PART B
STUDY DESCRIPTION

TITLE OF PROTOCOL	**A prospective study of patterns, predictors, and mechanisms of weight loss with exenatide treatment in overweight and obese women without diabetes**		
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Sponsor/Funding Source	**AstraZeneca**		

B1. PURPOSE OF PROTOCOL

Purpose

We recently completed a 35-week double-blind, placebo-controlled, crossover study investigating weight loss with exenatide treatment in a group of 41 overweight and obese women without diabetes. We found that a subset of women, approximately 30%, lost 5-13% of their body weight during the exenatide treatment period (average weight loss 8% at 16 weeks). We designated this subgroup "high responders." We found that weight loss with exenatide treatment could be identified as early as 4 weeks and continued throughout the 16 week treatment period.

We are now conducting a followup study that will investigate the possible mechanisms of weight loss associated with exenatide treatment and the metabolic characteristics of high responders to exenatide treatment. We will also examine the magnitude and duration of weight loss among a cohort of high responders over 52 weeks of treatment, and at 3 and 6 months following treatment.

Hypothesis:

The mechanisms of weight loss with exenatide are not fully understood, and weight loss responses to exenatide are highly variable, possibly reflecting distinct metabolic parameters. By identifying and following a group of obese women who lose $\geq$ 5% body weight after short-term exenatide treatment, we can gain insights into the possible mechanisms of weight loss and assess long-term weight loss with this pharmcotherapeutic intervention.

Primary Outcomes

The primary objectives of this study are:
1. To investigate possible mechanisms of weight loss with exenatide treatment
2. To determine long-term patterns of weight loss among individuals who have robust (>5%) early weight loss with exenatide

Secondary Outcomes

Our secondary objective is to identify metabolic characteristics that predict robust response to exenatide treatment.

Outcome measurements:

Weight: We will compare the duration and magnitude of weight loss among exenatide responders with the

duration and magnitude of weight loss among subjects assigned to placebo with a calorie-restricted diet over 52 weeks. We will also compare changes in weight at 3 and 6 months after the cessation of exenatide treatment or diet. Weight loss will be correlated to baseline BMI.
Body composition: Baseline body composition may predict response to exenatide treatment, and weight loss with exenatide may be associated with decreased fat versus lean body mass compared to diet-induced weight loss. We will compare the effect of exenatide treatment versus caloric reduction on body composition over 52 weeks using bioelectrical impedance analysis (BIA) and by measuring waist circumference.
Resting energy expenditure (REE): Our initial data suggest that exenatide may blunt the decrease in resting energy expenditure that is typically associated with diet-induced weight loss. We will measure resting energy expenditure (REE) via indirect calorimetry at baseline, at weeks 12, 24, and 52, and after 5%, 10%, 15% weight loss is achieved, and at additional 5% weight loss timepoints, as applicable (i.e., 20%, 25%, etc).
Mixed meal test: Exenatide may improve beta cell function and lower postprandial triglycerides in nondiabetic individuals. Measurement of fasting insulin and triglyceride levels does not capture these effects. We will administer a mixed liquid meal (Boost) and measure serial postprandial insulin, , and triglyceride levels. Subjects will have a mixed meal test at baseline, and at weeks 12, 24, and 52.
Thermic effect of food: Exenatide treatment may result in an increase in the thermic effect of food, which could explain, at least in part, why we did not see a significant reduction in energy expenditure among exenatide high responders in our initial study. We will measure the thermic effect of food using indirect calorimetry following the mixed meal challenge. Energy expenditure will be measured for 15-20 minutes every hour for four hours after the mixed meal challenge. The thermic effect of food will be measured in a subset of subjects at baseline, and at weeks 12, 24, and 52.
Serum metabolic parameters: Subjects will have blood drawn to measure leptin, soluble leptin receptor, insulin, cortisol, adiponectin, CRP, and FGF21. Blood will also be banked to measure other metabolic parameters in the future. Serum metabolic parameters will be measured at baseline and at weeks 12, 24, and 52. Serum metabolic parameters will also be measured when weight loss at a 5% increment has been achieved, or upon study completion if weight loss targets are not achieved.
Hunger/Nausea/Satiety visual analog scales (VAS): Perceptions of hunger, nausea or satiety early during exenatide treatment may predict and/or explain weight loss response. We will assess hunger, nausea and satiety at each study visit using standard 10cm horizontal visual analog scales.
Physical activity monitoring with Actigraph accelerometers: Subjects may be given wrist-worn accelerometers (Actigraph, MiniMitter) at week 0 to measure baseline physical activity levels. The will allow us to compare and control for baseline physical activity level differences between the placebo and exenatide groups. Subjects may be asked to wear the monitors again at study week 12, at study week 24, and after achieving 5%, 10%, 15%, weight loss, or weight loss > 15% at a 5% increment.

Delayed Gastric Emptying Substudy
Delayed gastric emptying is a known effect of exenatide treatment. Delayed gastric emptying can cause early and prolonged satiety, both of which may contribute to exenatide-induced weight loss. There is no literature on the effect of delayed gastric emptying on energy expenditure, in particular the thermic effect of food. Preliminary data from this study indicate that exenatide treatment is associated with a blunting of the thermic effect of food. This blunting is seen among exenatide responders (> 5% weight loss after 3 months of treatment) and among nonresponders (< 5% weight loss at 3 months). In contrast, individuals assigned to the placebo group maintain a 100-300 calorie increase in resting energy expentidure (the thermic effect of food, TEF) even in the setting of weight loss comparable to exenatide responders.

These intriguing data are the rationale behind a substudy that will further examine the effect of delayed gastric emptying on TEF. This substudy will specifically examine the effect of low-dose morphine, an agent that also delays gastric emptying, on TEF. By studying another agent known to delay gastric emptyingthrough a different pharmacologic mechanism, we can determine whether the blunted TEF that we see with exenatide is due to delayed gastric emptying or another mechanism of action of exenatide. For the substudy, we will recruit women who have completed treatment in the main study, either at 3 months (nonresponders) or at 12 months (responders). As mentioned, we have observed a blunting in TEF among both responders and nonresponders to exenatide, indicating that this effect is due to exenatide and independent of weight loss. Our current study population excludes women with diabetes or gastroparesis, both of which we also want to exclude in this substudy.
Study Population

Our study population will be generally healthy, non-diabetic women age 18-70 years with BMI 28-50 kg/m^2.

B2. SIGNIFICANCE AND BACKGROUND FOR THE STUDY

Incretin mimetics, medications that mimic the effects of incretin hormones produced by the L cells of the small intestine, are gaining popularity for the treatment of type 2 diabetes. Incretin mimetics are typically associated with more weight loss than any other class of antidiabetic agents. Exenatide, a glucagon-like peptide 1 (GLP-1) receptor agonist, was the first incretin mimetic approved in 2005. Liraglutide, a GLP-1 analog, was approved in 2010, and there are several additional incretin mimetics in development. Exenatide causes glucose dependent insulin secretion, restoration of the first phase insulin response, and reduction of postprandial glucagon secretion. Exenatide also causes delayed gastric emptying and decreases food intake through mechanisms that are not completely understood (Drucker et al., 2003; Iltz et al., 2006; Palamara et al.,2006). Exenatide is currently approved as a twice daily injection.

Exenatide is associated with weight loss among individuals with type 2 diabetes when used as monotherapy or in conjunction with metformin or a sulfonylurea (Buse 2004; Defronzo 2005; Kendall 2005; Riddle 2006; Moretto 2008; Buse 2009). Exenatide and liraglutide have also been associated with weight loss among obese individuals without diabetes (Rosenstock 2010; Astrup 2010). Retrospective analysis has shown that weight loss is greater among diabetic individuals with BMI > 30 compared to those with BMI < 30, however there are no published prospective studies that have characterized individuals who have robust weight loss with exenatide. Similarly, there are no studies that have examined weight trajectories following termination of exenatide treatment among individuals without diabetes.

