of ACTH from the pituitary gland follows normal circadian patterns, with ACTH typically rising during the late night/early morning hours and peaking around the habitual time of waking, although the exact timing varies by individual sleep schedules. EX1006, ¶ [0066]. The typical rise of ACTH in the early morning hours leads to elevated ACTH

levels throughout the morning in CAH patients. In attempts to counteract the excessive androgen production that follows due to inappropriately high ACTH, physicians often prescribe supraphysiological (*i.e.*, larger) glucocorticoid doses. EX1014, 8. However, this increased exposure to glucocorticoids may lead to debilitating side effects including increased cardiovascular disease risk, glucose intolerance, and bone density loss in CAH patients. EX1014, 8; EX1001, 1:61–65, 90:24–26. Elevated cortisol levels resulting from excessive glucocorticoid dosing can also lead to Cushing’s syndrome. EX1006, ¶ [0045].

24. Beyond the problems associated with overexposure to glucocorticoids, insufficient cortisol levels in CAH patients can lead to the development of adrenal insufficiency. Failure to reduce the ACTH levels in CAH patients can result in problems associated with the overproduction of androgens, including abnormal puberty, abnormal linear growth, excessive hair growth, virilization, and infertility. EX1016, 2130-32. Balancing the risks between excessive cortisol or excessive androgens in CAH patients is difficult for physicians and patients alike.

B. The Use of CRF1 Receptor Antagonists to Treat CAH

25. Corticotropin-release hormone (CRH), interchangeably referred to as corticotropin-releasing factor (CRF), is a polypeptide hormone secreted by the hypothalamus that increases ACTH secretion by the pituitary gland. EX1049, 102. In turn, CRF may act directly on adrenocortical cells to increase cortisol secretion

and expression of *CYP21A2*. EX1049, 102. CRF receptors include two main subtypes, CRF1 and CRF2. EX1018, 270. It has been understood in the field since at least 2002 that CRF is the main regulator of the release of ACTH from the pituitary gland. EX1019, 333; EX1020, 322.

26. CRF1 receptor antagonists specifically bind to CRF1, thus blocking the ability of the agonist to bind to the receptor, therefore directly reducing ACTH secretion. There is a large variety of CRF1 receptor antagonists with different structural properties and different binding affinities for the receptor. In patients with CAH this could in turn decrease the downstream production of androgens and reduce symptoms of hyperandrogenism, while also potentially allowing for the administration of glucocorticoids at physiological doses. EX1048, 802. This normalization of androgen production coupled with lower doses of glucocorticoids has the potential to reduce some of the treatment-associated side effects discussed above.

27. In 2016, Turcu et al. published the results of a Phase I clinical study evaluating the safety and efficacy of a CRF1 receptor antagonist developed by Neurocrine Biosciences, NBI-77860 (which I understand is also called verucerfont), in adult patients with 21-hydroxylase enzyme deficiency CAH. EX1008. Turcu and colleagues found that administration of 300 mg and 600 mg doses of NBI-77860 resulted in meaningful reductions in ACTH and 17-OHP in 6

of 8 patients. EX1008, 1179-80. The clinical report also detailed that the administration of 300 mg and 600 mg doses of NBI-77860 reduced androstenedione levels in 6 of 8 patients. EX1008, Table 3. Compared to placebo, administration of 300 mg and 600 mg NBI-77860 reduced androstenedione in the 6:00 to 10:00 a.m. timeframe (referred to as the “morning window” to note the time of peak ACTH elevation in CAH patients) in 6 of 8 patients, including one patient who achieved 57.9% reduction in androstenedione levels after a 600 mg dose and another patient who achieved a 27.9% reduction in androstenedione levels after a 300 mg dose. EX1008, Table 3.

28. Subsequently, several CAH review articles also cited the Turcu 2016 study as the first clinical evidence showing that a CRF1 receptor antagonist lowered ACTH and 17-OHP concentrations in patients with 21-hydroxylase deficiency CAH. EX1015, 2205; EX1014, 8; EX1025, 6; EX1049, 123.

29. In January 2015, Neurocrine Biosciences filed PCT Patent Application No. PCT/US2015/012315, titled “CRF1 Receptor Antagonists for the Treatment of Congenital Adrenal Hyperplasia.” EX1004. The U.S. Patent Application published on January 26, 2017, as Publication No. US 2017/0020877. EX1006. US 2017/0020877 to Grigoriadis (“Grigoriadis”) discloses that “CRF₁ receptor antagonists have the potential to directly inhibit ACTH release in patients with CAH and thereby allow normalization of androgen production while using

lower, more physiologic doses of hydrocortisone, and thus reducing treatment-associated side effects.” EX1006, Abstract, ¶¶ [0006], [0040]. Grigoriadis discloses a number of specific CRF1 receptor antagonists as useful for the treatment of CAH based on their dissociation half-life, including NBI-77860 (verucerfont) and SSR-125543 [4-(2-chloro-4-methoxy-5-methylphenyl)-N-(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl) ethyl-5-methyl-N-(2-propyn-1-yl)-2-thiazolamine]. EX1006, ¶¶ [0051], [0054], [0077]-[0083]. SSR-125543 is also known as crinecerfont. *See* EX1033. Crinecerfont was developed by Neurocrine Biosciences for the treatment of CAH (EX1027, 2) and is now FDA approved, as of December 13, 2024. EX1058; EX1089.

30. Neurocrine has studied crinecerfont as a treatment for CAH. On October 15, 2021, Neurocrine published the results of a Phase II clinical study evaluating crinecerfont for the treatment of CAH. EX1048. The Phase II study was an open-label, multiple-dose study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of crinecerfont in adult subjects with a documented medical diagnosis of classic 21-hydroxylase deficiency CAH. *Id.*, 2-4. The study reported that the administration of crinecerfont to CAH patients resulted in reduction of ACTH, 17-OHP and A4 levels, compared to those patients’ baseline hormone levels. *Id.*, 3-11, Tables 2-3, Figs. 2-4.

31. Neurocrine also studied crinecerfont for the treatment of CAH in adult and pediatric Phase III clinical studies. EX1052; EX1053. The Phase III studies were multi-dose studies to evaluate the efficacy, safety, and tolerability of crinecerfont versus placebo administered for 28 weeks in pediatric subjects, and 24 weeks in adult subjects with classic CAH due to 21-hydroxylase deficiency. EX1052; EX1053. The adult Phase III study found the use of crinecerfont resulted in a greater decrease from baseline in the mean daily glucocorticoid dose, including a reduction to the physiologic range, than placebo following evaluation of adrenal androgen levels. EX1052, Abstract. The pediatric study found crinecerfont was superior to placebo in reducing elevated A4 levels in pediatric participants with CAH and was also associated with a decrease in the glucocorticoid dose from supraphysiologic to physiologic levels while A4 control was maintained. EX1053, Abstract. Both of these Phase III studies were published in the New England Journal of Medicine.

32. Crinecerfont was approved by the FDA on December 13, 2024, as an adjunctive treatment to glucocorticoid replacement to control androgens in adults and pediatric patients 4 years of age and older with classic CAH. EX1058.

33. Spruce Biosciences, Inc. (“Spruce”) studied another CRF1 receptor antagonist, tildacerfont, as a potential treatment for CAH. Spruce announced its first “proof of concept” results of tildacerfont in March 2019. EX1043. In March

2024, Spruce announced results from a Phase IIb clinical study evaluating tildacerfont for the treatment of CAH. EX1044. Tildacerfont did not meet its primary efficacy endpoint in this study. *Id.* On December 10, 2024, Spruce announced results from a second Phase IIb clinical study evaluating the safety and efficacy of tildacerfont in reducing supraphysiologic glucocorticoid usage in 100 adults with classic CAH. EX1045. Tildacerfont also did not meet its primary efficacy endpoint in the Phase IIb study. *Id.* At the same time Spruce announced results from its second Phase IIb clinical study, Spruce stated “we will be winding down Spruce’s investment in tildacerfont for the treatment of CAH as we conserve financial resources and look to maximize shareholder value.” *Id.*

C. Testicular and Ovarian Adrenal Rest Tumors

34. Adrenal rest tumors are a recognized serious complication of CAH. In males, these tumors occur in the testes and are referred to as testicular adrenal rest tumors (“TARTs”). TARTs originate from aberrant adrenal cells in the testes; they can interfere with normal testicular structure and sperm production and are a proven risk factor for infertility. EX1064 (Delfino), 278; EX1067 (Yu), 156. Advanced or persistent TARTs may cause lasting damage to the testes. Long-standing TART with fibrotic changes may lead to irreversible testicular damage due to chronic obstruction and scarring. EX1068 (Aycan), 668. These changes would not be expected to regress with medical therapy.

35. TARTs are a frequently detected complication in males with CAH. Published studies report that TARTs occur in a substantial proportion of male CAH patients, with reported prevalence varying by age, hormonal control, and screening practices. One study reported prevalence of 94% in adult males with CAH. Aycan (2013), 3. A 2024 study reported a prevalence of TARTs in 66% of male patients (53 out of 80). Auchus (2024), Table 1. A 2015 study reported that TARTs were detected in 61.5% of male CAH patients evaluated (8 out of 13). Yu (2015) at 157-58. Similarly, a 2012 study of adult CAH patients identified TARTs in 61.1% of patients (11 of 18) and concluded that the findings “confirm[] the high prevalence of testicular adrenal rest tumors in patients with CAH.” Delfino (2012), 1-2. Earlier studies likewise reported variable prevalence across different study populations, with higher rates observed in adult patients and lower rates in younger patients. Yu (2015) at 157-58; *see also* Aycan (2013) at 2-3 (reporting a prevalence of 18.3% among male CAH patients aged 2 to 18 years).

36. The development and growth of TARTs in CAH patients has been linked with chronically elevated ACTH levels. Persistent ACTH stimulation in CAH has been reported to promote hyperplasia of adrenal rest tissue within the testes and contribute to tumor formation and progression. Yu (2015) at 156–159. Clinical studies report elevated ACTH levels and corresponding elevated androgens in CAH patients with TARTs and characterize TARTs as a

manifestation of inadequate hormonal suppression. Aycan (2013) at 667–669; Delfino (2012) at 383–388. Based on these observations, clinicians and researchers have hypothesized that therapies capable of lowering ACTH levels could reduce the development, size, or progression of TARTs. Yu (2015) at 158–159; Aycan (2013) at 669. In 2012, one study linked reduction or disappearance of TARTs after adequate replacement therapy to reduced plasma ACTH levels. Delfino (2012), 5.

37. However, some studies have reported that TARTs may persist or fail to regress even when ACTH levels are reduced through intensified glucocorticoid therapy, indicating that biochemical improvement does not consistently translate into tumor shrinkage. Yu (2015) at 158–159. This may be due to irreversible scarring that occurs with more advanced stages of TARTs. Some clinical studies further describe variability in tumor response despite hormonal control. *Id.*; Aycan (2013) at 668–669.

38. In females, adrenal rest tumors occur in the ovaries and are referred to as ovarian adrenal rest tumors (“OARTs”). OARTs are characterized by the presence of extra-adrenal tissue in the ovaries of females with CAH. Chronic elevation of ACTH—resulting from impaired cortisol synthesis in CAH—is thought to stimulate the proliferation of these ectopic adrenal rests, leading to

tumor formation. EX1069, R91 (Claahsen-van der Grinten 2021); EX1038, e70 (Zaarour).

39. OARTs are rare. As of the earliest priority date of the '084 patent in April 2018, only a handful of OART cases had been reported in the medical literature. Zaarour reported in 2014 that “only 11 cases of OART have been described in the English-language literature,” the majority of which involved patients with CAH. EX1038, e69, e72. Zaarour concluded that this scarcity “mak[es] it difficult to choose an optimal treatment approach for affected patients” and that “[t]he optimal treatment of the ovaries in cases of OART remains unclear.” EX1038, e72. Chen reported in 2017 that OARTs were “very rare,” that “[c]linical studies of this condition have not been performed,” and that “only a few cases have been published.” EX1040, 146. Chen further explained that “OARTs are seldom revealed with standard imaging techniques, making their diagnosis and subsequent treatment difficult.” EX1040, 147.

40. The diagnostic challenges associated with OARTs are significant. Unlike TARTs, which can often be detected by scrotal ultrasound—a well-established and widely available technique—OARTs are far more difficult to identify. Standard pelvic imaging, including transvaginal ultrasound, may not reliably distinguish OARTs from other ovarian pathology, such as polycystic ovaries, ovarian cysts, or gonadal neoplasms.

41. The limited literature addressing OARTs suggests that they may arise through persistent stimulation by elevated ACTH levels. Consistent with this mechanism, it has been hypothesized that suppression of ACTH may reduce OART size, with Zaarour stating that “[i]f an OART is detected early enough and glucocorticoid therapy is received, it is possible that the OART will decrease in size following suppression of adrenocorticotrophic hormone levels.” EX1038, e72. However, there is no controlled clinical evidence demonstrating that any pharmacological agent—including any CRF1 receptor antagonist—can treat OARTs.

42. Although TARTs and OARTs share a common embryological origin in ectopic adrenal cortical tissue, they are clinically distinct conditions. The anatomical, hormonal, and reproductive environments of the testes and ovaries are different, and these differences have meaningful implications for how adrenal rest tumors behave and respond to treatment in each setting. In my opinion, a person of ordinary skill in the art would not assume that findings from a single TART observation in a male patient could be extrapolated to predict outcomes in female patients with OARTs, particularly given the extreme rarity of OARTs, the diagnostic challenges, and the complete absence of controlled clinical trials.

D. Metabolic Parameters

43. In my clinical and research experience, I am familiar with various metabolic parameters, including fasting glucose, hemoglobin A1C (“HbA1C”), measures of insulin sensitivity, body mass index (“BMI”), and lipid profiles. Each of these metrics reflects a different aspect of metabolic health and is influenced by distinct physiological processes. For example, HbA1c reflects average blood glucose levels over approximately the prior two to three months and is commonly used as a marker of glycemic control. BMI, by contrast, reflects body weight relative to height and is influenced by numerous factors, including diet, physical activity, genetics, and other underlying conditions. Lipid profiles likewise are affected by a wide range of variables, including underlying metabolic disorders and comorbid diseases. Accordingly, while these parameters may be related in some patients, they are independent metrics, and changes in one do not necessarily predict or reflect changes in another. EX1104 (Sacks).

44. Because these metabolic parameters capture different physiological phenomena, they cannot be treated as interchangeable indicators of a single underlying condition. For instance, a patient may have diabetes or impaired glucose regulation without being overweight, or may have abnormalities in lipid levels independent of glycemic control. In my experience, clinicians evaluate each of these parameters individually and in context, recognizing that they reflect

distinct and multifactorial aspects of metabolic health rather than a single unified disease state.

45. In my opinion, the evaluation and treatment of TARTs and OARTs are fundamentally different from the assessment of metabolic parameters such as HbA1c, BMI, or lipid levels. Whereas metabolic parameters are surrogate biochemical or physiologic markers that can fluctuate based on a wide range of factors, TARTs and OARTs involve discrete anatomical changes in specific tissues. As a result, changes in metabolic markers do not necessarily correlate with the presence, absence, or progression of TARTs or OARTs, and these conditions must be evaluated and managed on their own clinical and biological bases.

46. Although expressed in opposite terms, insulin sensitivity and insulin resistance refer to the same underlying physiologic phenomenon, i.e., how effectively the body responds to insulin. Increased insulin resistance corresponds to decreased insulin sensitivity, and vice versa. Both represent a recognized metabolic parameter reflecting the body's physiologic response to insulin.

EX1105 (Fujimoto).

47. Similarly, fasting glucose is a specific measurement of blood glucose after fasting. Patients with glucose intolerance typically have elevated postprandial (post-meal) glucose levels, and may or not have elevated fasting glucose otherwise.

EX1106 (Abdul-Ghani). However, a POSA would have understood that elevated fasting glucose is an indication of glucose intolerance. EX1105 (Fujimoto), 9S.

E. Astressin and Small-Molecule CRF1 Receptor Antagonists

48. Astressin is a peptide-based, nonselective corticotropin-releasing hormone (CRH) antagonist. It is not considered a small molecule. The '084 patent describes astressin as “a nonselective corticotropin releasing hormone [CRH] antagonist that reduces the synthesis of ACTH and cortisol.” EX1001, 43:40–42. As a nonselective CRH antagonist, astressin acts broadly across CRH receptor subtypes, including both CRF1 and CRF2 receptors. EX1030, 373 (Zorrilla & Koob, 2010). Astressin is a different compound than the compounds claimed in the '084 patent, which are described as *selective* small-molecule antagonists of the CRF1 receptor subtype.

49. The distinction between a nonselective peptide CRH antagonist like astressin and a selective small-molecule CRF1 receptor antagonist is clinically significant. The CRF1 and CRF2 receptors have different tissue distributions and mediate different physiological responses. EX1088 (Deussing & Chen), 2233-2235. For example, a compound that blocks both receptor subtypes may produce different effects—including off-target effects—than a compound that selectively targets only CRF1.

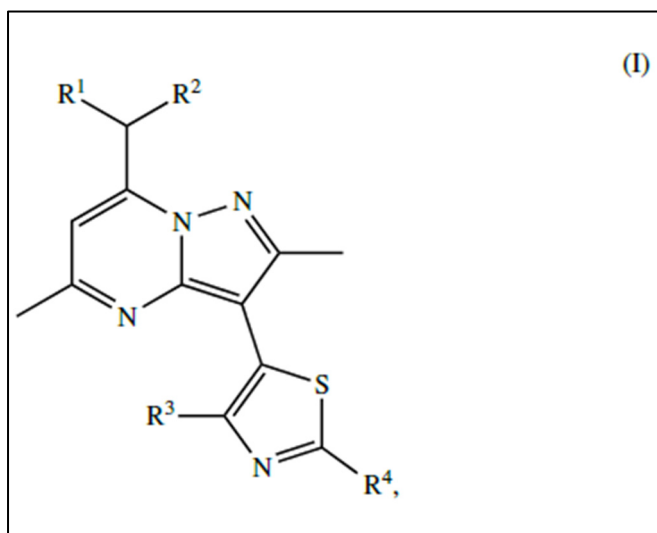
V. THE '084 PATENT

50. I have reviewed the '084 patent and portions of its prosecution history. The '084 patent issued on March 17, 2026. EX1001, cover page, (45). Spruce is listed as assignee on the front page of the '084 patent. *Id.* I understand from counsel that the '084 patent claims priority to provisional application no. 62/663,951, filed on April 27, 2018, and provisional application no. 62/822,815, filed on March 23, 2019. EX1001, cover page, (63).

A. '084 Patent Specification

51. The '084 patent relates to the use of compounds, namely CRF1 receptor antagonists encompassed within structural Formula (I), reproduced below, to treat TARTs or OARTs. EX1001, Abstract, 1:55-2:52.

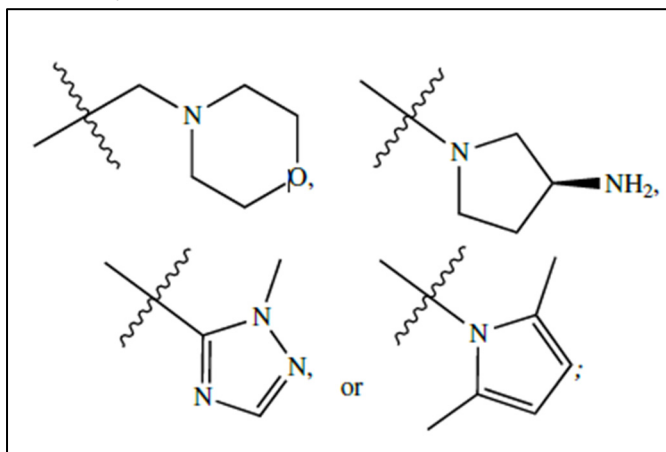
Formula (I):



or a pharmaceutically acceptable salt thereof,
wherein:

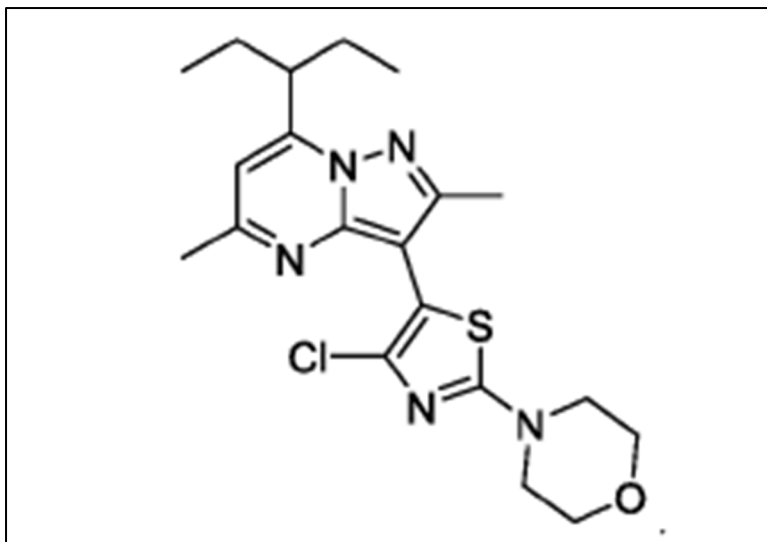
R¹ and R² are independently ethyl or n-propyl;

R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and
 R^4 is hydrogen, Br, R^aR^bN —, methoxymethyl, n-butyl, acetamido,
 pyridin-4-yl, morpholin-4-yl,



R^a and R^b are independently hydrogen, C_1 - C_3 alkyl, $H_2NCH_2CH_2$ —, $(CH_3)_3COC(O)NHCH_2CH_2$ —, or $CH_3CH_2CH_2NHCH_2CH_2$ —.

52. Formula (I) encompasses Compound 1, described in the '084 patent as “a potent, selective, nonsteroidal, oral corticotropin-releasing factor type-1 (CRF1) receptor antagonist that reduces excess ACTH, 17OHP, and A4 to improve clinical and biochemical sequelae of CAH.” EX1001, 1:66-2:2. The structure of Compound 1 is reproduced below. EX1001, 90:46–63. I understand that this compound is also known as tildacerfont. See EX1001, 96:64-97:2; EX1059, 1.



53. The '084 patent contains four examples. Of those, Example 1 and Example 3 relate specifically to the treatment of TARTs. None of the examples relate to the treatment of OARTs or contain any data related to the treatment of OARTs. EX1001, 90:8–98:35.

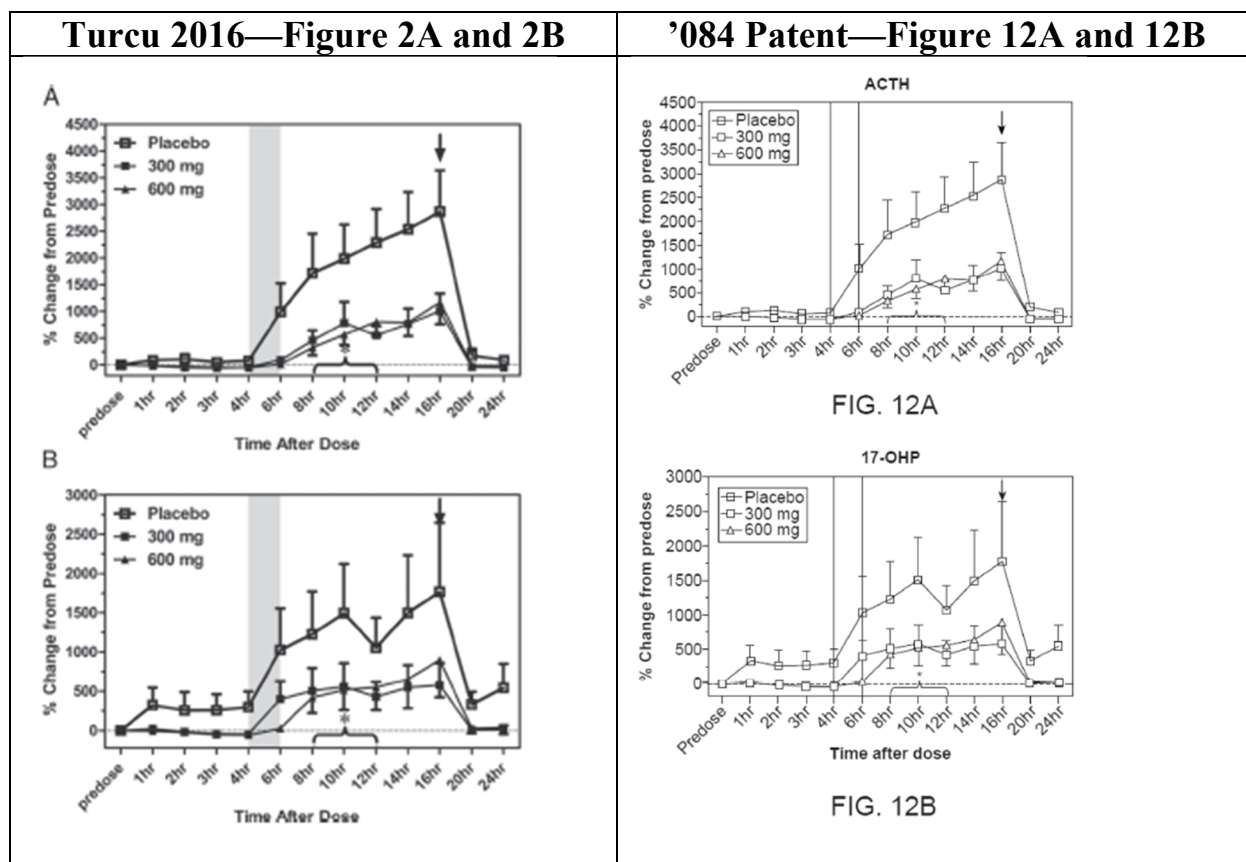
54. Example 1 describes a prophetic Phase 2, Open-Label Study of Compound 1 (tildacerfont) “specifically in male CAH subjects with TART.” EX1001, 90:66–67. I understand from counsel that a prophetic example is one that has not actually been performed and is conceptional. The '084 patent states that this study builds “upon the 2 completed Phase 1 studies of Compound 1 in healthy volunteers and the ongoing Phase 2 proof-of-concept study of Compound 1 in subjects with CAH.” EX1001, 90:63–67. As discussed in paragraph 33 above, tildacerfont (Compound 1) did not meet its primary efficacy endpoints in the Phase 2b CAH studies. EX1044; EX1045. Because it is prophetic, the '084 patent does

not include any data generated for the study described in Example 1. EX1001, 90:8–93:67.

55. Example 1 states that one of the secondary objectives of the prophetic Phase 2, Open-Label Study of Compound 1 (tildacerfont) is to “assess changes in metabolism.” EX1001, 91:60-64. The ’084 patent lists changes in metabolic parameters as “including fasting glucose, HbA1c, insulin sensitivity, and lipid profile (including LDL cholesterol, HDL cholesterol, and triglycerides), from baseline to Week 12.” *Id.*

56. Example 2 starts by noting that “[s]ince elevated ACTH is the primary driver for TART growth, blocking ACTH synthesis using Compound 1 [tildacerfont], a small-molecule antagonist of the CRF1 receptor, may be effective in reducing ACTH levels, thereby reducing the size of testicular lesions in TART and reducing the need for chronic supraphysiologic doses of GCs.” EX1001, 94:3–8. However, Example 2 does not include any data showing that the administration of Compound 1, or any other CRF1 receptor antagonist, would reduce or otherwise treat TARTs. EX1001, 94:1–96:2. It refers to Figure 2, which shows pharmacokinetic data following once-daily dosing for Compound 1 (tildacerfont). EX1001, 94:63–95:3. Example 2 also refers to Figure 3, which mentions once-daily and twice-daily dosing, but contains no data. *Id.*

57. Example 2 also notes that “this mechanism of action has been validated in a previous proof-of-concept study using a similar small-molecule CRF₁ receptor antagonist, which produced dose-dependent reductions in ACTH and 17-OHP in subjects with CAH” and cites to Figures 12A and 12B. EX1001, 95:40–44. While the ’084 patent does not identify the “similar small-molecule CRF₁ receptor antagonist,” I believe it is referring to NBI-77860 (verucerfont), the drug that Neurocrine has studied for the treatment of CAH, as described above. Indeed, in Spruce’s Clinical Study Report for its SPR001-202 study, the same statement is accompanied by a reference to the Turcu 2016 publication, which reports on clinical results of verucerfont (NBI-77860). EX1072, 13; EX1008, 14, 75. Figures 12A and 12B of the ’084 patent are essentially identical to Figures 2A and 2B of the Turcu 2016 publication, respectively, except for some minor shading.

