BRIEF SUMMARY

[0006a] In one aspect of the present disclosure, there is provided a use of a glucocorticoid receptor antagonist (GRA) having a non-steroidal backbone in the manufacture of a medicament for the treatment of a patient having secondary adrenal insufficiency due to prolonged use of a glucocorticoid, wherein the medicament is to be co-administered with a glucocorticoid (GC).

[0007] The present disclosure provides a method for treating a patient suspected of having secondary adrenal insufficiency. In some embodiments, the patient has secondary adrenal insufficiency. The method comprises co-administering a therapeutically effective amount of a glucocorticoid (GC) and a glucocorticoid receptor antagonist (GRA) to a patient in need thereof to increase the patient's morning plasma level of cortisol to at least about 12 μg/dL or a standard control level. In some cases, the patient's morning plasma level of cortisol increased to about 12 μg/dL, about 13 μg/dL, about 14 μg/dL, about 15 μg/dL, about 16 μg/dL, about 17 μg/dL, about 18 μg/dL¸ about 19 μg/dL¸ about 20 μg/dL¸ about 21 μg/dL¸ about 22 μg/dL¸ about 23 μg/dL¸ about 24 μg/dL¸ about 25 μg/dL¸ or more. In some embodiments, if the patient suffering from secondary insufficiency has a cortisol level below 12 μg/dL, *e.g.*, from about 5 μg/dL to about 11.9 μg/dL, administration of GC and GRA can increase the patient's cortisol level to about 18 μg/dL or more, *e.g.*, 18 μg/dL¸ about 19 μg/dL¸ about 20 μg/dL¸ about 21 μg/dL¸ about 22 μg/dL¸ about 23 μg/dL¸ about 24 μg/dL¸ about 25 μg/dL¸ or more, after ACTH administration (Cosyntropin stimulation test). In some embodiments, the subject is not otherwise in need of a combination treatment with a glucocorticoid and glucocorticoid receptor antagonist.

[0008] In some embodiments, the patient is suspected of having secondary adrenal insufficiency due to exogenous Cushing's syndrome (*e.g.*, due to prolonged use of a glucocorticoid). In other embodiments, the patient is suspected of having secondary adrenal insufficiency after surgery for endogenous Cushing's syndrome. In some cases, the patient is suspected of having secondary adrenal insufficiency after successful surgery of a pituitary ACTH secreting tumor. In other cases, the patient is suspected of having secondary adrenal insufficiency after successful surgery for an extra-adrenal cortisol secreting tumor (*e.g.*, ovarian cancer). In some cases, the patient is suspected of having secondary adrenal insufficiency after

WHAT IS CLAIMED IS:

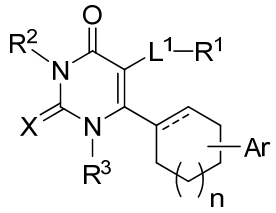
1. Use of a glucocorticoid receptor antagonist (GRA) having a non-steroidal backbone in the manufacture of a medicament for the treatment of a patient having secondary adrenal insufficiency due to prolonged use of a glucocorticoid, wherein the medicament is to be co-administered with a glucocorticoid (GC).

2. The use as in claim 1, wherein the patient has not received glucocorticoid and glucocorticoid receptor antagonist treatment, wherein preferably the patient has not been treated for a disorder or condition selected from the group consisting of glaucoma, inflammatory diseases, rheumatoid arthritis, asthma and rhinitis, chronic pulmonary disease, allergies, and autoimmune diseases, wherein the patient has not been treated to reduce a side effect of glucocorticoid treatment,

wherein more preferably the side effect is selected from the group consisting of weight gain, glaucoma, fluid retention, increased blood pressure, mood swings, cataracts, high blood sugar, diabetes, infection, loss of calcium from bones, osteoporosis, menstrual irregularities, fat redistribution, growth retardation, and cushingoid appearance.

3. The use as in claim 1 or 2, wherein the glucocorticoid receptor antagonist is a selective inhibitor of the glucocorticoid receptor.

