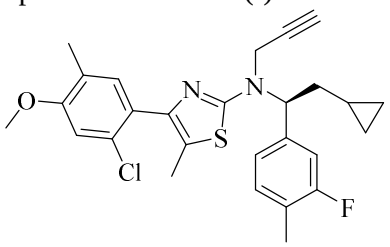
Provided herein is a compound of Formula (I):



(I),

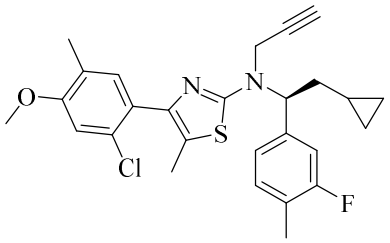
or a pharmaceutically acceptable salt thereof;

for use in a method of treating congenital adrenal hyperplasia in a subject,

wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a frequency of not less than twice daily; and

wherein the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the first administration is less than the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the second and any subsequent administrations.

In one aspect, the present disclosure refers to use of a compound of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for treating congenital adrenal hyperplasia in a subject,

wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is to be administered twice daily; and

wherein the ratio of the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the first daily administration to the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the second daily administration is 1:2; and wherein the subject is concurrently receiving a dose of a glucocorticoid.

Provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt thereof for use in a method of treating congenital adrenal hyperplasia in a subject,

wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a frequency of not less than twice daily; and

wherein the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, administered daily is greater than 200 mg based on the weight of the free base.

Provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in a method of reducing the severity of one or more symptoms selected from hirsutism, precocious puberty, fertility problems, acne, and growth impairment in a subject having classic congenital adrenal hyperplasia,

wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a frequency of not less than twice daily; and

wherein the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the first administration is less than the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the second and any subsequent administrations.

Provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in method of reducing the level of one or more biomarkers of congenital adrenal hyperplasia in a subject having congenital adrenal hyperplasia,

wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a frequency of not less than twice daily; and

wherein the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the first administration is less than the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the second and any subsequent administrations.

Provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in a method of reducing the dosage of corticosteroid administered to a subject having congenital adrenal hyperplasia for controlling congenital adrenal hyperplasia,

wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a frequency of not less than twice daily; and

wherein the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the first administration is less than the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the second and any subsequent administrations.

Provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in a method of reducing the severity of one or more side effects of glucocorticoid treatment in a subject having congenital adrenal hyperplasia,

wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a frequency of not less than twice daily;

wherein the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the first administration is less than the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the second and any subsequent administrations; and

wherein the side effect is selected from osteoporosis, avascular necrosis of bone, myopathy, hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression, gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis, hypertension, coronary heart disease, ischemic heart disease, heart failure, dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, hair loss, mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety,

cognitive impairment, psychosis, dementia, delirium, cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy, suppression of cell-mediated immunity, predisposition to infections, and reactivation of latent infections.

Provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia in a subject, the method comprising:

(a) selecting a subject who has a glucocorticoid dose of greater than 11 $mg/m^2/day$ after a time period of being administered a compound of Formula (I), or a pharmaceutically acceptable thereof, at an amount of about 100 mg twice daily based on the weight of the free base;

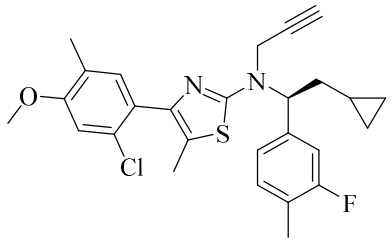
and

(b) administering to the subject the compound of Formula (I), or a pharmaceutically acceptable salt thereof, at a frequency of twice daily;

wherein the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the first administration is less than the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the second administration;

and wherein the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, administered daily is greater than or equal to about 200 mg based on the weight of the free base.

Provided herein is a method of treating congenital adrenal hyperplasia in a subject in need thereof comprising administering to the subject a compound of Formula (I):



(I),

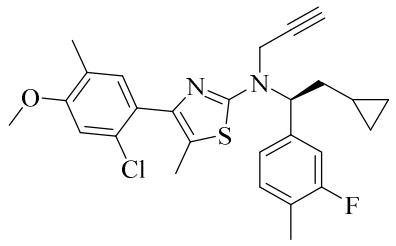
or a pharmaceutically acceptable salt thereof;

wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a frequency of not less than twice daily; and

wherein the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the first administration is less than the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the second and any subsequent administrations.

WHAT IS CLAIMED IS:

1. Use of a compound of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for treating congenital adrenal hyperplasia in a subject,

wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is to be administered twice daily; and

wherein the ratio of the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the first daily administration to the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the second daily administration is 1:2, and

wherein the subject is concurrently receiving a dose of a glucocorticoid.

