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Comparison of dapagliflozin (DAPA) and once-weekly exenatide (EQW), co-administered or alone, combination tablet dapagliflozin/ extended release metformin (DAPA/MET XR) and the weight loss drug, combination phentermine (PHEN)/topiramate (TPM) extended release (ER), on metabolic profiles and body composition in overweight/obese PCOS women

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
PCOS	Polycystic ovary syndrome
T2DM	Type 2 diabetes mellitus
β-cell	Pancreatic beta cell
GLP1	Glucagon-like peptide 1
SGLT2	Sodium/glucose cotransporter 2
OGTT	Oral glucose tolerance test
BMI	Body mass index
WC	Waist circumference
WHR	Waist to hip ratio
WHtR	Waist to height ratio
DEXA	Dual-energy X-ray absorptiometry
Metformin XR	Metformin extended release
DAPA	Dapagliflozin
EQW	Exenatide once weekly
PHEN/TPM ER	Phentermine/topiramate extended release

INTRODUCTION

Background

Polycystic ovary syndrome (PCOS) is a heterogeneous condition characterized by disordered reproductive and metabolic function that accounts for the myriad of clinical features including androgen excess, chronic anovulation, hyperinsulinemia, adiposity, and dyslipidemia. This syndrome is highly prevalent, affecting between 8 and 18% of the female population, depending on the diagnostic criteria used. Hyperandrogenism, ovarian dysfunction and metabolic abnormalities - the main determinants of PCOS – all appear to be involved in a synergistic way in the pathophysiology of PCOS. Women with PCOS are more likely to be obese: between 38 and 88% of women with PCOS are overweight or obese, although PCOS can also manifest in lean women. Obesity, particularly abdominal obesity, plays a central role in the development of PCOS, and exacerbates the reproductive and metabolic dysfunction. Rather than absolute body weight, it is the distribution of fat that is important with central (visceral) adiposity being a risk factor. Compared with weight-matched healthy women, those with PCOS have a similar amount of total and trunk fat, but a higher quantity of central abdominal fat. Visceral adipose tissue is more metabolically active than subcutaneous fat and the amount of visceral fat correlates with insulin resistance and hyperinsulinemia. Weight gain is also often an important pathogenic factor, with PCOS usually becoming clinically manifest in women with a presumable genetic predisposition for PCOS who subsequently gain weight. Therefore, environmental (particularly dietary) factors are important. However, BMI is also influenced by genetic factors such as the fat mass and obesity-associated protein, and obesity is a highly heritable condition. Therefore, the weight gain responsible for the manifestation of PCOS in many women with this condition is itself influenced by genetic factors. Ethnicity, genetic background, personal and family history, degree of obesity must all be taken into account because they might aggravate or even trigger metabolic disturbances women with PCOS. Moreover, the incidence of glucose intolerance, dyslipidemia, gestational diabetes, and type 2 diabetes (T2DM) is increased in women with PCOS at all weight levels and at a young age. Several studies have demonstrated that T2DM occurs with increased frequency in women with PCOS so that recently the American Diabetes Association and the International Diabetes Federation have identified PCOS as a significant non-modifiable risk factor associated with type 2 diabetes. PCOS may be a more important risk factor than ethnicity or race for glucose intolerance in young women. The exact factors responsible for this excess risk in women with PCOS have not been identified; family history of T2DM, obesity, insulin resistance, beta cell (ß-cell) secretory dysfunction, and hyperandrogenism are possible candidates. With better understanding of its pathophysiology, the metabolic consequences of the syndrome are now evident. Therefore, these patients need to be followed up even after their presenting complaint has been adequately resolved.

Multiple metabolic aberrations, such as insulin resistance (IR) and hyperinsulinemia, impaired glucose tolerance, visceral obesity, hypertension and dyslipidemia are associated with polycystic ovary syndrome. Current research has shown that the use of diabetes management practices aimed at

reducing IR and hyperinsulinemia (such as weight reduction and the administration of antidiabetic drugs) in non-diabetic women with PCOS can not only improve glucose and lipid metabolism but can also reverse testosterone abnormalities and restore menstrual cycles. Weight reduction through lifestyle modification is strongly advocated for PCOS to alleviate metabolic and cardiovascular risk. Lifestyle interventions remain essential to the management of women with PCOS; however, the majority of non-diabetic overweight/obese PCOS patients do not reach their therapeutic goals with these interventions alone and will require pharmacologic therapies.

Until a few years ago, the treatment for women with PCOS consisted exclusively of a combination of estrogen and progestins. Over the last years, considering the importance given to insulin resistance in the pathogenesis of the syndrome, clinical studies have focused on insulin sensitizing drugs for the treatment of women with PCOS, with metformin being the drug most extensively studied in this syndrome. Although no antidiabetic agents have US Food and Drug Administration approval for the treatment of PCOS, metformin was preferred due to the fact that it had the safest risk-benefit ratio, and could cause weight loss, while thiazolidinediones increased weight as a result of fluid retention. Metformin acts by decreasing hepatic gluconeogenesis and free fatty acid oxidation while increasing peripheral glucose uptake. Early studies in PCOS suggested that metformin indirectly reduces insulin levels, dyslipidemia and systemic inflammation; however, recent placebo-controlled trials failed to demonstrate significant metabolic benefit. Considerable variability in the metabolic responses to metformin has been observed in women with PCOS, attributable to several potential factors such as different doses of the drug and genetic background. Weight loss has been claimed to be a beneficial secondary effect of metformin extended release (metformin XR) but the effect is not very consistent. Interestingly, most studies have not found any beneficial effects of metformin treatment in obese patients with PCOS. It is possible that the weight loss that often accompanies protracted metformin therapy may account for some of the beneficial effects observed in many studies. Irrespective of treatment group (after adjustment for baseline BMI and age), only weight loss, but not the use of metformin, was associated with a significant improvement in metabolic and reproductive function in obese women with PCOS. Furthermore, a number of studies have substantiated the view that obesity may reduce the benefit of metformin treatment.

Novelty of Study

The realization that hyperinsulinemia is a key component in the pathogenesis of PCOS provided a basis for advances in treatment strategies for women with the disorder. Lifestyle modification, including diet and exercise, is considered a cornerstone of the management of women with PCOS presenting with obesity, particularly the abdominal phenotype. PCOS is characterized by a vicious cycle whereby androgen excess favors abdominal fat deposition, which in turn aggravates insulin resistance and compensatory hyperinsulinism, further enhancing ovarian androgen secretion. Hence, therapeutic strategies ameliorating abdominal adiposity and weight excess may inhibit this vicious cycle, improving not only the metabolic co-morbidities of PCOS but also androgen excess and reproductive aberrations

for overweight, anovulatory women with PCOS. Even a modest weight loss of 5% of total body weight can restore ovulation in overweight women with PCOS. Most characteristics of PCOS (e.g., hirsutism, testosterone levels, insulin resistance, menstrual cyclicity and ovulation) showed marked improvements, and PCOS frequently resolved after substantial weight loss induced by bariatric surgery. While weight loss is the key in the treatments of overweight/obese patients with PCOS, current non-pharmacologic management of body weight is hard to achieve. Thus, in the majority of patients with PCOS pharmaceutical intervention is an additional essential therapeutic aid to lifestyle changes.