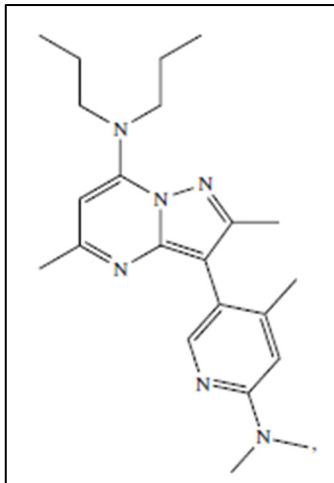


58. Example 3, titled “Congenital Adrenal Hyperplasia (CAH),” includes a series of figures related to CRF1 receptor antagonists and CAH. EX1001, 96:5–60. The only data in the '084 patent related to the treatment of TART with a CRF1 receptor antagonist appears in Example 3. It is a single figure with two panels (Figure 10A and Figure 10B) that purports to “show approximately 25% shrinkage in TART in a 25 year old male with classic congenital adrenal hyperplasia following 6 weeks treatment with a CRF1 receptor antagonist.” EX1001, 96:39–42. The '084 patent does not indicate what specific CRF1 receptor antagonist the patient received in Example 3, but states in another section titled “Brief

Description of the Drawings” that Figures 10A and 10B provide “[i]mages of a patient with TART pre-treatment with a CRF1 antagonist (Compound 1) (A) and 6-weeks post-treatment with a CRF1 antagonist (Compound 1) (B). EX1001, 10:20-23. The ’084 patent does not include any description of how the study was carried out. *Id.* The same image appears in Spruce’s 2021 Sarafoglou publication (EX1041) as Figure 6. It is unclear from the ’084 patent when, how, or how much tildacerfont was administered to this patient.

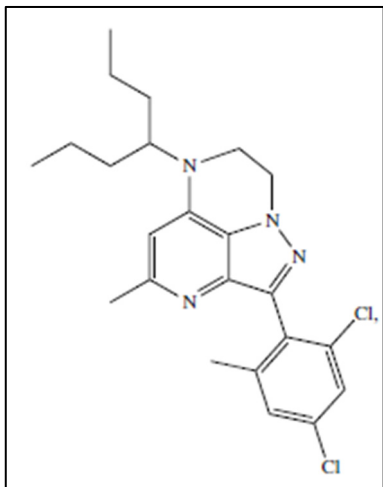
59. I understand that Spruce stated in a provisional application to which the ’084 claims priority, “it [was] not known whether Compound 1 [could] successfully treat TART.” EX1055 (U.S. Provisional Patent Application No. 62/663,951), [0287]. Although this statement does not appear in the ’084 patent, the ’084 patent provides no additional data regarding the efficacy of Compound 1 for the treatment of TART.

60. Example 4 describes a study “to assess the ability of Compound 1 to reduce excess ACTH and adrenal steroid production in participants with classic CAH on a stable [glucocorticoid (*sic*)] regimen; to evaluate the safety and tolerability of tildacerfont in participants with classic CAH, and to evaluate the pharmacokinetics (PK) of tildacerfont.” EX1001, 96:61–98:34. It does not contain any mention of TARTs or OARTs. *Id.*



EX1001, 7:20–35, 82:1–20; EX1093.

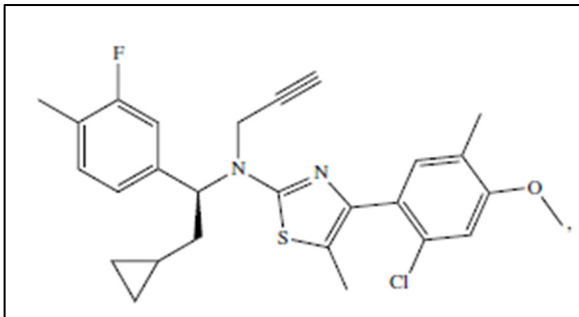
64. The third is Neurocrine's NBI-34041:



EX1001, 7:36–55, 82:20–37; EX1094.

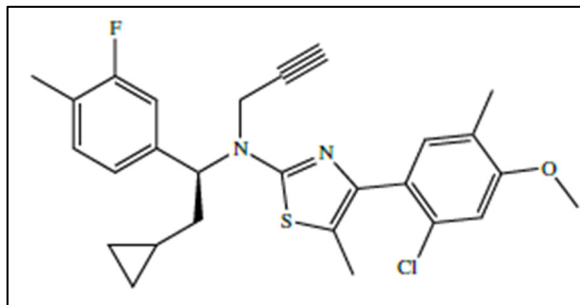
65. The fourth is SSR-126374. EX1001, 7:47, 8:32. The '084 patent does not depict the structure of SSR-126374. I understand from counsel that the structure has not been publicly disclosed.

66. The fifth is Neurocrine's crinecerfont, which is also referred to as SSR-125543 and NBI-74788 and has the IUPAC name 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine:



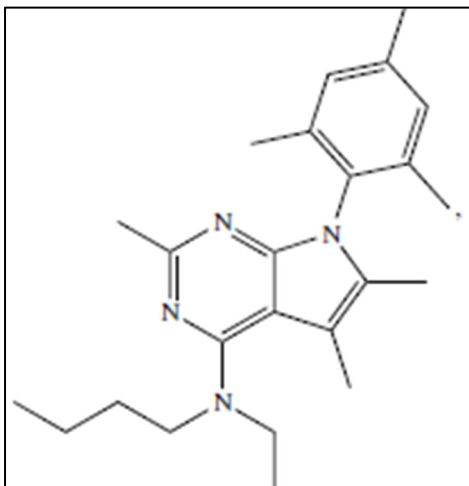
EX1001, 7:57–66, 82:40-50; EX1033

However, in another portion of the '084 patent the fifth structure is a structure that is drawn as containing a three carbon side chain with a 4-carbon bond, which I believe is physically impossible:



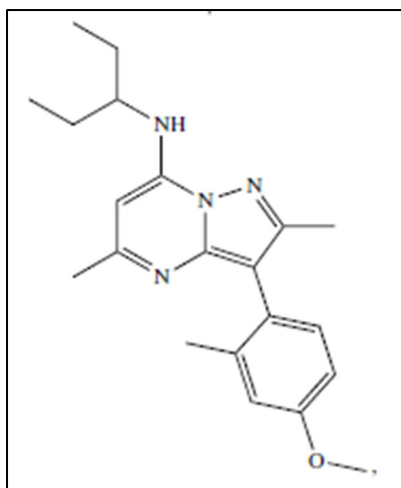
EX1001, 82:40-50.

67. The sixth is antalarmin:



EX1001, 8:1–15, 82:52–66; EX1096.

68. The seventh is DMP-904:



EX1001, 8:15–30, 83:1–16; EX1095.

69. The '084 patent does not contain any data related to any of those molecules, except with respect to the figures that appear to be reproduced from the Turcu 2016 publication and depict data related to verucerfont, as noted above in paragraph 57.

70. None of these compounds are identified in the '084 patent as compounds that can change a metabolic parameter in a TARTs or OARTs patient. Rather, they are taught only as “additional chemotherapeutic agent[s]” that can be administered in addition to a CRF1 receptor antagonist in the claimed methods. EX1001, 6:65–8:33, 81:44–83:19. The '084 patent also identifies other “additional chemotherapeutic agent[s]” as a glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, and an anti-androgen. EX1001, 6:65–8:33, 81:44–83:19.

71. The '084 patent also states that, in one aspect, “there is a method of treating a subject in need thereof comprising administering an astressin or a pharmaceutically acceptable salt or solvate thereof.” EX1001, 43:38-40. The '084

patent states that an “astressin generally refers to a nonselective corticotropin releasing hormone antagonist that reduces the synthesis of ACTH and cortisol.”

EX1001, 43:40-43. The '084 patent states that “astressin or a variant having at least 70% identity thereto” may be used to (1) treat CAH (EX1001, 43:44-48), (2) improve “hyperandrogenic symptoms” (EX1001, 43:58-62), (3) treat “menstrual irregularity, ovulatory dysfunction or infertility” (EX1001, 43:62-67), (4) improve “metabolic symptoms” (EX1001, 43:67-44:5), and (5) improve “quality of life” (EX1001, 44:6-10).

B. '084 Patent Claims

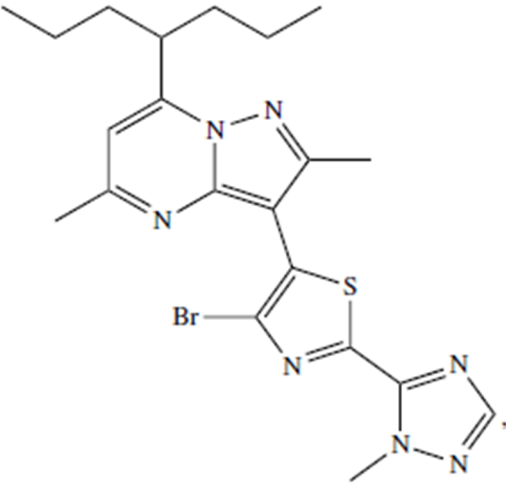
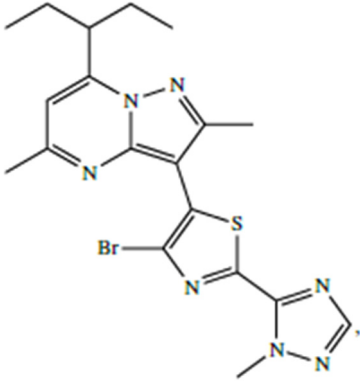
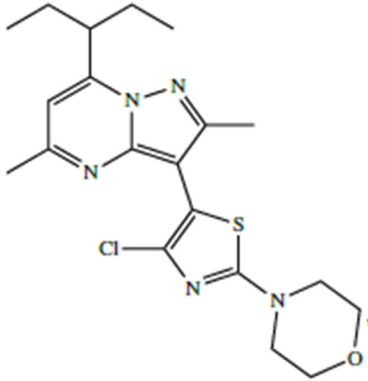
72. I understand from Neurocrine’s counsel that the claims of the '084 patent define the scope of the legal rights of the patent. Specifically, claim 1, the only independent claim, recites a method of changing a metabolic parameter of a subject having a TART or an OART as follows:

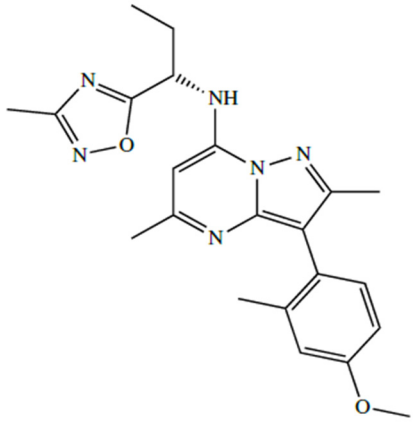
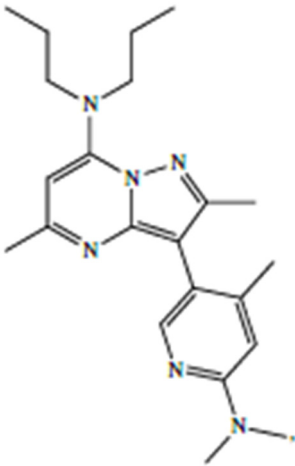
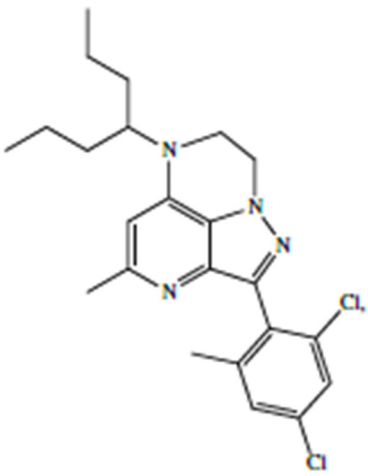
1. A method of changing a metabolic parameter of a subject having a testicular adrenal rest tumor (TART) or an ovarian adrenal rest tumor (OART), comprising administering to a subject in need thereof a small molecule corticotropin-releasing factor type-1 (CRF₁) antagonist, or a pharmaceutically acceptable salt thereof, wherein the small molecule CRF₁ antagonist is:

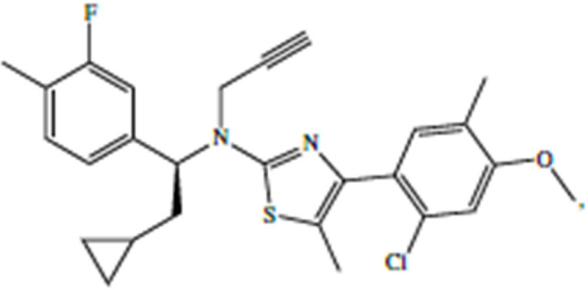
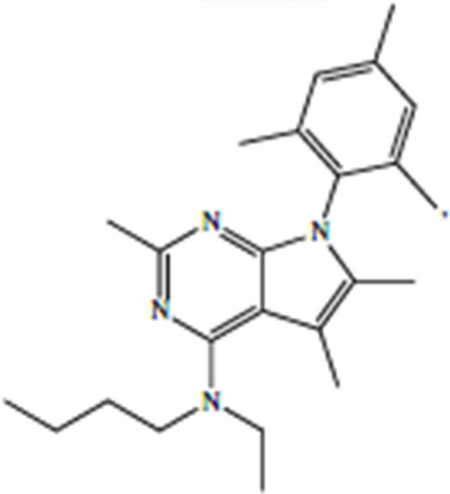
[one of the ten compounds structures set forth in the table below and labeled with letter designations (A–J)], or a pharmaceutically acceptable salt thereof,

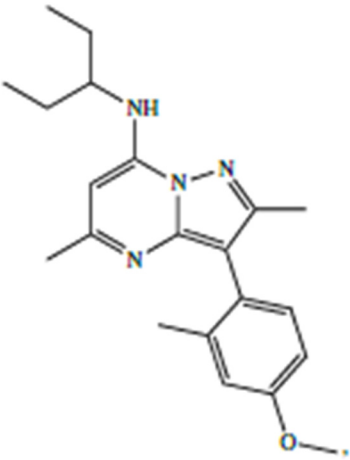
wherein the metabolic parameter comprises fasting glucose, HbA1c level, insulin sensitivity, or a lipid profile, or a combination thereof.

EX1001, 99:2–101:22; *see also* Appendix B (attached).

Compound Structure in Claim 1	Letter Designation
	A
	B
	C

Compound Structure in Claim 1	Letter Designation
	D
	E
	F

Compound Structure in Claim 1	Letter Designation
SSR-126374,	G
	H
	I

Compound Structure in Claim 1	Letter Designation
	J

73. Of the ten compounds in claim 1, only the first three, designated **A**, **B**, and **C** in the table, are compounds within the scope of Formula (I). The compound designated “**C**” in the table above is Spruce’s tildacerfont and is also referred to in the ’084 patent as “Compound 1.” *See* above, paragraph 52. The rest are described in the ’084 patent only as “additional chemotherapeutic agents” and include, among others, Neurocrine’s verucerfont (“**D**” in the table above) and crinecerfont (“**H**” in the table above). *See* above, paragraphs 61-68. Claim 2 limits the CRF1 antagonist to tildacerfont. EX1001, 101:23–47. Claim 3 limits it to crinecerfont. EX1001, 101:50–102:12.

74. The first dependent claim specifies the metabolic parameter is insulin sensitivity (claim 4); claim 5 recites that the subject has CAH; claims 6 and 7 recite reducing the size and number, respectively of the TART or OART; claims 8–16

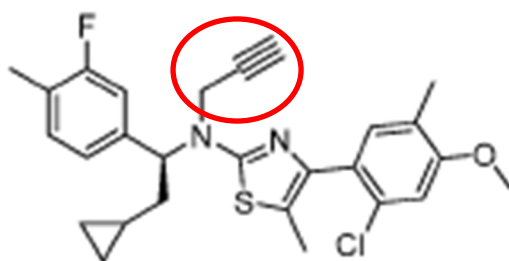
specify dosing characteristics; and claims 17 – 19 recite limitations related to reducing a plasma concentration of a biomarker. EX1001, 102:13–50.

VI. THE '084 PATENT PROSECUTION HISTORY

75. The application that led to the '084 patent was filed on January 31, 2025, as U.S. Patent Application No. 19/043,303 (“the '303 application”). *See* EX1001, cover page, (21), (22). I understand that this application was filed after the approval of CRENESSITY®, and the publication of the CRENESSITY® prescribing information, on December 13, 2024. EX1089; EX1010. I understand from counsel that the '303 application claims priority to U.S. Provisional Patent Application No. 62/822,815, filed March 23, 2019 (“the '815 Provisional”), and U.S. Provisional Patent Application No. 62/663,951, filed April 27, 2018 (“the '951 Provisional”) as well as a number of intervening applications including U.S. Patent Application No. 17/081,694 (“the '694 Application”). EX1001, cover page, (60), (63).

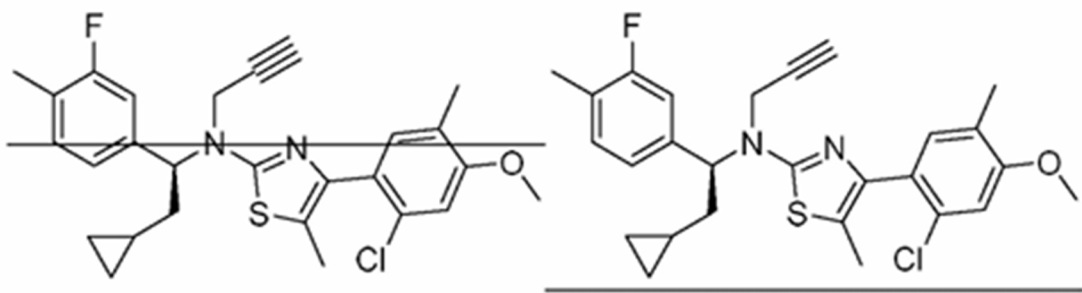
76. I have reviewed portions of the prosecution history of the '084 patent and of the applications to which the '084 patent claims priority. Of particular relevance to my opinions, I note that the initial filing of the '084 application did not include crinecerfont in the claims or in the specification. Instead, Spruce disclosed a compound having the following chemical structure, which included a

three carbon side chain with a carbon-carbon quadruple bond, as highlighted by the red circle below:



EX1002, 36-37 (¶27), 123 (¶261). That structure is not crinecerfont. Moreover, I understand that it is not chemically possible to have a carbon-carbon quadruple bond.

77. I understand that on November 13, 2025, Spruce filed an Amendment in the '084 application in which it amended claims 1 and 3 to replace the structure of one of the originally claimed small molecule CRF1 antagonists to the structure of crinecerfont, as follows:



78. I understand that the Examiner issued a “Notice of Allowance and Fees Due” (EX1002, 410-417) in the '303 application on December 19, 2025, with the following “Reasons for Allowance”:

[T]he claimed method is not taught or suggested by the prior art. Grigoriadis, US 20170020877, cited in an IDS, represents the closest prior art. Grigoriadis teaches CRF1 receptor antagonists, including several encompassed by the instantly claimed method, for treating a subject having congenital adrenal hyperplasia. However, Grigoriadis doesn't teach or suggest administering the CRF₁ receptor antagonists for treating a subject having testicular or ovarian adrenal rest tumors, as claimed.

79. I note that the Examiner issued another Notice of Allowance on January 29, 2026. EX1002, 418-424. This Notice does not contain a statement on the reasons for allowance.

80. I understand from counsel that the application leading to the '084 patent is a "continuation" of other applications filed in the Patent Office. I understand that one of those applications was U.S. Patent Application No. 17/081,694 ("the '694 application"). I understand that in the '694 application Spruce submitted a declaration from one of its employees, Dr. Barnes (Vice President and Project Team Leader of Spruce Biosciences, Inc.) ("Barnes Declaration"). EX1061, 19-22. Relevant to my opinions, Dr. Barnes stated that the "declaration [was] submitted to provide further description of the uncertainty and unpredictability of treating TART in patients with CAH." EX1061, 20 (¶4). In particular, Dr. Barnes stated that "[w]hile glucocorticoid (GC) therapy has been shown to reduce ACTH blood levels in CAH patients, the reduction of ACTH level alone does not always lead to inhibition or reduction of TART growth." *Id.* Dr. Barnes concluded that "based on various studies in the field of treating or

preventing TARTs development in CAH male patients, it is not clear whether reduced ACTH levels can lead to reduced TART growth.” *Id.* Dr. Barnes concluded that:

While it is certain that GC therapy can lead to controlled ACTH levels, it is unlikely for a person skilled in the art to arrive at a reasonable expectation that treating CAH patients with GC can achieve reduced TART growth. It is less likely for the person to replace GC with a CRF1 antagonist to treat TARTs in CAH patients with a reasonable expectation of success.

Id. Dr. Barnes’ declaration did not include any discussion of the data included in the ’084 patent (including Figures 10A and 10B) and whether it demonstrated that Compound 1 reduced ACTH levels and/or lead to reduced TART growth. *Id.*

81. Also relevant to my opinions, Dr. Barnes discussed two journal articles: Reisch *et al.*, Testicular Adrenal Rest Tumors Develop Independently of Long Term Disease Control: A Longitudinal Analysis of 50 Adult Men With Congenital Adrenal Hyperplasia due to Classic 21-Hydroxylase Deficiency, *J Clin Endocrinol Metab*, 98: E1820-E1826 (2013) (“Reisch”) and Mendes-dos-Santos *et al.*, Prevalence of Testicular Adrenal Rest Tumor and Factors Associated with Its Development in Congenital Adrenal Hyperplasia, *Horm Res Paediatr*, 90:161-168 (2018) (“Mendes-dos-Santos”). EX1070 (Reisch); EX1071 (Mendes-dos-Santos). About Reisch, Dr. Barnes stated that, “[a]lthough no definitive conclusion can be drawn from Reisch, based on this longitudinal investigation and analysis, it is clear

to conclude that the group of patients with TARTs were exposed to similar glucocorticoid (hydrocortisone, prednisolone, or dexamethasone) dose over a lifetime compared to patient without TART.” About Mendes-dos-Santos, Dr. Barnes stated that “[t]he presence of TARTs is not associated with doses of GCs prescribed or ACTH levels.”

82. Subsequently, the Examiner issued a Notice of Allowability (EX1077, 6-8), with the following “Reasons for Allowance”:

[T]he claimed method of treating or preventing TART or OART comprising administering to a subject in need thereof a CRF1 antagonist is not taught or suggested by the prior art. The closest prior art is [Grigoriadis (EX1006), Smeets (EX1078), and Zaarour (EX1038)], all of previous record. Grigoriadis teaches CRF1 antagonists to inhibit ACTH release in patients with congenital adrenal hyperplasia (CAH), and further teaches glucocorticoids are used to inhibit the formation of TARTs in men, but treatment or prevention of TARTs in a subject by administering a CRF1 antagonist is not taught or suggested. Smeets teaches subjects with CAH are at risk of developing TARTs, and that TARTs are treated with high doses of glucocorticoids, but treatment or prevention of TARTs in a subject by administering a CRF1 antagonist is not taught or suggested. Zaarour teaches OARTs as rare but can develop in female patients with CAH, with treatment of OARTs involving glucocorticoids. However, Zaarour doesn’t teach or suggest treatment or prevention of OARTs with a CRF1 antagonist.

The 1.132 declaration of Dr. Barnes, filed on 12/31/21 discloses that the treatment of TARTs is unpredictable, and although glucocorticoids were used clinically to suppress the formation of or for treating TARTs in subjects with CAH by reducing blood ACTH levels, this

therapy doesn't provide consistent results, as TARTs occur in subjects that are sufficiently treated with glucocorticoids (see paragraph sections 6-9). See Mendes-dos-Santos [EX1071] and Reisch [EX1070] (referred to in sections 6-8 of declaration). Mendes-dos-Santos teaches the prevalence of TARTs in subject with CAH was studied, and no association between TART development and sufficient glucocorticoid therapy or ACTH levels was found. Reisch teaches TARTs occur in patients over-treated with glucocorticoids and having suppressed ACTH levels, and no statistical differences were found between glucocorticoid doses in patients with or without TARTs having CAH. Applicants have shown that unexpectedly, CRF1 antagonist therapy was found to suppress the growth of TART in treated subjects (Figs. 10A-B).

83. I understand that the Examiner did not issue any claim rejections during prosecution of either the '303 application (leading to this '084 patent) or the '694 application based on lack of written description or lack of enablement.

VII. LEVEL OF KNOWLEDGE OF ONE OF ORDINARY SKILL IN THE ART PERTAINING TO THE '084 PATENT

84. A hypothetical person of ordinary skill in the art ("POSA") would have a medical degree or a Ph.D. in a field related to endocrinology, and would have knowledge of hormone regulation and disorders, and knowledge of the treatment regimens employed to treat such disorders. The hypothetical POSA would also have at least three years of experience conducting research concerning endocrine disorders, which might include TARTs, OARTs, and/or other adrenal disorders. In my opinion, a POSA in the field of the '084 patent may have also

worked as part of a multi-disciplinary team and drawn upon not only his or her own skills, but also consulted with others on the team having specialized skills to solve a problem, including analytical chemistry, pharmaceutical design, development, and formulation, clinical trials, and diagnostic medical sonography. Based on my review of the '084 patent specification, the patent prosecution history, the prior art, and my experience and general knowledge, I believe this definition of a POSA is applicable to the '084 patent.

VIII. INTERPRETATION OF THE '084 CLAIMS AT ISSUE

85. I have been informed by counsel for Neurocrine that for purposes of my analysis, the terms appearing in the '084 patent claims should be interpreted according to their ordinary and customary meaning as understood by a POSA in view of the patent's disclosure and prosecution history. In that regard, I understand that the best indicator of claim meaning is its usage in the context of the patent specification as understood by a POSA.

86. I understand that the words of the claims should be given their plain meaning unless that meaning is inconsistent with the patent specification or the patent's history of examination before the Patent Office. I also understand that the words of the claims should be interpreted as they would have been interpreted by a POSA as of the effective filing date of the claimed invention.

87. The term “baseline” appears in dependent claim 19 of the ’084 patent. EX1001, 102:63-49:50. I understand from counsel that Neurocrine previously challenged two other Spruce patents, U.S. Patent No. 10,849,908 (“the ’908 patent”) and U.S. Patent No. 11,007,201 (“the ’201 patent”) in Post-Grant Review proceedings before the Patent Office’s Patent Trial and Appeal Board (“the Board”) that resulted in Final Written Decisions determining that all claims of those patents were unpatentable. I understand from counsel that, in those previous proceedings, the Board construed the term “baseline” as meaning “a series of samples taken from an untreated patient with CAH, prior to treatment at intervals that are time-matched to the sampling intervals to be taken from the patient treated with either a CRF1 receptor antagonist or placebo.” EX1005, 25-26; EX1007, 24-25. The Board determined that no claim construction was necessary to resolve the written description issue in the prior PGRs. EX1005, 26; EX1007, 25.

IX. LEGAL STANDARDS

88. I am not an attorney, and I will offer no opinion on the law. I am, however, informed by counsel and understand several principles concerning patentability that I have used in arriving at my opinions.