An important clinical consideration with all pharmacotherapeutic agents, and especially those that are associated with weight loss, is identifying as early as possible individuals who do and do not respond to treatment. In our recently completed study of 41 overweight and obese women without diabetes, we found that exenatide treatment was associated with a significant decrease in weight, BMI, and waist circumference compared to placebo. There was also a trend towards decreased sleep latency (how long it takes to fall asleep) with exenatide treatment compared to placebo. We did not find any significant differences in blood pressure, body composition, lipid parameters, leptin levels, insulin levels or resting energy expenditure when we compared exenatide treatment to placebo overall, but we did note that a few subjects had dramatic changes in fasting insulin, glucose, leptin, or triglyceride levels.

In our initial study we also made the interesting observation that exenatide high responders did not have a significant decrease in resting energy expenditure (REE) despite an average 8% weight loss. Whereas diet-induced weight loss of this magnitude has been shown to result in a decrease in resting energy expenditure, which facilitates weight regain, our data suggest that exenatide may blunt this decrease in REE and thereby permit ongoing weight loss. In the present study, we will compare resting energy expenditure as well as the thermic effect of food among exenatide high responders, nonresponders, and subjects with diet-induced weight loss**.**

Another mechanism of weight loss may be a change in leptin sensitivity. Serum leptin levels have been shown to fall in obese individuals with diet-induced weight loss (Crujeiras 2010), and in our initial study, we found that high responders had a significant decrease in leptin levels compared to nonresponders. While this decrease may reflect weight loss, it may also reflect sensitization to leptin. Furthermore, measurement of total serum leptin levels may not be the best tool for assessing leptin sensitivity. In a cohort of lean males fasted for 72 hours, leptin levels fell while levels of the soluble leptin receptor increased (Chan et al, 2002). Measurement of both total leptin and soluble leptin receptor levels, and in turn calculation of the free leptin index, can provide more a more detailed assessment of leptin resistance.

Rationale for study population:

In this study, as in our initial study, we will enroll only obese women without diabetes. Certainly obesity is not a disease limited to women, but we have chosen to enroll only women because we do not wish to examine differences in the mechanisms and rate of weight loss between men and women. In addition, differences in body fat distribution between men and women may affect timing, duration, and amount of weight loss, which would introduce additional variability in our data. Future studies addressing weight loss among obese men treated with exenatide and/or studies comparing men and women treated with exenatide may follow from this study. By excluding women with diabetes, we aim to minimize the presence of co-morbidities associated with diabetes and insulin resistance that may mitigate the effects of exenatide on energy expenditure and serum

metabolic parameters.

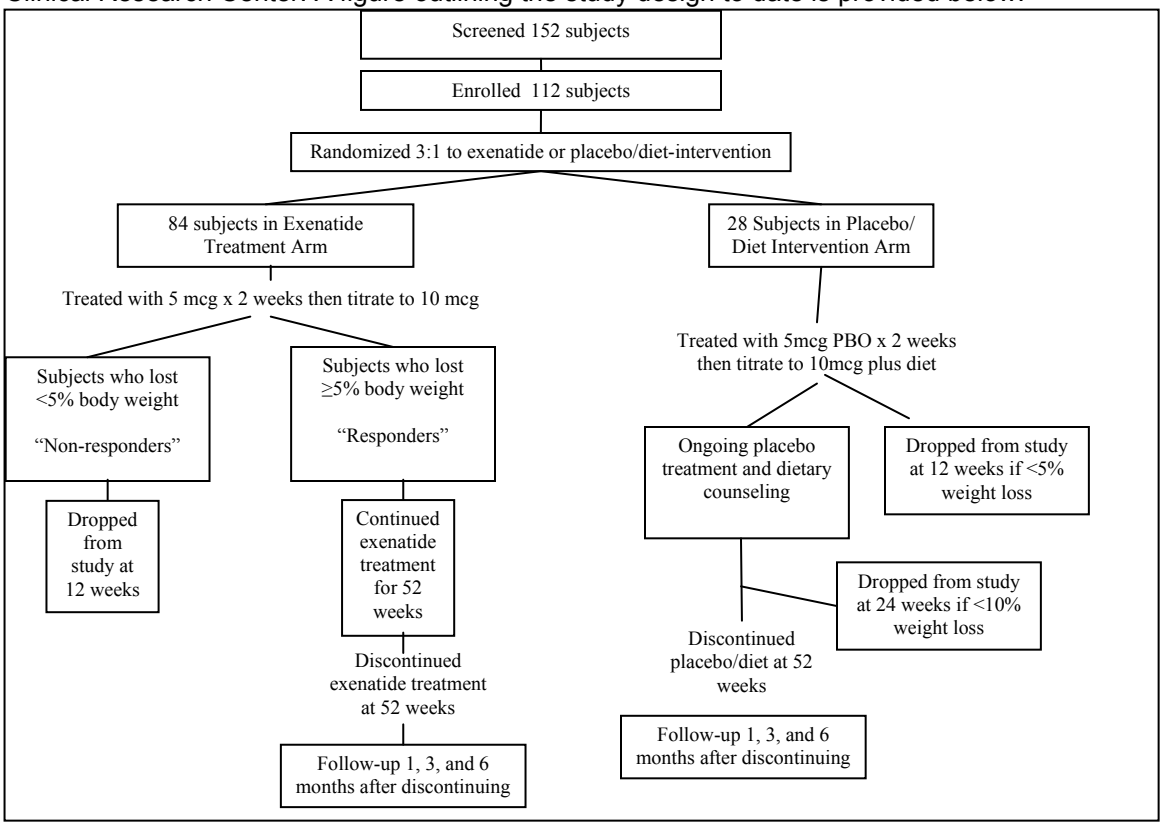
B3. DESCRIPTION OF RESEARCH PROTOCOL

A. Study Design – Overview, Methods, Procedures

Overview

We propose a 52-week randomized, placebo-controlled, single-blind interventional study. Eligible subjects will be randomized in a 2:1distribution to exenatide or placebo treatment. Subjects in the placebo treatment group will be given specific dietary counseling and meal plans aimed at achieving at least 5% weight loss (approximately 500-1000 cal/day caloric reduction). Subjects in the exenatide treatment group will be advised to follow a eucaloric diet and will not be given a diet plan. Subjects will be blinded to their treatment arm but investigators will not.

