PROTOCOL TITLE PAGE

Official Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of SkeetSteph, a Once-Weekly Subcutaneous GLP-1 Receptor Agonist, for Chronic Weight Management in Adults with Obesity
NCT Number:	[TBD - to be assigned upon ClinicalTrials.gov registration]
Document Date:	11-FEB-2026

Protocol Number: PROTO-SKST-OBE-001

Product Name: SkeetSteph (GLP-1 Receptor Agonist)

Protocol/Amendment Number: Protocol No.: 001-00 (Original)

CONFIDENTIALITY STATEMENT

SPONSOR: [Sponsor Name/Institution] (hereafter referred to as the Sponsor)

[Institution Address Line 1] [Institution Address Line 2] [City, State, ZIP]

Protocol-specific Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

TITLE:

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of SkeetSteph, a Once-Weekly Subcutaneous GLP-1 Receptor Agonist, for Chronic Weight Management in Adults with Obesity

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IND NUMBER: [TBD - to be assigned by FDA upon IND submission]

EudraCT NUMBER: [TBD - if applicable for international sites]

PROTO-SKST-OBE-001 | Version 1.0 Draft | 11-FEB-2026 Confidential

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312)
- International Council for Harmonisation (ICH) Guidelines including ICH E6(R2) Good Clinical Practice, ICH E9(R1) Statistical Principles for Clinical Trials, and ICH E10 Choice of Control Group and Related Issues in Clinical Trials
- Applicable local, state, and federal laws and regulations

All investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of this clinical trial have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent using a previously approved consent form.

The Principal Investigator will assure that no deviation from, or changes to, the protocol will take place without prior agreement from the IND sponsor and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants.

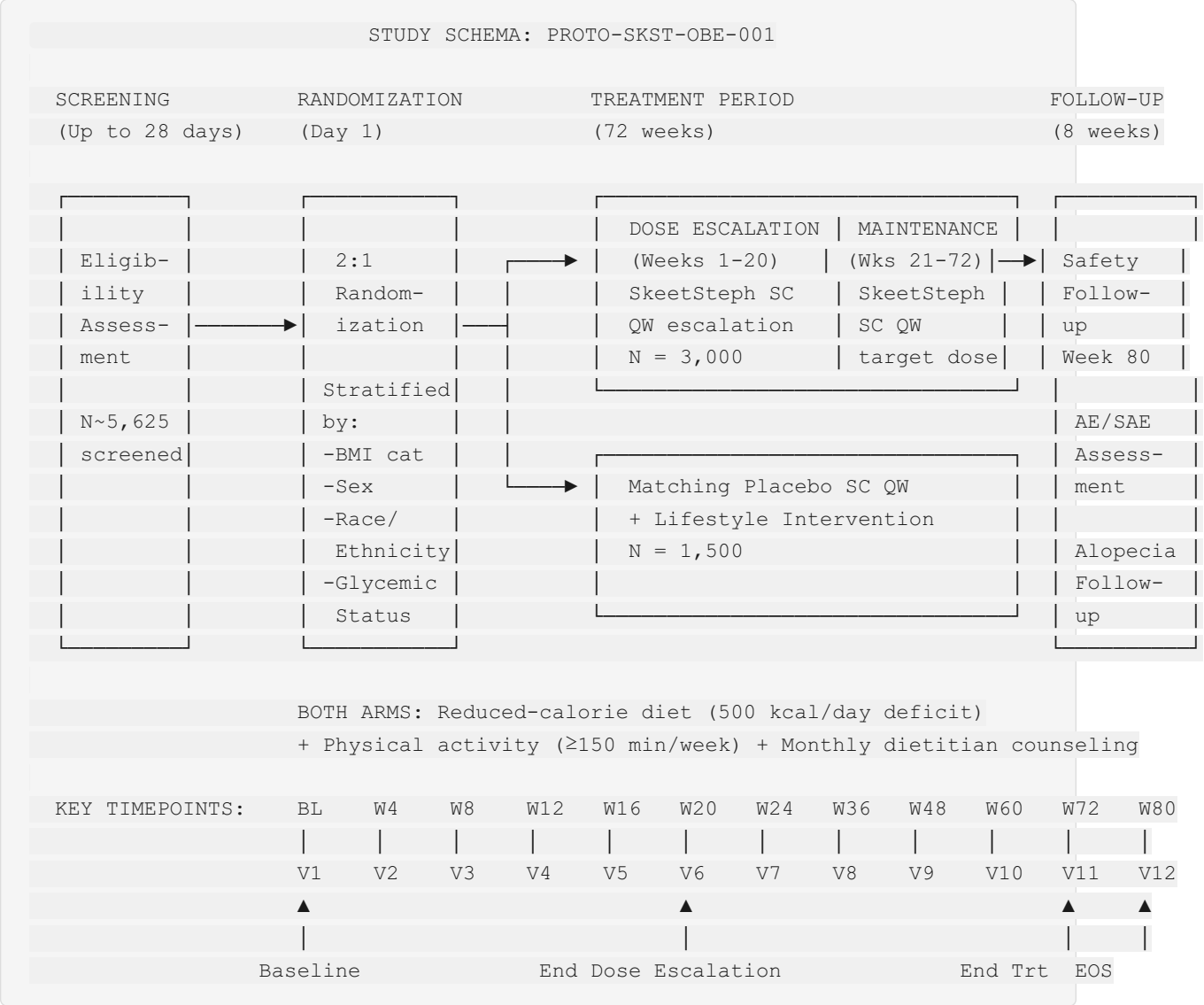
1 PROTOCOL SUMMARY

1.1 Synopsis

Field	Content
Title	A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of SkeetSteph, a Once-Weekly Subcutaneous GLP-1 Receptor Agonist, for Chronic Weight Management in Adults with Obesity
Short Title	SkeetSteph Phase 3 Obesity Trial
Protocol Version and Date	Version 1.0 Draft, 11-FEB-2026
Study Description	This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of SkeetSteph, a novel GLP-1 receptor agonist administered as a once-weekly subcutaneous injection, for chronic weight management in adults aged 30-39 years with obesity (BMI ≥30 kg/m²) without type 2 diabetes mellitus. Participants will be randomized in a 2:1 ratio to receive SkeetSteph or matching placebo, both as adjuncts to a reduced-calorie diet and increased physical activity program. The study hypothesis is that SkeetSteph will produce statistically significant and clinically meaningful weight reduction compared to placebo over 72 weeks.
Primary Objective	To evaluate the efficacy of once-weekly subcutaneous SkeetSteph compared to placebo in reducing body weight in adults with obesity
Secondary Objectives	- To evaluate the proportion of participants achieving clinically meaningful weight loss thresholds (≥5%, ≥10%, ≥15%) - To assess the effect of SkeetSteph on cardiometabolic risk factors (waist circumference, blood pressure, lipids, glycemic parameters) - To evaluate the safety and tolerability of SkeetSteph, with specific focus on alopecia as an adverse event of special interest (AESI) - To assess patient-reported outcomes related to weight-related quality of life
Exploratory Objectives	- To evaluate the effect of SkeetSteph on body composition (lean mass vs fat mass) via DXA substudy - To explore the relationship between weight loss magnitude and alopecia incidence/severity - To evaluate nutritional biomarkers (ferritin, zinc, biotin, vitamin D) as predictors of alopecia
Primary Endpoint	Percent change in body weight from baseline to Week 72

Field	Content
Co-Primary Endpoint	Proportion of participants achieving ≥5% body weight reduction from baseline at Week 72
Secondary Endpoints	- Proportion achieving ≥10% weight reduction at Week 72 - Proportion achieving ≥15% weight reduction at Week 72 - Change in waist circumference from baseline to Week 72 - Change in systolic blood pressure from baseline to Week 72 - Change in fasting plasma glucose and HbA1c from baseline to Week 72 - Change in lipid panel (LDL-C, HDL-C, triglycerides) from baseline to Week 72 - Incidence and severity of alopecia (graded by CTCAE v5.0 and SALT score) through Week 72 - Change in Impact of Weight on Quality of Life-Lite (IWQOL-Lite) score from baseline to Week 72
Exploratory Endpoints	- Change in total body fat mass and lean mass (DXA substudy) at Week 72 - Correlation between rate of weight loss and alopecia onset/severity - Change in nutritional biomarkers (ferritin, zinc, biotin, vitamin D) over time - Change in Hairdex questionnaire score from baseline to Week 72
Study Population	N=4,500 (3,000 SkeetSteph : 1,500 placebo). Adults aged 30-39 years with BMI ≥30 kg/m² without type 2 diabetes mellitus who have not achieved adequate weight loss with diet and exercise alone. Key exclusions: type 1 or 2 diabetes, prior bariatric surgery, history of pancreatitis, MTC/MEN2 history, active alopecia areata.
Phase	Phase 3
Description of Sites	Multicenter study conducted at approximately 150-200 clinical sites across the United States, Canada, and Europe. Sites will include academic medical centers, community-based clinical research sites, and endocrinology/obesity specialty clinics.
Description of Study Intervention	SkeetSteph: Once-weekly subcutaneous injection, dose-escalation over 20 weeks to target maintenance dose, administered in the abdomen, thigh, or upper arm. Placebo: Matching once-weekly subcutaneous injection (volume-matched, visually identical). Both arms: Standardized lifestyle intervention including reduced-calorie diet (500 kcal/day deficit) and increased physical activity (≥150 min/week moderate-intensity) with monthly dietitian counseling.
Study Duration	Enrollment period: ~18 months. Treatment period: 72 weeks (20-week dose escalation + 52-week maintenance). Follow-up period: 8 weeks post-treatment. Total study duration: ~30 months.
Participant Duration	Screening: Up to 28 days. Treatment: 72 weeks. Follow-up: 8 weeks. Total participation: ~82 weeks (~19 months).

1.2 Schema



1.3 Schedule of Activities (SoA)

Procedure	Screening (Day -28 to -1)	Baseline / V1 (Day 1)	V2 (Wk 4 ±3d)	V3 (Wk 8 ±3d)	V4 (Wk 12 ±7d)	V5 (Wk 16 ±7d)	V6 (Wk 20 ±7d)	V7 (Wk 24 ±7d)	V8 (Wk 36 ±7d)	V9 (Wk 48 ±14d)	V10 (Wk 60 ±14
ADMINISTRATIVE											

Procedure	Screening (Day -28 to -1)	Baseline / V1 (Day 1)	V2 (Wk 4 ±3d)	V3 (Wk 8 ±3d)	V4 (Wk 12 ±7d)	V5 (Wk 16 ±7d)	V6 (Wk 20 ±7d)	V7 (Wk 24 ±7d)	V8 (Wk 36 ±7d)	V9 (Wk 48 ±14d)	V10 (Wk 60 ±14
Informed consent	X										
Inclusion/ Exclusion	X	X									
Demographics	X										
Medical/surgical history	X										
Randomization		X									
STUDY INTERVENTION											
SkeetSteph or Placebo SC QW		X	X	X	X	X	X	X	X	X	X
Dose escalation assessment		X	X	X	X	X	X				
LIFESTYLE INTERVENTION											
Dietitian counseling		X	X	X	X	X	X	X	X	X	X
Physical activity log review		X	X	X	X	X	X	X	X	X	X
CONCOMITANT MEDS											

Procedure	Screening (Day -28 to -1)	Baseline / V1 (Day 1)	V2 (Wk 4 ±3d)	V3 (Wk 8 ±3d)	V4 (Wk 12 ±7d)	V5 (Wk 16 ±7d)	V6 (Wk 20 ±7d)	V7 (Wk 24 ±7d)	V8 (Wk 36 ±7d)	V9 (Wk 48 ±14d)	V10 (Wk 60 ±14
Concomitant medication review	X	X----------X----------X----------X----------X----------X----------X----------X----------X----------X									
CLINICAL ASSESSMENTS											
Physical exam (complete)	X	X									
Physical exam (directed)			X	X	X	X	X	X	X	X	X
Vital signs ^a^	X	X	X	X	X	X	X	X	X	X	X
Height	X										
Body weight ^b^	X	X	X	X	X	X	X	X	X	X	X
Waist circumference		X			X		X	X	X	X	X
HAIR ASSESSMENTS (AESI)											
Hair density assessment ^c^		X			X		X	X	X	X	X
Scalp photography ^d^		X					X		X		X
SALT score		X			X		X	X	X	X	X

Procedure	Screening (Day -28 to -1)	Baseline / V1 (Day 1)	V2 (Wk 4 ±3d)	V3 (Wk 8 ±3d)	V4 (Wk 12 ±7d)	V5 (Wk 16 ±7d)	V6 (Wk 20 ±7d)	V7 (Wk 24 ±7d)	V8 (Wk 36 ±7d)	V9 (Wk 48 ±14d)	V10 (Wk 60 ±14
Hairdex questionnaire (PRO)		X					X		X		
LABORATORY											
Hematology (CBC + diff)	X	X			X		X		X		
Chemistry panel ^e^	X	X			X		X		X		
Lipid panel (fasting)	X	X					X		X		
HbA1c	X	X					X		X		
Fasting plasma glucose	X	X	X	X	X	X	X	X	X	X	X
Fasting insulin		X					X		X		
Nutritional panel ^f^		X			X		X		X		X
Amylase/Lipase	X	X	X	X	X	X	X	X	X	X	X
Calcitonin	X	X					X		X		
Thyroid function (TSH, fT4)	X						X				
Pregnancy test (WOCBP) ^g^	X	X			X		X		X		
Urinalysis	X						X				
DIAGNOSTICS											
12-lead ECG	X	X					X				
DXA body composition ^h^		X									

Procedure	Screening (Day -28 to -1)	Baseline / V1 (Day 1)	V2 (Wk 4 ±3d)	V3 (Wk 8 ±3d)	V4 (Wk 12 ±7d)	V5 (Wk 16 ±7d)	V6 (Wk 20 ±7d)	V7 (Wk 24 ±7d)	V8 (Wk 36 ±7d)	V9 (Wk 48 ±14d)	V10 (Wk 60 ±14
EFFICACY											
Primary: Body weight % change		X	X	X	X	X	X	X	X	X	X
≥5%/10%/15% responder status			X	X	X	X	X	X	X	X	X
SAFETY											
AE assessment		X---------- X---------- X---------- X---------- X---------- X---------- X---------- X---------- X---------- X---------- X									
SAE assessment		X---------- X---------- X---------- X---------- X---------- X---------- X---------- X---------- X---------- X---------- X---------- X									
C-SSRS (suicidality)	X	X			X		X		X		

Procedure	Screening (Day -28 to -1)	Baseline / V1 (Day 1)	V2 (Wk 4 ±3d)	V3 (Wk 8 ±3d)	V4 (Wk 12 ±7d)	V5 (Wk 16 ±7d)	V6 (Wk 20 ±7d)	V7 (Wk 24 ±7d)	V8 (Wk 36 ±7d)	V9 (Wk 48 ±14d)	V10 (Wk 60 ±14
PATIENT-REPORTED OUTCOMES											
IWQOL-Lite		X					X		X		
SF-36		X							X		
EQ-5D-5L		X					X		X		

Footnotes:

^a^ Vital signs include systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature. Blood pressure measured in triplicate after 5 minutes seated rest.

^b^ Body weight measured on calibrated scale, in light clothing, shoes removed, at approximately the same time of day. Fasting preferred.

^c^ Hair density assessment using trichoscopy or standardized hair pull test performed by trained dermatology assessor.

^d^ Standardized scalp photography using reproducible positioning device; global photographs (vertex, frontal, temporal, occipital views).

^e^ Chemistry panel includes: sodium, potassium, chloride, bicarbonate, BUN, creatinine, eGFR, glucose, calcium, phosphorus, magnesium, total protein, albumin, total bilirubin, ALT, AST, alkaline phosphatase, GGT.

^f^ Nutritional panel includes: ferritin, serum iron, TIBC, zinc, biotin, vitamin D (25-OH), vitamin B12, folate. Monitored for potential nutritional deficiency contributing to alopecia.

^g^ Serum beta-hCG at screening; urine pregnancy test at subsequent visits for women of childbearing potential (WOCBP).

^h^ DXA body composition scan at substudy sites only (approximately 500 participants).

