An Oral GnRH Antagonist to Treat Mild Autonomous Cortisol Excess (MACE) Due to Adrenal Adenomas in Postmenopausal Women
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EXHIBIT A

PROTOCOL

Section		
1.0	**General Information**	
1.1	**Study Title:**	Pilot study of Elagolix for the treatment of autonomous cortisol secretion (ACS) due to adrenal adenomas in postmenopausal women (SA- 002509, Protocol # A19-745)
1.2	**1.2 Institution Name:**	Icahn School of Medicine at Mount Sinai Hospital
1.3	**Investigator Contact Information:**	Alice C. Levine, MD Alice.levine@mountsinai.org (212) 241-3422 Contact: Regina Belokovskaya, DO (regina.belokovskaya@mountsinai.org)
2.0	**Background Information**	
2.1	**Rationale & Background Information**	The rationale specifies the reasons for conducting the research in light of current knowledge. It should include a well-documented statement of the need/problem that is the basis of the project, the cause of this problem and its possible solutions. It should answer the question of why and what: why the research needs to be done and what will be its relevance. Selected literature references critical to the study design, dosage selection, or rationale for the study should be cited, as appropriate. Increasingly, patients are found to have incidentally found adrenal adenomas on imaging performed for other purposes. The most common secretory syndrome in adrenal nodules is autonomous cortisol secretion (ACS) where patients lack the typical clinical stigmata of overt hypercortisolism (1). Exposure to even low levels of excess cortisol can result in long term metabolic and cardiovascular effects which may not be completely reversible. Subclinical hypercortisolism due to adrenal incidentalomas has been shown in multiple, large retrospective studies to be associated with an increased prevalence of hypertension and type 2 diabetes mellitus (T2DM) and cardiovascular risk (2, 3, 4, 5). Morelli et al. reported that cardiovascular event prevalence was higher in patients with subclinical hypercortisolism, regardless of age and the presence of T2DM (6). Most notably, a study by Di Dalmazi et al. demonstrated increased mortality due to cardiovascular disease in patients with even mild cortisol excess due to adrenal adenomas (2). Mild, chronic cortisol excess is particularly toxic to bone resulting in increased bone demineralization and increased risk of vertebral fractures (7,8). There are limited studies regarding outcomes after unilateral adrenalectomy or medical management to treat this disorder. A recent publication demonstrated that adrenalectomy for patients with adenomas resulting in ACS reduces the risk of vertebral fractures (9). Current options for medical treatment of Cushing syndrome include steroidogenesis enzyme inhibitors suitable for all causes of CS (ketoconazole, metyrapone, the glucocorticoid receptor antagonist, mifepristone), agents to

suppress ACTH in Cushing's disease, such as dopamine agonists and pasireotide, and the adrenolytic and steroidogenic enzyme inhibitor mitotane for adrenal cortical carcinomas that secrete cortisol. Mifepristone is currently the only FDA approved medication for Cushing's syndrome with the specific indication for the treatment of elevated blood sugar in patients with Cushing's syndrome and type 2 diabetes mellitus (24). We recently completed a pilot study that demonstrates that Mifepristone treatment of ACS is associated with a statistically significant decrease in fasting glucose and insulin resistance as measured by HOMA-IR scores (25). With various insurance policies it is sometimes difficult to get these medications approved. Often time, ketoconazole, though not FDA approved, may be the first one covered by the insurance. However side effects are common, with the most limiting one being elevation in LFTs with ketoconazole.

The incidence of adrenal adenomas and ACS is higher in women than men with peak incidence at ages 50-70. In addition, several case reports have demonstrated luteinizing hormone/human chorionic gonadotropin receptor (LH/HCG-R) expression in adrenal secretory tumors in postmenopausal and pregnant females . A report by Teo et al. described a post-menopausal and 2 pregnant women with aldosterone-producing adrenal adenomas, each of which harbored activating mutations of *CTNNB1*, the gene encoding β-catenin. The mutations stimulate Wnt activation and cause adrenocortical cells to de-differentiate toward their common adrenal-gonadal precursor cell type including the expression of LH/hCGR and GATA-4 [10].

