somatotrophs, lactotrophs, or gonadotrophs (Kovacs et al., *Endocrine Pathology* **11(3)**:2670275 (2000)). First-line treatment for Cushing's Disease typically involves surgery to remove the pituitary tumor; however, in many cases, the patient is unable to undergo surgery, or not all of the tumor is able to be resected (e.g., if the tumor has invaded cranial regions outside the *sella turcica*, or has invaded bone, or for other reasons), or it may grow back, or may have metastasized. In some cases, radiation treatment is applied, e.g., following surgery. Conventional chemotherapy treatment often used for other tumors may be inapplicable for pituitary tumors, or may not be suitable for patients suffering from pituitary tumors. Medical treatment to reduce cortisol production has been prescribed to treat Cushing's syndrome. Medical treatment to reduce the effects of excess cortisol is often administered, particularly when symptoms persist following surgery (e.g., mifepristone (prescribed as KORLYM®); see also U.S. 9,956,216). However, surgery, radiation and standard chemotherapy may be incompletely effective, and may have severe side-effects, which may make them unsuitable for Cushing's patients. Thus, medical (i.e., non-surgical) treatments for pituitary tumors which cause Cushing's Disease remain lacking.

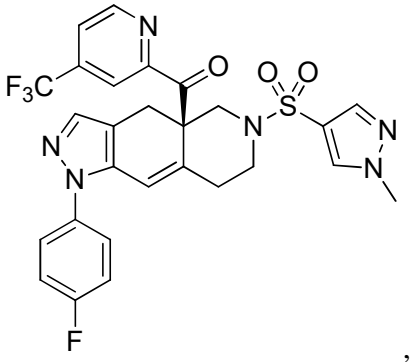
[0005] Accordingly, new medical treatments for pituitary tumors are required, including new medical treatments for pituitary tumors causing Cushing's Disease are required.

SUMMARY

[0006] Applicant discloses herein that administration of relacorilant may be effective to shrink (i.e., reduce the size of) a pituitary tumor. In example, the pituitary tumor to be shrunken by administration of relacorilant is visible using clinical imaging techniques. In example, the methods include selecting a patient suffering from a pituitary tumor that is visible, and which may be measurable, using clinical imaging techniques. In example, the patient suffers from a symptom of Cushing's syndrome. In example, the patient suffers from Cushing's Disease. In example, the methods include selecting a patient for whom the present methods are suitable, and in example, for whom the present methods are preferable to other methods, whether provided as first line treatment, or in conjunction with other treatments. Accordingly, Applicant discloses herein new and surprising treatment methods directed to patients suffering from pituitary tumors. These novel methods may be the sole treatment used to treat pituitary tumors, and may also be used along with other treatments, including surgical treatments, radiation treatment, and other treatments.

[0007] The pituitary tumor to be treated (i.e., shrunk) may be a non-functional (non-secreting) tumor, a hormone-secreting tumor, a benign tumor, or a malignant tumor, with or without metastasis. The pituitary tumor is typically not a non-pituitary metastatic tumor. However, in example, the pituitary tumor may be an invasive tumor. Thus, the pituitary tumor to be treated may be an adenoma or carcinoma, a non-functional (non-secreting) tumor, a hormone-secreting tumor (e.g., a hormone-secreting neuroendocrine tumor), or other tumor. In example, the pituitary tumor to be treated is a pituitary adenoma. In example, the pituitary adenoma to be treated is a macroadenoma. In example, the pituitary adenoma is an adenoma selected from a corticotroph (including a corticotroph with significant amounts of Crooke's hyalinazation, a corticotroph with little or no Crooke's hyalinization, and a silent corticotroph); a somatotroph; a lactotroph; a thyrotroph; a gonadotroph; and an oncocytoma. In example, the pituitary tumor to be reduced in size is pituitary tumor selected from a nonfunctional pituitary tumor; a growth hormone-secreting tumor; a gonadotropin-secreting tumor (e.g., secreting LH or FSH); or other tumor.

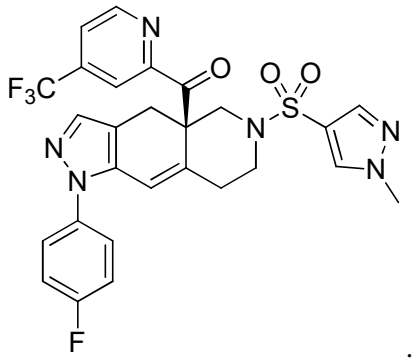
[0007a] In one aspect, the present disclosure refers to a use of relacorilant in the manufacture of a medicament for reducing the size of a visible pituitary tumor in a patient, the use comprising selecting a patient suffering from a pituitary tumor suitable for reduction in size, said selecting comprising imaging said pituitary tumor effective to determine that said tumor is visible, and that an effective amount of relacorilant is to be administered to the selected patient, wherein relacorilant is ((R)-(1-(4-fluorophenyl)-6-((1-methyl-1H-pyrazol-4-yl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone), which has the following structure:



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effective to reduce the size of the pituitary tumor.