2 INTRODUCTION

2.1 Study Rationale

Obesity is a chronic, relapsing, multifactorial disease characterized by abnormal or excessive fat accumulation that presents a risk to health. Globally, obesity prevalence has nearly tripled since 1975, with the World Health Organization estimating that over 890 million adults were living with obesity in 2022. In the United States, the prevalence of obesity among adults aged 20 and over exceeds 42%, with the highest rates of increase observed in younger adults aged 25-44 years. Obesity is independently associated with increased risk of type 2 diabetes, cardiovascular disease, obstructive sleep apnea, nonalcoholic fatty liver disease, certain cancers, and all-cause mortality. The economic burden is substantial, with obesity-related medical costs estimated at over $170 billion annually in the US alone.

Current pharmacological options for chronic weight management, while transformative compared to earlier agents, leave significant unmet needs. Approved GLP-1 receptor agonists (semaglutide, liraglutide) and the dual GIP/GLP-1 agonist tirzepatide have demonstrated 15-22% mean body weight reductions in Phase 3 trials. However, individual response varies considerably, gastrointestinal tolerability remains a barrier to optimal dosing for many patients, and long-term data beyond 2-3 years remains limited. Additionally, the emergence of alopecia as a safety signal across the GLP-1 class — with over 1,000 reports in the FDA FAERS database — highlights the need for agents with improved safety profiles and for clinical programs that prospectively characterize hair loss risk.

SkeetSteph is a novel GLP-1 receptor agonist designed to address these unmet needs. Preclinical and early clinical data suggest a favorable efficacy-to-tolerability ratio with once-weekly subcutaneous dosing. This Phase 3 study is designed to confirm the efficacy and safety of SkeetSteph for chronic weight management while prospectively characterizing the incidence, severity, and natural history of alopecia — a first for a GLP-1 weight management pivotal program. The study design aligns with the FDA's January 2025 draft guidance on developing drugs for weight reduction, incorporating updated endpoints, estimand frameworks, and sample size requirements.

Results from this study will inform an NDA submission for chronic weight management and contribute novel safety data on the relationship between GLP-1-mediated weight loss and hair loss, informing clinical risk-benefit discussions and future product labeling.

2.2 Background

A. Disease/Condition Overview

Obesity is defined by the World Health Organization as a body mass index (BMI) ≥30 kg/m² and is classified into three classes: Class 1 (BMI 30-34.9), Class 2 (BMI 35-39.9), and Class 3 (BMI ≥40). The underlying pathophysiology involves a complex interplay of genetic susceptibility, neurohormonal signaling (including the incretin system, leptin resistance, and hypothalamic appetite regulation), environmental factors (caloric excess, sedentary behavior), and epigenetic modifications. Adipose tissue dysfunction leads to chronic low-grade inflammation, insulin resistance, and metabolic dysregulation that drives comorbid disease development.

The natural history of obesity is characterized by progressive weight gain with periods of partial weight loss followed by regain. Without intervention, patients with obesity face a relentless trajectory toward metabolic and cardiovascular complications. The disease course is influenced by age of onset, severity, duration, fat distribution (visceral vs subcutaneous), and the presence and severity of comorbidities.

Epidemiologically, obesity disproportionately affects younger adults in the US, with prevalence in the 20-39 age group reaching approximately 40%. This population faces decades of exposure to obesity-related risks and represents a critical target for early intervention. Risk factors include genetic predisposition, sedentary lifestyle, high-calorie diet, sleep disruption, stress, certain medications (antipsychotics, corticosteroids, some antidepressants), and socioeconomic factors limiting access to healthy food and physical activity.

The disease burden of obesity extends beyond mortality to encompass significant morbidity: reduced quality of life, functional impairment, psychological distress (depression, anxiety, weight stigma), reduced productivity, and healthcare utilization. Adults with obesity have medical costs approximately 30% higher than those with normal weight.

Diagnosis is established by BMI calculation, supplemented by waist circumference measurement (≥102 cm in men, ≥88 cm in women indicating central obesity), assessment of comorbidities, and evaluation of secondary causes (hypothyroidism, Cushing syndrome, medications).

B. Current Standard of Care

First-line management of obesity consists of comprehensive lifestyle intervention including dietary modification (500-750 kcal/day energy deficit), increased physical activity (≥150 minutes/week moderate-intensity aerobic activity), and behavioral counseling. Lifestyle intervention alone typically achieves 3-5% weight loss, which while clinically meaningful, is insufficient for many patients.

Pharmacotherapy is recommended as adjunctive to lifestyle intervention for adults with BMI ≥30 or BMI ≥27 with weight-related comorbidities who have not achieved sufficient weight loss with lifestyle changes alone. Currently approved agents for chronic weight management include:

- **Semaglutide 2.4 mg SC weekly (Wegovy):** Approved 2021. The STEP 1 trial (NCT03548935, N=1,961) demonstrated 14.9% mean weight loss vs 2.4% placebo over 68 weeks. Approved in 2025 as oral formulation (25 mg daily) based on OASIS 4 trial (NCT05564117). Common AEs: nausea (44%), diarrhea (30%), vomiting (24%).
- **Tirzepatide SC weekly (Zepbound):** Dual GIP/GLP-1 agonist approved 2023. SURMOUNT-1 (NCT04184622, N=2,539) showed 15.0-20.9% mean weight loss across doses (5/10/15 mg) vs 3.1% placebo over 72 weeks. Similar GI AE profile.
- **Liraglutide 3.0 mg SC daily (Saxenda):** Approved 2014. Demonstrated ~8% weight loss. Generic now available (Teva).
- **Orlistat, phentermine/topiramate, naltrexone/bupropion:** Older agents with more modest efficacy (5-10% weight loss) and varying tolerability profiles.

Bariatric surgery remains the most effective intervention for severe obesity (BMI ≥40 or ≥35 with comorbidities) with 20-35% sustained weight loss, but is limited by surgical risk, irreversibility, access barriers, and patient acceptance.

Limitations of current pharmacotherapy include: variable individual response (10-30% of patients are non-responders), GI tolerability as a dose-limiting factor, high cost, need for chronic administration, incomplete understanding of long-term safety, and the emerging alopecia safety signal across the GLP-1 class.

C. Drug Background

C1. Drug Description

Generic Name: SkeetSteph (investigational) **Drug Class:** Glucagon-like peptide-1 (GLP-1) receptor agonist **Molecular Category:** [TBD - peptide analog or small molecule] **Formulation:** Sterile, clear to slightly opalescent, colorless to slightly yellow solution for subcutaneous injection **Dosage Form:** Pre-filled single-dose pen for subcutaneous injection **Strengths:** [TBD - multiple dose strengths for dose escalation, e.g., 0.25 mg, 0.5 mg, 1.0 mg, 1.7 mg, 2.4 mg] **Route of Administration:** Subcutaneous injection (abdomen, thigh, or upper arm) **Frequency:** Once weekly

C2. Mechanism of Action

SkeetSteph is an agonist of the GLP-1 receptor, a G-protein-coupled receptor expressed in pancreatic beta cells, the gastrointestinal tract, the central nervous system (hypothalamus, brainstem), and other tissues. By binding to and activating the GLP-1 receptor, SkeetSteph mimics the physiological effects of endogenous GLP-1, an incretin hormone secreted by intestinal L-cells in response to nutrient intake.

The weight loss mechanism of GLP-1 receptor agonism operates through multiple complementary pathways:

1. **Central appetite regulation:** GLP-1 receptor activation in the hypothalamic arcuate nucleus and paraventricular nucleus suppresses orexigenic (appetite-stimulating) neuropeptide Y/agouti-related peptide (NPY/AgRP) signaling and enhances anorexigenic (appetite-suppressing) proopiomelanocortin (POMC) signaling, reducing hunger and increasing satiety.

2. **Brainstem signaling:** Activation of GLP-1 receptors in the nucleus tractus solitarius and area postrema mediates satiety signals and contributes to reduced food intake and potential nausea (which also limits intake).

3. **Delayed gastric emptying:** GLP-1 receptor activation slows gastric motility, promoting prolonged gastric distension and early satiety after meals.

4. **Glucose-dependent insulin secretion:** Enhanced insulin secretion in the postprandial state improves glycemic control and may contribute to metabolic improvements independent of weight loss.

5. **Glucagon suppression:** Reduced glucagon secretion contributes to improved hepatic glucose output and metabolic profile.

These mechanisms are directly relevant to obesity pathophysiology, targeting the neurohormonal dysregulation that drives excessive caloric intake and metabolic dysfunction in patients with obesity.

C3. Pharmacology

Pharmacokinetics (Projected based on GLP-1 RA class and preclinical data):

- **Absorption:** Following subcutaneous injection, SkeetSteph is slowly absorbed from the injection site, achieving peak plasma concentration (Tmax) at approximately [TBD] hours post-dose. Absolute bioavailability following SC injection is estimated at [TBD]%. The slow absorption supports once-weekly dosing.

- **Distribution:** Volume of distribution (Vd) estimated at [TBD] L. Plasma protein binding is approximately [TBD]%. SkeetSteph crosses the blood-brain barrier to access central GLP-1 receptors, which is critical for appetite-suppressing effects.
- **Metabolism:** SkeetSteph is metabolized through general proteolytic degradation pathways. It is not primarily metabolized by CYP450 enzymes, reducing potential for drug-drug interactions. No active metabolites have been identified.
- **Excretion:** Terminal elimination half-life (t1/2) is approximately [TBD] hours, supporting once-weekly dosing. Elimination is primarily through peptide degradation with renal and fecal excretion of metabolites.

Pharmacodynamics:

- **Dose-response:** Preclinical studies demonstrated a dose-dependent reduction in food intake and body weight in diet-induced obese rodent models, with a plateau at doses corresponding to approximately [TBD] mg human equivalent dose.
- **Time course:** Weight loss onset expected within 4-8 weeks, with progressive weight loss through 52-72 weeks of treatment, consistent with the GLP-1 RA class.
- **Target engagement:** Receptor occupancy studies indicate [TBD]% GLP-1 receptor occupancy at projected therapeutic doses.

C4. Nonclinical Studies

Preclinical Efficacy:

- In vitro binding studies demonstrated high-affinity GLP-1 receptor binding with [TBD] nM EC50 in cAMP assay.
- Diet-induced obese (DIO) mouse model: [TBD]% body weight reduction over 8 weeks at human-equivalent therapeutic dose.
- DIO rat model: [TBD]% weight reduction with improvements in glucose tolerance, insulin sensitivity, and hepatic steatosis.
- Dose-response characterization across multiple animal models established therapeutic window and maximum effective dose.

Preclinical Safety/Toxicology:

- **Acute toxicity:** Single-dose toxicity studies in rats and dogs established no-observed-adverse-effect level (NOAEL) at [TBD] mg/kg (approximately [TBD]x human dose on mg/m^2 basis).

- **Chronic toxicity:** 26-week repeat-dose toxicity studies in rats and dogs. Key findings consistent with GLP-1 RA class: dose-dependent weight loss, reduced food intake, gastrointestinal effects. NOAEL at [TBD] mg/kg.
- **Carcinogenicity:** 2-year carcinogenicity study in rats revealed thyroid C-cell tumors (follicular cell adenomas and carcinomas) at doses ≥[TBD]x human dose, consistent with the GLP-1 RA drug class. This finding is attributed to sustained GLP-1 receptor activation in rodent thyroid C-cells and its clinical relevance to humans is uncertain. Carcinogenicity study in mice: [TBD].
- **Genotoxicity:** Negative in standard battery (Ames test, in vitro chromosomal aberration, in vivo micronucleus).
- **Reproductive toxicity:** Embryo-fetal development studies in rats and rabbits showed [TBD]. SkeetSteph is contraindicated in pregnancy. Males: no effect on fertility parameters at doses up to [TBD]x human dose.
- **Hair follicle observations:** [TBD - preclinical observations regarding hair/fur changes, if any, in chronic toxicity studies would be documented here. This is particularly relevant given the clinical alopecia signal.]

Translation to Humans:

- Human equivalent dose (HED) calculated from NOAEL using body surface area conversion.
- Starting dose for Phase 1 selected at [TBD] mg based on 1/10th of HED, consistent with ICH S9 guidance.
- Dose escalation strategy designed to optimize tolerability while achieving therapeutic exposure.

C5. Prior Clinical Experience

Phase 1 Studies:

- [TBD - First-in-human, single ascending dose (SAD) and multiple ascending dose (MAD) studies establishing safety, tolerability, PK, and preliminary PD in healthy volunteers and patients with obesity. Include NCT numbers when available.]
- Safety profile: [TBD - GI events (nausea, vomiting) consistent with class; any hair-related observations]
- PK/PD: Dose-proportional exposure; half-life supporting QW dosing confirmed.

Phase 2 Studies:

- [TBD - Dose-finding study establishing recommended Phase 3 dose. Include NCT number, N, design, key efficacy and safety results. Expected to show dose-dependent weight loss with identification of optimal efficacy:tolerability ratio.]
- Recommended Phase 3 dose: [TBD] mg SC QW based on Phase 2 efficacy, safety, and PK/PD data.
- Alopecia observations in Phase 2: [TBD - any hair loss events observed, incidence, severity, reversibility]

D. Rationale for Current Study Intervention

SkeetSteph is expected to produce clinically meaningful weight loss in adults with obesity based on the well-established efficacy of GLP-1 receptor agonism for weight management. The biological plausibility is firmly established: GLP-1 receptor activation reduces appetite, slows gastric emptying, and modulates central energy homeostasis — mechanisms validated by the clinical success of semaglutide (14.9% weight loss, STEP 1), tirzepatide (15.0-20.9%, SURMOUNT-1), and other GLP-1 RAs.

SkeetSteph may differentiate from existing GLP-1 RAs through [TBD - potential differentiating features such as improved tolerability, enhanced efficacy, novel receptor binding properties, or favorable safety profile]. This trial is specifically designed to address the alopecia safety signal prospectively, which has been retrospectively identified across the class but never systematically characterized in a pivotal trial.

The randomized, double-blind, placebo-controlled design is the gold standard for demonstrating efficacy in chronic weight management and is required by FDA guidance. A 72-week treatment duration (including 20-week dose escalation) is consistent with all major recent GLP-1 RA weight management programs (STEP, SURMOUNT, ATTAIN) and meets the 2025 FDA guidance requirement for ≥1 year of maintenance treatment. Placebo plus lifestyle intervention as the comparator is standard and ethically appropriate, as there is no single established standard of care for pharmacological weight management.

E. Similar Clinical Trials and Lessons Learned

The following pivotal trials directly inform the design of this study:

1. **STEP 1 (NCT03548935):** Semaglutide 2.4 mg, N=1,961, 68 weeks, 14.9% weight loss. *Lessons:* Established co-primary endpoints (% change + ≥5% responder). 2:1 randomization is feasible. GI AEs peak during escalation and attenuate. Lifestyle intervention in both arms is essential.

2. **SURMOUNT-1 (NCT04184622):** Tirzepatide, N=2,539, 72 weeks, 15-21% weight loss. *Lessons:* Multi-dose arms can differentiate dose-response. 20-week escalation improves GI tolerability. Stratification by sex, BMI, and glycemic status improves balance. Large sample sizes are feasible across multinational sites.

3. **ATTAIN-1 (NCT05869903):** Orforglipron, N=3,127, 72 weeks. *Lessons:* Sample sizes approaching FDA 2025 guidance (≥3,000 on drug) are achievable. Newer GLP-1 RAs may show different efficacy ranges (7.5-11.2% in this case). Oral formulations are viable competitors.

4. **STEP UP (NCT05646706):** Semaglutide 7.2 mg, N=1,407, 72 weeks. *Lessons:* Higher doses can achieve greater weight loss. Dose-response relationship within GLP-1 RA class persists at higher doses.