The growing body of evidence linking PCOS to an inherited resistance to insulin action, aggravated by lifestyle problems such as obesity, poor diet and physical inactivity has led to trials of diabetic therapies in patients with the polycystic ovary syndrome. Currently, a number of anti-diabetes medications have been approved that facilitate weight loss and improve the underlying insulin resistance. Glucagon-like peptide 1 (GLP-1) agonists evolved as therapeutic options for the treatment of T2DM primarily because of their effects on insulin and glucagon secretion, with weight loss as an additional benefit. Early studies of human GLP-1 showed that continuous peripheral infusion was associated with decreased appetite and increased satiety. Continuous infusion of GLP-1 also was shown to improve insulin sensitivity, glycemic control, and β-cell function in individuals with T2DM. Weight loss ranging from 2 to 6 kg has been a consistent finding in studies designed to investigate the glycemic benefits of GLP-1 agonists in individuals with T2DM. Additionally, this therapy has produced progressive weight loss in obese people without diabetes. The mechanisms of weight loss with GLP-1 agonists are not fully understood but may include changes in energy expenditure, changes in leptin sensitivity, or nausea resulting in decreased food intake. We found that treatment with the GLP-1 agonist exenatide for 24 weeks was superior to single agent metformin treatment in improving insulin action and reducing body weight and hyperandrogenism in obese women with PCOS. Similarly, a recent study showed that a 12-week treatment with another GLP1 agonist, liraglutide was associated with significantly greater weight loss in a subset of obese patients with PCOS and higher metabolic risk profile when compared to metformin. Another preliminary report confirmed that liraglutide had an add-on effect on weight loss in obese women with PCOS who had lost <5% body weight during a 6-month pre-treatment with metformin. We further observed exenatide treatment in women with PCOS significantly improved first-phase insulin responses to oral glucose administration. Since aberrant first-phase insulin secretion and impaired suppression of endogenous glucose production are major contributors to postprandial hyperglycemia and development of T2DM, the effects of the long acting GLP-1 agonist, exenatide once weekly [EQW (2 mg)], to target these defects, and normalize glucose excursions are likely to be clinically significant in overweight/obese patients with PCOS. The potential efficacy of a long-acting once-weekly GLP-1 agonist has not yet been evaluated in the PCOS population. We hypothesize that intervention with long-acting exenatide once-weekly will result in reduced body weight and improved hormonal and metabolic parameters in overweight/obese women with PCOS.

Sodium/glucose cotransporter 2 (SGLT-2) inhibitors are the newest class of medications for diabetes management. The main advantage of SGLT-2 inhibitors is they have a completely different mechanism of action; SGLT2 inhibitors work primarily to lower the renal threshold to glucose, leading to

increased glucose in the urine and reduced glucose levels in the blood. In addition, this inhibitory action can induce mild osmotic diuresis and increase urinary excretion of glucose with modest caloric elimination leading to weight loss. Dapagliflozin is a highly potent selective and reversible inhibitor of SGLT2 that improves fasting and post-prandial plasma glucose levels. Orally administered dapagliflozin is rapidly absorbed generally achieving peak plasma concentrations within 2 h with a half-life of 12-13 hours; so that once-daily dosing is appropriate. In addition to the beneficial effects related to improved glycemic control, dapagliflozin induces weight loss via caloric loss from glycosuria; i.e., by passing glucose out of the body, the accompanying calories in the excreted glucose are also passed out. Consistent with this, 3-6 months treatment with dapagliflozin has been associated with weight losses of 2–3 kg. The weight loss seen with SGLT2 inhibitors is similar to that seen with GLP-1 agonists, and may be more acceptable because they are oral agents. In addition, dapagliflozin treatment has recently been shown to improve insulin resistance and B-cell function in patients with T2DM by correcting hyperglycemia, i.e., reversal of glucotoxicity. . Because the SGLT2 inhibitors have a distinct mechanism of action that is independent of insulin secretion, the efficacy of this class of drugs is not anticipated to decline in the presence of severe insulin resistance. In prior study trials, the SGLT 2 inhibitor dapagliflozin appears to be safe, effective and lead to weight loss. The reduction in central adiposity may be an advantage in non-diabetic patients with PCOS who have associated insulin resistance. This drug class has not been investigated for use in the women with PCOS. Weight reduction has a beneficial effect on hyperinsulinemia, hyperandrogenism and increased SHBG production in overweight/obese women with PCOS supporting that dapagliflozin may be an effective alternative for in this group of patients.

The potentially beneficial role of long-acting GLP1 receptor agonist, exenatide once weekly in combination with the SGLT2 inhibitor, dapagliflozin in PCOS has not yet been evaluated. SGLT-2 inhibitors are type 2 diabetes drugs with an action independent of insulin, whereas GLP-1 agonists are "insulin dependent." Both seem to invoke weight loss as a secondary outcome, but it is not known whether this is additive, given the differing mechanisms of action of the two drug classes. Early data suggests there are additive weight loss effects. A small UK study observed that adding a sodium glucose cotransporter 2 (SGLT-2) inhibitor to therapy for T2DM patients who are already taking a glucagon like peptide 1 (GLP-1) agonist can result in additive weight loss. There was twice as much weight loss in those taking both agents compared with those taking just one of the medications. This clinical profile suggests that co-administration of DAPA and exenatide once-weekly (EQW) would have additional weight loss benefits and be useful therapeutic intervention for the treatment of overweight/obese women with PCOS.

The single fixed-dose combination of SGLT2 inhibitor, dapagliflozin and metformin extended release (XR) will also provide two complementary therapeutic approaches and allow for another innovative option for treating women with PCOS. The new combination is indicated for use as an adjunct to diet and exercise in adults in whom treatment with both dapagliflozin and metformin is appropriate. Metformin reduces hepatic glucose production and to a lesser extent, increases peripheral glucose uptake. Dapagliflozin causes the kidney resorption of glucose in the kidney by blocking a renal

protein called human sodium-glucose cotransport 2 (SGLT-2) resulting in increased urinary glucose excretion, with a consequent lowering of plasma glucose levels as well as weight loss. In addition to the beneficial effects related to improved glycemic control, the SGLT2 inhibitors have a number of non-glycemic effects that make them desirable agents for combination treatment with other antidiabetic agents. The SGLT2 inhibitor, dapagliflozin has an insulin-independent action, promotes weight loss, has a low incidence of hypoglycemia, and complements the action of other antidiabetic agents In PCOS, metformin has become an established treatment. While metformin has been shown to be effective in reducing fasting insulin and total testosterone concentrations in overweight women with PCOS, it had no consistent effect on weight loss or waist circumference. The potential therapeutic add-on effect of treatment with dapagliflozin has not been evaluated in the subpopulation of overweight/obese women with PCOS. The fixed-dose combination of metformin plus dapagliflozin should be more convenient than taking the drugs separately and an oral pill a more acceptable route of administration for some patients.

