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 12,569,491 B2

DECLARATION OF MAYA LODISH, M.D.

IN SUPPORT OF PETITION FOR POST GRANT REVIEW OF U.S. PATENT NO. 12,569,491 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 Selna 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. 12,569,491 to Howerton et al. ("the '491 Patent")
1002	Excerpts from the Prosecution History of the '491 Patent ("the Prosecution History")
1004	PCT Publication WO/2015/112642 to Grigoriadis et al. ("Grigoriadis PCT").
1006	U.S. Patent Application Publication No. 2017/0020877 to Grigoriadis et al. ("Grigoriadis").

Exhibit No.	Exhibit Description
1008	Turcu et al., "Single-Dose Study of a Corticotropin-Releasing Factor Receptor-1 Antagonist in Women With 21-Hydroxylase Deficiency," *J. Clin. Endocrinol. Metab.*, 101(3):1174-80 (March 2016) ("Turcu 2016").
1010	CRENESSITY® (crinecerfont) Prescribing Label, U.S. Food and Drug Administration (Dec. 13, 2024).
1013	Speiser et al., "Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline," *J. Clin. Endocrinol. Metab.*, 95(9):4133-60 (2010) ("Speiser 2010").
1014	Turcu A.F. & Auchus R.J., "The Next 150 Years of Congenital Adrenal Hyperplasia," *J. Steroid. Biochem. Mol. Biol.,* 153:63-71 (Sept. 2015) ("Turcu & Auchus 2015").
1015	El Maouche et al., "Congenital Adrenal Hyperplasia," *Lancet* 390:2194-10 (2017) ("El Maouche 2017").
1016	Merke D.P. & Bornstein S.R., "Congenital Adrenal Hyperplasia," *Lancet,* 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," *J. Clin. Endocrinol. Metab.*, 103(11):4043-88 (2018) ("Speiser 2018").

Exhibit No.	Exhibit Description
1018	Fahmy et al., "Structure and Function of Small Non-Peptide CRF Antagonists and their Potential Clinical Use," *Curr. Mol. Pharmacol.,* 10(4): 270-281 (2017) ("Fahmy 2017").
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," *J. Pharmacol. Exp. Ther.,* 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," *J. Pharmacol. Exp. Ther.,* 301(1):322-32 (2002) ("Gully 2002").
1024	Merke D.P. & Auchus R.J., "Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency," *N. Engl. J. Med.* 383(13):1248-61 (2020) ("Merke & Auchus 2020").
1025	Turcu A.F. & Auchus R.J., "Novel Treatment Strategies in Congenital Adrenal Hyperplasia," *Curr. Opin. Endocrinol. Diabetes Obes.,* 23(3):225-32 (June 2016) ("Turcu & Auchus 2016").

Exhibit No.	Exhibit Description
1026	Webb E.A. & Krone N., "Current and Novel Approaches to Children and Young People with Congenital Adrenal Hyperplasia and Adrenal Insufficiency," *Best Pract. Res. Clin. Endocrinol. Metab.,* 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," *Expert Opin. Ther. Pat.,* 23(8):1057-68 (2013) ("Williams 2013").
1033	National Center for Biotechnology Information, PubChem Compound Summary for CID 5282340, Crinecerfont (2026).
1038	Zaarour et al., "Bilateral Ovary Adrenal Rest Tumor in a Congenital Adrenal Hyperplasia Following Adrenalectomy," *Endo. Prac.*, 20:4 (Apr. 2014).
1039	Sarafoglou et al., "Interpretation of Steroid Biomarkers in 21-Hydroxylase Deficiency and Their Use in Disease Management," *J. Clin. Endocrinol. Metabol.* 108:2154-75 (March 2023) ("Sarafoglou 2023").

Exhibit No.	Exhibit Description
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," *Endocr. Pathol.*, 28:146-151 (2017).
1041	Sarafoglou et al., "Tildacerfont in Adults With Classic Congenital Adrenal Hyperplasia: Results from Two Phase 2 Studies," *J. Clin. Endocrinol. Metabol.* 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").

Exhibit No.	Exhibit Description
1046	Turcu A.F. & Auchus R.J, "Adrenal Steroidogenesis and Congenital Adrenal Hyperplasia," *Endocrinol. Metabol. Clin. N. Am.,* 44:275-96 (2015) ("Turcu & Auchus 2015a").
1047	Mallappa A. & Merke D.P., "Management challenges and therapeutic advances in congenital adrenal hyperplasia," *Nature Reviews Endocrinol.*, 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," *J. Clin. Endocrinol. Metabol.*, 107(3):801-12 (2022) ("Auchus 2022").
1049	Claahsen-van der Grinten et al., "Congenital Adrenal Hyperplasia–Current Insights in Pathophysiology, Diagnostics, and Management," *Endocrine Reviews*, 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," *N. Engl. J. Med.,* 391(6):504-14 (June 2024) ("Auchus 2024").
1053	Sarafoglou et al., "Phase 3 Trial of Crinecerfont in Pediatric Congenital Adrenal Hyperplasia," *N. Engl. J. Med.*, 391(6):493-503 (June 2024) ("Sarafoglou et al. 2024").

Exhibit No.	Exhibit Description
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).
1064	Delfino et al., "Testicular Adrenal Rest Tumors in Patients With Congenital Adrenal Hyperplasia: Prevalence and Sonographic, Hormonal, and Seminal Characteristics," *J. Ultrasound Med.*, 31:383-88 (2012).
1067	Yu et al., "Clinical manifestations of testicular adrenal rest tumor in males with congenital adrenal hyperplasia," *Ann. Ped. Endocrinol. Metab.*, 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," *Clin. Endocrinol.*, 78, 667-72 (2013).

Exhibit No.	Exhibit Description
1069	Claahsen-van der Grinten et al., "Gonadal dysfunction in congenital adrenal hyperplasia," Eur. J. Endocrinol., 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," *J. Clin. Endocrinol. Metab.*, 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," *Horm. Res. Paed.*, 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").
1075	NCT00539136, "A Study to Examine the Absorption of GSK561679 in Healthy Male Volunteers," ClinicalTrials.gov., (GlaxoSmithKline) ("GSK Study").
1076	Wilson, JD, "Prospects for Research for Disorders of the Endocrine System," *JAMA*, 285(5):624-627 (2001) ("Wilson 2001").
1077	U.S. Pat. App. No. 17/081,694 ("the '694 Application"), Notice of Allowance and Reasons for Allowance (Feb. 1, 2022).

Exhibit No.	Exhibit Description
1078	Smeets et al., "Molecular Characterization of Testicular Adrenal Rest Tumors in Congenital Adrenal Hyperplasia: Lesions With Both Adrenocortical and Leydig Cell Features," *J. Clin. Endocrinol. Metab.*, 100(3):E524-E530 (Mar. 2015).
1080	Claahsen-van der Grinten et al., "Testicular Adrenal Rest Tumours in Congenital Adrenal Hyperplasia," *Best Prac. & Res. Clin. Endocrinol. & Metab.* 23(2):209-220 (Apr. 2009) ("Claahsen-van der Grinten 2009").
1081	O'Shea et al., "Food for thought: formulating away the food effect – a PEARRL review," *J. Pharmacy and Pharmacology*, 71:510-535 (2019).
1082	Tellew et al., "Discovery of NBI-77860/GSK561679, a potent corticotropin-releasing factor (CRF1) receptor antagonist with improved pharmacokinetic properties," *Bioorganic & Medicinal Chem. Ltrs.*, 20(24):7259-7264 (Dec. 2010).
1083	Chen et al., "Synthesis and SAR of 2-Aryloxy-4-alkoxy-pyridines as Potent Orally Active Corticotropin-Releasing Factor 1 Receptor Antagonists," *J. Med. Chem.* 51:1377-1384 (2008).
1086	Declaration of June Ann Munford (May 22, 2026)
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).

Exhibit No.	Exhibit Description
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).

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

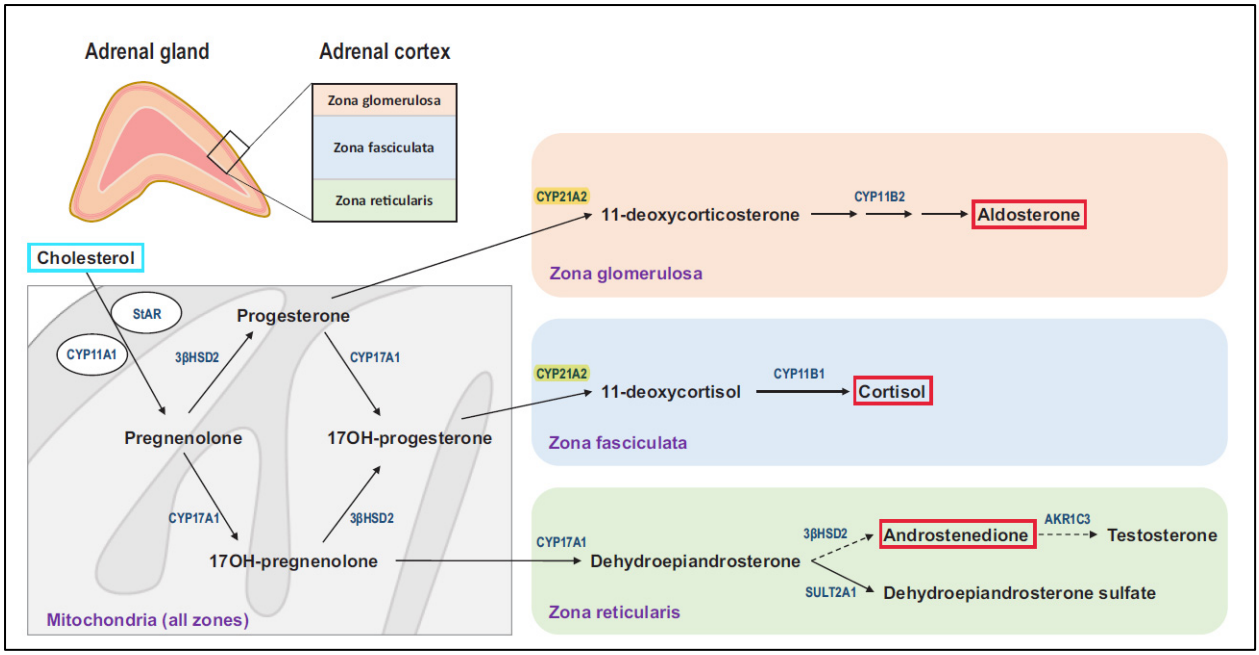
factor (CRF) and adrenocorticotropin (ACTH), which results in hyperplasia of the adrenal cortex. EX1046, 278; EX1053, 494. Approximately 90% to 99% of all CAH cases are caused by 21-hydroxylase deficiency (21OHD) due to mutations to the *CYP21A2* gene. EX1049, 93. CAH and 21OHD are often used interchangeably. 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 11β-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.

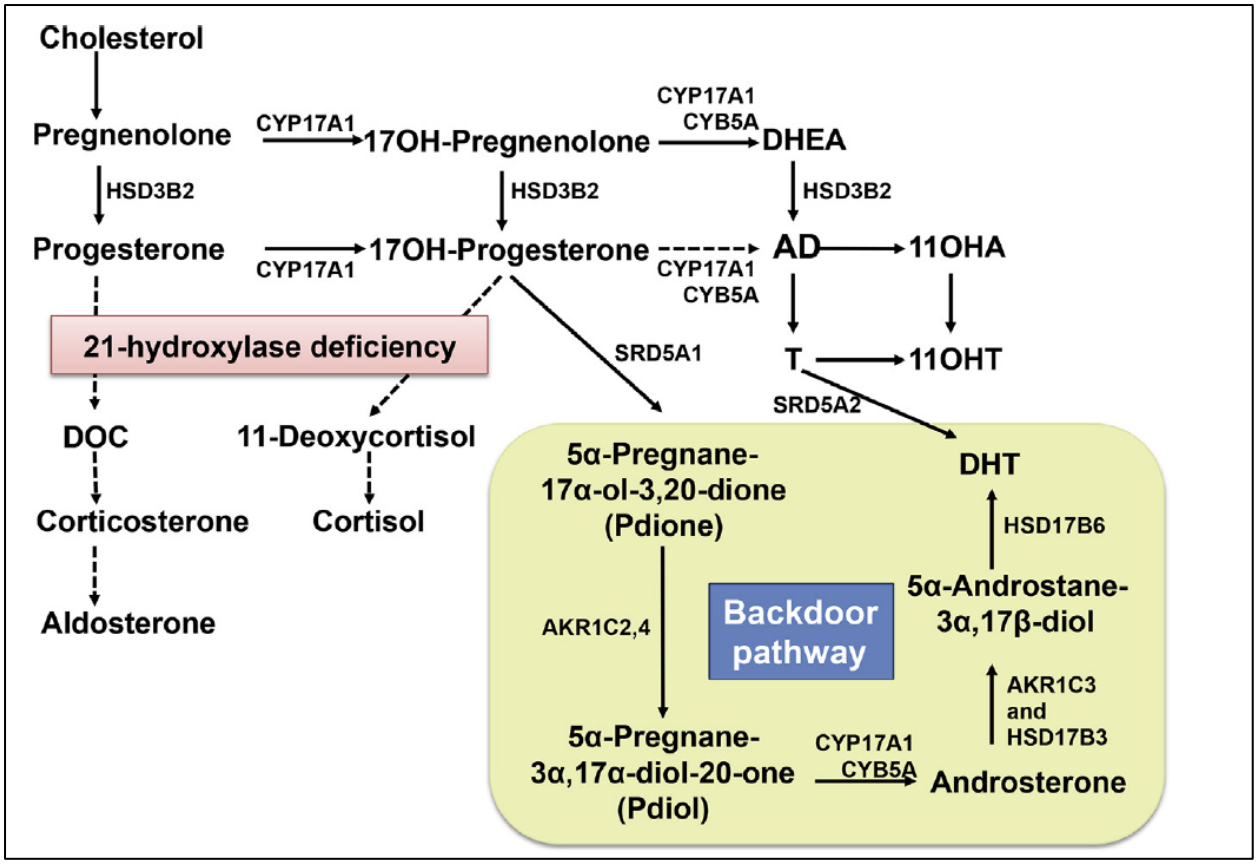


Adapted from EX1039, 2157, Fig. 3. Cholesterol (blue box) is enzymatically converted into various steroids, including aldosterone, cortisol, and androstenedione (red boxes). The protein encoded by the *CYP21A2* gene (yellow highlighting) is involved in the conversion of progesterone into aldosterone 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; 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, 90:20–22. 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 are 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 "CRF_1 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-hydroxlase 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.

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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 '491 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 adrenocorticotropic 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.

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D. Administration of Therapeutics With or Without Food

43. By 2018, the determination of any food effects, for example whether a medication should be administered with food (fed state) or without food (fasted state) was well within the skillset of the person of ordinary skill in the art.

44. A review article by O'Shea et. al. (EX1081) discusses how "[t]he concomitant administration of oral dosage forms with food can have a significant impact on drug pharmacokinetics and bioavailability relative to the fasted state." EX1081, 510. Medicines approved by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) that show altered bioavailability are "often required to be dosed, rather restrictively, in either the fed or the fasted state." *Id.* Because "[o]ral medicines are generally required to be repeatedly administered, often chronically and in multiple daily dosings [] it is inevitable that drugs will be administered in different prandial states." *Id.* Thus, understanding "the effects food has on pharmacokinetics is [] a critical factor in assessing the clinical potential of new medicines." *Id.* If a food effect is identified, drug development or regulatory scientists generally have three choices: (1) consider an alternative lead compound; (2) specify whether the medicine is to be taken with (fed) or without (fasted) food; or (3) design formulation(s) to overcome the food effect. *Id.* at 517.

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45. A food effect study was designed and published for GSK561679 (verucerfont). EX1075, 1; EX1082, 1-6; *see also* EX1006, [0084]. ClinicalTrials.gov study ID NCT00539136, titled "A Study to Examine the Absorption of GSK561679 in Healthy Male Volunteers," was carried out to examine the pharmacokinetic scope of GSK561679 formulated as either a solution or a tablet. EX1075. The secondary outcome measures included the AUC of GSK561679 "after administration of GSK561679 in a solution (fasted) and in a new 'optimized' tablet formulation (fasted and fed)." *Id.*, 1.

