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APPLICATION # 18/438,060	RECEIPT DATE / TIME 04/03/2026 03:47:40 PM Z ET	ATTORNEY DOCKET # 50535-716.302
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Title of Invention

METHODS OF TREATING CONGENITAL ADRENAL HYPERPLASIA

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	4456	FILED BY	JENNIFER VAIL
PATENT CENTER #	75151318	FILING DATE	02/09/2024
CUSTOMER #	21971	FIRST NAMED INVENTOR	Sangita GHOSH
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Kaia Parenti

Documents

TOTAL DOCUMENTS: 100

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT
Attorney Docket No. 50535-716.302

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: Inventors: Sangita Ghosh et al. Application No.: 18/438,060 Filing Date: February 9, 2024 Title: METHODS OF TREATING CONGENITAL ADRENAL HYPERPLASIA	Confirmation No.: 4456 Art Unit: 1623 Examiner: Lee, William Y. Customer No.: 21971 <u>Certificate of Electronic Filing</u> I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office's electronic filing system to the USPTO on <u>April 3, 2026</u> . By: _____ / Colleen Mensching / Colleen Mensching
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Mailstop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE TO NON-FINAL OFFICE ACTION

Dear Commissioner:

This paper responds to the Non-Final Office Action mailed October 7, 2025, the time period for response set for January 7, 2026. With payment of a 3-month extension of time, extending the period for response to April 7, 2026, this response is timely filed. Applicant respectfully requests reconsideration of the above-referenced application in view of the following amendments and remarks.

A Petition for Extension of Time is requested for a reply and the fee set forth under 37 C.F.R. §1.17(a)(3) is electronically submitted herewith.

Amendments to the Claims begin on page **2** of this paper.

Remarks begin on page **4** of this paper.

Conclusion begins on page **8** of this paper.

Atty. Docket No.: 50535-716.302

AMENDMENTS TO THE CLAIMS

Listing of the Claims

1.-105. **(Canceled)**

106. **(Currently Amended)** A method of treating congenital adrenal hyperplasia (CAH) in a subject, comprising administering to the subject a therapeutically effective amount of (S)-4-(2-chloro-4-methoxy-5-methylphenyl)-N-(2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl)-5-methyl-N-(prop-2-yn-1-yl)thiazol-2-amine (SSR125543) or salt thereof, at a frequency of at least twice per day, and a steroid or a pharmaceutically acceptable salt thereof, wherein the ~~steroid~~ glucocorticoid or pharmaceutically acceptable salt thereof is administered at a reduced dosage compared to a dosage of ~~steroid~~ the glucocorticoid or a pharmaceutically acceptable salt thereof administered alone, wherein the reduced dosage is in a 5 mg ~~increment~~ hydrocortisone equivalent, wherein the subject has a level of androstenedione (A4) that is less than two times an upper limit of a reference range of A4 and a level of adrenocorticotrophic hormone (ACTH) that is less than two times an upper limit of a reference range of ACTH.

107. **(Currently Amended)** The method of claim 106, wherein the SSR125543 or salt thereof, and the ~~steroid~~ glucocorticoid or pharmaceutically acceptable salt thereof are administered sequentially within 10 minutes to within about 24 hours.

108. **(Previously Presented)** The method of claim 106, wherein the CAH is non-classic CAH.

109. **(Previously Presented)** The method of claim 106, wherein the CAH is classic CAH.

110. **(Cancelled)**

111. **(Currently Amended)** The method of ~~claim 110~~ claim 106, wherein the glucocorticoid or a pharmaceutically acceptable salt thereof, is prednisone, cortisone, prednisolone, triamcinolone, methylprednisolone, betamethasone, dexamethasone, hydrocortisone or a pharmaceutically acceptable salt thereof.