[0008] The methods for reducing the size of pituitary tumors comprise administration of relacorilant ((R)-(1-(4-fluorophenyl)-6-((1-methyl-1H-pyrazol-4-yl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone), which has the following structure:



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Relacorilant is also known as CORT125134. Relacorilant is a glucocorticoid receptor modulator (GRM) that does not significantly affect progesterone, mineralocorticoid, androgen, or estrogen receptors (see, e.g., U.S. Patent 8,859,774; U.S. Patent 9,273,047; U.S. Patent 9,707,223; and U.S. Patent 9,956,216, the entire contents of all of which patents are hereby incorporated by reference in their entireties). In example, relacorilant is administered orally.

[0009] In example, an image (e.g., a magnetic resonance imaging (MRI), positron emission tomography (PET) image, computer assisted tomography (CAT) image, or other image) is made of the pituitary tumor, and then relacorilant is administered. The image of the pituitary tumor may be obtained from imaging at least a portion of the brain of, and nearby anatomical regions of, the patient. In example, such imaging may provide a general, and in example, a precise, localization of the tumor with respect to anatomical landmarks and anatomical regions at or near the pituitary of the patient. For example, such anatomical landmarks and anatomical regions may include, without limitation, the *sella turcia*, the pituitary stalk, the hypothalamus, a temporal lobe, a brain ventricle, the optic nerve or optic chiasm, the brainstem, the corpus callosum, and other anatomical structures near the pituitary gland or otherwise visible in an image that includes the pituitary. In example, a dimension of the tumor is measured using an image of the pituitary tumor. In example, a first image (e.g., an MRI, PET, CAT, or other image) is made of the pituitary tumor, relacorilant is then administered, and, after a period of time of relacorilant treatment, a second image (e.g., an MRI, PET, CAT, or other image) of the pituitary tumor is made. In example, a first image of the pituitary tumor is made, relacorilant is then administered, and, after a period of time of relacorilant treatment, a second image of the pituitary tumor is made, and then a further treatment is applied to the pituitary tumor. In example, such further treatment is surgical treatment; or radiation treatment; or pharmaceutical or chemotherapeutic treatment; or combinations thereof. The period of time may be, for example, a day, a week, or a month, or several months during which the patient receives relacorilant on a regular basis; such a regular basis may be, for example, daily relacorilant administration. Administration of relacorilant may be oral administration of relacorilant.

[0010] Accordingly, in example, Applicant discloses herein new and surprising treatment methods directed to patients suffering from pituitary tumors, the methods comprising administration of relacorilant to a patient suffering from a pituitary tumor effective to reduce the size of the pituitary tumor. Applicant discloses herein, for example, that a few months of relacorilant treatment was effective to reduce the size of pituitary tumors (both macroadenomas) in two Cushing's Disease patients.

[0011] These methods are surprising, for example, in view of the finding that there was no regression in any of 17 Cushing's Disease patients with visible tumors treated with mifepristone for 24 weeks (10 of which were macroadenomas). The tumors were imaged using magnetic resonance imaging (MRI); the MRI images were stable in all but one patient,

in whom the tumor increased in size with 10 weeks of mifepristone treatment (Fleseriu, et al., *J. Clin Endocrin Metab* 97(6):2039-2049 (2012)).

[0012] In example, Applicant discloses herein new and surprising treatment methods directed to the tumors of patients suffering from pituitary tumors, which may be, e.g., pituitary adenomas. In example, the treatment methods are directed to patients suffering from non-functional (i.e., non-secreting pituitary tumors). In example, the treatment methods are directed to patients suffering from hormone-secreting pituitary tumors, which may be, e.g., adrenocorticotrophic hormone (ACTH)-secreting pituitary tumors. In example, the treatment methods are directed to patients suffering from hormone-secreting pituitary tumors, which may be, e.g., GH, TSH, PRL, MSH, FSH, LH, or β-lipotropin -secreting pituitary tumors.