46. Based on the information in the '491 patent, it appears that such a study was also conducted for Spruce's CRF1 receptor antagonist, tildacerfont (Compound 1). The '491 patent explains that in Example 1—a study to assess the efficacy of Compound 1 in subjects with TART, "dosing at 10 pm and after consumption of a snack is based on information from the Phase 1 studies in healthy volunteers." EX1001, 91:14–29. The reason given for subjects to consume a snack first was "because the Phase 1 studies showed minimal study drug absorption when subjects were dosed in a fasted state." *Id.* There is nothing unexpected or surprising about that result.

47. Indeed, other studies had already been undertaken to determine (and improve) the positive food effects seen for other CRF1 receptor antagonists. For example, the review article Fahmy et. al. (EX1018) describes how many

compounds from a series of pyridine CRF receptor antagonists "showed a significant positive effect for food following oral administration in both humans and dogs." EX1018, 273. "In dogs, oral bioavailability was much lower during fasting than when the animals were fed." *Id.* In this case, "[t]o address the food effect concerns," one of the other three options was also used: "structural modifications were made in an effort to discover similar orally active compounds with an improved pharmacokinetic profile while retaining the desired pharmacological effect." *Id*; *see also* Chen et al., 2008 (EX1083) (original research article).

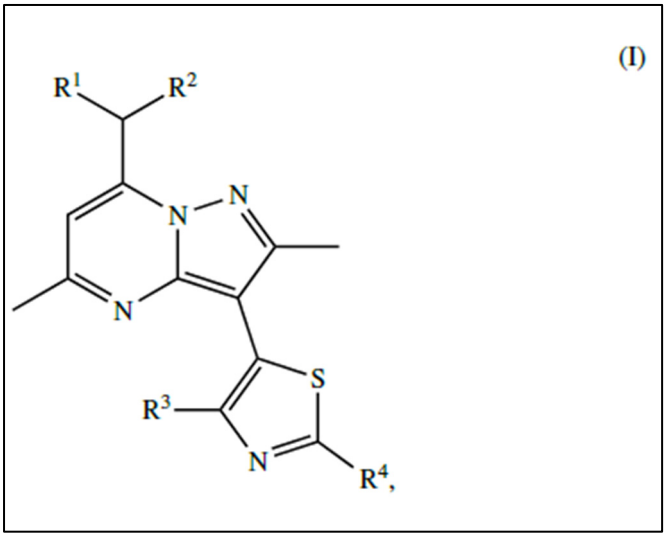
V. THE '491 PATENT

48. I have reviewed the '491 patent and portions of its prosecution history. The '491 patent issued on March 10, 2026. EX1001, cover page, (45). Spruce is listed as assignee on the front page of the '491 patent. *Id.* I understand from counsel that the '491 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, (60).

A. '491 Patent Specification

49. The '491 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):



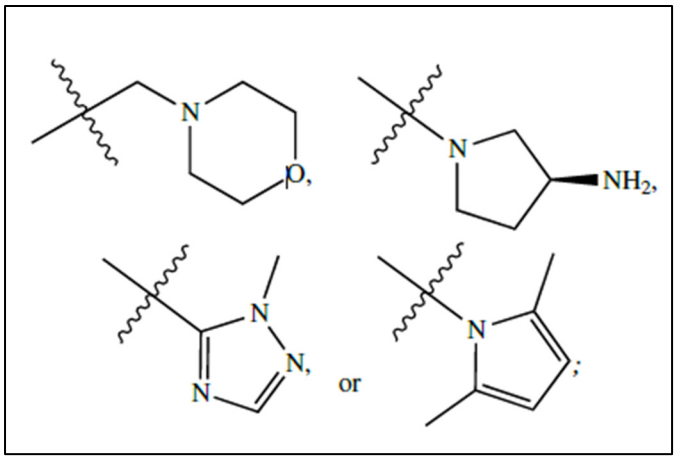
or a pharmaceutically acceptable salt thereof,

wherein:

R^1 and R^2 are independently ethyl or n-propyl;

R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and

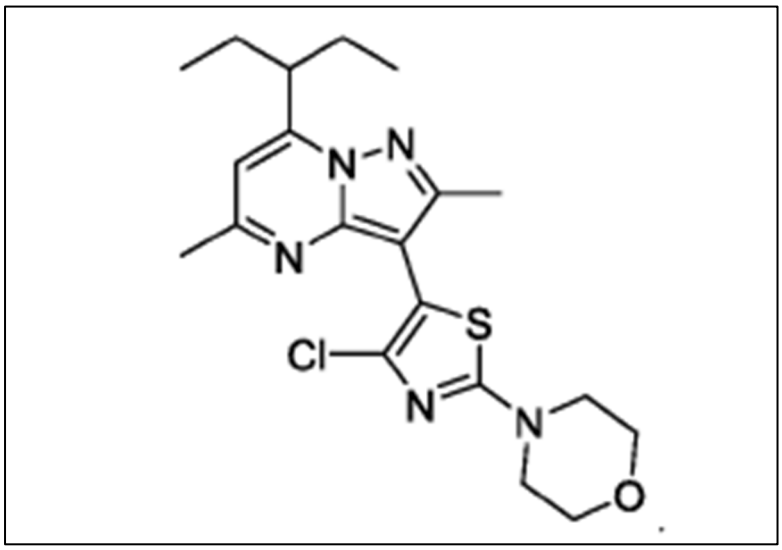
R^4 is hydrogen, Br, R^aR^bN—, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,



R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$—, $(CH_3)_3COC(O)NHCH_2CH_2$—, or $CH_3CH_2CH_2NHCH_2CH_2$—.

50. Formula (I) encompasses Compound 1, described in the '491 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, 90:42–58. I understand that this compound is also known as tildacerfont. *See* EX1001, 96:40-45; EX1059, 1.



51. The '491 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, 90:4–98:44.

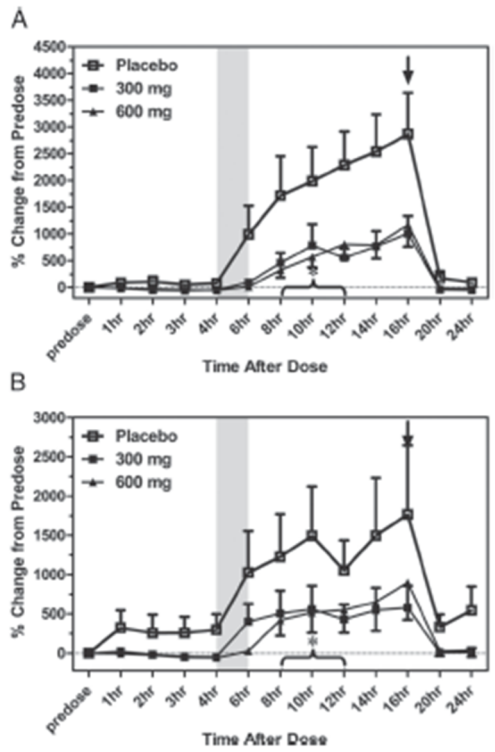
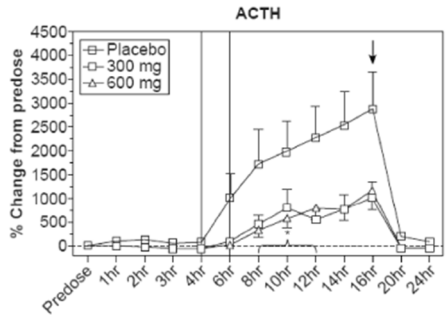
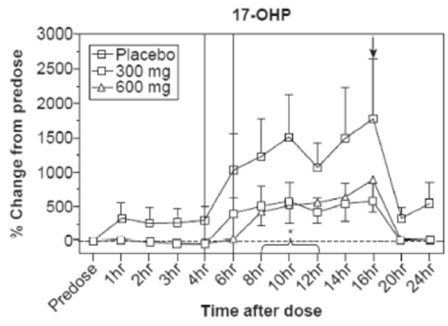
52. Example 1 describes a prophetic Phase 2, Open-Label Study of Compound 1 (tildacerfont) "specifically in male CAH subjects with TART." EX1001, 90:4–63. I understand from counsel that a prophetic example is one that has not actually been performed and is conceptual. The '491 patent states that this 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, 90:59–63. 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 '491 patent does not include any data generated for the study described in Example 1. EX1001, 90:4–93:52.

53. 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, 93:53–59. 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, 93:53–95:50. It refers to Figure 2, which shows pharmacokinetic data following once-daily dosing for Compound 1 (tildacerfont). EX1001, 94:46–53. Example 2 also refers to Figure 3, which mentions once-daily and twice-daily dosing, but contains no data. *Id*.

54. Example 2 also notes that "this mechanism of action has been validated in a previous proof-of-concept study using a similar small-molecule CRF_1 receptor antagonist, which produced dose-dependent reductions in ACTH

and 17-OHP in subjects with CAH" and cites to Figures 12A and 12B. EX1001, 95:19–26. While the '491 patent does not identify the "similar small-molecule CRF_1 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 '491 patent are essentially identical to Figures 2A and 2B of the Turcu 2016 publication, respectively, except for some minor shading.

Turcu 2016—Figure 2A and 2B	'491 Patent—Figure 12A and 12B
	 FIG. 12A  FIG. 12B

55. Example 3, titled "Congenital Adrenal Hyperplasia (CAH)," includes a series of figures related to CRF1 receptor antagonists and CAH. EX1001, 95:51–96:37. The only data in the '491 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, 96:17–20. The '491 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 '491 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 '491 patent when, how, or how much tildacerfont was administered to this patient.

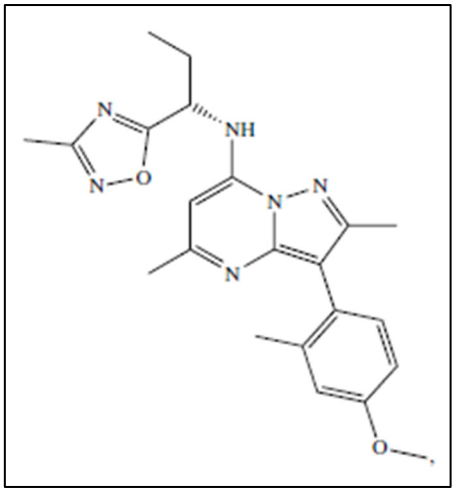
56. I understand that Spruce stated in a provisional application to which the '491 claims priority, "it [was] not known whether Compound 1 [could] successfully treat TART." EX1055 (U.S. Provisional Patent Application No. 62/663,951), [0287]. Although this statement does not appear in the '491 patent,

the ’491 patent provides no additional data regarding the efficacy of Compound 1 for the treatment of TART.

57. 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, 96:38–98:10. It does not contain any mention of TARTs or OARTs. *Id.*

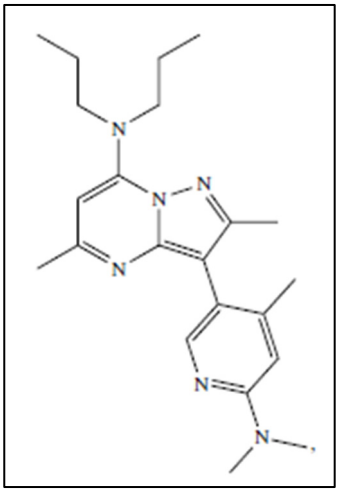
58. The ’491 patent also contemplates that additional chemotherapeutic agents may be co-administered with the compounds of Formula I (e.g., Compound 1 (tildacerfont)), in its methods. EX1001, 6:54–8:52; 81:37–83:38. Among those “additional chemotherapeutic agent[s]” are seven CRF1 receptor antagonists that are not identified in the ’491 patent as structures falling within the scope of Formula I. EX1001, 6:65–8:33; 81:47–83:38.

59. The first of these seven compounds described as “additional chemotherapeutic agents” is Neurocrine’s verucerfont, which is also known as NBI-77860 and GSK-561679:



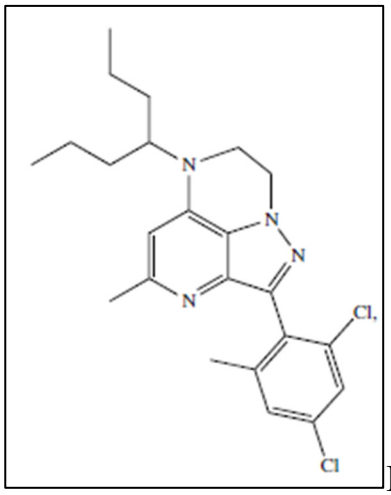
EX1001, 7:1–15; 81:50–65; EX1090.

60. The second is Neurocrine's NBI-30775:



EX1001, 7:20–35; 82:1–20; EX1093.

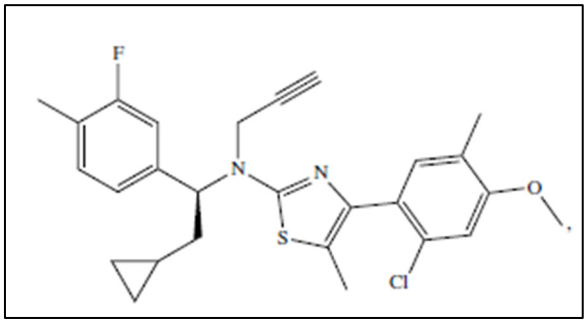
61. The third is Neurocrine's NBI-34041:



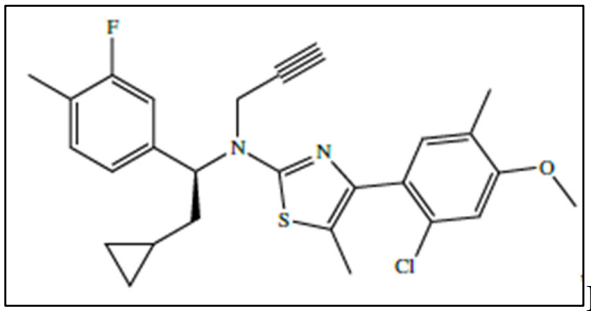
EX1001, 7:36–55; 82:20–37; EX1094.

62. The fourth is SSR-126374. EX1001, 7:47; 8:32. The ’491 patent does not depict the structure of SSR-126374. I understand from counsel that the structure has not been publicly disclosed.

63. The fifth, in one portion of the ’491 patent 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:

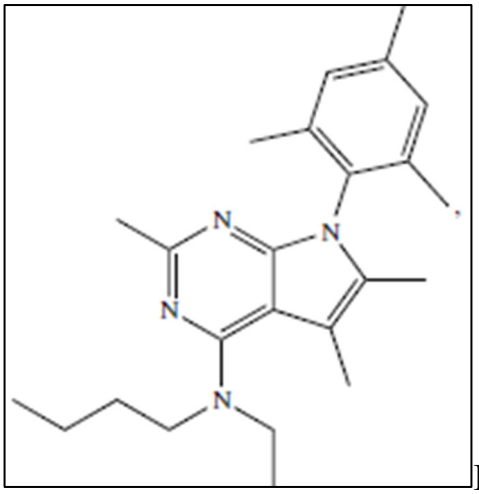


EX1001, 7:57–66; EX1033. However, in another portion of the ’491 patent the fifth structure is a structure that is drawn as containing a three carbon side chain with a 4-carbon bond, which I believe is physically impossible:



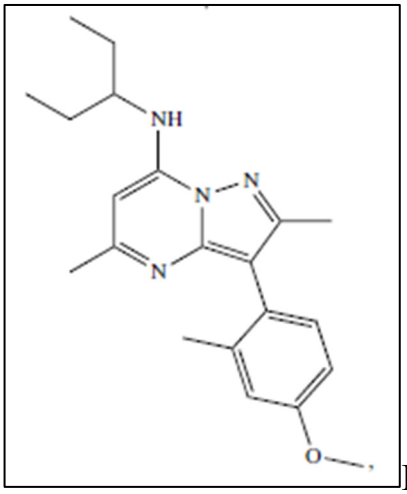
EX1001, 82:40–50.

