1 TITLE PAGE

CLINICAL STUDY PROTOCOL

A Phase IIb multicentre, double-blind, dose-ranging, randomised, placebo-controlled study evaluating safety and efficacy of BGS649 in male obese subjects with hypogonadotropic hypogonadism

Protocol No.: MBGS205	EUDRACT/IND No.: 2015-005760-42
Test Product:	BGS649
Indication:	Hypogonadotropic hypogonadism
Sponsor:	Mereo BioPharma 2 Ltd
Development Phase:	Phase IIb
Sponsor Signatory:	[redacted]
Sponsor Medical Expert:	
Date of the Protocol:	10 March 2017
Version of the Protocol:	Amended Protocol Version 6.0

The confidential information in this document is provided to you as an investigator, potential investigator or consultant for review by you, your staff and applicable Independent Ethics Committee and/or Institutional Review Board. It is understood that the information will not be disclosed to others without written authorisation from Mereo BioPharma 2 Ltd except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

SUMMARY AND JUSTIFICATION OF CHANGES

This amendment includes revisions to Protocol Version 5.0, dated 03 November 2016, summarized as follows

Change	Rationale
Clarification that the primary efficacy analysis and study unblinding will be performed when all data from Visit 8 (week 24) has been collected. The full 12 week follow up safety data will be separately analysed.	Performing the MBGS205 efficacy analysis at the earliest point will enable ineffective doses in MBGS206 to be discontinued and prevent subjects from MBGS205 transitioning an ineffective arm of MBGS206.
Limiting semen PK to Visit 8/EOT and removal of requirement for semen PK at Visits 9, 10 and 11.	To reduce burden of semen sampling on patients,as adequate follow up samples will be obtained through previously recruited patients and through the extension study MBGS206.
Screened subjects increased from 700 to 2000.	To reflect the screen failure rate.
Change in exclusion criterion to HbA1C from $\leq$8.5% to $\leq$10.5%.	To reflect the target population which includes a number of patients with type 2 diabetes and in light of no adverse effects on glucose control in >100 patients within the current trial.
Removal of monoclonal antibodies as exclusion criterion.	No clinical or scientific reason to exclude these treatments, apart from those that affect bone that are covered in a separate exclusion criterion.
Removal of use of insulin as exclusion criterion.	To enable recruitment of representative target population of obese men with type 2 diabetes requiring insulin.
Removal of exclusion critererion for new prescription or over-the-counter drug known to affect glucose homeostasis within the 4 weeks prior to first Screening Visit.	Already covered in exclusion criterion 7.
Change of exclusion of any history of weight reduction surgery or procedures, to surgeries and procedures that have occurred in the 3 months prior to Screening.	To enable inclusion of releavent patients in the target population. Ongoing significant weight effecta of surgeries prior to this time would be captured by weight loss or gain exclusion criterion 12.

Removal of change in smoking habit exclusion criterion.	Change in smoking not anticipated to affect study assessments or safety.
Only SAEs to be collected during screening.	No requirement to collects AEs prior to randomisation and dosing.
Increase semen sample timing window at baseline to 48 hours before/after baseline visit.	To increase flexibility of sampling date due to difficulty patients may have in providing sample and travel to specialist labs.
Plasma PK limited to testing at Visit 5 (week 12) and Visit 8 (EOT).	Adequate plasma PK data has now been collected to enable reduction in testing frequency to reduce burden on subject.
Visits 9 and 10 changed to telephone follow up.	Removal of requirement for semen PK at FU Visits 9 and 10 means these can be telephone only for assessment of AEs and concomitant medications.
Window for Baseline DEXA scan increased to be allowed any time in screening period and up to Day 8 after randomisation.	To overcome scheduling challenges with other assessments.
Window for EOT DEXA scan increased to up to 14 days before EOT.	To overcome scheduling challenges with other assessments and timelines to meet inclusion criteria for extension study MBGS206.
Ability to retest inclusion/exclusion laboratory tests under specific circumstances of technical failure or defined abherent results on agreement with medical monitor.	To prevent technical issues in laboratory measures inappropriately excluding subjects.
Ability to rescreen if change in clinical status $\geq$ 6 months after an initial screen failure if approved by medical monitor.	To enable previously screen failed subjects to be recruited when there has been a change in clinical statusover time.
Ability to rescreen if a subject previously failed due to a inclusion/exclusion or other study requirement than has been changed in subsequent protocols.	To enable previously screen failed subjects to be recruited when there has been a protocolised change in study requirements.
Clarification of follow up visits for early drug termination.	Clarification

Removal of Cyp3A4 modifying concomitant medications.	BGS649 has been shown not to be a substrate or inducer of major Cytochrome (CYP) 450 enzymes and is metabolised very slowly by CYPs. Therefore, the potential of BGS649 drug-drug interactions is low.
Clarification of worseining of lower limb oedema to exclude measurement artifacts and effects of restrictive clothing.	To prevent innapropriate drug interruption for artefactual worsening of leg oedema.
DEXA scan information changed to require same machine to the be used for baseline and follow up scans and greater details on technical requirements, including measurement of both femoral neck and total hip, requirement to apply the guidance given within the study imaging manual and to retain the primary source data from the scan.	DEXA scan procedures required to be tightened following variability of bone mineral density data from study to date.