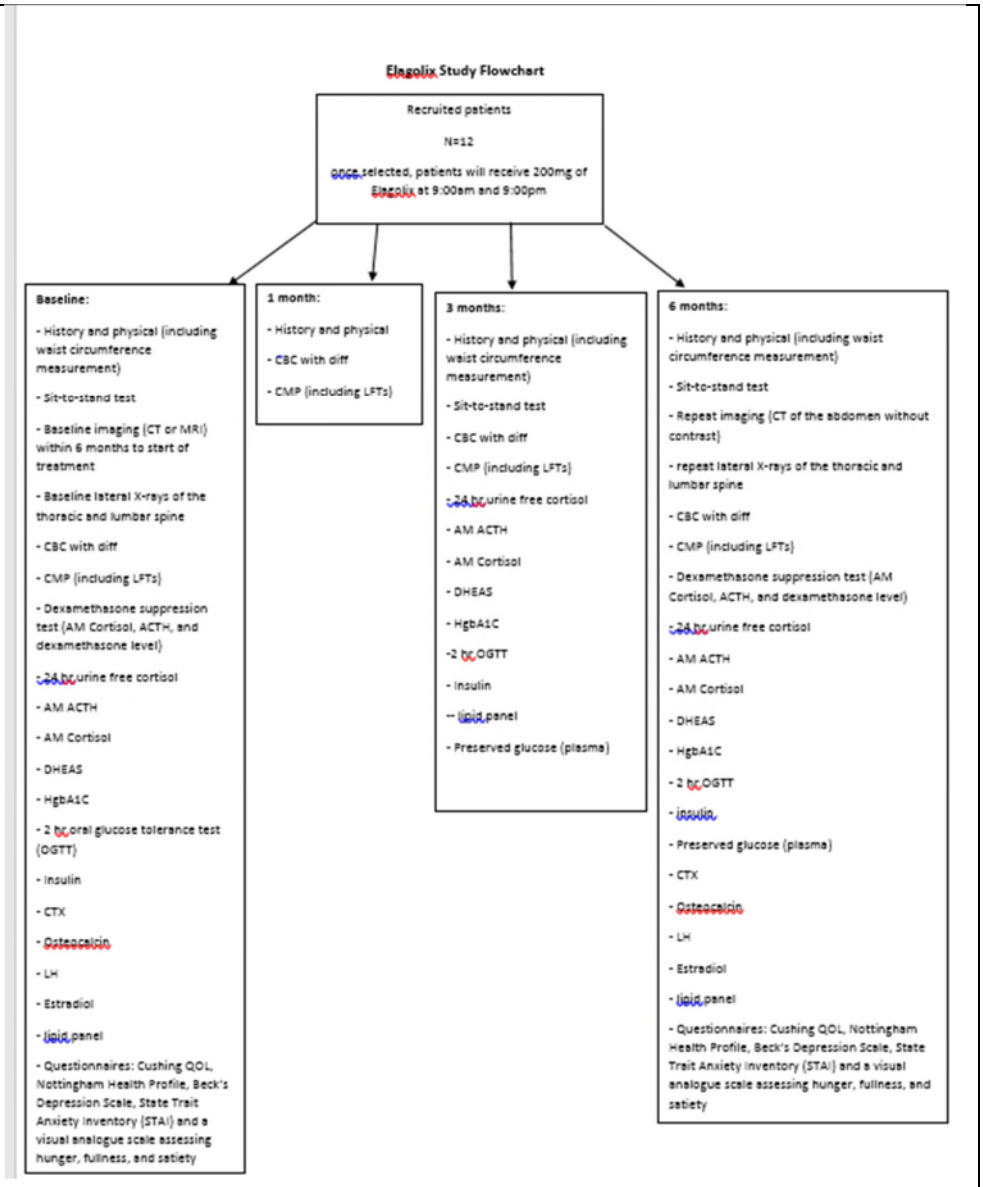
The adrenals and the gonads share a common lineage during embryogenesis (adrenogenital ridge). Adrenal cortex arises from the coelomic mesoderm of the urogenital ridge, and the medulla arises from neural crest tissue. We have recently demonstrated that adrenal adenomas overexpress LH/HCG-R and Gata-4 (gonadal differentiation factor) (11). As such, there is strong evidence that adrenal tumor development is at least partially driven by LH in postmenopausal women. We also will present data at The Endocrine Society 2019 demonstrating expression of LH/HCG-R in 24/24 adrenal adenomas derived from postmenopausal women (12). Such findings have also been seen in primate species. Lasley et al demonstrated the presence of luteinizing hormone/gonadal chorionic gonadotropin receptors in the adrenal cortex of ovarectomized female rhesus macaque (13). Further corroborating our data, Saxenda and Seely demonstrated a positive correlation between serum LH levels and urinary free cortisol levels in postmenopausal women (14).