89. I understand from counsel that the earliest possible effective filing date of the ’084 patent is April 27, 2018, which is the date the first provisional patent application in this patent family was filed.

A. Written Description

90. I understand that the specification must contain a “written description” of the claimed invention that allows a POSA to recognize that the inventor invented what is claimed. I understand that the test for written description is whether the disclosure in the specification reasonably conveys to a POSA that the inventor had possession of the full scope of the claimed invention as of the filing date. I understand that the written description requirement is applied in the context of the state of knowledge in the art at the time the patent application was filed.

91. The level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology. I understand that factors used to evaluate the sufficiency of a disclosure include: 1) the existing knowledge in the particular field; 2) the extent and content of the prior art; 3) the maturity of the science or technology; and 4) the predictability of the claimed method or invention.

B. Enablement

92. I understand that the specification must “enable” a POSA to make and use the full scope of the claimed invention. I understand that an enabling disclosure

is one which provides sufficient detail to allow a POSA to make and use the claimed invention without “undue experimentation.”

93. I understand that the following factors, sometimes called “*Wands* factors,” may be considered in deciding whether a POSA would have to engage in undue experimentation to make and use the invention: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

94. I understand that none of the above factors is alone dispositive. Rather, whether the degree of experimentation required is undue may involve weighing these factors in the context of the claimed invention and the state of the art at the time of the original application to determine whether a POSA would need to engage in undue experimentation to make and use the full scope of the claimed invention.

95. I further understand that the specification must enable a POSA to make and use the entire scope of the claimed invention.

C. Obviousness

96. I understand that a patent claim is invalid as obvious if the differences between the claimed subject matter and what is taught by the prior art are such that the subject matter as a whole would have been obvious to a POSA at the time the invention was made. I understand that four factual inquiries guide this determination: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the pertinent art; and (4) relevant secondary considerations (or objective criteria), such as unexpected results, commercial success, long-felt but unsolved needs, failure of others, copying by others, licensing, acclaim and awards, teaching away or skepticism in the art, and contemporaneous invention by others.

97. I understand that the obviousness analysis is done from the perspective of a POSA at the time of the invention. I understand that the relevant time period here is the 2018 timeframe.

98. I further understand that a POSA is presumed to have knowledge of the relevant prior art at the time of the claimed invention, and that the scope of the prior art comprises any prior art that was reasonably pertinent to the particular problems the inventor faced. I understand that a claimed invention may be found obvious based on a combination of prior art references. Further, I understand that there need not be an explicit teaching, suggestion, or motivation to combine those

references in order to determine that an invention is obvious. Nonetheless, I understand it is important that a POSA have a reason to combine the elements found in the prior art in the way the claimed invention does.

99. I understand that obviousness may be based on an inherent teaching of a prior art document if that prior art document contains necessarily discloses the claim limitation at issue. Stated another way, a result is inherent if it inevitably flows from practicing the claimed method taught in the prior art. I understand that additional references, including those that are not themselves prior art, may be used to show that a characteristic not expressly disclosed in a prior art document is an inherent result of practicing the method disclosed in the prior art document.

100. I understand that obviousness does not require absolute predictability of success. Rather, it is my understanding that a patent claim is obvious so long as there was a reasonable expectation of success.

X. OPINIONS REGARDING WRITTEN DESCRIPTION OF THE '084 PATENT

101. In my opinion, the claims of the '084 patent lack written description support for four reasons: (1) a POSA would not understand that the inventors had possession of a method of changing a metabolic parameter; (2) a POSA would not understand that the inventors had possession of crinecerfont in the application leading to the '084 patent as filed; (3) a POSA would not understand that the inventors had possession of any of the seven CRF1 receptor antagonists outside the

scope of Formula (I) for treating TARTs or OARTs; and (4) a POSA would not understand that the inventors had possession of changing a metabolic parameter in OARTs patients, specifically.

102. Independent claim 1 recites “[a] A method of changing a metabolic parameter of a subject having a testicular adrenal rest tumor (TART) or an ovarian adrenal rest tumor (OART), comprising administering to the subject in need thereof a small molecule corticotropin-releasing factor type-1 (CRF1) antagonist, or a pharmaceutically acceptable salt thereof, wherein the small molecule CRF1 antagonist is: *[one of the ten compounds reflected in the table above and labeled with letter designations (A–J)]*, or a pharmaceutically acceptable salt thereof, and wherein the metabolic parameter comprises fasting glucose, HbA1c level, insulin sensitivity, or a lipid profile, or a combination thereof.” EX1001, 99:2-101:22. I understand claim 1 encompasses a set of ten compounds that, when administered to a subject with a TART or an OART, purport to have the function of changing one or more of the listed metabolic parameters. I understand that dependent claims 4-19 also encompass the same set of compounds, whereas dependent claim 2 is narrowed to only one compound, Compound 1 (also known as tildacerfont), claim 3 is narrowed to only one compound, Neurocrine’s crinecerfont, and claims 2-19 all have the same requirement to change at least one of the enumerated

metabolic parameters in a subject with a TART or an OART. EX1001, 101:23-102:50.

A. The '084 patent lacks written description support for the claimed method of changing a metabolic parameter

103. I have reviewed the specification of the '084 patent to assess whether it provides written description support for a method of changing a metabolic parameter in a subject with a TART or OART. In my opinion, based on my review of the '084 patent and my experience, it does not. There are only two disclosures in the '084 patent related to changing metabolic parameters, and in my opinion, neither tells a POSA that, as of the priority date, the inventors were in possession of a method of changing a metabolic parameter using any of the claimed compounds.

104. The first disclosure is the passage describing the use of astressin: “In one aspect described herein, there is a method of improving metabolic symptoms in a subject in need thereof comprising administering an astressin or a variant having at least about 70% identity thereto; or a pharmaceutically acceptable salt or solvate thereof.” EX1001, 43:67–44:5. This disclosure linking “metabolic symptoms,” which can include the claimed metabolic parameters, is directed to a different compound than the CRF1 receptor antagonists that are claimed.

105. As I explained in the technology background above, Section IV.E, astressin is a nonselective peptide CRH antagonist that acts broadly across CRH

receptor subtypes, including both CRF1 and CRF2. EX1030, 373 (Zorrilla & Koob). The claimed compounds, by contrast, are selective small-molecule antagonists of the CRF1 receptor subtype. The CRF1 and CRF2 receptors have different tissue distributions and mediate different physiological responses. Thus, a compound that blocks both receptor subtypes (like the peptide astressin) may produce different effects—including off-target effects—than a compound that selectively targets only CRF1 (like a claimed small-molecule CRF1 receptor antagonist). EX1088 (Deussing & Chen), 2233-2235. A POSA would not have viewed astressin as interchangeable with any of the claimed CRF1 receptor antagonists for therapeutic purposes.

106. In my opinion, a POSA reading the '084 patent would not have understood the astressin disclosure as providing possession of a method of changing metabolic parameters with the claimed small-molecule CRF1 receptor antagonists. The '084 patent does not explain whether or how a selective CRF1 receptor antagonist could change a metabolic parameter. It does not identify any link between selective CRF1 antagonism and metabolic parameters. It presents no laboratory evidence or preclinical or clinical data suggesting that any of the claimed small-molecule CRF1 receptor antagonists would be effective for changing a metabolic parameter.

107. As noted above in § V.A, the '084 patent contains four examples. None of the examples contain any data showing a change in metabolic parameters in a subject with a TART or OART, and only Example 1 mentions metabolic parameters. EX1001, 89:63–98:33. Example 1 describes a Phase 2, Open-Label Study of Compound 1 (tildacerfont) “specifically in male CAH subjects with TART” and lists metabolic parameters as secondary outcome measures, but without any reported data because the Example is prophetic and, at the time of filing, had not been performed. EX1001, 90:10–91:3. Example 1 also does not contain any prediction on what the changes in any of the metabolic parameters would be following administration of Compound 1 (tildacerfont) and a POSA would not have been able to determine whether any change in any metabolic parameter would occur.

108. Example 2 does not describe or evaluate changing metabolic parameters. EX1001, 94:1–96:2. Example 3 claims to show an “approximately 25% shrinkage in TART in a 25 year old male with classic congenital adrenal hyperplasia following 6 weeks treatment with a CRF1 receptor antagonist.” EX1001, 96:2–96:59. Even assuming that the TART was, in fact, reduced in size, this is a morphological observation on an ultrasound and does not show a change in a metabolic parameter. Finally, Example 4 describes a study evaluating the effects of Compound 1 (tildacerfont) on ACTH and adrenal steroid levels, as well

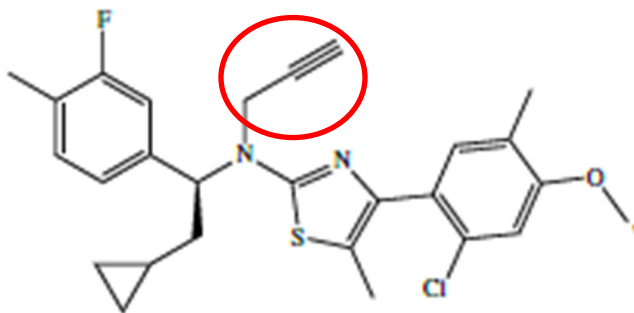
as its safety, tolerability, and pharmacokinetics, in participants with CAH, and does not mention anything about changing metabolic parameters. EX1001, 96:61–98:33.

109. In my opinion a POSA would not necessarily link a purported reduction in TART size with changes in metabolic parameters like fasting glucose, HbA1c levels, insulin sensitivity, or lipid profile. From a biological standpoint, treating TARTs or OARTs and changing a metabolic parameter such as fasting glucose, HbA1c, insulin sensitivity, or a lipid profile involve different physiological mechanisms. TARTs and OARTs are discrete anatomical structures that arise from ectopic adrenal rest cells present in the testes or ovaries, respectively. It is thought that these tumors enlarge primarily in response to chronically elevated ACTH levels. By contrast, metabolic parameters reflect systemic biochemical processes that are each independently regulated and influenced by a wide range of factors—for example, HbA1c reflects glycemic control over a period of months, and lipid profiles are affected by comorbid conditions and numerous metabolic pathways. Because the pathophysiology underlying TART growth is distinct from the diverse and independent mechanisms governing metabolic parameters, a POSA would not understand a disclosure directed to reducing the size or number of TARTs as necessarily describing or encompassing a method of changing a metabolic parameter. In my experience, a

patient's TART status does not necessarily predict or correlate with changes in these independent metabolic markers, and vice versa.

B. The '084 patent lacks written description support for crinecerfont

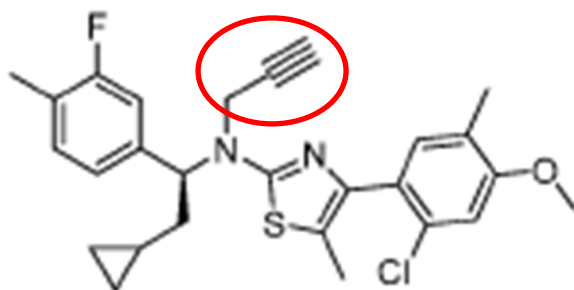
110. Crinecerfont is represented by the following chemical structure:



EX1033. Crinecerfont contains a propynyl moiety that I have circled in red, above.

A propynyl moiety is a three-carbon side chain that contains a carbon-carbon triple bond, i.e., ($-\text{CH}_2-\text{C}\equiv\text{CH}$).

111. I understand that in the originally filed application leading to the '084 patent, Spruce disclosed the following structure:



EX1002, 36-37 (¶27), 123 (¶261), 143 (claim 1), 144 (claim 3). This structure contains a three-carbon side chain that I have circled in red, above, with a chemically impossible carbon-carbon quadruple bond, i.e., ($-\text{CH}_2-\text{C}\equiv\text{C}$). This structure is not crinecerfont and cannot exist.

112. I have reviewed several documents that I understand from counsel the '084 patent claims priority to: International Application PCT/US2019/029486 (“the PCT application”), the '815 provisional, and the '951 provisional. None of these applications disclose crinecerfont. Instead, they all disclose a structure having the carbon-carbon quadruple bond that I have reproduced above. EX1051, ¶¶26-27, 260-261; EX1055, ¶¶231-232; EX1056, ¶¶4, 6, 9, 10, 11. I have also reviewed the original application leading to the '084 patent—the U.S. Application No. 19/043,303—and it also does not disclose crinecerfont. EX1002, 31-146.

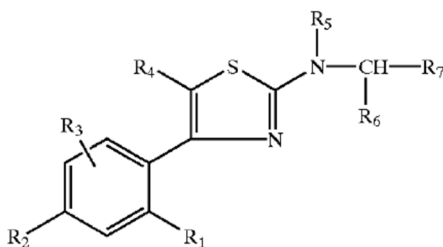
113. I understand from counsel that Spruce replaced the original structure (having a carbon-carbon quadruple bond) with a structure depicting crinecerfont during prosecution of the application leading to the '084 patent. I have been informed and understand from counsel that replacing the structure is impermissible “new matter” unless a POSA would consider that replacement to constitute an obvious correction of an obvious error.

114. In my opinion, the original structure has an obvious error: the carbon-carbon quadruple bond is chemically impossible. Nevertheless, crinecerfont would

not have been the obvious correction because nothing in the surrounding disclosure refers to or discloses crinecerfont and a POSA would have recognized that multiple chemical alternatives could replace the carbon-carbon quadruple bond.

115. For example, a POSA would have looked to U.S. Patent 6,586,456 assigned to Sanofi (“the Sanofi patent”) because the Sanofi patent discloses and teaches several aminothiazole derivatives as CRF receptor antagonists, including crinecerfont. I understand that this patent was licensed from Sanofi by Neurocrine.

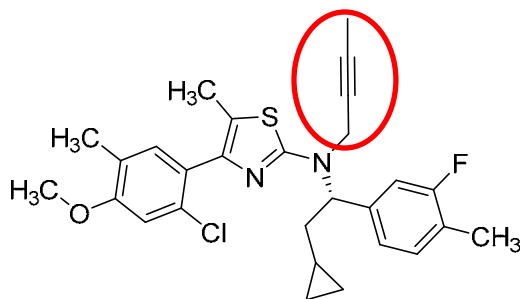
116. The Sanofi patent discloses aminothiazole derivatives having the following formula (I) as CRF receptor antagonists:



. EX1060, 4:5-14.

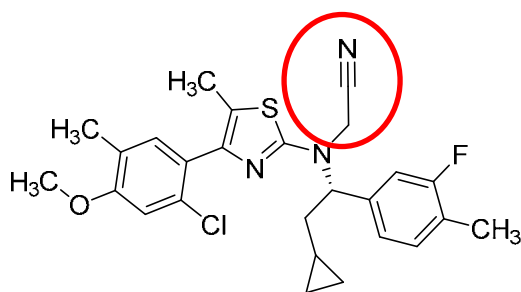
The '084 patent's original carbon-carbon quadruple bond is located at position R₅. The Sanofi patent teaches that R₅ may be “an alkenyl of 3 to 6 carbon atoms; an alkynyl of 3 to 6 carbon atoms; a cyano(C₁-C₆)alkyl; [or] a (C₁-C₄)alkoxy.” *Id.*, 4:45-47. Thus, a POSA would have understood that multiple alternative R₅ substituents could have served as a “correction” to the originally disclosed structure having the carbon-carbon quadruple bond.

117. For example, a POSA would have recognized from the Sanofi patent that R₅ could be corrected to a butynyl moiety (an alkynyl group of four carbon atoms). I have circled the butynyl moiety in red below:



In this case, the R₅ substituent is an “alkynyl of 3 to 6 carbon atoms,” which is represented by $-\text{CH}_2-\text{C}\equiv\text{C}-\text{CH}_3$. EX1060, 4:45-46.

118. As another example, a POSA would have recognized from the Sanofi patent that the carbon-carbon quadruple bond could be corrected to a nitrile (also called a cyano) moiety, which contains a carbon-nitrogen triple bond that I have circled in red below:



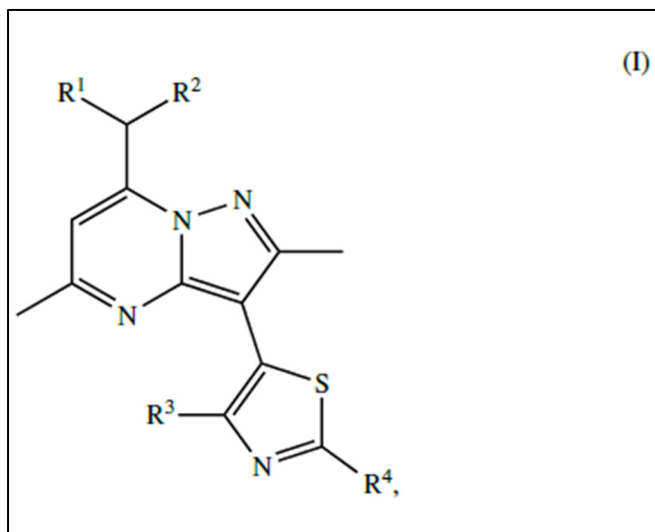
In this case, the R₅ substituent is “a cyano (C₁-C₆) alkyl,” which is represented by $-\text{CH}_2-\text{C}\equiv\text{N}$.

C. The '084 patent also lacks written description support for seven of the 10 claimed compounds for changing a metabolic parameter in a subject with TARTs or OARTs.

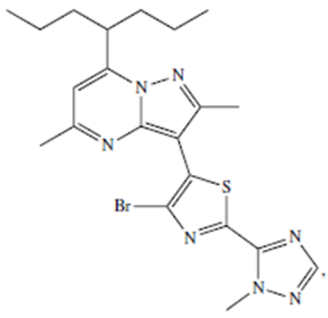
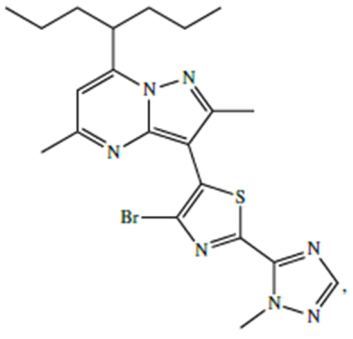
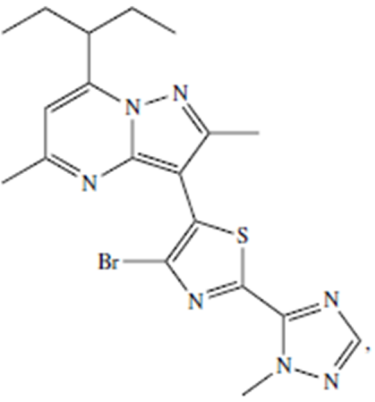
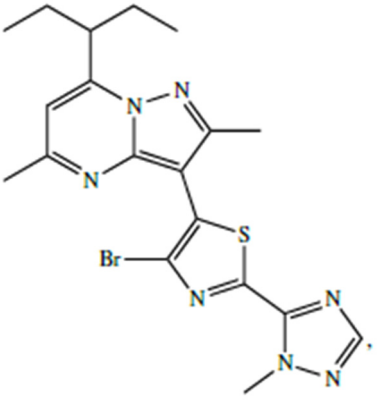
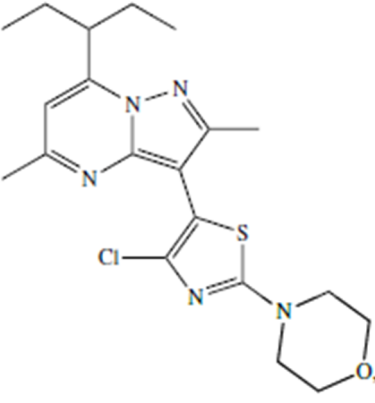
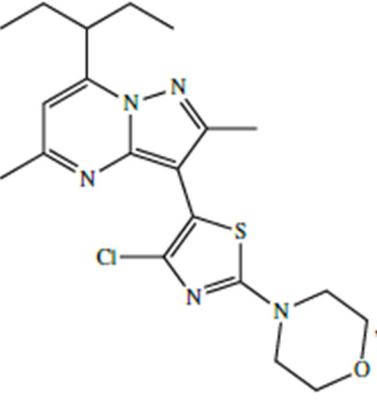
119. I have reviewed the specification of the '084 patent to assess whether it provides written description support for the full scope of the ten compounds identified in Claim 1. In my opinion, based on my review of the '084 patent and my experience, it does not. In my opinion, the '084 patent does not demonstrate that, as of the priority date, the inventors were in possession of a method for changing a metabolic parameter in a subject with a TART or an OART using all of claim 1 compounds. In addition, seven of the ten claimed compounds are not identified in the '084 patent as falling within the scope of Formula (I), and are described only as “additional chemotherapeutic agents,” to be co-administered with a compound of Formula (I), not as compounds for changing a metabolic parameter. One claimed compound, crinecerfont, was not disclosed in the original application leading to the '084 patent.

120. A POSA would view the '084 patent as directed to CRF1 receptor antagonists having a specific structural formula, referred to in the patent as Formula (I), which I've replicated below. EX1001, 2:13–33.

Formula (I):



121. The '084 patent defines Formula (I) by specifying particular substituents at positions R1, R2, R3, and R4. EX1001, 2:34–55. Based on these definitions, only three of the CRF1 receptor antagonists recited in claim 1 are identified in the '084 patent as falling within the scope of Formula (I). These three compounds are disclosed in column 3 of the patent and correspond to the first three compounds listed in claim 1, which I refer to as Compounds A, B, and C (for ease of reference only), respectively. Below is a chart showing that the compounds from column 3 are the same as those in claim 1:

	Column 3	Claim 1
A	R^a and R^b are independently C_1-C_3alkyl. In some embodiments, the compound is 	salt thereof, wherein the small molecule CRF₁ antagonist is: 
B	In some embodiments, the compound is 	-continued 
C	In some embodiments, the compound is 	 20 25 30

EX1001, 3:11–67; 98:51–99:30; EX1091 (compound **A**); EX1092 (compound **B**); EX1059 (compound **C**).

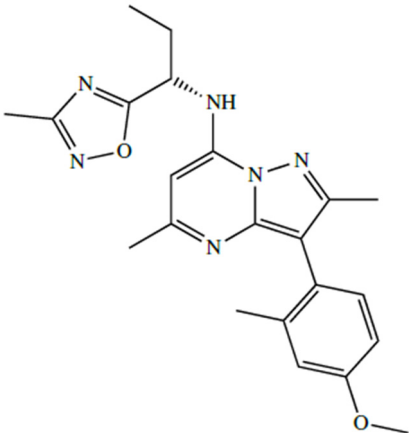
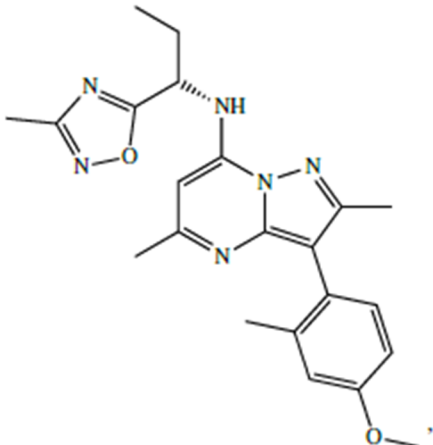
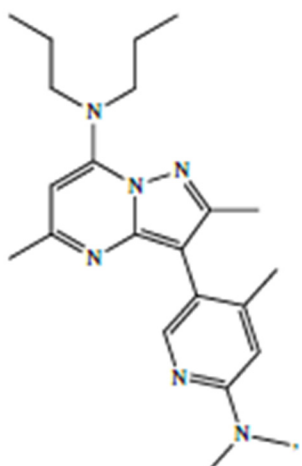
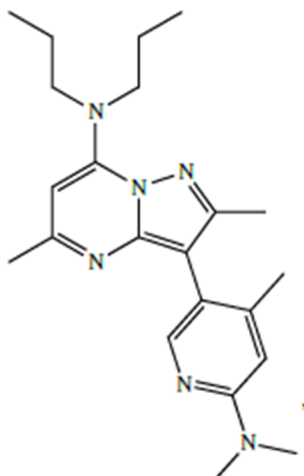
122. As noted above in § V.A, one of these Formula (I) compounds is identified in the '084 patent as “Compound 1,” which corresponds to tildacerfont and is the compound I have designated as “**C**,” for ease of reference. EX1001, 90:42-58; 96:40–45; EX1059.

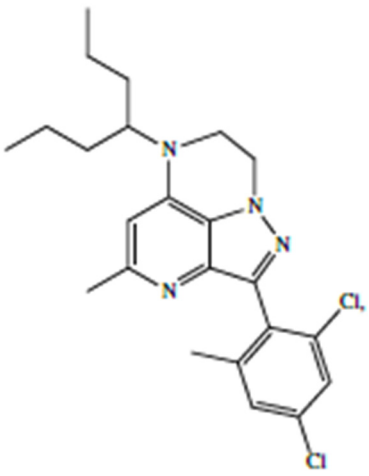
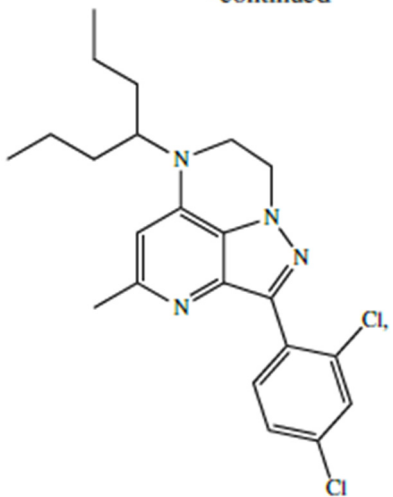
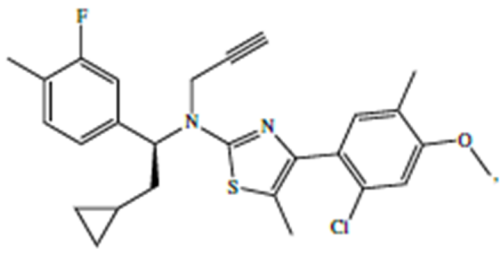
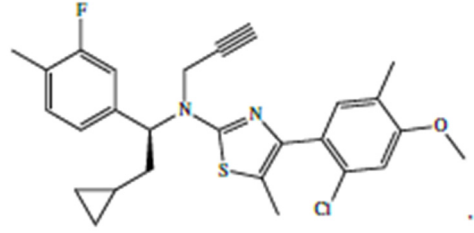
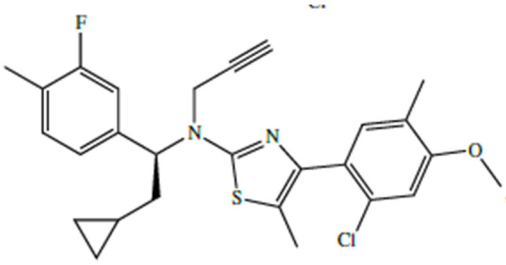
123. The '084 patent's discussion of CRF1 receptor antagonists focuses on compounds of Formula (I), and in particular on Compound 1 (tildacerfont). For example, the '084 patent states that Compound 1 “may be effective in blocking ACTH synthesis, thereby reducing the size of testicular lesions in TART,” and that pre-clinical and Phase 1 clinical results “provide a rationale for investigating the use of Compound 1 in the treatment of TART.” EX1001, 90:25–29, 90:38–41. These statements are specific to Compound 1 and at most for the treatment of TARTs, not OARTs, and do not show possession of changing a metabolic parameter in a subject with a TART or an OART using any of the seven claimed CRF1 receptor antagonists not identified as a Formula (I) structure.