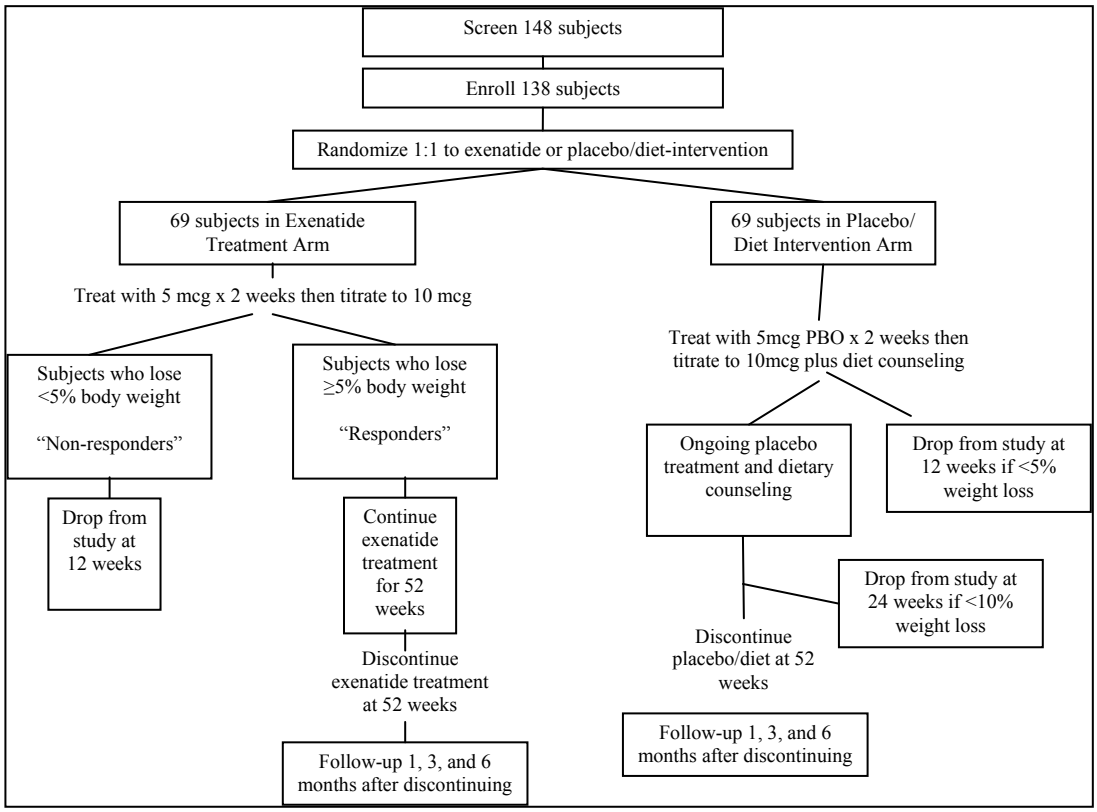
All subjects will receive twice daily treatment for 12 weeks. Subjects will inject 5 mcg exenatide or placebo twice a day for the first 2 weeks and then 10 mcg twice a day for the remainder of the study. We will identify subjects who lose ≥5% body weight at 12 weeks as *high responders* to exenatide or placebo, and such subjects will remain in the study for 52 weeks with monthly study visits. Subjects who lose < 5% body weight at 12 weeks will be considered *nonresponders* and will discontinue participation after 12 weeks. At 24 weeks, subjects in the placebo group who have not lost 10% of their body weight will discontinue participation. At 52 weeks, high responders in both treatment groups will discontinue treatment. Subjects will return at 3 and 6 months for post-treatment followup visits. All visits are outpatient visits that will take place in the Beth Israel Deaconess Medical Center Clinical Research Center. A figure outlining the study design to date is provided below.



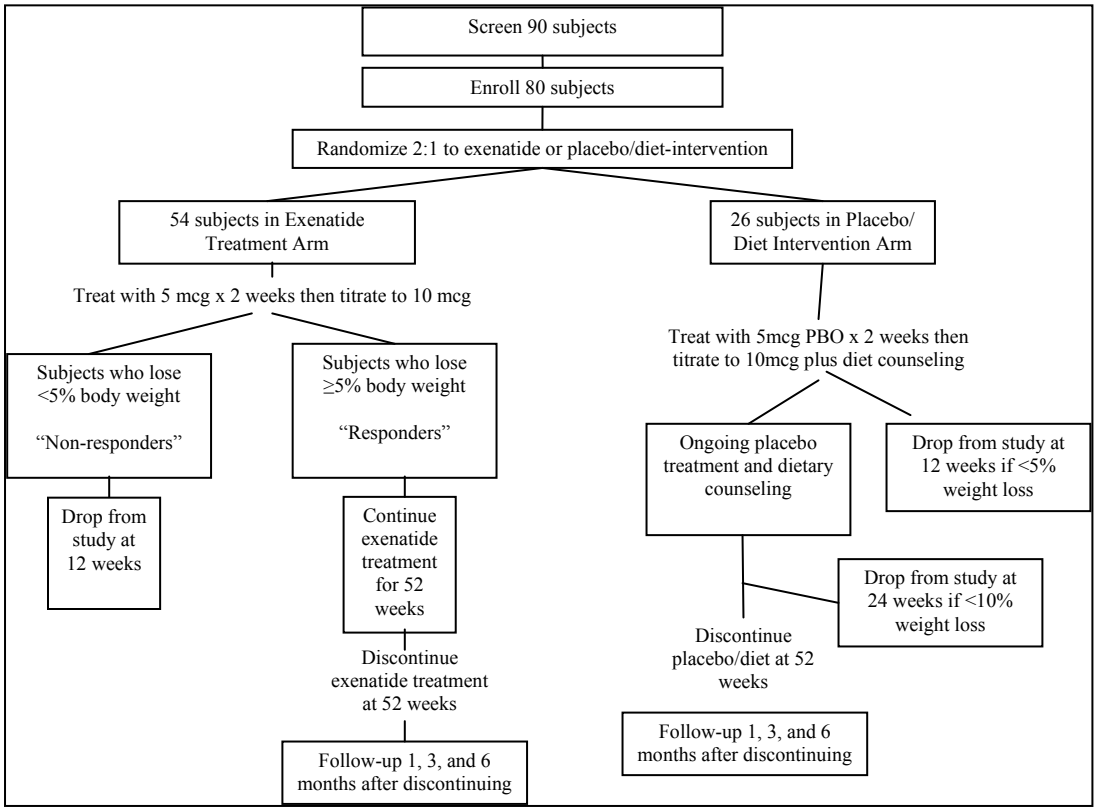
Rationale for study design:

Subjects are randomized to exenatide treatment with general dietary counseling or placebo treatment with aggressive dietary intervention. We are including placebo treatment with aggressive dietary intervention in order to minimize potentially unequal dropout rates in the exenatide versus dietary intervention arms. We will not be able to achieve our primary objectives without an adequate control group that loses at least 5% of body weight with dietary intervention alone.

As of 7/1/14, using a 3:1 randomization scheme, we have enrolled 84 subjects in the exenatide group and 28 in placebo. Due to a higher-than-expected exenatide high responder rate (approximately 60% compared to our prediction of 30%), we must change our randomization scheme to 1;1 to enroll enough subjects in the placebo group for comparison. The number of subjects screened will also be increased from 250 to 300 to achieve our enrollment goal of 250. Thus, we will screen 148 more subjects for a total of 300 screened.



As of 6/5/15, using a 1:1 randomization scheme, we enrolled 24 subjects in the exenatide group and 10 in placebo. Due to a higher than expected drop out rate in the exenatide group and a high response rate in the placebo group, we will change our randomization scheme to 2:1 to enroll enough subjects in both groups for comparison based on our original power calculation.
The following figure outlines the new changes:



The placebo arm will be used to study weight-loss induced metabolic changes that are independent of exenatide. Because the subjects in the placebo/dietary intervention arm serve as a weight-loss comparison group, these subjects will be dropped from the study at 12 weeks if they do not lose 5% of their body weight. Subjects in the exenatide treatment arm will be characterized as "non-responders" (<5% weight loss) or "responders" (≥5% weight loss) based on weight loss at 12 weeks. Data from our previous exenatide study in non-diabetic obese women shows that 12 weeks provides a reasonable timeframe to differentiate "non-responders" and "responders." Because this study focuses only on the characteristics of exenatide responders, subjects in the exenatide treatment arm with less than 5% weight loss at 12 weeks will be dropped from the study. Exenatide "responders" will continue treatment for 52 weeks to assess the magnitude and duration of weight loss in this subgroup. These subjects will also participate in 3-month and 6-month follow-up visits to assess weight changes post-treatment. Subjects in the dietary intervention arm will continue study participation for up to 52 weeks if they demonstrate ongoing weight loss and then attend 3-month and 6-month follow-up visits after returning to *ad-lib* eating.