Key design improvements in SkeetSteph trial: - Prospective alopecia characterization (AESI with standardized grading, photography, PROs) — novel for the class - Nutritional biomarker monitoring (ferritin, zinc, biotin, vitamin D) to elucidate alopecia mechanism - Sample size of 4,500 aligned with 2025 FDA guidance requirements - Updated statistical approach using estimand framework and multiple imputation per 2025 FDA guidance - DXA body composition substudy to assess lean mass preservation

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

Immediate Risks (occurring during or shortly after treatment initiation):

1. **Gastrointestinal events (Very common, >10%):** Nausea (40-44%), vomiting (15-24%), diarrhea (20-30%), constipation (10-24%), abdominal pain (10-20%), dyspepsia (5-10%). These are the most common AEs across the GLP-1 RA class, typically mild to moderate (Grade 1-2), occur predominantly during dose escalation, and frequently attenuate with continued treatment. Based on STEP and SURMOUNT programs, GI events lead to treatment discontinuation in 4-7% of participants.

2. **Injection site reactions (Common, 1-10%):** Pain, erythema, pruritus, swelling at the injection site. Generally mild and transient.

3. **Alopecia/Hair loss (Uncommon to Common, 1-10% estimated):** Telogen effluvium is the most likely mechanism, triggered by the metabolic stress of rapid weight loss and potential nutritional deficiencies. FDA FAERS data show elevated reporting for semaglutide (ROR 2.46) and tirzepatide (ROR 1.73). Hair loss may be diffuse, progressive, and distressing to participants. This is a key Adverse Event of Special Interest (AESI) in this study.

4. **Hypoglycemia (Uncommon, <5% in non-diabetic population):** GLP-1 RA-mediated insulin secretion is glucose-dependent, minimizing hypoglycemia risk in non-diabetic patients. Risk increases if combined with sulfonylureas or insulin (excluded in this population).

5. **Headache, dizziness, fatigue (Common, 5-15%):** Generally mild and self-limiting.

6. **Increased heart rate (Common, 1-5 bpm increase):** Dose-dependent, mechanism not fully understood, generally not clinically significant.

7. **Risks from study procedures:** Blood draws (bruising, discomfort), DXA scan (minimal radiation exposure in substudy), psychological impact of regular weight monitoring.

Long-Range Risks:

1. **Pancreatitis:** Acute pancreatitis has been reported with GLP-1 RAs at rates of approximately 0.1-0.3%. The causal relationship remains debated but requires monitoring (amylase/lipase at each visit).

2. **Gallbladder events:** Cholelithiasis, cholecystitis, and biliary events occur at increased rates (1.5-2.5%) with GLP-1 RAs, likely related to rapid weight loss altering bile composition.

3. **Thyroid C-cell tumors:** GLP-1 RAs cause thyroid C-cell tumors in rodents (class effect). Clinical relevance in humans is uncertain, but a boxed warning applies to all GLP-1 RAs. Baseline and periodic calcitonin monitoring included.

4. **Renal impairment:** Dehydration from GI events (vomiting, diarrhea) may exacerbate renal insufficiency. Renal function monitored throughout.

5. **Suicidal ideation/behavior:** FDA has evaluated reports of suicidal ideation with GLP-1 RAs; no definitive causal link established, but C-SSRS monitoring included as a precaution.

6. **Unknown long-term risks:** As a novel compound, long-term safety beyond the study duration cannot be fully characterized. This is an inherent limitation of all investigational drug studies.

2.3.2 Known Potential Benefits

Immediate Potential Benefits:

1. **Clinically meaningful weight loss:** Based on the GLP-1 RA class, participants randomized to SkeetSteph may achieve 10-20% weight reduction from baseline, exceeding what is achievable with lifestyle intervention alone (2-5%). Weight loss of ≥5% is associated with improvements in obesity-related comorbidities.

2. **Cardiometabolic improvements:** Weight loss with GLP-1 RAs is associated with reductions in blood pressure, improvements in lipid profile (reduced LDL-C and triglycerides, increased HDL-C), improved glycemic control (reduced fasting glucose, HbA1c), and reduced risk of progression to type 2 diabetes in patients with prediabetes.

3. **Improved quality of life:** Weight loss is associated with improvements in physical functioning, mobility, self-esteem, body image, and social participation. Patient-reported outcome improvements documented across GLP-1 RA trials.

4. **Close medical monitoring:** Study participants benefit from regular medical assessments, laboratory monitoring, dietitian counseling, and clinical oversight that may not be available in routine clinical care.

Important: No guarantee of benefit. Participants may be randomized to placebo. Individual responses to GLP-1 RAs vary, and some participants may not achieve clinically meaningful weight loss.

Long-Range Potential Benefits:

1. **Sustained weight management:** If efficacy is maintained, long-term weight reduction may reduce lifetime risk of type 2 diabetes, cardiovascular events, certain cancers, and all-cause mortality.

2. **Reduced need for more invasive interventions:** Effective pharmacotherapy may reduce the need for bariatric surgery in some patients.

3. **Contribution to generalizable knowledge:** Data generated will inform the understanding of GLP-1 RA efficacy, safety (particularly alopecia), and optimal use for weight management, benefiting future patients.

2.3.3 Assessment of Potential Risks and Benefits

Risk-Benefit Balance:

The anticipated risks of SkeetSteph are consistent with the well-characterized safety profile of the GLP-1 RA class. The most common risks (GI events) are generally mild to moderate, manageable with dose escalation, and self-limiting. The more serious potential risks (pancreatitis, gallbladder events, thyroid C-cell concern) are uncommon and are mitigated by careful participant selection (exclusion criteria) and monitoring (amylase/lipase, calcitonin).

Alopecia, while distressing, is generally non-life-threatening and potentially reversible. The prospective characterization of this risk in the current study represents a significant advance over prior programs that reported it only retrospectively. Detailed monitoring will enable informed risk-benefit discussions for prescribers and patients.

The potential benefits — meaningful weight reduction with associated cardiometabolic improvements — are well-established for the GLP-1 RA class and address a serious chronic disease with limited treatment options. The risks of untreated obesity (cardiovascular disease, diabetes, mortality) substantially outweigh the known risks of GLP-1 RA therapy. The 2:1 randomization ratio maximizes the number of participants receiving active treatment while maintaining adequate placebo exposure for statistical rigor.

Risk Minimization Strategies:

1. **Patient selection:** Stringent eligibility criteria exclude participants at elevated risk (pancreatitis history, MTC/MEN2, active alopecia areata, severe renal impairment, suicidal ideation).
2. **Dose escalation:** 20-week escalation mitigates GI AE severity by allowing physiologic adaptation.
3. **Frequent monitoring:** Schedule of Activities includes regular safety assessments (amylase/lipase, calcitonin, C-SSRS, hair assessments, nutritional biomarkers) at defined intervals.
4. **Stopping rules:** Prespecified discontinuation criteria for individual participants (severe pancreatitis, clinically significant calcitonin elevation, severe alopecia per protocol-defined thresholds) and study-wide stopping rules per DSMB charter.
5. **DSMB oversight:** Independent Data Safety Monitoring Board will conduct regular safety reviews with predefined futility and harm boundaries.
6. **Informed consent:** Comprehensive consent process including detailed discussion of alopecia risk, class-specific risks, and participant rights.
7. **Training:** All site staff trained in AE recognition, grading, and reporting, with specific training on alopecia assessment.

3 OBJECTIVES AND ENDPOINTS

Category	Objective	Endpoint	Justification
Primary	To evaluate the efficacy of once-weekly subcutaneous SkeetSteph compared to placebo, as an adjunct to diet and exercise, in reducing body weight in adults aged 30-39 with obesity (BMI ≥30 kg/m²)	Percent change in body weight from baseline to Week 72	Continuous weight change is the recommended primary endpoint per FDA 2025 draft guidance for weight management drugs. Consistent with STEP 1, SURMOUNT-1, and ATTAIN-1 co-primary endpoint. Clinically meaningful and directly interpretable.
Co-Primary	To evaluate the proportion of participants achieving clinically meaningful weight reduction	Proportion of participants achieving ≥5% body weight reduction from baseline at Week 72	Co-primary responder endpoint per FDA guidance. ≥5% threshold is the minimum for clinically meaningful improvements in comorbidities. Used as co-primary in all approved GLP-1 RA programs.
Secondary	To evaluate the proportion achieving higher weight loss thresholds	Proportion achieving ≥10% weight reduction at Week 72	Higher thresholds (10%, 15%) associated with greater improvements in cardiometabolic risk. Recommended as responder analyses in 2025 FDA guidance.
Secondary	To evaluate the proportion achieving substantial weight loss	Proportion achieving ≥15% weight reduction at Week 72	≥15% threshold associated with near-normalization of metabolic parameters. Differentiates more effective agents.
Secondary	To assess the effect on central adiposity	Change in waist circumference from baseline to Week 72	Waist circumference is an independent predictor of cardiometabolic risk beyond BMI. Recommended in 2025 FDA guidance.

Category	Objective	Endpoint	Justification
Secondary	To assess the effect on cardiovascular risk factors	Change in systolic blood pressure, fasting glucose, HbA1c, and lipid panel (LDL-C, HDL-C, triglycerides) from baseline to Week 72	Standard cardiometabolic secondary endpoints in weight management trials. Support labeling claims and clinical outcome assessment.
Secondary	To evaluate the safety and tolerability of SkeetSteph, with focus on alopecia	Incidence and severity of alopecia (CTCAE v5.0 grade, SALT score) through Week 72; time to onset; reversibility during follow-up	Alopecia is a prespecified AESI based on class safety signal (semaglutide ROR 2.46, >1,000 FAERS reports). Prospective characterization is novel and essential for informed prescribing.
Secondary	To assess the impact on weight-related quality of life	Change in IWQOL-Lite total score from baseline to Week 72	IWQOL-Lite is a validated weight-specific QoL instrument. COAs recommended by 2025 FDA guidance for labeling claims.
Exploratory	To evaluate body composition changes	Change in total body fat mass and lean body mass by DXA at Week 72 (substudy, N~500)	Understanding fat vs lean mass loss informs clinical significance and addresses concern about muscle wasting with rapid weight loss.
Exploratory	To explore relationship between weight loss and alopecia	Correlation between rate of weight loss (% per month) and alopecia incidence/ severity/onset	May elucidate whether alopecia is driven by rapidity of weight loss vs direct drug effect, informing risk mitigation strategies.
Exploratory	To evaluate nutritional predictors of alopecia	Change in ferritin, zinc, biotin, vitamin D over time; correlation with alopecia events	Nutritional deficiency from caloric restriction is a proposed mechanism for GLP-1 RA-associated alopecia. May identify modifiable risk factors.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter clinical trial evaluating the efficacy and safety of SkeetSteph administered as a once-weekly subcutaneous injection for chronic weight management in adults aged 30-39 years with obesity.

Key Design Features:

- **Study Type:** Interventional clinical trial
- **Phase:** Phase 3 (pivotal)
- **Design:** Randomized, double-blind, placebo-controlled, parallel-group
- **Blinding:** Double-blind (participants, investigators, site staff, sponsor study team, and outcome assessors are blinded to treatment assignment). An unblinded pharmacist or designee at each site will manage study drug dispensing.
- **Randomization:** 2:1 (SkeetSteph : Placebo) using an interactive web response system (IWRS). Stratified by BMI category (30-34.9 vs 35-39.9 vs ≥40 kg/m²), sex (male vs female), race/ethnicity, and glycemic status (normoglycemia vs prediabetes, defined as HbA1c 5.7-6.4% or FPG 100-125 mg/dL).
- **Study Arms:**
- **Arm A (SkeetSteph):** SkeetSteph SC QW with 20-week dose escalation to target maintenance dose + lifestyle intervention. N=3,000.
- **Arm B (Placebo):** Matching placebo SC QW + lifestyle intervention. N=1,500.
- **Number of Sites:** Approximately 150-200 clinical sites
- **Geographic Distribution:** United States (~60% of sites), Canada (~15%), Europe (~25%)
- **Study Duration:**
- Enrollment period: ~18 months
- Treatment period: 72 weeks (20-week dose escalation + 52-week maintenance)
- Post-treatment follow-up: 8 weeks
- Total study duration from first participant enrolled to last participant last visit: ~30 months
- **Target Enrollment:** N=4,500 (3,000 SkeetSteph : 1,500 Placebo)

Study Periods:

1. **Screening (Day -28 to Day -1):** Eligibility assessment, informed consent, baseline assessments, medical history, laboratory evaluations.
2. **Dose Escalation Period (Weeks 1-20):** Gradual dose increase to minimize GI side effects. Dose increments every 4 weeks per protocol-specified escalation schedule.
3. **Maintenance Period (Weeks 21-72):** Treatment at target maintenance dose with regular efficacy and safety assessments.
4. **Post-Treatment Follow-up (Weeks 73-80):** Safety follow-up after last dose, including alopecia assessment for recovery.

4.2 Scientific Rationale for Study Design

Randomized controlled trial (RCT): A randomized, double-blind, placebo-controlled design is the gold standard for demonstrating efficacy in chronic weight management, is required by the FDA 2025 draft guidance, and is consistent with all pivotal GLP-1 RA weight management programs (STEP, SURMOUNT, ATTAIN, OASIS). Randomization and blinding minimize selection bias, confounding, and placebo effects, which are particularly relevant for subjective endpoints and self-reported outcomes.

Placebo comparator: Placebo (with lifestyle intervention in both arms) is the appropriate comparator for several reasons: (1) there is no single established standard-of-care pharmacotherapy for obesity; (2) placebo-controlled design is mandated by FDA guidance for weight management drugs; (3) the effect size of lifestyle intervention alone provides a clinically relevant control; (4) active comparator trials (e.g., head-to-head vs semaglutide) may be appropriate for subsequent studies but are not required for initial approval.

2:1 randomization ratio: Selected to maximize the number of participants exposed to SkeetSteph, meeting the FDA 2025 guidance requirement of ≥3,000 subjects on the investigational drug while limiting total enrollment. This ratio is ethically favorable (greater chance of receiving active treatment) and improves safety database characterization with modest loss of statistical power.

Double-blind design: Essential for weight management trials because body weight measurement can be influenced by participant behavior (diet adherence, exercise) and subjective outcomes (PROs, AE reporting) may be affected by knowledge of treatment assignment. Matching placebo injections ensure blinding integrity.

72-week treatment duration: Selected to provide a 20-week dose escalation period (consistent with SURMOUNT-1 and optimal for GI tolerability) plus a 52-week maintenance period, meeting the FDA 2025 guidance requirement of ≥1 year maintenance treatment. The 72-week total is consistent with SURMOUNT-1 and ATTAIN-1 trial durations.

8-week post-treatment follow-up: Provides safety data on treatment discontinuation effects (weight regain trajectory, AE resolution including alopecia recovery assessment) and contributes to understanding the durability of treatment effects.

4.3 Justification for Dose

The SkeetSteph dose for this Phase 3 trial was selected based on the totality of nonclinical and clinical data:

Nonclinical dose rationale: - Preclinical efficacy studies in DIO rodent models demonstrated dose-dependent body weight reduction, with maximum efficacy plateau at approximately [TBD] mg/kg (corresponding to approximately [TBD] mg human equivalent dose). - Chronic toxicology studies established the NOAEL at [TBD] mg/kg in rats and [TBD] mg/kg in dogs, providing a safety margin of approximately [TBD]-fold over the proposed clinical dose.

Clinical dose rationale: - Phase 1 SAD/MAD studies established safety and tolerability across the [TBD] mg dose range, with dose-limiting GI events at [TBD] mg. - Phase 2 dose-finding study evaluated [TBD] doses of SkeetSteph over [TBD] weeks in [TBD] participants with obesity. The [TBD] mg dose demonstrated the optimal efficacy-to-tolerability ratio, achieving [TBD]% mean body weight loss with acceptable GI AE rates of [TBD]%. - PK/PD modeling confirmed that the recommended dose achieves [TBD]% receptor occupancy throughout the dosing interval, consistent with the exposure-response relationship.

Dose escalation rationale: - A 20-week dose escalation schedule (dose increments every 4 weeks) is employed to minimize GI tolerability issues during treatment initiation. This approach is consistent with semaglutide (Wegovy) and tirzepatide (Zepbound) approved dose escalation schedules and reflects the GLP-1 RA class experience that gradual dose titration significantly reduces nausea, vomiting, and treatment discontinuation.