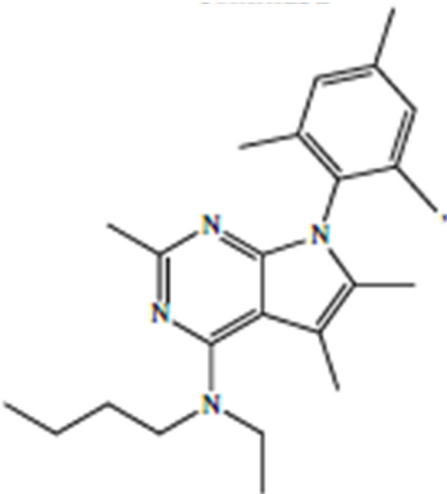
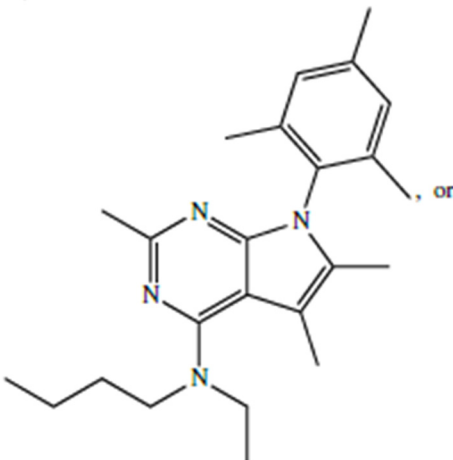
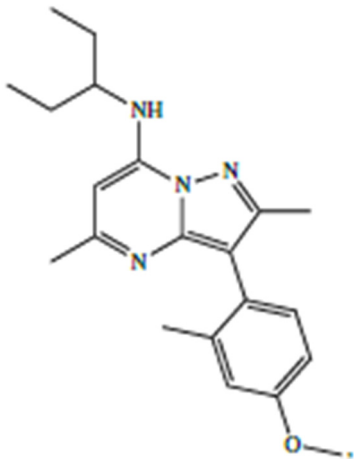
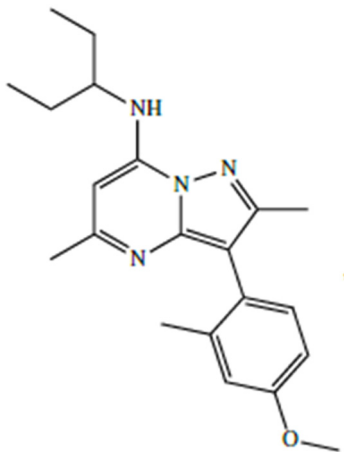
124. In addition to the three Formula (I) compounds, claim 1 of the '084 patent recites seven additional compounds that are not identified as Formula (I) compounds. These compounds are listed in the specification separately from the Formula (I) compounds, and specifically only as “additional chemotherapeutic

agents,” shown below, to be administered alongside those of Formula (I)

compounds:

	Specification (Columns 7-8 and 81-83)	Claim 1
D		
E		

	Specification (Columns 7-8 and 81-83)	Claim 1
F		-continued 
G	SSR-126374,	1, SSR-126374,
H	At Col. 7:55-65.  At Col. 82:40-50. 	

	Specification (Columns 7-8 and 81-83)	Claim 1
I		
J		

EX1001, 6:65–8:50; 81:50–83:38.

125. Five of these additional CRF1 receptor antagonists were developed by Neurocrine Biosciences for the treatment of congenital adrenal hyperplasia (“CAH”). For example, Compound **D** corresponds to verucerfont (NBI-77860) (EX1090), Compound **E** corresponds to NBI-30775 (EX1093), Compound **F** corresponds to NBI-34041 (EX1094), Compound **G** is SSR-126374, and Compound **H** corresponds to crinecerfont (also referred to as SSR-125543)

(EX1033). The remaining two compounds from claim 1 are Compound **I**, which is antalarmin (EX1001, 8:1–15; 82:52–66; EX1096) and Compound **J** (EX1095).

Based on their chemical structures, none of compounds **D-F** and **H-J** falls within the scope of Formula (I). The '084 patent fails to disclose the structure of the remaining compound **G**, SSR-126374. Nevertheless, it is not identified in the '084 patent as a Formula (I) compound.

126. These seven compounds are not described in the '084 patent as compounds for changing a metabolic parameter. Instead, they appear only in two sections of the specification describing optional co-therapies. Specifically, the patent states that, “[i]n some embodiments, the method further comprises administering to the subject an additional chemotherapeutic agent.” EX1001, 6:54-56, 81:37-40. The patent further states that, “[i]n some embodiments, the additional chemotherapeutic agent is another CRF1 antagonist,” and then lists the seven compounds not identified as Formula (I) compounds. EX1001, 6:65–8:50; 81:48–83:38. Six of these compounds are CRF1 receptor antagonists that I identified above as compounds **D-G** and **I-J**. I understand that one of these compounds was amended during prosecution to be Neurocrine’s crinecerfont, which I have identified above as compound **H**. In my opinion, a POSA would understand that these compounds are additional chemotherapeutic agents that may optionally be administered in combination with a compound of Formula (I), not as stand-alone

compounds for changing a metabolic parameter in a subject with a TART or an OART, as I understand are required by claims 1 and 3-19.

127. I did not identify any portion of the '084 patent that describes the compounds that I have designated **D-J** as compounds used to changing a metabolic parameter themselves. Instead, the '084 patent treats these compounds the same as other “additional chemotherapeutic agents” (identified as glucocorticoids, mineralocorticoids, ACAT1 inhibitors, and anti-androgens) that may also optionally be co-administered with a compound of Formula (I). EX1001, 6:54-8:52, 81:36-83:38. The specification also does not provide any experimental data, clinical results, or discussion linking these additional compounds to changing a metabolic parameter in a subject with a TART or an OART.

128. I have reviewed the entire specification of the '084 patent specification, and considered it from the vantage point of a POSA at the priority date. Every figure, description, and example refers exclusively to Compound 1 (tildacerfont). EX1001, 9:55-10:47, Figs. 1-11, 13-17. The TART data presented in the examples is expressly identified as data for Compound 1 (tildacerfont). EX1001, 89:59-98:22. I did not identify any experimental data, figures, or clinical observations relating to any other CRF1 receptor antagonist in connection with changing a metabolic parameter. In my opinion, a POSA reviewing the '084 patent would understand that the patent's disclosure is limited to CRF1 receptor

antagonists having the structure of Formula (I), and in particular to Compound 1 (tildacerfont), for, at most, treating TARTs.

129. A POSA would understand that disclosure of data for a Compound 1 (tildacerfont) does not establish that other CRF1 receptor antagonists will necessarily have the same pharmacological or clinical properties as Compound 1. This is particularly true where the additional CRF1 receptor antagonists differ in chemical structure from the disclosed Compound 1 (tildacerfont), which as Spruce admitted, has unique structural features. EX1041 (Sarafoglou), 4667.

130. Structural differences may affect, for example, receptor binding and clinical performance. For example, a 2013 review article by Williams concluded that “antagonists of the CRF1 receptor have not demonstrated clinical utility despite over 30 years of research and hundreds of patents.” EX1029, 1065. Williams also describes several clinical studies in which CRF1 receptor antagonists failed to demonstrate utility in treating depression and anxiety disorder. EX1029, 1058. Williams concludes that “[f]urther clinical evaluation of new compounds appears unlikely unless novel structures are identified that interact with the receptor distinct to the first-generation antagonists.” EX1029, 1057.

131. In a scientific publication, Spruce described Compound 1 (tildacerfont) as having “unique structural features,” further underscoring that it is not representative of all CRF1 receptor antagonists. EX1041 (Sarafoglou), 4667.

The '084 patent does not provide guidance for identifying other CRF1 receptor antagonists that might share the features of Compound 1 (tildacerfont) for changing a metabolic parameter in a subject with a TART or an OART. I also note that the '084 patent does not reference or describe any “unique structural features” for Compound 1.

132. The histories of these compounds in clinical development also reflect their functional differences. In contrast to Compound 1 (tildacerfont), which failed in clinical development for treating CAH, Neurocrine’s CRENESSITY achieved clinical success and ultimately received FDA breakthrough designation for the treatment of CAH. EX1058 (Dec. 13, 2024, Neurocrine Press Release); EX1044; EX1045. In my opinion, a POSA would view these divergent outcomes as further confirmation that the properties and performance of the other claimed CRF1 receptor antagonists cannot be assumed based on data from Compound 1 (tildacerfont).

133. For these reasons, it is my opinion that a POSA reviewing the '084 patent would not understand the disclosure of Compound 1 (tildacerfont) or of Formula (I) to describe or support methods of changing a metabolic parameter using the full scope of the claimed CRF1 receptor antagonists that differ structurally and clinically from Compound 1, like Compounds **D-J** do.

D. The '084 patent lacks written description support for performing any of the claimed methods in a subject having an OART.

134. I have reviewed the specification of the '084 patent to assess whether it provides written description support for a method of changing a metabolic parameter in a subject with an OART. In my opinion, based on my review of the '084 patent and my experience, it does not. In my opinion, the '084 patent does not demonstrate that, as of the priority date, the inventors were in possession of a method for changing a metabolic parameter in a subject with an OART using any compound. Rather, OARTs are mentioned only at a high level, without any technical detail, examples, experimental data, clinical evidence, or any other evidence directed to OARTs themselves.

135. The '084 patent refers to OARTs in only two limited ways. First, it includes general background statements describing adrenal rest tumors as occurring in both testes and ovaries. EX1001, 1:41-51, 24:7-10. Second, it recites generic method statements reciting treatment of “testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART).” EX1001, 2:4-6, 2:13-15, 24:26-29, 38:62-63, 39:30-36, 39:45-52, 50:47-49, 50:59-60, 51:41-42, 55:33-36, 79:21-23. These references are not accompanied by any OART-specific examples, experimental data, clinical or laboratory observations, or technical discussion. In my opinion, a POSA would not have understood the inventors of the '084 patent to

have actually invented or possessed a method for changing a metabolic parameter in a subject with an OART based on these disclosures.

136. As noted above in § V.A, the '084 patent contains four examples. None of the examples relate specifically or even generally to OARTs or contain any data related to OARTs. EX1001, 90:4–98:44. Example 1 describes a Phase 2, Open-Label Study of Compound 1 (tildacerfont) “specifically in male CAH subjects with TART” but without any outcome data or information because it is prophetic. EX1001, 90:4–63. Example 2 is limited to hormonal pharmacodynamic data for Compound 1 (tildacerfont) in subjects with CAH and does not describe or evaluate changing a metabolic parameter in a subject with an OART. EX1001, 93:53-95:50. Example 3 claims to show results from treating CAH patients with CRF1 receptor antagonists, including a description of Figures 10A and 10B as showing “approximately 25% shrinkage in TART in a 25 year old male with classic congenital adrenal hyperplasia following 6 weeks treatment with a CRF1 receptor antagonist,” but Example 3 does not include any information relating to OARTs. EX1001, 95:51-96:37. Finally, Example 4 describes a study evaluating the effects of Compound 1 (tildacerfont) on ACTH and adrenal steroid levels, as well as its safety, tolerability, and pharmacokinetics, in participants with CAH, and does not mention anything about OARTs. EX1001, 96:38-98:10.

137. The '084 patent's lack of OART-specific disclosure is particularly significant given what was known in the art as of 2018, the earliest priority date of the '084 patent. At that time, OARTs were understood to be exceedingly rare and poorly characterized, with only a small number of reported cases, limiting clinical experience. For example, Zaarour reported in 2014 that "only 11 cases of OART have been described in the English-language literature" and explained that this scarcity made it "difficult to choose an optimal treatment approach for affected patients." EX1038, e70. The Zaarour authors concluded that "[t]he optimal treatment of the ovaries in cases of OART remains unclear." EX1038, e72. Similarly, Chen reported in 2017 that OARTs were "very rare," that "[c]linical studies of this condition have not been performed," and that "only a few cases have been published." EX1040, 146. Chen further explained that OARTs are "seldom revealed with standard imaging techniques," which makes their diagnosis and subsequent treatment particularly unpredictable and difficult compared to TARTs. EX1040, 147. Accordingly, a POSA would have understood at the time of the invention that treating OARTs was unpredictable. A POSA would have expected additional detail, such as clinical data, laboratory data, or other evidence, to show that an inventor had actually invented a method for changing a metabolic parameter in a subject with an OART. In my opinion, the '084 patent does not convey that the inventor possessed a method for doing so in a subject with OARTs.

138. The '084 patent's limited discussion of OARTs also contains a basic anatomical error. In the Definition section, the patent states that both TARTs and OARTs "may develop from ectopic remnants of intra-testicular adrenal tissue." EX1001, 25:4-8. From a biological and anatomical standpoint, that statement is incorrect as applied to OARTs. OARTs arise in the ovaries of females, and ovarian adrenal rest tissue cannot derive from intra-testicular adrenal tissue because females do not have testicular tissues. A POSA would immediately recognize this mistake, and in my opinion, the presence of this error further indicates that the inventors did not possess a developed scientific or clinical understanding of changing a metabolic parameter in a patient with an OART.

XI. OPINIONS REGARDING ENABLEMENT OF THE '084 PATENT

139. I understand that claims 1-19 of the '084 patent encompass methods of changing a metabolic parameter in a subject with a TART or an OART by administering one of ten specified CRF1 receptor antagonists. Dependent claims 2 is limited to a single compound (tildacerfont) and dependent claim 3 is limited to a single compound (crinecerfont), respectively, but still require changing a metabolic parameter in a subject with a TART or an OART. Based on my review of the '084 patent, my familiarity with the relevant scientific literature, and my clinical experience, I do not believe the '084 patent provides sufficient technical teaching to allow a POSA to carry out these methods across the full scope of the claims

without undertaking extensive, iterative experimentation that goes well beyond what a POSA would consider routine.

140. In forming this opinion, I have considered what I understand from counsel to be factors relevant to whether undue experimentation would be required, including: the breadth of the claims, the nature of the invention, the nascent state of the art, the level of one of ordinary skill, the unpredictability in the art, the amount and degree of guidance provided in the patent, whether there are working examples, and the quantity of experimentation that would be needed to practice the claimed methods. I address each of these considerations below from a clinical and scientific perspective.

141. In short, it is my opinion that a POSA would have to perform undue experimentation to practice the invention as claimed. From a clinical perspective, a POSA would need to determine whether any of the claimed CRF1 receptor antagonists meaningfully change a metabolic parameter in a subject with a TART or an OART, which is not disclosed in the '084 patent.

142. The scope of what the claims require is significant. Each claim requires a method of changing a metabolic parameter in a subject with a TART or an OART. The metabolic parameter is defined to include fasting glucose, HbA1c level, insulin sensitivity, or a lipid profile, or a combination thereof. Claims 1 and 4-19 encompass ten CRF1 receptor antagonists, each of which would need to be

capable of achieving the claimed result of changing a metabolic parameter. From a clinical standpoint, the claims are broad in at least three ways: they cover ten different compounds, two distinct patient populations (subjects with a TART or subjects with an OART), and multiple metabolic endpoints. The '084 patent does not contain laboratory or clinical evidence addressing any claimed metabolic parameter in any subject or patient population using any of the claimed compounds, let alone across that full scope.

143. In my review of the '084 patent, I did not identify any example, laboratory evidence, clinical observation, dosing protocol, monitoring strategy, response criteria, or treatment outcome data related to changing a metabolic parameter in a subject with an OART. As I explained above in § X.D, the patent's references to OARTs are limited to generic statements that merely recite the claim language. EX1001, 1:41–51, 2:4–6, 2:13–15, 24:27–30, 38:63–64, 39:31–35, 39:45–52, 50:45–47, 50:52–53, 51:41–42, 55:33–36, 79:23–25. It does not provide any example, laboratory evidence, clinical observation, dosing regimen, response criteria, or treatment outcome relating to an OART subject. A POSA attempting to practice the claimed methods in a subject with an OART using any of the claimed CRF1 receptor antagonists would therefore lack practical guidance regarding diagnosis, monitoring, treatment endpoints, and expected clinical response based on the '084 patent's disclosure.

144. This omission is significant in view of the clinical reality that OARTs are rare, difficult to diagnose and study, and represent an unpredictable area of endocrine medicine. EX1038, e70, e72 (Zaarour); EX1040, 146-147 (Chen). In clinical practice, OARTs are often not detected unless imaging is performed for unrelated reasons, and even when suspected, distinguishing adrenal rest tissue from other ovarian or adrenal pathology can be challenging. EX1040, 147 (Chen). As a result, a POSA would not be able to fill the disclosure gaps with routine clinical practice and would instead be forced to design and undertake additional study—potentially including multicenter efforts or long-term case accumulation—to determine whether any claimed CRF1 receptor antagonist could reliably change any of the claimed metabolic parameters in a subject with an OART and what dosing and monitoring would be required.

145. Similarly, the patent provides no experimental or clinical guidance for changing metabolic parameters with any of the ten claimed CRF1 receptor antagonists in a subject with an OART. The only passage in the specification that connects any compound to metabolism describes the use of astressin—a nonselective peptide CRH antagonist that is pharmacologically distinct from every compound recited in the claims. EX1030, 373 (Zorrilla & Koob). As I discussed in the technology background section of this declaration, Section IV.E, astressin acts broadly across both CRF1 and CRF2 receptor subtypes and has different

pharmacokinetic properties from the claimed selective small-molecule CRF1 receptor antagonists. EX1030, 373 (Zorrilla & Koob). In my opinion, a POSA could not rely on a single, unsupported reference to astressin as a basis for understanding or practicing how to change a metabolic parameters with the full scope of the claimed CRF1 receptor antagonists.

146. I also note that changing a metabolic parameter and treating OARTs are clinically distinct objectives with different underlying pathophysiology. Metabolic parameters such as fasting glucose, HbA1c, insulin sensitivity, and lipid profiles reflect systemic biochemical processes, each independently regulated and influenced by a wide range of factors including diet, genetics, comorbid conditions, and hormonal status. OARTs, by contrast, are structural lesions consisting of ectopic adrenal cortical tissue within the ovaries that enlarge primarily in response to chronically elevated ACTH levels. Improving one does not necessarily improve the other. A subject may have OARTs without any abnormality in a given metabolic parameter, or may have impaired metabolic parameters without any detectable OARTs. In my opinion, a POSA attempting to both change a metabolic parameter in a subject with an OART and/or also trying to treat OARTs would need experimental or clinical evidence that a given therapeutic intervention addresses each condition's distinct mechanism—and the '084 patent does not provide such evidence for any CRF1 antagonist.

147. The sole data in the '084 patent relating to any adrenal rest tumor is the disclosure in Example 3 describing Figures 10A and 10B, which purport to show approximately 25% shrinkage of a TART in a single 25-year-old male patient following six weeks of treatment with a CRF1 receptor antagonist identified as Compound 1 (tildacerfont). In my clinical judgment, this disclosure does not provide the information a POSA would need to reproduce or evaluate this result, much less to design a method for changing fasting glucose, HbA1c, insulin sensitivity, or lipid profile in a subject with a TART or an OART.

148. This observation involves a male patient with a testicular tumor. Males do not have ovaries and cannot develop OARTs. The '084 patent does not disclose any corresponding metabolic data for this patient. It does not report fasting glucose, HbA1c level, insulin sensitivity, lipid profile, or any change in any of those parameters. In my opinion, a POSA would not consider a single ultrasound observation in one male patient with a TART to provide sufficient experimental or clinical guidance for changing a metabolic parameter in subjects with a TART or an OART. EX1107 (Merkatz). As I discussed above in section X.A, tumor size on ultrasound is a morphological observation, not a metabolic endpoint.

149. The lack of experimental or clinical evidence regarding OARTs makes the patent's lack of OART-specific disclosure significant. Because OART cases are so infrequently encountered, even identifying suitable patients for clinical

study would require extended screening across multiple institutions. EX1038, e70, e72 (Zaarour); EX1040, 146-147 (Chen). A POSA would likely need years of effort to locate a sufficient number of subjects with OARTs, standardize diagnostic and imaging approaches, and assess whether any of the claimed compounds could change one or more of the claimed metabolic parameters in such subjects. From a clinical trial standpoint, that would be costly, difficult, and unpredictable, and it is not the type of routine follow-on testing a POSA could perform based on the disclosure in the '084 patent.

150. A POSA would not be able to fill in the gaps in the '084 patent's disclosure through routine clinical practice. Instead, in my opinion, a POSA would need to design and conduct dedicated clinical studies—potentially requiring multi-center recruitment and long-term follow-up—to determine whether any CRF1 receptor antagonist could reliably change a metabolic parameter in a subject with TARTs or OARTs, and what dosing, monitoring, and response criteria would be appropriate. From a clinical-trial standpoint, such studies would be costly, time-consuming, and uncertain in outcome.

151. I understand that the '084 defines a “subject in need thereof” as “a living organism suffering from or prone to a disease or condition that can be treated by administration of a pharmaceutical composition as provided herein.” EX1001, 27:55-61. This could include administration to non-humans, such as in an

animal model. *Id.* For the same reasons as for human subjects as described above, in my opinion it would likewise be costly, difficult, and unpredictable to determine whether each of the claimed CRF1 receptor antagonists can change a metabolic parameter in an animal with a TART or an OART. That would not be routine testing a POSA could perform based on the disclosure of the '084 patent.

152. Even if the '084 patent disclosed that Compound 1 (tildacerfont) had an effect on adrenal rest tumors, which in my opinion it does not, the patent does not provide any disclosure of why a POSA would expect the other nine claimed CRF1 receptor antagonists, many of which are structurally distinct from Compound 1, to produce the any effect on the claimed metabolic parameters. As a result, a POSA would be left to determine, through additional research and testing, whether any of the other compounds could achieve the claimed metabolic changes.

153. The '084 patent's examples and discussion focus on Compound 1 (tildacerfont) and do not provide any experimental or clinical data for the other claimed CRF1 receptor antagonists. Example 1 describes a study protocol "specifically in male CAH subjects with TART," but it is prophetic, limited to Compound 1, and includes no clinical results. EX1001, 90:10–91:3. Example 2 and Example 4 describe studies focused on hormone measures and pharmacokinetics for Compound 1 in CAH participants and do not mention, much less evaluate, changing a metabolic parameter in subjects with TARTs or OARTs. EX1001,

94:1–96:2, 96:61–98:33. Example 3 presents images from a single TART patient and is limited to Compound 1, without any specifics as to the method of treatment other than that it was with Compound 1 and lasted 6-weeks. EX1001, 96:4–96:59. In my opinion, these disclosures do not teach a POSA how to change a metabolic parameter in a subject with TARTs or OARTs using any CRF1 receptor antagonist, and certainly not claimed CRF1 receptor antagonists beyond Compound 1 (tildacerfont).

154. In my opinion, a POSA attempting to practice the claimed methods across the full set of ten CRF1 receptor antagonists would necessarily have to engage in an extensive and iterative, trial and error process. At a minimum, a POSA would need to: (i) define experimental or clinically meaningful response criteria for the claimed metabolic parameters in subjects with a TART and subjects with an OART; (ii) design monitoring protocols (including metabolic endpoints); and (iii) test each compound to determine whether it produces a reliable change in one or more of the claimed metabolic parameters. The specification does not provide sufficient instruction to allow those steps to be carried out without substantial additional work. These steps would require sequential clinical testing, rather than routine bench-level experimentation.

155. A POSA would also understand that CRF1 receptor antagonists may not be interchangeable in terms of clinical efficacy. Differences in chemical

structure may lead to differences in receptor binding and clinical performance. For example, published structure–activity relationship studies of non-peptide CRF1 receptor antagonists demonstrate that structural differences may lead to substantial differences in CRF1 receptor binding affinity, subtype selectivity, and functional antagonism. EX1018 (Fahmy), Sections 4–5. Additionally, reviews of CRF1 receptor antagonists report that structurally distinct compounds can exhibit different receptor binding kinetics, including differences in dissociation rates and residence time at the CRF1 receptor, which are understood to influence biological activity. EX1029 (Williams), Section 3. Because of this, where the patent provides tumor related disclosure only for Compound 1 (tildacerfont), a POSA would not be able to predict that the other claimed compounds would produce changes to the claimed metabolic parameters without trial-and-error testing.

156. Spruce itself has described Compound 1 (tildacerfont) as having “unique structural features” compared to other CRF1 receptor antagonists. EX1041, 4667. A POSA would understand such “unique structural features” to suggest that Compound 1 is not representative of the broader class of CRF1 receptor antagonists. The '084 patent does not identify what those features are or provide guidance for determining whether other claimed CRF1 receptor antagonists share them. In my opinion, that further limits a POSA’s ability to extrapolate from Compound 1 to other compounds without extensive testing.

157. I recognize, as explained above in § VII, that a POSA in this field would have substantial education and experience, namely a Ph.D. or a medical degree. However, high skill does not substitute for missing disclosure about how to select and use each of ten CRF1 receptor antagonists to change one or more of the claimed metabolic parameters in subjects with a TART or an OART. In my opinion, a POSA, even a highly skilled one, would still need extensive additional work to practice the claimed methods across their full breadth.

158. In summary, based on my review of the '084 patent and my clinical and scientific experience, the patent does not teach a POSA how to change a metabolic parameter in subjects with a TART or an OART using each of the ten claimed CRF1 receptor antagonists without undue experimentation. A POSA would need to conduct substantial original experimental and/or clinical research to determine which, if any, of these compounds could change a metabolic parameter in a subject with a TART or an OART. In practical terms, the '084 patent would be understood by a POSA as outlining a research hypothesis rather than providing an enabling teaching for a completed method of changing a metabolic parameter in a subject with a TART or an OART by administering the 10 claimed compounds.

XII. OPINIONS REGARDING OBVIOUSNESS OF THE '084 PATENT

A. PRIOR ART

159. As discussed below, it is my opinion that claims 1 and 3–19 of the '084 patent would have been obvious over the work that Neurocrine and others carried out and published before Spruce filed the application for its '084 patent. Specifically, over Grigoriadis (EX1006), Richard (EX1012), Yu (EX1067), Delfino (EX1064), and Howerton (EX1074), each of which is summarized in this section.

1. Grigoriadis (EX1006)

160. Grigoriadis is a U.S. Patent Publication (2017/0020877) that published on January 26, 2017. EX1006, cover page, (10) and (43). Grigoriadis relates to “[c]ompositions and methods for treating congenital adrenal hyperplasia” and describes a number of different CRF1 receptor antagonists for treatment of CAH, including NBI-77860 (verucerfont) and SSR-125543 (crinecerfont). EX1006, [0002], [0051], [0054] and table on pages 4 and 6.

161. Grigoriadis states that treatment goals include improving CAH patients’ “health, well-being, [and] quality of life,” and to “manage [their] related disorders.” EX1006, [0002]; [0005]. Grigoriadis identifies some of those related disorders as “testicular adrenal rest tumors in men.” EX1006, [0044]. Grigoriadis discusses how to determine optimal dosing of its CRF1 receptor antagonists (*see*,

e.g., EX1006, [0061]–[0074]), and also identifies one specific dose range as of about 50–1000 mg. EX1006, [0063].

162. Grigoriadis teaches that patients with CAH have an increased prevalence of negative side effects due to conventional treatment with supraphysiologic doses of glucocorticoids. EX1006, [0045-0047]. Grigoriadis teaches that CAH patients “require lifelong management with glucocorticoids and the attendant problems associated with such treatment.” EX1006, [0005]. Grigoriadis teaches that administration of supraphysiologic glucocorticoids in adults elevates the risk of cardiovascular disease, obesity, hypertension, insulin resistance, glucose intolerance, and decreased bone-mineral density. EX1006, [0046–0047]. Grigoriadis teaches that, in children, administration of supraphysiologic glucocorticoids “can impede statural growth.” EX1006, [0069]. Statural growth means the increase in height over time. Grigoriadis teaches that use of a CRF1 for treating CAH and its related disorders (*e.g.*, TARTs) enables administration of lower, more physiologic doses of hydrocortisone in CAH patients, thereby reducing these treatment-associated side effects. EX1006, [0040].