[0013] The present methods may be applied to patients suffering from a pituitary tumor effective to shrink the pituitary tumor, as a first-line treatment of the tumor; as neo-adjuvant treatment of the tumor (i.e., preceding a subsequent treatment such as radiation, surgical, or other treatment of the tumor (e.g., as preparation for such treatment)); as adjuvant treatment of the tumor (i.e., following surgical, radiation, or other treatment of the pituitary tumor); and in other uses and combinations. The present methods may be applied to patients suffering from a pituitary tumor that is visible using clinical imaging. The present methods may be applied to patients suffering from a pituitary tumor the size of which is measurable using clinical imaging. Pituitary tumors are often treated surgically; such surgical treatment for pituitary tumors may be, e.g., transsphenoidal surgery. In example, the treatment methods are directed to patients suffering from pituitary tumors, who are not candidates for surgery, or who have refused surgery, or who have failed surgery, where the surgery may be transsphenoidal surgery or may be other surgery for treatment of the pituitary tumor. In example, the treatment methods are directed to patients suffering from pituitary tumors, who are candidates for surgery, who have not yet undergone surgery, where the surgery may be transsphenoidal surgery or may be other surgery for treatment of the pituitary tumor. In example, the treatment methods are directed to patients suffering from pituitary tumors, for whom surgery is planned, but who have not yet undergone surgery, in which administration of relacorilant comprises preparation or pre-treatment for surgery, where the surgery may be transsphenoidal surgery or may be other surgery for treatment of the pituitary tumor. In example, the treatment methods are directed to patients suffering from pituitary tumors, which patients have previously undergone surgery for treatment of the

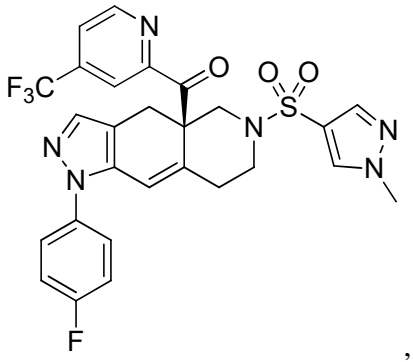
pituitary tumors, which treatment was not successful, or was incompletely successful, or following which the tumors have regrown, where the surgery may be transsphenoidal surgery or may be other surgery for treatment of the tumor. In example, the treatment methods are directed to patients suffering from pituitary tumors, which patients have previously undergone radiation treatment for the pituitary tumors, which treatment was not successful, or was incompletely successful, or following which the tumors have regrown.

[0014] Accordingly, Applicant discloses herein methods of treating a visible pituitary tumor comprising administering relacorilant to the patient, effective treat the pituitary tumor, wherein said treatment comprises reducing the size of the pituitary tumor. Applicant discloses herein methods of reducing the size of a pituitary tumor comprising administering relacorilant to the patient, effective to reduce the size of the pituitary tumor; such reduction of the size of the pituitary tumor may be irrespective of the functional status of the pituitary tumor. Applicant discloses herein methods of treatment of a visible pituitary tumor comprising administering relacorilant to the patient, effective to reduce the size of the visible pituitary tumor. Applicant discloses herein methods of treatment of a pituitary tumor comprising administering relacorilant to the patient, effective to reduce hormone secretion from the pituitary tumor. Applicant discloses herein methods of treatment of a pituitary tumor comprising administering relacorilant to the patient, effective to treat the pituitary tumor to reduce ACTH secretion from the pituitary tumor. The methods may include selecting a patient for such treatment, where the patient suffers from such a pituitary tumor; where the patient suffers from a visible pituitary tumor; where the patient suffers from a measurable pituitary tumor. The methods may include selecting a patient for such treatment, where the patient suffers from such a pituitary tumor and suffers from symptoms of Cushing's syndrome; or suffers from excess ACTH levels; or from excess cortisol levels; or from a pituitary tumor that causes symptoms of Cushing's syndrome.

[0015] Relacorilant administration may comprise oral administration of relacorilant, and may be to a patient in the fasted, or in the fed, condition. The pituitary tumor may be an adenoma, and may be a hormone-secreting pituitary tumor. The pituitary tumor may be an ACTH-secreting pituitary tumor. The treatment may comprise relacorilant administration prior to pituitary surgery, during pituitary surgery, after pituitary surgery, and combinations thereof (where such pituitary surgery may include, e.g., surgical resection of the tumor). In example, the treatment methods may further comprise radiation, or (for pituitary

CLAIMS:

1. Use of relacorilant in the manufacture of a medicament for reducing the size of a visible pituitary tumor in a patient, the use comprising selecting a patient suffering from a pituitary tumor suitable for reduction in size, said selecting comprising imaging said pituitary tumor effective to determine that said tumor is visible, and that an effective amount of relacorilant is to be administered to the selected patient, wherein relacorilant is ((R)-(1-(4-fluorophenyl)-6-((1-methyl-1H-pyrazol-4-yl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone), which has the following structure:



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effective to reduce the size of the pituitary tumor.

2. The use of claim 1, wherein said selecting further comprises determining that said patient suffers from a symptom of Cushing's syndrome.

3. The use of claim 1, further comprising measuring said pituitary tumor.

4. The use of claim 1, further comprising measuring said pituitary tumor following relacorilant administration, wherein said measuring comprises a second imaging of the pituitary tumor.

5. The use of claim 1, wherein said relacorilant administration comprises that relacorilant is to be administered orally.