Route and frequency rationale: - Once-weekly subcutaneous injection was selected to maximize adherence (reduced injection frequency) while maintaining sustained therapeutic drug levels throughout the dosing interval. This frequency is established for the GLP-1 RA class (semaglutide QW, tirzepatide QW) and preferred by patients over daily injections.

4.4 End of Study Definition

Individual participant completion: A participant is considered to have completed the study upon completion of the Week 80 (end-of-study) follow-up visit, including all required assessments. A participant is considered to have completed the treatment period upon completion of the Week 72 visit.

Global study end: The study will be considered complete when the last randomized participant has completed the last study visit (Week 80), all data queries have been resolved, the database is locked, and the final clinical study report is issued.

Early termination criteria for the study: - The DSMB recommends termination based on prespecified safety stopping boundaries (unacceptable rate of SAEs, unexpected safety signal, or unacceptable risk-benefit ratio) - Futility analysis at interim demonstrates no reasonable probability of achieving primary endpoint - Sponsor decision based on regulatory action, business considerations, or external data rendering the study no longer necessary or feasible - Regulatory authority (FDA or other) mandates study discontinuation

In the event of early termination, all enrolled participants will be offered a final safety visit and appropriate transition of care.

5 STUDY POPULATION

5.1 Inclusion Criteria

Participants must meet ALL of the following criteria to be eligible for enrollment:

1. **Informed Consent:** Able to understand and willing to provide written informed consent and comply with all study procedures and visit schedule.
2. **Age:** Adults aged 30-39 years (inclusive) at the time of informed consent.
3. **BMI:** Body mass index ≥30.0 kg/m² at screening, as calculated from height and weight measured at the screening visit. Class 3 obesity (BMI ≥40 kg/m²) participants must comprise at least 15% of total enrollment per FDA 2025 guidance recommendation for representative sampling.
4. **Weight Stability:** Stable body weight (self-reported change of ≤5 kg within 90 days prior to screening).
5. **Prior Weight Management Attempt:** History of at least one failed dietary effort to lose weight, as documented in medical records or by participant self-report.
6. **Glycemic Status:** No diagnosis of type 1 or type 2 diabetes mellitus. Participants with prediabetes (HbA1c 5.7-6.4% or fasting plasma glucose 100-125 mg/dL) are eligible and will be stratified.
7. **Adequate Organ Function:** As defined in the following table:

Parameter	Requirement
eGFR (CKD-EPI)	≥30 mL/min/1.73 m²
ALT	≤3.0 × ULN
AST	≤3.0 × ULN
Total Bilirubin	≤1.5 × ULN (unless Gilbert syndrome)
Amylase	≤2.0 × ULN
Lipase	≤2.0 × ULN

Parameter	Requirement
Calcitonin	<50 pg/mL (ng/L)
TSH	Within normal reference range (or clinically stable on thyroid replacement)

1. **Contraception (WOCBP):** Women of childbearing potential must agree to use a highly effective method of contraception (combined hormonal contraception, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, or vasectomized partner) during the study and for at least 8 weeks after the last dose of study drug. Women who are postmenopausal (≥12 consecutive months of amenorrhea without alternative medical cause) or permanently sterilized (bilateral salpingectomy, bilateral oophorectomy, or hysterectomy) are not considered WOCBP.

2. **Contraception (Male participants):** Male participants with female partners of childbearing potential must agree to use effective contraception (condom plus partner use of a highly effective method) during the study and for at least 8 weeks after the last dose.

3. **Pregnancy Testing:** WOCBP must have a negative serum beta-hCG pregnancy test at screening and a negative urine pregnancy test at baseline (Day 1) prior to randomization.

4. **Willingness to Comply with Lifestyle Intervention:** Willing and able to participate in a standardized lifestyle modification program, including reduced-calorie diet (500 kcal/day deficit from estimated energy requirements) and increased physical activity (≥150 minutes/week moderate-intensity aerobic activity), with monthly dietitian counseling sessions.

5. **Injection Self-Administration:** Willing and able to self-administer once-weekly subcutaneous injections (or have a caregiver available to assist) following training at the baseline visit.

5.2 Exclusion Criteria

Participants meeting ANY of the following criteria will be excluded:

Prior/Current Therapy: 1. Use of any prescription or over-the-counter weight loss medication (including orlistat, phentermine, phentermine/topiramate, naltrexone/bupropion, semaglutide, liraglutide, tirzepatide, or any other GLP-1 RA) within 90 days prior to screening. 2. Prior bariatric surgery (gastric bypass, sleeve gastrectomy, gastric band, biliopancreatic diversion) or planned bariatric surgery during the study period. 3. Receipt of any investigational drug, device, or biologic within 30 days or 5 half-lives (whichever is longer) prior to screening, or concurrent enrollment in another interventional clinical trial. 4. Current use of systemic corticosteroids (>7.5

mg prednisone equivalent/day for >14 consecutive days), atypical antipsychotics, or other medications known to cause significant weight gain, within 90 days prior to screening. Inhaled, topical, or intranasal corticosteroids are permitted. 5. Current use of medications known to cause alopecia (e.g., certain chemotherapy agents, lithium, valproic acid, high-dose retinoids, anticoagulants at supratherapeutic doses) within 6 months prior to screening.

Endocrine/Metabolic: 6. Diagnosis of type 1 or type 2 diabetes mellitus, or HbA1c ≥6.5% at screening. 7. History of secondary obesity due to endocrine disorder (e.g., Cushing syndrome, untreated hypothyroidism [TSH >10 mIU/L], hypothalamic obesity) unless adequately treated and stable for ≥6 months. 8. History of pancreatitis (acute or chronic). 9. Personal or family history of medullary thyroid carcinoma (MTC) or Multiple Endocrine Neoplasia type 2 (MEN2). 10. Calcitonin ≥50 pg/mL (ng/L) at screening.

Hair/Dermatologic: 11. Current or history of alopecia areata, alopecia totalis, alopecia universalis, frontal fibrosing alopecia, or other autoimmune-mediated hair loss disorders. 12. Current active scalp condition (e.g., severe seborrheic dermatitis, scalp psoriasis, folliculitis) that would confound alopecia assessment. 13. Use of finasteride, minoxidil, or other hair loss treatments within 6 months prior to screening.

Cardiovascular: 14. Uncontrolled hypertension (systolic BP ≥160 mmHg and/or diastolic BP ≥100 mmHg) despite antihypertensive therapy at screening. 15. History of myocardial infarction, stroke, unstable angina, coronary artery bypass grafting, or percutaneous coronary intervention within 6 months prior to screening. 16. New York Heart Association Class III or IV heart failure. 17. Clinically significant cardiac arrhythmia or QTcF >500 msec on screening ECG.

Gastrointestinal: 18. History of inflammatory bowel disease (Crohn disease, ulcerative colitis). 19. History of gastroparesis or other severe GI motility disorder. 20. History of bowel obstruction or ileus within 12 months prior to screening.

Psychiatric: 21. History of suicidal behavior within 12 months prior to screening, or any suicidal ideation with intent or plan (corresponding to C-SSRS score of 4 or 5) within 12 months prior to screening. 22. History of major depressive disorder with active symptoms not adequately controlled on stable medication for ≥3 months. 23. Current substance use disorder (moderate or severe per DSM-5 criteria) within 12 months prior to screening. Tobacco use disorder is permitted.

Hepatic/Renal: 24. Known history of chronic liver disease (cirrhosis, hepatitis B, hepatitis C), ALT or AST >3.0 × ULN, or total bilirubin >1.5 × ULN at screening (Gilbert syndrome excepted). 25. Severe renal impairment (eGFR <30 mL/min/1.73 m^2) or end-stage renal disease requiring dialysis.

Reproductive: 26. Pregnant or breastfeeding, or planning to become pregnant during the study period and through 8 weeks after the last dose.

Allergies/Hypersensitivity: 27. Known hypersensitivity to SkeetSteph, any GLP-1 receptor agonist, or any excipient of the study drug formulation.

Other: 28. Active malignancy or history of malignancy within 5 years prior to screening, with the exception of adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other non-invasive or indolent malignancy. 29. Any other medical condition that, in the investigator's opinion, would pose an unacceptable risk to the participant or confound interpretation of study data. 30. Inability or unwillingness to comply with the study protocol, visit schedule, or lifestyle intervention requirements.

5.3 Lifestyle Considerations

All participants (both SkeetSteph and placebo arms) will participate in a standardized lifestyle modification program for the duration of the study:

Dietary Intervention: - Reduced-calorie diet targeting approximately 500 kcal/day deficit from estimated total daily energy expenditure (calculated using Mifflin-St Jeor equation adjusted for activity level) - General dietary composition guidance: emphasis on whole foods, fruits, vegetables, lean proteins, whole grains, limited processed foods and added sugars - No specific macronutrient ratio mandated (to reflect real-world primary care setting per FDA guidance) - Monthly counseling sessions with a registered dietitian (in-person or telehealth)

Physical Activity Intervention: - Target: ≥150 minutes/week of moderate-intensity aerobic physical activity (e.g., brisk walking, cycling, swimming) - Gradual progression for sedentary participants (start at 75 min/week, increase by 25 min/week) - Physical activity logged using participant diary and reviewed at each study visit - Resistance/strength training encouraged but not mandated

Contraception: - WOCBP and male participants with WOCBP partners must use highly effective contraception as specified in Inclusion Criteria 8-9 - Pregnancy testing at scheduled visits as specified in the SoA

Nutritional supplementation: - Participants found to have nutritional deficiencies (ferritin <30 ng/mL, zinc <60 mcg/dL, vitamin D <20 ng/mL) at any study visit will be referred to their primary care provider for supplementation per standard of care. Supplementation is permitted and will be documented as a concomitant medication.

Alcohol and substance use: - Moderate alcohol consumption is permitted (≤1 drink/day for women, ≤2 drinks/day for men) - Tobacco cessation is encouraged but not required; changes in tobacco use will be documented

5.4 Screen Failures

A screen failure is defined as a participant who provides informed consent and undergoes screening assessments but is determined to be ineligible for randomization based on the inclusion/exclusion criteria.

- All screen failures will be documented with the primary reason for screen failure in the screening log
- Screen failure rates are expected at approximately 20-25% based on similar GLP-1 RA trials
- Re-screening is permitted once, after a minimum washout of 30 days, only if the initial screen failure reason was for a potentially correctable condition (e.g., elevated liver enzymes, uncontrolled blood pressure). Re-screening requires new informed consent.
- Screen failures will not be assigned a randomization number
- Screen failure data will be retained in the study database for regulatory reporting purposes

5.5 Strategies for Recruitment and Retention

Recruitment Methods: - Identification of potentially eligible participants from investigator patient panels and referral networks - Electronic health record (EHR) screening at participating sites - Physician referral from endocrinology, primary care, and obesity medicine clinics - IRB-approved advertisements (print, digital, social media) targeting the 30-39 age demographic - Community outreach through health fairs, employer wellness programs, and community health centers - Partnership with obesity advocacy organizations - ClinicalTrials.gov posting per regulatory requirements

Diversity and Inclusion: - Recruitment strategies will ensure enrollment reflective of the demographic composition of the target population per FDA Diversity Action Plan requirements - Sites selected to include geographic and socioeconomic diversity - Materials provided in English and Spanish (additional languages per site needs) - Enrollment monitoring by race/ethnicity, sex, and BMI class with targeted recruitment if underrepresentation is identified

Retention Strategies: - Flexible scheduling (including evening and weekend appointments where possible) - Telehealth options for dietitian counseling and non-laboratory visits - Reminder systems (automated calls, texts, emails) for upcoming visits - Reimbursement for study-related travel and time (per IRB-approved amounts, not coercive) - Participant appreciation

communications and study newsletters - Consistent study coordinator contact (dedicated point of contact per participant) - Prompt response to participant questions and concerns - Clear communication about study duration and expectations during informed consent

Enrollment Targets: - Target enrollment of 4,500 participants over approximately 18 months - Average enrollment rate: ~250 participants/month across all sites - Average per-site enrollment: 23-30 participants per site over the enrollment period - Enrollment dashboards monitored weekly by the sponsor with site-level follow-up for underperforming sites

6 STUDY INTERVENTION

6.1 Study Intervention(s) Administration

6.1.1 Study Intervention Description

Feature	SkeetSteph (Investigational)	Placebo (Comparator)
Description	Novel GLP-1 receptor agonist	Matching placebo
Dosage Form	Solution for subcutaneous injection	Solution for subcutaneous injection
Appearance	Clear to slightly opalescent, colorless to slightly yellow	Visually identical to active drug
Delivery Device	Pre-filled single-dose pen	Identical pre-filled single-dose pen
Dose Strengths	[TBD - e.g., 0.25 mg, 0.5 mg, 1.0 mg, 1.7 mg, 2.4 mg]	Volume-matched to each dose strength
Route	Subcutaneous (abdomen, thigh, or upper arm)	Subcutaneous (abdomen, thigh, or upper arm)
Frequency	Once weekly	Once weekly
Injection Volume	[TBD] mL	Matched to active

6.1.2 Dosing and Administration

Dose Escalation Schedule:

Period	Weeks	Dose	Pen Strength
Escalation Step 1	Weeks 1-4	[TBD] mg SC QW	[TBD]
Escalation Step 2	Weeks 5-8	[TBD] mg SC QW	[TBD]
Escalation Step 3	Weeks 9-12	[TBD] mg SC QW	[TBD]
Escalation Step 4	Weeks 13-16	[TBD] mg SC QW	[TBD]

Period	Weeks	Dose	Pen Strength
Escalation Step 5	Weeks 17-20	[TBD] mg SC QW	[TBD]
Maintenance	Weeks 21-72	[TBD] mg SC QW (target dose)	[TBD]

Administration Instructions: - Injections are administered subcutaneously in the abdomen (≥5 cm from umbilicus), front of thigh, or upper arm - Injection site should be rotated with each dose - Injections are administered on the same day each week, at any time of day, with or without meals - If a dose is missed, it should be administered as soon as possible within 5 days of the scheduled day. If more than 5 days have elapsed, the missed dose should be skipped and the next dose administered on the regularly scheduled day. - Participants will be trained on self-injection technique at the baseline visit using training pens, and proficiency will be confirmed before first dose administration

Dose Modification: - If a participant does not tolerate a dose escalation step (persistent Grade ≥2 GI AEs for >2 weeks despite supportive management), the dose may be reduced to the previous tolerated level. One re-escalation attempt is permitted after ≥4 weeks at the reduced dose. - Participants unable to escalate to the target maintenance dose may continue on the highest tolerated dose. These participants will remain in the study and be analyzed per the ITT population.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and Accountability

Study drug (SkeetSteph and matching placebo) will be manufactured by [TBD - sponsor or CMO] and supplied to study sites by the sponsor. Drug accountability logs will be maintained at each site documenting receipt, dispensation, return, and destruction of all study drug. The investigator or designee is responsible for study drug accountability and must ensure that study drug is used only in accordance with this protocol. Unused study drug must be returned to the sponsor or destroyed per site-specific procedures.

6.2.2 Formulation, Appearance, Packaging, and Labeling

SkeetSteph is formulated as a sterile, clear to slightly opalescent, colorless to slightly yellow aqueous solution for subcutaneous injection in a pre-filled single-dose pen. Matching placebo pens are visually identical in appearance, packaging, and labeling (other than the blinded

treatment code). All study drug is labeled in accordance with 21 CFR 312.6 and applicable local regulations, including protocol number, batch number, storage conditions, expiration date, "For Clinical Trial Use Only" statement, and sponsor contact information.

6.2.3 Product Storage and Stability

- Store refrigerated at 2-8°C (36-46°F) in original carton to protect from light
- Do not freeze. Discard if product has been frozen.
- May be stored at room temperature (up to 30°C / 86°F) for up to [TBD] days for participant convenience. Once removed from refrigeration, do not return to refrigerator.
- Shelf life: [TBD] months when stored at 2-8°C
- Each pen is for single use only. Discard after use.
- Do not use if solution is discolored, cloudy, or contains visible particles.

6.2.4 Preparation

No reconstitution or dilution is required. The pre-filled pen is ready for use. Participants should allow the pen to reach room temperature for approximately 30 minutes prior to injection. The injection area should be cleaned with an alcohol swab. Detailed instructions for use are provided in the participant pen instruction guide.

