1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Study to Assess the Efficacy and Safety of PF-08653944 in Female Participants with Urinary Incontinence and with Obesity or Overweight (VESPER-UI)

Protocol Brief Title: A Study of PF-08653944 in Women with Urine Leakage and with Obesity or Overweight (VESPER-UI)

Regulatory Agency Identification Number(s):

US IND Number:	181430
EU Clinical Trial (CT) Number:	TBD
ClinicalTrials.gov ID:	TBD
Pediatric Investigational Plan Number:	TBD
Protocol Number:	C6491036
Phase:	3

Rationale:

Glucagon-like peptide 1 receptor agonists (GLP-1 RA) are an established therapeutic mechanism for weight management in patients with obesity or overweight. Overweight and obesity are important and modifiable risk factors for urinary incontinence (UI) due to increased intra-abdominal pressure and weakened pelvic floor muscle. A weight loss of 5% to 10% shows comparable efficacy to surgical treatment and can significantly reduce, or even resolve, incontinence episodes. Existing evidence suggests that GLP-1 RA treatment may benefit patients with UI. PF-08653944 is a GLP-1 RA that is being developed for chronic weight management and multiple weight related comorbidities.

The purpose of the VESPER-UI Phase 3 study is to investigate the efficacy and safety of once monthly (QM) dosing of PF-08653944 in women with UI and with obesity or overweight.

Objectives and Endpoints:

The primary endpoints and all key secondary endpoints will be evaluated using the on-study estimands and on-treatment estimands. The on-study estimand is the difference between PF-08653944 maximum tolerated dose (MTD) and placebo in female participants with UI and overweight/obesity regardless of treatment discontinuation, weight reduction procedures, or initiation of prohibited weight management medications or UI therapy, exercise, or surgery. The on-study estimand is the primary analysis, where all data collected after such events are included. The on-treatment estimand will also be used as a supplementary estimand, which estimates the difference between PF-08653944 MTD and placebo in female participants with UI and overweight/obesity had they remained on randomized treatment for 52 weeks without weight reduction procedures or initiation of prohibited weight management

medications or UI therapy, exercise, or surgery, where all data collected after such events are set to missing.

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary**
• To demonstrate the superiority of PF-08653944 maximum tolerated dose (MTD) once-monthly (QM) compared to placebo in urinary incontinence (UI)	• Change from Baseline (CFB) at Week 52 in incontinence episodes frequency (IEF) per week as measured with a 3-day voiding electronic diary (e-diary)	• Population-level summary: The difference in mean percent CFB at Week 52 in IEF per week between PF-08653944 and placebo • On-study estimand (primary) • On-treatment estimand (supplementary)
Key Secondary:	**Key Secondary:**	**Key Secondary**
• To demonstrate the superiority of PF-08653944 MTD QM versus placebo in anthropometric parameters	• Body weight percent CFB at Week 52	• Population-level summary: The difference in mean body weight percent CFB at Week 52 between PF-08653944 and placebo • On-study estimand (primary) • On-treatment estimand (supplementary)
• To demonstrate the superiority of PF-08653944 MTD QM versus placebo in stress and urgency UI	• CFB at Week 52 in stress-only IEF per week as measured by 3-day voiding electronic diary (e-diary) • CFB at Week 52 in urgency-only IEF per week as measured by 3-day voiding e-diary	• Population-level summary: The difference in mean percent CFB at Week 52 in stress and urgency IEF per week between PF-08653944 and placebo • On-study estimand (primary) • On-treatment estimand (supplementary)
• To demonstrate the superiority of PF-08653944 MTD QM versus placebo in UI-related quality of life (QoL)	• CFB at Week 52 in Incontinence Quality of Life Questionnaire (I-QoL) subscales: o Avoidance and limiting behavior o Social embarrassment	• Population-level summary: The difference in mean I-QoL CFB at Week 52 between PF-08653944 and placebo • On-study estimand (primary) • On-treatment estimand (supplementary)
Other Secondary:	**Other Secondary:**	**Other Secondary:**
• To compare changes in UI signs of PF-08653944 MTD QM versus placebo	• CFB at Week 52 in number of continence pads used per week	• Population-level summary: The difference in mean number of continence pads used per week CFB at Week 52 between PF-08653944 and placebo • On-study estimand (primary) • On-treatment estimand (supplementary)