64. The sixth is antalarmin:



EX1001, 8:1–15; 82:52–66; EX1096.

65. The seventh is DMP-904:



EX1001, 8:15–30; 83:1–16; EX1095.

66. The ’491 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 54.

67. None of these compounds are identified in the ’491 patent as compounds that can treat TARTs or OARTs. 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, 6:54-8:31, 81:37-83:39. The '491 patent also identifies other "additional chemotherapeutic agent[s]" as a glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, and an anti-androgen. EX1001, 6:56-58, 81:40-42.

B. '491 Patent Claims

68. I understand from Neurocrine's counsel that the claims of the '491 patent define the scope of the legal rights of the patent. Specifically, claim 1, the only independent claim, recites a method for treating a testicular adrenal rest tumor (TART) or an ovarian adrenal rest tumor (OART) as follows:

> 1. A method of treating an endocrine disorder associated with corticotropin-releasing factor type-1 (CRF_1) activity, comprising administering to a subject in need thereof a small molecule CRF_1 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 small molecule CRF_1 antagonist is administered to the subject twice per day, and
> wherein the subject is in the fed state,
> wherein the endocrine disorder associated with CRF_1 activity is a testicular adrenal rest tumor (TART) or an ovarian adrenal rest tumor (OART).

EX1001, 98:47–100:67.

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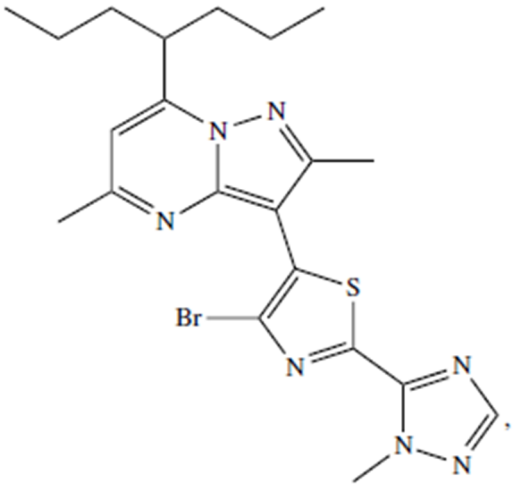
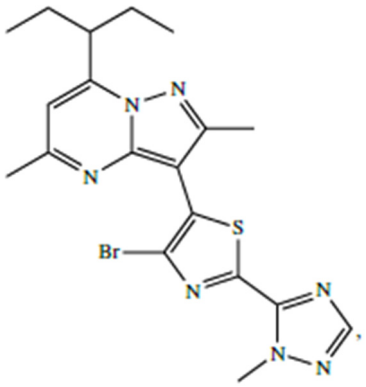
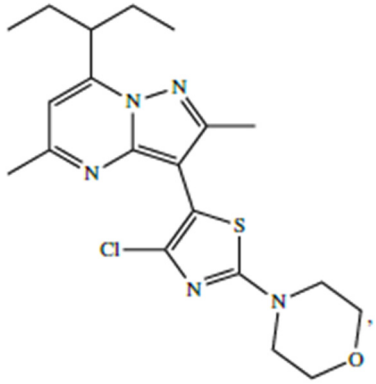
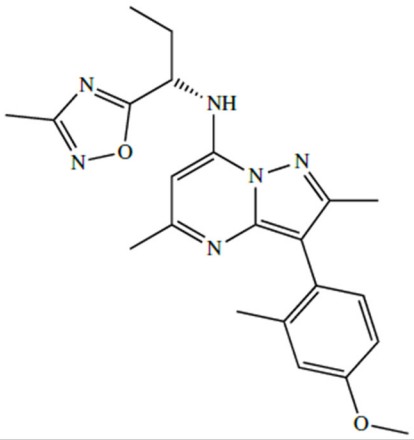
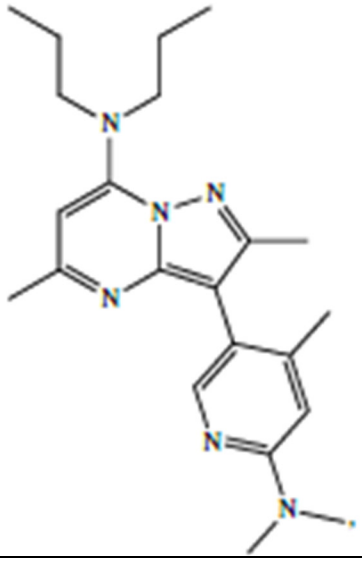
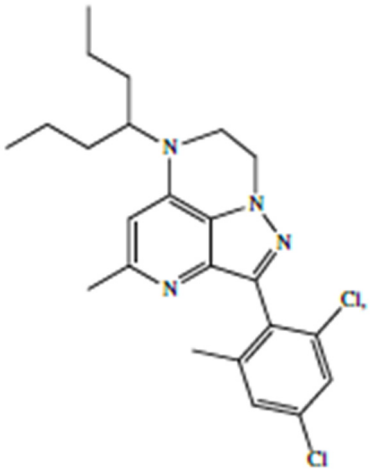
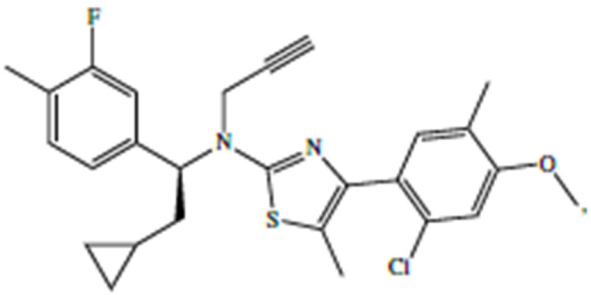
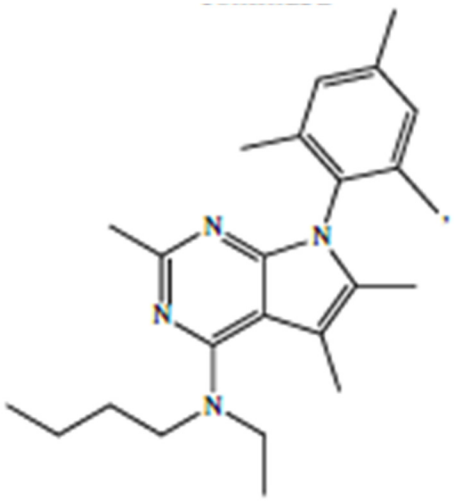
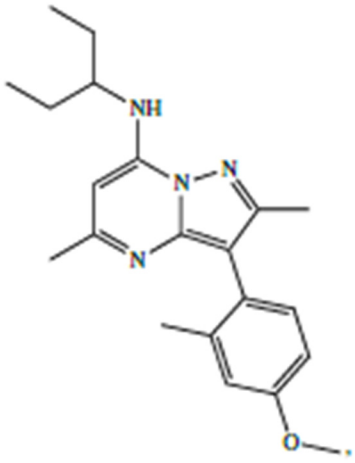
Compound Structure in Claim 1	Letter Designation
	**A**
	**B**
	**C**

Compound Structure in Claim 1	Letter Designation
	**D**
	**E**
	**F**

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

69. 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 '491 patent as "Compound 1." *See* above, paragraph 50. The rest are described in the '491 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 58-67. Claim 2 limits the CRF1 antagonist to tildacerfont. EX1001, 101:1–19. Claim 3 limits the CRF1 receptor antagonist to crinecerfont. EX1001, 101:20–35

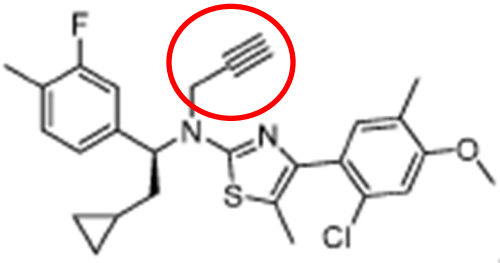
70. A first set of dependent claims specify details about the subject: has CAH (claim 4), is receiving a glucocorticoid in conjunction with the CRF_1 antagonist (claims 5–7), is an adolescent or at least 18 years old (claims 8 and 9). The remainder of the dependent claims specify details about the dose (claims 10-14), format (claims 15 and 16), and timing (claims 17–19) of the CRF_1 antagonist administration. EX1001, 102:14–36.

VI. THE '491 PATENT PROSECUTION HISTORY

71. The application that led to the '491 patent was filed on January 31, 2025, as U.S. Patent Application No. 19/043,275 ("the '275 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®

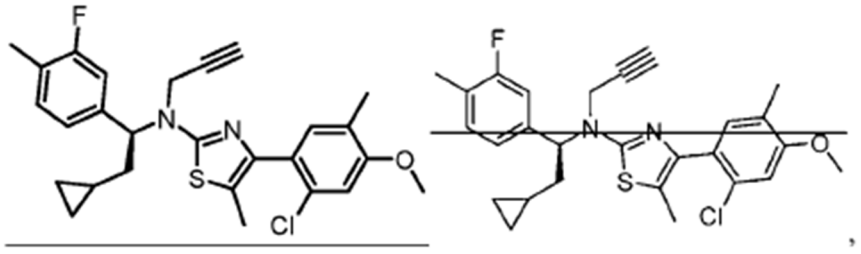
prescribing information, on December 13, 2024. EX1089; EX1010. I understand from counsel that the ’275 application claims priority to U.S. Provisional Patent Application No. 62/822,815, filed March 23, 2019 (“the ’815 Provisional”), and U.S. Provisional Patent Application No. 62/663,951, filed April 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”), filed October 27, 2020. EX1001, cover page, (60), (63).

72. I have reviewed portions of the prosecution history of the ’491 patent and of the applications to which the ’491 patent claims priority. Of particular relevance to my opinions, I note that the initial filing of the ’275 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, 35 (¶27), 93 (¶261). That structure is not crinecerfont. Moreover, I understand that it is not chemically possible to have a carbon-carbon quadruple bond.

73. I understand that on August 15, 2025, Spruce filed an Amendment in the ’275 application in which it amended claim 1 to replace the structure of one of the originally claimed small molecule CRF1 antagonists to the structure of crinecerfont, as follows:



74. I understand that the Examiner issued a “Notice of Allowance and Fees Due” on December 23, 2025. In that Notice, the Examiner provided the following “Reasons for Allowance”:

> [T]he claimed method is not taught or suggested by the prior art. Howerton, WO 2019036503; and Grigoriadis, US 20170020877, both of record, represent the closest prior art. Howerton and Grigoriadis teach treatment of congenital adrenal hyperplasia by administering a CRF1 receptor antagonist, however, treatment of a subject having an ovarian adrenal rest tumor or a testicular adrenal rest tumor, as required by the claims, is not taught or suggested.

I understand that the claims that the Examiner refers to are the claims of the ’491 patent, as issued.

75. I note that the Examiner issued a "Corrected Notice of Allowability" on January 21, 2026. EX1002, 435-436. This Corrected Notice does not contain a statement on the reasons for allowance.

76. I understand from counsel that the application leading to the '491 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 '491 patent (including Figures 10A and 10B) and whether it demonstrated that Compound 1 reduced ACTH levels and/or lead to reduced TART growth. *Id.*

77. 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: El820-El826 (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"). 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."

78. 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. Mendos-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).

79. I understand that the Examiner did not issue any claim rejections during prosecution of either the ’275 application (leading to this ’491 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 ’491 PATENT

80. 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 ’491 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 ’491 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 '491 patent.

VIII. INTERPRETATION OF THE '491 CLAIMS AT ISSUE

81. I have been informed by counsel for Neurocrine that for purposes of my analysis, the terms appearing in the '491 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.

82. 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.

IX. LEGAL STANDARDS

83. 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.

84. I understand from counsel that the earliest possible effective filing date of the ’491 patent is April 27, 2018, which is the date the first provisional patent application in this patent family was filed.

A. Written Description

85. 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.

86. 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

87. 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."

88. 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.

89. 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.

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

C. Obviousness

91. 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.

92. 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.

93. 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.

94. 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.

95. 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 '491 PATENT

96. In my opinion, the claims of the '491 patent lack written description support for four reasons: (1) a POSA would not understand that the inventors had possession of a method of treating OARTs; (2) a POSA would not understand the single-TART patient example in the '491 patent to convey that the inventors had possession of a method of treating TARTs or OARTs with the full scope of the CRF1 receptor antagonists recited in the claims; (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 crinecerfont in the application leading to the '491 patent as filed.

97. Independent claim 1 recites "[a] method of treating an endocrine disorder associated with corticotropin-releasing factor type-1 (CRF_1) activity, comprising administering to a subject in need thereof a small molecule CRF_1 antagonist, or a pharmaceutically acceptable salt thereof, wherein the small molecule CRF_1 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, wherein the small molecule CRF_1 antagonist is administered to the subject twice per day, and wherein the subject is in the fed state, wherein the endocrine disorder associated with CRF_1 activity is a testicular adrenal rest tumor (TART) or an ovarian adrenal rest tumor (OART)." EX1001, 98:46-100:67. I understand claim 1 encompasses a set of ten compounds that, when administered to a subject twice per day and in the fed state, purport to have the function of treating both TARTs and OARTs. 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 treat a TART or an OART. EX1001, 101:20-102:36.

A. The '491 patent lacks written description support for the claimed method of treating OARTs.

98. I have reviewed the specification of the '491 patent to assess whether it provides written description support for a method of treating OARTs. In my

opinion, based on my review of the ’491 patent and my experience, it does not. In my opinion, the ’491 patent does not demonstrate that, as of the priority date, the inventors were in possession of a method for treating OARTs 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.

99. The ’491 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 observations or laboratory observations, or technical discussion. In my opinion, a POSA would not have understood the inventors of the ’491 patent to have actually invented or possessed a method for treating OARTs based on these disclosures.

100. As noted above in § V.A, the ’491 patent contains four examples. None of the examples relate specifically or even generally to the treatment of OARTs or contain any data related to the treatment of 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 treatment of OARTs. 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.

101. The '491 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 '491 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

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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 treating OARTs. In my opinion, the '491 patent does not convey that the inventors possessed a method for treating OARTs.

102. The '491 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 female patients, and ovarian adrenal rest tissue cannot derive from intra-testicular adrenal tissue

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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 OARTs or their treatment.

B. The ’491 patent lacks written description support for methods of treating TARTs.

103. I have reviewed the ’491 patent’s disclosure relating to the treatment of TARTs. The patent describes only a single patient with classic CAH who purportedly had a TART and was treated with Compound 1 (tildacerfont). The patient is referenced in the specification in only two places, and in my opinion, this limited disclosure is insufficient to convey to a POSA as of the priority date that the inventors had possession of the method of treating TARTs as claimed in claims 1-19.