6.3 Measures to Minimize Bias: Randomization and Blinding

Randomization: - Participants will be randomized in a 2:1 ratio (SkeetSteph : placebo) using a centralized interactive web response system (IWRS) - Randomization will use permuted blocks (block sizes will not be disclosed to site personnel to preserve blinding) stratified by: - BMI category (30-34.9 vs 35-39.9 vs ≥40 kg/m²) - Sex (male vs female) - Race/ethnicity (as defined per site demographics) - Glycemic status (normoglycemia [HbA1c <5.7% and FPG <100 mg/dL] vs prediabetes [HbA1c 5.7-6.4% or FPG 100-125 mg/dL])

Blinding: - This is a double-blind study. The following individuals are blinded: participants, investigators, site staff, sponsor clinical team, and outcome assessors (including dermatology assessors for alopecia grading). - An unblinded pharmacist or IWRS designee at each site will manage study drug dispensation. - SkeetSteph and placebo pens are identical in appearance, packaging, and labeling. - The IWRS assigns treatment and manages drug supply without revealing allocation. - Emergency unblinding is available 24/7 through the IWRS for medical emergencies where knowledge of treatment assignment is required for participant safety. Any unblinding event must be documented and reported to the sponsor within 24 hours. - The independent DSMB may review unblinded data per the DSMB charter.

6.4 Study Intervention Compliance

- Study drug compliance will be assessed at each visit by reviewing the participant injection diary and counting used/unused pens
- Compliance is defined as ≥80% of scheduled doses administered
- Site staff will address compliance barriers (injection technique issues, scheduling difficulties, side effects) through counseling and dose modification if appropriate
- Participants with compliance <80% over any 12-week period will receive enhanced adherence counseling
- Compliance data will be summarized and included in the statistical analysis plan

6.5 Concomitant Therapy

Permitted Concomitant Medications: - All medications for pre-existing conditions that are stable for ≥30 days prior to screening (including antihypertensives, statins, antidepressants on stable dose, inhaled/topical corticosteroids, thyroid replacement, oral contraceptives) - Over-the-counter analgesics (acetaminophen, NSAIDs) for acute symptomatic relief - Anti-emetic medications for GI symptom management (e.g., ondansetron) at investigator discretion - Nutritional supplements for identified deficiencies (per Section 5.3) - Vaccinations per standard of care schedule

Prohibited Concomitant Medications: - Other GLP-1 receptor agonists (semaglutide, liraglutide, dulaglutide, exenatide, tirzepatide, etc.) - Other prescription weight loss medications (orlistat, phentermine, phentermine/topiramate, naltrexone/bupropion) - Insulin - Sulfonylureas - Systemic corticosteroids >7.5 mg prednisone equivalent/day for >14 consecutive days - Other investigational agents - Any medication specifically prohibited due to potential drug interactions [TBD based on final drug interaction data]

All concomitant medications and changes will be documented at each study visit. Initiation of new antidiabetic, antihypertensive, or lipid-lowering medications during the study will be captured as potential intercurrent events per the estimand framework.

6.5.1 Rescue Medicine

Anti-emetic therapy (ondansetron 4-8 mg orally as needed, or alternative per investigator preference) is permitted for management of nausea and vomiting during the dose escalation period. Use of rescue anti-emetics will be documented and reported in the safety analysis.

If a participant develops type 2 diabetes during the study (confirmed HbA1c ≥6.5% on two occasions), the participant will be referred to their primary care provider for diabetes management. The participant may continue in the study, and initiation of antidiabetic medication (excluding prohibited medications) will be documented as an intercurrent event. Preferably, metformin would be initiated as first-line per standard of care.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

A participant may discontinue study intervention (SkeetSteph or placebo) while remaining in the study for continued follow-up assessments. Reasons for discontinuation of study intervention include:

1. **Unacceptable toxicity:** - Acute pancreatitis (confirmed by imaging and clinical presentation) - Clinically significant calcitonin elevation (≥100 pg/mL confirmed on repeat testing) or thyroid nodule suspicious for MTC on ultrasound - Severe hypersensitivity reaction (anaphylaxis, angioedema) to study drug - Persistent Grade ≥3 gastrointestinal adverse events despite dose reduction to the lowest dose level and adequate supportive care for ≥4 weeks - Severe alopecia meeting protocol-defined stopping criteria: SALT score >50% (loss of >50% of scalp hair) confirmed on two assessments ≥4 weeks apart, or CTCAE Grade 3 alopecia with significant psychological distress documented by the investigator - Hepatic injury: ALT or AST >5× ULN, or ALT or AST >3× ULN with total bilirubin >2× ULN (Hy's Law criteria) - Suicidal ideation with intent or plan (C-SSRS score 4 or 5) or any suicidal behavior

2. **Intercurrent illness or condition:** Development of a medical condition that contraindicates continued treatment (e.g., new diagnosis of MTC/MEN2, new diagnosis of pancreatitis, development of severe renal impairment [eGFR <15 mL/min])

3. **Pregnancy:** Positive pregnancy test at any time during the study. Study drug must be discontinued immediately. Participant enters pregnancy follow-up per Section 8.3.9.

4. **Investigator decision:** The investigator determines that continued study drug administration poses an unacceptable safety risk to the participant.

5. **Participant decision:** The participant requests to stop study drug but agrees to continue study visits and assessments.

6. **Persistent non-compliance:** Compliance <50% of scheduled doses over any 12-week period despite enhanced adherence counseling, or failure to attend ≥3 consecutive scheduled study visits.

7. **Sponsor decision:** Study termination by sponsor based on DSMB recommendation, regulatory authority action, or other safety-related considerations.

Procedures After Study Intervention Discontinuation:

Participants who discontinue study intervention should continue to attend all scheduled study visits per the Schedule of Activities (Section 1.3) whenever possible. This includes: - Continued body weight measurements at all scheduled visits (primary endpoint data collection) - Continued safety assessments including AE/SAE monitoring through the end-of-study visit (Week 80) - Continued hair assessments at scheduled timepoints to characterize alopecia resolution/persistence - Continued laboratory monitoring (including nutritional panel) at scheduled visits - Continued patient-reported outcomes (IWQOL-Lite, Hairdex) at scheduled visits - An end-of-treatment (EOT) visit should be conducted within 7 days of the last dose of study drug, including all assessments specified for the EOT visit in the SoA - Documentation of the reason for intervention discontinuation and the date of last dose in the eCRF

Participants who discontinue study intervention early will be followed for the remainder of the 72-week treatment period and through the 8-week follow-up period, unless they withdraw consent for all study participation.

7.2 Participant Discontinuation/Withdrawal from the Study

Complete withdrawal from the study means no further study visits, assessments, or data collection will occur.

Criteria for Study Withdrawal:

1. **Withdrawal of consent:** The participant voluntarily withdraws consent for all study procedures. Participants have the right to withdraw at any time without prejudice to their medical care. The investigator should make every reasonable effort to ascertain the reason for withdrawal and document it in the eCRF, but participants are not required to provide a reason.

2. **Lost to follow-up:** Unable to contact the participant despite documented contact attempts per Section 7.3.

3. **Death:** All deaths are reported as SAEs per Section 8.3.6. Date and cause of death are documented from available sources (death certificate, hospital records, autopsy report, investigator assessment).

4. **Investigator decision:** Rare circumstances where the investigator determines that continued study participation (not just study drug) is inappropriate for the participant's safety.

5. **Sponsor decision:** Study termination by the sponsor.

Procedures for Withdrawn Participants:

- Encourage participants to complete an early termination visit with all assessments specified for the EOT visit in the SoA
- Document the reason for withdrawal and date of last contact in the eCRF
- All data collected up to the time of withdrawal will be retained and included in analyses per the statistical analysis plan
- Withdrawn participants will not be replaced
- Participants who withdraw consent for study participation will be included in the Intent-to-Treat (ITT) population based on data collected prior to withdrawal
- Per the informed consent form, previously collected data may continue to be used for study analyses unless the participant specifically requests destruction of their data (to the extent permitted by applicable law)

Partial Withdrawal Options:

Participants may choose partial withdrawal: - **Withdraw from study drug only:** Continue study visits and assessments (preferred option — see Section 7.1) - **Withdraw from in-person visits:** Continue remote data collection (telephone, electronic PROs) if willing - **Complete withdrawal:** No further contact or data collection

The investigator should clearly discuss these options with any participant considering withdrawal and document the participant's preference.

7.3 Lost to Follow-Up

Definition: A participant is considered lost to follow-up (LTFU) when they fail to attend scheduled study visits and cannot be contacted despite documented attempts using all available methods.

Contact Attempt Procedures:

A minimum of 3 documented contact attempts using at least 2 different methods must be made over a period of at least 4 weeks before a participant is classified as LTFU:

1. **Telephone contact:** At least 2 calls at different times of day (morning and evening) on different days of the week. Leave voicemail messages if possible.
2. **Written communication:** One certified letter (or equivalent trackable mail) sent to the participant's last known address.

3. **Electronic communication:** Email and/or text message (if participant has consented to electronic contact).
4. **Emergency contact:** Contact the emergency contact person listed in the participant's study file (per signed consent).
5. **Medical records review:** Check institutional medical records for recent healthcare encounters.

Documentation: Each contact attempt must be documented in the study source documents with: date, time, method used, person making the attempt, and outcome.

Classification: If all contact attempts are exhausted without successful contact, the participant is classified as LTFU. The date of the last successful contact is recorded as the date of withdrawal from the study.

Analysis: LTFU participants are included in the ITT population. Data collected up to the last contact are used in analyses. Missing data after LTFU are handled per the multiple imputation methodology specified in the statistical analysis plan (Section 9).

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8 STUDY ASSESSMENTS AND PROCEDURES

8.1 Efficacy Assessments

Primary Efficacy Assessment: Body Weight

Body weight is the primary efficacy measure for this study. Accurate and consistent weight measurement is critical.

Measurement Procedures: - Body weight measured at every scheduled visit (Screening through Week 80) as specified in the SoA - Calibrated digital scale used at each site; scale must be calibrated per manufacturer instructions and documented at least quarterly - Same scale should be used for a given participant throughout the study whenever possible - Measurements taken in light indoor clothing (no shoes, coats, heavy accessories) - Fasting preferred (≥8 hours) for consistency; fasting status documented - Measured at approximately the same time of day when possible - Weight recorded to the nearest 0.1 kg - If the first measurement appears inconsistent with prior measurements (>2 kg change from last visit for visits <4 weeks apart), a second measurement should be taken and both recorded

Primary Endpoint Derivation: - Percent change from baseline: ((Weight at Week 72 - Weight at Baseline) / Weight at Baseline) × 100 - Baseline weight defined as the Day 1 (randomization) body weight measurement - Co-primary endpoint: Binary response (≥5% weight reduction from baseline at Week 72: Yes/No)

Secondary Efficacy Assessments

Responder Analyses: - Proportion achieving ≥10% weight reduction at Week 72 - Proportion achieving ≥15% weight reduction at Week 72 - Assessed using the same weight measurements as the primary endpoint

Waist Circumference: - Measured at Baseline, Weeks 12, 24, 36, 48, 60, 72, and 80 (per SoA) - Measured at the midpoint between the lowest palpable rib and the iliac crest, at the end of normal expiration, using a non-stretchable tape measure - Recorded to the nearest 0.1 cm - Two measurements taken; if they differ by >1 cm, a third measurement is taken and the median value is recorded

Cardiometabolic Parameters: - Systolic and diastolic blood pressure: Triplicate measurements after 5 minutes seated rest, recorded at every visit. Mean of 3 readings used for analysis. - Fasting plasma glucose: Measured at every visit during dose escalation; every 12 weeks during maintenance - HbA1c: Measured at Screening, Baseline, Weeks 24, 48, and 72 - Fasting lipid panel (total cholesterol, LDL-C, HDL-C, triglycerides): Measured at Screening, Baseline, Weeks 24, 48, and 72

Patient-Reported Outcomes (PROs):

Instrument	Description	Timepoints
IWQOL-Lite (Impact of Weight on Quality of Life - Lite)	31-item weight-specific QoL measure assessing physical function, self-esteem, sexual life, public distress, and work. Total score 0-100 (higher = better).	Baseline, Weeks 24, 48, 72
SF-36 (Short Form 36 Health Survey)	Generic health-related QoL measure with 8 domains and 2 composite scores (Physical Component Summary, Mental Component Summary).	Baseline, Weeks 48, 72
EQ-5D-5L	Generic health utility measure for health economic analyses. 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) with visual analogue scale.	Baseline, Weeks 24, 48, 72
Hairdex	Hair-specific quality of life questionnaire assessing emotional, functional, and social impact of hair problems.	Baseline, Weeks 24, 48, 72, 80

PRO assessments should be completed by the participant at the beginning of the study visit, before any clinical assessments or discussions with study staff, to minimize bias.

Exploratory Efficacy Assessments

DXA Body Composition (Substudy, ~500 participants): - Dual-energy X-ray absorptiometry (DXA) whole-body scan at Baseline and Week 72 - Performed at substudy-qualified sites with standardized DXA equipment (Hologic or GE Lunar) - Measures: Total body fat mass, lean body mass, bone mineral content, percentage body fat, regional fat distribution (android/gynoid ratio) - All DXA scans read by a central imaging core laboratory for consistency - Participants provide separate consent for DXA substudy

8.2 Safety and Other Assessments

Physical Examination

- **Complete physical examination:** Screening, Baseline, and Week 72 (EOT). Includes examination of all major body systems: general appearance, HEENT, cardiovascular, respiratory, abdominal, musculoskeletal, neurological, skin (including scalp), and lymph nodes.
- **Directed physical examination:** All other scheduled visits. Focused on any new or worsening symptoms, AE-related findings, and assessment relevant to the study intervention (GI system, injection sites, scalp/hair).

