Mifepristone Dynamic Testing for Diagnosis for Central Adrenal Insufficiency

NCT04588688

IRB Approval Date: March 18, 2020

CLINICAL PROTOCOL

Mifepristone Dynamic Testing for Diagnosis for Central Adrenal Insufficiency

Study Agents: Mifepristone

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Version 1.5, February 17th, 2020

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PROTOCOL SYNOPSIS

Financial Sponsor: Corcept Therapeutics, Inc.
Name of Finished Product: Mifepristone (Korlym)
Study Title: Mifepristone Dynamic Testing for Diagnosis for Central Adrenal Insufficiency
Study Phase: Phase II
Primary Objective: Phase I of the study is to determine whether recruitment at our institution is sufficient for a study for mifepristone use as a diagnostic tool to diagnose central adrenal insufficiency and to generate data to inform a post-pilot study. Phase II of the study involves taking those recruited and having them complete the study to generate the data.
Study Design: Single-center pilot feasibility study of mifepristone to evaluate the recruitment of participants with the diagnosis of confirmed or suspected secondary adrenal insufficiency. Cortisol (secondary endpoint), ACTH and other steroid responses (exploratory endpoints) to mifepristone in participants with normal insulin tolerance testing (ITT) and participants with confirmed or suspected adrenal insufficiency will be analyzed. The study will test primarily for feasibility of recruitment (phase 1) and provide preliminary data for planning a post-pilot study (phase 2).
Study Population: Subjects with normal ITT and subjects with confirmed or suspected diagnosis of central adrenal insufficiency.
1. **Criteria for Inclusion and Exclusion: Please see section 4.**
Test Product; Dose; and Mode of Administration: Single dose of mifepristone 600mg, administered orally
Reference or Placebo Therapy; Dose; and Mode of Administration: None
Duration of Treatment: One day
Variables: Cortisol, ACTH

Statistical Methods:

- For the primary endpoint of recruitment actual recruitment will be compared to target recruitment (1 patient per 6 weeks). Actual and target recruitment per month will be plotted and visually compared. Recruitment of ≥ 26 participants and study completion and complete data on ≥ 22 patients will be a success regarding the primary endpoint.
- For the secondary endpoint the day 2 cortisol level will be compared to the maximal ITT cortisol level to determine if and to what degree there is a correlation between the two measurements.
- Receiver operating characteristic (ROC) curve will be created with the day 2 cortisol level as the variable, and the ITT result as the “gold standard” test for adrenal insufficiency, to analyze the performance of cortisol as a diagnostic test.
- T-tests will be used to compare cortisol, ACTH, and other hormone levels between healthy individuals and those with diagnosed with central adrenal insufficiency.

1 INTRODUCTION

1.1 Indication

Central adrenal insufficiency (CAI) is the inadequate production of cortisol in the setting of physiologic stress. In contrast to primary adrenal insufficiency, CAI is due to pituitary or hypothalamic dysfunction. Today, CAI has a prevalence of roughly 150-280 per million.[i] The most common cause of CAI is administration of exogenous glucocorticoids. Other common pharmacologic causes of CAI include synthetic progestins and opiates, which can suppress the hypothalamic-pituitary-adrenal (HPA) axis. Primary pituitary pathologies include tumors, congenital or developmental causes, and hypophysitis. Brain trauma, radiation, and granulomatous diseases can also affect the neuroendocrine components of the (HPA) axis.

1.2 Background and Rationale

Central adrenal insufficiency can be challenging to diagnose, as patients often present with nonspecific symptoms of weakness, malaise, and nausea. Furthermore, patients with partial adrenal insufficiency may be asymptomatic until they encounter major physiologic stress. Currently, CAI is diagnosed with basal testing and/or dynamic testing. Basal testing that reveals low morning cortisol and ACTH suggests CAI. If basal testing is equivocal, dynamic testing is typically completed with cosyntropin stimulation test. Cosyntropin stimulation testing can diagnose or rule out primary adrenal insufficiency, but can also be equivocal in CAI. The gold standard for diagnosing CAI is dynamic testing with the insulin tolerance test (ITT); metyrapone testing is also used. ITT protocol requires administration of

insulin to induce hypoglycemia, followed by serial measurements of cortisol and ACTH response. However, ITT is uncomfortable for patients and poses risks associated with hypoglycemia, such as precipitation of cardiac events or seizures. Metyrapone testing is challenging, because it requires measurement of 11-deoxycortisol, and there is often cross-reactivity between 11-deoxycortisol with cortisol in commercial immunoassays.[ii]

Secondary adrenal insufficiency is a rare diagnosis and data on mifepristone use as a diagnostic tool is unavailable in these patients. Therefore, the current study will test recruitment of this population as the primary endpoint.