• To compare changes in UI-related QoL of PF-08653944 MTD QM versus placebo	• CFB at Week 52 in I-QoL: o Total score o Psychosocial impact	• Not applicable
• To compare the efficacy of PF-08653944 MTD QM versus placebo on lipids	• CFB at Week 52 in fasting lipids (mg/dL) o Total cholesterol o High-density lipoprotein cholesterol (HDL-C) o Low-density lipoprotein cholesterol (LDL-C) o Non-HDL-C o Very low-density lipoprotein cholesterol (VLDL-C)	• Not applicable
• To compare changes in participant reported urinary incontinence symptoms and impact between PF-08653944 MTD QM and placebo	• CFB at Week 52 in: o International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-UI-SF) score o Urinary Incontinence Impact Questionnaire Short Form (IIQ-7) score o Urogenital Distress Inventory, Short Form (UDI-6) score	• Not applicable
• To compare changes in other patient reported outcomes of PF-08653944 MTD QM versus placebo	• CFB at Week 52 in: o % of participants with a categorical improvement in Patient Global Impression of Severity (PGI-S) for UI o % of participants with a categorical improvement in Patient Global Impression of Change (PGI-C) for UI	• Not applicable
• To compare changes in additional parameters between PF-08653944 MTD QM versus placebo	• CFB at Week 52 in: o Body weight (kg) o BMI (kg/m^2) o Waist circumference (cm)	• Not applicable
• To compare changes in patient-reported QoL of PF-08653944 MTD QM versus placebo	• CFB at Week 52 in score of all domains and component summaries of Short Form 36-Item (SF-36) acute questionnaire	• Not applicable
• To compare changes in EuroQol 5-Dimension 5-Level (EQ5D-5L) for PF-08653944 MTD QM versus placebo	• CFB at Week 52 in EQ-5D-5L score	• Not applicable
• To compare the safety and tolerability of PF-08653944 MTD QM versus placebo	• Presence/absence of: o Treatment-Emergent Adverse Event (TEAE) o Serious Adverse Event (SAE)	• Not applicable

	○ AE leading to permanent discontinuation from study intervention or study ○ Adverse Events of Special Interest (AESI) ○ Clinical laboratory abnormalities	
Exploratory	**Exploratory:**	**Exploratory:**
• To assess the effect of PF-08653944 MTD QM on inflammation	• CFB at Week 52 in: ○ High-sensitivity C-reactive protein (hsCRP) ○ Interleukin 6 (IL-6) ○ Interleukin 1 beta (IL-1β)	• Not applicable
• To assess the pharmacokinetics (PK) of PF-08653944	• PF-08653944 plasma concentrations	• Not applicable
• To assess the immunogenicity of PF-08653944	• Incidence of anti-drug antibodies (ADAs), and neutralizing antibodies (NAbs), if applicable	• Not applicable

Overall Design:

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of PF-08653944 in female adults who have a body mass index (BMI) ≥27 kg/m^2 with UI.

The study consists of the following:

- Up to 4 weeks of screening, 52 weeks of treatment, and 7 weeks of follow-up.

Approximately 780 eligible participants will be randomized in a 2:1 ratio to receive the maximum tolerated dose (MTD) of PF-08653944 or placebo. If all eligibility criteria are met, participants will initiate study intervention after randomization and will be dose escalated over 20 weeks for QM dosing to reach 9.6 mg QM (or MTD) and will be maintained at this MTD for the remaining duration of the 52-week treatment period. Participant follow-up through Week 59 will provide a total of 11 weeks of follow-up after the last study drug dose administration at Week 48, corresponding to 7 weeks after the End of Treatment (EOT) visit at Week 52.

All participants will be counseled to follow a hypocaloric diet based on baseline body weight and will receive initial lifestyle counseling, including promotion of increased physical activity. Diet/exercise/lifestyle counseling will be reinforced throughout the study.

Dose escalation for PF-08653944 will follow a predefined scheme to reach the target dose level of 9.6 mg QM or MTD.

A program-level External Data Monitoring Committee (E-DMC) will review unblinded data from all ongoing Phase 3 studies to evaluate the safety of participants and the overall benefit:risk profile for the duration of the studies. In addition, an independent external Adjudication Committee blinded to treatment assignment, will adjudicate prespecified events.

Number of Participants:

Approximately 780 participants will be enrolled in the study.

Note: "Enrolled" means a participant's agreement to participate in this clinical study following completion of the informed consent process and randomization to study intervention.