104. The ’491 patent states that Figures 10A and 10B show “[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. In Example 3, the patent states that Figures 10A and 10B “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, 96:17–20. Figures 10A and 10B are reproduced below:

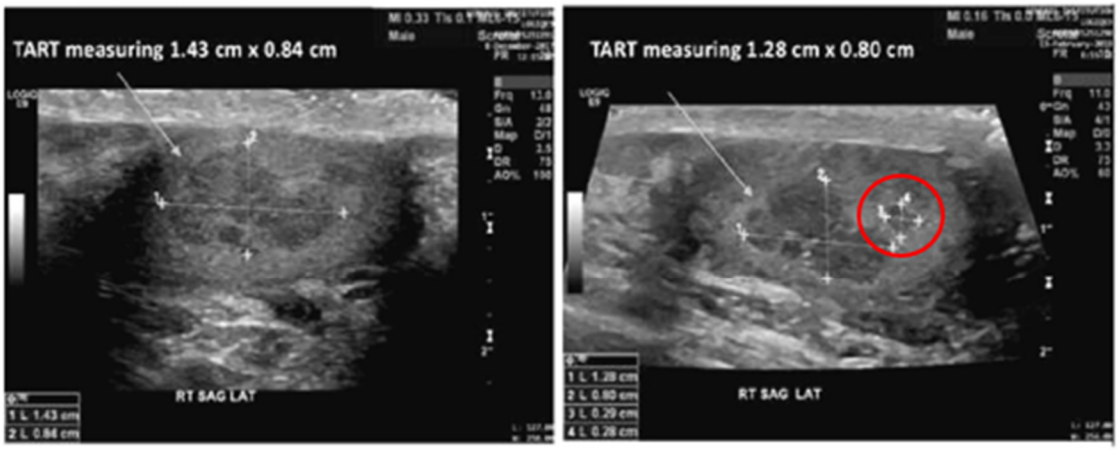

FIG. 10A *FIG. 10B*

105. The ’491 patent does not state that this patient reflected in Figure 10 was among the subjects reflected in Figure 4, which presents ACTH data for a group of ten CAH patients. Nor does the ’491 patent disclosure link the ACTH data shown in Figure 4 to the single patient described in Example 3. I did not identify any disclosure indicating that the patient with the TART experienced reduced ACTH levels as a result of treatment with Compound 1. Although the ’491 patent hypothesizes that Compound 1 “may be effective in reducing ACTH levels, thereby reducing the size of testicular lesions in TART” (EX1001, 93:56-58), it provides no information about the degree of ACTH reduction necessary to achieve TART shrinkage. In my opinion, a POSA would have expected this information given that Figure 4 shows some of the CAH patients treated with Compound 1

(tildacerfont) exhibited no improvement in ACTH levels at all, and one of those patients exhibited an increase in ACTH levels.

106. Other than noting that the Figure 10 patient was treated with Compound 1, nowhere does the '491 patent disclose the treatment method or dosing regimen used to administer Compound 1, the duration or frequency of dosing beyond mentioning a six-week treatment period, or any treatment protocol defining how Compound 1 was administered. The specification likewise does not disclose whether the patient received Compound 1 alone or in combination with concomitant glucocorticoids or other therapies. A POSA would have understood that a patient with classic CAH must receive additional glucocorticoids to survive, and glucocorticoids were already known to affect TARTs, as shown by Yu (EX1067, table 3) and the '491 patent (EX1001, 90:20-22). The specification does not provide any statistical or comparative analysis showing that the purported shrinkage in tumor size was, in fact, due to treatment with Compound 1 (tildacerfont). Because of this, a POSA would not know whether Compound 1 affected the TART or if some co-therapy, such as glucocorticoids, did.

107. In my opinion, a POSA would not have understood Figures 10A-10B to demonstrate any therapeutic difference in TART size between the purported pre-treatment and post-treatment images. The '491 patent does not define any response criteria for assessing treatment of a TART in this patient. The

specification does not describe how TART size was measured, what degree of change would be considered clinically meaningful, or whether the reported change was statistically significant or reproducible. The Figures 10A and 10B simply purport to show a change in size based on ultrasound measurements: "TART measuring 1.43 cm x 0.84 cm" for Fig. 10A and "TART measuring 1.28 cm x. 0.80 cm" for Fig. 10B.

108. The '491 patent fails to provide any analysis of the ultrasound images shown in Figures 10A and 10B. For example, the '491 patent does not describe, and it is unclear, how the "approximately 25% shrinkage" was calculated. As noted above, the only measurements disclosed in the written description are "TART measuring 1.43 cm x 0.84 cm" in Figure 10A and "TART measuring 1.28 cm x 0.80 cm" in Figure 10B. EX1001, 96:17-20. One standard approach for measuring a change in tumor size is to calculate the change in the longest diameter of the tumor. If a POSA were to calculate change in that way here, the longest diameter in Figure 10A is 1.43 cm and the longest diameter in Figure 10B is 1.28 cm. The percent change in diameter is thus ~10.5 % [(1.43 cm – 1.28 cm) / 1.43 cm = 10.48 %]. Another approach would be to measure a change in tumor size by the reduction, if any, in the area of the tumor. If a POSA were to calculate a change in area, the area of the TART in Figure 10A is ~1.20 cm^2 [1.43 cm x 0.84 cm ≈ 1.20 cm^2] and the area of the TART in Figure 10B is ~ 1.02 cm^2 [1.28 cm x

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0.80 cm ≈ 1.02 cm^2]. The decrease in area is ~0.18 cm^2 [1.20 cm^2 - 1.02 cm^2 ≈ 0.18 cm^2]. The percent shrinkage therefore is ~14.8% [(0.18 ÷ 1.20) × 100 ≈ 14.8%]. Accordingly, the reduction in TART size between Figure 10A and 10B is at most, between approximately 10.5% to approximately 15%, not 25% as the '491 patent states. This is an additional reason why a POSA would not have considered Figure 10A-10B as demonstrating a therapeutic response to treatment with Compound 1.

109. Moreover, based on my review, a POSA would observe several ambiguities in those images. For example, Figure 10A appears to mark and measure a single lesion, whereas Figure 10B appears to mark two lesions (the second lesion circled in red above), making it unclear whether Figure 10B reflects the same lesion or a different lesion altogether. For instance, if the ultrasound technician gathering the images moves the probe, it is possible that the lesions would merge and the diameter would be the same. A POSA would have considered this lack of explanation regarding measurements and analysis of the ultrasound images critical because the alleged changes in dimensions are only a few millimeters—approximately 1.5 mm on the x-axis and 0.4 mm on the y-axis.

110. A POSA would also recognize that the measurements shown in Figures 10A and 10B reflect changes on the order of only a few millimeters. In my experience, such small differences are within the range of variability commonly

observed in ultrasound imaging, particularly where imaging planes and measurement axes are not standardized.

111. Further, the depth at which the measurements were taken appears to differ between Figures 10A and 10B (10A shows a depth of 2.5 cm while 10B shows a depth of 3.3 cm), suggesting that the TART was not imaged or measured in a consistent manner. TARTs are nodular lobulated masses. And so measuring at different depths (or imaging planes) can result in different widths and lengths for the same tumor. This lack of consistency would make it difficult for a POSA to determine whether any apparent size difference reflects an actual change in tumor size. These differences do not necessarily reflect a difference in tumor size; instead, they only reflect a difference in the imaging planes.

112. Figures 10A and 10B also depict imaging of only one testicle, even though TARTs are typically bilateral tumors, meaning they are commonly present in both testes. EX1001, 25:9–10; EX1080, 211 (Claahsen-van der Grinten 2009). The ’491 patent does not provide any information regarding the status of the patient’s other testicle, which a POSA would consider critical and necessary in evaluating whether a treatment affected or had a clinical impact on TARTs size.

113. Even assuming that the images in Figures 10A and 10B show some reduction in the size of a TART in this single patient, the ’491 patent does not provide any information indicating whether such a reduction was clinically

meaningful, durable, or attributable to treatment with Compound 1 rather than natural variation, imaging variability, or other factors such as increased compliance with the patient's glucocorticoid dose or increased dosage of glucocorticoids. The patent does not include a control, comparator, or analysis across additional patients which, ordinarily, would provide a POSA with important context for assessing the clinical impact of a treatment modality like Compound 1.

114. In my opinion, a POSA would not extrapolate from the limited disclosure relating to this single patient to conclude that Compound 1 is effective for treating TARTs generally, particularly given the short treatment duration (only six weeks) and absence of supporting clinical or biochemical data. The '491 patent also does not provide any data or disclosure relating to the treatment of TARTs using CRF1 receptor antagonists other than Compound 1 (tildacerfont). As discussed below, the additional CRF1 receptor antagonists recited in the claims are not evaluated in the context of TART treatment in the specification.

115. I also understand that the '491 patent claims priority to U.S. Provisional Application 62/663,951 which stated that "it is not known whether Compound 1 can successfully treat TART." EX1055, ¶¶287, 296. This is so even though the Provisional Application contains the same data—Figures 10A and 10B—as the '491 patent. I understand that this statement does not appear in the '491 patent. Nevertheless, in my opinion, this earlier acknowledgment supports

my opinion that a POSA would not have reasonably concluded that all of the claimed compounds are effective to treat TARTs based on a single result from one patient under these circumstances.

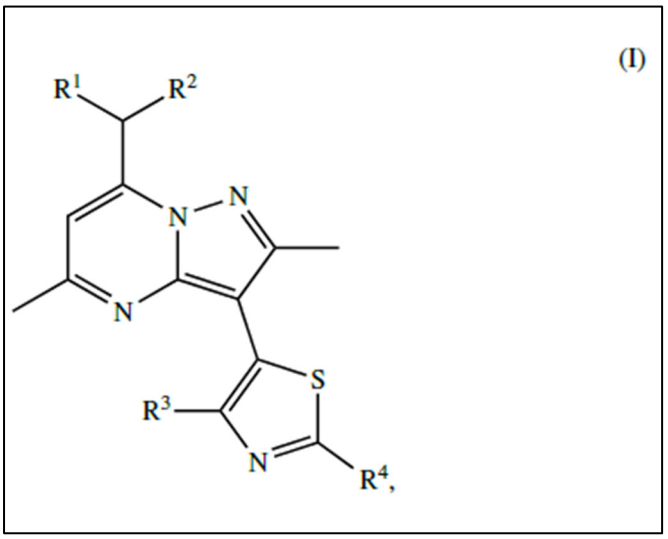
116. For these reasons, a POSA reviewing the ’491 patent would understand that the disclosure relating to treatment of TARTs is limited to a single, briefly described patient treated with Compound 1, without sufficient information to assess treatment efficacy, reproducibility, or applicability to other patients or other CRF1 receptor antagonists.

C. The ’491 patent also lacks written description support for seven of the ten claimed compounds for treating TARTs or OARTs.

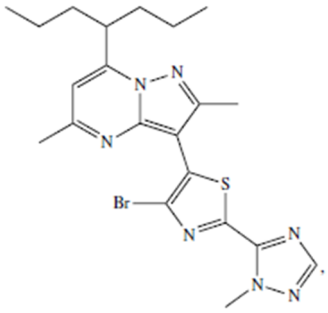
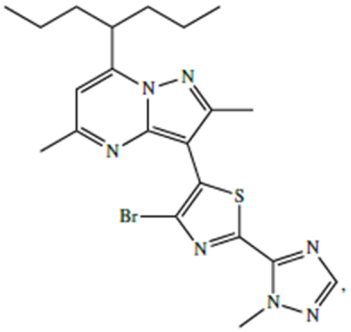
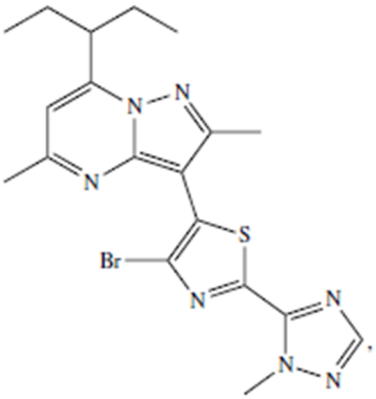
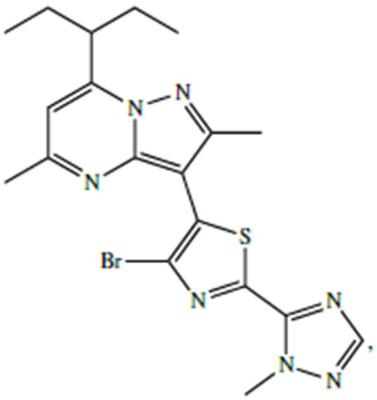
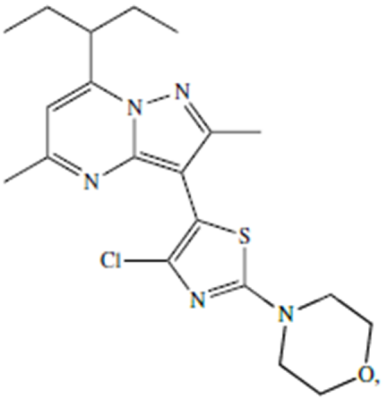
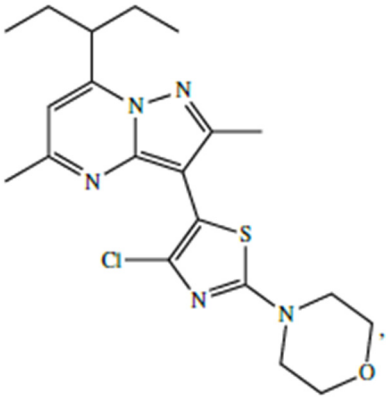
117. I have reviewed the specification of the ’491 patent to assess whether it provides written description support for the full scope of the ten compounds identified in Claim 1. In my opinion, based on my review of the ’491 patent and my experience, it does not. In my opinion, the ’491 patent does not demonstrate that, as of the priority date, the inventors were in possession of a method for treating TARTs or OARTs using all of claim 1 compounds. In addition, seven of the ten claimed compounds are not identified in the ’491 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 treating TARTs or OARTs. One claimed compound, crinecerfont, was not disclosed in the original application leading to the ’491 patent.

118. A POSA would view the '491 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):



119. The '491 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 '491 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 CRF_1 antagonist is: 
B	In some embodiments, the compound is 	-continued 
C	In some embodiments, the compound is 	

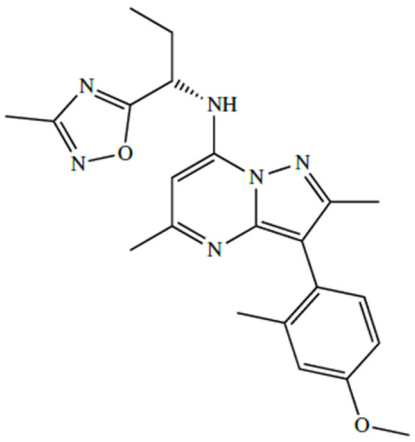
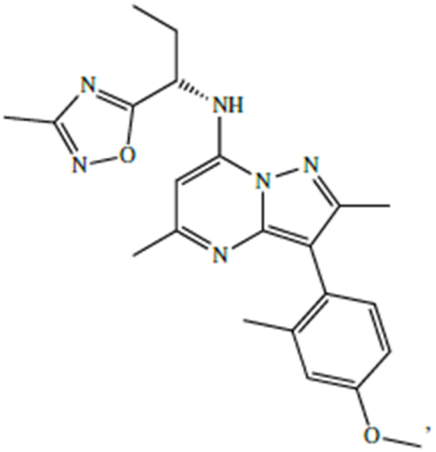
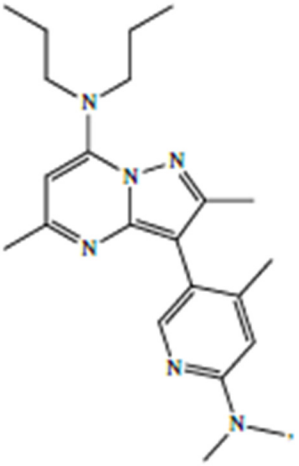
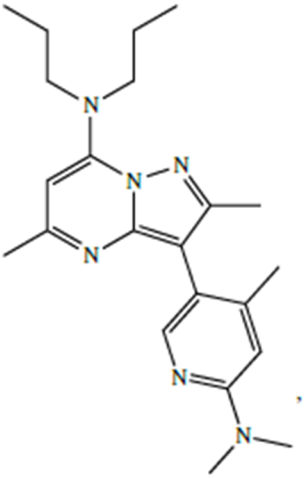
EX1001, 3:11–67; 98:51–99:30; EX1091 (compound **A**); EX1092 (compound **B**); EX1059 (compound **C**).