Recruiting and randomization:

The study will be advertised in local print media and on the radio, and flyers will be posted in Boston, including the Longwood Medical Area. The study will also be advertised via the internet with clinicaltrials.gov, TrialX, and on CraigsList. Participants may also be referred for participation by their primary care physicians or

endocrinologists. Individuals who respond to advertisements will first have a brief telephone screen, which will include questions about past medical history, medication use and the ability to travel to Boston for study visits. Subjects who have been deemed appropriate for enrollment after a telephone screen will be scheduled for a screening visit. After they have completed the screening visit, and once the results of all of their screening labs have been reviewed, they will be asked to enroll in the study. If they agree to enroll, they will now be randomized in a 2:1ratio to the exenatide treatment arm or placebo/diet treatment arm of the study, respectively. The research pharmacy at the Beth Israel Deaconess Medical Center will randomize patients and allocate exenatide or placebo to subjects in the at the enrollment visit.

Study duration:

All subjects randomized to exenatide treatment will continue participation for 12 weeks. At 12 weeks, subjects who are high responders will continue participation for 52 weeks plus followup visits at 3 and 6 months. Exenatide high responders will remain in the study even if weight loss plateaus or if there is weight regain. Exenatide nonresponders will discontinue participation after 12 weeks.

Subjects in the placebo/diet intervention arm will discontinue participation if they fail to lose 5% of their body weight after 12 weeks or 10% of their body weight after 24 weeks. Subjects who demonstrate ongoing weight loss will continue placebo/dietary intervention for up to 52 weeks, plus follow-up visits at 3 and 6 months. Metabolic monitoring will occur when subjects have lost 5% and 10% of their body weight.

Dosing of exenatide and placebo:

Subjects will inject 5mcg of exenatide or identically dispensed placebo subcutaneously 15 minutes before the morning and evening meal for the first 2 weeks of the study. At study week 2, subjects will increase to 10 mcg twice daily, which is the standard treatment dose of exenatide used for the treatment of type 2 diabetes.

Dietary counseling:

Caloric requirements for weight maintenance will be calculated at the enrollment visit for each subject. Subjects who are receiving exenatide will receive general nutrition counseling without caloric restriction. Subjects who are receiving placebo will be instructed to reduce their intake by 500-1000 calories/day below the weight maintenance level. These subjects will be provided with sample menus and the approximate caloric content of common foods, and they will have the option of receiving weekly nutrition counseling (vie email or in person). No exercise counseling will be provided to any subjects in the study, and subjects should maintain baseline physical activity throughout the study.

Safety variables:

Subjects will provide informed consent in a quiet, private area in the presence of a study investigator. Subjects will be given ample time to read the informed consent document and ask questions. Inclusion and exclusion criteria will be reviewed prior to the screening visit and again confirmed at the screening visit. Subjects will be reminded that participation is voluntary and that they are able to withdraw participation at any time.

A complete physical exam will be done at the screening visit, study week 12, study week 24, and study week 52. Vital signs (body weight, heart rate, blood pressure, and oxygen saturation using pulse oximetry) will be done at every study visit. A urine pregnancy test will be done at every visit. A hematology panel (white blood cell count with differential, hemoglobin, hematocrit, platelet count), serum chemistries (sodium, potassium, chloride, bicarbonate, urea nitrogen, creatinine, calcium, phosphorous, magnesium), lipase, transaminases, and a lipid panel will be drawn at baseline, study week 12, study week 24 and study week 52. Hemoglobin A1C and TSH will also be measured at baseline.

Potential side effects of exenatide and a reduced energy diet will be reviewed at the enrollment visit. At every visit subjects will be asked about adverse events and concomitant medications.

Gastric Emptying Substudy
Subjects, all of whom met eligibility criteria for and participated in the main study, will report to the CRC after an overnight fast. Women of childbearing potential (menstrual period within the past 2 years) will have a urine

pregnancy test. After vital signs are obtained, including weight, blood pressure, heart rate, and oxygen saturation, we will place an IV and subjects will rest for 15-20 minutes. After this rest period we will measure baseline resting energy expenditure using indirect calorimetry. Subjects will then receive a single bolus dose of IV morphine, 0.05mg/kg, followed by a mixed meal challenge (single serving of Boost). We will measure the thermic effect of food using indirect calorimetry for 15-20 minutes every hour for up to six hours after the mixed meal challenge, as is done in the main study. Subjects will have vital signs monitored every 30 minutes following administration of morphine and immediately prior to discharge from the CRC. Subjects will not be permitted to drive home after discharge, they will either have a ride or will be provided with compensation for transportation.

All adverse events reported spontaneously by the subject, as well as those noted by the investigator or study site staff, will be recorded. In order to avoid vague, ambiguous, or colloquial expressions, the adverse event term will be recorded using standard medical terminology rather than the subject's own words. Every attempt will be made to describe the adverse event in terms of a diagnosis. Whenever the investigator is confident in making a unifying diagnosis, all related signs, symptoms and abnormal test results should be grouped together and recorded as a single adverse event.

All subjects who have adverse events, whether or not the adverse events are considered associated with the use of the study medication, will be monitored until the adverse event resolves, stabilizes, or becomes chronic. The clinical course of the adverse event will be followed according to accepted standards of medical practice, even after the end of the observation period, until a satisfactory explanation for the adverse event is found or the investigator considers it medically justifiable to terminate follow-up. All adverse events will be evaluated for intensity and causal relationship with use of the study medication.

Collection of serious adverse event information will begin at the signing of informed consent and continue through 30 days after administration of the last dose of exenatide or placebo. Serious adverse events are defined as death, life threatening, requiring inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, and congenital anomaly or birth defect. If a serious adverse event occurs, the investigators will initiate appropriate support procedures. Unexpected, related serious adverse events will be reported to the FDA in an expedited manner.

The following sections (1-1.7) contain information about adverse events from the sponsor. The sponsor requested that this information be included in the protocol submitted to the BIDMC IRB.

1 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or 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 (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

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.)

1.1 Serious Adverse Events

A ***serious AE (SAE)*** is any untoward medical occurrence that at <u>any dose</u>:

- 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 [eg, 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 1.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, any organism, virus or infectious particle, pathogenic or non-pathogenic) 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 1.4 for reporting pregnancies.)

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered "important medical event" or event life threatening)
- 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 (eg, routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state and was 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 (eg, lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

1.1.1 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. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the investigator believes that an SAE is not related to the 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.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). When using paper forms, the reports are to be transmitted via email or

confirmed facsimile (fax) transmission to:

SAE Email Address: worldwide.safety@bms.com

SAE Facsimile Number: 1-609-818-3804

For studies capturing SAEs/pregnancies through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

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 BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

1.2 Nonserious Adverse Events

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

1.2.1 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 1.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug, or those that are 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 (paper or electronic).

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

1.3 Laboratory Test Abnormalities

The following laboratory abnormalities should be captured on the nonserious AE CRF Page or SAE Report Form (paper or electronic) as appropriate:

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

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

1.4 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 (eg, 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 (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section 1.1.1.

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.

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 (eg, 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 (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section 1.1.1.

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.

Any pregnancy that occurs in a female partner of a male study participant should be reported to the sponsor. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

1.5 Overdose

All occurrences of overdose must be reported as SAEs (see Section 1.1.1 for reporting details).

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 6.1.1 for reporting details.).

1.6 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 1.1.1. for reporting details).

Potential drug induced liver injury is defined as

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

AND

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

AND

3. 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.