163. Grigoriadis also includes clinical data that relate to its methods of treating CAH with CRF1 receptor antagonists. Grigoriadis’ Example 6 describes “A Phase 1, Single-Blind Placebo-Controlled, Fixed-Sequence, Single-Dose Study to Evaluate the Safety and Tolerability of NBI-77860 [verucerfont] in Adult

Females with [CAH].” EX1006, [0090]. “It was designed to assess the safety, tolerability, and plasma exposure of NBI-77860, as well as the effect of this compound on endogenous levels of HPA axis hormones.” EX1006, [0090]. Each patient received, during three different treatment periods, a single dose of placebo, 300 mg, and 600 mg of NBI-77860. EX1006, [0091]; FIG. 4. Blood samples were collected 16 hours post-dose and analyzed for the HPA axis biomarkers including 17-OHP and ACTH. EX1006, [0092]. Both the 300 mg and 600 mg doses resulted in “[c]onsistent and clinically meaningful reductions from predose levels of both 17-OHP and ACTH” relative to placebo at the population level. EX1006, [0093]; FIG. 5. Furthermore, an individual responder rate of 50% (defined as at least a 50% decrease in 17-OHP and ACTH relative to placebo) was achieved for both the 300 mg and 600 mg doses. EX1006, [0093], FIG. 6.

2. Richard (EX1012)

164. Richard is a World Intellectual Property Organization Publication that published on September 20, 2007. EX1012, cover page, (43) and (54). Richard relates to “use of a compound of formula (I) [] or one of its pharmaceutically acceptable salts, for the manufacture of a medicament for the prevention and/or the treatment of metabolic syndrome and/or obesity and/or dyslipoproteinemia.” EX1012, cover page, (57).

165. Richard describes the results of tests performed in Zucker rats—a rat model of obesity—with “compound A,” a compound of Richard’s formula (I). EX1012, 14:4–31. Richard’s “Compound A” has the IUPAC name “[4-(2-chloro-4-methoxy-5-methylphenyl)-5-methylthiazol-2-yl][(1 S)-(2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl)]prop-2-ynylamine hydrochloride.” EX1012, 14:28–31. Compound A is the hydrochloride salt form of crinecerfont, which I confirmed by entering the IUPAC name into the program ChemDraw and comparing it with the PubChem entry for crinecerfont (EX1033).

166. Richard tested the effect of “compound A”—crinecerfont—on several metabolic parameters in the Zucker rat model. EX1012, 14:9-31. The Zucker rats are “characterized by a massive obesity that develops early after birth,” are “hyperlipidemic, hyperinsulinemic, glucose intolerant, and insulin resistant.” These rats also have very high levels of corticosterone due to an overstimulated hypothalamo-pituitary-adrenal (HPA) axis. EX1012, 14:18-26. Richard reports that administration of crinecerfont to these rats prevented “the fasting-induced increase in corticosterone levels in obese rats,” reduced circulating glucose levels “to values similar to those of lean and untreated food-deprived obese rats,” “improved insulin sensitivity,” “reduced circulating triglyceride levels in lean rats,” and prevented “fasting-induced reduction of triglycerides in obese rats.” EX1012, 16:13-24, 17:35-18:18, Figs. 3a-3g.

3. Yu (EX1067)

167. Yu is a 2015 publication from the *Annals of Pediatric Endocrinology & Metabolism* titled “Clinical manifestations of testicular adrenal rest tumor in males with congenital adrenal hyperplasia.” EX1067, 155.

168. Yu describes a study that “was conducted to investigate the prevalence of TARTs in male patients with CAH, and characterize the manifestations to identify contributing factors to TART.” *Id.* (Purpose). The study “detected TARTs in 8 of the 13 patients (61.5%)” using scrotal ultrasound. *Id.*, 155 (Results); 156 (Materials and Methods). Yu also examined clinical characteristics and found that CAH patients with TARTs exhibited elevated serum ACTH levels compared to those without TARTs (statistically significant at $P < 0.05$). *Id.*, 157–158. Yu characterizes serum ACTH levels above 70 pg/mL as being representative of uncontrolled disease. *Id.*, 157. The median value in CAH patients with TARTs was 144.6 pg/mL (above Yu’s threshold); the median value in CAH patients without TARTs, was 36.5 pg/mL (below Yu’s threshold). *Id.*, 158. Yu observed “no clear differences in other laboratory values” between the two groups of CAH patients. *Id.*

169. Follow-up ultrasounds were performed on five of Yu’s patients between 6 months to 1 year after the initial diagnostic ultrasound. *Id.*, 158. Three of the patients’ TARTs decreased in size; one slightly increased; and one had no

changes. *Id.*, 158. Each of the CAH patients whose tumor size decreased over time “demonstrated significantly decreased ACTH levels compared to the baseline study,” whereas the single patient whose tumor size increased “did not show a significant decrease in serum ACTH level.” *Id.*, 158.

170. Yu explains, citing earlier publications, that previous studies had identified ACTH “the most frequently suggested causative and growth promoting factor in TARTs.” *Id.*, 159. Yu concludes that the results of its study “support[s] the previous hypothesis that exposure to high concentrations of the serum ACTH level can be a major factor in the development of TARTs” and that “[t]his hypothesis could be taken in consideration for the treatment of TARTs.” *Id.*, 159.

4. Delfino (EX1064)

171. Delfino is a 2012 *Journal of Ultrasound Medicine* article titled “Testicular Adrenal Rest Tumors in Patients with Congenital Adrenal Hyperplasia.” EX1064, 383. Delfino’s work: (1) evaluated “the prevalence of testicular adrenal rest tumors in patients with CAH”; (2) studied their “hormonal profile”; (3) defined their “sonographic features”; (4) assessed their “seminal profile”; and (5) initiated a “longitudinal study on the possible role of corticotropin (ACTH) plasma levels in the induction and persistence of testicular adrenal rest tumors.” *Id.*

172. Delfino studied 18 patients with CAH, of which 11 (61.1%) had observable TARTs. EX1064, 384. Delfino's hormonal evaluation showed that all 11 patients with TARTs had elevated ACTH levels, despite long-term cortisone acetate therapy. EX1064, 385. Preliminary results from Delfino's longitudinal study showed, however, that "after 6 months of modified cortisone acetate therapy," three patients' ACTH levels returned to normal. *Id.* In two cases, tumors disappeared; in one, the tumor was reduced in size. *Id.*; *see also id.*, 386.

5. Howerton (EX1074)

173. Howerton is a World Intellectual Property Organization Publication (WO 2016/065177 A1) dated April 28, 2016, and titled "Method of Treating Depression and Other Stress Related Disorders." EX1074, cover page, (10), (43), (54); 1. It relates to "a method of treating a disorder in a male subject, comprising administering to the male subject a pharmaceutically effective amount of a CRF1 [CRF1] antagonist, wherein the disorder manifests hypersecretion of corticotropin-releasing factor (CRF)." *Id.*, cover page (57, Abstract); 2:1–5. Howerton lists a variety of such disorders, including anxiety related and stress related disorders (*Id.*, 2:5–19) alongside a list of dozens of CRF1 receptor antagonists (*Id.*, 2:20–24). Among the CRF1 receptor antagonists are Neurocrine's NBI-77860 (verucerfont). *Id.*, 2:20–24; *see also* 13:12–17 and table spanning pages 13–32. Also among the CRF1 receptor antagonists are LY2371712 (tildacerfont). *Id.*

174. Howerton describes how to administer the CRF1 receptor antagonists to humans. *Id.*, 23:16–17. In particular, “using known procedures, at dosages and for periods of time effective to treat a disease or disorder in the patient.” *Id.*, 17–18. Particular embodiments described in Howerton include administering dosages “that range from one to five times per day or more,” which Howerton considers to “specifically disclose” the sub-ranges within. *Id.*, 12:14–22. Howerton also describes how the dose of a compound “may be administered in a single dose or in multiple doses, for example from 1 to 4 or more times per day.” *Id.*, 30:28–31:3; 31:16–17. As one example, a dose of 1 mg per day may be administered as two 0.5 mg doses, with about a 12-hour interval between doses.” *Id.*, 31:4–5.

B. OBVIOUSNESS OF CLAIMS 1, 3–5, 8–13, AND 15–19

175. It is my opinion that independent claim 1 and dependent claims 3–5, 8–13, and 15–19 of the '084 patent would have been obvious over Neurocrine's Grigoriadis (EX1006), especially in view of Richard (EX1012), and Yu (EX1067).

176. At the time the application for the '084 patent was filed, Grigoriadis (EX1006) had already not only disclosed using several CRF1 receptor antagonists (including crinecerfont and verucerfont) to treat CAH, but also presents data from a Phase I clinical study demonstrating that administering an effective amount of verucerfont (NBI-77860) directly inhibits ACTH release in patients with CAH. *See above*, paragraphs 160-163; EX1006, [0002], [0005], [0051], [0054], [0090]–

[0093] table on pages 4 and 6. Grigoriadis also teaches that suppression of ACTH treats CAH-related disorders such as “testicular adrenal rest tumors in men.” EX1006, [0044]. Yu (EX1067) also teaches that CAH patients with TARTs have elevated ACTH levels, and suggests reducing ACTH levels as a therapeutic approach to treating TARTs. *See above*, paragraphs 167–170, EX1067, 155–159. Combining Grigoriadis with Yu would have provided a POSA, at the time that the application for the ’084 patent was filed, with a reason to use one of the ’084 patent’s claimed CRF1 receptor antagonists to lower ACTH in TART patients and treat the TARTs, as well as a reasonable expectation of success in treating TARTs with a CRF1 receptor antagonist.

177. Grigoriadis also teaches that inhibiting ACTH release in patients with CAH allows for the administration of “lower, more physiologic doses of hydrocortisone”—a well-known glucocorticoid used to treat CAH patients—“thus reducing treatment-associated side effects.” EX1006, Abstract. A POSA understands that such treatment-associated side effects include cardiovascular disease, obesity, hypertension, insulin resistance, glucose intolerance, and decreased bone-mineral density in adults, EX1006, [0046]–[0047], and inhibition of statural growth in children, EX1006, [0069]. Richard (EX1012) tested the effect of crinecerfont on metabolic parameters including fasting glucose, insulin sensitivity, and plasma triglycerides in a rat model of obesity and found that it

prevented fasting-induced increase in corticosterone levels, reduced circulating glucose levels “to values similar to those of lean and untreated food-deprived obese rats,” “improved insulin sensitivity,” “reduced circulating triglyceride levels in lean rats,” and prevented “fasting-induced reduction of triglycerides in obese rats.” EX1012, 14:9-31, 16:13-24, 17:35-18:18, Figs. 3a-3g.

178. A POSA would have understood from the combination of Grigoriadis and Richard that the administration of a CRF1 receptor antagonist, such as Grigoriadis’s crinecerfont or verucerfont, to a CAH patient would have not only allowed for the administration of more physiologic doses of glucocorticoids to the patient, but also would have led to other positive outcomes in metabolic parameters, such as improved insulin sensitivity and reduced fasting glucose. EX1012, 18:13-14. Based on Richard’s results, a POSA would have had a reasonable expectation that administration of crinecerfont or verucerfont would change the metabolic parameters of insulin sensitivity and glucose intolerance.

179. As discussed in more detail below, the remaining requirements of dependent claims 3-5, 8-13, 15-19 would have been obvious to a POSA.

C. Claim 1

180. Claim 1 recites

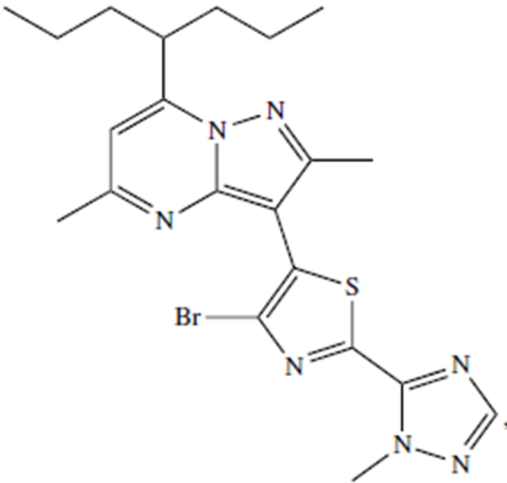
1. A method of changing a metabolic parameter of a subject having a testicular adrenal rest tumor (TART) or an ovarian adrenal rest tumor (OART), comprising administering to the subject in need thereof a small

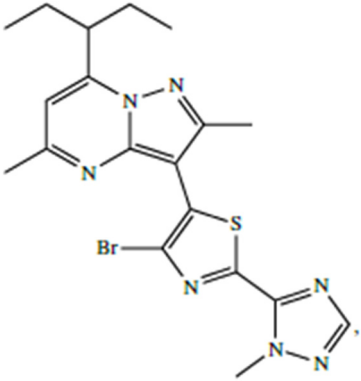
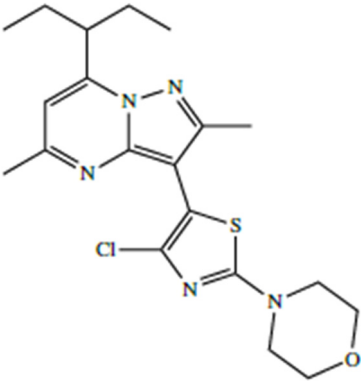
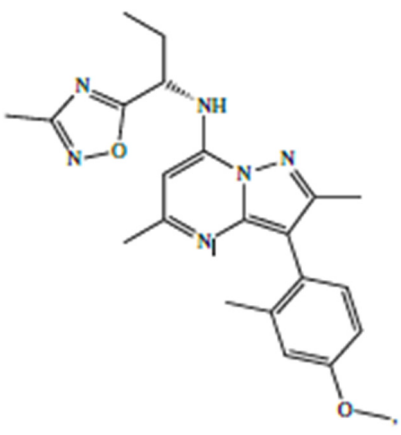
molecule corticotropin-releasing factor type-1 (CRF₁) antagonist, or a pharmaceutically acceptable salt thereof, wherein the small molecule CRF₁ antagonist is:

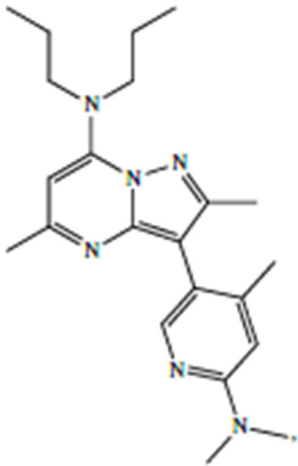
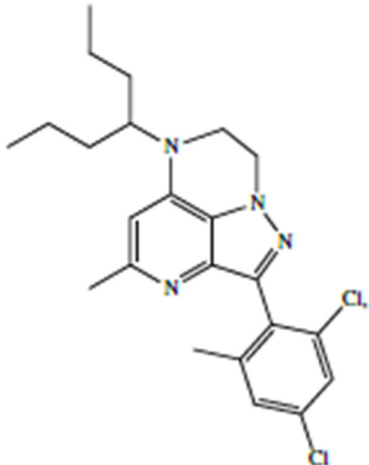
[one of the ten compounds structures set forth in the table below and labeled with letter designations (A–J) and common synonyms which do not appear in the claims, for easy reference], or a pharmaceutically acceptable salt thereof,

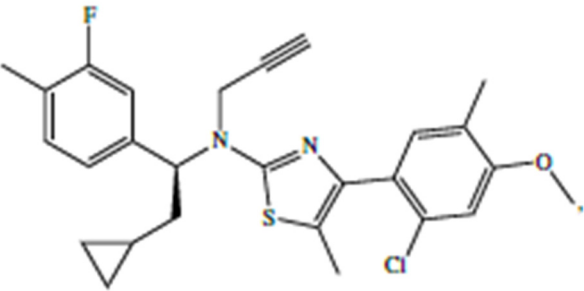
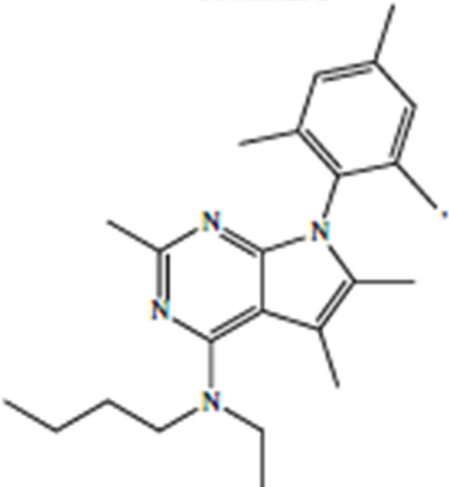
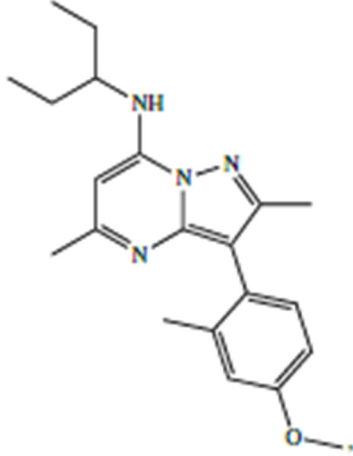
wherein the metabolic parameter comprises fasting glucose, HbA1c level, insulin sensitivity, or a lipid profile, or a combination thereof.

EX1001, 99:1–101:22; *see also* Appendix B (attached)..

Compound Structure in Claim 1	Letter Designation	Synonyms and/or IUPAC name (Provided for Easy Reference)
	A	3-[4-Bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-a]pyrimidine] EX1091 (PubChem CID 24758885)

Compound Structure in Claim 1	Letter Designation	Synonyms and/or IUPAC name (Provided for Easy Reference)
	B	3-(4-Bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine EX1092 (PubChem CID 24898976)
	C	Tildacerfont SPR-001 LY-2371712 EX1059 (PubChem CID 134694266)
	D	Verucerfont NBI-77860 GSK-561679 EX1090 (PubChem CID 11596613)

Compound Structure in Claim 1	Letter Designation	Synonyms and/or IUPAC name (Provided for Easy Reference)
	E	NBI-30775 R-121919 EX1093 (PubChem CID 9821250)
	F	NBI-34041 SB-723620 EX1094 (PubChem CID 9888194)
SSR-126374,	G	

Compound Structure in Claim 1	Letter Designation	Synonyms and/or IUPAC name (Provided for Easy Reference)
	H	Crinecerfont SSR-125543 EX1033 (PubChem CID 5282340)
	I	Antalarmin EX1096 (PubChem CID 177990)
	J	DMP-904 EX1095 (PubChem CID 9884878)

181. It is my opinion that Claim 1 is obvious over Grigoriadis (EX1006), Richard, (EX1012), and Yu (EX1067).

1. “A method of changing a metabolic parameter of a subject having a testicular adrenal rest tumor (TART) or an ovarian adrenal rest tumor (OART)”

182. As described above in paragraphs 160–163, Grigoriadis teaches “[c]ompositions and methods for treating congenital adrenal hyperplasia” and describes a number of different CRF1 receptor antagonists for treatment of CAH, including NBI-77860 (verucerfont) and SSR-125543 (crinecerfont). EX1006, [0002], [0051], [0054] and table on pages 4 and 6. And, as Grigoriadis describes, the goals of CAH treatment include “improv[ing] the health, well-being, quality of life, and [managing] related disorders.” EX1006, ¶ [0002], [0005]. Such related disorders include “testicular adrenal rest tumors in men.” EX1006, ¶ [0044]. A POSA reading Grigoriadis would understand that it teaches treating not just CAH, but also its related disorders including “testicular adrenal rest tumors in men.”

183. As Grigoriadis discusses, conventional treatment for CAH patients requires lifelong treatment with supraphysiological doses glucocorticoids. EX1006, ¶ [0005]. But the supraphysiological doses of glucocorticoids used to treat CAH patients increase the prevalence of negative side effects such as cardiovascular disease, obesity, hypertension, insulin resistance, glucose intolerance, and decreased bone-mineral density. EX1006, ¶ [0046]–[0047]. They

can also impede “statural growth” (increase in height over time) in children.

EX1006, ¶¶ [0069]. However, as Grigoriadis describes, administering a CRF1 receptor antagonist for treating CAH and its related disorders “permits use of lower, more physiological doses of hydrocortisone in subjects with CAH and thus reduces treatment-associated side effects.” *Id.*, ¶ [0040]. Again, hydrocortisone is a glucocorticoid commonly used to treat CAH patients. EX1006, ¶¶ [0047], [0070].

184. A POSA would understand that Grigoriadis teaches (or at least suggests) that administering a CRF1 receptor antagonist such as verucerfont or crinecerfont to a TART patient is paired with a decrease in glucocorticoid administration, and that this reduction in glucocorticoid administration is associated with a decreased risk of cardiovascular disease, obesity, hypertension, insulin resistance, glucose intolerance, decreased bone-mineral density, and statural growth inhibition. Of these side effects, insulin resistance and glucose intolerance are well-known metabolic parameters or metabolic abnormalities. EX1012, 2:34-38.

185. Accordingly, a POSA would have reasonably expected a change in a metabolic parameter based on the teachings of Grigoriadis, i.e., a lowered risk of insulin resistance (which corresponds to improved insulin sensitivity) and a lowered risk of glucose intolerance. As explained above (paragraph 47), glucose

intolerance can be measured by the amount of fasting glucose in the plasma. The greater the amount of fasting glucose, the higher the level of glucose intolerance, and vice versa. *See* paragraph 196, below.

186. Richard confirms the teachings of Grigoriadis. Richard describes “changing a metabolic parameter” by administering a CRF1 receptor antagonist. Richard’s Compound A (crinecerfont—*see* paragraph 165, above), when administered to Zucker rats (a rat model of obesity), reduced circulating glucose levels, improved insulin sensitivity, reduced circulating triglyceride levels, and prevented fasting-induced reduction of triglycerides in obese rats. EX1012, 18:2-18, Figs. 3a-3g. A POSA would have had a reason to look to Richard to confirm that crinecerfont, in addition to treating a TART in a patient with CAH (as taught by Grigoriadis), would also change a metabolic parameter and, therefore, address the negative side-effects of supraphysiological glucocorticoid doses such as insulin resistance and glucose intolerance.

187. A POSA would have also had a reasonable expectation of success in changing such a metabolic parameter in a subject with TARTs by administering a CRF1 receptor antagonist such as verucerfont or crinecerfont. First, I note that claim 1 does not specify any particular direction, amount, or time of change. Grigoriadis teaches administering a CRF1 receptor antagonists to reduce ACTH levels, which serves as a treatment of CAH-related disorders, including TARTs.

EX1006, ¶¶ [0006], [0007], [0012], [0013], [0044]. Richard demonstrates that administration of crinecerfont changes fasting glucose levels, insulin sensitivity, and a lipid profile. EX1012, 18:2-18, Figs. 3a-3g. Together, this provides a POSA with a reasonable expectation that administering a CRF1 receptor antagonist will lower ACTH levels and change fasting glucose, insulin sensitivity, and/or a lipid profile in a patient with a TART.

188. While claim 1 requires only that the administration of the CRF1 receptor antagonist changes one of the recited metabolic parameters, it is also my opinion that it would also have been obvious to *treat* the TART. Yu (EX1067), as described above (paragraphs 167-170) describes a study that “was conducted to investigate the prevalence of TARTs in male patients with CAH, and characterize the manifestations to identify contributing factors to TART.” EX1067, 155. Yu’s study found a 61.5% prevalence of TARTs (8/13 male patients) using scrotal ultrasound. *Id.*, 155 (Results); 156 (Materials and Methods). On average, the patients with TARTs had a statistically higher serum ACTH level (which was above Yu’s threshold for “uncontrolled disease”) than patients without TARTs (which was below Yu’s threshold for “uncontrolled disease”). *Id.*, 157–158. Five of the 8 TART patients were examined for TART development after initial diagnosis. *Id.*, 158. Of those five, three patients had a decrease in TART size, one slightly increased, and one had no changes. *Id.* Based on these results, and

previous studies that identified ACTH as “the most frequently suggested causative and growth promoting factor in TARTs,” Yu concluded that the study “support[ed] the previous hypothesis that exposure to high concentrations of the serum ACTH level can be a major factor in the development of TARTs,” which “could be taken into consideration for the treatment of TARTs.” *Id.*, 159.

189. A POSA would have understood from Yu that elevated ACTH levels are associated with TART prevalence and size in male CAH patients—in line with Yu’s results. A POSA, with the understanding that CRF1 receptor antagonists lower ACTH levels as taught by Grigoriadis, and Yu’s teachings directly linking TARTs to elevated ACTH levels, would have been motivated to treat a subject with TARTs by administering Grigoriadis’ CRF1 receptor antagonists (e.g., verucerfont or crinecerfont) to reduce ACTH levels and, as a result, treat TARTs.

190. I note the ’084 patent states that “treating” can refer to “any indicia of success in the therapy or amelioration of an injury, disease, pathology or condition.” EX1001, 26:60-62. As discussed above, and as Grigoriadis teaches, biomarkers such as ACTH levels can be used to monitor treatment efficacy. EX1006, [0060]. And, in the context of treating CAH and its related disorders, reduction of ACTH is an indication of treatment efficacy. *See, e.g.*, EX1006, [0044]. Furthermore, Grigoriadis contains human clinical data that demonstrates that the CRF1 receptor antagonist NBI-77860 (verucerfont) lowers ACTH levels

compared to placebo. *See, e.g.*, EX1006 at Examples 5 and 6 (paragraphs [0087]-[0092] and Figures 4–5). These teachings provide a POSA with a reasonable expectation that TARTs can be treated with a CRF1 receptor antagonist disclosed in Grigoriadis, such as crinecerfont or verucerfont.

191. Taken together, the teachings of Grigoriadis and Yu provide a POSA with a reasonable expectation that administering a CRF1 receptor antagonist will lower ACTH levels, and accordingly, treat TARTs.

2. “comprising administering to the subject in need thereof a small molecule corticotropin-releasing factor type-1 (CRF₁) antagonist, or a pharmaceutically acceptable salt thereof,”

192. Grigoriadis teaches administering “an effective amount of” its CRF1 receptor antagonists (as well as pharmaceutical compositions comprising them) to a “subject in need thereof.” EX1006, ¶ [0040], [0049], [0050], [0061], [0070]. As one example, Grigoriadis teaches administering an effective amount of the “potent” CRF1 receptor antagonist NBI-77860, also referred to as verucerfont—labeled as Compound “D” in the chart of claim 1 molecules above. *Id.* at ¶ [0051], [0052], [0061], [0070], [0090]–[0093]. As another example, Grigoriadis teaches administering crinecerfont—labeled as Compound “H” in the chart of claim 1 molecules above. *Id.* ¶ [0054]. Grigoriadis reports that administration of CRF1 receptor antagonists was “found to directly inhibit ACTH release in patients with

CAH,” thereby allowing normalization of androgen production. *Id.* at ¶ [0007]; *see also* ¶¶ [0040], [0050], [0051], [0052], [0061], [0070], [0090]–[0093].

3. “wherein the small molecule CRF₁ antagonist is: . . . ”

193. Grigoriadis teaches administering at least two of the small molecule CRF₁ antagonists listed in claim 1 (and depicted in the table following paragraph 180 above). For example, NBI-77860 (verucerfont, claimed compound “**D**” in the table above) and SSR-125543 (crinecerfont, claimed compound “**H**” in the table above). EX1006, [0013], [0051]. While the ’084 patent provides only the structure and not the name of compound “**D**,” a POSA would have compared the compound described and depicted in paragraph [0051] of Grigoriadis with the claimed structure “**D**” and readily understood that these are the same compound. Likewise, while the ’084 patent provides only the structure and not the name of compound “**H**,” a POSA would have compared the compound “SSR-125543” on page 6 of Grigoriadis (middle) and readily understood that these are the same compound.