As such, there is strong evidence that adrenal tumor development is at least partially driven by LH in postmenopausal women. Most recently, Doroszko et al studied the effects of the GnRH antagonist cetrorelix acetate (CTX) on adrenocortical tumor cells from mouse and human subjects *in vitro* and in transgenic mice *in vivo*, demonstrating that CTX decreased cell viability and proliferation *in vitro* and tumor size *in vivo* (15).

		Thus, we hypothesize that LH/HCG-R is a viable target for the treatment of ACS due to adrenal adenomas in postmenopausal women. In this study, we propose the use of elagolix, an oral GnRH antagonist recently approved for the treatment of endometriosis, to treat ACS in postmenopausal women with adrenal adenomas.
3.0	**Core Protocol**	
3.1	**Study Objectives and Purpose**	Objectives should be simple (no complex) and specific (no vague). After the statement of the primary objective, secondary objectives may be mentioned The goal of this pilot study is to determine if treatment of postmenopausal women with adrenal incidentaloma and ACS with elagolix for 6 months leads to a decrease in adrenal adenoma size, reduction in hypercortisolism leading to improvement in metabolic, bone, mood and quality of life measures.
3.2	**Study Design**	This section is a concise overview of the study design and should include the following: ● Type of experimental design (observational or interventional, randomized block, crossover, etc.); ● Whether the study is controlled (treatments other than the test product and/or placebo); ● Description of the type/design of the study to be conducted (e.g., open-label, single or double-blind); ● A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the study; and, ● The number of the study centers (single or multi-center). The number of study centers (single or multi-center) and the total number of subjects included in the study and how they will be assigned to treatment groups must be indicated. When appropriate, state if the subjects will be stratified. This is a pilot, open-label, interventional study. Subjects will be recruited from The Mount Sinai Adrenal Center, Mount Sinai Internal Medicine Associates (IMA) and Faculty Practice Associates (FPA). A total of 12 patients will be enrolled and all patients enrolled will receive study drug. This will be a change-from-baseline approach. Primary Endpoints: To determine the effects of elagolix treatment on 1) adrenal adenoma size 2) cortisol secretion 3) metabolic parameters and 4) bone turnover markers and vertebral fractures rates between baseline and 6 months treatment. Secondary Endpoints: To determine the effects of elagolix treatment on mood and quality of life.
3.3	**Inclusion Criteria**	Eligible post-menopausal women that have incidentally found adrenal adenomas with benign appearing characteristics on imaging (<4 cm, non-contrast CT <10 HU and/or lipid rich and benign appearing on MRI), the absence