6. The use of claim 1, wherein said pituitary tumor is a non-secreting pituitary tumor.

7. The use of claim 1, wherein said pituitary tumor is a hormone-secreting tumor, and said treatment is effective to reduce the size of the pituitary tumor and to reduce hormone secretion from said pituitary tumor.

8. The use of claim 1, wherein said relacorilant administration comprises that between about 20 milligrams (mg) to about 800 mg of relacorilant is to be administered daily.

9. The use of claim 1, wherein said relacorilant administration comprises that relacorilant is to be administered daily in single unit dosage forms each containing an amount of relacorilant selected from 50 milligrams (mg), 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, and 500 mg of relacorilant.

10. The use of claim 4, further comprising application of a further pituitary tumor targeting treatment following said second imaging of the pituitary tumor.

11. The use of claim 10, wherein said pituitary tumor targeting treatment comprises surgical treatment.

12. The use of claim 5, wherein said administration of relacorilant comprises that relacorilant is to be administered orally to a fasted patient.

13. The use of claim 12, wherein said fasted patient is a patient who has not eaten a meal or otherwise ingested food for at least two hours prior to the administration of relacorilant.

14. The use of claim 5, wherein said administration of relacorilant comprises that relacorilant is to be administered orally to a fed patient.

15. The use of claim 14, wherein said fed patient is a patient who has begun eating a meal about 30 minutes or less prior to the administration of relacorilant.

16. The use of claim 14, wherein a fed patient is a patient who has begun eating a meal about one hour or less prior to the administration of relacorilant.

17. The use of claim 1, wherein said administration of relacorilant comprises that relacorilant is to be administered prior to surgery for resection of the pituitary tumor.

18. The use of claim 1, wherein said administration of relacorilant comprises that relacorilant is to be administered following surgery for resection of the pituitary tumor.

19. The use of claim 18, wherein said relacorilant administration following surgery for resection of the tumor is effective to reduce the size of, or growth of, tumor tissue remaining in the patient following said surgical treatment.

20. The use of claim 19, further comprising that radiation treatment or cancer chemotherapy treatment, or both, is to be administered to said patient.

21. The use of claim 1, wherein said administration of relacorilant comprises that relacorilant is to be administered to a patient who has been administered another pharmaceutical or medical treatment prior to, or at the same time as, said relacorilant.

22. The use of claim 1, wherein said administration of relacorilant comprises that relacorilant is to be administered to a patient, followed by surgical treatment in that said pituitary tumor is to be resected, then followed by a further step that relacorilant is to be administered.

23. The use of claim 1, wherein said administration of relacorilant comprises that relacorilant is to be administered to a patient, followed by surgical treatment in that said pituitary tumor is to be resected, then followed by radiation treatment targeting the pituitary tumor and/or regions near the location previously occupied by said pituitary tumor.

24. The use of claim 5, wherein said administration of relacorilant comprises that relacorilant is to be administered to a patient, followed by surgical treatment in that said pituitary tumor is to be resected, then followed by a further step that relacorilant is to be administered.

25. The use of claim 5, wherein said administration of relacorilant comprises that relacorilant is to be administered to a patient, followed by surgical treatment in that said pituitary tumor is to be resected, then followed by radiation treatment targeting the pituitary tumor and/or regions near the location previously occupied by said pituitary tumor.

26. The use of claim 14, wherein said administration of relacorilant comprises that relacorilant is to be administered to a patient, followed by surgical treatment in that said pituitary tumor is to be resected, then followed by a further step that relacorilant is to be administered.

27. The use of claim 14, wherein said administration of relacorilant comprises that relacorilant is to be administered to a patient, followed by surgical treatment in that said pituitary tumor is to be resected, then followed by radiation treatment targeting the pituitary tumor and/or regions near the location previously occupied by said pituitary tumor.

28. The use of claim 1, wherein said pituitary tumor is hormone-secreting tumor, and said tumor secretes a hormone selected from adrenocorticotrophic hormone, prolactin, growth hormone, thyroid stimulating hormone, follicle stimulating hormone, luteinizing hormone, melanocyte stimulating hormone, β-lipotropin, oxytocin, and vasopressin.

29. The use of claim 5, wherein said pituitary tumor is hormone-secreting tumor, and said tumor secretes a hormone selected from adrenocorticotrophic hormone, prolactin, growth hormone, thyroid stimulating hormone, follicle stimulating hormone, luteinizing hormone, melanocyte stimulating hormone, β-lipotropin, oxytocin, and vasopressin.

30. The use of claim 7, wherein said pituitary tumor is hormone-secreting tumor, and said tumor secretes a hormone selected from adrenocorticotrophic hormone, prolactin, growth hormone, thyroid stimulating hormone, follicle stimulating hormone, luteinizing hormone, melanocyte stimulating hormone, β-lipotropin, oxytocin, and vasopressin.