2. The use of claim 1, wherein the congenital adrenal hyperplasia is classic congenital adrenal hyperplasia.

3. The use of claim 1 or 2, wherein the use comprises reducing the dose of the glucocorticoid to be administered to the subject after a time period of administration of the composition, wherein the decrease in glucocorticoid burden is relative to the glucocorticoid burden prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

4. The use of any one of claims 1 to 3, wherein the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to be administered daily is from 50 mg to 1000 mg based on the weight of the free base.

5. The use of claim 4, wherein the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to be administered daily is about 300 mg based on the weight of the free base.

6. The use of claim 5, wherein the first administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof is about 100 mg based on the weight of the free base and the second administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof is about 200 mg based on the weight of the free base.

7. The use of any one of claims 1 to 6, wherein the subject weighs greater than or equal to about 55 kg.

8. The use of claim 4, wherein the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to be administered daily is about 75 mg based on the weight of the free base.

9. The use of claim 8, wherein the subject weighs from 10 kg to 20 kg.

10. The use of claim 4, wherein the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to be administered daily is about 150 mg based on the weight of the free base.

11. The use of claim 10, wherein the subject weighs from 20 kg to 55 kg.

12. The use of any one of claims 1 to 3, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is to be administered in an amount sufficient to reduce the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in the subject.

13. The use of any one of claims 1 to 3, wherein treating congenital adrenal hyperplasia in a subject comprises reducing the severity of one or more symptoms selected from hirsutism, precocious puberty, fertility problems, acne, and growth impairment in the subject having classic congenital adrenal hyperplasia.

14. The use of any one of claims 1 to 3, wherein treating congenital adrenal hyperplasia in a subject comprisesreducing the severity of one or more side effects of glucocorticoid treatment in the subject having congenital adrenal hyperplasia, and

wherein the side effect is selected from osteoporosis, avascular necrosis of bone, myopathy, hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression, gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis, hypertension, coronary heart disease, ischemic heart disease, heart failure, dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, hair loss, mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, delirium, cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy, suppression of cell-mediated immunity, predisposition to infections, and reactivation of latent infections.

15. The use of any one of claims 1 to 14, wherein the compound of Formula (I) is to be administered in the free base form.

16. The use of any one of claims 1 to 15, wherein the subject is in a fed state.

17. The use of any one of claims 1 to 16, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is to be administered to the subject with a meal.

18. The use of any one of claims 1 to 17, wherein the first daily administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof is with a morning meal.

19. The use of any one of claims 1 to 17, wherein the second daily administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof is with an evening meal.

20. The use of any one of claims 1 to 17, wherein the first daily administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is with a morning meal and the second daily administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof is with an evening meal.

21. The use of any one of claims 1 to 20, wherein the glucocorticoid is selected from cortisol (hydrocortisone), cortisone, prednisone, prednisolone, methylprednisolone, dexamethasone, betamethasone, triamcinolone, fludrocortisone acetate, and deoxycorticosterone acetate.

22. The use of any one of claims 1 to 21, wherein the compound of Formula (I) is to be administed as a pharmaceutical composition comprising: (a) the compound of Formula (I), or a pharmaceutically acceptable salt thereof; and (b) one or more of an oily phase vehicle, an emulsifying agent, a nonionic surfactant, and a solubilizing agent.

23. The use of claim 22, wherein the pharmaceutical composition comprises 1 wt% to 20 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

24. The use of claim 22 or 23, wherein the pharmaceutical composition comprises the compound of Formula (I) as a free base.

25. The use of any one of claims 22 to 24, wherein the pharmaceutical composition is formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of 5 mg to 200 mg, based on the weight of the free base.

26. The use of any one of claims 22 to 25, wherein the pharmaceutical composition is in the form of a tablet, capsule, sachet, powder, granules, coated particle, coated tablet, enterocoated tablet, enterocoated capsule, melting strip, or melting film.

27. The use of any one of claims 1 to 21, wherein the compound of Formula (I) is to be administered as a pharmaceutical composition in oral solution dosage form comprising:

(a) the compound of Formula (I), or a pharmaceutically acceptable salt thereof;

(b) one or more of a sweetener, an anti-oxidant, and a flavor; and

(c) a liquid vehicle.

28. The use of claim 27, wherein the pharmaceutical composition comprises the compound of Formula (I) as a free base.

29. The use of claim 27 or 28, wherein the pharmaceutical composition is formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of 5 mg/mL to 200 mg/mL, based on the weight of the free base.