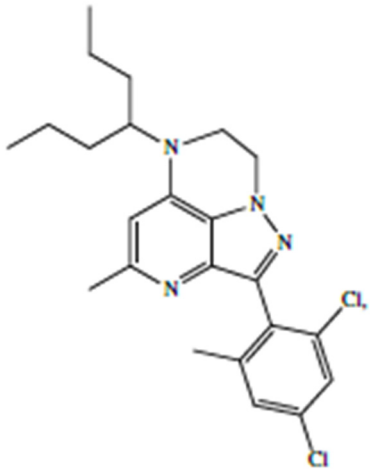
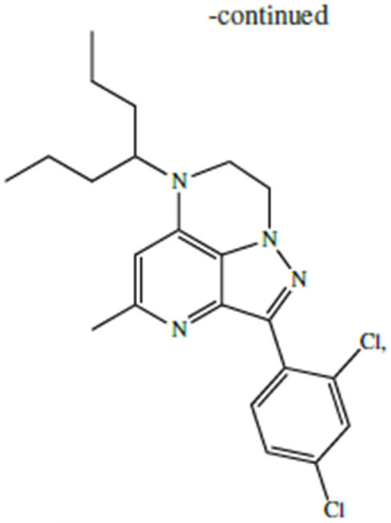
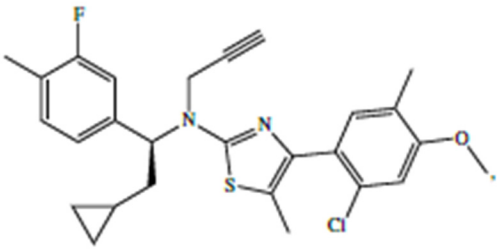
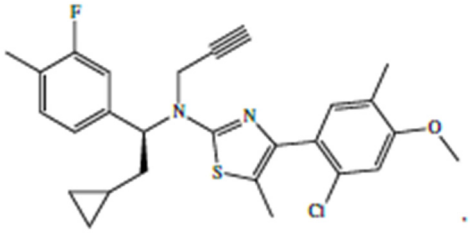
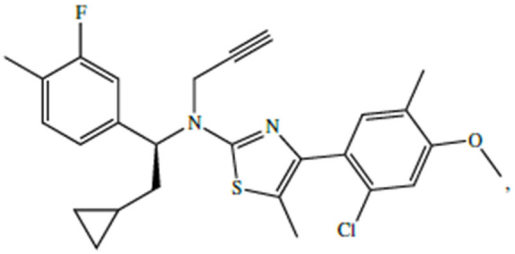
120. As noted above in § V.A, one of these Formula (I) compounds is identified in the '491 patent as "Compound 1," which corresponds to tildacerfont and is the compound designated as "**C**," for ease of reference. EX1001, 90:42-58; 96:40–45; EX1059.

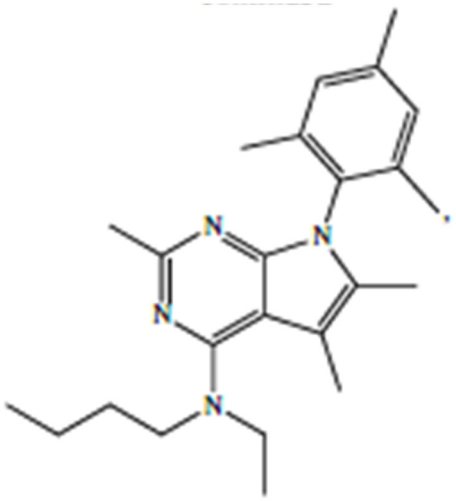
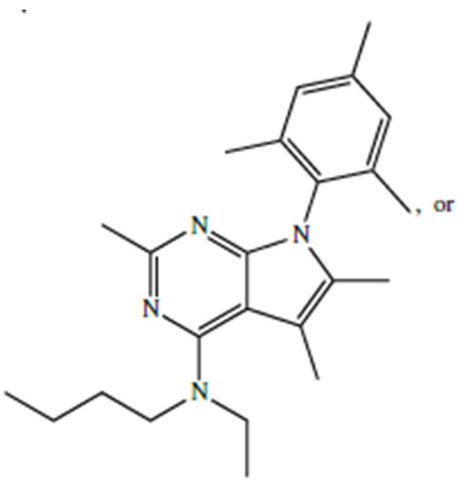
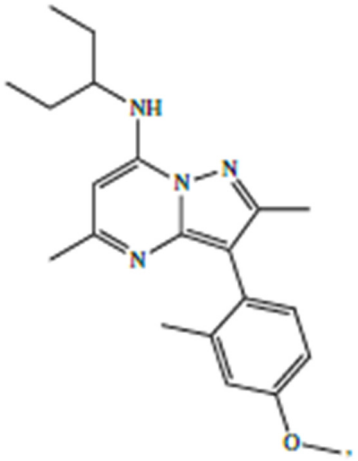
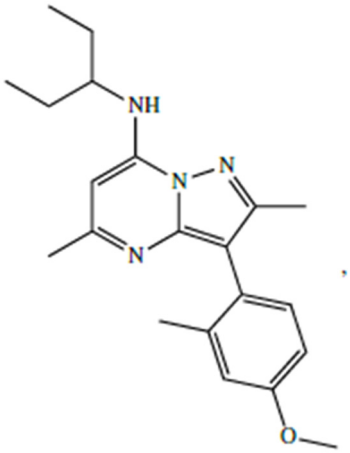
121. The '491 patent's discussion of CRF1 receptor antagonists focuses on compounds of Formula (I), and in particular on Compound 1 (tildacerfont). For example, the '491 patent states that Compound 1 "may be effective in blocking ACTH synthesis, thereby reducing the size of testicular lesions in TART," 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. These disclosures do not show possession of treatment of TARTs or OARTs using any of the seven claimed CRF1 receptor antagonists not identified as a Formula (I) structure.

122. In addition to the three Formula (I) compounds, claim 1 of the '491 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,	], SSR-126374,
H	 At Col. 7:55-65.  At Col. 82:40-50.	

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

EX1001, 6:65–8:50; 81:50–83:38.

123. 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). EX1006, [0054]-[0056]. 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 '491 patent fails to disclose the structure of the remaining compound **G**, SSR-126374. Nevertheless, it is not identified in the '491 patent as a Formula (I) compound.

124. These seven compounds are not described in the '491 patent as compounds for treating TARTs or OARTs. 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; see also id., 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 treating TARTs or OARTs, as I understand are required by claims 1 and 3-19.

125. I did not identify any portion of the '491 patent that describes the compounds designated **D-J** as compounds used to treat TARTs or OARTs themselves. Instead, the '491 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 the treatment of TARTs or OARTs.

126. I have reviewed the entire specification of the '491 patent specification, and considered it from the vantage point of a POSA at the priority date. Every figure, description, and example relating to purportedly treating TARTs or OARTs 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 the treatment of TARTs or OARTs. In my opinion, a POSA reviewing the '491 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.

127. A POSA would understand that disclosure of data for 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.

128. 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.

129. In a scientific publication, Spruce described Compound 1 (tildacerfont) as having "unique structural features," further underscoring that it is

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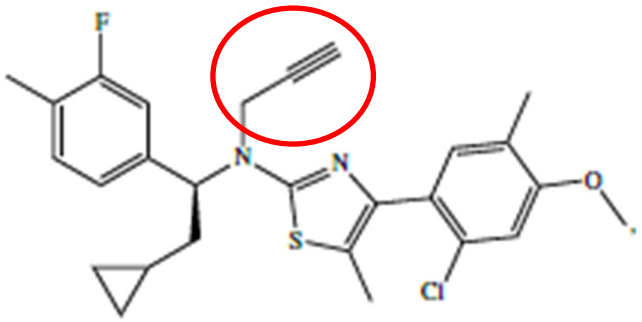
not representative of all CRF1 receptor antagonists. EX1041 (Sarafoglou), 4667. The '491 patent does not provide guidance for identifying other CRF1 receptor antagonists that might share the features of Compound 1 (tildacerfont) for treatment of TARTs or OARTs. I also note that the '491 patent does not reference or describe any "unique structural features" for Compound 1.

130. 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).

131. For these reasons, it is my opinion that a POSA reviewing the '491 patent would not understand the disclosure of Compound 1 (tildacerfont) or of Formula (I) to describe or support methods of treating TARTs or OARTs using the full scope of the claimed CRF1 receptor antagonists that differ structurally and clinically from Compound 1, like Compounds **D**-**J** do.

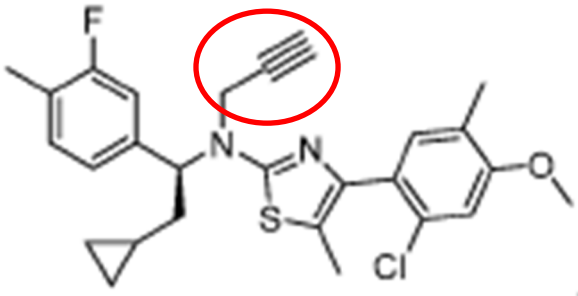
D. The ’491 patent lacks written description support for crinecerfont

132. 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., (−CH_2−C≡CH).

133. I understand that in the originally filed application leading to the ’491 patent, Spruce disclosed the following structure:



EX1002, 35 (¶27), 93 (¶261), 141 (claim 1), 142 (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., (–CH_2-C≡C). This structure is not crinecerfont and cannot exist.

134. I have reviewed several documents that I understand from counsel the '491 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 '491 patent—the U.S. Application No. 19/043,275—and it also does not disclose crinecerfont. EX1002, 29-145.

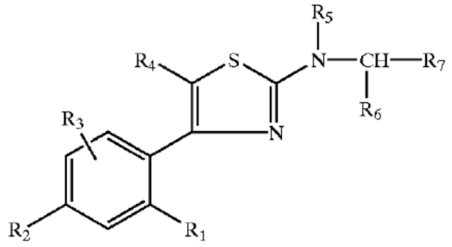
135. I understand from counsel that Spruce replaced the original structure (having a carbon-carbon quadruple bond) with a structure depicting crinecerfont during prosecution of the application leading to the '491 patent. I have been informed and understand from counsel that replacing the structure is impermissible "new matter" unless a POSA would consider that replacement to constitute an obvious correction of an obvious error.

136. 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.

137. 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.

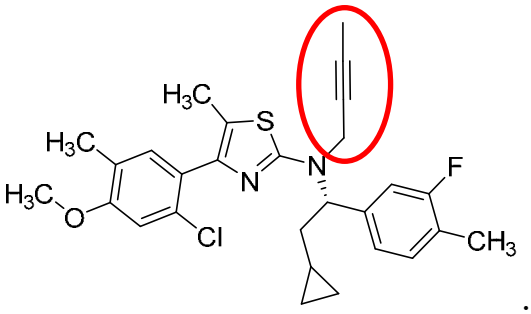
138. The Sanofi patent discloses aminothiazole derivatives having the following formula (I) as CRF receptor antagonists:



.

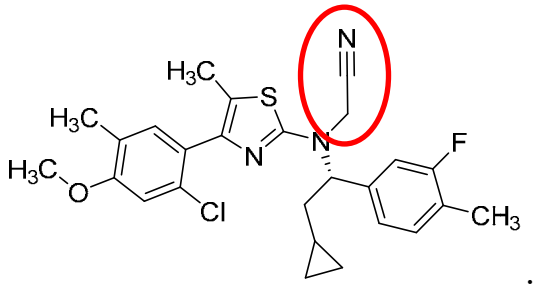
EX1060, 4:5-14. The '491 patent's original carbon-carbon quadruple bond is located at position R_5. The Sanofi patent teaches that R_5 may be "an alkenyl of 3 to 6 carbon atoms; an alkynyl of 3 to 6 carbon atoms; a cyano(C_1-C_6)alkyl; [or] a (C_1-C_4)alkoxy." *Id.*, 4:45-47. Thus, a POSA would have understood that multiple alternative R_5 substituents could have served as a "correction" to the originally disclosed structure having the carbon-carbon quadruple bond.

139. For example, a POSA would have recognized from the Sanofi patent that R_5 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 R_5 substituent is an "alkynyl of 3 to 6 carbon atoms," which is represented by $–CH_2–C\equiv C–CH_3$. EX1060, 4:45-46.

140. As another example, a POSA would have recognized from the Sanofi patent that R_5 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 R_5 substituent is "a cyano (C_1-C_6) alkyl," which is represented by $–CH_2–C\equiv N$.

XI. OPINIONS REGARDING ENABLEMENT OF THE '491 PATENT

141. I understand that claims 1-19 of the '491 patent encompass methods of treating both TARTs and OARTs using any one of ten recited CRF1 receptor

antagonists, subject to certain dosing conditions. Dependent claim 2 is limited to a single compound (tildacerfont) and dependent claim 3 is limited to a single compound (crinecerfont), but still require treatment of both TARTs or OARTs. Based on my review of the '491 patent, my familiarity with the relevant scientific literature, and my clinical experience, I do not believe the specification provides sufficient technical teaching to allow a POSA to practice these methods across the full scope of the claims without extensive, iterative experimentation that goes well beyond what a POSA would consider routine.

142. 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.

143. 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 first need to determine whether any of the claimed CRF1 receptor antagonists meaningfully suppress ACTH in patients with TARTs or OARTs,

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whether such suppression is durable, and whether any degree of ACTH suppression correlates with measurable changes in adrenal rest tissue for both TARTs and OARTs—none of which is disclosed in the ’491 patent.

144. The scope of what the claims require is significant. Each claim requires a method that treats two distinct clinical conditions—TARTs or OARTs. No dependent claim narrows the method to treating TARTs only. In addition, claims 1 and 4-19 encompass ten CRF1 receptor antagonists, each of which would need to be capable of treating TARTs or OARTs. The ’491 patent does not contain clinical evidence addressing treatment of OARTs.

145. In my review of the ’491 patent, I did not identify any example, laboratory evidence, clinical observation, dosing protocol, monitoring strategy, response criteria, or treatment outcome data related to the treatment of OARTs. As I explained above in § X.A, 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, 24:7-10, 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. It does not provide any example, laboratory evidence, clinical observation, dosing regimen, response criteria, or treatment outcome relating to an OART patient. A POSA attempting to treat OARTs using any of the claimed CRF1 receptor antagonists would therefore lack practical

guidance regarding diagnosis, monitoring, treatment endpoints, and expected clinical response for OARTs based on the ’491 patent’s disclosure.

146. 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, ovarian adrenal rest tumors 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 CRF1 receptor antagonist could reliably treat OARTs and what dosing and monitoring would be required.

147. As explained above in § X.B, even with respect to TARTs, the ’491 patent does not provide key details that a POSA would need to reproduce or evaluate the alleged treatment effect in the single referenced patient. EX1001, Figs. 10A-B, Example 3. The specification does not disclose the dosing regimen used for that patient (including dose amount, dose frequency, timing relative to meals, or treatment protocol), does not describe the concomitant glucocorticoids

administered, and does not provide response criteria defining what constituted "treatment" of a TART in that case.

148. In my experience, reliable assessment of tumor size by ultrasound typically requires standardized imaging planes, repeated measurements, and documentation of inter-observer variability, none of which are described in the '491 patent. The '491 patent also does not provide statistical or comparative analysis supporting the alleged change in tumor size in that patient, does not provide any analysis of the ultrasound images presented, and does not provide objective criteria for interpreting what is shown in Figures 10A–10B (including whether the images were captured in consistent planes, whether lesions were measured consistently, and what degree of measurement variability would be expected). In my opinion, these omissions would prevent a POSA from using the single-patient disclosure as a reproducible, enabling teaching for treating TARTs.

149. Moreover, as I explained above in § X.B, the '491 patent's examples and discussion relating to TARTs treatment 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, 90:4-63. 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, TARTs/OARTs or tumor outcomes. EX1001, 93:53-95:50, 96:38-98:10. 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, 95:51-96:37. In my opinion, these disclosures do not teach a POSA how to treat TARTs or OARTs using any CRF1 receptor antagonist, and certainly not the claimed CRF1 receptor antagonists beyond Compound 1 (tildacerfont).

150. Even if the ’491 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 claimed CRF1 receptor antagonists, many of which are structurally distinct from Compound 1, to produce the same effects. 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 tumor-treatment outcomes.

151. 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 TARTs and OARTs; (ii) design monitoring protocols (including

imaging approach and hormone endpoints); and (iii) test each compound to determine whether it produces a reliable tumor response. 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.

152. With respect to OARTs, the lack of 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 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 patients with OARTs, standardize diagnostic and imaging approaches, and assess whether any of the claimed compounds treat OARTs. 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 '491 patent.

