Cushing's syndrome that are caused by non-pituitary sources of cortisol are termed "ectopic Cushing's syndrome". Endogenous Cushing's syndrome is an orphan disease that most often affects adults aged 20-50. In the United States, an estimated 20,000 patients have Cushing's syndrome, with about 3,000 new patients being diagnosed each year. Symptoms vary, but most people experience one or more of the following manifestations: high blood sugar (hyperglycemia), diabetes, high blood pressure, upper-body obesity, rounded face, increased fat around the neck, thinning arms and legs, easy bruising, facial plethora, acne, red purple stripes across the body, severe fatigue and weak muscles. Irritability, anxiety, cognitive disturbances and depression are also common. Cushing's syndrome can affect every organ system in the body and can be lethal if not treated effectively. One cause of death in Cushing's syndrome patients is due to emboli caused by hypercoagulopathy associated with the syndrome. Hypercoagulopathy is associated with, and may cause, emboli associated with arterial thrombosis or venous thromboembolism (VTE), including pulmonary emboli and deep vein thrombosis. Such emboli may occur and are often fatal. Stroke is another common result of emboli due to hypercoagulopathy.

[0004] Cushing's syndrome patients may be treated surgically to remove, as much as possible, the source of the excess cortisol, and by other means. Cushing's syndrome patients may receive medical treatment, such as by administration of glucocorticoid receptor modulators, such as mifepristone, to reduce or block the effects of excess cortisol (see, e.g., U.S. Patent 9,943,526; U.S. Patent 9,956,216, both of which patents are hereby incorporated by reference in their entireties). However, the hypercoagulopathy experienced by Cushing's syndrome patients often persists following surgery for Cushing's syndrome. The coagulation factors Factor VIII and von Willebrand Factor ***increased*** one month after surgery, and took six months or more to decline below the levels found prior to surgery (Casonato, et al. Blood Coagulation and Fibrinolysis 10(3):145-151 (1999)).

[0005] Accordingly, methods for treating Cushing's syndrome patients in order to reduce the risk of developing hypercoagulopathy, DVT, PE, VTE, or other embolic disorder are lacking in the art and are required.

SUMMARY

[0005a] In an aspect of the present disclosure, there is provided a use of a glucocorticoid receptor modulator (GRM) in the manufacture of a medicament for reducing the risk of hypercoagulopathy in a Cushing's syndrome patient, wherein:

said patient is determined to be at elevated risk of suffering from hypercoagulopathy as compared to other Cushing's syndrome patients,

an effective amount of a glucocorticoid receptor modulator (GRM) is to be administered to said patient, wherein said GRM administration comprises a first anticoagulation therapy,

Whereby said risk of developing hypercoagulopathy is reduced as compared to the risk of developing hypercoagulopathy in a Cushing's syndrome patient who has not received said first anticoagulation therapy.

[0005b] In another aspect of the present disclosure, there is provided a use of a glucocorticoid receptor modulator (GRM) in the manufacture of a medicament for reducing risk of developing deep vein thrombosis (DVT), pulmonary embolism (PE), or venous thromboembolism (VTE) in a Cushing's syndrome patient, wherein:

said patient is determined to be at elevated risk of suffering from at risk of developing DVT, PE, or VTE as compared to other Cushing's syndrome patients,

an effective amount of a glucocorticoid receptor modulator (GRM) is to be administered to said patient, wherein said GRM administration comprises a first anticoagulation therapy,

Whereby said risk of developing DVT, PE, or VTE is reduced as compared to the risk of developing DVT, PE, or VTE in a Cushing's syndrome patient who has not received said first anticoagulation therapy.

[0006] Applicant provides novel methods for preventing or treating hypercoagulopathy. In examples, these novel methods are effective for preventing or treating hypercoagulopathy in Cushing's syndrome patients at risk of, or suffering from, a disease or condition associated

with an elevated risk of developing hypercoagulopathy, or from a disease or condition associated with an elevated risk of developing deep vein thrombosis (DVT), pulmonary embolism (PE), and venous thromboembolism (VTE). In examples, these novel methods are effective for treating an inflammatory state in Cushing's syndrome patients suffering from a disease or condition associated with an elevated risk of developing hypercoagulopathy, or from a disease or condition associated with an elevated risk of developing DVT, PE, and VTE. In examples, these novel methods are effective for unmasking an inflammatory state in Cushing's syndrome patients suffering from, or at risk of developing, hypercoagulopathy, DVT, PE, or VTE.