4. The use as in claims 1, 2 or 3, wherein the glucocorticoid receptor antagonist backbone is a cyclohexyl pyrimidine, wherein the cyclohexyl pyrimidine has preferably the following formula:



wherein

the dashed line is absent or a bond;

X is selected from the group consisting of O and S;

R^1 is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl and heteroaryl, optionally substituted with from 1 to 3 R^{1a} groups;

each R^{1a} is independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkyl OR^{1b}, halogen, C_{1-6} haloalkyl, C_{1-6} haloaloxy, OR^{1b}, $NR^{1b}R^{1c}$, $C(O)R^{1b}$, $C(O)OR^{1b}$, $OC(O)R^{1b}$, $C(O)NR^{1b}R^{1c}$, $NR^{1b}C(O)R^{1c}$, SO_2R^{1b}, $SO_2NR^{1b}R^{1c}$, cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

R^{1b} and R^{1c} are each independently selected from the group consisting of H and C_{1-6} alkyl;

R^2 is selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} alkyl-OR^{1b}, C_{1-6} alkyl $NR^{1b}R^{1c}$ and C_{1-6} alkylene heterocycloalkyl;

R^3 is selected from the group consisting of H and C_{1-6} alkyl;

Ar is aryl, optionally substituted with 1-4 R^4 groups;

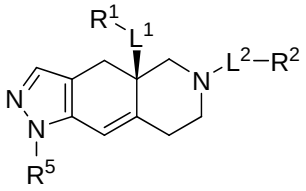
each R^4 is independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} alkoxy, halogen, C_{1-6} haloalkyl and C_{1-6} haloalkoxy;

L^1 is a bond or C_{1-6} alkylene; and

subscript n is an integer from 0 to 3,

or salts and isomers thereof.

5. The use as in claims 1, 2 or 3, wherein the glucocorticoid receptor antagonist backbone is a fused azadecalin, wherein the fused azadeclin is preferably a compound having the following formula:



wherein

L^1 and L^2 are members independently selected from a bond and unsubstituted alkylene;

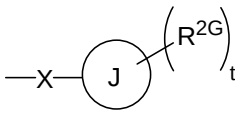
R^1 is a member selected from unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted heterocycloalkyl, $-OR^{1A}$, $NR^{1C}R^{1D}$, $-C(O)NR^{1C}R^{1D}$, and $-C(O)OR^{1A}$, wherein

R^{1A} is a member selected from hydrogen, unsubstituted alkyl and unsubstituted heteroalkyl,

R^{1C} and R^{1D} are members independently selected from unsubstituted alkyl and unsubstituted heteroalkyl,

wherein R^{1C} and R^{1D} are optionally joined to form an unsubstituted ring with the nitrogen to which they are attached, wherein said ring optionally comprises an additional ring nitrogen;

R^2 has the formula:



wherein

R^{2G} is a member selected from hydrogen, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, -CN, and $-CF_3$;

J is phenyl;

t is an integer from 0 to 5;

X is $-S(O_2)-$; and

R^5 is phenyl optionally substituted with 1-5 R^{5A} groups, wherein

R^{5A} is a member selected from hydrogen, halogen, $-OR^{5A1}$, $S(O_2)NR^{5A2}R^{5A3}$, -CN, and unsubstituted alkyl, wherein

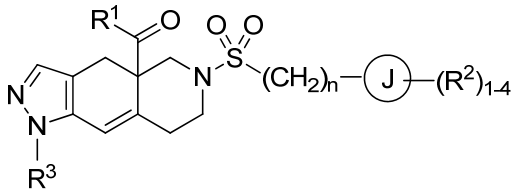
R^{5A1} is a member selected from hydrogen and unsubstituted alkyl, and

R^{5A2} and R^{5A3} are members independently selected from hydrogen and unsubstituted alkyl,

or salts and isomers thereof.

6. The use as in claims 1, 2 or 3, wherein the glucocorticoid receptor antagonist backbone is a heteroaryl ketone fused azadecalin or an octahydro fused azadecalin.