		of anti-anabolic clinical features of overt Cushing's signs (proximal muscle weakness, >three ecchymoses, hyperpigmented striaie) and 2 of 3 of the following: 1) elevated 24 hr urine free cortisol (UFC) above the upper limit of normal (>50 mcg/24 hours) in at least two complete 24-hour tests and/or 2) late night salivary cortisol more than upper limit of normal in at least two tests and/or 3) an abnormal dexamethasone suppression defined as post 1mg dexamethasone suppression test serum cortisol concentration of >1.8 mcg/ml will be eligible for inclusion (2). Post-menopausal is defined as: clinic status of cessation of menses for 12 mo in a previously cycling woman and reflecting complete or nearly complete permanent cessation of ovarian function and fertility (26). Patients with osteoporosis can be included in the study. However, if they are receiving treatment with either antiresorptive medications (bisphosphonates, denosumab) or anabolic agents (teriparitide, abaloparatide or romosozumab) any bone related data will be excluded from their analysis.
3.4	**Exclusion Criteria**	Subjects receiving medications for chronic medical problems that may interact with elagolix, untreated hypothyroidism or hypopituitarism, known pituitary disorder, dexamethasone or CRH in the week prior to testing, use of elagolix, ketoconazole, metyrapone or mifepristone for one month prior, or known allergy to elagolix. In addition patients will be excluded if they have poorly controlled hypertension (mean systolic BP >170 mm Hg or mean diastolic BP >110 mm Hg) at screening, poorly controlled diabetes mellitus (Hemoglobin A1C >12% at screening), abnormal liver test results (total bilirubin >1.5 x upper limit normal or elevated alanine aminotransferase or aspartate amino transferase >3X upper limit normal at baseline), severe renal insufficiency (GFR <= 29 ml/min) at baseline. Patients will be excluded if they use or plan to use somatostatin analogues (octreotide, lanreotide or pasireotide) or have used these drugs within 8 months prior to study start. Patients with adrenal cortical carcinoma will also be excluded. Patients with a history of malabsorption will be excluded. Patients on HRT will be excluded. Elagolix is also a substrate of CYP3A and therefore should not be used concomitantly with drugs that are strong CYP3A inhibitors including: clarithromycin, telithromycin, nefazodone, itraconazole, ketoconazole, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir. **Drug interactions of note (not Exclusion Criteria):** Elagolix is also a *substrate* of CYP3A and therefore should not be used concomitantly with drugs that are strong CYP3A inhibitors including: clarithromycin, telithromycin, nefazodone, itraconazole, ketoconazole, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir. Elagolix is also a *substrate* of organic anion transporting polypeptide (OATP) therefore the concomitant use of strong OATP

		1B1 inhibitors (e.g., cyclosporine and gemfibrozil) is contraindicated as they may increase plasma concentrations of elagolix. Elagolix is a weak to moderate *inducer* of cytochrome P450 (CYP) 3A. Co-administration with Elagolix may *decrease* plasma concentrations of drugs that are substrates of CYP3A (i.e. amlodipine and atorvastatin). Elagolix is a weak *inhibitor* of CYP 2C19. Co-administration with Elagolix may increase plasma concentrations of drugs that are substrates of CYP2C19 (e.g., omeprazole) but this only requires attention if very high doses are used such as in Zollinger-Ellison syndrome.
3.5	**Study Flowchart**	A study flow chart is highly recommended. It should display all clinical and laboratory measurements and the time periods (e.g., hours, days, and/or weeks) at which data are to be collected.

		
3.6	**Study Procedures**	This section is a detailed explanation of the experimental design. The use of subheadings, lists, tables, or outlines are recommended. Describe the initial screening period(s), baseline period(s), treatments to be compared, study configuration (e.g., parallel, crossover, etc.), duration of the treatment period(s), control group(s), follow-up procedures, and length of time specified for washout intervals and safety follow-up. This section should also include subject withdrawal criteria (e.g, terminating investigational product treatment/trial treatment) and procedures specifying: a) When and not to withdraw subjects from the trial/investigational product treatment; b) The type and timing of the data to be collected for withdrawn subjects;

c) Whether and how subjects are to be replaced;

d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

The study will be submitted for IRB approval by the Mount Sinai Institutional Review Board and registered with the clinical trials office. A determination will be made regarding eligibility of this study for an Investigational New Drug (IND) exemption.

The following parameters will be measured:

Adenoma Size: All patients will have baseline imaging (CT or MRI) within 6 months to start of treatment and then will have repeat imaging with CT abdomen without contrast at 6 months to determine the effect of elagolix treatment on adrenal adenoma size and imaging characteristics. The images will be reviewed by a dedicated adrenal radiologist for consistency.

Clinical Exam and parameters: At baseline, one month, 3 months and 6 months patient will have full physical exam include measurement of vital signs. Body weight and waist circumference will be measured. Weight will be measured without overcoat and shoes and with only light clothing. Waist circumference measurements will be obtained to the nearest 0.5 cm following removal of clothing from the waistline. Waist circumference will be measured in centimeters (cm) in the horizontal plane midway between the lowest ribs and the iliac crest (16).