1.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

Study Visits:

- **Screening visit**
  - Informed consent obtained in writing
  - Standard measurements (blood pressure, heart rate, height, weight, waist circumference, body composition)
  - Physical exam and medical history
  - 24h food recall
  - Fasting safety labs (CBC, metabolic panel, transaminases, lipid panel, lipase, TSH, A1c)
  - Urine pregnancy test for premenopausal women

- **Week 0—Enrollment and randomization visit**
  - **Start exenatide or placebo at 5 mcg twice daily dose**
  - Standard measurements
  - Dietary counseling
  - Visual analog scales (VAS) to measure nausea, satiety, hunger
  - 24h food recall
  - Resting energy expenditure using indirect calorimetry
  - Fasting leptin, soluble leptin receptor, insulin, cortisol, adiponectin, CRP, FGF21 (draw before meal test)
  - Mixed meal test with serial measurements of postprandial insulin, and triglyceride levels
  - Measurement of thermic effect of food (TEF) in subset of subjects
  - Distribute Actical physical activity monitor to subjects if device is available
  - Urine pregnancy test for premenopausal women

- **Week 2—Titration visit**
  - Titrate dose of exenatide or placebo to 10mcg twice daily
  - Standard measurements
  - Dietary counseling
  - VAS to measure nausea, satiety, hunger
  - 24-hr food recall
  - Assessment of symptoms, adverse events, and diet/medication compliance
  - Urine pregnancy test for premenopausal women

- **Weeks 4 & 8—Follow-up visits**
  - Standard measurements
  - Dietary counseling
  - VAS for nausea, satiety, hunger
  - 24-hr food recall
  - Assessment of symptoms, adverse events, and diet/medication compliance
  - If subject has attained 5% or 10% weight loss, follow “5% or 10% weight loss procedures”
  - Urine pregnancy test for premenopausal women

- **Week 12—Exenatide and placebo nonresponders (<5% weight loss) discontinue participation**
  - Fasting safety labs for all subjects (CBC, metabolic panel, transaminases, lipid panel, lipase)
  - Fasting leptin, soluble leptin receptor, insulin, cortisol, adiponectin, CRP, FGF21 levels
  - Standard measurements

- Physical exam
- Dietary Counseling
- VAS for nausea, satiety, hunger
- 24-hr food recall
- Assessment of symptoms, adverse events, and diet/medication compliance
- Resting energy expenditure
- Mixed meal test
- Thermic effect of food (TEF) in a subset of subjects
- Physical activity monitoring with Actical monitor if device is available
- Urine pregnancy test for premenopausal women

- **Weeks 16 and 20 — Follow-up visits**
  - Standard measurements
  - Dietary counseling
  - VAS for nausea, satiety, hunger
  - 24-hr food recall
  - Assessment of symptoms, adverse events, and diet/medication compliance
  - If subject has attained 10%, 15%, or > 15% weight loss in a 5% increment, follow 10% weight loss procedures"
  - Urine pregnancy test for premenopausal women

- **Week 24 — Follow-up visit with safety labs; discontinue <10% weight loss on placebo**
  - Fasting safety labs (CBC, metabolic panel, transaminases, lipid panel, lipase)
  - Fasting leptin, soluble leptin receptor, insulin, cortisol, adiponectin, CRP, FGF21 levels
  - Physical exam
  - Standard measurements
  - Dietary counseling
  - VAS for nausea, satiety, hunger
  - 24-hr food recall
  - Assessment of symptoms, adverse events, and diet/medication compliance
  - Resting energy expenditure
  - Mixed meal test
  - Thermic effect of food (TEF) in subset of subjects
  - Subjects who have not lost 10% body weight on placebo treatment discontinue participation at 24 weeks
  - Physical activity monitoring in subjects continuing participation if device is available
  - Urine pregnancy test for premenopausal women

- **Weeks 28, 32, 36, 40, 44, 48 — Followup visits**
  - Standard measurements
  - Dietary counseling
  - VAS for nausea, satiety, hunger
  - 24-hr food recall
  - Assessment of symptoms, adverse events, and diet/medication compliance
  - If subject has attained 10%, 15%, or > 15% weight loss in a 5% increment, follow 10% weight loss procedures"
  - Urine pregnancy test for premenopausal women

- **Week — 52 Final Treatment visit**
  - **Discontinue exenatide treatment or placebo intervention**
  - Fasting safety labs (CBC, metabolic panel, transaminases, lipid panel, lipase)
  - Fasting leptin, soluble leptin receptor, insulin, cortisol, adiponectin, CRP, FGF21 levels
  - Physical exam
  - Standard measurements
  - VAS for nausea, satiety, hunger
  - 24-hr food recall
  - Assessment of symptoms, adverse events, and diet/medication compliance
  - Resting energy expenditure

  - Mixed meal test
  - Thermic effect of food (TEF) in subset of subjects
  - Urine pregnancy test for premenopausal women

- **1, 3, and 6 month follow-up visits**
  - Standard measurements

- **5% Weight Loss Procedures**
  - Fasting lipid panel
  - Fasting leptin, soluble leptin receptor, insulin, cortisol, adiponectin, CRP, FGF21 levels
  - Standard measurements
  - VAS for nausea, satiety, hunger
  - 24-hr food recall
  - Assessment of symptoms, adverse events, and diet/medication compliance
  - Resting energy expenditure
  - Physical activity monitoring if device is available

- **10% Weight Loss Procedures**
  - Fasting lipid panel
  - Fasting leptin, soluble leptin receptor, insulin, cortisol, adiponectin, CRP, FGF21 levels
  - Standard measurements
  - VAS for nausea, satiety, hunger
  - 24-hr food recall
  - Assessment of symptoms, adverse events, and diet/medication compliance
  - Resting energy expenditure
  - Physical activity monitoring if device is available

- **15% Weight Loss Procedures**
  - Fasting lipid panel
  - Fasting leptin, soluble leptin receptor, insulin, cortisol, adiponectin, CRP, FGF21 levels
  - Standard measurements
  - VAS for nausea, satiety, hunger
  - 24-hr food recall
  - Assessment of symptoms, adverse events, and diet/medication compliance
  - Resting energy expenditure
  - Physical activity monitoring if device is available

- **15% % Weight Loss Procedures (20%, 25%, 30% etc)**
  - Fasting lipid panel
  - Fasting leptin, soluble leptin receptor, insulin, cortisol, adiponectin, CRP, FGF21 levels
  - Standard measurements
  - VAS for nausea, satiety, hunger
  - 24-hr food recall
  - Assessment of symptoms, adverse events, and diet/medication compliance
  - Resting energy expenditure
  - Physical activity monitoring if device is available
- **Substudy Procedures**
  - Overnight fast
  - Urine pregnancy test if applicable
  - Standard measurements
  - Measurement of baseline resting energy expenditure
  - Administration of a single dose of morphine, 0.05mg/kg
  - Oral ingestion of Boost (mixed meal)
  - Measurement of TEF hourly for 4 hours with indirect calorimetry
  - Vital signs every 30 minutes following administration of morphine and prior to discharge from CRC

The 5%, 10%, 15%, and > 15% weight loss procedures will not occur within 2 weeks of starting the treatment, as acute weight loss within this time frame is likely due to fluid shifts rather than fat loss.

Explanations of measurements and assessments:

Labs for exenatide and diet interventions: The placebo of this study allows us to compare metabolic changes that occur with exenatide versus diet-induced weight loss. We are particularly interested in the 5% and 10% weight loss timepoints and will measure metabolic parameters when that degree of weight loss is achieved. However, the 5%, 10%, 15%, and > 15% weight loss metabolic visits will not be scheduled within 2 weeks of starting the treatment, as acute weight loss within this time frame is likely due to fluid shifts rather than fat loss.