[0007] In examples, the methods comprise prophylactic methods suitable for, and effective for, reducing the risk of development of hypercoagulopathy in Cushing's syndrome patients. In examples, the methods comprise prophylactic methods suitable for, and effective for, reducing the risk of development of DVT, PE, and VTE in Cushing's syndrome patients.

[0008] In examples, Applicant discloses herein methods of treating hypercoagulopathy in a patient suffering from Cushing's syndrome, comprising: Administering an effective amount of a glucocorticoid receptor modulator (GRM) to said patient, whereby said hypercoagulopathy is treated. In examples, the methods of treating hypercoagulopathy in a patient suffering from Cushing's syndrome further comprise determining that the Cushing's syndrome patient is suffers from, or is at elevated risk of developing, hypercoagulopathy. In examples, the GRM is a glucocorticoid receptor antagonist (GRA). In examples, the GRM is mifepristone. In examples, the GRM or GRA is a heteroaryl-ketone fused azadecalin GRM (HKGRM). In examples, the HKGRM is relacorilant.

[0009] In examples, Applicant discloses herein methods of reducing the risk of developing DVT, PE, or VTE in a patient suffering from Cushing's syndrome, comprising: Administering a medical treatment for Cushing's syndrome, said medical treatment comprising administering an effective amount of a glucocorticoid receptor modulator (GRM) to said patient, Whereby said risk of developing DVT, PE, or VTE is reduced as compared to the risk of developing DVT, PE, or VTE in a Cushing's patient who had not previously received said medical treatment for Cushing's syndrome. In examples, the risk of developing DVT, PE, or VTE in the Cushing's syndrome patient is reduced at one month of medical treatment as compared to the risk, one month following surgery, of developing DVT, PE, or VTE in a Cushing's patient who has received surgical treatment for Cushing's

syndrome. In examples, the methods of reducing the risk of developing DVT, PE, or VTE in a patient suffering from Cushing's syndrome further comprise determining that the Cushing's syndrome patient is suffers from, or is at elevated risk of developing, hypercoagulopathy.

[0010] In examples, Applicant discloses herein methods of unmasking and subsequently reducing an inflammatory state in a patient suffering from Cushing's syndrome, comprising: Administering an effective amount of a GRM to said patient, Effective to increase inflammatory symptoms in said patient within about 4 weeks of beginning said administration, and Effective to subsequently decrease said inflammatory symptoms in said patient by about 3 to 4 months after beginning said administration, Whereby said inflammatory state is reduced in Cushing's syndrome. In examples of the methods of unmasking and subsequently reducing an inflammatory state in a patient suffering from Cushing's syndrome, the inflammatory symptoms comprise greater than normal C-Reactive protein levels. In examples, the methods of unmasking and subsequently reducing an inflammatory state in a patient suffering from Cushing's syndrome further comprise determining that the Cushing's syndrome patient suffers from, or is at elevated risk of developing, hypercoagulopathy.

[0011] In examples of the methods disclosed herein, the GRM is a heteroaryl ketone fused azadecalin GRM, and may be relacorilant. In examples of the methods disclosed herein, the GRM is a steroidal GRM, and may be mifepristone.

[0012] Applicant discloses herein that the coagulation profile of the Cushing's patients treated with relacorilant was improved compared to baseline. In contrast to prior observations of Cushing's syndrome patients treated surgically, relacorilant administration did not lead to an increase in either Factor VIII or von Willebrand's Factor, and declined with only a few months of relacorilant treatment. APTT measurements increased in Cushing's patients receiving relacorilant, indicating that the risk of coagulation and of risk of DVT, PE, and VTE was reduced. These results show that relacorilant treatment improves the coagulation profile of Cushing's patients. These results further suggest that relacorilant treatment of Cushing's patients provides a better coagulation factor profile, earlier after treatment, than does surgery.