1.3 Hypothesis

With regards to the primary endpoint we propose that we can reach a target average recruitment of one patient every 6 weeks for a time study duration of 36 months.

With regards to the secondary endpoint we propose the use of mifepristone as an alternative dynamic testing reagent for CAI. Mifepristone is a glucocorticoid and progesterone receptor antagonist. In normal participants, mifepristone would be expected to cause a rise in morning cortisol. In subjects with CAI, morning cortisol will remain low. This alternative test would avoid patient discomfort associated with hypoglycemia required with insulin tolerance testing, and avoid the need to measure surrogate parameters, such as 11-deoxycortisol required with metyrapone testing.

1.4 Previous Human Experience

Mifepristone is a glucocorticoid and progesterone receptor antagonist. While it is well-known as an abortifacient agent, it is also used and FDA-approved for medical management of Cushing's syndrome. Prior studies have demonstrated that administration of mifepristone causes a dose-dependent increase in morning ACTH and cortisol starting at a dose of 4.5mg/kg.[iii] Furthermore, the concurrent administration of mifepristone and evening dexamethasone 1mg resulted in normal morning ACTH and cortisol, indicating that mifepristone disinhibits HPA suppression by dexamethasone. Of note, these effects of mifepristone on ACTH and cortisol levels were only noted in hormone levels in the morning.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

This study can be viewed as having two phases. The primary (first phase) objective of this pilot-feasibility study is to evaluate, whether recruitment of participants can be reached.

The secondary (phase II) objective is analysis of cortisol response to mifepristone in participants without history of adrenal insufficiency compared to participants with confirmed or suspected adrenal insufficiency. The cortisol response with mifepristone administration will be compared with the maximal cortisol response of the insulin tolerance test to determine whether there is any correlation between the two values.

Another objective of the study is to evaluate the effects of mifepristone on other steroid hormones and metabolites. The last objective is to determine whether there is a statistically large enough difference between the ACTH and cortisol response in healthy participants and those with adrenal insufficiency, to indicate that mifepristone could be used as an agent for diagnosis of central adrenal insufficiency.

2.2 Endpoints

2.2.1 Primary Endpoint

The primary endpoint of this pilot feasibility study is actual study participant recruitment. Reaching the target recruitment rate of one patient every 6 weeks over a 36-month period will be regarded as successful in reaching the primary endpoint.

2.2.2 Secondary Endpoint

The secondary endpoint is the correlation between the peak cortisol measured in ITT (the gold standard) and the cortisol measured the day after mifepristone administration. We will assess whether there is a strong relationship between ITT peak cortisol and the cortisol measured after mifepristone administration. We hypothesize that the Pearson's correlation coefficient (r) for this correlation will be > 0.7. The results of the ITT will be regarded as the gold standard in the diagnosis of secondary adrenal insufficiency. As the true cut-off for diagnosis of adrenal insufficiency using post-mifepristone cortisol is unknown we will analyze the data using ROC c-statistics for different cut-offs.

2.2.3 Exploratory Endpoints

Exploratory endpoints include the impact of mifepristone on ACTH and other steroid hormones and metabolites, such as but not limited to corticosterone, aldosterone, androstenedione, 11-deoxycortisol, 11-deoxycorticosterone, DHEAS, DHEA, 17-hydroxyprotesterone, 17-hydroxypregnenolone. Analysis will be done by c-statistics in comparison the gold standard of ITT peak cortisol as well.