In addition at baseline, three month and 6 month study visits patients will have a measurement of proximal muscle strength utilizing **the sit to stand test.** The test evaluates the ability of patients to go from standing to sitting in a chair and then getting up again with/without the use of their arms or other aids. Patients seated in a chair will be asked to fold their arms across their chests and to stand up from the seated position once. If they are able to successfully rise from the chair, they will be asked to sit down again and then stand up and sit down, a total of 5 times as quickly as possible. Study staff will use a stopwatch to measure the total time it takes for the patient to stand up and sit down five times. Start time is in the seated position and stop time is in the final standing position. The total time of the test is measured.

Cortisol Secretion and Metabolic Parameters: At the baseline, 3 and 6 month study visits, patients will undergo a history and physical examination, including measurement of weight, blood pressure and waist circumference. Fasting 8AM laboratory testing will be obtained, including a comprehensive metabolic panel, cortisol, ACTH, DHEAS, hemoglobin A1c, preserved glucose and insulin levels, 2 hour oral glucose tolerance test, lipid profile, LH and estradiol. Fasting glucose and insulin level will be used to calculate HOMA-IR (Homeostatic Model Assessment for Insulin Resistance). Results of oral glucose tolerance testing and C-peptide values to calculate a Matsuda index, oral disposition index, and HOMA IR (all measures of insulin resistance). Dexamethasone

		suppression test will be performed at baseline and completion of the study. In addition, 24 hour urine free cortisol measurements will be done at time 0, 3 and 6 months. **Bone turnover markers and vertebral fracture rate:** At the baseline and 6 months determination of serum c-telopeptide (CTX), a marker of osteoclastic activity and osteocalcin (a marker of osteoblastic activity) will be determined. Previous studies have demonstrated a suppressive effect of high cortisol on osteocalcin with return to normal levels after treatment (17). Fragility, or low traumatic fractures, which are fractures associated with either minimal or no discernible trauma, is a common complication of endogenous Cushing's syndrome (1). Mild hypercortisolism has also been shown to increase vertebral fracture rates and a recent study demonstrated that surgical adrenalectomy for SH due to adrenal adenomas reduces vertebral fractures. Interestingly, bone density measurements may underestimate the deleterious effects of glucocorticoids on bone quality (9). Accordingly, baseline and 6 month vertebral fractures rates will be assessed by lateral X-rays of thoracic and lumbar spine. Study subjects are allowed to take Calcium and Vitamin D. **Mood and Quality of Life Measures:** Patients will also complete several validated surveys at baseline and 6 months' treatment, including Cushing QOL (18), Nottingham Health Profile (19), Beck's Depression Scale (20), State Trait Anxiety Inventory (STAI) (21) and a visual analogue scale assessing hunger, fullness, and satiety (22). The surveys will be scored based on validated scoring system. **Safety Monitoring and Subject Withdrawal Criteria:** Patients will be assessed at baseline, one month, three months and six months including history, physical, and laboratory testing (comprehensive metabolic panel and complete blood count with differential). Study drug will be discontinued for any adverse reactions including nausea, vomiting, and/or diarrhea, a single episode occurring within 6-8 hours after administration of Elagolix. Drug will also be discontinued for elevations greater than 3-4x normal in liver function tests, any abnormalities in electrolytes (above or below normal range) or kidney function (elevation of BUN and/or creatinine above normal range) and any abnormalities in hematologic parameters. **Procedures for Reporting a Serious Adverse Event (SAE):** Any SAE occurring from the time of signing of the informed consent form (ICF) and for at least 30 days after the last dose of study drug must be *reported within 24 hours* to the designated safety contact and recorded on the SAE form. The investigator will supply the sponsor and the IRB/IEC with any additional requested information. **Adverse Event Follow-up:** All adverse events will be followed until resolution, until deemed stable by the Principal Investigator, or until the patient is deemed by the Principal Investigator to be lost to follow-up.