Study Population:

Inclusion Criteria:

Participants are eligible to be included in this study only if all the following criteria apply **at Screening**:

Age and Sex

1. ≥18 years of age (or the minimum age requirement for provision of consent in a participating country).

   Refer to Protocol (Appendix 4) for reproductive criteria for female participants.

2. Female sex assigned at birth.

Disease Characteristics

3. Have BMI ≥27 kg/m^2.

4. Urinary incontinence, for any type (ie, stress, urgency, or mixed), for at least 90 days.

Other Inclusion Criteria

5. At Screening (Visit 1) and in the investigator's opinion, participants are well-motivated, capable, and willing to follow study procedures for the duration of the study.

Exclusion Criteria:

Participants are excluded from the study if any of the following criteria apply:

Obesity-Related

1. A self-reported body weight change ([increase or decrease] greater than 5%) within 90 days prior to Screening.

2. Have obesity induced by other endocrinologic disorders (eg, Cushing's syndrome) or diagnosed monogenetic or syndromic forms of obesity (eg, Melanocortin 4 Receptor deficiency or Prader-Willi Syndrome).

3. Have a prior or planned surgical treatment for obesity (excluding liposuction or abdominoplasty if performed >1 year prior to Screening).

4. Have or plan to have endoscopic and/or device-based therapy for obesity or have had device removal within the last 6 months prior to Screening (for example, mucosal ablation, gastric artery embolization, intragastric balloon and duodenal-jejunal bypass sleeve).

Diabetes- and Endocrine-Related

5. Medical history of diabetes or laboratory assessments indicative of diabetes.

   - Diagnosis of any form of diabetes (resolved gestational diabetes is permitted)
   - HbA1c ≥6.5% (48 mmol/mol) at Screening
   - Fasting glucose ≥126 mg/dL (≥7 mmol/L) or random glucose ≥200 mg/dL (≥11.1 mmol/L) with classic symptoms of hyperglycemia at Screening

6. Thyroid-stimulating hormone (TSH) level <0.4 mIU/L or >6 mIU/L at the Screening visit.

   Note: participants receiving treatment for hypothyroidism may be included, provided their thyroid hormone replacement dose has been stable for at least 90 days and Screening TSH falls within the range indicated above.

7. Calcitonin level of ≥35 ng/L at Screening.

Gastrointestinal-Related

8. Currently known clinically significant gastric emptying abnormality (eg, severe gastroparesis or gastric outlet obstruction) or chronically take drugs that directly affect gastrointestinal (GI) motility.

9. History of acute or chronic pancreatitis. Participants with gallstone-associated pancreatitis who have undergone cholecystectomy are eligible for this trial.

10. Active/current symptomatic gallbladder disease.

Hepatic- and Renal-Related

11. Have significant hepatic dysfunction (eg, Child-Pugh Class C).

12. Estimated glomerular filtration rate (eGFR) (using Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] Scr-Scys Combined) <30 mL/min/1.73 m^2 at Screening.

Cardiovascular-Related

13. Have New York Heart Association (NYHA) Functional Classification IV heart failure.

14. Significant cardiovascular event within 90 days prior to randomization including but not limited to unstable angina, myocardial infarction, coronary artery bypass graft, percutaneous coronary artery re-vascularization, or hospitalization due to congestive heart failure.

15. Poorly controlled hypertension, defined as mean seated systolic blood pressure (BP) ≥180 mm Hg or mean seated diastolic BP ≥120 mm Hg (1 retest is permitted) at Screening visit.

16. Presence of clinically significant ECG abnormalities at the Screening visit or prior to dosing on Day 1, or any abnormalities that interfere with measurement of QT interval.

Hematologic- and Malignancy-Related

17. Personal or relevant family history (first degree relatives) of medullary thyroid carcinoma (MTC) or Multiple Endocrine Neoplasia Type 2 (MEN2).

18. History of neoplastic disease within the last 5 years prior to screening, with the exception of adequately treated basal or squamous cell skin cancer or carcinoma in situ of the cervix, or in situ prostate cancer.

Psychobehavioral

19. Have a history of significant active or unstable Major Depressive Disorder (MDD) or other severe psychiatric disorder (eg, schizophrenia, bipolar disorder, or other serious mood or anxiety disorder) within the last 2 years.

    Note: Participants with MDD or generalized anxiety disorder whose disease state is considered stable and expected to remain stable throughout the course of the study, in the opinion of the investigator, may be considered for inclusion if they are not on excluded medications.