3 STUDY DESIGN

This will be a single-center trial of mifepristone to evaluate the ACTH and cortisol response to mifepristone in participants without history of adrenal insufficiency and participants with confirmed or suspected adrenal insufficiency. All adult participants who have undergone ITT from 2012 to present, are scheduled to undergo ITT in the future, or are clinically suspected to have adrenal insufficiency, will be approached for this study. There will be at least a one-week interval between ITT and mifepristone testing.

Subjects who meet inclusion criteria and agree to participation will undergo the study conducted over two days: baseline hormone labs will be obtained on the morning of day 1. A single dose of 600mg mifepristone is to be orally taken at 10PM on day 1. Participants will then return for repeat lab work on day 2.

4 SUBJECT SELECTION

4.1 Subject Recruitment

The study population will include adult male and female patients (n = 20), who underwent ITT from 2012 to present, are scheduled to undergo ITT in the future, or are clinically suspected to have adrenal insufficiency.

Eligible participants will be identified through a EMERSE and Data Direct search of individuals who have undergone ITT between 2012 and present, who have ITT ordered to be completed, or who have adrenal insufficiency listed as a clinical diagnosis. In addition, eligible participants will be recruited through physician referral and through review of clinic schedules listing individuals scheduled for ITT.

Patients will be called and offered participation by the study staff.

4.1.1 Inclusion Criteria

Adult (ages ≥ 18 years of age) male and female subjects who:

1. Completed ITT at University of Michigan from 2012 to present.

   OR

2. Are scheduled to complete ITT.

   OR

3. Are clinically suspected to have adrenal insufficiency but have not undergone ITT.

4.1.2 Exclusion Criteria

1. Female patients who are of child-bearing potential (defined as a sexually mature woman who has not undergone hysterectomy, bilateral oophorectomy bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 12 weeks prior to screening, or who has not been naturally postmenopausal for at least 24 consecutive months prior to study enrollment) and not using non-hormonal contraception.

2. Female patients not willing to use non-hormonal contraception for one month following treatment.

3. Women who are breast feeding.

4. Female patients who have a positive pregnancy test. L SEP

5. Female patients with unexplained vaginal bleeding or history of endometrial hyperplasia with atypia or carcinoma. L SEP

6. Patients with an existing diagnosis of adrenal insufficiency who are on any glucocorticoid replacement other than oral hydrocortisone or prednisone.

7. Patients with hypokalemia < 3.5 mEq/L on lab work completed on Day 1 or obtained within 3 months prior to Day 1.

8. Patients with AST or ALT greater than 3 times the upper limit of normal on lab work completed on Day 1 or obtained within 3 months prior to Day 1.

9. Hypertensive patients with uncontrolled blood pressure defined as SBP > 180 and/or DBP > 100.

10. Patients on medications that are CYP3A substrates with narrow therapeutic ranges, such as cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus.

11. Patients on medications that are strong CYP3A inhibitors (such as itraconazole, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir, fosamprenavir, boceprevir, clarithromycin, conivaptan, lopinavir, mibefradil, posaconazole, saquinavir, telaprevir, telithromycin, and voriconazole) or inducers (such as rifampin, rifabutin, rifapentine, phenobarbital, phenytoin, carbamazepine, St. John’s wort).

12. Patients taking other medications metabolized by CYP3A, such as simvastatin, lovastatin.

13. Patients who are not euthyroid as judged by the investigator.

14. Patients with history of hypersensitivity to mifepristone or the tablet components

15. Patients who have a history of QT prolongation and patients with any recent abnormal ECG.

5 STUDY TREATMENTS

5.1 Allocation to Treatment

All subjects will be in the treatment group.

5.2 Breaking the Blind

Not applicable.