The non-diabetic female with PCOS offers a unique model to study the relationship between insulin resistance and adiposity. Women with PCOS demonstrate abnormal body composition characterized by a greater percent body fat, body fat mass, and increased ratio of fat to lean mass (F/L ratio). Studies using DEXA methodology report a higher degree of metabolic dysfunction in patients with PCOS which appears be directly associated with their higher F/L ratio. Given that monotherapy and combined therapy with exenatide once weekly (EQW), and dapagliflozin (DAPA) along with DAPA/ metformin XR therapy are associated with weight loss introduces a confounder to the current study since it prevents distinguishing direct effects of the compounds on β-cell function vs. effects due to reduced adiposity. To control for loss of body mass and provide appropriate intervention in the remaining study arm we propose the use of a comparator weight loss drug alone, combination phentermine (PHEN)/topiramate (TPM) extended release (ER). Combination phentermine (PHEN)/topiramate (TPM) extended release (ER) is a is a fixed combination oral weight-loss medication comprised of immediate-release phentermine hydrochloride and extended-release topiramate approved by the U.S. Food and Drug Administration in 2012 as an adjunct to lifestyle modification for long-term treatment of overweight and obesity. Phentermine, a sympathomimetic drug, has been widely used as short-term appetite suppressant. Topiramate is an antiepileptic drug. The anorectic effect of phentermine is mediated by catecholamine release in the hypothalamus. The exact mechanism underlying the weight loss action of topiramate is not known; however, it may be associated with a combination of features such as an effect on sodium channels, enhancement of γ-aminobutyric acid (GABA) activated chloride channels, and inhibition of carbonic anhydrase isoenzymes. This fixed combination uses lower doses of phentermine (titration dose at 3.75 mg, recommended dose at 7.5 mg) than as a single agent. Topiramate is an ER formulation. Its dose in the fixed combination (titration dose at 23 mg, recommended dose at 46 mg) is lower than that when it is used for migraine prophylaxis or to control seizures. Both medications reduce appetite and in addition, topiramate produces a sense of satiety (feeling of fullness), and in some people, induce a negative energy balance. PHEN/TPM ER has been shown to improve cardiometabolic parameters and prevent progression to T2DM in patients with

prediabetes and/or metabolic syndrome. This treatment will allow us to examine the independent impact of reduction in body weight on improved insulin sensitivity in this non-diabetic patient population.

Study Rationale

We propose a randomized, single-blind, parallel 5 treatment group 24-week trial designed to directly compare the therapeutic effects of exenatide once weekly (EQW), dapagliflozin (DAPA), EQW plus DAPA, combined DAPA/metformin XR and the weight loss medication, phentermine/topiramate extended release (PHEN/TPM ER) on metabolic and endocrinological parameters in overweight/obese non-diabetic women with PCOS. To avoid the confounding relationship of body fat and insulin resistance, we will enroll only overweight/obese non-diabetic insulin-resistant women with PCOS. All patients will receive diet and lifestyle counseling, including advice on exercise, according to usual clinical routine commencing during the lead-in period and continuing throughout the study. In this study, we will examine the efficacy of these therapies on metabolic parameters, body weight and body composition, anthropometric measurements, and reproductive function in a well-defined group of pre-menopausal overweight/obese, non-diabetic women with PCOS, focusing on their relationship to insulin resistance and obesity. We hope to determine which treatment(s) addressing the multifaceted disturbances of individual subgroups emerge as the preferable therapy.

There is a growing need to develop pharmacologic interventions to improve metabolic function in women with PCOS. Use of the combination of GLP-1 agonists/SGLT2 inhibitors, compared to either of the individual components as monotherapy or dapagliflozin combined with metformin, will likely induce greater weight loss. The resulting weight loss will further assist in decreasing insulin resistance leading to increased glucose disposal thus contributing to an increased insulin secretion-insulin sensitivity (ISSI) index, the primary outcomes measure. More germane to the current application is the fact that all therapies are associated with weight loss, which in and of itself introduces a confounder to the current study since it prevents distinguishing direct effects of the compounds on β cell function vs. effects due to a reduction in adiposity. To control for weight loss due to exenatide once-weekly, dapagliflozin, exenatide once-weekly plus dapagliflozin and combination dapagliflozin/metformin XR, as well as provide appropriate intervention in the remaining arm requires use of a weight loss drug alone. There are very limited data on weight loss with phentermine/topiramate extended release in non-diabetic females with PCOS treated with this agent. The use of DEXA technology that is simple, operator independent, safe, accurate and cost-effective will be used to assess fat quantity and distribution.

Benefit/Risk and Ethical Assessment

GLP-1 receptor agonists are peptides that mimic native GLP-1, binding to its receptors to elicit the same effects, but at much higher pharmacological levels than the physiological profiles. The most common treatment-related adverse effects of GLP-1 receptor agonists are gastrointestinal in nature and include nausea, vomiting, and diarrhea, which are usually mild and tend to subside over time. Other documented but infrequent concerns with GLP-1 receptor agonists include injection site reactions and,

particularly with exenatide extended-release, the development of transient small nodules around injection sites related to the microsphere technology of delivery. When looking at the benefit–risk assessment, the GLP-1 receptor agonists demonstrate clinical advantages such as reduced risk for drug-related hypoglycemia and often favorable effects on body weight.

Dapagliflozin is an SGLT2 inhibitor that works by targeting and helping to stop sodium-glucose transport proteins from allowing glucose that has been filtered out of the blood by the kidneys to be reabsorbed back into the blood. Its efficacy and safety has been studied in multiple randomized controlled trials including an add-on to metformin compared with a placebo. Clinical trials with dapagliflozin have demonstrated that treatment in healthy subjects results in continuously excreted glucose in the absence of hyperglycemia. The increased glucose excretion with the SGLT2 inhibitors leads to increased urogenital infections. Genital mycotic infections, increased urination and urinary tract infection are the most common side effects associated with dapagliflozin. In clinical studies, subjects receiving SGLT2 inhibitors compared with placebo were reported to have an increase in the rate of genital and urinary tract infections with a greater percentage of women diagnosed than men. These fungal infections were reported to subside spontaneously or to respond to local antifungal treatment. Genital mycotic infections and urinary tract infections were usually mild to moderate and responsive to treatment, and they rarely resulted in discontinuation of therapy. Studies have also shown that some adverse events related to osmotic diuresis (e.g., polyuria) are greater with SGLT2 inhibitors than with placebo but these agents remain well tolerated and beneficial. Currently available data on dapagliflozin, the most clinically advanced of the SGLT2 inhibitors, has demonstrated efficacy and consistent safety across a wide range of patient populations. In addition, the asymptomatic clinical presentation of subjects with familial renal glycosuria despite multiple generations of the disease suggests that chronic inhibition of renal glucose reabsorption and the associated chronic glycosuria may not be associated with adverse effects. Based on the efficacy of SGLT2 inhibition on weight reduction and safety, the benefits of this treatment far outweigh the risk of increased urogenital infections that can be minimized by meticulous genital hygiene.