112. **(Cancelled)**

113. **(Cancelled)**

114. **(Cancelled)**

115. **(Cancelled)**

116. **(Cancelled)**

117. **(Previously Presented)** The method of claim 112, wherein levels of the steroid hormone in the subject is determined from a biological sample from the subject.
118. **(Previously Presented)** The method of claim 117, wherein the biological sample is selected from the group of blood, blood fractions, plasma, serum, and saliva.
119. **(Previously Presented)** The method of claim 106, wherein the SSR125543 or salt thereof, is administered in a dose of about 50 mg to about 200 mg total daily dose to the subject.
120. **(Previously Presented)** The method of claim 106, wherein the SSR125543 or salt thereof, is administered in a dose of about 200 mg total daily dose to the subject.
121. **(Previously Presented)** The method of claim 106, wherein the SSR125543 or salt thereof, is administered in a dose of about 100 mg total daily dose to the subject.
122. **(Currently Amended)** The method of claim 106, wherein the SSR125543 or salt thereof, is in the form of ~~microparticles~~ a tablet or capsule.
123. **(Previously Presented)** The method of claim 106, wherein the subject is tested to determine morning levels of A4 and ACTH.
124. **(Previously Presented)** The method of claim 106, wherein the subject is an adult patient.
125. **(Previously Presented)** The method of claim 106, wherein the subject is a pediatric patient.
126. **(New)** The method of claim 106, wherein the subject is in a fed state.
127. **(New)** The method of claim 106, wherein the reference range of ACTH is about 7 to 63.3 pg/mL.
128. **(New)** The method of claim 106, wherein the reference range of A4 is about 50 to 220 ng/dL, about 40 to 190 ng/dL, about 51 to 213 ng/dL, about 73 to 230 ng/dL, about 73 to 184 ng/dL, or about 20 to 75 ng/dL.
129. **(New)** The method of claim 111, wherein the glucocorticoid is hydrocortisone.



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APPLICATION # 18/438,060	RECEIPT DATE / TIME 04/03/2026 02:13:02 PM Z ET	ATTORNEY DOCKET # 50535-716.302
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Title of Invention

METHODS OF TREATING CONGENITAL ADRENAL HYPERPLASIA

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	4456	FILED BY	Colleen Mensching
PATENT CENTER #	75147670	AUTHORIZED BY	Kaia Parenti
CUSTOMER #	21971	FILING DATE	02/09/2024
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Sangita GHOSH

Payment Information

PAYMENT METHOD DA / 232415	PAYMENT TRANSACTION ID E202643E14147427	PAYMENT AUTHORIZED BY Colleen Mensching
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FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
1253	EXTENSION FOR RESPONSE WITHIN THIRD MONTH, EXCEPT PROVISIONAL APPLICATIONS	1590.00	1	1590.00
TOTAL AMOUNT:				\$1,590.00

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If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C.

371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

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UNITED STATES
PATENT AND TRADEMARK OFFICE

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION # 18/438,060	RECEIPT DATE / TIME 04/03/2026 02:13:02 PM Z ET	ATTORNEY DOCKET # 50535-716.302
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CUSTOMER #	21971	FIRST NAMED INVENTOR	Sangita GHOSH
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Kaia Parenti

Documents

TOTAL DOCUMENTS: 3

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
Spruce 50535-716.302 Response to NFOA mailed 10.07.2025.pdf	8	-	123 KB
Spruce 50535-716.302 Response to NFOA mailed (1-1) 10.07.2025-A....pdf	1	Amendment/Request for Reconsideration-After Non- Final Rejection	82 KB
Spruce 50535-716.302 Response to NFOA mailed (2-3) 10.07.2025-CLM.pdf	2	Claims	84 KB
Spruce 50535-716.302 Response to NFOA mailed (4-8) 10.07.2025-REM.pdf	5	Applicant Arguments/Remarks Made in an Amendment	113 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
Spruce 50535-716.302 Response to NFOA mailed 10.07.2025.pdf	8990DB7A00BC03F844E8989EA87076B24F76A6AE4752451C7 78C77DC4F6226350952A0106292294FD617F048A791A249FC4 B0011A9BFC0FF18A4487ADBC845AA
Spruce 50535-716.302 Response to NFOA mailed 10.07.2025-A....pdf	F109E67471F9EF2FFAC360F12A1A0DDE7D4F3EEB398737F7F 747EC85A1200609A7E9D503AADEE47AAD3675AC42B110A4A FB9B0329233820C97D43C13011275E1
Spruce 50535-716.302 Response to NFOA mailed 10.07.2025-CLM.pdf	D5C77421A217A1D149C8FCAD43134C703A72787DC5B5C93B 04E58867A60DAB9EA29547D19AE0C46DCCE980FAB3A8B2CF 40919A09FDE0EE1524AEA2435C8D42C1
Spruce 50535-716.302 Response to NFOA mailed 10.07.2025-REM.pdf	CB0E589257A60579D2D62D36EB3AA94B9841C0A2D8EE7E06 3419F9502842AD85D5E6DBAEB2297B0E17ECD2AFC0C3B7C1 BC30E576B9DE69DFAF207A6FF113848B