5.3 Drug Supplies-Mifepristone

- Other names for the drug: KORLYM®, C1073, RU486
- Description: 300 mg tablets are light yellow to yellow, oval-shaped, film-coated tablets debossed with “Corcept” on one side and “300” on the other. Each bottle contains 28 tablets.
- Mode of action: Mifepristone is a selective antagonist of the progesterone receptor at low doses and blocks the glucocorticoid receptor (GR-II) at higher doses. Mifepristone has high affinity for the GR-II receptor but little affinity for the GR-I (MR, mineralocorticoid) receptor.
- Pharmacokinetics:
  Absorption
  Following oral administration pf mifepristone to healthy volunteers, time to peak plasma concentrations of mifepristone occurred between 1 and 2 hours following single dose, and between 1 and 4 hours following multiple doses of 600 mg. The mean plasma concentrations of the three active metabolites of mifepristone peak between 2 and 8 hours after multiple doses of 600 mg/day, and the combined concentrations of the metabolites exceed that of the parent mifepristone. Exposure to mifepristone is substantially less than dose proportional. Time to steady state is within 2 weeks, and the mean (SD) half-life of the parent mifepristone was 85 (61) hours following multiple doses of 600 mg/day of mifepristone. Studies evaluating the effects of food on the pharmacokinetics of mifepristone demonstrate a significant increase in plasma levels of mifepristone when dosed with food.

  Distribution
  Mifepristone is highly bound to alpha-1-acid glycoprotein (AAG) and approaches saturation at doses of 100 mg (2.5 μM) or more. Mifepristone and its metabolites also bind to albumin and are distributed to other tissues, including the central nervous system (CNS).

Metabolism
Cytochrome P450 3A4 (CYP3A4) has been shown to be involved in mifepristone metabolism in human liver microsomes. Two of the known active metabolites are the product of demethylation (one monodemethylated and one di-demethylated), while a third active metabolite results from hydroxylation (monohydroxylated).

Elimination and Excretion
Excretion is primarily (approximately 90%) via the fecal route. Excretion in the urine accounts for less than 10%.

- Side effects: The most common adverse reactions reported in patients with Cushing's syndrome (≥ 20%) include: nausea, fatigue, headache, decreased blood potassium, arthralgia, vomiting, peripheral edema, hypertension, dizziness, decreased appetite, and endometrial hypertrophy. Refer to the current FDA-approved label of Korlym® for the most comprehensive and up to date information on side effects. However, these adverse reactions are observed in patients with Cushing syndrome and are likely due to a contribution by steroid withdrawal syndrome.

- Drug Interactions:
  CYP3A
  - The use of mifepristone with drugs whose metabolism is primarily mediated by CYP3A (substrates) is likely to result in increased plasma concentrations of the drug. Mifepristone is contraindicated in patients taking simvastatin, lovastatin, and CYP3A substrates with narrow therapeutic ranges. Instructions on handling drugs with high or low first pass metabolism in which CYP3A is the primary or the minor route of metabolism are provided in the current FDA-approved label of Korlym®.
  - Medications that inhibit CYP3A could increase plasma mifepristone concentrations and dose reduction of mifepristone may be required.
  - Mifepristone has not been studied with CYP3A inducers. CYP3A inducers could decease the plasma concentration of mifepristone and therefore, co-administration should be avoided.

  Cytochrome P450 (CYP) 2C8/2C9
  - Co-administration of mifepristone with drugs primarily metabolized by CYP2C8/2C9 (substrates) would be expected to result in an increased plasma concentration of that drug. For example, mifepristone significantly increased exposure of the CYP2C8/2C9 substrate fluvastatin. Substrates of these enzymes (e.g., non-steroidal anti-inflammatory drugs, warfarin, repaglinide) should be used at the smallest recommended doses and

monitored closely for adverse effects.

CYP2B6 substrates

- No study has been conducted on the effects of mifepristone on CYP2B6 substrates. Mifepristone is a CYP2B6 inhibitor and may cause significant increase in exposure to drugs that are metabolized by CYP2B6. Caution should be exercised when mifepristone is used concomitantly with CYP2B6 substrates such as bupropion.

Hormonal Contraceptives

- Mifepristone is a progesterone-receptor antagonist and will interfere with the effectiveness of hormonal contraceptives. Therefore, non-hormonal contraceptive methods should be used.

Refer to the current FDA-approved label of Korlym® for the most comprehensive and up to date information on drug-drug interactions with mifepristone.

- Storage and stability: Mifepristone tablets should be stored at controlled room temperature, 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F). [See USP Controlled Room Temperature]. Mifepristone bottles must be stored in a secure, limited access area.

- Preparation and Dispensing: Count the appropriate number of tablets into a prescription bottle and label with a patient-specific label.