The side effect profile in patients treated with PHEN/TPM ER is well tolerated and consistent among all phase III and post-marketing reports. The most commonly reported treatment-related adverse events (AEs) in clinical trials include paraesthesia, dizziness, dysgeusia (altered taste), insomnia, constipation, and dry mouth. The majority of reported adverse events have been mild and discontinuation of study drug due to AEs was rare. In clinical studies, PHEN/TPM ER showed a significant weight loss across all doses studied that exceed both FDA efficacy benchmarks for weight loss. PHEN/TPM ER is a safe and effective medication in managing weight loss as adjunct therapy to diet and exercise for the obese or overweight patient with at least one weight-related comorbidity. Benefits may extend to improve and reduce the risk of cardiovascular disease in obese and overweight patients with co-morbidities. PHEN/TPM ER is contraindicated in pregnancy because of concerns about the teratogenicity of topiramate. Topiramate is associated with oral clefts if used during pregnancy. It requires a negative pregnancy test before treatment and monthly thereafter.

Women with PCOS are at substantially increased risk of T2DM. Compared with the general population, these women are more likely to be overweight or obese. Taken together, the data support increased abdominal fat as the strongest factor associated with declining B-cell compensation for insulin resistance in PCOS women at high risk for Type 2 DM. Although no pharmacological agent is without some risk, DAPA, EQW, combination DAPA/metformin XR, and PHEN/TPM ER appear to have wide margins of safety when used appropriately. The robust clinical benefits observed with these pharmacologic agents may confer a significant advantage to improve outcomes in patients at high risk of developing type 2 diabetes.

STUDY OBJECTIVES

Primary Objective:

- The primary aim of this study is to compare the efficacy of dapagliflozin, exenatide once-weekly, dapagliflozin plus exenatide once-weekly, combination dapagliflozin/metformin XR and phentermine/topiramate extended release in improving the oral disposition index (product of Matsuda index and insulinogenic index; SI_{OGTT} x Δinsulin30–0 min to glucose30–0 min)], modeled from a simple 2-h oral glucose tolerance test (OGTT) in obese non-diabetic female subjects with polycystic ovary syndrome (PCOS).

Secondary Objective(s)

- We will further examine the impact of the administration of these pharmacotherapies on insulin sensitivity, first phase insulin response, glycemic parameters determined with a 75-g OGTT, total fat mass and fat distribution evaluated by DEXA and other anthropometric parameters, cardiometabolic markers (lipid fractions and blood pressure) and reducing hyperandrogenism in non-diabetic PCOS women using the following parameters:
    - Surrogate measures of insulin action derived from OGTT [insulin sensitivity index (HOMA-IR, Matsuda index), corrected early insulin secretory response (insulinogenic index/HOMA-IR)
    - Fasting and 2 hour glucose levels after an OGTT
    - Plasma lipid fractions
    - Liver enzymes
    - Blood pressure
    - Anthropometric parameters, including body mass index [BMI], absolute body weight, waist circumference, waist: hip ratio, waist-height ratio and trunk fat mass and truck fat/extremities fat ratio by DEXA,
    - Free androgen index (total testosterone and SHBG) and DHEAS
    - Menstrual diaries

Safety Measures:

Safety and tolerability will be assessed by collating data on adverse events (AEs), laboratory tests, physical examinations, and vital signs. Patients will be educated about the side effects and use of exenatide extended-release and the injection delivery system. Patients will be asked about the most common adverse events related to exenatide such as headache, nausea, dyspepsia and vomiting if not volunteered. In addition, patients will be actively questioned at each study visit to assess signs, symptoms, and reports suggestive of genital infection and of urinary tract infection (UTI). These responses and those obtained spontaneously will be categorized in the database using a predefined list suggestive of vulvovaginitis, and related genital infection and UTI. If patients become pregnant during the study, all medications will be stopped immediately.

This protocol and the associated Informed Consent as well as any addenda or amendments, must be reviewed and approved by the Woman's Hospital Institutional Review Board (WHIRB) review committee prior to the start of the study. All revisions to this Protocol are considered "protocol amendments; these must be approved in advance, in writing, by the WHIRB. Every patient will have given her written informed consent prior to participating in the study. Prior to participation in this trial, each subject will have an opportunity to ask questions and will sign (and date) a written Informed Consent, which must be witnessed. The signed consent forms will be filed with the investigator's study charts for each subject. Any subject may voluntarily withdraw from the study at any time without prejudicing treatment.

STUDY PLANS AND PROCEDURES

Randomized, Single-blind, Parallel, Prospective Study Trial

All patients will randomly be assigned to one of 5 investigation product treatment groups-–exenatide once weekly (EQW), dapagliflozin (DAPA), EQW plus DAPA, combined DAPA/metformin XR and the weight loss medication, phentermine/topiramate extended release (PHEN/TPM ER); all subjects will be allocated to one of these 5 groups based on computer-generated random numbers using a block randomization method. The pharmacy will "single-blind" all the treatment arms to the primary investigators by filling color-coded bags (A, B, C, D, E) with 1 of 5 medications-A) exenatide once weekly (EQW), B) dapagliflozin, C) EQW plus DAPA, D) DAPA/metformin XR and E) PHEN/TPM ER and dispensing open-label medications to study patients in color-coded bags with instructions on how to take the medicine**.**

Treatment Regimen

Overweight/obese non-diabetic women with PCOS will be treated for 24 weeks with exenatide once weekly (EQW), dapagliflozin (DAPA), dapagliflozin plus exenatide once weekly, combination dapagliflozin/metformin XR or the weight loss medication, phentermine/topiramate extended release (PHEN/TPM ER). (See separate page with Figure 1 flowchart).

Inclusion Criteria

1. Non-diabetic women (18-45 years)
2. PCOS- NIH criteria hyperandrogenism and irregular menses
3. Overweight/obese (BMI $\geq$25$\leq$45)
4. Written consent for participation in the study