Vital Signs

Measured at every study visit: - Systolic and diastolic blood pressure (triplicate, seated, after 5 min rest) - Pulse/heart rate - Respiratory rate - Body temperature (oral) - Orthostatic blood pressure and heart rate at Screening only (supine to standing after 3 minutes)

Hair and Alopecia Assessments (Adverse Event of Special Interest)

Given the identified alopecia safety signal with the GLP-1 RA class, this protocol includes comprehensive, prospective hair assessments:

Hair Density Assessment (Trichoscopy): - Performed by a trained dermatology assessor (or site staff trained per protocol-specific training module) - Trichoscopy of standardized scalp regions (vertex, frontal, temporal) using dermoscopic imaging device - Hair density (hairs/cm^2), hair diameter, and vellus-to-terminal hair ratio documented - Standardized hair pull test: gentle traction on 50-60 hairs from 3 scalp regions; >10% extracted hairs is positive (suggestive of active telogen effluvium) - Timepoints: Baseline, Weeks 12, 24, 36, 48, 60, 72, and 80

Standardized Scalp Photography: - Global photographs: 4 standardized views (vertex, frontal hairline, right temporal, left temporal) using a reproducible positioning device - Photographs taken under consistent lighting conditions with color calibration card - All photographs reviewed by central dermatology reader for blinded assessment of hair loss progression/resolution - Timepoints: Baseline, Weeks 24, 48, 72, and 80

Severity of Alopecia Tool (SALT) Score: - Quantitative assessment of percentage of scalp affected by hair loss - Score 0-100 (0 = no hair loss, 100 = complete scalp hair loss) - Calculated by trained assessor at each scheduled hair assessment visit - Used for alopecia severity grading and stopping rule assessment - Timepoints: Baseline, Weeks 12, 24, 36, 48, 60, 72, and 80

CTCAE v5.0 Alopecia Grading: - Grade 1: Hair loss of <50% of normal that is not obvious from a distance but only on close inspection; a different hairstyle may be required to cover the hair loss but it does not require a wig or hairpiece - Grade 2: Hair loss of ≥50% normal that is readily apparent to others; a wig or hairpiece is necessary to completely camouflage - Grade 3: Not defined for alopecia in CTCAE v5.0; for this protocol, Grade 3 is defined as SALT score >75% with significant psychological impact requiring referral for psychological support

Alopecia AESI Reporting: - Any new-onset alopecia or worsening of pre-existing subclinical hair thinning is reported as an AESI - AESI report includes: date of onset, CTCAE grade, SALT score, hair pull test result, nutritional biomarker values at most recent assessment, associated symptoms (scalp pruritus, tenderness), hair loss pattern (diffuse, patterned, patchy), rate of weight loss at time of onset - All alopecia AESIs reviewed by the sponsor's dermatology safety consultant within 5 business days

Laboratory Assessments

Hematology (CBC with differential): - WBC with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), RBC, hemoglobin, hematocrit, platelet count, MCV, MCH, MCHC - Timepoints: Screening, Baseline, Weeks 12, 24, 48, 72

Comprehensive Chemistry Panel: - Sodium, potassium, chloride, bicarbonate, BUN, creatinine, eGFR (CKD-EPI), glucose, calcium, phosphorus, magnesium, total protein, albumin, total bilirubin, direct bilirubin, ALT, AST, alkaline phosphatase, GGT - Timepoints: Screening, Baseline, Weeks 12, 24, 48, 72

Pancreatic Enzymes (Amylase and Lipase): - Monitored for pancreatitis risk per GLP-1 RA class labeling - Elevation >3× ULN triggers enhanced monitoring; elevation >5× ULN with compatible symptoms triggers study drug hold and clinical evaluation per Section 7.1 - Timepoints: Screening, Baseline, and every visit through Week 72

Calcitonin: - Monitored for thyroid C-cell tumor risk per GLP-1 RA class labeling - Calcitonin ≥100 pg/mL on confirmed repeat testing triggers thyroid ultrasound and referral to endocrinologist - Timepoints: Screening, Baseline, Weeks 24, 48, 72

Thyroid Function (TSH, free T4): - Screening, Weeks 24, 72 - Abnormalities evaluated and managed per standard of care

Nutritional Panel (ferritin, serum iron, TIBC, zinc, biotin, vitamin D [25-OH], vitamin B12, folate): - Monitored to identify nutritional deficiencies that may contribute to alopecia - Deficiencies managed per Section 5.3 (Lifestyle Considerations) - Timepoints: Baseline, Weeks 12, 24, 48, 60, 72, 80

Fasting Lipid Panel and Glycemic Parameters: - Per efficacy assessments schedule (Section 8.1)

Pregnancy Testing: - Serum beta-hCG at Screening; urine HCG at Baseline and Weeks 12, 24, 48, 72 (WOCBP only) - Positive pregnancy test triggers immediate study drug discontinuation and pregnancy follow-up

Urinalysis: - Screening and Week 72

12-Lead ECG

- Standard 12-lead ECG performed at Screening, Baseline, Week 24, and Week 72
- ECG reviewed locally by the investigator and centrally by an independent cardiologist (central ECG core laboratory)
- QTcF interval calculated using Fridericia correction
- QTcF >500 msec or increase from baseline >60 msec triggers enhanced cardiac monitoring and clinical evaluation

Columbia-Suicide Severity Rating Scale (C-SSRS)

- Baseline version administered at Screening and Baseline
- Since-last-visit version administered at Weeks 12, 24, 48, and 72
- Any positive response for suicidal ideation with intent (Type 4), suicidal ideation with plan (Type 5), or any suicidal behavior triggers immediate psychiatric evaluation, study drug discontinuation per Section 7.1, and SAE reporting

8.3 Adverse Events and Serious Adverse Events

8.3.1 Definition of Adverse Events (AE)

An adverse event is any untoward medical occurrence in a clinical trial participant administered a study intervention and which does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study intervention, whether or not considered related to the study intervention.

This includes: - Any new condition or worsening of a pre-existing condition - Clinically significant abnormal laboratory values or diagnostic test results - Events resulting from protocol-mandated interventions (e.g., blood draws) - Pre-existing conditions that worsen in severity or frequency during the study

This does NOT include: - Medical or surgical procedures (the condition leading to the procedure is the AE) - Situations where no untoward medical occurrence has occurred (e.g., hospitalization for elective surgery planned before study entry) - Disease progression or worsening of the condition under study (unless unexpected in nature or severity)

8.3.2 Definition of Serious Adverse Events (SAE)

An SAE is any AE that: - Results in death - Is life-threatening (places the participant at immediate risk of death at the time of the event) - Requires inpatient hospitalization or prolongation of existing hospitalization - Results in persistent or significant disability or incapacity - Is a congenital anomaly or birth defect - Is an important medical event that may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Note: Planned hospitalizations for study procedures or pre-existing conditions (planned before study entry) are not SAEs unless the condition worsens unexpectedly.

8.3.3 Classification of an Adverse Event

Each AE must be classified by the investigator for:

Severity (CTCAE v5.0): - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated - Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation indicated; disabling; limiting self-care ADL - Grade 4: Life-threatening consequences; urgent intervention indicated - Grade 5: Death related to AE

Relationship to Study Intervention (Investigator Assessment): - Not related: No reasonable possibility that the study intervention caused the AE - Possibly related: There is a reasonable possibility that the study intervention caused the AE (temporal relationship and/or biological plausibility, but alternative explanations exist) - Probably related: Strong temporal relationship and biological plausibility; unlikely to be explained by another cause - Definitely related: Clear temporal relationship, confirmed by rechallenge or dechallenge, no other plausible explanation

Outcome: - Recovered/Resolved - Recovering/Resolving - Not recovered/Not resolved - Recovered/Resolved with sequelae - Fatal - Unknown

Action Taken with Study Intervention: - None - Dose reduced - Drug interrupted (temporarily held) - Drug withdrawn (permanently discontinued) - Not applicable

8.3.4 Time Period and Frequency for Event Assessment and Follow-Up

AE Collection Period: - AE collection begins at the time of informed consent (for procedure-related AEs) or at the time of first dose of study intervention (for treatment-emergent AEs) - AEs are collected continuously through the end-of-study visit (Week 80) - SAEs are collected from the time of informed consent through 30 days after the last dose of study intervention, or through the end-of-study visit, whichever is later

Assessment Frequency: - AEs assessed at every study visit by open-ended questioning ("Have you experienced any new symptoms or changes in your health since your last visit?") - Between visits: Participants instructed to contact the study site for any new or worsening symptoms - AE assessment includes review of concomitant medications, laboratory results, vital signs, physical examination findings, and participant reports

Follow-Up: - All AEs followed to resolution, stabilization, return to baseline, or determination that the event is chronic/irreversible - SAEs followed until resolution regardless of timing relative to study visits - Alopecia AESIs followed through the end-of-study visit (Week 80) and beyond if not resolved, with extended follow-up per sponsor agreement

8.3.5 Adverse Event Reporting

- All AEs recorded in the eCRF with: verbatim term (MedDRA coding applied by data management), onset date, resolution date (or ongoing), severity grade (CTCAE v5.0), seriousness criteria (if SAE), relationship to study intervention, action taken, outcome, and concomitant treatment administered
- AEs coded using MedDRA (Medical Dictionary for Regulatory Activities), latest version available at database lock

8.3.6 Serious Adverse Event Reporting

- All SAEs must be reported to the sponsor within 24 hours of the investigator becoming aware of the event
- SAEs reported via the electronic SAE reporting system provided by the sponsor
- Initial report: Complete SAE form with all available information within 24 hours
- Follow-up reports: Submit updated information as it becomes available within 5 calendar days

- The sponsor will report all applicable SAEs to the FDA per 21 CFR 312.32 (IND safety reports) within the required timeframes:
- Unexpected fatal or life-threatening suspected adverse reactions: 7 calendar days
- All other reportable SAEs: 15 calendar days
- The sponsor will distribute IND safety reports to all participating investigators and relevant IRBs

8.3.7 Reporting Events to Participants

If the DSMB or sponsor identifies a safety signal that may affect the risk-benefit assessment for enrolled participants, the following actions will be taken: - Updated risk information communicated to all participating investigators - IRBs notified per regulatory requirements - Informed consent form revised if needed - Enrolled participants re-consented with updated risk information if the safety signal materially changes the risk-benefit profile - Decision to continue, modify, or terminate the study made in consultation with the DSMB

8.3.8 Events of Special Interest

The following are designated as Adverse Events of Special Interest (AESI) for this study and require enhanced data collection and expedited reporting to the sponsor within 72 hours:

1. **Alopecia** (any grade): New-onset hair loss or worsening of pre-existing subclinical hair thinning. Enhanced data collection includes SALT score, CTCAE grade, hair pull test result, photographic documentation, nutritional biomarker values, and patient-reported hair impact (Hairdex).

2. **Pancreatitis** (acute or chronic): Any event of pancreatitis regardless of severity. Enhanced data collection includes amylase/lipase values, imaging results (CT/MRI), clinical presentation, and hospitalization details.

3. **Thyroid neoplasm or calcitonin elevation:** Any thyroid nodule detected during the study, any calcitonin elevation ≥50 pg/mL, or any diagnosis of thyroid cancer.

4. **Gallbladder events:** Cholelithiasis, cholecystitis, biliary colic, or other gallbladder-related events.

5. **Severe gastrointestinal events:** Any GI event requiring hospitalization (severe nausea/vomiting with dehydration, bowel obstruction, severe constipation/ileus).

6. **Acute kidney injury:** Any event of acute kidney injury (KDIGO criteria: serum creatinine increase ≥0.3 mg/dL within 48 hours, or ≥1.5× baseline within 7 days, or urine output <0.5 mL/kg/h for ≥6 hours).

7. **Suicidal ideation or behavior:** Any positive C-SSRS response for suicidal ideation with intent (Type 4), plan (Type 5), or any suicidal behavior.

8. **Severe injection site reactions:** Any injection site reaction Grade ≥3 or requiring medical intervention.

8.3.9 Reporting of Pregnancy

- Pregnancy is not an AE but must be reported to the sponsor within 24 hours of awareness
- Study drug must be discontinued immediately upon confirmation of pregnancy
- Pregnancy outcomes will be followed to completion (delivery, spontaneous abortion, elective termination)
- Pregnancy outcome data collected: gestational age at delivery, mode of delivery, infant weight, congenital anomalies (if any), neonatal complications
- Any pregnancy complication or adverse outcome reported as an AE or SAE as appropriate
- Male participants whose partners become pregnant: Pregnancy outcome followed and reported to the sponsor
- Participants should contact the study site immediately if they suspect pregnancy

8.4 Unanticipated Problems

8.4.1 Definition of Unanticipated Problems (UP)

An unanticipated problem (UP) is any incident, experience, or outcome that meets ALL THREE of the following criteria: 1. **Unexpected** (in terms of nature, severity, or frequency) given the procedures described in the protocol, the known characteristics of the study intervention, and the characteristics of the study population 2. **Related or possibly related** to participation in the research 3. **Suggests that the research places participants or others at a greater risk of harm** (including physical, psychological, economic, or social harm) than was previously known or recognized

8.4.2 Unanticipated Problem Reporting

- UPs reported to the IRB and the sponsor within the timeframes specified by the reviewing IRB (typically within 5-10 business days of the investigator becoming aware of the event)
- For federally funded research: UPs involving risks to participants or others reported to OHRP per 45 CFR 46.108(a)(4) and 46.103(b)(5)
- UPs reported to the FDA as appropriate per 21 CFR 312.32
- UP reports include: description of the event, assessment of expectedness, assessment of relatedness to the research, assessment of increased risk, corrective actions taken or proposed

8.4.3 Reporting Unanticipated Problems to Participants

If an UP is identified that may affect the safety or willingness of current participants to continue in the study: - Participants are informed of the new information in a timely manner - Informed consent form revised to reflect the new information - Participants are re-consented with updated consent form - Participants given the opportunity to withdraw from the study based on new information

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

Primary Hypothesis (Continuous Co-Primary Endpoint)

- **Null Hypothesis (H_0):** There is no difference between SkeetSteph and placebo in mean percent change in body weight from baseline to Week 72 (μ_SkeetSteph - μ_Placebo = 0).
- **Alternative Hypothesis (H_1):** SkeetSteph is superior to placebo in mean percent change in body weight from baseline to Week 72 (μ_SkeetSteph - μ_Placebo ≠ 0).
- **Testing:** Two-sided test at alpha = 0.05 (adjusted per hierarchical testing procedure below).

Co-Primary Hypothesis (Binary Co-Primary Endpoint)

- **Null Hypothesis (H_0):** There is no difference between SkeetSteph and placebo in the proportion of participants achieving ≥5% body weight reduction at Week 72 (π_SkeetSteph - π_Placebo = 0).
- **Alternative Hypothesis (H_1):** SkeetSteph is superior to placebo in the proportion achieving ≥5% weight reduction at Week 72 (π_SkeetSteph - π_Placebo ≠ 0).
- **Testing:** Two-sided test at alpha = 0.05.

Multiplicity Adjustment for Co-Primary Endpoints

Both co-primary endpoints must be statistically significant ($p < 0.05$) for the study to be declared positive. This intersection-union testing approach controls the overall Type I error rate at 0.05 without requiring further alpha adjustment, as both hypotheses must be rejected for success.

Key Secondary Hypotheses (Hierarchical Testing)

If both co-primary endpoints are statistically significant, the following secondary endpoints will be tested in a pre-specified hierarchical (fixed-sequence) order at alpha = 0.05:

1. Proportion achieving ≥10% weight reduction at Week 72
2. Proportion achieving ≥15% weight reduction at Week 72
3. Change in waist circumference from baseline to Week 72

4. Change in systolic blood pressure from baseline to Week 72
5. Change in IWQOL-Lite total score from baseline to Week 72

Testing proceeds sequentially; if any test in the sequence fails ($p \geq 0.05$), all subsequent endpoints are considered exploratory (descriptive only). This hierarchical procedure controls the familywise Type I error rate at 0.05.

9.2 Sample Size Determination

Primary Endpoint for Sample Size Calculation

The sample size is based on the continuous co-primary endpoint: percent change in body weight from baseline to Week 72. The continuous endpoint was selected as the basis for powering because it provides greater sensitivity to detect treatment differences than the binary responder endpoint.

Assumptions

Effect Size: - Expected mean percent change in body weight with SkeetSteph: -12.0% - Expected mean percent change in body weight with placebo: -2.5% - Expected treatment difference: 9.5 percentage points - Basis: Conservative estimate informed by STEP 1 (semaglutide: -14.9% vs placebo: -2.4%, NCT03548935), SURMOUNT-1 (tirzepatide: -15.0% to -20.9% vs placebo: -3.1%, NCT04184622), and ATTAIN-1 (orforglipron: -7.5% to -11.2% vs placebo: -2.1%, NCT05869903). A conservative 12% weight loss assumption for SkeetSteph accounts for the possibility of lower efficacy compared to established agents.

Standard Deviation: - Common standard deviation: 8.5% - Basis: Standard deviations observed in STEP 1 (~7-9%) and SURMOUNT-1 (~8-10%) for the primary weight change endpoint.

Statistical Parameters: - Statistical test: Mixed Model for Repeated Measures (MMRM) with ANCOVA at Week 72 as confirmatory - Significance level: Two-sided alpha = 0.05 (no adjustment required for co-primary intersection-union test) - Power: 90% - Allocation ratio: 2:1 (SkeetSteph : Placebo)

Sample Size Calculation

Using a two-sample t-test approximation (conservative relative to MMRM/ANCOVA which provides higher power by leveraging repeated measures):

- **Unadjusted sample size:** Approximately 2,400 (SkeetSteph) and 1,200 (Placebo) = 3,600 total
- **Dropout adjustment:** 20% expected dropout rate based on similar trials (STEP 1: ~14%, SURMOUNT-1: ~15%, with conservative margin for a novel agent)
- **Adjusted sample size:** 3,600 / (1 - 0.20) = 4,500
- **Final enrollment target:** N = 4,500 (3,000 SkeetSteph : 1,500 Placebo)

This enrollment target also meets the FDA 2025 draft guidance requirements of ≥3,000 subjects randomized to the investigational drug and ≥1,500 subjects on placebo for ≥1 year of maintenance treatment.