- Administration: Mifepristone tablets should not be crushed, split, or chewed.

- Availability: The investigational drug will be provided by Corcept from the same supply as the commercial drug. Under no circumstance will the study medication, mifepristone, be used other than as directed by the protocol.

- Return and Retention of Study Drug: Drug that expires during the study or remains at the site at the end of the study should be discarded on site according to the institutional standard operating procedure for drug destruction. The drug disposition should be documented in the drug accountability logs. The logs including the quantity and lot number of the destroyed drug should be provided to the sponsor.

- Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the investigational drug, mifepristone. The drug accountability records will capture drug receipt, drug dispensing, and final disposition.

5.4 Concomitant medications

Patients on medications listed in the exclusion criteria will not be included in the study.

6 STUDY PROCEDURES- SEE THE SCHEDULE OF ACTIVITIES

6.1 Screening Visit

Potential subjects will be contacted over the phone to review their past medical history and current medications. If the potential participant is a woman of childbearing potential, she will be asked to take an at-home urine pregnancy test or come in for a urine or serum pregnancy test one week prior to visit 1. If they do not meet any pre-screening exclusion criteria, they will present for Day 1 of the study and complete screening labs on this day.

6.2 Treatment Study Period

6.2.1 Visit 1 (Day 1)

Subject will be presented the consent document prior to any procedures on this day. Between 7AM and 9AM, baseline labs, including morning cortisol, ACTH, and other steroid hormones and metabolites (5ml serum, 5ml EDTA) and a serum pregnancy test will be obtained. A comprehensive metabolic panel and complete blood count will be obtained if not already performed in the prior 3 months. Patients will be provided a single dose of 600mg mifepristone to be administered orally, and subjects will be instructed to take the drug between 10PM and 11PM on Day 1.
If the participant is scheduled for an ITT as part of their medical care and is consented for this study prior to completing ITT, the study team will attempt to obtain left over blood samples for measurement of baseline labs relevant for

mifepristone testing, if the serum is drawn before 10AM, the lab draw that is part of Day 1 of the study could be omitted in this scenario.

6.2.2 Follow-up

On Day 2, subjects will return to the clinic. it will be confirmed with the participants that they took mifepristone at the recommended time the previous night. We will obtain vital signs. Between 7AM and 9AM, repeat complete blood count (CBC), serum chemistry and hormone labs will be obtained. Adverse events will be collected.

On Day 7 and Day 30, participants will be contacted by phone to assess for any adverse events that occurred since Day 1.

6.2.3 Subjects with history of adrenal insufficiency

Subjects with confirmed history of adrenal insufficiency (AI) on glucocorticoid replacement at baseline will be instructed on the following protocol for glucocorticoid dosing during testing. All components of the study protocol are otherwise the same as above.

- Day 0: Take the morning dose of glucocorticoid and hold the afternoon dose.
- Day 1: Hold the morning dose until labs are drawn, then take the morning dose. Hold the afternoon dose.
- Day 2: Hold the morning dose until labs are drawn, then take the morning dose and resume baseline dosing schedule.

- Withholding afternoon doses of glucocorticoids for testing is routinely done in clinical practice and considered safe. Participants with diagnosed AI will be provided with a prescription for 4 mg of dexamethasone. Participants will be

provided with two 24-hour phone numbers to call if/when they experience any side effects. . Participants will be instructed to take 4mg of dexamethasone in case they experience significant signs of acute adrenal insufficiency [increasing nausea, lethargy, diarrhea, fever]. Participants are encouraged to contact one of the 24-hour phone numbers prior to taking the dexamethasone and are advised to call the number after taking the dexamethasone. As participants are scheduled for a blood draw the next morning they will be clinically assessed for adrenal insufficiency in case overnight concerns occur and further management will depend on this clinical evaluation. On day 2, participants with adrenal insufficiency will resume their usual dose of hydrocortisone replacement therapy and occurrence of adrenal insufficiency will become less likely. However, participants will remain advised to keep the dexamethasone emergency dosing and to contact the study team in case of any symptoms and signs of adrenal insufficiency