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REMARKS

Claims 106-125 were pending prior to entry of the amendments presented in this response. Claims 106, 107, 111, and 122 have been amended herein. New claims 126-128 have been added. These amendments are fully supported by the application as originally filed. No new matter is added by the amendments made herein. Claims 110 and 112-116 are herein canceled without prejudice or disclaimer of its subject matter. Applicant reserves the right to pursue the subject matter deleted from the pending or canceled claims in this or any other appropriate patent application. Accordingly, upon entry of the proposed amendments, claims 106-109, 111, and 117-128 will be under examination.

The listing of claims provided herein will replace all prior versions and listings of claims in this application. Reconsideration and allowance are respectfully requested in light of the abovementioned amendments and the following remarks.

Claim Rejections Under 35 U.S.C. § 112(a)

Claims 106-125 are rejected under 35 U.S.C. § 112(a).

The Office alleges that the specification does not reasonably provide enablement for the full scope of the claimed method, citing that the claimed method “would entail 5 mg reductions of any steroid with concomitant CRF1 antagonist therapy.” (Office Action, Page 3).

Without acquiescing to the basis of the rejection, and solely to advance the application to allowance, Applicant has amended the independent claim to recite in part:

“ . . . wherein the ~~steroid~~ glucocorticoid or pharmaceutically acceptable salt thereof is administered at a reduced dosage compared to a dosage of ~~steroid~~ the glucocorticoid or a pharmaceutically acceptable salt thereof administered alone, wherein the reduced dosage is in a 5 mg ~~increment~~ hydrocortisone equivalent . . . ”

Applicant submits the presently amended claims are enabled by the specification and that a person of skill in the art can make and use the invention without undue experimentation. Only “reasonable detail must be provided in order to enable members of the public to understand and

carry out the invention.” *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997).

Glucocorticoid therapy is a known treatment option for patients with CAH. The specification explains that treatment of CAH is based on normalization of hormone and steroid levels and that glucocorticoids are the current standard treatment (para. [0051]). The specification provides an exemplary embodiment of specific glucocorticoids, which includes prednisone, cortisone, prednisolone, triamcinolone, methylprednisolone, betamethasone, dexamethasone, and hydrocortisone (para. [0032]). A person of skill in the art would understand that the potency and duration of action of different glucocorticoids can vary and that a dosage conversion may be necessary to convert between doses of different glucocorticoids (para. [0068]). A person of skill in the art could readily convert dose reductions among different glucocorticoids based on a reference value of a 5 mg hydrocortisone equivalent, and this would not amount to undue experimentation.

CRF₁ antagonists are a well-known class of compounds. The specification describes a working example of a clinical trial for subjects with CAH that are administered different doses of a CRF₁ antagonist while on a stable glucocorticoid regimen is described in Example 1. The specification provides representative examples of CRF₁ antagonists, reciting over 10 specific compounds, including the instantly claimed SSR125543 (see, e.g., para. [0071]-[0072] and [00104]-[00106]).

Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. §112(a).

Claim Rejections Under 35 U.S.C. §102

Claims 106-111, 119-121 and 124-125 is/are rejected under 35 U.S.C. 102(a)(1) as being anticipated by Grigoriadis (aka US 877) (U.S. 2017/0020877). Without acquiescing to the basis of the rejection, and solely to advance the application to allowance, Applicant has amended claim 106 to incorporate the limitations of dependent claim 116, which was not rejected under 35 U.S.C. §102. Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. §102.

Claim Rejections Under 35 U.S.C. §103

Claims 106-121 and 123-125 are rejected under 35 U.S.C. 103 as being unpatentable over Grigoriadis (aka US 877) (US20170020877). Claims 106-125 are rejected under 35 U.S.C. 103 as being unpatentable over Grigoriadis (aka US 877) (US20170020877) in view of Dhoot et al (aka US 623) (US 2006/0078623 A1).

To establish a *prima facie* case of obviousness, the cited references must provide all elements and limitations of the claims with a motivation to modify or combine the references with a reasonable expectation of success.