Sensitivity Analyses for Sample Size

Scenario	Effect Size	SD	Power	N Total (Adjusted)	Conclusion
Base case	9.5%	8.5%	90%	4,500	Adequately powered
Conservative effect (20% lower)	7.6%	8.5%	~85%	4,500	Adequately powered
Higher variance (20% higher SD)	9.5%	10.2%	~82%	4,500	Adequately powered
Both conservative	7.6%	10.2%	~75%	4,500	Borderline; may require sample increase

The proposed sample size of 4,500 provides robust power (≥80%) under moderately conservative assumptions. If actual effect size is smaller than anticipated, the interim analysis (Section 9.4.6) will provide an opportunity for sample size re-estimation.

Power for Co-Primary Binary Endpoint

- Expected proportion achieving ≥5% weight loss: ~85% (SkeetSteph) vs ~35% (Placebo)
- At N = 4,500 (2:1), power exceeds 99% for the binary endpoint using Chi-square test
- The binary co-primary endpoint is not the power-limiting endpoint

Power for Key Secondary Endpoints

The study is formally powered for the continuous co-primary endpoint. Key secondary endpoints are expected to have sufficient power (>80%) based on effect sizes observed in similar trials, though formal power calculations for each secondary endpoint are not presented. Analyses of secondary endpoints that do not achieve statistical significance in the hierarchical testing procedure will be considered exploratory.

IMPORTANT DISCLAIMER: Sample size calculations are preliminary estimates based on pattern analysis of similar trials. Formal sample size calculation using validated statistical software (nQuery, PASS, or SAS PROC POWER) and review by a qualified biostatistician is required before study initiation. Final sample size may be adjusted based on updated assumptions, Phase 2 data, or regulatory feedback from the Pre-IND meeting.

9.3 Populations for Analyses

Population	Definition	Primary Use
Intent-to-Treat (ITT)	All randomized participants, analyzed per randomization assignment regardless of treatment received	Primary population for all efficacy analyses
Modified ITT (mITT)	All randomized participants who received ≥1 dose of study drug and had ≥1 post-baseline body weight measurement	Supportive efficacy analysis
Per-Protocol (PP)	All mITT participants who completed ≥52 weeks of treatment (maintenance period), had ≥80% compliance with study drug, had body weight measured at Week 72 (±14 days), and had no major protocol deviations	Supportive efficacy analysis; sensitivity analysis
Safety	All participants who received ≥1 dose (or partial dose) of study drug, analyzed per treatment actually received	All safety analyses
DXA Substudy	All randomized participants at DXA-qualified sites who consented to DXA substudy and completed baseline DXA	Exploratory body composition analyses

Major Protocol Deviations (excluding from PP): - Enrollment of participant not meeting inclusion/exclusion criteria (eligibility violation) - Use of prohibited concomitant medication (other GLP-1 RA, other prescription weight loss medication) - Study drug compliance <80% - Missing primary endpoint assessment (no body weight at Week 72 ± 14 days)

9.4 Statistical Analyses

9.4.1 General Approach

All statistical analyses will be conducted using SAS version 9.4 or later (SAS Institute, Cary, NC) and/or R version 4.0 or later (R Foundation for Statistical Computing). A detailed Statistical Analysis Plan (SAP) will be finalized prior to database lock.

Descriptive Statistics: - Continuous variables: N, mean, standard deviation, median, Q1, Q3, minimum, maximum - Categorical variables: N, n (frequency), percentage (%)

Inferential Statistics: - Two-sided tests at alpha = 0.05 unless otherwise specified - 95% confidence intervals for treatment effects - P-values reported to 4 decimal places

Pre-Specified Covariates for Primary Analyses: - Baseline body weight (continuous) - Stratification factors: BMI category, sex, race/ethnicity, glycemic status - Age (continuous)

Estimand Framework (per FDA 2025 Guidance and ICH E9(R1)):

The primary estimand is the **treatment policy estimand**, which estimates the treatment effect regardless of adherence to study drug (intent-to-treat principle). This includes all data regardless of treatment discontinuation, use of rescue medication, or initiation of prohibited concomitant medications.

Attribute	Definition
Population	Adults aged 30-39 with BMI ≥30 without T2DM
Treatment	SkeetSteph SC QW vs. Placebo SC QW + lifestyle intervention
Endpoint	Percent change in body weight from baseline to Week 72
Intercurrent Events	Treatment discontinuation: included under treatment policy; Initiation of prohibited weight loss medication: included under treatment policy; Bariatric surgery: composite strategy (treatment failure)
Summary Measure	Difference in means between treatment groups

A **supplementary estimand** (hypothetical estimand) will estimate the treatment effect assuming all participants adhered to study drug for the full 72 weeks, using MMRM under the MAR assumption.

9.4.2 Analysis of the Primary Efficacy Endpoint(s)

Co-Primary Endpoint 1: Percent Change in Body Weight from Baseline to Week 72

- **Population:** ITT
- **Statistical Model:** Mixed Model for Repeated Measures (MMRM)
- Model: % Change from Baseline = Treatment + Visit + Treatment × Visit + Baseline Weight + BMI Category + Sex + Race/Ethnicity + Glycemic Status
- Covariance structure: Unstructured (selected based on model fit criteria; compound symmetry and AR(1) as sensitivity)
- Visits included: Weeks 4, 8, 12, 16, 20, 24, 36, 48, 60, 72
- Primary inference: Least squares mean difference at Week 72 (SkeetSteph minus Placebo) with 95% CI and p-value
- **Confirmatory Analysis:** ANCOVA at Week 72 with multiple imputation for missing data (treatment policy estimand)
- Multiple imputation: 50 imputations using Markov Chain Monte Carlo (MCMC) method under MAR assumption
- Imputation model includes: treatment, baseline weight, all observed post-baseline weights, stratification factors
- Combined using Rubin's rules
- **Sensitivity Analyses:**
- Per-protocol population
- Complete case analysis (participants with observed Week 72 weight)
- Tipping point analysis: Determine what imputed values for missing data in the SkeetSteph arm would change the conclusion
- Pattern-mixture model: Impute missing data using reference-based imputation (placebo-based pattern for SkeetSteph dropouts)
- Delta-adjusted analysis: Add progressively larger penalties (delta = 0, 1, 2, 3, 4 percentage points) to imputed values in the SkeetSteph arm

Co-Primary Endpoint 2: Proportion Achieving ≥5% Weight Reduction at Week 72

- **Population:** ITT
- **Statistical Model:** Logistic regression
- Model: logit(P[≥5% reduction]) = Treatment + Baseline Weight + BMI Category + Sex + Race/Ethnicity + Glycemic Status

- Primary inference: Odds ratio (SkeetSteph vs. Placebo) with 95% CI, p-value, and estimated proportions with 95% CI for each arm
- Risk difference and relative risk also reported
- **Missing Data:** Participants with missing Week 72 weight are classified as non-responders (conservative, aligned with FDA 2025 guidance treatment policy estimand)
- **Sensitivity Analysis:** Multiple imputation approach (impute missing weight, then classify responder status)

9.4.3 Analysis of the Secondary Endpoint(s)

Secondary endpoints tested in hierarchical order (Section 9.1) at alpha = 0.05:

#	Secondary Endpoint	Statistical Method
1	Proportion achieving ≥10% weight reduction at Week 72	Logistic regression (same covariates as co-primary); non-responder imputation for missing data
2	Proportion achieving ≥15% weight reduction at Week 72	Logistic regression; non-responder imputation
3	Change in waist circumference baseline to Week 72	MMRM (same structure as primary); LS mean difference with 95% CI
4	Change in systolic blood pressure baseline to Week 72	MMRM; LS mean difference with 95% CI
5	Change in IWQOL-Lite total score baseline to Week 72	MMRM; LS mean difference with 95% CI; MCID = 7.7 points

Additional secondary endpoints (not in hierarchical gate, reported as descriptive): - Change in fasting plasma glucose and HbA1c from baseline to Week 72 - Change in lipid panel (LDL-C, HDL-C, triglycerides) from baseline to Week 72 - Incidence and severity of alopecia through Week 72 (see Safety Analyses) - Hairdex questionnaire change from baseline to Week 72

9.4.4 Safety Analyses

Population: Safety population (all participants receiving ≥1 dose)

Adverse Events: - Treatment-emergent AEs (TEAEs): Events with onset after first dose or worsening of pre-existing condition after first dose - Summary tables by System Organ Class (SOC) and Preferred Term (PT), sorted by decreasing frequency in the SkeetSteph arm: - Any TEAE - Treatment-related TEAEs (investigator-assessed possible, probable, or definite relationship) - TEAEs by maximum severity (CTCAE Grade 1-5) - Serious TEAEs - TEAEs leading

to dose reduction - TEAEs leading to study drug discontinuation - Fatal TEAEs - Denominators: Number of participants in the safety population per treatment arm - Between-group comparison: Descriptive (no formal statistical testing); risk differences with 95% CI may be calculated for key AEs

Adverse Events of Special Interest (AESI): - Dedicated summary tables for each AESI category (alopecia, pancreatitis, thyroid neoplasm/calcitonin elevation, gallbladder events, severe GI events, acute kidney injury, suicidal ideation/behavior, severe injection site reactions) - For alopecia specifically: - Incidence by CTCAE grade (1, 2, protocol-defined Grade 3) - Time to onset (Kaplan-Meier estimate) - SALT score over time (mean, median, range) - Association between rate of weight loss and alopecia (logistic regression: alopecia yes/no ~ rate of weight loss per month, adjusting for baseline covariates) - Nutritional biomarker levels at time of alopecia onset vs. non-alopecia participants (descriptive) - Resolution/persistence at end of follow-up (Week 80)

Serious Adverse Events: - Separate detailed table by SOC and PT - Individual participant narratives for all SAEs

Laboratory Data: - Shift tables: Baseline CTCAE grade to worst post-baseline CTCAE grade for amylase, lipase, ALT, AST, bilirubin, calcitonin, eGFR - Potentially clinically significant (PCS) values: frequency by treatment arm (e.g., amylase >3× ULN, lipase >3× ULN, ALT >3× ULN, calcitonin ≥50 pg/mL) - Nutritional panel parameters (ferritin, zinc, biotin, vitamin D): mean change from baseline over time by treatment arm

Vital Signs: - Mean change from baseline in SBP, DBP, and heart rate at each visit - Frequency of clinically notable values (SBP >160, HR >100 bpm)

ECG: - Mean change from baseline in QTcF; frequency of QTcF >480 ms or >500 ms or increase >60 ms

C-SSRS: - Shift from baseline in suicidal ideation category; frequency of any positive ideation or behavior

9.4.5 Baseline Descriptive Statistics

Table 1: Baseline Characteristics by Treatment Arm (ITT Population)

Three columns: SkeetSteph (N=3,000), Placebo (N=1,500), Total (N=4,500)

Variables: - Demographics: Age (mean ± SD, range), Sex (n, %), Race (n, %), Ethnicity (n, %), Region (US, Canada, Europe; n, %) - Anthropometric: Body weight (kg; mean ± SD), BMI (kg/m²; mean ± SD), BMI category (30-34.9, 35-39.9, ≥40; n, %), Waist circumference (cm; mean ± SD) -

Glycemic status: Normoglycemia vs prediabetes (n, %), FPG (mg/dL; mean ± SD), HbA1c (%; mean ± SD) - Cardiometabolic: SBP, DBP (mmHg; mean ± SD), Total cholesterol, LDL-C, HDL-C, triglycerides (mg/dL; mean ± SD) - Hair baseline: Hair density (hairs/cm²; mean ± SD), SALT score (mean ± SD), Hair pull test positive (n, %) - Nutritional biomarkers: Ferritin, zinc, vitamin D, biotin (mean ± SD; n (%) below normal) - Prior weight management: Prior diet attempts (n, %), Prior pharmacotherapy (n, %) - Medical history: Hypertension (n, %), Dyslipidemia (n, %), Obstructive sleep apnea (n, %), NAFLD (n, %)

No statistical testing between arms. Baseline comparisons are descriptive only. Randomization ensures balance; hypothesis testing at baseline is methodologically inappropriate.

9.4.6 Planned Interim Analyses

One planned interim analysis will be conducted when approximately 50% of participants (N ≈ 2,250) have completed the Week 72 assessment.

Purpose: Efficacy and futility assessment

Conduct: The independent Data Safety Monitoring Board (DSMB) will conduct the interim analysis. The DSMB biostatistician will prepare unblinded analyses. The sponsor, investigators, and study team will remain blinded.

Methods:

Parameter	Detail
Alpha spending function	Lan-DeMets (O'Brien-Fleming type)
Information fraction	0.50
Efficacy boundary	z = 2.96 (approximately p = 0.003) at interim; z = 2.01 (approximately p = 0.044) at final
Futility boundary	Conditional power < 20% under the current trend
Overall alpha preserved	0.05 (two-sided)

DSMB Recommendations: - Continue as planned - Continue with sample size re-estimation (increase enrollment if effect size smaller than expected) - Stop for efficacy (crosses efficacy boundary) - Stop for futility (conditional power < 20%) - Stop for safety (unacceptable risk-benefit ratio)

Safety Reviews: The DSMB will also conduct safety reviews approximately every 6 months (independent of the efficacy interim). Safety reviews will assess overall AE/SAE rates, mortality, alopecia incidence, and any emerging safety signals.

Impact on Final Analysis: Final analysis p-value boundary adjusted per the alpha spending function. All CIs adjusted accordingly.

9.4.7 Sub-Group Analyses

Pre-specified subgroups (exploratory, not adjusted for multiplicity):

1. **Age:** 30-34 vs 35-39 years
2. **Sex:** Male vs Female
3. **Race:** White vs Black/African American vs Asian vs Other
4. **Ethnicity:** Hispanic/Latino vs Not Hispanic/Latino
5. **BMI category:** 30-34.9 vs 35-39.9 vs ≥40 kg/m²
6. **Glycemic status:** Normoglycemia vs Prediabetes
7. **Baseline waist circumference:** Below vs above median
8. **Region:** US vs Canada vs Europe

Analysis Method: - Treatment × subgroup interaction test in MMRM model (or logistic regression for binary endpoints) - Interaction $p < 0.10$ considered suggestive of heterogeneity (given limited power) - Forest plots: Treatment effect (LS mean difference or OR) with 95% CI for each subgroup level, with overall effect for reference - Consistency assessment: Visual and qualitative evaluation of whether treatment benefit is maintained across subgroups

Interpretation: Subgroup analyses are hypothesis-generating. Results are reported descriptively and are not used for confirmatory inference. Risk of false-positive and false-negative findings due to multiplicity and low power is acknowledged.

9.4.8 Tabulation of Individual Participant Data

Individual participant data listings will be provided in appendices: 1. **Demographics and baseline characteristics** (all randomized participants) 2. **Adverse event listings** (all AEs, SAEs, AEs leading to discontinuation, deaths — with individual narratives for SAEs and deaths) 3. **Concomitant medication listings** (all medications during study) 4. **Laboratory data listings** (all values at all timepoints) 5. **Body weight over time** (all measurements for each participant) 6. **Alopecia event listings** (all alopecia AESIs with SALT scores, CTCAE grades, hair pull test

results, nutritional biomarker values, onset timing, resolution status) 7. **Protocol deviation listings** (all deviations with impact assessment) 8. **Study drug exposure and compliance** (doses received, compliance percentage)

Listings sorted by treatment arm, then participant ID, then visit/date.