4. “and wherein the metabolic parameter comprises fasting glucose, HbA1c level, insulin sensitivity, or a lipid profile, or a combination thereof”

194. As described above, Grigoriadis teaches that CAH patients have an increase in the prevalence of insulin resistance and glucose intolerance due to supraphysiological doses of glucocorticoids. EX1006, [0046]–[0047]. Richard

describes “changing a metabolic parameter” by administering a CRF1 receptor antagonist alone. Richard’s Compound A (crinecerfont—*see* paragraph 165, above), when administered to Zucker rats (a rat model of obesity), reduced circulating glucose levels, improved insulin sensitivity, reduced circulating triglyceride levels, and prevented fasting-induced reduction of triglycerides. EX1012, 18:2-18, Figs. 3a-3g.

195. While Grigoriadis uses the term “insulin resistance,” a POSA would have understood that “insulin resistance” and “insulin sensitivity” are two ends of the spectrum of a patient’s response to insulin. Insulin resistance refers to the body’s inability to respond properly to insulin and the resulting need for higher amounts of insulin to lower blood glucose levels. Insulin sensitivity refers to the normal responsiveness of target tissues to insulin, including glucose uptake into muscle and fat tissue, suppression of glucose production in the liver, and inhibition of the synthesis of fat. If a person is insulin resistant, that person would also have impaired sensitivity to insulin. A POSA would have understood that as insulin resistance increases, insulin sensitivity decreases. EX1108 (Moller), 941.

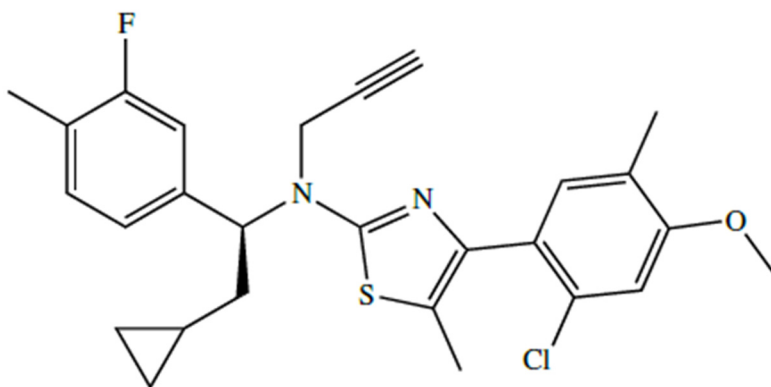
196. Similarly, while Grigoriadis uses the term “glucose intolerance,” a POSA would have understood that glucose intolerance can be measured by two hour post-load glucose of 140-199 mg/dl. Impaired glucose tolerance and impaired fasting glucose are distinct but overlapping categories. A POSA would

have understood that elevated fasting glucose is an indication of glucose intolerance. EX1105 (Fujimoto), 9S.

D. Dependent Claims

1. **Claim 3 — “wherein the small molecule CRF1 antagonist is [crinecerfont] or a pharmaceutically acceptable salt thereof”**

197. Claim 3 recites: “[t]he method of claim 1, wherein the small molecule CRF₁ antagonist is:



or a pharmaceutically acceptable salt thereof. EX1001, 101:50–102:12.

198. As discussed above, this structure is Neurocrine’s crinecerfont, which is disclosed in Grigoriadis as a CRF1 receptor antagonist that inhibits ACTH release in patients with CAH. Crinecerfont is compound “**H**” in the chart of claim 1 molecules above. *See* above, paragraph 66; EX1006, ¶¶ [0013], [0054], page 6.

2. **Claim 4 — “wherein the metabolic parameter is insulin sensitivity”**

199. As described above, Grigoriadis teaches that CAH patients have an increase in the prevalence of insulin resistance and glucose intolerance due to

supraphysiological doses of glucocorticoids. EX1006, [0046]-[0047]. Richard describes “changing a metabolic parameter” by administering a CRF1 receptor antagonist alone. Richard’s Compound A (crinecerfont—*see* paragraph 165, above), when administered to Zucker rats (a rat model of obesity), improved insulin sensitivity. EX1012, 18:2-18, Figs. 3a-3g.

200. While Grigoriadis uses the term “insulin resistance,” a POSA would have understood that “insulin resistance” and “insulin sensitivity” are two ends of the spectrum of a patient’s response to insulin. Insulin resistance refers to the body’s inability to respond properly to insulin and the resulting need for higher amounts of insulin to lower blood glucose levels. Insulin sensitivity refers to the normal responsiveness of target tissues to insulin, including glucose uptake into muscle and fat tissue, suppression of glucose production in the liver, and inhibition of the synthesis of fat. If a person is insulin resistant, that person would also have impaired sensitivity to insulin. A POSA would have understood that as insulin resistance increases, insulin sensitivity decreases. EX1108 (Moller), 941.

3. Claim 5 — “wherein the subject has congenital adrenal hyperplasia (CAH)”

201. Claim 5 recites “[t]he method of claim 1, wherein the subject has congenital adrenal hyperplasia (CAH).” EX1001, 102:16–17.

202. Grigoriadis teaches a method of treating CAH by administering an effective amount of a CRF1 receptor antagonist, which directly inhibits ACTH

release in patients with CAH, leading to normalizing the production of androgen hormones. EX1006, ¶¶ [0007], [0040].

4. Claims 8–12 — “wherein the small molecule antagonist is administered at a dose of . . .”

203. Claims 8-12 relate to doses. Claim 8 recites “[t]he method of claim 1, wherein the small molecule CRF₁ antagonist is administered at a dose of about 10 mg/day to about 400 mg/day to the subject.” EX1001, 102:21–23. Claim 9 recites “[t]he method of claim 10, wherein the small molecule CRF₁ antagonist is administered at a dose of about 50 mg.” EX1001, 102:24–25. Claim 10 recites “[t]he method of claim 8, wherein the small molecule CRF₁ antagonist is administered at a dose of about 100 mg.” EX1001, 102:26–27. Claim 11 recites “[t]he method of claim 8, wherein the small molecule CRF₁ antagonist is administered at a dose of about 200 mg.” EX1001, 102:28–29. Claim 12 recites “[t]he method of claim 8, wherein the small molecule CRF₁ antagonist is administered at a dose of about 400 mg.” EX1001, 102:30–31.

204. Grigoriadis teaches that a dose of a CRF1 receptor antagonist “is about 50 to 1000 mg.” EX1006, ¶ [0063]. In Example 5, Grigoriadis discloses the administration of single doses (50 mg and 400 mg) of NBI-77860 (verucerfont, compound **D** in the Table following paragraph 180). EX1006, ¶¶ [0088]–[0089]. A POSA would have understood that the single doses (50 mg and 400 mg) were administered once per day. Grigoriadis explicitly mentions that the CRF1 receptor

antagonist is administered in single doses in various embodiments. EX1006, ¶ [0063]. For example, Example 6 discloses the administration of single doses (300 mg and 600 mg) of NBI-77860 (verucerfont). EX1006, ¶¶ [0091]–[0093].

205. While Grigoriadis does not expressly disclose administration of a daily dose of “about 100 mg” (claim 10) or “about 200 mg” (claim 11) of the CRF1 receptor antagonist, these doses would have been obvious, for example based on Grigoriadis’s dose range of “about 50 to 1000 mg” and/or Grigoriadis’s disclosure of individual doses of 50 mg and 300 mg. EX1006, ¶¶ [0063], [0088]–[0089], [0091]–[0093]. I find nothing in the ’084 patent teaching or suggesting to a POSA that a dose of 100 mg or of 200 mg produces any unique or unexpectedly improved result compared to Grigoriadis’ “about 50 to 1000 mg” range or the 50 mg or 300 mg single doses. I also find nothing in Grigoriadis suggesting that a POSA should not use a dose of “about 100 mg” or “about 200 mg.” Rather, Grigoriadis teaches that the use of the minimum effective dose is preferred. EX1006, ¶ [0063]. Thus, a POSA would have looked to the lower end of the range disclosed in Grigoriadis to determine appropriate dosing.

5. Claim 13 — “wherein the small molecule CRF₁ antagonist is administered to the subject once per day”

206. Claim 13 recites “wherein the small molecule CRF₁ antagonist is administered to the subject once per day.” EX1001, 102:32–33. Grigoriadis teaches this. In Example 5, Grigoriadis discloses the administration of single doses

(50 mg and 400 mg) of NBI-77860 (verucerfont, compound D in the Table following paragraph 180). EX1006, ¶¶ [0088]–[0089]. A POSA would have understood that the single doses (50 mg and 400 mg) were administered once per day. For example, Example 5 discloses “single oral doses” of NBI-77860 (verucerfont). EX1006, ¶ [0087]. As another example, Example 6 discloses the administration of single doses (300 mg and 600 mg) of NBI-77860 (verucerfont). EX1006, ¶¶ [0091]–[0093].

6. Claims 15 and 16 — “administered orally” / “formulated as a capsule or tablet”

207. Claim 15 recites “[t]he method of claim 1, wherein the small molecule CRF₁ antagonist is administered orally.” EX1001, 102:35-36. Claim 16 recites “[t]he method of claim 1, wherein the small molecule CRF₁ antagonist is formulated as a capsule or tablet.” EX1001, 102:37–38.

208. These claims relate to the route of administration (orally) or the dosage form (capsule or tablet). Grigoriadis teaches each. For example, Grigoriadis states that a CRF₁ receptor antagonist “may be administered to a subject in need by any one of several routes that effectively deliver an effective amount of the compound” including “for example, oral” administration. EX1006, [0065]. Grigoriadis also teaches that the “oral formulations” may be in the form of “tablets, powders, granules, or capsules.” EX1006, [0074].

7. Claims 17–19 — “wherein the administering reduces a plasma concentration of a biomarker comprising . . .”

209. Claim 17 depends from claim 1 and specifies that “administering reduces a plasma concentration of a biomarker comprising” 17-OHP, ACTH, or A4, among others. EX1001, 102:39-45. Claim 18, which depends on claim 17, requires that the biomarker “is selected from the group consisting of 17-OHP, ACTH, and A4.” EX1001, 102:46-48. Claim 19, which also depends on claim 17, specifies that the plasma concentration of the biomarker is at least 10% “from baseline.” EX1001, 102:49-50.

210. As Grigoriadis explains, 17-OHP, androstenedione (A4), testosterone, cortisol and ACTH are standard biomarkers that are used by endocrinologists to monitor the effects CRF1 receptor antagonists. EX1006, ¶ [0060]. Grigoriadis teaches that these biomarkers are “easily measured in both children and adults giving rapid and meaningful data regarding treatment impact.” *Id.*

211. In Example 6, Grigoriadis demonstrated the administration of NBI-77860 (verucerfont) to CAH patients resulted in “consistent and clinically meaningful reductions from predose levels of both 17-OHP and ACTH” as compared to placebo. *Id.*, ¶¶ [0090]-[0093], FIG. 5, FIG. 6. Following administration, 50% of patients had “at least a 50% decrease in 17-OHP and ACTH.” *Id.* A POSA would have understood that Grigoriadis’ Example 6 shows reduction of the plasma concentration of both 17-OHP and ACTH.

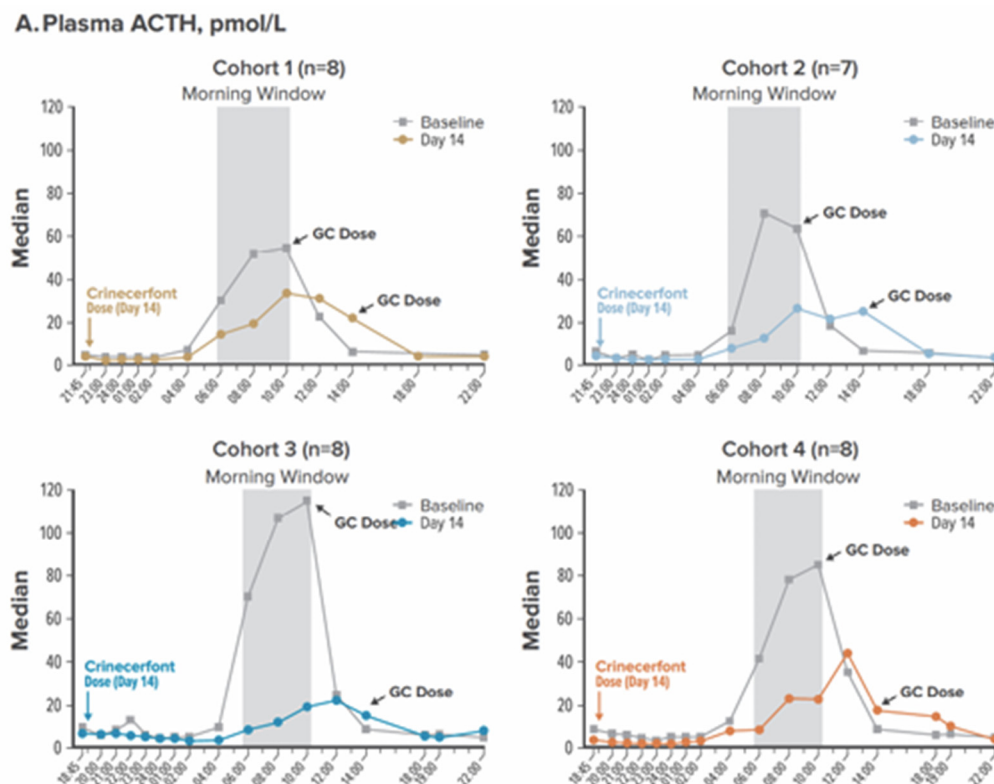
212. I understand from Neurocrine’s counsel that “baseline” in this context means “a series of samples taken from an untreated patient with CAH, prior to treatment at intervals that are time-matched to the sampling intervals to be taken from the patient treated with either a CRF1 receptor antagonist or placebo.” Grigoriadis teaches administering the CRF1 receptor antagonist crinecerfont to a CAH patient. EX1006, ¶ [0054]. In clinical trials, administration of crinecerfont to patients with classic CAH resulted in median reductions of approximately 50-70% in both ACTH and 17-OHP from baseline. EX1048, Figs. 2, 4. The administration of crinecerfont to CAH patients would necessarily result in an at least 10% reduction from baseline in both ACTH and 17-OHP in a patient. As discussed below, administration of crinecerfont leads to a greater than 10% reduction in a majority of patients. EX1048, Figs. 2, 4.

213. That crinecerfont causes a reduction of at least 10% from baseline compared to the patient’s pre-treatment baseline levels for both ACTH and 17-OHP is demonstrated by Auchus et al., “Crinecerfont Lowers Elevated Hormone Markers in Adults with 21-Hydroxylase Deficiency Congenital Adrenal Hyperplasia,” *The Journal of Clinical Endocrinology & Metabolism* 107(3) 801–812 (2022) (“Auchus”). EX1048, Figs. 2, 4. I understand that Auchus is not prior art to the ’084 patent. I rely on data from Auchus merely as confirmation that

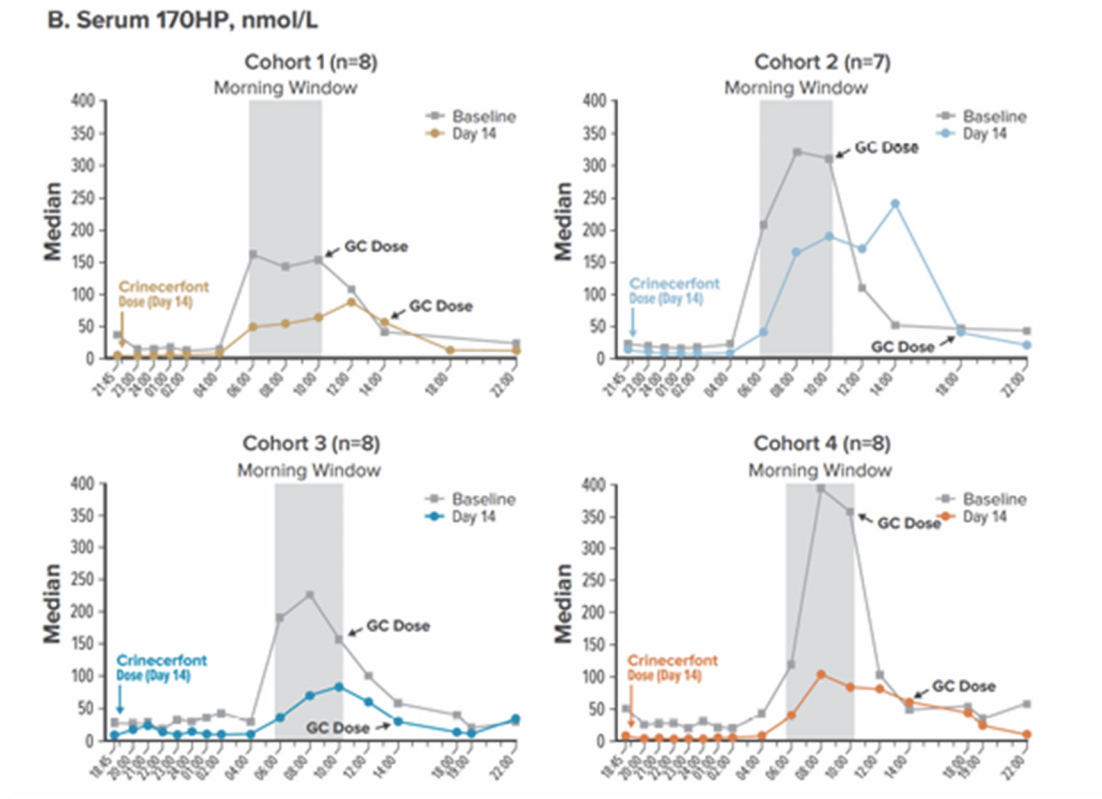
administration of crinecerfont to CAH patients as taught by Grigoriadis results in the hormone reductions claimed in the '084 patent.

214. Auchus' Figure 2 shows time-matched 24-hour profile data for four patient cohorts (1-4). EX1048, Fig. 2. As depicted in Figure 2, after 14 days of treatment with crinecerfont, all four of the patient cohorts showed a median percent reduction in morning-window ACTH and 17-OHP levels of greater than 10% (orange), relative to the patients' baseline (untreated) measurements (gray).

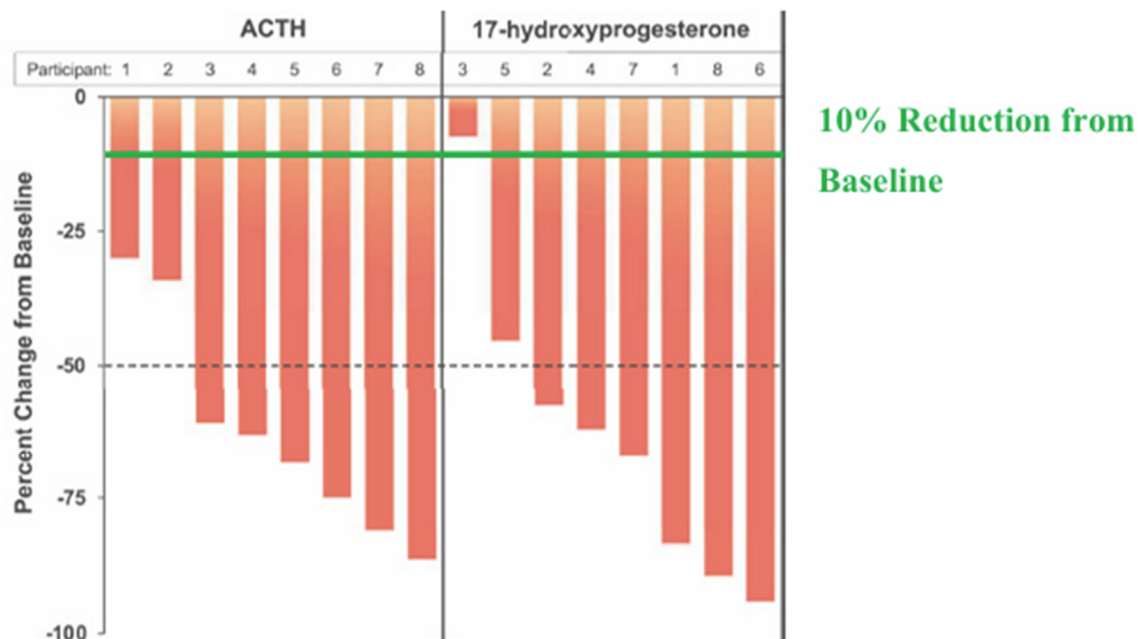
EX1048, Fig. 2. Panel A of Figure 2 (excerpted below) shows the decrease in biomarker ACTH.



215. Panel B of Figure 2 (excerpted below) shows the decrease in biomarker 17-OHP.



216. As show in Auchus' Figure 4 (reproduced below, with added annotation showing 10% reduction from baseline), every patient in Cohort 4 achieved over 10% reduction in ACTH following treatment with crinecerfont, as compared to the time-matched "baseline" samples. And 7 of 8 patients achieved over 10% reduction in 17-OHP. EX1048, Fig. 4.



217. Therefore, Auchus confirms that the administration of crinecerfont (as taught by Grigoriadis) reduces the plasma concentration of these biomarkers by at least 10%.

E. OBVIOUSNESS OF CLAIMS 6 AND 7

218. It is my opinion that dependent claims 6 and 7 would have been obvious over Neurocrine’s Grigoriadis (EX1006), especially in view of Richard (EX1012), Yu (EX1067), and Delfino (EX1064).

219. Claims 6 and 7 recite that the administration of the CRF1 antagonist “reduces a size of the TART or the OART” or “reduces a number of the TART or the OART,” respectively. EX1001, 102:17–20.

220. There is explicit disclosure of reduction in the size or number of tarts in, for example, Delfino (EX1064). As discussed above in Section XII.C., with respect to claim 1, it would have been obvious for a POSA to administer a CRF1 receptor antagonist to lower ACTH in TART patients, with a reasonable expectation of success at changing a metabolic parameter in the patient. Delfino describes clinical outcomes for such TART patients and, therefore, a POSA would have looked to Delfino for its teachings regarding those clinical outcomes.

221. Delfino and Yu both teach that TARTs are associated with elevated ACTH levels. EX1064 (Delfino), EX1067 (Yu), 157-158. Delfino, in conjunction with its longitudinal study, describes how normalizing ACTH levels in TART patients led to the disappearance of the TART or reduction in the diameter of the TART. EX1064, 386-387 (discussing the “reduction or disappearance” of TARTs after reduction of plasma ACTH levels). Disappearance of a TART is a reduction in the number of TARTs. Reduction in the diameter of a TART is a reduction in the size of the TART. Thus, a POSA would have had a reasonable expectation of success in reducing the size or the number of TARTs based on Delfino’s results.

F. OBVIOUSNESS OF CLAIM 14

222. It is my opinion that dependent claim 14 would have been obvious over Neurocrine’s Grigoriadis (EX1006), especially in view of Richard (EX1012), Yu (EX1067), and Howerton (EX1074).

223. Claim 14 specifies that the “CRF₁ antagonist is administered” “twice per day.” EX1001, 102:33–34. In my opinion, this limitation would have been obvious to a POSA at the time the application for the ’084 patent was filed, for example from the teachings of Grigoriadis as combined with Howerton.

224. There is explicit disclosure of administering a CRF₁ receptor antagonist twice per day in, for example, Howerton (EX1074, WO 2016/065177), which, as described above in paragraphs 173–174, also relates to administration of CRF₁ receptor antagonists, including some of the compounds in claim 1 of the ’084 patent. EX1074, cover page (57, Abstract); 2:1–24; 13:12–17; table spanning pages 13–32. Thus, in my opinion, a POSA seeking guidance on dosing regimens for Grigoriadis’s compounds would have looked to Howerton because it teaches dosing regimens for many of the same compounds. Howerton teaches that administration of a CRF₁ receptor antagonist to a human “may be carried out using known procedures, at dosages and for periods of time effective to treat a disease or disorder in the patient.” EX1074, 23:16-18.

225. Howerton explicitly describes one common way of dosing: using staggered or divided dosages (e.g., administering a total daily dose across multiple administrations throughout the day). *See* EX1074, 23:11–13; 23–25; 13–14; 31:2–5; 31:17–18. For example, dividing a daily dose between 1 to 4 times per day. EX1074, 31:2–3. As one specific example, Howerton describes dividing a daily

dose of 1 mg into two administrations of 0.5 mg with about a 12-hour interval between doses. *See* EX1074, 23:2–5. A POSA would have understood that this specific example is a twice-daily dosing regimen.

226. Howerton also describes administering the CRF1 receptor antagonists “in dosages that range from one to five times per day or more.” EX1074, 25:13–14. Howerton states that “all values that fall within [its] ranges” are “also contemplated by the present application.” EX1074, 31:29–33. Therefore, a POSA would have understood that dividing a daily dose between 1 to 4 times per day includes, for example, between 1 to 3 and 1 to 2 times per day as well as once, twice, three times, or four times daily.

227. A POSA would have readily combined Grigoriadis with Howerton’s explicit disclosure of dosing regimens (including a twice-daily dosing regimen) and found it obvious to administer the CRF1 receptor antagonists twice per day. A POSA would have reasonably expected that twice-daily dosing would be successful with Grigoriadis’s compounds because Howerton teaches a POSA to use twice-daily dosing with Grigoriadis’s compounds, such as verucerfont. I see nothing in the ’084 patent teaching that twice-daily dosing is anything new or produces any result that a POSA would not have already expected. From the viewpoint of a POSA, the ’084 patent treats the dosing regimens (once-daily, twice-daily, and thrice-daily) the same. EX1001, 59:39-60:16, 63:35-65:58, 68:20-

70:46 (once-daily), 60:16-53, 65:59-68:19, 70:58-73:8 (twice-daily), 60:53-61:22 (thrice-daily).

228. As a POSA would have understood that the dose and dosing regimen (including time of administration—*see, e.g.*, EX1074, 24:9–14), is a matter of determining the appropriate dose and dosing regimen for a particular patient or patient group.

229. Normally, the pituitary gland secretes ACTH in rhythmic pulses throughout the day based on CRF agonism, circadian regulation, and cortisol-mediated negative feedback. In CAH, patients, however, regulation is disrupted and ACTH levels remain chronically elevated. Moreover, the rhythmic ACTH pulses become both larger and more frequent.

230. Grigoriadis teaches that in some cases, a CRF1 receptor antagonist is administered prior to an expected circadian release of ACTH, for example, at bedtime. EX1006, ¶¶ [0007], [0066]. Grigoriadis’ generalization is based on the observation that “since most orally administered drugs have a Tmax [(the time it takes for a drug to reach its maximum concentration (Cmax) in the bloodstream after administration)] of several hours, dosing at 10 P.M., for example, which is 3-4 hours in advance of the expected circadian release of ACTH is desirable.” *Id.* ¶ [0066]. Treatment of CAH requires “normalization of hormone and steroid levels using a variety of medications from diagnosis in infancy through adulthood.”

EX1006, ¶ [0044]. Thus, a goal for ongoing treatment of CAH patients is not just to avoid individual ACTH spikes, but to regulate ACTH levels on a continual basis. *See, e.g.*, EX1006, ¶¶ [0004]–[0007], [0040], [0044].

231. A POSA would have recognized that in the case of small molecule drugs that require repeated oral intermittent dosing for continuous control (such as CRF1 receptor antagonism to control ACTH release), the goal is to reach a steady-state, i.e., the dose amount and timing needs to maintain consistent ACTH suppression throughout the day. Maintaining steady doses twice daily is more important than timing to the ACTH surge. A twice-daily dosing regimen (e.g., approximately every twelve hours, as taught by Howerton) is commonly used for small molecule therapeutics to maintain this pattern of stable and therapeutic drug levels. A twice-daily dosing regimen is also practical because it links doses to daily routines and improves patient adherence to further increase the consistency in controlling ACTH levels.

232. For at least these reasons, it would have been obvious to a POSA to provide for consistent control of ACTH levels throughout the day—by administering a CRF1 receptor antagonist in a twice-daily divided dose as taught by Howerton.