Table 1. Schedule of Activities

Protocol Activity	Screening Phone Call	Screening / Day 1[a]	Day 2	Day 7 (+/- 3 days) Phone Call	Day 30 Phone Call (+/- 3 days)
Visit # / Phone call	**1**	**1**	**2**	**3**	**4**
Informed Consent		X			
Medical History	X	X			
Vitals Signs [b]		X	X		
Serum Chemistry [c]		X	X		
Complete Blood Count		X	X		
Pregnancy Test [d]	X	X			
Hormone Labs [e]		X	X		
Treatment with study agent (10 pm)		X			
Adverse Event Assessment		X	X	X	X

a. There will be at least a one-week interval between ITT and mifepristone testing.
b. Vital signs: height (Day 1 only), weight (Day 1 only), temperature, heart rate, blood pressure.
c. Serum chemistry: comprehensive metabolic panel. Day 1 labs will be omitted if completed and documented in the patient electronic medical record within the prior 3 months. Day 2 labs will be obtained in all cases.
d. Urine pregnancy test at home 1 week before scheduled visit or come in to have urine or serum pregnancy test. Day 1 visit will include a Serum pregnancy test (women of childbearing potential)
e. Hormone labs: ACTH, cortisol and steroid profile (including but not limited to corticosterone, aldosterone, androstenedione, 11-deoxycortisol, 11-deoxycorticosterone, DHEAS, DHEA, 17-hydroxyprotesterone, 17-hydroxypregnenolone). These must be drawn between 7 and 9 AM.

7 ASSESSMENTS

7.1 Primary Endpoint Assessments

The primary endpoint of this pilot feasibility study is the rate of actual study participant recruitment. Reaching the target recruitment rate of one patient per 6 weeks over a 36-month period will be regarded as successfully in reaching the primary endpoint.

7.2 Secondary Assessments

The secondary endpoint is the correlation between cortisol measured after mifepristone administration and the peak cortisol measured in ITT. The results of the ITT will be regarded as the gold standard in diagnosis of diagnosis of secondary adrenal insufficiency. We expect that this correlation, as measured with the Pearson correlation coefficient (r) will be > 0.7. As the true cut-off for diagnosis of adrenal insufficiency using post-mifepristone cortisol is unknown, we will analyze the data using ROC c-statistics for different cut-offs.

7.3 Exploratory Assessments

Exploratory endpoints include the impact of mifepristone on ACTH and other steroid hormones and metabolites, such as but not limited to corticosterone, aldosterone, androstenedione, 11-deoxycortisol, 11-deoxycorticosterone, DHEAS, DHEA, 17-hydroxyprotesterone, 17-hydroxypregnenolone. Analyses will be completed with c-statistics as well.

8 ADVERSE EVENT REPORTING

8.1 Adverse Event Definition

An adverse event (AE) is any untoward medical occurrence in a subject participating in an investigational study or protocol regardless of causality assessment. An adverse event can be an unfavorable and unintended sign (including an abnormal laboratory finding), symptom, syndrome or disease associated with or occurring during the use of an investigational product whether or not considered related to the investigational product.

These events may be:

a. *Definitely related:* clearly associated with study drug/treatment

b. *Probably related*: likely associated with study drug/treatment

c. *Possibly related*: may be associated with study drug or other treatment

d. *Unlikely to be related*, or

e. *Definitely not related* to the study drug/treatment

For reporting purposes, an AE should be regarded as definitely or probably related to the regimen if the investigator believes that at least one of following criteria are met:

a. There is a clinically plausible time sequence between onset of the AE and the administration of the study drug or treatment.

b. There is a biologically plausible mechanism for the study drug or treatment causing or contributing to the AE.

c. The AE cannot be attributed solely to concurrent/underlying illness, other drugs, or procedures.

d. A potential alternative cause does not exist.

Serious Adverse Events (SAE): An adverse drug experience occurring at any dose that results in any of the following outcomes:

a. Death

b. A life-threatening adverse drug experience

c. Inpatient hospitalization or prolongation of existing hospitalization

d. A persistent or significant disability &/or incapacity

e. A congenital anomaly or birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. A serious adverse experience includes any experience that is fatal or immediately life threatening, results in a persistent or significant disability/incapacity, requires or prolongs in-patient hospitalization, or is a congenital anomaly, cancer, or overdose.