7. The use as in claim 6, wherein the heteroaryl ketone fused azadecalin has the formula:



wherein

R^1 is a heteroaryl ring having from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O and S, optionally substituted with 1-4 groups each independently selected from R^{1a};

each R^{1a} is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, CN, N-oxide, C_{3-8} cycloalkyl, and C_{3-8} heterocycloalkyl;

ring J is selected from the group consisting of a cycloalkyl ring, a heterocycloalkyl ring, an aryl ring and a heteroaryl ring, wherein the heterocycloalkyl and heteroaryl rings have from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O and S;

each R^2 is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halogen, $C_{1\ 6}$ haloalkyl, $C_{1\ 6}$ alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkyl-C_{1-6} alkoxy, CN, OH, $NR^{2a}R^{2b}$, $C(O)R^{2a}$, $C(O)OR^{2a}$, $C(O)NR^{2a}R^{2b}$, SR^{2a}, $S(O)R^{2a}$, $S(O)_2R^{2a}$, C_{3-8} cycloalkyl, and C_{3-8} heterocycloalkyl, wherein the heterocycloalkyl groups are optionally substituted with 1-4 R^{2c} groups;

alternatively, two R^2 groups linked to the same carbon are combined to form an oxo group (=O);

alternatively, two R^2 groups are combined to form a heterocycloalkyl ring having from 5 to 6 ring members and from 1 to 3 heteroatoms each independently selected from the group consisting of N, O and S, wherein the heterocycloalkyl ring is optionally substituted with from 1 to 3 R^{2d} groups;

R^{2a} and R^{2b} are each independently selected from the group consisting of hydrogen and C_{1-6} alkyl;

each R^{2c} is independently selected from the group consisting of hydrogen, halogen, hydroxy, C_{1-6} alkoxy, C_{1-6} haloalkoxy, CN, and $NR^{2a}R^{2b}$;

each R^{2d} is independently selected from the group consisting of hydrogen and C_{1-6} alkyl, or two R^{2d} groups attached to the same ring atom are combined to form (=O);

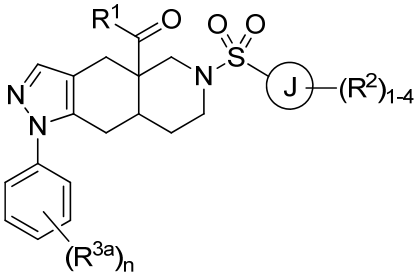
R^3 is selected from the group consisting of phenyl and pyridyl, each optionally substituted with 1-4 R^{3a} groups;

each R^{3a} is independently selected from the group consisting of hydrogen, halogen, and C_{1-6} haloalkyl; and

subscript n is an integer from 0 to 3;

or salts and isomers thereof.

8. The use as in claim 6, wherein the octahydro fused azadecalin has the formula:



wherein

R^1 is a heteroaryl ring having from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O and S, optionally substituted with 1-4 groups each independently selected from R^{1a};

each R^{1a} is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, N-oxide, and C_{3-8} cycloalkyl;

ring J is selected from the group consisting of an aryl ring and a heteroaryl ring having from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O and S;

each R^2 is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkyl-C_{1-6} alkoxy, CN, OH, $NR^{2a}R^{2b}$, $C(O)R^{2a}$, $C(O)OR^{2a}$, $C(O)NR^{2a}R^{2b}$, SR^{2a}, $S(O)R^{2a}$, $S(O)_2R^{2a}$, C_{3-8} cycloalkyl, and C_{3-8} heterocycloalkyl having from 1 to 3 heteroatoms each independently selected from the group consisting of N, O and S;

alternatively, two R^2 groups on adjacent ring atoms are combined to form a heterocycloalkyl ring having from 5 to 6 ring members and from 1 to 3 heteroatomps each independently selected from the group consisting of N, O and S, wherein the heterocycloalkyl ring is optionally substituted with from 1 to 3 R^{2c} groups;

R^{2a}, R^{2b} and R^{2c} are each independently selected from the group consisting of hydrogen and C_{1-6} alkyl;

each R^{3a} is independently halogen; and

subscript n is an integer from 0 to 3,

or salts and isomers thereof.

9. The use as in claims 1 to 8, wherein the glucocorticoid is selected from the group consisting of hydrocortisone, prednisone, dexamethasone, cortisone, and methylprednisone.