153. I understand that the '491 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 treat TARTs or OARTs in an animal. That would not be routine testing a POSA could perform based on the disclosure of the '491 patent.

154. 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 anti-tumor-related disclosure only for Compound 1 (tildacerfont), a POSA would not be able to predict that any of the other claimed compounds would produce the same anti-tumor effect without trial-and-error testing.

155. 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 '491 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.

156. 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 treat OARTs (a disease that is rare and not well understood), how to reproduce or evaluate the claimed tumor effects in TARTs, or how to select and use each of the ten CRF1 receptor antagonists to achieve the claimed methods of treating TARTs or OARTs. 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.

157. In sum, based on my review of the '491 patent and my clinical and scientific experience, a POSA would understand that the specification provides, at most, a starting point focused on Compound 1, but does not teach how to treat TARTs or OARTs using 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 treat

TARTs or OARTs. In practical terms, the '491 patent would be understood by a POSA as outlining a research hypothesis rather than providing an enabling teaching for a completed method of treating TARTs or OARTs by administering the claimed 10 compounds.

XII. OPINIONS REGARDING OBVIOUSNESS OF THE '491 PATENT

A. PRIOR ART

158. As discussed below, it is my opinion that claims 1 and 3–19 of the '491 patent would have been obvious over the work that Neurocrine and others carried out and published before Spruce filed the application for its '491 patent. Specifically, over Grigoriadis (EX1006), Yu (EX1067), Howerton (EX1074), and GSK Study (EX1075), each of which is summarized in this section.

1. Grigoriadis (EX1006)

159. 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.

160. 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].

161. 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. Yu (EX1067)

162. 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.

163. 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.*

164. 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.

165. 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.

3. Howerton (EX1074)

166. 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 CRFr1 [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).

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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.*

167. 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.

4. GSK Study (EX1075)

168. The GSK Study reference (EX1075) is a clinicaltrials.gov entry for Clinical Trial NCT00539136, which is a Phase 1 study carried out from 2007 to 2008 to examine the absorption of GSK561679 (verucerfont) in healthy male volunteers. EX1075, 1-2. GSK561679 and NBI-77860 are verucerfont. EX1082, 1-6; EX1006 at [0084]. I understand from the declaration of June Ann Munford that the GSK Study was publicly available at least by July 3, 2013. EX1086, ¶11.

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In this study, verucerfont was administered to the male volunteers in either tablet or solution format. EX1075, 1. The solution was administered in the fasted state; the tablet was administered in both the fed and fasted state. *Id.* The study's primary endpoints were pharmacokinetic scope, complete gastric emptying of radioactive marker, and complete tablet breakdown. *Id.* The study's secondary endpoints included Area Under the plasma concentration-time Curve (AUC) for three time periods: AUC (0–24), AUC (0-t) and AUC (0-∞) to evaluate drug exposure over time, as well as other pharmacokinetic parameters including: lambda_Z (drug elimination), t1/2 (half-life), tlag (lag time), Ka (absorption rate constant), and the time to absorb the 25, 50 and 90% of the total absorbed dose. *Id.*

B. OBVIOUSNESS OF CLAIMS 1 AND 3-19

169. It is my opinion that independent claim 1 and dependent claims 3–19 of the '491 patent would have been obvious over Neurocrine's Grigoriadis (EX1006), especially in view of Yu (EX1067), Howerton (EX1074), and the GSK Study (EX1075).

170. At the time the '491 application 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 159–161; 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 162–165, EX1067, 155–159. Combining Grigoriadis with Yu would have provided a POSA at the time that the '491 application was filed with a reason to use one of the '491 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.

171. As discussed in more detail below, the remaining requirements of claim 1 (administration "twice per day" and "in the fed state")—as demonstrated for example in Howerton (EX1074) and the GSK study (EX1075)—would have been obvious to a POSA. A POSA would have combined Grigoriadis with references like Howerton and the GSK study to arrive at these claimed parameters, as well as those of dependent claims 3–19.

C. Claim 1

172. Claim 1 recites

> 1. A method of treating an endocrine disorder associated with corticotropin-releasing factor type-1

(CRF_1) activity, comprising administering to a subject in need thereof a small molecule CRF_1 antagonist, or a pharmaceutically acceptable salt thereof, wherein the small molecule CRF1 antagonist is:

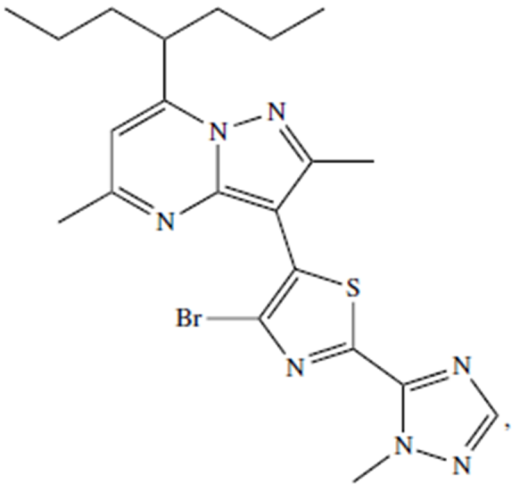
[*one of the ten compounds structures set forth in the table below and labeled with letter designations (A–J) and common synonyms which do not appear in the claims, for easy reference*], or a pharmaceutically acceptable salt thereof,

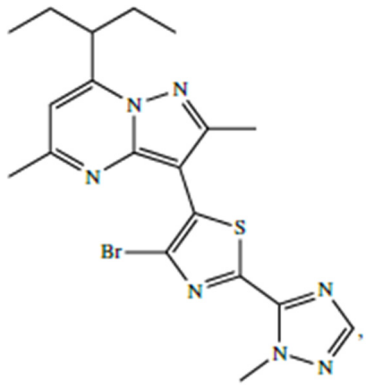
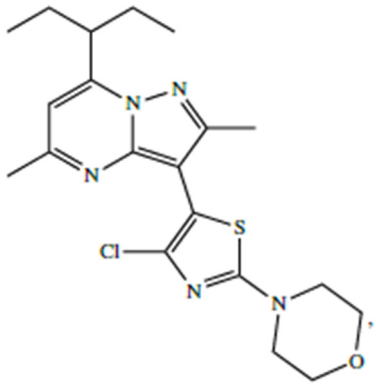
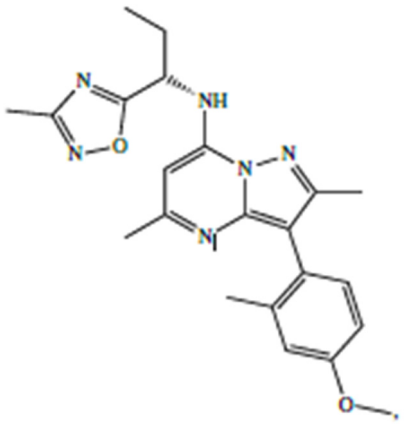
wherein the small molecule CRF_1 antagonist is administered to the subject twice per day, and

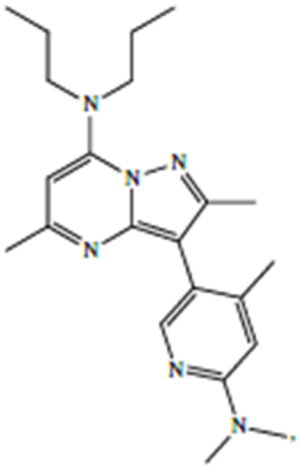
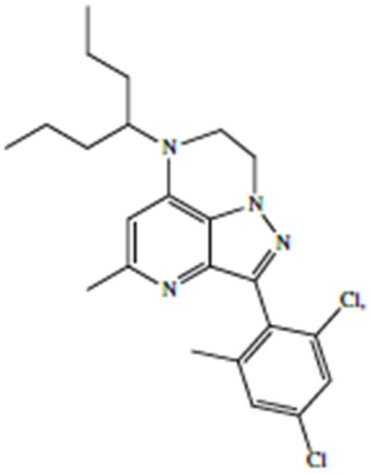
wherein the subject is in the fed state,

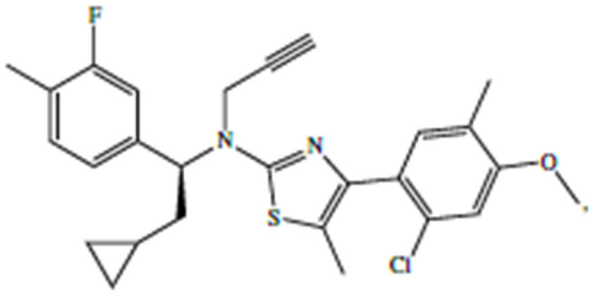
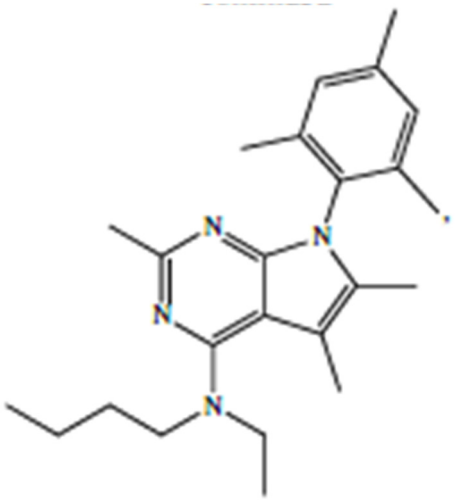
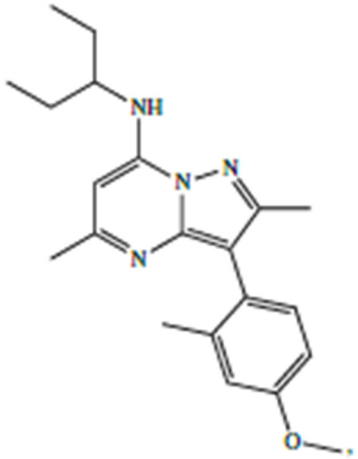
wherein the endocrine disorder associated with CRF_1 activity is a testicular adrenal rest tumor (TART) or an ovarian adrenal rest tumor (OART).

EX1001, 98:47–100:67; *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-2*H*-[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)

173. It is my opinion that Claim 1 is obvious over Grigoriadis (EX1006), Yu (EX1067), Howerton (EX1074), and the GSK study (EX1075).

1. "A method of treating an endocrine disorder associated with corticotropin-releasing factor type-1 (CRF1) activity"

174. Grigoriadis teaches a method of treating an endocrine disorder associated with CRF1 activity.

175. First, Grigoriadis teaches that congenital adrenal hyperplasia (CAH) is an endocrine disorder associated with CRF1 activity, and that "testicular adrenal rest tumors in men" are a known complication of CAH. *See* paragraphs 159–161 and 169–171 above; EX1006, [0002], [0005], [0044], [0051], [0054], [0090]–[0093] table on pages 4 and 6.

176. The endocrine system refers to the network of glands and organs that produce and regulate hormones in the body. An endocrine disorder is a condition that disrupts the normal production, release, or action of hormones, disrupting normal bodily functions. EX1076, 624-625.

177. As Grigoriadis describes, within the steroid synthetic pathway in the adrenal glands (as depicted in FIG. 1), corticotropin releasing factor (CRF, a hormone produced by the hypothalamus) "has been found to produce profound alterations in endocrine, nervous, and immune system functions," and is "believed to be the major physiological regulator" of ACTH (a hormone produced by the pituitary gland—*see* FIG. 1). *Id.* at [0034], [0048], FIG. 1. Binding of secreted

CRF to the CRF1 receptor (a member of the class B family of G-protein coupled receptors), causes ACTH to be released from corticotrophs in the anterior pituitary. *Id.*

178. CAH is a genetic disorder that results in dysregulation of this steroid synthetic pathway. EX1006, [0004], [0005] [0034], FIG. 1. The most prevalent form of CAH is caused by a deficiency in the enzyme 21-hydroxylase (also referred to as 21-a-hydroxylase), which results in a decrease of cortisol (a glucocorticoid hormone produced by the adrenal glands), an increase in androgens (sex hormones) such as testosterone, and excessive ACTH production. *See id,* ¶¶ [0004], [0005], [0034], [0050]. As Grigoriadis also explains, this weakens the negative feedback loop of cortisol on hypothalamic and CRF secretion and pituitary ACTH release, whereby the decrease in cortisol causes a concomitant increase in the production of ACTH, which also contributes to the overproduction of androgens. Id., [0050].

179. As discussed above (*see* paragraphs 159–161), 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]. As Grigoriadis notes, goals of CAH treatment include inhibiting "testicular adrenal rest tumors in men." EX1006, [0044]. A POSA reading Grigoriadis would understand that the methods described for treating CAH and its related disorders

include "testicular adrenal rest tumors in men." Therefore, Grigoriadis teaches "an endocrine disorder associated with corticotropin-releasing factor type-I (CRF1) activity."

180. As also discussed above (*see* paragraphs 159–161), Grigoriadis also teaches methods of treating CAH by administering an effective amount of a CRF1 receptor antagonist and that the goal of treating CAH is not simply to correct the dysregulation, but also to manage its related disorders, such as "testicular adrenal rest tumors in men." EX1006, [0002], [0005]. Clinicians evaluating the effectiveness of such a CRF1 receptor antagonist treatment, as Grigoriadis explains, can use biomarkers such as plasma levels of 17–OHP, androstenedione, testosterone, cortisol, and ACTH to monitor treatment efficacy. EX1006, [0060]. For example, as was done in the clinical study described in Grigoriadis' Example 6. *See* paragraphs 159–161 above; EX1006, [0092].

2. "comprising administering to a subject in need thereof a small molecule CRF1 antagonist, or a pharmaceutically acceptable salt thereof,"

181. 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," allowing normalization of androgen hormones. *Id.* at ¶ [0007]; *see also* ¶¶ [0040], [0050], [0051], [0052], [0061], [0070], [0090]–[0093].

3. "wherein the small molecule CRF1 antagonist is: . . . "

182. Grigoriadis teaches administering at least two of the small molecule CRF1 antagonists listed in claim 1 (and depicted in the table following paragraph 172 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 '491 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 '491 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.

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4. "wherein the small molecule CRF1 antagonist is administered to the subject twice per day" and "wherein the subject is in the fed state"

183. Claim 1 also recites "wherein the small molecule CRF1 antagonist is administered to the subject twice per day" and "wherein the subject is in the fed state." In my opinion, these limitations would have been obvious to a POSA at the time the '491 patent was filed, for example from the teachings of Grigoriadis as combined with Howerton and the GSK study.

"Twice per day" Administration

184. 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 166–167, also relates to administration of CRF1 receptor antagonists, including some of the compounds in claim 1 of the '491 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.

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185. 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.

186. 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.

187. 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 '491 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 '491 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).

188. 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.

189. 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.

190. 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].

191. 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.

192. 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.

"Fed State" Administration

193. As discussed above in paragraphs 43–47, by 2018 the optimization of any food effects and, as a result, administration with food (fed state) or without food (fasted state) was considered routine and well within the skillset of the POSA.

194. Grigoriadis notes, for example, that "[o]ptimal doses may generally be determined using experimental models and/or clinical trials." EX1006, ¶ [0063]. As discussed above, the GSK study describes a clinical trial designed to measure the absorption of verucerfont in healthy male volunteers, measuring drug exposure over time as well as other pharmacokinetic parameters under both fed and fasted conditions. *See* paragraph 168, above. That is, the GSK Study expressly teaches administering verucerfont in both the fasted and fed states. A POSA, as Grigoriadis teaches, would have performed a clinical trial such as the one described in the GSK Study to determine whether there were any food effects and, if so, adjust administration accordingly (e.g., specifying administration in either the fed or fasted state).

195. As discussed above in paragraphs 43–47, if a drug has a food effect, there are just three choices: choose a different drug, re-formulate the drug, or specify administration in the fed or fasted state. Practically speaking, for a given drug formulation, that means there is just one choice: specify whether the medicine should be taken with or without food. A POSA would have recognized that this leaves two options: with food (fed) or without food (fasted). A POSA would have a reasonable expectation of success with either dosing option because there is nothing innovative in determining whether a food effect is observed and, if so, what type, and choosing between those two options.