3.7	**Statistical Analysis and Sample Size Justification**	The statistical methods proposed to be used for the analysis of data should be clearly outlined, including reasons for the sample size selected, power of the study, level of significance to be sued, procedures for accounting for any missing or spurious data, etc. For projects involving qualitative approaches, specify in sufficient detail how the data will be analyzed. State who will be responsible for analyzing the study data (e.g., investigator, contract CRO, etc.). Investigator will be responsible for analyzing the study data. The significance of the effect of elagolix treatment on different outcome measures will be assessed with the Wilcoxon matched-pairs signed rank test to generate a two-tailed p-value. Calculations will be performed with Prism 6 (Graphpad Software, Inc.). Sample Size Justification: No hypothesis testing, pilot study.
3.8	**Specific Drug Supply Requirements**	The investigator is responsible for keeping accurate records of the clinical supplies, the amount dispensed to and returned by the subjects, and the disposition at the end of the study. Clinical supplies must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Clinical supplies are dispensed in accordance with the protocol. The investigator will be responsible for the destruction of the supplies at the study center pursuant to the ICH/GCP Guidelines, local regulations, and the investigator's institutional policies. Elagolix 200 mg BID has an acceptable safety profile and results in rapid suppression of LH (23). We selected this dose because it has been deemed to be safe and we are aiming for maximal efficacy. Once screened and with informed consent, patients will be administered elagolix 200 mg orally twice daily for a total of 6 months.
3.9	**Safety Reporting**	In addition to compliance with all FDA reporting requirements pursuant to 21 CFR 312, the Principal Investigator shall: a) Report to AbbVie all serious adverse events (SAEs) experienced by a study subject receiving an AbbVie product within 24 hours of learning of the event regardless of the relationship of the event to the AbbVie product. Principal Investigator shall make available to AbbVie promptly such records as may be necessary and pertinent to investigate any such event, if specifically requested by AbbVie, and, b) Copy AbbVie on the submission to the FDA of events meeting the definition of IND safety reports at the time of submission to the Agency; and, c) Notify AbbVie upon any subjects receiving an AbbVie Product whose pregnancy has resulted in a negative outcome or untoward event during the course of pregnancy or upon delivery.

		s contact for reporting serious adverse drug experiences, pregnancy experiences, and communications of FDA submissions of IND safety reports shall be PPDINDPharmacovigilance@abbvie.com : Complaints: In addition to compliance with all FDA requirements pursuant to 21 CFR 211 and 21 CFR 820, Principal Investigator will report to AbbVie within 24 hours any suspected quality defect in an AbbVie Product or its AbbVie-provided packaging, labeling, or medical device component (collectively, "Product Complaint"). Principal Investigator will report Product Complaints that involve an AbbVie Product, whether AbbVie has supplied the AbbVie Product used in the Study or not. AbbVie's contact for reporting Product Complaints shall be RD_PQC_QS@abbvie.com *llection of non-serious adverse events may be added per product-specific requirements. The events to be collected and the timing of this reporting should be included in this section as required.>* Patients will be evaluated and questioned to identify AEs during the study. Collection of AEs will start immediately following the signing of the informed consent forms. Illnesses present before the patient signs the consent are considered pre-existing conditions and are documented on the medical history. Adverse events that occur after the start of the study drug and up to and including 30 days after administration of the last dose of study drug will be considered treatment emergent adverse events. Any adverse events reported more than 30 days after the last dose of study drug will be considered post treatment AEs. Any AEs/SAEs occurring from the time of signing the ICF and for at least 30 days after the last dose of study drug will be reported within 24 hours to the designated safety contact and recorded on the SAE form. All patients with an SAE will be followed and the outcomes will be reported. All AEs will be followed until resolution or until deemed stable by the Principal Investigator or until the patient is deemed to be lost to follow-up. SAEs will be reported in accordance to FDA requirements and AbbVie will be informed on these cases.
3.10	**References**	All literature references cited in the protocol should be listed accordingly in the reference section. 1. Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. The Journal of clinical endocrinology and metabolism. 2008;93(5):1526-40. 2. Di Dalmazi G, Vicennati V, Garelli S, Casadio E, Rinaldi E, Giampalma E, et al. Cardiovascular events and mortality in patients with adrenal incidentalomas that are either non-secreting or associated with

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