Bioelectrical impedance: Bioelectric impedance analysis (BIA) measures the opposition of bodily tissues to the flow of a mild (less than one milliAmp) alternating electric current (Gudivaka et al., 1999). Impedance is a function of two components (vectors): the resistance of the tissues themselves and the additional opposition (reactance) due to the capacitant effect of membranes, tissue interfaces, and nonionic tissues. Electrodes are typically placed on a wrist and an ankle and change in voltage between electrodes is measured. RJL system Quantum II Bioelectrical Body Composition Analyzer Testing using Cyprus software will be used in this study. The subject is generally tested using the right arm and foot. She will be in a supine position with arms 30 degrees from the body and legs not touching. The testing time takes less than 2 minutes and results are immediately available from software program. Resistance and reactance are used to calculate % body fat (Kotler et al., 1996).

Visual Analog Scales: Visual analogue scales are used to measure subjective satiety and hunger (Cornier et al., 1994). Satiety will be defined as the sensation of fullness after eating so that a person does not feel the need to eat for some time afterward. Hunger will be defined as the subjective driving force for the search for, choice of, and ingestion of food. Subjects will be instructed to make a single vertical mark on a horizontal 10-cm bar to indicate their current feelings, ranging between "not hungry at all" and "really hungry", between "empty" and "full" and between “not at all nauseated” and “extremely nauseated.” Subjects will complete the VAS the day prior to the study visit, once in the morning in the fasted state and a second time 2 hours after eating their evening meal. The visual analog packet will also include questions about eating habits, including overeating and binge eating. The entire packet will take less than 5 minutes to complete.

Resting energy expenditure: Indirect calorimetry calculates heat production by measuring gas exchange. During resting conditions, food sources are broken down to produce energy (heat or KCALS). The oxygen consumed and the carbon dioxide produced are measured to provide an indirect assessment of caloric expenditure. Resting energy expenditure (REE) provides the total energy expenditure in 24 hours and is calculated from the gas exchange data (VO2, VCO2) collected by the Vmax. When obtaining a subject’s REE, the subject reaches a steady state condition, which is defined as five consecutive minutes in which the VO2 and VE are within 10% and the RQ (respiratory quotient) is within 5%. Subjects in the fasted state will lay face up on an examination bed for approximately 20-30 minutes with a mask over the nose and mouth while measurements of gas exchange are taken. The use of indirect calorimetry to measure REE has been used as a measure of energy expenditure in clinical studies with obese subjects (Perseghin, 2001; Smith et al., 2005).

Mixed meal test: After an overnight fast, subjects will consume a standardized liquid test meal containing 35% of their calculated 24-hour energy requirements distributed as 40% of total calories from fat, 40% from carbohydrate, and 20% from protein. After the meal, serum insulin and triglyceride levels will be measured.

Physical activity monitoring with actigraph watches: If the device is available, subjects will be given actigraph monitors at week 0 to measure baseline physical activity levels. The will allow us to compare and control for baseline physical activity level differences between the placebo and exenatide groups. Subjects will be asked to wear the monitors again at week 12, at week 24, and after achieving 5%, 10%, 15%, and > 15% weight loss.

Thermic effect of food: Immediately after the mixed meal is consumed, subjects will remain supine for 4 hours while energy expenditure is measured using indirect calorimetry. Resting energy expenditure will be measured for 15-20 minutes every hour for four hours in a subset of subjects. Blood will be drawn between these REE measurements.

Laboratory studies:

- Analysis of the CBC, standard chemistries, lipid panel, transaminases (AST and ALT), lipase, TSH, and hemoglobin A1c will be performed at LabCorp.

- Analysis of leptin, insulin, cortisol, adiponectin, and CRP will be performed at the Harvard Catalyst Core Laboratory (HCCL). CRP may be analyzed at LabCorp as well.
- Analysis of soluble leptin receptor and FGF21 will be performed in the laboratory of Dr. Maratos-Flier using commercially available ELISA kits.
- Blood will also be banked at enrollment (week 0), week 12, week 24, week 52, 5% weight loss, 10% weight loss, 15% weight loss, and > 15% weight loss in 5% increments for future measurement of incretin levels or other proteins or hormones involved in metabolism. The banked blood may be analyzed in the HCCL, the laboratory of Dr. Maratos-Flier, or in collaboration with other researchers.

B. Statistical Considerations

Statistical methods:

For the first objective of this study, we will examine the patterns of weight loss (termed "trajectories") for the subjects with robust weight loss in the exenatide group (A), and also those in diet-induced weight loss group (B). We expect to see that in group A, the trajectory of weight loss for the majority of subjects will be consisted of 2 linear segments (T1). The first segment starting at week 12 will have a steeper negative slope (rate of weight loss decrease) than that of the second linear segment, which would have a less steep slope and plateau out toward week 52. However, individual subjects are expected to follow different trajectories. For example, some may have a constant gradual negative slope from week 12 to week 52 (one single linear segment), some may have three segments (plateau at first, then decrease, then plateau), and some may have no change at all after week 12 (one single plateau). The trajectory analysis will allow us to first assess the number of possible trajectories, and second, the shapes of the trajectories of weight loss. We are most interested in trajectory T1 which would allow us to estimate not just the rate of change over time for each of the two linear segments, but also the duration of time for each of the two segments.

To estimate the number and shape of the weight loss trajectories, we will use a mixture modeling technique of the longitudinal data of monthly weights for each subject. We will first plot the data for each subject over time. The graphs will allow us to have some understanding of the shape of the observed trajectories, and how the curves cluster. We will assume that the number of clusters ranges from one to six, but we expect the optimal estimate of the number of clusters is three or four, as described above, with the largest cluster consisting of trajectory of shape T1. The marginal density of a subject having weight measurement at a particular time point is modeled as a function of the product of two densities: the probability of the weight measurement belonging to a particular group, and the probability of observing such a measurement conditioning on the particular group. The first probability is modeled using a generalized logit model since the outcome is categorical (from 1 to 6 categories/types of trajectories), and the second probability is a polynomial linear regression of the weight measurement as a function of time (linear, quadratic, cubic). To select the optimal number of trajectories, we will compare the Bayesian Information Criteria (BIC) value from the six models (corresponding to 1 to 6 types of trajectories). The algorithm and the SAS macro for this type of modeling has been published (Jones 2007). We will repeat the modeling technique above for group B in order to assess the number and shapes of the trajectories in this group.

For aim 2, we will first create a binary outcome variable. The outcome is 1 if the weight loss difference between 12-week and 52-week is at least 1 kg; otherwise, it is 0. We will perform multivariable logistic regression to assess the association between metabolic parameters and this outcome. We consider the association to be statistically significant if the p-value is less than 0.05, and the overall model c-statistic is above 0.8. Once these metabolic parameters have been identified and quantified, we will also use the result from the trajectory analysis (aim 1) to assess the distribution of the metabolic parameters across different trajectories. We will model the likelihood of falling into a particular trajectory as a function of metabolic parameters (i.e. the change in a particular metabolic parameter may affect a certain trajectory but not all trajectories of weight loss).

We will repeat these models for the subjects in group B. The difference in the estimates of the model coefficients between the two groups (A and B) implies the potential effect of exenatide.

Expected attrition rate:

We expect a 20-25% attrition rate based on the literature and our experience with our initial study. We plan to enroll an additional 50 subjects to account for this expected attrition rate.