Grigoriadis, alone or in combination with Dhoot, does not provide all the limitations of claims. The claims recite administration of SSR125543 “at a frequency of at least twice per day”. Grigoriadis does not disclose dosing twice per day or more than twice per day. As the Office recognized, Grigoriadis also does not disclose that the monitored A4 and ACTH levels of the subject are less than two times an upper limit of a reference range of A4 and ACTH (Office Action, Page 16). The deficiencies of Grigoriadis are not cured by Dhoot, which describes microparticle and nanoparticle pharmaceutical formulations. Dhoot does not disclose the claimed dosing frequency or levels of A4 and ACTH in the subject, let alone treatment of CAH with a CRF₁ antagonist. By failing to provide all elements and limitations of the claims as amended herewith, a *prima facie* case of obviousness has not been established.

Example 1 of the present application identifies distinct subgroups of CAH patients based on levels of A4 and ACTH. In defining subgroups based on levels of A4 and ACTH, “the inclusion of 17-OHP as an input occluded the identification of clear subgroups which was **non-obvious**” (specification para. [0191], emphasis added). Different therapeutic outcomes among subgroups based on levels of A4 and ACTH were observed. FIGS. 2-4 of the present application show differences in biomarker levels following administration with a CRF₁ antagonist between a treatment group having highly elevated ACTH and A4 levels (“poor disease control”) and a treatment group having ACTH and A4 levels that are near normal or below (“good disease control”). Both groups had elevated 17-OHP. Levels of ACTH, 17-OHP, and A4 were assessed overnight from 10 pm to 8 am in non-dexamethasone subjects. Patients with highly elevated levels of A4 and ACTH at baseline (“poor control”) showed reduction in ACTH, 17-OHP, and

A4 levels (Figure 2A, 3A, and 4A) throughout the overnight period. Patients with normal or near normal levels of A4 and ACTH at baseline (“good control”) did not exhibit meaningful reduction of levels of ACTH and A4 (Figure 2B and 4B) and exhibited only a modest reduction in levels of 17-OHP (Figure 3B). This data shows that administration of a CRF₁ antagonist to patients with highly elevated levels of A4 and ACTH does not necessarily result in the same therapeutic outcome as patients with normal or near-normal levels of A4 and ACTH. As described in the application, subgroups based on A4 and ACTH “provide a basis for different, yet sequential methods of treatment.” Example 3 of the instant application describes a prophetic study to assess the impact of reduction of glucocorticoid dose to subjects in one of these subgroups. For at least the reasons described above, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. §103.

Application No. 18/438,060
Office Action Mailed October 7, 2025
Amendment dated: April 3, 2026

CONCLUSION

In light of the remarks set forth above, Applicant believes that the pending claims are under condition for allowance. Applicant respectfully solicits the Examiner to expedite the prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned at (212) 453-2852

The Commissioner is authorized to charge any underpayment or credit any overpayment to Deposit account No. 23-2415 (Attorney Docket No. 50535-716.302).

Respectfully submitted,

Date: April 3, 2026

By: /Kaia R. Parenti/
Kaia R. Parenti, Reg. No. 81,050

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Phone: (650) 493-9300
Customer No. 21971

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875				Application or Docket Number 18/438,060		Filing Date 02/09/2024		☐ To be Mailed		
ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO										
APPLICATION AS FILED - PART I										
		(Column 1)	(Column 2)							
FOR		NUMBER FILED	NUMBER EXTRA		RATE (\$)		FEE (\$)			
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))		N/A	N/A		N/A					
☐ SEARCH FEE (37 CFR 1.16(k), (l), or (m))		N/A	N/A		N/A					
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))		N/A	N/A		N/A					
TOTAL CLAIMS (37 CFR 1.16(j))		minus 20 =	*		x \$100 =					
INDEPENDENT CLAIMS (37 CFR 1.16(h))		minus 3 =	*		x \$480 =					
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))		If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).								
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))										
* If the difference in column 1 is less than zero, enter "0" in column 2.					TOTAL					
APPLICATION AS AMENDED - PART II										
		(Column 1)	(Column 2)		(Column 3)					
AMENDMENT	04/03/2026	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)			
	Total (37 CFR 1.16(i))	* 18	Minus	** 20	= 0	x \$200 =	0			
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0	x \$600 =	0			
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))									
						TOTAL ADD'L FEE	0			
AMENDMENT		(Column 1)	(Column 2)		(Column 3)					
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)			
	Total (37 CFR 1.16(i))	*	Minus	**	=	x \$0 =				
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x \$0 =				
	☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))										
						TOTAL ADD'L FEE				
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.						LIE				
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".						/CAROLYN E THOMAS/				
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".										
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.										

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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