G. The '084 Patent's Allegedly "Unexpected Results" Would Not Have Been Unexpected

233. As discussed above in paragraphs 80–82 (Prosecution History), during the prosecution of an earlier application (the '694 application), Spruce submitted a Declaration from Dr. Chris Barnes, who was Spruce's Vice President and Project Team Leader at the time. EX1061, 19-22. Dr. Barnes stated that "treating TART in patients with CAH" was "uncertain[]" and "unpredictabl[e]" and, therefore, a POSA would not have believed that controlling ACTH levels (with either glucocorticoid therapy or CRF1 receptor antagonists) would treat TARTs in CAH patients with a reasonable expectation of success. EX1061, 20 (¶4), 21-22 (¶19). The Examiner credited Dr. Barnes' testimony, stating that it "discloses that the treatment of TARTs is unpredictable." EX1077, 7-8. However, in my opinion, Dr. Barnes' declaration and supporting references do not support the notion that reducing ACTH levels to treat TARTs would have been unexpected to a POSA.

234. First, as discussed in paragraphs 34–42, multiple references had already reported that TARTs are connected to elevated ACTH levels. Delfino reports that "[t]his study confirms the high prevalence of testicular adrenal rest tumors in patients with CAH and the major role played in its pathogenesis by high plasma ACTH levels." EX1064, 383. Yu likewise shows that male CAH patients with TARTs had elevated ACTH levels, as discussed above. EX1067, 156–59. Aycan reports that TARTs "are suppressed if serum ACTH is suppressed by the

higher-dose glucocorticoid treatment.” EX1068, 669. Clinical studies on CAH patients had also shown elevated ACTH levels in CAH patients with TARTs. EX1067 (Yu), 156–159. Furthermore, by the time of Spruce’s application, numerous clinicians and researchers had proposed reducing the development, size, or progression of TARTs by lowering ACTH levels in CAH patients. EX1067 (Yu), 158–159; EX1068 (Aycan), 669, EX1064 (Delfino), 386-387. For example, Delfino reports that TARTs “are reversible lesions, as shown by the reduction or disappearance after adequate replacement therapy to reduce plasma ACTH levels.” EX1064, 386-387.

235. Second, two of the references cited in Dr. Barnes’ declaration appear to be mischaracterized: Reisch (EX1070) and Mendes-dos-Santos (EX1071).

236. In the Examiner’s “Reasons for Allowance,” Reisch is described as teaching that “TARTs occur in patients over-treated with glucocorticoids and having suppressed ACTH levels, and no statistical differences were found between glucocorticoid doses in patients with or without TARTs having CAH.” EX1077, 7-8. The Examiner thus interpreted Reisch as teaching no connection between TARTs and ACTH levels. But this is incorrect. Reisch teaches that “TARTs are ACTH responsive” and that “ACTH-suppressive glucocorticoid treatment with dexamethasone efficiently reverses TART growth and restores sperm count and fertility.” EX1070, E1821. In my opinion, Reisch does not teach or suggest that

suppressing ACTH cannot treat TARTs. Reisch hypothesizes that TARTs are induced during fetal development, but not that TARTs cannot be “treated” by lowering ACTH levels.

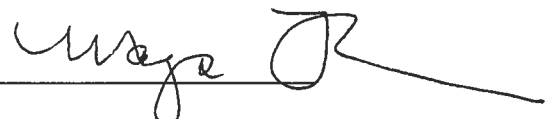
237. In the Examiner’s “Reasons for Allowance,” the Examiner describes Mendes-dos-Santos as teaching that “no association between TART development and...ACTH levels was found.” EX1077, 7-8. Mendes-dos-Santos did not study whether treatment of TARTs could be achieved by lowering ACTH levels. Mendes-dos-Santos studied when TARTs develop and factors associated with its development, including the clinical form of disease, CYP21A2 genotype, disease control, and presence of puberty. EX1071, 162. Further, Mendes-dos-Santos states that TARTs “are ACTH responsive” and that “intensifying treatment can lead to the regression of lesions.” *Id.* Mendes-dos-Santos also expressly teaches that “[s]tudies have shown that...suppressing ACTH, can lead to tumor regression in the short term and even to normal sperm count.” EX1071, 167. Thus, I do not agree with the Examiner or Dr. Barnes that Mendes-dos-Santos teaches a POSA that lowering ACTH levels will not lead to treatment of TARTs.

238. As discussed above in paragraphs 175–176, a POSA would have had a reasonable expectation that lowering ACTH levels by administering a CRF1 receptor antagonist (such as crinecerfont or verucerfont) would successfully treat TARTs.

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

240. I currently hold the opinions expressed in this declaration. My analysis may continue, and I may acquire additional information and/or attain supplemental insights that may result in additional observations. I reserve the right to offer additional opinions regarding the subject matter set forth in this declaration, including in response to any argument raised by Spruce, or in response to expert opinions offered on behalf of Spruce.

Date: 6/16/26

By: 
Maya Lodish, M.D.

APPENDIX A – CURRICULUM VITAE OF MAYA LODISH, M.D.

Name: Maya Beth Lodish, MD

Position: Professor of Clinical Pediatrics
Selna L. Kaplan Chair Distinguished Professorship in Pediatric
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Pediatrics
School of Medicine

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San Francisco, CA 94143
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EDUCATION

1994 - 1998	Dartmouth College, Hanover NH	B.A.	Cum Laude, Biochemistry and Molecular Biology
1999 - 2003	Yale University School of Medicine, New Haven, CT	M.D.	
2003 - 2006	Johns Hopkins Hospital, Baltimore, MD	Intern/ Resident	Internship & Residency in Pediatrics
2006 - 2009	National Institutes of Health, Bethesda, MD	Fellow	Fellowship in Pediatric Endocrinology
2010 - 2013	Duke University, Durham NC	M.H.Sc.	

LICENSES, CERTIFICATION

2006 Diplomate, American Board of Pediatrics

2006 Maryland Board of Physicians, License # 1124596

2009 Diplomate of the American Board of Pediatrics Sub-board of Pediatric Endocrinology

2011 Commonwealth of Virginia, Board of Medicine License #0101246122

2018 Medical Board of California, License #155103

PRINCIPAL POSITIONS HELD

2018 - present UCSF	Professor of Clinical Pediatrics Pediatrics; Selna Kaplan Distinguished Professorship
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OTHER POSITIONS HELD CONCURRENTLY

1998 - 1999	Boston Children's Hospital	Research Assistant	Division of Hematology-Oncology
2009 - 2012	National Institute of Child Health and Human Development (NICHD)	Assistant Clinical Investigator	Program on Developmental Endocrinology and Genetics (PDEGEN)
2009 - 2014	NICHD	Deputy Program Director	Fellowship in Pediatric Endocrinology
2012 - 2017	NICHD	Staff Clinician	PDEGEN
2015 - 2018	NICHD	Program Director	Fellowship in Pediatric Endocrinology
2017 - 2018	NICHD	Associate Research Physician	Developmental Endocrine Oncology and Genetics
2019 - present	UCSF	Chief, Division of Endocrinology	Pediatrics

HONORS AND AWARDS

1997	Tucker Foundation Community Service Fellowship	Dartmouth College
1998	Cum Laude	Dartmouth College
1998	Presidential Scholar	Dartmouth College
2000	NIH Medical Student Research Training Fellowship	Yale University School of Medicine
2003	William U. Gardner Thesis Prize	Yale University School of Medicine
2008	Clinical Category Poster Competition Award	Endocrine Society
2009	Presidential Poster Award	Lawson Wilkins Pediatric Endocrine Society
2012	Mentor Award	National Institute of Child Health and Human Development
2013	Merit Award for exceptional clinical support and management of in pediatrics	National Institute of Child Health and Human Development
2014	Elected to Society for Pediatric Research	Society for Pediatric Research

2014	Outstanding Reviewer Recognition Award	The Journal of Clinical Endocrinology and Metabolism
2015	Certificate of Appreciation for Valuable Contribution as IRB Member	Combined NeuroScience IRB
2015	John D. Crawford Visiting Professor	Massachusetts General Hospital
2016	Nominated by the NIH Fellows Committee for the Distinguished Clinical Teacher Award	Fellows Committee, NIH
2018	Society For Endocrinology Journal award: Endocrine Related Cancer	Society for Endocrinology
2020	President's Innovation Fund-San Francisco (PIF-SF) Grant Award	UCSF
2023	Invited Professorship, Sick Kids Hospital	University of Toronto, Sick Kids Division of Pediatric Endocrinology
2023	Excellence in Teaching Award in health professions education	UCSF Academy of Medical Educators
2024	Fellows leadership and advocacy group mentorship award	Fellows leadership and advocacy group, UCSF

CLINICAL SERVICES

2009 - 2018	Teaching Attending, Pediatric Endocrinology Service, NIH Clinical Center	3 months per year
2009 - 2018	Attending, Fellow's Outpatient Endocrine Clinic, NIH Clinical Center	44 sessions per year
2018 - present	Inpatient consult attending, Pediatric Endocrinology Service, Benioff Children's Hospital and Children's Hospital Oakland	1 month per year
2018 - present	Neuro-oncology multidisciplinary clinic team Endocrinologist	once per month
2018 - present	Outpatient clinical endocrinology attending physician, Benioff Children's Hospital SF and Benioff Children's Hospital Oakland	3-4 sessions per week
2025 - present	Pediatric thyroid nodule and cancer multidisciplinary clinic	once per month

MEMBERSHIPS

2002 - present American Academy of Pediatrics
 2006 - present Endocrine Society
 2008 - present Pediatric Endocrine Society
 2011 - present Children's Oncology Group
 2014 - present Society for Pediatric Research

2018 - present American Thyroid Association
 2019 - present American Diabetes Association
 2021 - present International Thyroid Oncology Group

SERVICE TO PROFESSIONAL ORGANIZATIONS

2010 - 2017	Hope for Hypothalamic Hamartoma	Board Member
2014 - 2017	Pediatric Endocrine Society	Leader, Sub-committee on Fellow Education
2015 - 2018	The Endocrine Society	Member, Clinical Endocrine Education Committee
2017 - 2020	Pediatric Endocrine Society	Leader, Sub-committee on Regional Meetings
2017 - present	The Endocrine Society	Strategic Planning Committee Invited Member
2017 - present	American Multiple Endocrine Neoplasia Support	Member, Medical Advisory Board
2017 - present	The Endocrine Society	Abstract Review
2018 - 2018	The Endocrine Society Annual Meeting Session: Pituitary Function and dysfunction	Session co-chair/moderator
2018 - 2018	NIH Center for Cancer Research: Cancer, Autoimmunity and Immunology, Autoimmune Endocrinopathies	Session co-chair/moderator
2019 - present	Children's Oncology Group Long-Term Follow-Up Guidelines Taskforce, Endocrine Late Effects Working Group – Pituitary Thyroid-Adrenal Silo	Member
2019 - present	Children's Oncology Group Executive Committee	Member
2019 - present	Endocrine Society Leadership Task Force	Member
2020 - present	American Thyroid Association Education Leadership Committee	Member
2021 - present	Children's Oncology Group Long-Term Follow-Up Guidelines Taskforce, Late Effects Working Group New Anticancer Agents	Silo Leader
2021 - 2022	THE GROWTH HORMONE RESEARCH SOCIETY: Safety of growth hormone replacement in survivors of cancer and intra-cranial and pituitary tumours	Committee member
2021 - 2022	Prolactin-Secreting Adenomas Consensus Workshop, the Pituitary Society	Committee Member
2023 - 2025	Pediatric Endocrine Society Annual Meeting Planning Committee	Committee Member

2023 - 2025	American Thyroid Association Annual Meeting Planning Committee	Committee Member
2023 - present	Pediatric Endocrine Society TRENDS Special Interest Group (Tumor Related Endocrine and Neuroendocrine Disorders)	co-chair
2024 - present	American Thyroid Association	Executive Board Member

SERVICE TO PROFESSIONAL PUBLICATIONS

2012 - 2016	Editorial Board Member Journal of Clinical Endocrinology & Metabolism
2012 - present	Ad Hoc Reviewer Pediatric Blood & Cancer
2013 - present	AdHoc Reviewer PLOS ONE
2015 - present	AdHoc Reviewer Journal of Clinical Oncology
2016 - present	AdHoc Reviewer Molecular and Cellular Endocrinology
2016 - present	AdHoc Reviewer The Journal of Pediatrics (2016, 2017, 2018)
2016 - present	AdHoc Reviewer Endocrinology, Diabetes and Metabolism Case Reports
2017 - present	AdHoc Reviewer Endocrine (2017)
2017 - present	AdHoc Reviewer BMC Medical Genetics (2017)
2017 - present	AdHoc Reviewer Endocrine-Related Cancer (2017)
2017 - present	AdHoc Reviewer Endocrine (2017)
2018 - present	AdHoc Reviewer Thyroid (2018)
2018 - present	AdHoc Reviewer JNCI Cancer Spectrum
2019 - present	AdHoc Reviewer The Lancet
2021 - present	Ad-Hoc Reviewer Journal of the American Medical Association

INTERNATIONAL INVITED PRESENTATIONS

2009	European Society for Paediatric Endocrinology and Lawson Poster Wilkins Pediatric Endocrine Society	
2011	The Endocrine Society	Invited Speaker
2015	The Endocrine Society	Invited Speaker
2015	Joint meeting of International Society for Pediatric and Adolescent Diabetes & Australasian Paediatric Endocrine Group	Invited Speaker
2016	European Congress of Endocrinology	Invited Speaker
2017	10th International Meeting of Pediatric Endocrinology	Poster
2018	The Endocrine Society	Speaker, Poster, Session Moderator

2020	The Endocrine Society	Invited Speaker
2022	The Pituitary Society	Invited Speaker
2023	McGill University	Invited Speaker
2023	University of Toronto	Invited Speaker
2023	Mexican Society of Pediatric Endocrinology	Invited Speaker
2023	The Endocrine Society	Invited Speaker
2024	The Endocrine Society	Invited Speaker
2025	International Pituitary Society Annual Meeting	Invited Speaker

NATIONAL INVITED PRESENTATIONS

2010	Children's Tumor Foundation	Invited Speaker
2010	Life With Cancer	Invited Speaker
2011	Childhood Cancer Survivorship Conference	Invited Speaker
2013	Department of Pediatrics-Division of Academics and Research Children's Hospital of the Greenville SC Hospital System	Invited Speaker
2014	Pediatric Academic Society	Invited Speaker
2014	Johns Hopkins University School of Medicine	Invited Speaker
2015	Society of Inborn Errors of Metabolism	Invited Speaker
2015	University of Maryland, Division of Endocrinology	Invited Speaker
2015	Massachusetts General Hospital	Invited Speaker
2015	Cornell University School of Medicine	Invited Speaker
2015	Riley Hospital for Children, Indiana University School of Medicine,	Invited Speaker
2017	Thyroid Cancer Survivors' Association	Invited Speaker
2017	University of California, San Francisco	Invited Speaker
2018	National Cancer Institute, Bethesda Maryland NCI Cancer Moonshot Initiative: Medullary Thyroid Cancer	Invited panel member
2018	Thyroid Cancer Survivor's Association	Invited Speaker
2018	St. Jude Children's Research Hospital	Invited Speaker
2018	Children's Hospital of Philadelphia Neuroendocrinology Symposium	Invited Speaker
2018	Children's Hospital Oakland Research Institute	Invited Speaker
2019	52nd Annual Advances & Controversies in Clinical Pediatrics	Invited Speaker
2019	Pediatric Academic Society Meeting	Invited Speaker

2019	Baylor College of Medicine, Texas Children's Hospital	Invited Speaker
2020	Pediatric Endocrine Society Meeting	Invited Speaker
2021	PEARL Pediatric Endocrine Association for Research and Learning, Seattle, Washington	Invited Speaker
2022	Pediatric Endocrinologists of the Rocky Mountains Annual Meeting October 2022	Invited Speaker
2022	New York University School of Medicine Department of Pediatrics Grand Rounds	Invited Speaker
2023	Pediatric Grand Rounds New York University School of Medicine	Invited Speaker
2023	Pediatric Endocrine Society Meeting	Symposium Leader
2023	American College of Surgeons Annual Meeting, Boston, MA	Invited Speaker
2024	Pediatric Endocrine Society Meeting	Symposium Leader
2025	Pediatric Endocrine Society Meeting	Invited Speaker
2026	American Thyroid Association Meeting, Scottsdale, AZ	Invited Speaker

REGIONAL AND OTHER INVITED PRESENTATIONS

2010	NICHD Scientific Retreat for Investigators	Invited Speaker
2013	NICHD Exchange: "Pediatric Cancer: Perspectives and Promises"	Invited Speaker
2014	NIH Research Festival	Invited Speaker
2014	Combined Neuroscience IRB Retreat	Invited Speaker
2016	NIH Clinical Center Grand Rounds	Invited Speaker
2016	National Cancer Institute Symposium on Cancer Health Disparities	Invited Speaker
2017	Johns Hopkins University School of Medicine and National Institutes of Health Joint Perioperative Medicine Conference.	Invited Speaker
2017	Children's National Health Systems Pediatric Endocrine Conference	Invited Speaker
2017	NIH Clinical Center Pediatric Nursing Team	Invited Speaker
2017	Pediatric Endocrinology Metabolism and Genetics Research Conference	Invited Speaker
2018	Symposium to honor Dr. Felix Conte	Invited Speaker
2019	Advances and Controversies in Clinical Pediatrics	Invited Speaker
2019	Pediatric Oncology Grand Rounds UCSF	Invited Speaker
2020	Pediatric Genetics Educational Conference	Invited Speaker

2020	Stanford University Endocrine Grand Rounds	Invited Speaker
2021	Pediatric Grand Rounds, Benioff Children's hospital Oakland	Invited Speaker
2021	Child and Adolescent Health Equity in Scholarship (SIP) Session Speaker	Invited Speaker
2021	Early Career Forum (ECF) Workshop. Your session, Know Your Options: Career Paths within Clinical Endocrinology and Research, Endocrine Society	Invited Speaker
2022	Annual meeting of the Organization of Pediatric Endocrinologists (OPEC)	Invited Speaker
2022	Pediatric Endocrinologists of the Rocky Mountains (PERM)	Invited Speaker
2025	Pediatric Interest Group UCSF School of Medicine	Invited Speaker
2026	Western Medical Research Conference	Invited Speaker

CONTINUING EDUCATION AND PROFESSIONAL DEVELOPMENT ACTIVITIES

2018 Academy of Medical Educators: Narrative in Medicine Workshop, UCSF

2018 Research-Related Resources Symposium at UCSF

2018 Completed courses in Collaborative Institutional Training Initiative to be approved as an investigator in CTEP / Children's Oncology Group

2020 Diversity, Equity, and Inclusion Championing Training

2020 Leadership Development Course through Pediatric Endocrine Society

2022 AMSPDC Pediatric Division Directors Leadership Program.

2024 UCSF Connected Leadership Development Program

2024 Educator Essentials: Teach for UCSF Certificate Program UCSF center for faculty educators

2025 Alabama pilgrimage through UCSF Office of Diversity and Outreach and the Center for Community Engagement, and GLIDE's Center for Social Justice

GOVERNMENT AND OTHER PROFESSIONAL SERVICE

2009 - 2018	Graduate Medical Education Committee, NIH Clinical Center	Member
2014 - 2014	European Research Council	Grant Reviewer
2016 - 2016	NIDDK Institutional K12	Grant Review Committee Member
2016 - 2016	Luxembourg National Research Fund	Grant Reviewer
2018 - 2018	Children with Cancer UK Clinical PhD & Training Studentships	Grant Reviewer
2018 - present	UpToDate	Peer Reviewer

2018 - 2018	Association for Clinical and Translational Science	Mock Study Section Member
2019 - 2019	Fanconi Anemia Research Fund 2019 grant review process	Grant Reviewer
2020 - 2020	French National Research Agency	Grant Reviewer
2021 - 2021	NIDDK T32 Training Grant	Grant Reviewer
2022 - 2022	NIDCR Study Section	Invited Member
2025 - 2025	Pediatric Cancer Research Foundation grant review committee	Grant Reviewer
2025 - 2025	Albert Einstein College of Medicine K23 Mock Study Section review	Mock Study Section Member

UNIVERSITY SERVICE - SYSTEM

2022 - 2023	California Children's Services (CCS)	Medical Consultant Corrective Action Plan
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UNIVERSITY SERVICE - SCHOOL OF MEDICINE

2018 - present	UCSF Pediatric Residency Selection Committee	Interviewer for residency candidates
2018 - present	Pediatric Endocrinology Fellowship Program Annual Evaluation Committee	Committee Member
2019 - present	CMC preceptorship for medical students	preceptor
2021 - 2021	Search Committee for the Director of the Diabetes Center	Selection Committee Member
2023 - present	Search Committee for Adult Endocrinology Faculty Position	Selection Committee Member
2026 - present	UCSF School of Medicine Admissions Interview Committee	Interviewer

DEPARTMENTAL SERVICE

2019 - present	Division Chief, Pediatric Endocrinology	Division Chief
2021 - 2021	Search Committee, Division Chief of Pediatric Hematology	committee member
2020 - 2021	Department of Pediatrics Faculty Incentive Committee	committee member
2022 - present	Department of Pediatrics Senate Series Promotion Committee	committee member, co-chair since 2024
2023 - 2025	Department of Pediatrics Compensation Committee	committee member
2025 - present	Pediatric Complex Care Committee	committee member
2025 - present	Miller Endowed Chair Search Committee	Chair

2025 - present President's Physician Executive Council	member
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UNIVERSITY SERVICE - OTHERS

2004 - 2006	Johns Hopkins Pediatric Residency Curriculum Committee Member	Baltimore, MD
2006 - 2008	NICHD annual fellows retreat steering committee member	Bethesda, MD
2007 - 2009	NICHD Quality Assurance Committee Fellows Representative	Bethesda, MD
2009 - 2018	Member, Graduate Medical Education Committee, National Institutes of Health Clinical Center (NIH CC)	Bethesda, MD
2010 - 2015	Member, Combined Neuroscience Institutional Review Board, NIH CC	Bethesda, MD
2012 - 2018	Member, Tenure and Promotion Committee, National Institute of Child Health and Human Development	Bethesda, MD
2014 - 2018	Member, Pediatric Care Committee, NIH Clinical Center	Bethesda, MD
2017 - 2018	Member, NICHD Scientific Retreat Planning Committee	Bethesda, MD
2022 - 2023	Member, Scholarship Oversight Committee, Children's Hospital of Philadelphia	Philadelphia, PA

COMMUNITY & PUBLIC SERVICE

2006 - 2006	Mercy Medical Mission / Johns Hopkins Tropical Medicine Elective	Physician member team in Chulucanas, Peru
2013 - 2013	Johns Hopkins Women's Pre-Health Leadership Society	Invited Speaker
2013 - 2015	Montgomery County Public Schools	Led STEM classes for first graders
2015 - 2016	The Children's Inn at NIH	Marathon Team Member
2016 - 2018	Montgomery County Public Schools Health Council	Physician Member
2017 - 2017	American Red Cross	Blood Drive Leader
2018 - 2018	The Gift of Life Bone Marrow Registry	Leader of Drive to enroll participants into registry
2018 - present	Swim Across America	Team member
2019 - present	Bearskin Meadow Diabetes Camp	camp physician
2019 - 2019	Berkeley High School "STEMINISM" club	invited speaker
2025 - present	UCSF Pediatric Brain Tumor Family Day	Invited Speaker

FORMAL TEACHING

Date	Course No. & Title	Teaching Contribution	School	Class Size
2019 - 2019	Pediatrics 110 Small Group Teaching	Small Group leader	Medicine	15
2020 - 2022	121C Small Group Teaching	small group leader	Medicine	15
2021 - present	Foundations 1 Course IDS 122A Renal, Endocrine, GI, Nutrition (REGN)	Small Group Leader	Medicine	15
2022 - 2023	Foundations 1 Course IDS 121C REGN MS1 core lecture on Diabetes	Lecture	Medicine	120
2023 - present	Foundations 1 Course IDS 121C REGN MS1 core lecture on Thyroid, core lecture on disorders of Adrenal, Pituitary and Hypothalamus	Lecture	Medicine	120
2026 - present	PEDS 130.17 CIEEx - Pediatric Endocrinology Subspecialty Elective	Elective Director	Medicine	1-3

INFORMAL TEACHING

2007 - 2011 Becoming an Effective Scientist, Lecture and Journal Club Leader at NIH CC

2009 - 2015 Clinical Protocol Mechanics- Advanced Nursing Seminar at NIH CC

2009 - 2018 2-3 months per year in-patient teaching attending for Pediatric Endocrinology at NIH CC

2009 - 2018 Supervision of fellows, visiting residents, rotating medical students in the Pediatric Endocrinology Outpatient Clinic, 44 sessions per year

2009 - 2018 Weekly Pediatric Endocrinology rounds, Research Conference, Endocrine grand Rounds, and Research conference, 4 hours per week

2009 - 2018 Lectures to pediatric endocrine and adult endocrine fellows, as well as board - review interactive question sessions 2 hours per week

2009 - 2018 Consultations from referring physicians at NIH Clinical Center

2018 - present weekly case conference + monthly journal club

2018 - present Adolescent health Seminar, Division of Adolescent and Young Adult Medicine lecture on Abnormal Puberty for Nursing School

2018 - present Pediatric Residency Noon Conference

2019 - present Endocrinology Fellowship Didactic Series

2021 - present Preceptor for IDS 125 SPAN: Specialty Practice Ambulatory Sub-Internship for a 4th year medical student

PREDOC STUDENTS SUPERVISED/MENTORED

Date	Name	Program or School	Mentor Type	Role	Current Position
2011- 2011	Brooke (Lokie) Clampitt	Penn State College of Medicine Summer Internship Program at NIH	Research/Scholarly Mentor	Mentor for scholarly activity, on BMD in NF-1	Pediatrician in practice
2011- 2013	Urania Dagalakis	Albany College of Medicine Intramural Research Training Award NIH	Research/Scholarly Mentor	Mentor for scholarly activity on puberty and tumor growth in NF-1	Asst Prof of Peds, George Washington on SOM
2012- 2012	Laura Libuit	Howard U. Medical Student	Research/Scholarly Mentor	Supervise summer research project: Gender differences in pediatric Cushing disease	Anesthesiologist at Virginia Commonwealth University
2013- 2013	Juliana Biro	Bard College Undergraduate Summer Student	Research/Scholarly Mentor	Supervise summer research project: Ectopic ACTH/CRH tumors	Fellow in Peds Endo Children's Hospital of Orange County
2015- 2017	Cynthia Tsay	Medical Student, Yale University	Research/Scholarly Mentor	Thesis advisor: Genetics of pituitary adenomas in Harvey Cushing's collection	Assistant Professor of Medicine at Weill Cornell Medicine

Date	Name	Program or School	Mentor Type	Role	Current Position
2015- 2015	Sara Rahman	Medical Student, Quinnipiac University	Research/Scholarly Mentor	Supervise clinical research project: Kidney Stones in pediatric Cushing Syndrome	Fellow in Urogynecology Cleveland Clinic
2015- 2016	Leah Birdwell	U. of Maryland Undergraduate Senior Project mentee	Research/Scholarly Mentor	Supervise clinical research project: Coagulation abnormalities in pediatric Cushing Syndrome	Practicing pediatrician in Roanoke, VA
2021- 2022	Taylor Vasquez	Medical Student UCSF	Co-Mentor/Clinical Mentor	SPAN mentor	Resident in Peds, Stanford University
2026- 2026	Sebastian Castillo	Medical Student UCSF	Co-Mentor/Clinical Mentor	SPAN mentor	In training