9.4.9 Exploratory Analyses

1. **Body Composition (DXA Substudy, N ≈ 500):** - Change in total fat mass (kg), lean body mass (kg), percentage body fat from baseline to Week 72 - ANCOVA adjusted for baseline, sex, and treatment - Ratio of fat mass loss to lean mass loss (fat:lean ratio) by treatment arm - Descriptive statistics and treatment comparisons

2. **Alopecia — Weight Loss Rate Correlation:** - Logistic regression: Alopecia (yes/no) ~ average monthly % weight loss + baseline BMI + age + sex + nutritional biomarkers - Cox regression: Time to alopecia onset ~ rate of weight loss (time-varying covariate) - Threshold analysis: Identify rate-of-weight-loss threshold associated with increased alopecia risk

3. **Nutritional Biomarker Predictors of Alopecia:** - Comparison of baseline and time-varying nutritional biomarker levels (ferritin, zinc, biotin, vitamin D) between participants who develop alopecia and those who do not - ROC analysis for baseline biomarker values predicting alopecia development - Mixed model: Nutritional biomarker trajectory over time by alopecia status

4. **Responder Analyses:** - Proportion achieving ≥20% weight reduction at Week 72 - Time to achieve ≥5% weight reduction (Kaplan-Meier, log-rank) - Characteristics of "super-responders" (≥20% loss) vs "non-responders" (<5% loss): descriptive comparison of demographics, baseline characteristics, and alopecia incidence

5. **Weight Loss Trajectory:** - Growth curve modeling of weight change over time - Latent class analysis to identify distinct trajectory subgroups (e.g., early responders, gradual responders, non-responders) - Characterization of trajectory classes by baseline factors

6. **Weight Regain After Treatment Discontinuation:** - Descriptive analysis of weight change from Week 72 to Week 80 (follow-up period) - Comparison of weight regain trajectory between SkeetSteph and placebo arms

9.4.10 Missing Data Handling (per FDA 2025 Guidance)

Primary Approach: Treatment Policy Estimand with Multiple Imputation

Consistent with FDA 2025 draft guidance, the primary analysis uses a treatment policy estimand that includes all data regardless of treatment adherence. Missing data are handled using multiple imputation:

- **Method:** Multiple imputation by chained equations (MICE) under the missing-at-random (MAR) assumption
- **Number of imputations:** 50
- **Imputation model variables:** Treatment arm, baseline weight, all observed post-baseline weights, age, sex, BMI category, glycemic status, race/ethnicity
- **Combination:** Rubin's rules for combining estimates across imputations
- **Software:** SAS PROC MI and PROC MIANALYZE (or R mice package)

Sensitivity Analyses for Missing Data:

1. **Complete case analysis:** Only participants with observed Week 72 weight (MCAR assumption)
2. **Reference-based imputation (jump-to-reference):** Missing SkeetSteph data imputed from placebo distribution (conservative for treatment policy estimand)
3. **Copy increments in reference (CIR):** Missing SkeetSteph data imputed assuming post-discontinuation trajectory matches placebo trajectory
4. **Tipping point analysis:** Progressively increase imputed values for SkeetSteph missing data (delta = 0, 1, 2, 3, 4 percentage points added) to identify assumptions that would change the primary conclusion
5. **Pattern-mixture model:** Model missing data patterns and assess sensitivity to the MAR assumption

Missing Data Monitoring: - Missing data rates monitored quarterly by the sponsor data management team - If missing data rate exceeds 25% in either arm, the DSMB will be notified and retention strategies intensified - Missing data reasons (withdrawal of consent, LTFU, AE-related discontinuation) will be tabulated by treatment arm and compared descriptively

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Informed Consent Process

The informed consent process will be conducted in accordance with 21 CFR Part 50, ICH E6(R2), and applicable local regulations. The informed consent form (ICF) will be written at an appropriate reading level (8th grade or lower) in the participant's primary language.

Process: - The Principal Investigator or a qualified, trained designee will explain the study to potential participants - Participants will be given adequate time (at least 24 hours recommended) to review the ICF and discuss with family members or personal physicians - All questions will be answered to the participant's satisfaction before consent is obtained - The voluntary nature of participation, the right to withdraw at any time without penalty, and the alternatives to study participation will be emphasized - The ICF will describe all known risks, including the alopecia safety signal, in clear language

Documentation: - The ICF is signed and dated by the participant (or legally authorized representative) and the person obtaining consent - The original signed ICF is maintained in the study regulatory file - A copy is provided to the participant - The consent process is documented in the participant's medical record

Re-Consent: If the protocol is amended with changes that materially affect participant risk or benefit, a revised ICF will be submitted to the IRB for approval. Currently enrolled participants will be re-consented with the updated ICF.

Special Consents: - DXA substudy: Separate consent section or addendum for body composition substudy - Future use of specimens: Optional consent for storage and future research use of biological specimens - HIPAA Authorization: Separate HIPAA authorization form (US sites)

10.1.2 Study Discontinuation and Closure

The study may be discontinued early if: - The DSMB recommends termination based on safety or futility analysis - The FDA or other regulatory authority requests or orders study discontinuation - The sponsor determines that continued conduct of the study is not in the best interest of participants or is not feasible

Closure procedures: - All enrolled participants notified and offered a final safety visit - IRBs notified with reason for early termination - FDA notified per regulatory requirements (IND safety report or annual report) - ClinicalTrials.gov updated with "Terminated" status and reason - All data collected through termination analyzed and reported - Final clinical study report prepared and submitted to the FDA

10.1.3 Confidentiality and Privacy

Participant confidentiality is protected through: - Assignment of unique numeric participant identifiers (site number + sequential ID) - No personal identifiers (names, dates of birth, medical record numbers) included in the study database or transmitted to the sponsor - Site master identification log linking participant ID to identity maintained separately in a locked location with restricted access - All electronic data stored on password-protected, encrypted, access-controlled servers - Data transmitted via secure encrypted channels - HIPAA authorization obtained at US sites - GDPR compliance at European sites, including Data Processing Agreements between sponsor and sites - All study personnel sign confidentiality agreements

10.1.4 Future Use of Stored Specimens and Data

Participants may optionally consent to the storage and future use of biological specimens (blood samples) collected during the study. Future research may include biomarker discovery, pharmacogenomic analyses, or other exploratory investigations. Specimens will be coded (linked to study ID only, not personal identifiers) and stored at a sponsor-designated biorepository for up to 15 years. Participants may withdraw consent for future specimen use at any time, at which point remaining specimens will be destroyed.

Deidentified study data may be made available to qualified researchers upon reasonable request for secondary analyses, meta-analyses, or regulatory submissions, subject to a data use agreement. Individual participant data sharing will comply with applicable regulations (ICH E6, GDPR) and will not occur until after publication of the primary study results.

10.1.5 Key Roles and Study Governance

Sponsor: Responsible for overall study oversight, IND submission and maintenance, regulatory correspondence, study drug supply, site selection and qualification, clinical monitoring, data management, pharmacovigilance, statistical analysis, and the final clinical study report.

Principal Investigator (Site PI): Responsible for the conduct of the study at their site in accordance with the protocol, ICH-GCP, and applicable regulations. Duties include: IRB submissions, informed consent, participant safety, AE/SAE reporting, data accuracy, study drug accountability, staff supervision and training, and cooperation with monitoring and audits.

Global Coordinating Investigator: Provides scientific leadership, chairs the Steering Committee, leads publication efforts, and serves as the primary clinical interface with the sponsor.

Steering Committee: Provides scientific oversight of the study. Comprises the Global Coordinating Investigator, 4-6 key opinion leaders in obesity medicine, a biostatistician representative, and sponsor medical representatives. Meets quarterly.

DSMB: See Section 10.1.6.

Contract Research Organization (CRO): [TBD] — may be contracted by the sponsor to perform clinical monitoring, data management, biostatistics, pharmacovigilance, and/or regulatory submissions.

10.1.6 Safety Oversight

Data Safety Monitoring Board (DSMB):

A DSMB is required for this study given its large sample size, Phase 3 pivotal design, blinded treatment assignment with interim analysis, and the novel alopecia safety signal requiring ongoing monitoring.

Composition: 5 members — 2 clinical experts in obesity medicine/endocrinology, 1 dermatologist (for alopecia safety oversight), 1 independent biostatistician, 1 ethicist/clinical trialist. All members are independent of the sponsor and investigators with no financial conflicts of interest.

Charter: The DSMB operates under a formal charter that specifies membership, meeting procedures, data access, confidentiality requirements, voting rules, and reporting procedures. The charter is finalized before the first participant is enrolled.

Meetings: Approximately every 6 months, or more frequently if safety concerns arise. Meetings include: - Open session: Aggregate blinded safety data presented to DSMB and sponsor - Closed session: Unblinded safety and efficacy data reviewed by DSMB only

Recommendations: After each review, the DSMB provides one of the following recommendations to the sponsor: - Continue study as planned - Continue with modifications (protocol amendment, enhanced monitoring) - Suspend enrollment pending further evaluation - Terminate the study

Stopping Rules:

Rule	Trigger	Action
Safety	Mortality rate >1% in SkeetSteph arm (not attributed to non-study causes)	DSMB convenes emergency review
Safety	Acute pancreatitis rate >2% in SkeetSteph arm	DSMB convenes emergency review
Safety	Severe alopecia (SALT >75%) rate >5% in SkeetSteph arm	DSMB convenes emergency review
Futility	Conditional power <20% at interim (Section 9.4.6)	DSMB may recommend termination
Efficacy	Efficacy boundary crossed at interim (Section 9.4.6)	DSMB may recommend early success

10.1.7 Clinical Monitoring

A risk-based monitoring approach per FDA guidance ("Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring") will be implemented.

On-Site Monitoring: - Site initiation visit (SIV): Before first participant enrolled at each site - Periodic monitoring visits: Quarterly during active enrollment, transitioning to semi-annual during follow-up - Close-out visit (COV): After last participant completes study at each site

Key monitoring activities: - 100% source data verification for: informed consent, eligibility criteria, primary endpoint (body weight), SAEs, study drug accountability - Targeted SDV (~20%) for: secondary endpoints, laboratory data, concomitant medications, non-serious AEs

Central/Remote Monitoring: - Real-time eCRF data review for data quality, completeness, and consistency - Statistical monitoring for site-level outliers (enrollment patterns, AE rates, data distributions) - Risk indicators tracked: query rates, protocol deviation rates, SAE reporting timeliness, enrollment vs. target

10.1.8 Quality Assurance and Quality Control

Quality System: - Study conducted per sponsor and CRO SOPs - All study staff complete ICH-GCP training and protocol-specific training before study involvement - Protocol-specific training includes: SkeetSteph injection administration, alopecia assessment (trichoscopy, SALT scoring, scalp photography), C-SSRS administration, lifestyle intervention delivery, EDC system use

Audits: - Sponsor QA may conduct audits of selected sites, the CRO, central laboratories, and the DSMB process - Sites maintain inspection-ready regulatory files at all times - FDA may conduct routine or for-cause inspections at any time

10.1.9 Data Handling and Record Keeping

Electronic Data Capture: - EDC system: [TBD — e.g., Medidata Rave, Oracle Clinical, Veeva, or REDCap] - 21 CFR Part 11 compliant with audit trail, electronic signatures, role-based access control - Data entered within 3 business days of each visit - Data queries resolved within 5 business days

Source Documentation: - Source documents include: medical records, laboratory reports, ECG printouts, DXA reports, scalp photographs, PRO questionnaires, pharmacy dispensing records - Source data verification performed per monitoring plan

Database Lock: - All data entered, queries resolved, monitoring complete - Medical and statistical review complete - Database lock meeting conducted - Database frozen for analysis

Record Retention: - Study records retained for a minimum of 2 years after the last approval of a marketing application, or 2 years after the IND is closed, or per local regulations (whichever is longest) - Sponsor will notify sites when records may be destroyed

10.1.10 Protocol Deviations

All protocol deviations are documented, classified (major vs minor), and reported to the sponsor and IRB per applicable requirements.

Major deviations (affecting participant safety, rights, or data integrity): Reported to the sponsor within 24 hours and to the IRB per IRB-specific timelines. Examples: enrollment of ineligible participant, administration of incorrect study drug, failure to obtain informed consent, missed SAE reporting.

Minor deviations (not affecting safety or data integrity): Documented and reported to the sponsor during routine data transmission. Examples: visit conducted outside the protocol-specified window, minor documentation omission.

Root cause analysis is performed for all major deviations and for patterns of minor deviations. Corrective and preventive actions (CAPA) are implemented as needed.

10.1.11 Publication and Data Sharing Policy

Publication: Study results will be published in a peer-reviewed journal per ICMJE guidelines. The primary manuscript is targeted within 12 months of study completion. Authorship will follow ICMJE criteria. The sponsor has the right to review manuscripts before submission for accuracy and protection of confidential information (review period: 30 days).

ClinicalTrials.gov: Results posted per 42 CFR Part 11 requirements within 1 year of primary completion date.

Data Sharing: Deidentified individual participant data may be made available to qualified researchers upon reasonable request after publication of the primary manuscript, subject to a data use agreement.

10.1.12 Conflict of Interest Policy

All investigators and sub-investigators will complete financial disclosure forms per 21 CFR Part 54 at study initiation and at study completion. Disclosable financial interests include compensation tied to study outcome, proprietary interest in SkeetSteph, equity interest in the sponsor exceeding $50,000, and significant payments exceeding $25,000 annually. The sponsor will review all disclosures and implement conflict management strategies as needed (increased monitoring, independent data verification, or investigator exclusion).

10.2 Additional Considerations

Alopecia Assessment Training: All sites will designate at least one trained assessor for hair/alopecia assessments. Training will include standardized trichoscopy technique, SALT scoring, hair pull test procedure, and scalp photography positioning. A training module and certification quiz will be provided by the sponsor. Assessor certification must be completed before the first participant undergoes baseline hair assessment at each site.

Lifestyle Intervention Standardization: Monthly dietitian counseling sessions will follow a standardized curriculum developed by the sponsor in consultation with obesity medicine experts. Training for site dietitians/nutritionists will be provided during the SIV. Lifestyle intervention adherence will be documented via participant food diaries and physical activity logs reviewed at each visit.

Emergency Procedures: A 24/7 emergency contact line is available for investigators to reach the sponsor medical monitor for urgent safety questions, emergency unblinding requests, and guidance on management of study-related medical emergencies.

10.3 Abbreviations

Abbreviation	Full Term
ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CAPA	Corrective and Preventive Action
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CI	Confidence Interval

Abbreviation	Full Term
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMO	Contract Manufacturing Organization
COV	Close-Out Visit
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DIO	Diet-Induced Obese (animal model)
DSMB	Data Safety Monitoring Board
DXA	Dual-Energy X-ray Absorptiometry
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EOT	End of Treatment
EOS	End of Study
EQ-5D-5L	EuroQol 5-Dimension 5-Level
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
GLP-1	Glucagon-Like Peptide-1
HbA1c	Glycated Hemoglobin

Abbreviation	Full Term
hCG	Human Chorionic Gonadotropin
HDL-C	High-Density Lipoprotein Cholesterol
HED	Human Equivalent Dose
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard Ratio
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
IWQOL-Lite	Impact of Weight on Quality of Life - Lite
IWRS	Interactive Web Response System
KDIGO	Kidney Disease: Improving Global Outcomes
LDL-C	Low-Density Lipoprotein Cholesterol
LTFU	Lost to Follow-Up
MAR	Missing at Random
MCAR	Missing Completely at Random
MCID	Minimal Clinically Important Difference
MedDRA	Medical Dictionary for Regulatory Activities
MEN2	Multiple Endocrine Neoplasia Type 2
MICE	Multiple Imputation by Chained Equations
mITT	Modified Intent-to-Treat
MMRM	Mixed Model for Repeated Measures
MOA	Mechanism of Action
MTC	Medullary Thyroid Carcinoma

Abbreviation	Full Term
NDA	New Drug Application
NOAEL	No-Observed-Adverse-Effect Level
OHRP	Office for Human Research Protections
OR	Odds Ratio
PD	Pharmacodynamics
PHI	Protected Health Information
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per-Protocol
PRO	Patient-Reported Outcome
PT	Preferred Term
QTcF	QT Interval Corrected by Fridericia Formula
QW	Once Weekly
RA	Receptor Agonist
RCT	Randomized Controlled Trial
ROC	Receiver Operating Characteristic
ROR	Reporting Odds Ratio
SAE	Serious Adverse Event
SALT	Severity of Alopecia Tool
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SDV	Source Data Verification
SF-36	Short Form 36 Health Survey
SIV	Site Initiation Visit

Abbreviation	Full Term
SoA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
T2DM	Type 2 Diabetes Mellitus
TEAE	Treatment-Emergent Adverse Event
TIBC	Total Iron-Binding Capacity
TSH	Thyroid-Stimulating Hormone
ULN	Upper Limit of Normal
UP	Unanticipated Problem
WOCBP	Women of Childbearing Potential

10.4 Protocol Amendment History

Amendment #	Date	Description	Sections Affected
Original	11-FEB-2026	Original protocol (Version 1.0 Draft)	All

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