196. As with twice-daily dosing, I see nothing in the '491 patent teaching that dosing in the fed state represents anything new, or produces any result that a POSA would not have already expected. From the viewpoint of a POSA, the '491 patent treats administration in the fed and fasted states interchangeably by stating that the CRF1 receptor antagonist is "administered in the fed state" in some embodiments and "in the fasted state" in other embodiments. EX1001, 6:35-39, 78:54-58, 81:4-7.

5. "wherein the endocrine disorder associated with CRF1 activity is a testicular adrenal rest tumor (TART) or an ovarian adrenal rest tumor (OART).

197. As described above in paragraphs 159–161, 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."

198. Likewise, Yu (EX1067), as described above (paragraphs 162–165) 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.

199. 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 TARTs by administering Grigoriadis' CRF1 receptor antagonists (e.g., verucerfont or crinecerfont) to reduce ACTH levels and, as a result, treat TARTs.

200. I note that claim 1 of the '491 patent does not specify what "treating" means in the context of "treating an endocrine disorder." However, elsewhere, the '491 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

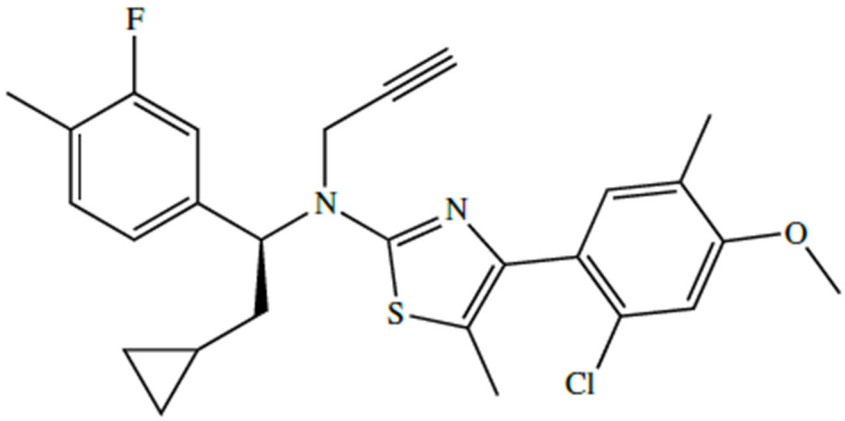
human clinical data that demonstrates that the CRF1 receptor antagonist NBI-77860 (verucerfont) lowers ACTH levels compared to placebo. *See, e.g.,* EX1006 at Examples 5 and 6 (paragraphs [0087]-[0092] and Figures 4–5). These teachings provide a POSA with a reasonable expectation that TARTs can be treated with a CRF1 receptor antagonist disclosed in Grigoriadis, such as crinecerfont or verucerfont.

201. 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.

D. Dependent Claims

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

202. Claim 3 recites: "[t]he method of claim 1, wherein the small molecule CRF_1 antagonist is:



or a pharmaceutically acceptable salt thereof. EX1001, 101:20–35.

203. 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 172; EX1006, ¶¶ [0013], [0054], page 6.

2. Claim 4 — "wherein the subject has congenital adrenal hyperplasia (CAH)"

204. Claim 4 recites "[t]he method of claim 1, wherein the subject has congenital adrenal hyperplasia (CAH)." EX1001, 101:36–37.

205. 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].

3. Claim 5 — "wherein the subject is receiving a glucocorticoid in conjunction with the administering of the small molecule CRF1 antagonist"

206. Claim 5 recites "[t]he method of claim 1, wherein the subject is receiving a glucocorticoid in conjunction with the administering of the small molecule CRF_1 antagonist." EX1001, 102:1–3.

207. Grigoriadis teaches that in some cases, its disclosed methods "may further comprise administering a GC [glucocorticoid] at a dose lower than the currently recommended dose of a GC for treating a subject who has CAH." EX1006, ¶ [0070].

4. Claims 6 and 7 — "wherein the glucocorticoid comprises . . ."

208. Claim 6 recites "[t]he method of claim 5, wherein the glucocorticoid comprises beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisone, or triamcinolone, or a combination thereof." EX1001, 102:4–8.

209. Grigoriadis teaches the co-administration of several glucocorticoids, including hydrocortisone, prednisone, prednisolone, dexamethasone, and fludrocortisone. EX1006, ¶ [0070].

210. Claim 7 recites "[t]he method of claim 6, wherein the glucocorticoid is hydrocortisone." EX1001, 102:9–10.

211. Grigoriadis teaches the co-administration of hydrocortisone. EX1006, ¶ [0070].

5. Claims 8 and 9 — "wherein the subject is . . . "

212. Claim 8 recites "[t]he method of claim 1, wherein the subject is an adolescent." EX1001, 102:11–12. Claim 9 recites "[t]he method of claim 1, wherein the subject is at least 18 years old." EX1001, 102:12–13.

213. Grigoriadis teaches administration of CRF1 receptor antagonist to block the release of ACTH and that treatment efficacy can be "easily measured in both children and adults." EX1006, ¶ [0060]. A POSA understands that "children" includes an adolescent and "adults" includes a subject who is at least 18

years old. Grigoriadis teaches that treatment of CAH occurs throughout "diagnosis in infancy through adulthood," and that one of the factors a POSA considers when determining CRF1 receptor antagonist dosage is the subject's age. EX1006, ¶¶ [0044], [0064]. In some cases, Grigoriadis' CRF1 receptor antagonist is co-administered with a glucocorticoid, and the dosage of glucocorticoid depends on whether the subject "is a fully grown patient" or "a growing patient" with CAH. EX1006, ¶ [0070]. Moreover, in Example 6, Grigoriadis teaches the administration of NBI-77860 (verucerfont) to CAH patients "ages 19 to 58." EX1006, ¶ [0091]. A POSA would not consider the subject matter in either claims 8 or 9 new or nonobvious.

6. Claims 10–14 — "wherein the small molecule antagonist is administered at a dose of . . . "

214. Claims 10-14 relate to doses. Claim 10 recites "[t]he method of claim 1, wherein the small molecule CRF_1 antagonist is administered at a dose of about 10 mg/day to about 400 mg/day to the subject." EX1001, 102:14–16. Claim 11 recites "[t]he method of claim 10, wherein the small molecule CRF_1 antagonist is administered at a dose of about 50 mg." EX1001, 102:17–18. Claim 12 recites "[t]he method of claim 10, wherein the small molecule CRF_1 antagonist is administered at a dose of about 100 mg." EX1001, 102:19–20. Claim 13 recites "[t]he method of claim 10, wherein the small molecule CRF_1 antagonist is administered at a dose of about 200 mg." EX1001, 102:21–22. Claim 14 recites

"[t]he method of claim 1, wherein the small molecule CRF_1 antagonist is administered at a dose of about 400 mg." EX1001, 102:23–24.

215. 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 single doses (50 mg and 400 mg) of NBI-77860 (verucerfont, compound **D** in the Table following paragraph 172). 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].

216. While Grigoriadis does not expressly disclose administration of a daily dose of "about 100 mg" (claim 12) or "about 200 mg" (claim 13) 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 '491 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.

7. Claims 15 and 16 — "administered orally" / "formulated as a capsule or tablet"

217. Claim 15 recites "[t]he method of claim 1, wherein the small molecule CRF_1 antagonist is administered orally." EX1001, 102:25–26. Claim 16 recites "[t]he method of claim 1, wherein the small molecule CRF_1 antagonist is formulated as a capsule or tablet." EX1001, 102:27–28.

218. 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 the form of "tablets, powders, granules, or capsules." EX1006, [0074].

8. Claims 17–19 — "administered . . . before sleep" / "in the evening"

219. Claim 17 recites "[t]he method of claim 1, wherein the small molecule CRF_1 antagonist is administered less than about 6 hours before sleep." EX1001,

102:29–31. Claim 18 recites "[t]he method of claim 1, wherein the small molecule CRF_1 antagonist is administered less than about 3 hours before sleep." EX1001, 102:32–34. Claim 19 recites "[t]he method of claim 1, wherein the small molecule CRF_1 antagonist is administered in the evening." EX1001, 102:35–36.

220. These claims relate to the timing of administration. Grigoriadis teaches each.

221. Grigoriadis teaches that its CRF1 receptor antagonists can be administered at "nighttime," "prior to sleep (i.e., bedtime administration), and at 10 P.M." EX1006, [0066]. A POSA would consider 10 P.M. in particular to be "in the evening" as recited in claim 19. EX1001, 4:58-60, 6:49-53, 79:18-20; EX1006, [0066].

222. Claims 17 and 18 simply provide a window for administration, and that window spans from "less than" 6 or 3 hours before sleep to right before sleep. A POSA would understand that Grigoriadis's "prior to sleep (i.e., bedtime administration)" falls within the windows of administration recited in claims 17 and 18.

E. The '491 Patent's Allegedly "Unexpected Results" Would Not Have Been Unexpected

223. As discussed above in paragraphs 71–79, 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.

224. First, as discussed in paragraphs 34–42, multiple references had already reported that TARTs are connected to elevated ACTH levels. Delfino reports that "[t]This 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,

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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.

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

226. 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.

227. 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.

228. As discussed above in paragraphs 170–171, 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.

***

229. 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

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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.

230. 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:

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

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Prepared: March 10, 2026

Name: **Maya Beth Lodish, MD**

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

Address: University of California, San Francisco
Mission Hall 550 16th St., 4th Floor, Box 0434
San Francisco, CA 94143
Tel: (415) 476-3310
maya.lodish@ucsf.edu

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

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 Endocrinolgy 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 Wilkins Pediatric Endocrine Society	Poster
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 Adolscent 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

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

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 CIEx - 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 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 prioject: 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. Judes

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 Sinaii 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 Correra	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

1. 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 Study to Evaluate the Safety and Efficacy of Crinecerfont (NBI-74788) in Pediatric Subjects with Classic Congenital Adrenal Hyperplasia, Followed by Open-Label Treatment $ 135,106.73 direct/yr 1 $ 784,487 total
   Clinical Trial of novel oral medication in children with CAH
   PI

2. A145565 1112923 PI 0% % effort Lodish (PI)
   DHCS California Department of Health and Children's Services 9/1/2024 8/31/2026
   California Youth Behavioral Health Initiative (CYBHI) Evidence-Based Practices and Community-Defined Evidence Practices Grant Program $ 725,351 total
   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 Development 10/30/2011 10/30/2013
Detection and treatment of endocrine abnormalities in childhood cancer survivors $ 120,796 direct/yr 1 $ 537,688 total
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 and pharmacodynamics of mifepristone in children with refractory Cushing disease $ 200,000 direct/yr 1 $ 400,000 total
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 (DIPHR), NIH 07/01/2014 01/01/2018
Genetic Factors in Cushing Disease: Whole Exome Sequencing $ 78,381 direct/yr 1 $ 365,738 total
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 date, 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 direct/yr 1 $ 4,481,953 total
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 RARγ-Specific Agonist (Palovarotene) in the Treatment of Preosseous Flare-ups in Subjects with Fibrodysplasia Ossificans Progressiva (FOP)

9. A140504 Primary Investigator 0% % effort Lodish (PI)
Lily Pharma 10/10/2022 10/10/2024
UCSF pediatric thyroid cancer experience registry $ 125,953 direct/yr 1
Funding to allow for data entry and specimen processing and tissue analysis to study pediatric thyroid cancer
Primary Investigator

10. A140562 Primary Investigator 0% % effort Lodish (PI)
Alameda Alliance for Health 07/01/2022 6/30/2024
AGREEMENT between NOVEL INTERVENTIONS IN CHILDREN'S HEALTH CARE and ALAMEDA ALLIANCE FOR HEALTH $ 428,000 direct/yr 1 $ 856,000 total
Grant to support program at UCSF to provide wrap-around care for children with chronic illness and high burden of social needs
PI

11. Award ID 139743A Primary Investigator 0.5% % effort Lodish (PI)
IBSA 08/10/2022 1/1/2026
A Randomized Comparative Study Between Liquid (Tirosint®-SOL) and Tablet Formulations of Levothyroxine in Neonates and Infants with Congenital Hypothyroidism (CH) $ 63,913.77 direct/yr 1 $ 95,151.39 total
A research study comparing Tirosint®-SOL oral solution as thyroid hormone (TH) replacement therapy in infants with Congenital Hypothyroidism (CH) to the conventional treatment with crushed levothyroxine sodium (LT4) tablets.
PI

PEER REVIEWED PUBLICATIONS

1. Crispino JD, **Lodish** M, MacKay JP, Orkin SH 1999 Use of altered specificity mutants to probe a specific protein-protein interaction in differentiation: the GATA-1:FOG complex. Molecular cell 3:219-228. PMID: 10078204
2. Crispino JD, **Lodish** M, Thurberg BL, Litovsky SH, Collins T, Molkentin JD, Orkin SH 2001 Proper coronary vascular development and heart morphogenesis depend on interaction of GATA-4 with FOG cofactors. Genes & development 15:839-844. PMID: 11297508
3. Chang AN, Cantor AB, Fujiwara Y, **Lodish** M, Droho S, Crispino JD, Orkin SH 2002 GATA-factor dependence of the multitype zinc-finger protein FOG-1 for its essential role in megakaryopoiesis. Proceedings of the National Academy of Sciences of the United States of America 99:9237-9242. PMID: 12077323
4. **Lodish** M, Powell AC, Abu-Asab M, Cochran C, Lenz P, Libutti SK, Pingpank JF, Tsokos M, Gorden P 2008 Insulinoma and gastrinoma syndromes from a single intrapancreatic neuroendocrine tumor. The Journal of clinical endocrinology and metabolism 93:1123-1128. PMID: 18252785

5. Drori-Herishanu L, Horvath A, Nesterova M, Patronas Y, **Lodish** M, Bimpaki E, Patronas N, Agarwal S, Salvatori R, Martari M, Mericq V, Stratakis CA 2009 An Intronic mutation is associated with prolactinoma in a young boy, decreased penetrance in his large family, and variable effects on MEN1 mRNA and protein. Hormone and metabolic research 41:630-634. PMID: 19391077
6. **Lodish** M, Sinaii N, Patronas N, Batista DL, Keil M, Samuel J, Moran J, Verma S, Popovic J, Stratakis CA 2009 Blood pressure in pediatric patients with Cushing syndrome. The Journal of clinical endocrinology and metabolism 94:2002-2008. PMID: 19293264
7. Nguyen JH, **Lodish** M*, Patronas NJ, Ugrasbul F, Keil MF, Roberts MD, Popovic J, Stratakis CA 2009 Extensive and largely reversible ischemic cerebral infarctions in a prepubertal child with hypertension and Cushing disease. The Journal of clinical endocrinology and metabolism 94:1-2. PMID: 19126630. (*corresponding author)
8. Drori-Herishanu L, **Lodish** M, Verma S, Bimpaki E, Keil MF, Horvath A, Stratakis CA 2010 The growth hormone receptor (GHR) polymorphism in growth-retarded children with Cushing disease: lack of association with growth and measures of the somatotropic axis. Hormone and metabolic research 42:194-197. PMID: 20013551
9. Kiehna EN, Keil M, **Lodish** M, Stratakis C, Oldfield EH 2010 Pseudotumor cerebri after surgical remission of Cushing's disease. The Journal of clinical endocrinology and metabolism 95:1528-1532. PMID: 20164289
10. **Lodish** M, Patronas NJ, Stratakis CA 2010 Reversible posterior encephalopathy syndrome associated with micronodular adrenocortical disease and Cushing syndrome. European journal of pediatrics 169:125-126. PMID: 19415327
11. **Lodish** M, Adams KT, Huynh TT, Prodanov T, Ling A, Chen C, Shusterman S, Jimenez C, Merino M, Hughes M, Cradic KW, Milosevic D, Singh RJ, Stratakis CA, Pacak K 2010 Succinate dehydrogenase gene mutations are strongly associated with paraganglioma of the organ of Zuckerkandl. Endocrine-related cancer 17:581-588. PMID: 20418362
12. **Lodish** M, Gartner LA, Albini P, Sabnis G, Brodie A, Meck JM, Meloni-Ehrig AM, Hill S, Tsilou E, Valera VA, Walter BA, Merino MJ, Stratakis CA 2010 Intrauterine growth retardation associated with precocious puberty and sertoli cell hyperplasia. Hormone and metabolic research 42:682-688. PMID: 20411478
13. **Lodish** M, Hsiao HP, Serbis A, Sinaii N, Rothenbuhler A, Keil MF, Boikos SA, Reynolds JC, Stratakis CA 2010 Effects of Cushing disease on bone mineral density in a pediatric population. The Journal of pediatrics 156:1001-1005. PMID: 20223476
14. Stratakis CA, Tichomirowa MA, Boikos S, Azevedo MF, **Lodish** M, Martari M, Verma S, Daly AF, Raygada M, Keil MF, Papademetriou J, Drori-Herishanu L, Horvath A, Tsang KM, Nesterova M, Franklin S, Vanbellinghen JF, Bours V, Salvatori R, Beckers A 2010 The role of germline AIP, MEN1, PRKAR1A, CDKN1B and CDKN2C mutations in causing pituitary adenomas in a large cohort of children, adolescents, and patients with genetic syndromes. Clinical genetics 78:457-463. PMID: 20507346
15. Gaal J, Stratakis CA, Carney JA, Ball ER, Korpershoek E, **Lodish** M, Levy I, Xekouki P, van Nederveen FH, den Bakker MA, O'Sullivan M, Dinjens WN, de Krijger RR 2011 SDHB immunohistochemistry: a useful tool in the diagnosis of Carney-Stratakis and Carney triad gastrointestinal stromal tumors. Modern pathology: an official journal of the United States and Canadian Academy of Pathology, Inc 24:147-151. PMID: 20890271
16. Janeway KA, Kim SY, **Lodish** M, Nose V, Rustin P, Gaal J, Dahia PL, Liegl B, Ball ER, Raygada M, Lai AH, Kelly L, Hornick JL, O'Sullivan M, de Krijger RR, Dinjens WN,