Exclusion Criteria

1. Presence of significant systemic disease, heart problems including congestive heart failure, unstable angina or acute myocardial infarction, current infectious liver disease, acute stroke or transient ischemic attacks, history of pancreatitis, or diabetes mellitus (Type 1 or 2)
2. Any hepatic diseases in the past (infectious liver disease, viral hepatitis, toxic hepatic damage, jaundice of unknown etiology) or severe hepatic insufficiency and/or significant abnormal liver function tests defined as aspartate aminotransferase (AST) >3x upper limit of normal (ULN) and/or alanine aminotransferase (ALT) >3x ULN
3. Renal impairment (e.g., serum creatinine levels ≥1.4 mg/dL for women, or eGFR <60 mL/min/1.73 m2) or history of unstable or rapidly progressing renal disease or end stage renal disease.
4. Uncontrolled thyroid disease (documented normal TSH), Cushing's syndrome, congenital adrenal hyperplasia or hyperprolactinemia
5. Significantly elevated triglyceride levels (fasting triglyceride > 400 mg/dL)
6. Untreated or poorly controlled hypertension (sitting blood pressure > 160/95 mm Hg)
7. Use of hormonal medications, lipid-lowering (statins, etc.), anti-obesity drugs or weight loss medications (prescription or OTC) and medications known to exacerbate glucose tolerance (such as isotretinoin, hormonal contraceptives, GnRH agonists, glucocorticoids, anabolic steroids, C-19 progestins) stopped for at least 8 weeks. Use of anti-androgens that act peripherally to reduce hirsutism such as 5-alpha reductase inhibitors (finesteride, spironolactone, flutamide) stopped for at least 4 weeks
8. Prior history of a malignant disease requiring chemotherapy
9. Patients at risk for volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics should have careful monitoring of their volume status
10. History of unexplained microscopic or gross hematuria, or microscopic hematuria at visit 1, confirmed by a follow-up sample at next scheduled visit.
11. Presence of hypersensitivity to dapagliflozin or other SGLT2 inhibitors (e.g. anaphylaxis, angioedema, exfoliative skin conditions
12. Known hypersensitivity or contraindications to use GLP1 receptor agonists (exenatide, liraglutide)
13. Use of metformin, thiazolidinediones, GLP-1 receptor agonists, DPP-4 inhibitors, SGLT2 inhibitors or weight loss medications (prescription or OTC) stopped for at least 4 weeks.
14. Prior use of medication to treat diabetes except gestational diabetes
15. Eating disorders (anorexia, bulimia) or gastrointestinal disorders
16. Suspected pregnancy (documented negative serum β-hCG test), desiring pregnancy in next 6 months, breastfeeding, or known pregnancy in last 2 months
17. Active or prior history of substance abuse (smoke or tobacco use within past 3 years) or significant intake of alcohol

18. Having a history of bariatric surgery
19. Patient not willing to use barrier contraception during study period (unless sterilized or have an IUD) Debilitating psychiatric disorder such as psychosis or neurological condition that might confound outcome variables
20. Inability or refusal to comply with protocol
21. Current participation or participation in an experimental drug study in previous three months

Method

Following written consent, all study patients will undergo the following clinical, metabolic and laboratory evaluations before and during treatment (see separate page with Figure 2 study schedule). All study subjects will be assigned an individual study identifier that includes the study acronym, patient initials, and unique number. All blood samples will be obtained and results identified and reported using this unique study identifier. A full physical examination will be performed and vital signs (blood pressure, respiration and temperature) determined. Trained personnel using standardized protocols at the baseline and follow-up examination will obtain anthropometric measurements and blood specimens. Absolute body weight, height, waist and hip circumference, body fat distribution (waist/hip {WHR}) and waist/height ratio ({WHtR}) and blood pressure (BP) will be determined. Body weight will be measured to the nearest 0.1 kg using a calibrated digital scale with participants in light clothing and no shoes. Height will be measured to the nearest centimeter. The total body adiposity (total fatness), defined as the accumulation of body fat without regard to regional distribution, will be expressed as BMI and calculated as weight (kg)/ height (m) ^{2}. The circumference measurements will be taken in the upright position using a 15-mm width flexible metric tape held close to the body but not tight enough to indent the skin. Waist circumference (WC) will be measured at the narrowest level midway between the lowest ribs and the iliac crest and hip circumference measured at the widest level over the buttocks while the subjects are standing and breathing normally. The WHR and WHtR will be calculated for measure of body fat distribution.

All patients will randomly be assigned to one of 5 investigation product treatment groups-–exenatide once weekly (EQW), dapagliflozin (DAPA), EQW plus DAPA, combined DAPA/metformin XR and the weight loss medication, phentermine/topiramate extended release (PHEN/TPM ER); all subjects will be allocated to one of these 5 groups based on computer-generated random numbers using a block randomization method. Oral glucose tolerance tests (OGTTs) with glucose (G) and insulin (I) measured at 0, 30, 60, and 120 after glucose load to assess diabetes, fasting (FBG) and mean blood glucose (MBG) concentrations, insulin resistance and pancreatic ß-cell function will be determined prior to randomization and at 20-24 weeks after full doses of study medications are reached. Mean blood glucose (MBG) concentrations will be calculated by summing glucose values obtained at 0,30,60 and 120 minutes during the OGTT and dividing by 4. At the initial lab evaluation, creatinine and calculated eGFR, TSH, prolactin and ß-hCG will be determined for study inclusion. Baseline blood samples will also be analyzed for lipid profiles and liver enzymes. A baseline blood sample will also be used to measure an

androgen profile (total testosterone [T], dehydroepiandrosterone sulfate [DHEAS], sex hormone-binding globulin [SHBG]), a lipid panel (total cholesterol, high-density lipoprotein [HDL-C], low-density lipoprotein [LDL-C], and triglycerides [TRG] and liver enzymes.

Body composition analyses will be performed using dual-energy x-ray absorptiometry (DEXA) (Hologic Discovery A model, software version 12.5; Hologic, Inc., Waltham, MA) at the start and completion of the study trial. For the scan, the participants will be asked to change into a hospital gown and asked to lie supine on on the table with hands by the side palms facing down away from the thighs and look at the ceiling to maintain head position. DEXA can estimate 3 body compartments consisting of fat mass, lean body mass, and bone mass. The relative attenuation of two different x-ray energies by body tissues produces a three-component model comprising total fat mass (FM), total lean mass (LM including fluid and muscle), and total body bone mineral content (BMC) and density. DEXA also has the ability to determine body composition in defined regions such as the arms, legs, and trunk. DEXA measurements are based in part on the assumption that the hydration of fat-free mass remains constant at 73%. Total body fat mass [FM]) and fat content of head, trunk and extremities (arms+ legs) is provided by the software. Default software readings provide lines positioned to divide the body into six compartments, i.e. head, trunk, arms and legs. The trunk is defined by a horizontal line below the chin, vertical lines between trunk and arms and oblique lines passing through the colli femuri. The region below this lower border of the trunk, including both legs and the hip region is called lower body region. For each region of the whole body, fat and lean body mass and BMC are determined. . Standard software options are used to calculate the total fat-free mass (FFM), fat mass (FM) *vs.* lean mass (LM).

For a better description of the sex specific fat distribution the fat distribution index (FDI) will be calculated as:

FDI = Upper body fat mass in kg/Lower body fat mass in kg

A fat distribution index below 0.9 indicates a gynoid fat distribution, i.e. the fat mass of the lower body surpassed the fat mass of the upper body. A fat distribution index >1.1 defines an android fat distribution. In this case the amount of fat tissue of the abdominal region surpassed the fat mass of the lower body. An FDI between 0.9 and 1.1 is classified as an intermediate stage of fat distribution. We will use the FDI for further quantification of the fat distribution compared to the widely used waist to hip ratio. The WHR describes body shape and silhouette while the FDI provides the quantitative amount of fat distribution. Nevertheless we have to be aware that the FDI describes not the ratio of abdominal fat to gluteal-femoral fat, but the ratio between upper body fat, including abdominal fat and breast fat mass, and lower body fat.