POSTDOC FELLOWS/RESIDENTS SUPERVISED/MENTORED

Date	Name	Fellow	Mentor Type	Faculty Role	Current Position
2009- 2010	Radha Nandagopal	Pediatric Endocrine Fellow	Co-Mentor/Clinical Mentor	Clinical supervision	Asst Professor of Medicine Washington State University
2009- 2011	Angela Delaney	Pediatric Endocrine Fellow	Co-Mentor/Clinical Mentor	Clinical supervision	Director, Division of Endocrinology St. Jude

Date	Name	Fellow	Mentor Type	Faculty Role	Current Position
2009- 2011	Melissa Crocker	Pediatric Endocrine Fellow	Co-Mentor/Clinical Mentor	Clinical Supervision	Asst Prof of Peds, Children's Hospital Boston
2009- 2012	Alison Boyce	Pediatric Endocrine Fellow	Co-Mentor/Clinical Mentor	Clinical supervision	Staff Clinician in Skeletal Clinical Studies Unit at NIH
2010- 2013	Youn Hee Jee	Pediatric Endocrine Fellow	Co-Mentor/Clinical Mentor	Clinical supervision	Assoc prof Children's National
2010- 2013	Evgenia Gourgari	Pediatric Endocrine Fellow	Research/Scholarly Mentor, Project Mentor, Career Mentor, Co-Mentor/Clinical Mentor	Clinical supervision, research mentor adrenal phenotype in PCOS	Asst. Prof of Peds Georgetown University SOM
2011- 2014	Lars Ola Nilsson	Pediatric Endocrine Fellow	Co-Mentor/Clinical Mentor	Clinical supervision	Asst. Prof Karolinska Institute, Stockholm, Sweden
2011- 2014	Aikaterini Nella	Pediatric Endocrine Fellow	Research/Scholarly Mentor, Project Mentor, Career Mentor, Co-Mentor/Clinical Mentor	Clinical Supervision, research mentor on cushing syndrome in patient with MTC	Asst Prof Pediatrics , University of Texas

Date	Name	Fellow	Mentor Type	Faculty Role	Current Position
2012- 2015	Andrea Estrada	Pediatric Endocrine Fellow	Co-Mentor/Clinical Mentor	Clinical supervision	Asst Prof Peds George Washington, University SOM
2013- 2015	Mihail Zilbermint	Adult Endocrine Fellow	Research/Scholarly Mentor,Project Mentor,Career Mentor	Research Mentor, Genetics of Adrenal Hyperplasia	Assoc Prof Medicine, Johns Hopkins University
2013- 2016	Ovidiu Galescu	Pediatric Endocrine Fellow	Co-Mentor/Clinical Mentor	Clinical supervision	Medical Officer, FDA
2013- 2014	Roopa Kanakatti Shankar	Genetics Fellow	Research/Scholarly Mentor,Project Mentor,Career Mentor	Research Mentor, abnormalities in Fanconi Anemia	Assoc Prof Peds Children's National
2014- 2017	Cemre Robinson	Pediatric Endocrine Fellow	Research/Scholarly Mentor,Project Mentor,Career Mentor,Co-Mentor/Clinical Mentor	Clinical Supervision, Research mentor BMD in GVHD	Asst Prof Peds Mount Sinai Medical Center
2014- 2017	Miranda Broadney	Pediatric Endocrine Fellow	Co-Mentor/Clinical Mentor	Clinical Supervision	Program Director: Div. Diabetes, Endo & Metab, NIH
2014- 2015	Ricardo Herrera	Adult Endocrine Fellow	Research/Scholarly Mentor,Project Mentor,Career Mentor	Research Mentor, ARMC-5 in PPNAD	Assoc Prof of Medicine, Cleveland Clinic
2015- 2018	Marissa Lightbourne	Pediatric Endocrine Fellow	Research/Scholarly Mentor,Career Mentor,Co-Mentor/Clinical Mentor	Clinical Supervision	Staff Clinician, NIDDK

Date	Name	Fellow	Mentor Type	Faculty Role	Current Position
2016- 2018	Christina Tatsi	Pediatric Endocrine Fellow	Research/Scholarly Mentor,Project Mentor,Career Mentor	Research Mentor, Autoimmune disorders, lymphocyte Count infection Risk in Cushing Syndrome Chromosomal Abnormalities in Pediatric Pituitary Corticotropinomas	Staff Clinician, NICHD
2017- 2018	Rebecca Persky	Pediatric Endocrine Fellow	Research/Scholarly Mentor,Co-Mentor/Clinical Mentor	Clinical Supervision	Asst. Prof of Peds, George Washington SOM
2017- 2018	Abby Meyers	Pediatric Endocrine Fellow	Research/Scholarly Mentor,Co-Mentor/Clinical Mentor	Clinical Supervision	Instructor, Childrens National Medical Center
2017- 2017	Carolina Saldarriaga	Research Fellow	Research/Scholarly Mentor,Project Mentor,Career Mentor	Research Mentor, Postoperative Diabetes Insipidus and Hyponatremia in Children after Transsphenoidal Surgery	Pediatrician in primary care, Texas Children's

Date	Name	Fellow	Mentor Type	Faculty Role	Current Position
2017- 2018	Angeliki Makri	Pediatric Endocrine Fellow	Research/Scholarly Mentor, Project Mentor, Career Mentor	Research Mentor, Pheochromocytoma in children with MEN2, Lipoprotein Particles In Patients With Pediatric Cushing Disease	Asst. Professor of Peds, McGill University
2018- 2020	Armaiti Mody	Pediatric Endocrine Fellow	Research/Scholarly Mentor, Project Mentor, Career Mentor	Research mentor 11-oxygenated steroids in PCOS, Obesity in Pediatric Cancer Survivors	Assoc Prof UC Davis
2018- present	Caroline Schulmeister	Pediatric Endocrinology Fellow	Research/Scholarly Mentor	Career Mentor SOC Member	Asst Prof Peds UC Davis
2019- present	Angel Alvarez	Resident in Pediatrics, BCH Oakland	Project Mentor	PLUS project mentor	Pediatrician, Kaiser Permanente
2020- 2020	Namrata Patel	Pediatric Gastroenterology Fellow	Project Mentor	SOC Member	Asst. Prof of Pediatrics , UCSF
2020- present	Su Ying Nip	Resident in Pediatrics, UCSF	Project Mentor	incidence of DKA during emerging adulthood in the California State Registry 2014-2018	Asst Prof of Pediatrics , UCSF
2021- 2023	Kevin Yen	Fellow in Pediatric Endocrinology , UCSF	Project Mentor	SOC Member	Asst Prof of Pediatrics , UCSF

Date	Name	Fellow	Mentor Type	Faculty Role	Current Position
2021- 2023	Priya Srivastava	Fellow in Pediatric Endocrinology , UCSF	Project Mentor,Career Mentor	SOC Member	Asst Prof of Pediatrics , Stanford
2022- present	Tina Hu	Adult/Pediatric Endocrinology Fellow, UCSF	Research/Scholarly Mentor,Project Mentor	Pediatric Differentiated Thyroid Cancer	Asst Prof of Pediatrics , UCSF
2025- present	Austin Sanders	Fellow in Pediatric Endocrinology UCSF	Research/Scholarly Mentor,Project Mentor	Pituitary Tumors in Pediatrics (NUSPAR)	in training

FACULTY MENTORING

Date	Name	Position while Mentored	Mentor Type	Mentoring Role	Current Position
2023- present	Ayca Erkin-Cakmak	Assistant Professor of Pediatrics	Research/Scholarly Mentor	Clinical Research mentor	Assistant Professor of Pediatrics

RESEARCH AWARDS - CURRENT

- NBI-74788-CAH2006 Primary Investigator 2% % effort Lodish (PI)

Award ID: 132532A

Neurocrine Pharma 06/24/2021 6/6/2030

A Randomized, Double-Blind, Placebo-Controlled \$ 135,106.73 \$ 784,487 total

Study to Evaluate the Safety and Efficacy of direct/yr 1

Crinecerfont (NBI-74788) in Pediatric Subjects with Classic Congenital Adrenal Hyperplasia, Followed by Open-Label Treatment

Clinical Trial of novel oral medication in children with CAH

PI
- A145565 1112923 PI 0% % effort Lodish (PI)

DHCS California Department of Health and Children's 9/1/2024 8/31/2026

Services

California Youth Behavioral Health Initiative (CYBHI) \$ 725,351 total

Evidence-Based Practices and Community-Defined Evidence Practices Grant Program

Grant to support program to provide community health worker support to children with chronic illness

PI

3. A143632 CLCI699C2203	Primary Investigator	0% % effort	Lodish (PI)
Recordati		6/6/2024	6/6/2029
A phase II, multicenter, open-label, non-comparative study to evaluate the pharmacokinetics, pharmacodynamics, and tolerability of osilodrostat in children and adolescent patients with Cushing's syndrome		\$ 344,169 direct/yr 1	
Clinical trial of novel oral medication in children with Cushing's syndrome			
PI			

RESEARCH AWARDS - PAST

1. L30 Research Career Program	Clinical Fellow and Associate Clinical Investigator	100% % effort	Lodish (PI)
NIH office of Intramural Loan Repayment		07/01/2006	06/30/2011
L30 Research Career Program		\$ 20,000 direct/yr 1	\$ 90,000 total

The NIH Intramural loan repayment program covered the costs of medical school loans while I served as a clinical fellow and Associate Clinical Investigator
Served as Clinical Fellow and ACI with research contributing to the LRP mission

2. Bench-to-Bedside	Co-investigator	20 % effort	Stratakis (PI)
Office of Research on Women's Health, NIH		06/01/2010	06/01/2012
Adrenal Hyperplasia Among Adolescent Patients with Polycystic Ovarian Syndrome		\$ 135,000 direct/yr 1	\$ 270,000 total

Androgen excess may be adrenal and/or ovarian in origin; we hypothesized that a subgroup of patients with polycystic ovarian syndrome (PCOS) may have some degree of abnormal adrenocortical function. The objective of the study was to evaluate the pituitary adrenal axis with an oral low- and high-dose dexamethasone-suppression test (Liddle's test) in women with PCOS. This was a case-control study conducted at the National Institutes of Health Clinical Center. A total of 38 women with PCOS and 20 healthy volunteers (HV) aged 16-29 years participated in the study.

Led clinical care of patients with PCOS, mentored fellow (Dr. Gourgari) on study design and analysis plan, after Dr. Gourgari graduated from fellowship, I took on the role of primary investigator of the clinical protocol.

3. 1ZIAHD008894 PI 50 % effort Lodish (PI)
National Institute of Child Health and Human 10/30/2011 10/30/2013
Development
Detection and treatment of endocrine abnormalities \$ 120,796 direct/yr \$ 537,688 total
in childhood cancer survivors 1
Endocrine dysfunction is increasingly recognized as one of the most important aspects of
quality of life issues, physical and psychosocial development and overall prognosis in
pediatric patients diagnosed with neoplasms, as well as in patients s/p bone marrow
transplant throughout their lifespan. In addition, several of the new, molecularly designed
therapies for neoplasms may interact with endocrine signaling; these include receptors
and/or their ligands for growth and/or proliferation factors, and disruptors of steroid hormone
interaction. One of the aims of this protocol is in training our fellows, residents and students
in the identification and management of endocrine abnormalities developing in patients who
have been diagnosed with and treated for neoplasms and/or who have received HSCT at
the NIH-Clinical center.
Wrote protocol, web-based case report forms, responsible for all aspects of the protocol
including patient care, IRB submission and renewal

4. CRADA PI 20 % effort Lodish (PI)
Corcept Therapeutics 06/01/2012 06/01/2014
An open-label study of the safety, pharmacokinetics \$ 200,000 direct/yr \$ 400,000 total
and pharmacodynamics of mifepristone in children 1
with refractory Cushing disease
Study objectives are to characterize the safety profile of mifepristone in children with
Cushing's disease, to determine the pharmacokinetics of mifepristone in children with
Cushings disease, and to obtain pharmacodynamic data on the effect of mifepristone on
glucose metabolism, body weight and the growth-hormone-IGF-1 axis in children with
refractory Cushing Disease
As Primary Investigator of the clinical trial, I wrote the protocol, submitted it to the IRB,
trained nurses and physicians on protocol related issues, and led the patient care team.

5. HHSN275201300023I/27500003 Associate Investigator 20 % effort Mills (PI)
 Division of Intramural Population Health Research 07/01/2014 01/01/2018
 (DIPHR), NIH
 Genetic Factors in Cushing Disease: Whole Exome \$ 78,381 \$ 365,738 total
 Sequencing direct/yr 1

The major goal of this research initiative is to employ large scale genome analytic approaches to identify genetic factors associated with CD, associated phenotypes and clinical factors such as response to therapy

As primary investigator of the clinical study entitled "A CLINICAL AND GENETIC INVESTIGATION OF PITUITARY AND HYPOTHALAMIC TUMORS AND RELATED DISORDERS" at the NIH Clinical center, I am responsible for all aspects of the clinical protocol. We have stored samples from pediatric patients with Cushing Disease and have performed WES on these samples. We are identifying genetic variants are associated with phenotypic changes and clinical factors. My role is to link clinical data to genetic data, specifically, to see if gene variants are related to factors such as levels of cortisol, ACTH, response to provocative tests, facial dysmorphic features, tumor size, response to therapy and clinical features including growth trajectory, blood pressure, height percentile, and glucose tolerance.

6. 1ZIEHD008944 PI 50 % effort Lodish (PI)
 NIH 01/01/2015 06/29/2018
 Pediatric Endocrine Training Program \$ 1,539,035 \$ 4,481,953 total
 direct/yr 1

3 Year ACGME accredited fellowship program in pediatric endocrinology
 Oversight of fellowship training, mentor trainees in their scholarly activities

7. CRADA 03193 PI 20 % effort Lodish (PI)
 Pfizer 11/30/2017 01/01/2018

An open-label phase 2 study of the safety and efficacy of pegvisomant in children with refractory growth hormone excess

The objectives of the study are to characterize the safety profile of the pegvisomant in children with growth hormone excess, and to obtain pharmacodynamic data on the effect of pegvisomant on the growth-hormone-IGF-1 axis in children with refractory gigantism, as well as on their linear growth rate.

As the primary investigator on this study, I wrote the study protocol, submitted the draft for scientific review and to the IRB, am working with the FDA to obtain an IND, and will be responsible for all aspects of the protocol.

8. PVO-1A-202 Associate investigator 5% % effort Hsiao (PI)
 11/01/2019 11/01/2021

A Phase 2, Open-Label Extension, Efficacy and Safety Study of a RAR γ -Specific Agonist (Palovarotene) in the Treatment of Preosseous Flare-ups in Subjects with Fibrodysplasia Ossificans Progressiva (FOP)

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8. Makri A, **Lodish M**, Gigantism and Acromegaly Pituitary Disorders of Childhood: Diagnosis and Clinical Management, 2017 Springer Nature (in press)
9. **Lodish M**, Keil M, Stratakis C, Cushing Syndrome in Childhood Pediatric Endocrinology: A Practical Clinical Guide, 3ed. 2017 Springer (in press)
10. Stratakis, C and **Lodish M**: Cushing's Syndrome. In: The 5-Minute Pediatric Consult, Eighth Edition 2017, edited by Drs. Michael D. Cabana and Linda A. DiMeglio. Lippincott Williams & Wilkins
11. Almeida M, **Lodish M**, Stratakis C Cushing's Syndrome 2018 edition of Conn's Current Therapy, edited by Edward T. Bope and Rick D. Kellerman. Elsevier

OTHER PUBLICATIONS

1. Rivkees SA, Kelly M, **Lodish M**, Weiner D 2017 The Pediatric Medical Student Research Forum: Fostering Interest in Pediatric Research. J Pediatr;188:3-4. PMID: 28645440

SIGNIFICANT PUBLICATIONS

1. Tatsi C, Boden R, Sinaii N, Keil M, Lyssikatos C, Belyavskaya E, Rosenzweig S, Stratakis C, **Lodish M**. 2017 Decreased Lymphocyte Count and Increased Infection Risk are Common in Pediatric Endogenous Cushing Syndrome" Pediatric Research - 2018 Feb;83(2):431-437

I initiated this study to investigate the relationship between elevated cortisol and the immune system, specifically looking at infection risk. I mentored Christina Tatsi, pediatric endocrine fellow, who chose this as her scholarly project for fellowship. We describe the changes of the WBC lineages in pediatric endogenous hypercortisolemia, their associations with the markers of disease severity, and the presence of infections in 197 children with endogenous CS compared to 66 controls. The absolute lymphocyte count of CS patients was significantly lower than that of controls, while the total WBC and the absolute neutrophil counts were significantly higher. These changes correlated with several markers of CS severity and improved after resolution of hypercortisolemia. Infections were identified in 35 patients (17.8%), and their presence correlated to elevated serum morning cortisol, midnight cortisol, and urinary free cortisol levels, as well as with the decrease in absolute lymphocyte count. Children with endogenous CS have abnormal WBC counts, which correlate with the severity of CS, and normalize after cure. Infections are common in this population; clinicians should be aware of this complication of CS and have low threshold in diagnosis and treating infections in CS

2. Kraft IL, Akshintala S, Zhu YJ, Lei H, Derse-Anthony C, Dombi E, Steinberg SM, **Lodish M**, Waguespack S, Kapustina O, Fox E, Balis FM, Merino MJ, Meltzer PS, Glod J, Shern JF, Widemann BC. Outcomes of Children and Adolescents with Advanced Hereditary Medullary Thyroid Carcinoma Treated with Vandetanib. Clin Cancer Res. 2018 Feb 15;24(4):753-765

For the past 10 years, I have served as the pediatric endocrinologist on this collaborative study with the NCI, responsible for endocrine management of the 16 patients enrolled in study. We conducted the first phase I/II trial of vandetanib for children and adolescents with Medullary Thyroid Cancer to define a recommended dose and assess antitumor activity.

3. Saldarriaga, C, Lyssikatos C, Belyavskaya E, Keil M, Chittiboina P, Sinaii N, Stratakis CA, **Lodish M**. Postoperative Diabetes Insipidus and Hyponatremia in Children after Transsphenoidal Surgery for Adrenocorticotropin Hormone and Growth Hormone Secreting Adenomas. The Journal of Pediatrics. 2018 Apr;195:169-174

Post-operative management for children undergoing transsphenoidal surgery may be challenging. I initiated this study to define the incidence and risk factors of postoperative sodium alterations in pediatric patients undergoing transsphenoidal surgery for adrenocorticotrophic hormone and growth hormone secreting pituitary adenomas. Among 160 children who underwent TSS for pituitary adenomas, the incidence of DI and SIADH after TSS was 26% and 14%, respectively. Combined risk factors for DI and/or SIADH include female sex, manipulation of and/or tumor invasion into the PP, and CSF leak or lumbar drain. I mentored medical student Carolina Saldarriaga in all aspects of this project.

4. Sarafoglou K, Kim MS, Lodish M, Felner EI, Martinierie L, Nokoff NJ, Clemente M, Fechner PY, Vogiatzi MG, Speiser PW, Auchus RJ, Rosales GBG, Roberts E, Jeha GS, Farber RH, Chan JL; CAHtalyt Pediatric Trial Investigators. Phase 3 Trial of Crinecerfont in Pediatric Congenital Adrenal Hyperplasia. N Engl J Med. 2024 Jun 2.

.I am a co-author on this manuscript that describes our phase 3 trial of crinecerfont in

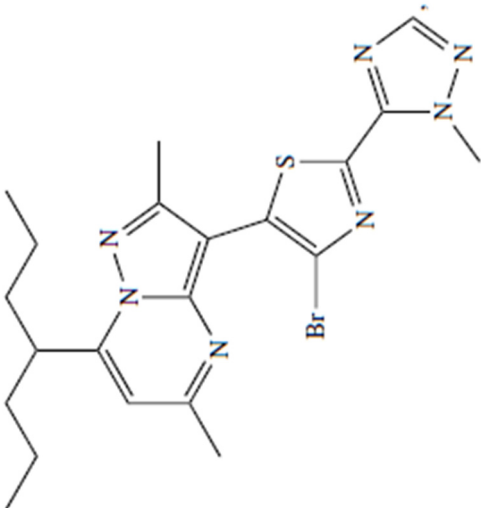
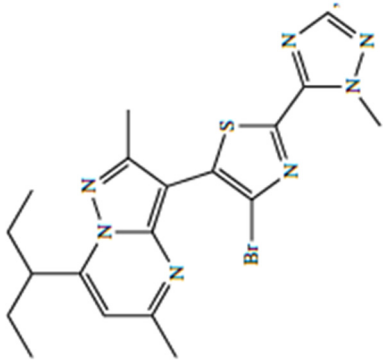
treating children with CAH that led to the FDA approval of this medication in children in 2025.

ACADEMIC LEADERSHIP

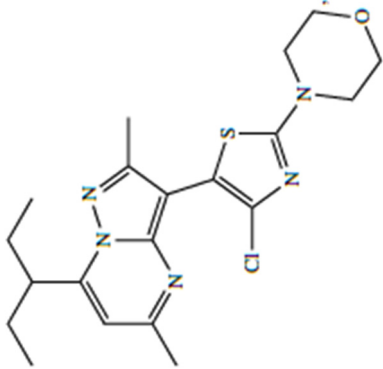
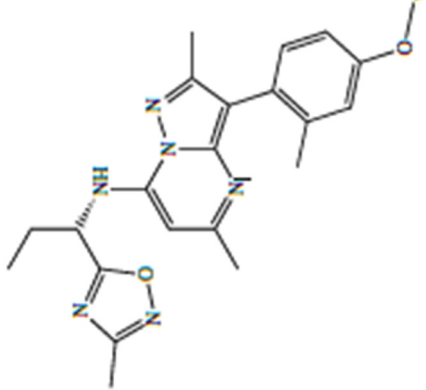
From January 2015 - June 2018, I served as director of the fellowship in Pediatric Endocrinology at the NIH. The fellowship is sponsored by the NICHD and Children's National Health Systems (CNHS) and is based at the NIH Clinical Center. I continue to expand my role as clinical educator and investigator; in 2013, I earned my masters degree in the NIH-Duke Training Program in Clinical Research, and in 2014 I became a member of the Society of Pediatric Research. I have been recognized as a leader in the field of medical education in pediatric endocrinology as an invited member of the Education Committee of the Pediatric Endocrine Society as well as the Clinical Education Committee of the Endocrine Society. Currently I serve as Division Chief of Pediatric Endocrinology at UCSF.

APPENDIX B – COMPOUND STRUCTURES IN CLAIM 1

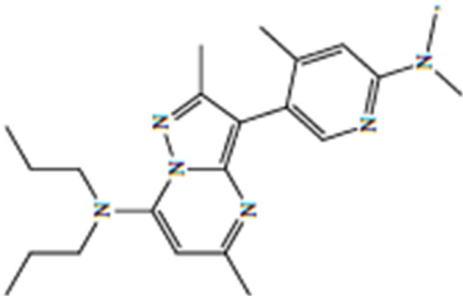
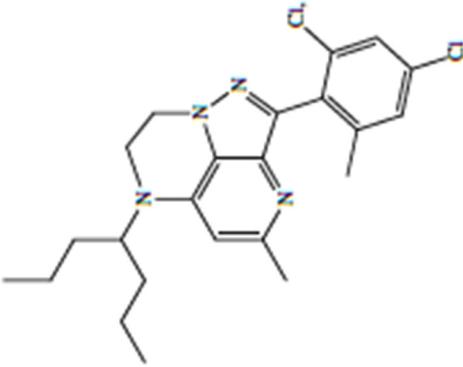
Appendix B – Compound Structures in Claim 1

Compound Structure in Claim 1	Letter Designation	Synonyms and/or IUPAC name (Provided for Easy Reference)	PubChem Entry
	A	3-[4-Bromo-2-(2-methyl-2H-[1,2,4]thiazol-3-yl)-2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-a]pyrimidine]	EX1091 (CID 24758885)
	B	3-(4-Bromo-2-(2-methyl-2H-[1,2,4]thiazol-3-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine	EX1092 (CID 24898976)

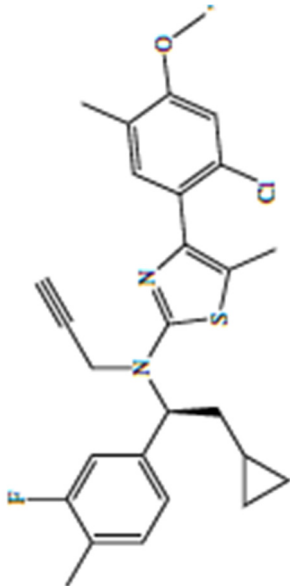
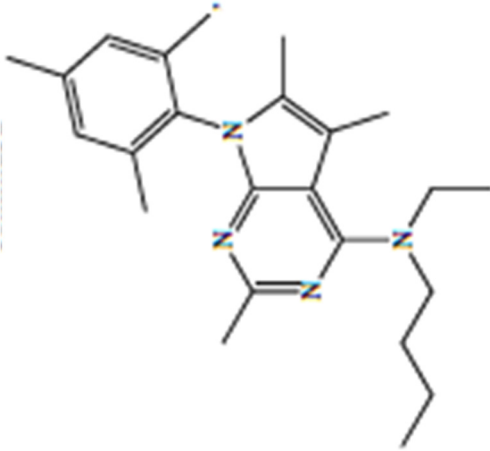
Appendix B – Compound Structures in Claim 1

Compound Structure in Claim 1	Letter Designation	Synonyms and/or IUPAC name (Provided for Easy Reference)	PubChem Entry
	C	Tildacerfont; SPR-001; LY-2371712 3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine	EX1059 (CID 134694266)
	D	Verucerfont; NBI-77860; GSK-561679 3-(4-methoxy-2-methylphenyl)-2,5-dimethyl-N-[(1S)-1-(3-methyl-1,2,4-oxadiazol-5-yl)propyl]pyrazolo[1,5-a]pyrimidin-7-amine	EX1090 (CID 11596613)

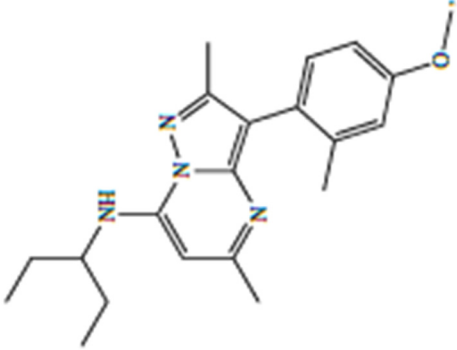
Appendix B – Compound Structures in Claim 1

Compound Structure in Claim 1	Letter Designation	Synonyms and/or IUPAC name (Provided for Easy Reference)	PubChem Entry
	E	NBI-30775; R-121919 3-[6-(dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl- <i>N,N</i> -dipropylpyrazolo[1,5-a]pyrimidin-7-amine	EX1093 (CID 9821250)
	F	NBI-34041; SB-723620 3-(2,4-dichlorophenyl)-9-heptan-4-yl-6-methyl-1,2,5,9-tetrazatricyclo[6.3.1.0 ^{4,12}]dodeca-2,4,6,8(12)-tetraene	EX1094 (CID 9888194)

Appendix B – Compound Structures in Claim 1

Compound Structure in Claim 1	Letter Designation	Synonyms and/or IUPAC name (Provided for Easy Reference)	PubChem Entry
	G		
	H	Crinecerfont; SSR-125543 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine	EX1033 (CID 5282340)
	I	Antalarmin N-butyl-N-ethyl-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)pyrrolo[2,3-d]pyrimidin-4-amine	EX1096 (CID 177990)

Appendix B – Compound Structures in Claim 1

Compound Structure in Claim 1	Letter Designation	Synonyms and/or IUPAC name (Provided for Easy Reference)	PubChem Entry
	J	DMP-904 3-(4-methoxy-2-methylphenyl)-2,5-dimethyl-N-pentan-3-ylpyrazolo[1,5-a]pyrimidin-7-amine	EX1095 (CID 9884878)