Other important medical events that may not result in death, not be life-threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject/patient and may require medical or surgical intervention to prevent one of the outcomes listed previously.

Expected adverse events are those adverse events that are listed in the protocol, the drug label, the Investigator's Brochure (version 18, June 2017), published literature, or in the study informed consent document.

Unexpected adverse events are those that:

a. are not described in the Investigator's Brochure or drug label as far as drug is concerned.

b. are not anticipated in the study informed consent. This includes adverse events for which the specificity or severity is not consistent with the description in the informed consent.

Unanticipated problem: Per FDA Procedural Guidance for Clinical Investigators, Sponsors, and IRBs (January 2009), A serious problem that has implications for the conduct of the study (requiring a significant and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent or investigator's brochure).

Unanticipated problem Reporting: Per 21 CFR 312.66, 312.53 (c)(1)(vii), and 56.108(b)(1), should an Unanticipated problem occur during the investigation, the investigator will promptly report all unanticipated problems involving risks to human subjects or others to IRBMED /FDA.

The severity or grade of an adverse event may be measured using the following definitions:

Mild: Noticeable to the subject, but does not interfere with subject's expected daily activities, usually does not require additional therapy or intervention, dose reduction, or discontinuation of the study.

Moderate: Interferes with the subject's expected daily activities, may require some additional therapy or intervention but does not require discontinuation of the study.

Severe: Extremely limits the subject's daily activities and may require discontinuation of study therapy, and/or additional treatment or intervention to resolve.

8.2 Event reporting:

The study will comply with the IRB & FDA reporting requirements and guidelines.

8.2.1 Serious Adverse Event Reporting Guidelines

The Principal Investigator must be notified within ONE business day of study team's knowledge of any event meeting the criteria and definition of a serious adverse event, regardless of attribution, occurring during the study or within 30 days of the last administration of the study related intervention.

The investigator must report all events meeting the criteria and definition of a serious adverse event as per the local IRB reporting requirements. Participants will be given contact information for study staff should they need to report any adverse events.

The Sponsor-Investigator will coordinate with the Michigan Institute for Clinical and Health Research (MICHR) IND/IDE Assistance Program (MIAP) office for the reporting of any and all IND safety reports to the FDA as per the requirements outlined in 21 CFR312.32 which include all SAEs that are both unexpected and related to the intervention/treatment.

8.2.2 Routine Reporting

Lab results that are out of normal range but not clinically significant will not be reported. All other adverse events, such as those that are expected, or are unlikely or definitely not related to the study participation, are to be reported annually as part of regular data.

9 DATA ANALYSIS/STATISTICAL METHODS

9.1 Sample Size Determination

This is a pilot-feasibility study with the primary endpoint of enrollment per month over a 36-month period. This study time frame was chosen due to the lack of any prior data regarding feasibility. Data required form this study will inform the planning of a post-pilot study.

9.2 Data Analysis

9.2.1 Analysis Populations

As the primary endpoint recruitment will be analyzed as a primary endpoint. The cortisol response with mifepristone administration will be compared with the maximal ITT cortisol level in all patients as a secondary endpoint. In addition, the hormone levels of participants with normal ITT will be compared to those with confirmed diagnosis of central adrenal insufficiency. Data from this study will inform planning of a larger post-pilot study.

9.2.2 Analysis of Primary Endpoint

The primary endpoint of this pilot feasibility study is actual study participant recruitment. Reaching the target recruitment of one participant every 6 weeks over a 36-month period (target n=26) will be regarded successful in reaching the primary endpoint. We estimate an enrollment of 90% of patients in this study. This is in accordance with our prior experience in patients with rare diseases, who are often motivated regarding study participation. We estimate a total of 85% of patients with complete data as we only anticipate minimal study drop out due to side effects of the drug or non-analyzable specimens. Study recruitment will be plotted over time and actual and target recruitment will be visually compared. We will regard a total of 22 patients as a target in meeting the primary endpoint.