Demetri GD, Antonescu CR, Fletcher JA, Helman L, Stratakis CA 2011 Defects in succinate dehydrogenase in gastrointestinal stromal tumors lacking KIT and PDGFRA mutations. Proceedings of the National Academy of Sciences of the United States of America 108:314-318. PMID: 21173220

17. King KS, Prodanov T, Kantorovich V, Fojo T, Hewitt JK, Zacharin M, Wesley R, **Lodish** M, Raygada M, Gimenez-Roqueplo AP, McCormack S, Eisenhofer G, Milosevic D, Kebebew E, Stratakis CA, Pacak K 2011 Metastatic pheochromocytoma/paraganglioma related to primary tumor development in childhood or adolescence: significant link to SDHB mutations. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 29:4137-4142. PMID: 21969497

18. Libe R, Horvath A, Vezzosi D, Fratticci A, Coste J, Perlemoine K, Ragazzon B, Guillaud-Bataille M, Groussin L, Clauser E, Raffin-Sanson ML, Siegel J, Moran J, Drori-Herishanu L, Faucz FR, **Lodish** M, Nesterova M, Bertagna X, Bertherat J, Stratakis CA 2011 Frequent phosphodiesterase 11A gene (PDE11A) defects in patients with Carney complex (CNC) caused by PRKAR1A mutations: PDE11A may contribute to adrenal and testicular tumors in CNC as a modifier of the phenotype. The Journal of clinical endocrinology and metabolism 96:E208-214. PMID: 21047926

19. Briassoulis G, Horvath A, Christoforou P, **Lodish** M, Xekouki P, Quezado M, Patronas N, Keil MF, Stratakis CA 2012 Lack of mutations in the gene coding for the hGR (NR3C1) in a pediatric patient with ACTH-secreting pituitary adenoma, absence of stigmata of Cushing's syndrome and unusual histologic features. Journal of pediatric endocrinology & metabolism: JPEM 25:213-219. PMID: 22570980

20. **Lodish** M, Dagalakis U, Chen CC, Sinaii N, Whitcomb P, Aikin A, Dombi E, Marcus L, Widemann B, Fox E, Chuk M, Balis F, Wells S, Jr., Stratakis CA 2012 (111)In-octreotide scintigraphy for identification of metastatic medullary thyroid carcinoma in children and adolescents. The Journal of clinical endocrinology and metabolism 97:E207-212. PMID: 22162469

21. **Lodish** M, Dunn SV, Sinaii N, Keil MF, Stratakis CA 2012 Recovery of the hypothalamic-pituitary-adrenal axis in children and adolescents after surgical cure of Cushing's disease. The Journal of clinical endocrinology and metabolism 97:1483-1491. PMID: 22399509

22. **Lodish** M, Dagalakis U, Sinaii N, Bornstein E, Kim A, Lokie KB, Baldwin AM, Reynolds JC, Dombi E, Stratakis CA, Widemann BC 2012 Bone mineral density in children and young adults with neurofibromatosis type 1. Endocrine-related cancer 19:817-825. PMID: 23089139

23. **Lodish** M, Mastroyannis SA, Sinaii N, Boikos SA, Stratakis CA 2012 Known VDR polymorphisms are not associated with bone mineral density measures in pediatric Cushing disease. Journal of pediatric endocrinology & metabolism: JPEM 25:221-223. PMID: 22570981

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25. Fox E, Widemann BC, Chuk MK, Marcus L, Aikin A, Whitcomb PO, Merino MJ, **Lodish** M, Dombi E, Steinberg SM, Wells SA, Balis FM 2013 Vandetanib in children and adolescents with multiple endocrine neoplasia type 2B associated medullary thyroid carcinoma.

Clinical cancer research: an official journal of the American Association for Cancer Research 19:4239-4248. PMID: 23766359

26. Crocker MK, Gourgari E, **Lodish** M*, Stratakis CA 2014 Use of aromatase inhibitors in large cell calcifying sertoli cell tumors: effects on gynecomastia, growth velocity, and bone age. The Journal of clinical endocrinology and metabolism 99:E2673-2680. PMID: 25226294. (*corresponding author)
27. Dagalakis U, **Lodish** M*, Dombi E, Sinaii N, Sabo J, Baldwin A, Steinberg SM, Stratakis CA, Widemann BC 2014 Puberty and plexiform neurofibroma tumor growth in patients with neurofibromatosis type I. The Journal of pediatrics 164:620-624. PMID: 24321536 (*corresponding author)
28. Faucz FR, Zilbermint M, **Lodish** M, Szarek E, Trivellin G, Sinaii N, Berthon A, Libe R, Assie G, Espiard S, Drougat L, Ragazzon B, Bertherat J, Stratakis CA 2014 Macronodular adrenal hyperplasia due to mutations in an armadillo repeat containing 5 (ARMC5) gene: a clinical and genetic investigation. The Journal of clinical endocrinology and metabolism 99:E1113-1119. PMID: 24601692
29. Gourgari E, **Lodish** M, Keil M, Wesley R, Hill S, Xekouki P, Lyssikatos C, Belyavskaya E, De La Luz SM, Stratakis CA 2014 Post-operative growth is different in various forms of pediatric Cushing's syndrome. Endocrine-related cancer 21:L27-31. PMID: 25258026
30. Gourgari E, Nella AA, **Lodish** M, Stratakis CA, Yanovski JA 2014 Vitamin B12 deficiency in an adolescent girl with polycystic ovarian syndrome. European journal of obstetrics, gynecology, and reproductive biology 179:254. PMID: 24933126
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32. London E, **Lodish** M, Keil M, Lyssikatos C, de la Luz Sierra M, Nesterova M, Stratakis CA 2014 Not all glucocorticoid-induced obesity is the same: differences in adiposity among various diagnostic groups of Cushing syndrome. Hormone and metabolic research 46:897-903. PMID: 25295416
33. London E, Rothenbuhler A, **Lodish** M, Gourgari E, Keil M, Lyssikatos C, de la Luz Sierra M, Patronas N, Nesterova M, Stratakis CA 2014 Differences in adiposity in Cushing syndrome caused by PRKAR1A mutations: clues for the role of cyclic AMP signaling in obesity and diagnostic implications. The Journal of clinical endocrinology and metabolism 99:E303-310. PMID: 24248186
34. Nella AA, **Lodish** M*, Fox E, Balis FM, Quezado MM, Whitcomb PO, Derdak J, Kebebew E, Widemann BC, Stratakis CA 2014 Vandetanib successfully controls medullary thyroid cancer-related Cushing syndrome in an adolescent patient. The Journal of clinical endocrinology and metabolism 99:3055-3059. PMID: 24617713 (* Corresponding Author)
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Gigantism and acromegaly due to Xq26 microduplications and GPR101 mutation. The New England journal of medicine 371:2363-2374. PMID: 25470569

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2. **Lodish** M "Multiple Endocrine Neoplasia Type 2." In Stratakis, C (Ed.), Endocrine Tumor Syndromes and Their Genetics. 2013 Basel, Switzerland: Karger.
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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 o define the incidence and risk factors of postoperative sodium alterations in pediatric patients undergoing transsphenoidal surgery for adrenocorticotropic 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, Martinerie L, Nokoff NJ, Clemente M, Fechner PY, Vogiatzi MG, Speiser PW, Auchus RJ, Rosales GBG, Roberts E, Jeha GS, Farber RH, Chan JL; CAHtalyst 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

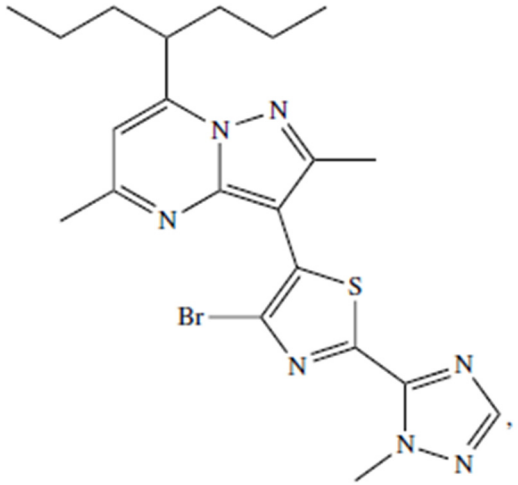
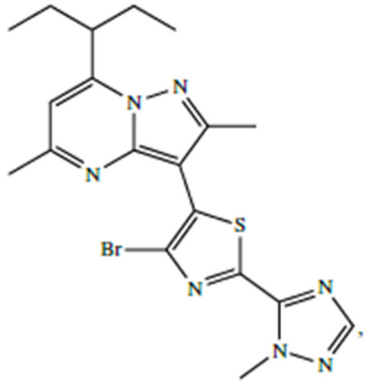
treating children with CAH that led to the FDA approval of this medication in children in 2025.

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-2*H*-[1,2,4]triazol-3-yl)-thiazol-5-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]triazol-3-yl)-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine	EX1092 (CID 24898976)

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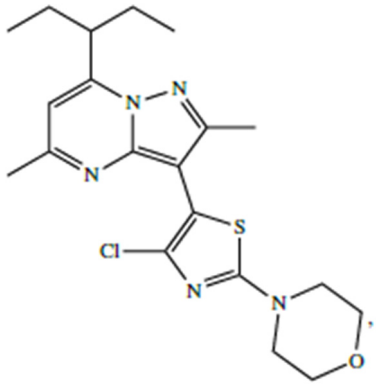
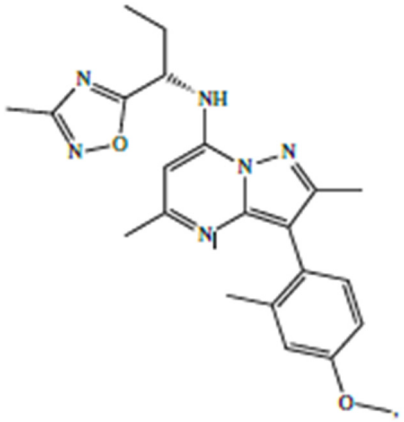
Appendix B – Compound Structures in Claim 1

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-morphlin-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*-[(1*S*)-1-(3-methyl-1,2,4-oxadiazol-5-yl)propyl]pyrazolo[1,5-a]pyrimidin-7-amine	EX1090 (CID 11596613)

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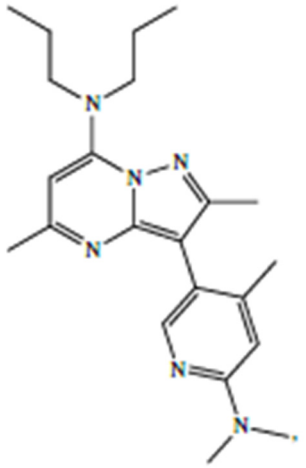
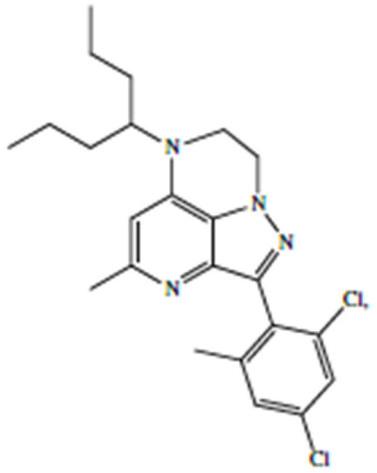
Appendix B – Compound Structures in Claim 1

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-*N*,*N*-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)

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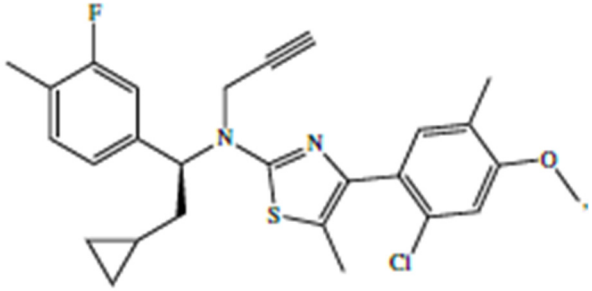
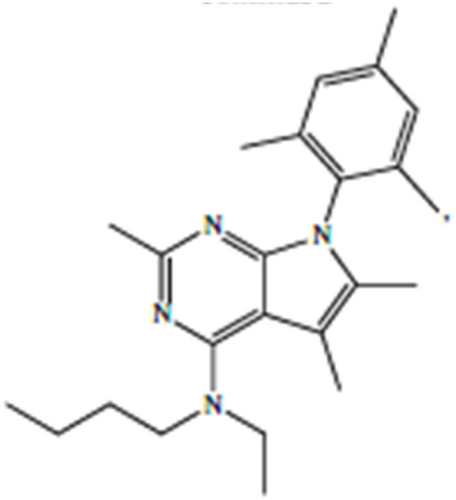
Appendix B – Compound Structures in Claim 1

Compound Structure in Claim 1	Letter Designation	Synonyms and/or IUPAC name (Provided for Easy Reference)	PubChem Entry
SSR-126374,	**G**		
	**H**	Crinecerfont; SSR-125543 4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-[(1*S*)-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)

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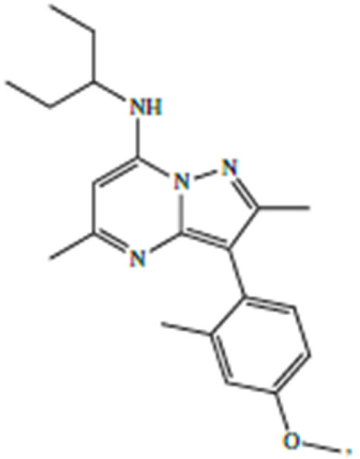
Compound Structure in Claim 1	Letter Designation	Synonyms and/or IUPAC name (Provided for Easy Reference)	PubChem Entry
	**J**	DMP-904 3-(4-methoxy-2-methylphenyl)-2,5-dimethyl-*N*-pentan-3-ylpyrazolo[1,5-a]pyrimidin-7-amine	EX1095 (CID 9884878)

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