All patients will receive the same counseling concerning the benefits of lifestyle modification through diet and exercise. The patients will be also encouraged to increase daily exercise (such as walking, using stairs), although this will not be formally assessed. The participants will receive further encouragement to adhere to the regime during follow-up phone calls. Side effects of the treatment and reason for any withdrawals from the study will be recorded.

After 24 weeks of treatment, all clinical and laboratory tests will be repeated. All anthropometric parameters and physical including vital signs and DEXA will again be performed and calculations will be repeated for post-treatment effects. In addition, the patient's record of menstrual cycle frequency- (#menses during study period [24 weeks]) will be reviewed and recorded. All side-effects will also be recorded and summarized for the 24 week-treatment period. During the whole study period, compliance to the treatment will be documented. Questioning regarding the occurrence of adverse events and use of concomitant medication will take place throughout the trial.

All investigational products (study drugs) will be stored under appropriate storage conditions in a secure area according to local regulations. The investigator is responsible for ensuring that it is dispensed only to study subjects and only from official study sites by authorized personnel, as dictated by local regulations. The investigator is responsible for ensuring that the investigational product is stored under the appropriate environmental conditions (temperature, light, and humidity), as noted in the product labeling: AstraZeneca and Vivus will provide Investigational product. The packing, labeling, and distribution of all medications are the sponsors' responsibility. Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines for labeling.

Study Drug Records - It is the responsibility of the investigator to ensure that the unblinded study coordinator maintains a current disposition record of investigational product. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area; amount currently in storage area
- label ID number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- non-study disposition (e.g., lost, wasted)
- amount destroyed at study site
- dates and initials of person responsible for Investigational Product dispensing/ accountability.

The pharmacy will "single-blind" all the treatment arms to the physicians and clinical coordinators (open-label study drugs to study patients) by color-coded bags (A, B, C, D, E) with 1 of 5 medications-A) exenatide once weekly (EQW) (Bydureon), B) dapagliflozin (Farxiga), C) EQW plus DAPA (Bydureon plus Farxiga), D) DAPA/metformin XR (Xigduo) and E) PHEN/TPM ER (Qsymia), and dispensing open-label medications to study patients in color-and letter coded bags with instructions on how to take the medicine**.**

Destruction of Investigational Product - If the study drugs are to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for disposal, and that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures. Appropriate records of the disposal will be maintained.

Study Endpoints and Assessments

Primary Endpoint

The primary efficacy endpoint is improvement in the oral disposition index as determined with the insulin secretion-insulin sensitivity (ISSI) index (β-cell compensatory function from an OGTT) which is analogous to the disposition index obtained from an IVGTT). The ISSI is defined as the product of insulin action (Matsuda index- SI_{OGTT}) and insulin secretion (insulinogenic index) derived from the OGTT (SI_{OGTT} x Δinsulin30–0 min to glucose30–0 min). Improving ß-cell compensatory function (increasing insulin sensitivity and enhancing insulin release after an oral glucose load) is reflective of improvement and/or delays in declining glucose tolerance.

Secondary Endpoints

Secondary outcome measures include mean blood glucose (MBG), fasting (HOMA) and glucose-stimulated insulin sensitivity (SI_{OGTT}) and early pancreatic ß-cell response (IGI/HOMA-IR), glycemic parameters (fasting blood glucose [FBG] and 2 hour post OGTT glucose), free androgen index (total testosterone and SHBG) and DHEAS. plasma lipid fractions, trunk fat mass and truck fat/extremities fat ratio by DEXA, anthropometric endpoints include percent change in body weight from baseline to week 12, absolute change in body weight and change in BMI, body fat distribution [waist circumference (WC), (waist/hip ratio [WHR] and waist/height ratio (WHtR)], and blood pressure (BP) from baseline to weeks 12 and 24 and menstrual cycle rates (menstrual cyclicity is determined by # menses/24 weeks pre- and post-treatment.

Biological Sampling Procedures

Laboratory Measures

Hormonal and metabolic parameters will be measured at baseline and 16 week follow-up following an overnight fast. Blood samples will be obtained in the fasting state and ½, 1 and 2 h after a standardized 75-g oral glucose load. Blood samples will be centrifuged, divided into aliquots, and stored at –70°C until assayed. Plasma glucose levels will be determined with a glucose analyzer using the glucose oxidase method (Glucose Reagent Kit, Bayer Newbury, UK). Serum insulin will be determined in all samples in duplicate by microparticle enzyme immunoassay (Abbott AxSYM System, Abbott Laboratories, Abbott Park, IL). Levels of total cholesterol, high-density lipoprotein cholesterol (HDL-C) and triglycerides will be determined in the initial basal sample using standard enzymatic colorimetric assays on an automated clinical chemistry analyzer whereas low-density lipoprotein cholesterol (LDL-C) will be calculated according to the Friedewald equation. Serum creatinine, liver enzymes, AST, and ALT will be measured using standard automated kinetic enzymatic assay. Circulating levels of TSH, prolactin, ß human chorionic gonadotropin (ßhCG), testosterone, sex-hormone binding globulin (SHBG) and DHEAS will be measured using a two-site sandwich immunoassay with direct chemiluminometric technology (Diagnostic Products, Los Angeles, CA). The intra- and interassay coefficients of variation are less than 7 and 11%, respectively, over the sample concentration range.

Assessment of insulin sensitivity and secretion

Indexes of insulin sensitivity and secretion using the serum glucose and insulin concentrations obtained in the fasting state and during the 2hr OGTT with INS will be computed by several measures previously validated in women. Fasting and glucose-stimulated insulin sensitivity will be estimated by homeostasis model assessment of insulin sensitivity (HOMA-IR) and by Matsuda's insulin sensitivity index (SI_{OGTT}). Early pancreatic β-cell response will be estimated as the insulinogenic index (IGI) derived from the ratio of the increment of insulin to that of glucose 30 minutes after a glucose load (insulin 30 min − insulin 0 min/glucose 30 min − glucose 0 min) corrected for by the relative level of insulin resistance (IGI/HOMA-IR). An estimation of β-cell compensatory function, the insulin secretion-sensitivity index (IS-SI) will be derived by applying the concept of the disposition index to measurements obtained during the 2-h OGTT and calculated as the index of insulin secretion factored by insulin resistance (ΔINS/ΔPG 30 x Matsuda SI_{OGTT}) from the OGTT.

Collateral Research

Several other endpoints will be assessed at each study visit. Baseline blood samples will also be collected for measurement of androgen profiles (DHEAS, total testosterone, SHBG and calculated FAI), lipid profiles (cholesterol, HDL and LDL cholesterol, and triglycerides) and liver enzymes (AST/ALT). The free androgen index (FAI) is calculated from the total T concentration (nmol/l)/ concentration of SHBG (nM/L) x100. Menstrual cycle frequency before and after medication treatments will be compared. Dyslipidemia is defined as the presence of at least one of the mentioned lipid parameters abnormalities.