Sample size calculation:

Based on published literature describing weight loss with exenatide treatment among individuals with type 2 diabetes, we hypothesize that responders will stratify into a plateau group and a continued weight loss group by 52 weeks of treatment. The sample size is based on the difference between two differences of weight. The first difference is the weight difference between week 12 and week 52 for the exenatide group (group A), and the second difference is the difference between week 12 and week 52 for the diet-induced group (group B). The difference in weight loss between these two groups is hypothesized to be 1 kg (i.e. the exenatide group between week 12 and 52 loses on the average 1 kg more than group B). The common standard deviation of the distribution of the weight loss difference is 1.2 kg. We plan to enroll 150 subjects in group A and 36 in group B. Given an expected dropout rate of 25% from the screening visit, we will screen 200 for group A, and 50 for group B. At 12 weeks, we expect that 30% of group A will be high responders (50 subjects). At 52 weeks, we expect the dropout rate to be 25% for group A and 50% for group B. Thus we will have 38 subjects left for group A, and 18 for group B for final data analysis. Given this sample size, we will still have a power of 0.83 to detect the difference of 1kg.

Data Analysis:

We consulted with Dr. Long Ngo through the Harvard Catalyst statistical consultation service for assistance with study design and sample size calculations. A project statistician will assist with statistical analyses.

Delayed Gastric Emptying Substudy
Preliminary data from our main study includes 41 individuals randomized to exenatide and 9 randomized to placebo. There is no difference in resting energy expenditure between exenatide and placebo-treated subjects. However, there are significant differences in TEF at 1 hour ($p< 0.009$), 2 hours ($p < 0.03$) and 4 hours ($p < 0.04$) postprandially. According to these data, we expect to observe a detectable difference in total TEF of about 674 kcal (SD 570 kcal) before and after treatment with morphine. A sample size of 12 individuals will have 80% power to detect this difference at a significance level of 5%. Student's t-test will be used to determine if morphine significantly suppresses TEF compared to baseline and compared to exenatide treatment.

Data management:

Data at each study visit will be collected by one of the investigators. Each subject will have her own binder with a numeric code and no other identifying information. The binder will contain data from all study visits. At each visit, the numeric code will be crosschecked with the name of the patient using a password secured list maintained on the hospital server. Whenever possible, data will be automatically recorded and filed in computer files from assays or automated equipment and entered into an access database by one of the study investigators. When this is not possible, data will be transcribed from laboratory printouts and entered into an access database. All subjects' binders will be stored in a locked file cabinet to which only the investigators have access. All electronic study data will be stored on a desktop and laptop computer used solely for this study.

C. Subject Selection

We expect that the racial distribution of subjects will reflect the diversity of the greater Boston population, which is 54% White, 25% Black, 14% Hispanic, and 7% Asian.

Inclusion/Exclusion Criteria

Inclusion Criteria
1. Females age 18-70
2. BMI 28-50 kg/m^2
3. Stable weight (< 3 kg weight gain or loss within 6 months of screening visit)
4. Ability to give informed consent and follow verbal and written instructions in English

Exclusion Criteria
1. Type 1 or type 2 diabetes mellitus diagnosed according to American Diabetes Association criteria
2. Unstable heart disease as evidenced by ongoing angina
3. Congestive heart failure
4. Uncontrolled hypertension (BP > 170/100 mmHg on or off antihypertensive medication)

5. Uncontrolled dyslipidemia (LDL > 200 or TG > 400 on or off lipid lowering medication)
6. cocaine, or intravenous drug use
7. Shift workers (night shift or alternating day/night shifts)
8. Gastroparesis
9. Inflammatory bowel disease
10. Malignancy treated with chemotherapy within the past 3 years
11. History of pancreatitis, with the exception of gallstone pancreatitis if the subject has had a cholycystectomy
12. diagnosis of psychosis
13. Renal insufficiency (eGFR < 50)
14. Transaminases > 2x above the normal range
15. Pregnancy within 6 months of the screening visit
16. Lactation
17. Failure to use medically approved contraceptive methods (monophasic oral contraception, intra uterine device, surgical sterilization or 2 combined barrier methods)
18. History of an eating disorder (anorexia, bulimia or laxative abuse) in past 5 years
19. Treatment with FDA-approved or over-the-counter weight loss medication within 6 months, with the exception of Xenical if there was no weight loss
20. History of gastric bypass surgery or gastric stapling
21. Biochemical evidence of hyper or hypothyroidism, 22. Previous treatment with exenatide
23. Discretion of the PI
24: Gastric emptying substudy: known hypersensitivity to morphine, chronic respiratory depression, acute asthma exacerbation, history of or current paralytic ileus, hypotension

Exclusionary Medications:

1. *Medications for gastrointestinal dysmotility or nausea*: The use of metoclopramide, marinol, prochlorperazine, and promethazine will not be permitted.
2. *Medications for weight loss*: The use of antiobesity medications (orlistat), medications to achieve weight loss (amphetamines, phenteramine), and nonprescription herbal supplements for weight loss will not be permitted.
3. *Medications for malignancy*: The use of chemotherapeutic agents will not be permitted.
4. PPARalpha agonists (such as fenofibrate) and PPARgamma agonists (such as pioglitazone or rosiglitazone) will not be permitted.
5. Coumadin is not permitted.
6. *Gastric emptying substudy:* Ongoing opioid or proton pump inhibitor use

Subjects enrolled in the study will be asked about concomitant medications at every study visit.

B4. POSSIBLE BENEFITS

Subjects may or may not experience benefits from exenatide or a low-calorie diet, including weight loss, increased insulin sensitivity, and favorable changes in blood pressure, lipids, and inflammatory markers. Participation in this research study may provide important new information regarding the effects of exenatide and diet-induced weight loss on obese patients without diabetes.

B5. POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO

Subjects will be extensively screened prior to being invited to participate in this study. A physical exam performed by a physician will be done at the screening visit, week 12, week 24, and week 52. Vital signs (heart rate, blood pressure, and oxygen saturation using pulse oximetry) will be done at every study visit. Laboratory tests will be drawn at baseline, week 12, week 24, and week 52. Subjects will have a urine pregnancy test at every visit. If the results of any of the laboratory tests are abnormal at the screening visit, the subject will be notified and she will be encouraged to follow up with her primary care physician.

Risks of exenatide treatment

Common side effects of exenatide (these occur in more than 5 out of 100 people): Nausea, vomiting, diarrhea, feeling jittery, dizziness, headache, dyspepsia (heartburn). Forty four percent of people (44 people out of 100) who have taken this medication in research studies have had mild to moderate nausea, 13 percent have had vomiting or diarrhea, and about 10 percent have felt jittery, dizzy or had a headache. Six percent of people have had heartburn while taking this medication. The nausea and vomiting is usually not severe and tends to go away over time.

Less common side effects of exenatide: Fewer than 5 in 100 people who have taken this medication have had skin irritation at the site where the medication is injected or have had bloating, belly pain, belching, constipation, a change in the sense of taste, flatulence (passing gas), or feeling sleepy.

Rare side effects of exenatide: Fewer than 1 in 10,000 people who have taken this medication have had an allergic reaction that may include itching, swelling or difficulty breathing.

In addition, the following rare adverse effects have been associated with use of exenatide among individuals with type 2 diabetes (taken from the Byetta® package insert, revised 10/09):

5 WARNINGS AND PRECAUTIONS

5.1 Acute Pancreatitis

Based on postmarketing data BYETTA has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. After initiation of BYETTA, and after dose increases, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting). If pancreatitis is suspected, BYETTA should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, BYETTA should not be restarted. Consider antidiabetic therapies other than BYETTA in patients with a history of pancreatitis.

5.3 Renal Impairment

BYETTA should not be used in patients with severe renal impairment (creatinine clearance < 30 mL/min) or end-stage renal disease and should be used with caution in patients with renal transplantation *[see Use in Specific Populations (8.6)]*. In patients with end-stage renal disease receiving dialysis, single doses of BYETTA 5 mcg were not well-tolerated due to gastrointestinal side effects. Because BYETTA may induce nausea and vomiting with transient hypovolemia, treatment may worsen renal function. Caution should be applied when initiating or escalating doses of BYETTA from 5 mcg to 10 mcg in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min).