[0013] Accordingly, Applicant provides herein methods to treat hypercoagulopathy seen in Cushing's syndrome patients in a way that is much safer than surgery. The acute decreases of

WE CLAIM:

1. Use of a glucocorticoid receptor modulator (GRM) in the manufacture of a medicament for reducing the risk of hypercoagulopathy in a Cushing's syndrome patient, wherein:

said patient is determined to be at elevated risk of suffering from hypercoagulopathy as compared to other Cushing's syndrome patients,

an effective amount of a glucocorticoid receptor modulator (GRM) is to be administered to said patient, wherein said GRM administration comprises a first anticoagulation therapy,

Whereby said risk of developing hypercoagulopathy is reduced as compared to the risk of developing hypercoagulopathy in a Cushing's syndrome patient who has not received said first anticoagulation therapy.

2. The use of claim 1, wherein said patient is determined to be at elevated risk of suffering from hypercoagulopathy, wherein:

a blood clotting marker is measured or a blood clot is identified in the patient, and

the measured blood clotting marker is compared to normal values of said blood clotting marker,

wherein the patient is determined to be at elevated risk of hypercoagulopathy from decreased blood clotting time, elevated platelet count, elevated fibronectin or D-dimer levels, or presence of a blood clot.

3. The use of claim 1, wherein the GRM is to be administered orally.

4. The use of claim 1, wherein the Cushing's syndrome patient suffers from Cushing's Disease.

5. The use of claim 1, wherein the GRM is mifepristone.

6. The use of claim 1, wherein the GRM is a non-steroidal GRM having a heteroaryl ketone fused azadecalin backbone.

7. The use of claim 5, wherein the GRM is selected from relacorilant, CORT122928, and CORT113176.

8. The use of claim 5, wherein the GRM is relacorilant.

9. The use of claim 1, wherein a second anticoagulation therapy is to be further administered.

10. Use of a glucocorticoid receptor modulator (GRM) in the manufacture of a medicament for reducing risk of developing deep vein thrombosis (DVT), pulmonary embolism (PE), or venous thromboembolism (VTE) in a Cushing's syndrome patient, wherein:

said patient is determined to be at elevated risk of suffering from at risk of developing DVT, PE, or VTE as compared to other Cushing's syndrome patients,

an effective amount of a glucocorticoid receptor modulator (GRM) is to be administered to said patient, wherein said GRM administration comprises a first anticoagulation therapy,

Whereby said risk of developing DVT, PE, or VTE is reduced as compared to the risk of developing DVT, PE, or VTE in a Cushing's syndrome patient who has not received said first anticoagulation therapy.

11. The use of claim 10, wherein said patient is determined to be at elevated risk of suffering from hypercoagulopathy, wherein:

a blood clotting marker is measured or a blood clot is identified in the patient, and

the measured blood clotting marker is compared to normal values of said blood clotting marker,

wherein the patient is determined to be at elevated risk of developing DVT, PE, or VTE from decreased blood clotting time, elevated platelet count, elevated fibronectin or D-dimer levels, or presence of a blood clot.

12. The use of claim 1, wherein the GRM is to be administered orally.

13. The use of claim 11, wherein the patient suffers from Cushing's syndrome.

14. The use of claim 11, wherein the GRM is a glucocorticoid receptor antagonist (GRA).

15. The use of claim 14, wherein the GRM is mifepristone.

16. The use of claim 14, wherein the GRM is a non-steroidal GRM having a heteroaryl ketone fused azadecalin backbone.

17. The use of claim 16, wherein the GRM is selected from relacorilant, CORT122928, and CORT113176.

18. The use of claim 17, wherein the GRM is relacorilant.

19. The use of claim 11, wherein a second anticoagulation therapy is to be further administered.

20. The use of claim 11, wherein said risk of developing DVT, PE, or VTE is reduced at one month of medical treatment as compared to the risk, one month following surgery, of developing DVT, PE, or VTE in a Cushing's syndrome patient who has received surgical treatment for Cushing's syndrome.

21. The use of claim 2, wherein said risk of developing hypercoagulopathy is reduced at one month of medical treatment as compared to the risk, one month following surgery, of developing hypercoagulopathy in a Cushing's syndrome patient who has received surgical treatment for Cushing's syndrome.