Safety assessments

The safety and tolerability assessments will include incidence and intensity of adverse events, withdrawals because of adverse events, physical exams, vital sign measurements and clinical laboratory parameters. Patients will be seen at 12-14 weeks to confirm they are not pregnant by laboratory evaluation and required to perform monthly home pregnancy tests.

Statistical Methods and Sample Size Calculations

A priori sample size analysis was performed using the online calculator provided by the Massachusetts General Hospital Mallinckrodt General Clinical Research Center (http://hedwig.mgh.harvard.edu/sample_size/size.html). Given there are no previous studies utilizing dapagliflozin, exenatide once-weekly or combination treatments for women with PCOS, sample size analysis was based on the assumption that the smallest mean difference between treatment groups is 20% with an with an average SE of 2.2% [average SD of 9.8%]; the sample size with a statistical power of 0.80 and two-sided P-value <0.05 is calculated to be 20-25 for each group. Using a 20% drop-out rate, the study is designed to recruit 25 patients in each arm to ensure that the number of subjects completing the study (22) as derived by the sample size calculation is met

All analyses will be conducted using SPSS for Windows (version 11.01, SPSS, Inc.; Chicago, Ill). The primary outcome measure is comparison of the insulin secretion-insulin sensitivity (ISSI) index (oral

disposition index) determined from a 75-g OGTT before and after treatment between non-diabetic women with PCOS treated with exenatide once weekly (EQW), dapagliflozin (DAPA), EQW plus DAPA, combined DAPA/metformin XR or combination phentermine (PHEN)/topiramate (TPM) extended release (ER). The secondary outcome measures include changes in surrogate measures of insulin action (HOMA-IR, SI_{OGTT}, IGI/HOMA-IR and oral DI) and glycemic parameters (fasting blood glucose [FBG] and 2 hour post OGTT glucose) mean blood glucose (MBG), anthropometric parameters (weight and fat distribution by DEXA), blood pressure, lipid profiles, liver enzymes, androgen levels (DHEAS, total testosterone, SHBG and calculated FAI) and menstrual cyclicity. Mean **blood glucose (**MBG) concentrations **will be calculated by summing glucose values obtained at 0,30,60 and 120 minutes** during the **OGTT and dividing by 4.** The normality of all variables will be checked using the Kolmogorov-Smirov test. Continuous variables will be tested for normality of distribution using the Kolmogorov-Smirov test. When necessary, non-normally distributed data will be subjected to logarithmic or square root transformation to obtain a normal distribution where necessary for subsequent analyses. Direct and indirect estimates of insulin sensitivity and secretion (HOMA, SI_{OGTT}, IGI/HOMA, ß-cell compensatory 3function, glycemic parameters (FBG, MBG, 2 hour post OGTT glucose level) anthropometric measurements (body weight, BMI), fat distribution (WC, WHR and WHtR), BP, androgen and lipid profiles will be considered as dependent variables.

For all analyses, in which the measures are continuous, data from evaluable subjects will be submitted to a repeated-measures general linear model (SS/ Drug treatments x repeated measures ANOVA) including the arm of drug treatment as the between-subjects effect, and the visit (baseline and 24 wks.) as the within-subjects effect. To evaluate the differences in the response to each treatment over visits, the interaction effect will be calculated. For both the primary and secondary outcome measures, if a statistically significant interaction effect is found ($P \leq 0.05$), a contrast analysis will be applied to locate the differences between the 5 medication groups. The pairwise contrasts of the average across the within –subject factors (drug treatment x time interaction) will be tested with the Bonferonni correction, which adjusts the significance level for multiple comparisons to better control for Type I errors. The Bonferroni test uses a straight-forward *t* test but then evaluates that *t* at $\alpha = .05/c$, where c is the number of comparisons. This test adjusts the critical value of the test statistic keeping the familywise error rate at, or near.05. The result is that this test is more conservative as the number of contrasts increases, which means a larger difference between means, is required for significance and each set of comparisons is protected against an increase in the risk of Type 1 errors by the nature of the test.

Dysglycemia occurrence before and after different treatment will be compared with the McNemar test (complex chi square for paired data), which formally tests for a change between the observed proportions of k related samples. Menstrual cycle rates before and after treatment will be compared with the McNemar test (complex χ^2 for paired data), which formally tests for a change between the observed proportions of 2 related samples.

Baseline comparisons between groups (intent-to treat population) will be made by one-way ANOVAs and post hoc comparisons performed with the Tukey test to analyze the variation among the 5

groups if the ANOVA shows overall baseline differences were significant ($p<0.05$). Data will be analyzed on the basis of intention to treat and also on completed treatment parameters where relevant. The intent-to-treat population (ITT) is defined as all randomized subjects who received one oral dose of medication starting from the evening of day 1. The evaluable population is defined as all randomized subjects who complete treatment through week 20-24 weeks. Results will be reported as mean +/- S.E.M unless otherwise noted. Categorical data will be presented as percentage.

Ethical and Regulatory Requirements

This protocol and the associated Informed consent as well as any addenda or amendments, must be reviewed and approved by the Woman's Hospital Foundation Institutional Review Board (WHIRB) review committee prior to the start of the study. Recruitment materials and advertising must be reviewed and approved by the WHIRB prior to use. All revisions to this Protocol are considered "protocol amendments" these must be approved in advance, in writing, by the WHIRB. Every patient will have given her written informed consent prior to participating in the study. Prior to participation in this trial, each subject will have an opportunity to ask questions and will sign (and date) a written Informed Consent, which must be witnessed. The signed consent forms will be filed with the investigator's study charts for each subject. A copy of the informed consent will be provided to the subject. Any subject may voluntarily withdraw from the study at any time without prejudicing treatment.

Good Clinical Practice - This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH) and in accordance with the ethical principles underlying the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50). The study will be conducted in compliance with the protocol. All potential serious breaches must be reported to AstraZeneca (AZ) immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study. Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure; debarment).

Patients starting all oral therapies will be advised that they may have minor gastrointestinal side effects. The most reported common adverse effects of dapagliflozin (Farxiga) are genital mycotic infections, lower urinary tract infections (UTIs), and those related to osmotic diuresis. Patients are strongly counseled on the practice of good genital hygiene in order to avoid yeast infections. That means, whenever possible, they should cleanse well after voiding to remove residual glucose. They are also taught to watch for signs-such as itching, burning and redness so they can get treated promptly. There is no need to stop the medication, just to treat the infection. In addition, the tablets contain lactose, which may cause discomfort in lactose-intolerant individuals. The most common side effects of metformin are diarrhea, nausea or vomiting, flatulence, indigestion, abdominal discomfort and rarely, a

metallic taste in the mouth. These acute reversible adverse effects occur in 5–20% of patients treated with metformin. The symptoms are dose related and remit if the dose is reduced, sometimes an increase in the dose can later be tolerated. Taking the drug with or after food, and starting therapy with low dosages that may be increased slowly can minimize these. The dose can then be increased slowly at intervals of two weeks. Lactic acidosis is the biguanide-related adverse effect of most concern with an estimated incidence of less than 0.01 to 0.08 cases. Should a patient have lactic acidosis attributable to metformin, the drug can be removed by hemodialysis. Other contraindications to the use of metformin include concurrent liver disease and a previous history of lactic acidosis. Oral therapy will also be stopped if the blood lactate concentration is substantially increased by any illness. Oral therapy will be temporarily suspended for all major surgical procedures that involve restriction of fluid intake.