20. Showing suicidal tendency as per the Columbia-Suicide Severity Rating Scale (C-SSRS) at Screening (Visit 1) or Baseline (Visit 2) visits (Applicable Version) or showing clinically significant depression as per the Patient Health Questionnaire 8 (PHQ-8) at Screening or Baseline visits as follows:

    - Suicidal ideation associated with actual intent and a method or plan in the past year: "Yes" answers on items 4 or 5 of the C-SSRS
    - Previous history of suicidal behaviors in the past 5 years: "Yes" answer to any of the suicidal behavior items of the C-SSRS
    - Any lifetime history of serious or recurrent suicidal behavior
    - Clinically significant depression: PHQ-8 total score ≥15

Urogenital Conditions

21. Severe pelvic prolapse, extending through the introitus, with self-reported difficulty in urination.

22. Active or chronic urinary tract infection (UTI) defined as >3 diagnosed UTIs within 12 months.

23. Neurologic (eg, stroke, spinal cord injury, multiple sclerosis) or functional (eg, physical, mental, environmental barriers) cause of UI.

Other Medical Conditions and Diagnostic Assessments

24. Consent to not initiate any new therapeutic treatment for UI or weight reduction for the duration of the study.

25. Have had a transplanted organ (corneal transplants [keratoplasty] allowed) or are awaiting an organ transplant.

26. Any medical or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

27. Any clinically significant illness or hospitalization in the 28 days prior to the first study intervention administration including acute infection (eg, influenza or Coronavirus Disease 2019 [COVID-19]).

Prior/Concomitant Therapy

28. Use of dietary weight loss supplements within 7 days or 5 half-lives (whichever is longer) of the first study drug administration.

29. Have taken within 90 days prior to randomization, medications (prescribed or over-the counter) intended to promote weight loss. Examples include but are not limited to:

    - Mounjaro®/Zepbound® (tirzepatide)
    - Ozempic®/Wegovy® (semaglutide)
    - Saxenda®/Victoza® (liraglutide)
    - Xenical®/Alli® (orlistat)
    - Meridia® (sibutramine)
    - Acutrim® (phenylpropanolamine)
    - Sanorex® (mazindol)
    - Adipex® (phentermine)
    - BELVIQ® (lorcaserin)
    - Qsymia® (phentermine/topiramate combination)
    - Contrave® (naltrexone/bupropion)

30. Chronic use of high dose systemically administered corticosteroids (>10 mg of prednisone or equivalent for more than a 14-day treatment course) within 90 days prior to Screening.

31. Change in dose, within 90 days prior to randomization, of any of the following medications that may cause significant weight gain, including but not limited to: tricyclic antidepressants, atypical antipsychotic, and mood stabilizers for example:

    - imipramine
    - amitriptyline
    - mirtazapine
    - paroxetine
    - phenelzine
    - chlorpromazine
    - thioridazine

- clozapine
- olanzapine
- zotepine (where approved)
- valproic acid and its derivatives
- lithium

32. Prior surgery for UI within 3 years (eg, midurethral sling surgery, retropubic suspension, urethral bulking) and/or prior surgery for obesity within 6 months.

33. Use of pelvic radiation that encompass the bladder, ovary, or uterine cervix within 6 months.

34. Are on a medication regimen of diuretics or sodium-glucose cotransporter 2 (SGLT2) inhibitors where dose and/or frequency has not been stable for at least 12 weeks prior to randomization, or is anticipated to significantly change during the course of the study.

35. Have received onabotulinumtoxin A (Botox®) in the past 6 months or are currently taking medications for UI.

36. Physical therapy to reduce urinary incontinence in the prior 6 weeks.

Prior/Concurrent Clinical Study Experience

37. Previous administration of an investigational product (drug or vaccine) within 30 days (or 5 half-lives, whichever is longer) preceding the first dose of study intervention used in this study. This exclusion is extended to 90 days (or 5 half-lives, whichever is longer) for studies investigating an IP intended to promote weight loss. Participation in studies of other investigational products (drug or vaccine) at any time during participation in this study.

38. Has participated in a clinical trial of PF-08653944 and received treatment, whether active or placebo.

Other Exclusion Criteria

39. Participants who are breastfeeding, pregnant, parturition in the past 12 months, planning to become pregnant in the following 12 months, or of childbearing potential and not using adequate contraception.

40. Hypersensitivity to drugs containing glucagon-like peptide-1 receptor agonists (GLP-1 RA) and its excipients.