There have been postmarketing reports of altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, sometimes requiring hemodialysis or kidney transplantation. Some of these events occurred in patients

receiving one or more pharmacologic agents known to affect renal function or hydration status, such as angiotensin converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, or diuretics. Some events occurred in patients who had been experiencing nausea, vomiting, or diarrhea, with or without dehydration. Reversibility of altered renal function has been observed in many cases with supportive treatment and discontinuation of potentially causative agents, including BYETTA. Exenatide has not been found to be directly nephrotoxic in preclinical or clinical studies.

We will not enroll subjects who have a GFR less than 50 ml/min.

5.4 Gastrointestinal Disease

BYETTA has not been studied in patients with severe gastrointestinal disease, including gastroparesis. Because BYETTA is commonly associated with gastrointestinal adverse reactions, including nausea, vomiting, and diarrhea, the use of BYETTA is not recommended in patients with severe gastrointestinal disease.

5.5 Immunogenicity

Patients may develop antibodies to exenatide following treatment with BYETTA, consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals. In a small proportion of patients, the formation of antibodies to exenatide at high titers could result in failure to achieve adequate improvement in glycemic control. If there is worsening glycemic control or failure to achieve targeted glycemic control, alternative antidiabetic therapy should be considered *[see Adverse Reactions (6.1)]*.

5.6 Hypersensitivity

There have been postmarketing reports of serious hypersensitivity reactions (e.g. anaphylaxis and angioedema) in patients treated with BYETTA. If a hypersensitivity reaction occurs, the patient should discontinue BYETTA and other suspect medications and promptly seek medical advice *[see Adverse Reactions (6.2)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Monotherapy

For the 24-week placebo-controlled study of BYETTA used as a monotherapy, Table 2 summarizes adverse reactions (excluding hypoglycemia) occurring with an incidence ≥2% and occurring more frequently in BYETTA-treated patients compared with placebo-treated patients.

Table 2: Treatment-Emergent Adverse Reactions ≥2% Incidence With BYETTA Used as Monotherapy (Excluding Hypoglycemia)*

Monotherapy	Placebo BID N = 77 %	All BYETTA BID N = 155 %
Nausea	0	8
Vomiting	0	4
Dyspepsia	0	3

* In a 24-week placebo-controlled trial.
BID = twice daily.

Adverse reactions reported in ≥1.0 to <2.0% of patients receiving BYETTA and reported more frequently than with placebo included decreased appetite, diarrhea, and dizziness. The most frequently reported adverse reaction associated with BYETTA, nausea, occurred in a dose-dependent fashion.

Two of the 155 patients treated with BYETTA withdrew due to adverse reactions of headache and nausea. No placebo-treated patients withdrew due to adverse reactions.

There is limited data on the use of exenatide among people without diabetes. There does not appear to be additional risk in this population but there may be other side effects in patients with normal or impaired glucose homeostasis that we cannot predict.

Risks of single dose low-dose morphine:

Common: Sedation, lightheadedness, dizziness, nausea, vomiting, constipation, and diaphoresis. These may be more prominent in ambulatory patients and in those who are not experiencing severe pain.

Central Nervous System – Euphoria, dysphoria, weakness, headache, agitation, tremor, uncoordinated muscle movements, visual disturbances, transient hallucinations and disorientation.

Gastrointestinal – Constipation, biliary tract spasm.

Cardiovascular – Tachycardia, bradycardia, palpitation, faintness, syncope, and orthostatic hypotension.

Genitourinary – Oliguria and urinary retention; an antidiuretic effect has been reported.

Allergic – Pruritus, urticaria, and skin rashes. Anaphylactoid reactions have been reported following intravenous administration.

Other – Opiate-induced histamine release may be responsible for the flushing of the face, diaphoresis, and pruritus often seen with these drugs. Wheals and urticaria at the site of injection may occur. Morphine may alter temperature regulation in susceptible individuals and will depress the cough reflex.

Less common: Respiratory depression, anaphylaxis

Reproductive Parameters: There are no adequate and well-controlled studies in pregnant women, and as such, women who are pregnant may not participate in this study. Women of childbearing potential must employ adequate and medically approved birth control measures for one month prior to being enrolled in the study, during the entire time that the study drug is being taken, and for three months post-study drug administration. If a patient becomes pregnant during study drug therapy, or if a pregnancy is suspected, the study drug must be discontinued immediately and the patient withdrawn from the study. A urine pregnancy test will be done at the screening visit for all subjects. A urine pregnancy test will be collected at every study visit.

Psychological Parameters: Subjects may become distressed or feel as though their privacy is threatened when they

are asked to perform food recalls and complete visual analog scales for nausea, satiety, and hunger. Subjects will be reassured that the information they report will be kept strictly confidential and will be permitted to decline completing questionnaires.

Blood drawing: The risks and discomforts of phlebotomy from a superficial vein include the possibility of pain or bruising at the site of the blood draw; occasional feeling of lightheadedness; and rarely, infection at the site of the blood draw. The risk of infection from phlebotomy will be minimized by using standard, sterile techniques.

Dietary counseling: All subjects will have an individualized diet formulated by CRC bionutritionists. Subjects on exenatide will receive general nutritional counseling. Subjects on placebo will be instructed to follow a reduced calorie diet. The diet will have balanced macronutrient content and will aim to reduce calories by 500-1000 cal/day. Meal replacements and/or commercially available meals may be used. This intervention should not pose any significant risk to subjects.

Side effects of placebo: Subjects may experience skin irritation at the site where the medication is injected.

B6. RECRUITMENT AND CONSENT PROCEDURES

We will advertise the study as a weight loss study using print media (local and university newspapers), internet (Clinicaltrials.gov, Craigslist, TrialX), radio advertising, brochures, and flyers placed widely in the Harvard Medical Area and in Boston (attached). We will not enroll Harvard Medical students or women who work directly for any of the study investigators. Participants may, however, be Beth Israel Deaconess Medical Center employees.

Initial telephone screening will be done by one of the study investigators. No telephone messages will be left on answering machines. If the subject states that she is not interested in participating after expressing an initial interest, she will not be contacted again. Once patients have passed the initial telephone screen (confirmation of age, weight, height, baseline medications, brief medical and social history), a screening visit with one of the study investigators will be scheduled. The Investigator will fully explain the purpose of this study to the subject prior to entering her in the study. The Investigator will be responsible for obtaining written informed consent from each subject at the beginning of the screening visit. Only individuals who are able to provide written informed consent will be enrolled in the study. The subject will be given a copy of the informed consent form.

B7. STUDY LOCATION

This is a single-center study that will be conducted only at the Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, MA 02215. All visits will take place in the General Clinical Research Center. Telephone screening will be done in the offices of one of the study investigators using standard procedures for privacy.

B8. DATA SECURITY

Data at each study visit will be collected by one of the investigators. Each subject will have his or her own binder with a numeric code and no other identifying information. The binder will contain data from all study visits. At each visit the numeric code will be crosschecked with the name of the patient using a password secured list maintained on the hospital server. Laboratory data without patient identifying information will be placed in the patient binder by one of the investigators. When possible, data will be automatically recorded and filed in computer files from assays or automated equipment and entered into an access database by one of the study investigators. When this is not possible, data will be transcribed from laboratory printouts and entered into an access database. All subjects' binders will be stored in a locked filing cabinet to which only the investigators have access. All electronic study data will be stored on a secure desktop computer to which only study investigators will have access.

B9 Multi-Site Studies

Is the BIDMC the coordinating site or is the BIDMC PI the lead investigator of the multi-site study?
☐ Yes ☒ No

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