9.2.3 Analysis of Secondary Endpoints

The secondary data point is day 2 cortisol and ACTH response to mifepristone administration. The day 2 cortisol level will be compared to the maximal ITT cortisol level to determine if and to what degree there is a correlation between the two measurements. In addition, a receiver operating characteristic (ROC) curve will be created with the day 2 cortisol level as the variable, and the ITT result as the “gold standard” test for adrenal insufficiency, to analyze the performance of cortisol as a diagnostic test. The cortisol and ACTH values in participants with normal ITT will be compared to those with confirmed diagnosis of central adrenal insufficiency, using a

t-test to determine whether there is statistically significant difference between the two populations.

9.2.4 Analysis of Secondary Endpoints

The secondary end points are levels of ACTH, other (than cortisol) steroid hormones and metabolites. These hormone levels will also be analyzed with t-tests to determine whether there is a statistically significant difference between participants with normal ITT and those with confirmed diagnosis of central adrenal insufficiency.

10 MONITORING

To assure adequate protection of the rights of human subjects, per 21 CFR §312.50, 312.53, this study will be monitored by the University of Michigan Institute for Clinical and Health Research (MICHR). Routine monitoring will be scheduled at appropriate intervals, with more frequent visits occurring at the beginning of the study. An initiation visit will take place, followed by routine monitoring visits. Additional visits can be scheduled at the request of the Project Manager.

The established monitoring plan will ensure the quality and integrity of the data through pre- investigation visits and periodic site visits to verify adherence to the protocol, completeness and accuracy of study data and samples collected, proper storage, dispensing and inventory of study medication, and compliance with regulations.

11 DATA HANDLING AND RECORD KEEPING

11.1 CRFs / Electronic Data Record

Data will be protected by several different measures throughout the life of the study. Paper documents and records will be stored in a secured location with restricted access to authorized personnel only. Electronic study documents and data will be kept in a password protected environment, whereby access rights will be terminated at the request of the PI when study members leave the project.

11.2 Record Retention

Per 21 CRF §312.62, study records will be retained for 2 years after the investigation is discontinued.

12 ETHICS

12.1 IRB/FDA

Prior to study commencement, an Investigator Initiated Investigational New Drug (IND) will be submitted to the Food and Drug Administration (FDA), for review and approval. Prior to study commencement, an Investigator Initiated Investigational New Drug (IND) will be submitted to the Food and Drug Administration (FDA), for review and approval. The study will also be reviewed and approved by the Institutional Review Board (IRBMED, University of Michigan, Ann Arbor, MI).

12.2 Institutional Review Board (IRB)

Before implementing this study, the protocol, the proposed informed consent form and other information to be provided to subjects, must be reviewed by a properly constituted Institutional Review Board (IRB). Any amendments to the protocol must be reviewed and approved by IRBMED.

12.3 Subject Information and Consent

The study team member will explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent will be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

The informed consent form is considered to be part of the protocol, and will be submitted for IRB approval.

12.4 STUDY DISCONTINUATION CRITERIA

12.4.1 Stopping Rules for Safety reasons

There will be no Data Safety Monitoring Board as this is a single site study. However, we will continuously review SAE. If a study related SAE occurs in 3 of 6 patients or in >50% of patients at any time, the study will be terminated.

12.4.2 Rules for Discontinuation of a Subject

In the event a patient drops out of the study or is discontinued due to protocol violations, all attempts will be made to exit the patient in accordance with the protocol requirements.

13 REFERENCES

[i] Charmandari E, Nicolaides NC, Chrousos GP. Adrenal insufficiency. Lancet. 2014 Jun 21;383(9935):2152-67.

[ii] Monaghan PJ, Owen LJ, Trainer PJ, Brabant G, Keevil BG, Darby D. Comparison of serum cortisol measurement by immunoassay and liquid chromatography-tandem mass spectrometry in patients receiving the 11β-hydroxylase inhibitor metyrapone. Annals of clinical biochemistry. 2011 Sep;48(Pt 5):441-6.

[iii] Gaillard RC, Riondel A, Muller AF, Herrmann W, Baulieu EE. RU 486: a steroid with antiglucocorticosteroid activity that only disinhibits the human pituitary-adrenal system at a specific time of day. Proc Natl Acad Sci U S A. 1984 Jun;81(12):3879-82.