The United States Food and Drug Administration (FDA) have assigned pregnancy category X to phentermine/topiramate (Qsymia). Data from pregnancy registries and epidemiology studies indicate an increased risk in oral clefts (cleft lip with or without cleft palate) with first trimester exposure to topiramate, a component of Qsymia. The US FDA classifies Farxiga and Xigduo as a pregnancy category C drugs (i.e., “potential benefit should outweigh the potential risk”). Women of childbearing potential are required to use adequate contraception during use (unless sterilized). Metformin is classified as a US FDA pregnancy category B drug (i.e., "no evidence of risk in humans"). This means that, while there is no evidence of teratogenesis or adverse fetal effects, insufficient data exist to state that harm does not occur. Metformin does cross the placenta, prompting a cautious approach to its use in pregnancy. There have been several published reports of the use of metformin during pregnancy, predominantly in women with insulin resistance and PCOS. Some clinicians routinely use metformin to treat diabetes in pregnant women. However, most experts believe that if medication is needed to control blood sugar during pregnancy, insulin is the drug of choice, not an oral antihyperglycemic agent. If patients become pregnant during the study, all medications will be stopped and the patient will discontinue from the study.

For safety, all subjects who enter the study are evaluable. Subjects will be monitored for safety by assessment of adverse events, physical exams, vital signs and laboratory values. Continued patient safety assessment will be carried out and all adverse events documented and reported to the WHIRB. On each visit, compliance with treatment will be checked with questions about the side-effects and a subjective evaluation of the tolerability of the administered drug; the patients will also asked about incidental missed administrations.

Adverse events will be evaluated on a continuous basis while the patient is on study and until 30 days after the last dose of study drug. Patients should be followed until all treatment-related adverse events have recovered to baseline or are deemed irreversible by the principal investigator.

Adverse Event Procedures

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

1. Serious Adverse Events

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 4 for reporting pregnancies).

NOTE:

The following hospitalizations are not considered SAEs:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

1A. Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuation of dosing. The investigator should report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure. All SAEs, whether related or not related to study drug, and pregnancies must be reported to AZ (or designee) within 24 hours. They will also be reported immediately to the Woman's Hospital Foundation Institutional Review Board at (225) 231-5296 and Woman's Health Research Institute at (225) 231-5275. SAEs must be recorded on an SAE Report Form or similar form (e.g. CIOMS, MedWatch); pregnancies on an AZ approved Pregnancy Surveillance Form. Reports are to be transmitted via email or confirmed facsimile (fax) transmission.

Investigators and other site personnel must inform the FDA, via a MedWatch/AdEERs form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to AZ. A copy of the MedWatch/AdEERs report must be faxed to AstraZeneca at the time the event is reported to the FDA. It is the responsibility of the investigator to compile all necessary information and ensure that the FDA receives a report

according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

When reporting to AstraZeneca, a cover page should accompany the MedWatch/AdEERs form indicating the following:

- Investigator Sponsored Study (ISS)
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number

Investigative site must also indicate, either in the SAE report or the cover page, the causality of events in relation to all study medications and if the SAE is related to disease progression, as determined by the principal investigator. An SAE report should be completed for any event where doubt exists regarding its seriousness. If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

Send SAE report and accompanying cover page by way of fax to AstraZeneca's designated fax line: 1-866-984-7229

Serious adverse events that do not require expedited reporting to the FDA need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events.
In the case of blinded trials, AstraZeneca will request that the Sponsor either provide a copy of the randomization code/ code break information or unblind those SAEs which require expedited reporting.

All SAEs have to be reported to AstraZeneca, whether or not considered causally related to the investigational product. All SAEs will be documented. The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements. If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to AZ (or designee) using the same procedure used for transmitting the initial SAE report.
In cases where the investigator learns of the SAE after its occurrence and resolution, the time and circumstances of the event will be recorded. The reporting requirements will still be followed

All SAEs should be followed to resolution or stabilization.

In addition, investigators will also follow 21 CFR 312.32 and notify Vivus, Inc. of Qsymia SAEs within 24 hours and receive a written report within 48. In accordance with 21 CFR 312.32, the investigators will notify FDA no later than 15 calendar days of all events that are serious, unexpected, and have possible

relationship to Qsymia. For unexpected fatal or life-threatening suspected adverse reaction reports related to Qsymia, the investigators will notify the FDA no later than 7 calendar days after the investigators initial receipt of the information.

Nonserious Adverse Events

A nonserious adverse event is an AE not classified as serious.

2A. Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 1A). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF.

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

2. Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

3. Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety).

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify AZ (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to AZ (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section 1A.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 1A for reporting details.).

4. Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 1A for reporting details).
Potential drug induced liver injury is defined as:

AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

5. Adverse Events of Special Interest

In this study, the following adverse events are to be reported to AZ, regardless of whether these reports are classified as serious or unexpected:

1. liver test abnormalities accompanied by jaundice or hyperbilirubinemia
2. opportunistic infections associated with the use of dapagliflozin
3. pancreatitis
4. anaphylaxis
5. angioedema

6. Steven-Johnson's Syndrome

When one of these events meets the criteria for a serious adverse event, report the event using SAE reporting procedures. When one of these events does not meet the criteria for a serious adverse event, report the event within 24 hours as a non-serious event.

6. Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate,

Discontinuations

The reason for a subject discontinuing from the study will be recorded in the patient chart. A discontinuation occurs when an enrolled subject ceases participation in the study, regardless of the circumstances, prior to completion of the protocol. The investigator must determine the primary reason for discontinuation. Withdrawal due to adverse event will be distinguished from withdrawal due to insufficient response according to the definition of adverse event noted earlier. The final evaluation required by the protocol will be performed at the time of study discontinuation. The investigator will record the reason for study discontinuation, provide or arrange for appropriate follow-up (if required) for such subjects, and document the course of the subject's condition. They will also to be reported to Woman's Hospital Foundation Institutional Review Board at (225) 231-5296 and Woman's Health Research Institute at (225) 231-5275.

Subjects MUST discontinue investigational product for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason).
- Any clinical adverse event, laboratory abnormality, or intercurrent illness, which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject.
- Pregnancy
    - Instruct subjects to contact the investigator or study staff immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation. Institutional policy and local regulations should determine the frequency of on-study pregnancy tests for subjects enrolled in the study.
    - The investigator must immediately notify AZ if a study subject becomes pregnant.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

All subjects who discontinue should comply with protocol-specified follow-up procedure. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

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