2 SPONSOR SIGNATURE PAGE

PROTOCOL TITLE: A Phase IIb multicentre, double-blind, dose-ranging, randomised, placebo-controlled study evaluating safety and efficacy of BGS649 in male obese subjects with hypogonadotropic hypogonadism

PROTOCOL NUMBER: MBGS205

Mereo BioPharma 2 Limited

[redacted]

6th APRIL 2017
Date (day/month/year)

[redacted]

6 APRIL 2017
Date (day/month/year)

3 GENERAL INFORMATION

A Phase IIb multicentre, double-blind, dose-ranging, randomised, placebo-controlled study evaluating safety and efficacy of BGS649 in male obese subjects with hypogonadotropic hypogonadism

Protocol No.:	MBGS205
Date of the Protocol:	28 December 2015
Date and Number of Amendment(s):	09 March 2016, Amendment 1.0 05 May 2016, Amendment 2.0 26 September 2016, Amendment 3.0 03 November 2016, Amendment 4.0 10 March 2017, Amendment 5.0
Sponsor:	Mereo BioPharma 2 Ltd 1 Cavendish Place London W1G 0QF
Clinical Research Organisation:	ICON Clinical Research Ltd South County Business Park Leopardstown Dublin 18 Ireland
Sponsor Signatory:	[redacted]
Sponsor Medical Expert:	[redacted]
Principal Investigator:	Professor T. Hugh Jones Robert Hague Centre for Diabetes and Endocrinology Barnsley Hospital NHS Foundation Trust Gawber Road Barnsely S25 2EP UK Tel No.: +44 (0) 1226 431896 Fax No.: +44 (0) 1226 434404

Biostatistics: [redacted]

4 STUDY SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
Mereo BioPharma 2 Ltd</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier:

Volume:

Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Product:
BGS649</td></tr>
<tr><td>Name of Active Ingredient:
4,4’-[fluoro-(1-H-1,2,4-triazol-1-yl)methylene]bisbenzonitrile</td></tr>
<tr><td colspan="3">Title of Study:
A Phase IIb multicentre, double-blind, dose-ranging, randomised, placebo-controlled study evaluating safety and efficacy of BGS649 in male obese subjects with hypogonadotropic hypogonadism.</td></tr>
<tr><td colspan="3">Principal Investigator:
Professor T. Hugh Jones</td></tr>
<tr><td colspan="3">Study Centre(s):
It is planned that approximately 75 centres will be initiated for this study in approximately five countries.</td></tr>
<tr><td colspan="3">Publication(s):
None</td></tr>
<tr><td colspan="2">Planned Study Period:
Jan 2016 to Feb 2017</td><td>Development Phase:
Phase IIb</td></tr>
<tr><td colspan="3">Objectives:
Primary Objectives
The primary objective is to demonstrate the efficacy of BGS649 to normalise total testosterone levels (300-1000 ng/dL [10.4-35 nmol/L]) in ≥ 75% of subjects after 24 weeks of treatment.
Secondary Objectives
1. To follow the time-course of normalisation in total testosterone levels
2. To demonstrate the efficacy of BGS649 to normalise total testosterone levels in ≥ 90% of subjects after 24 weeks of treatment
3. To evaluate the effect of BGS649 on luteinising hormone (LH) and follicle stimulating hormone (FSH)
4. To further determine the pharmacokinetics (PK) of BGS649.
Safety Objectives
1. To evaluate safety and tolerability of BGS649
Exploratory Objectives
1. To evaluate the effect of BGS649 on oestradiol, DHT and inhibins (A and B)
2. To evaluate the effect of BGS649 on testosterone/oestradiol ratio
3. To investigate the effect on patient reported outcomes (PROs) following treatment with BGS649. PRO measures will be:
o International Index of Erectile Function (IIEF) and PROMIS Sexual Function and Satisfaction (PROMIS SexFS): to assess improvement in erectile function
o IIEF and PROMIS SexFS: to assess improvement in sexual desire and satisfaction with sex life.
o 36-item Short Form Health Survey (SF-36): to assess general quality of life (QoL).
o Brief Fatigue Inventory (BFI), PROMIS Fatigue Short Form and the SF-36 Vitality: to assess improvement in energy levels.
o Patient Global Impression of Status items (PGI-S): to assess the patients’ overall impression of their current health status.
4. To determine any change in physical activity and sleeping pattern via wrist worn monitor
5. To determine any change in grip strength, as measured by a dynamometer</td></tr>
</table>

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6. To determine any associations between objective findings of improvement (e.g. testosterone, time in physical activity or sleep, and grip strength) and total and domain scores on PRO measures
7. To determine body composition change: waist circumference, BMI, body composition (as measured by impedance), and gynecomastia
8. To determine any associations between change in testosterone, body composition (as measured by BMI and waist circumference) and change in grip strength and wrist monitor data
9. To determine any associations between change in testosterone, body composition (as measured by impedance) and change in grip strength and wrist monitor data
10. To determine the effect of BGS649 on cardiometabolic parameters: systolic blood pressure (SBP) and diastolic blood pressure (DBP), lipid panel (total cholesterol, low density lipoprotein [LDL], triglycerides and HDL), glycosylated haemoglobin (HbA1c), fasting glucose and insulin, HOMA-IR and high sensitivity C-reactive protein (hs-CRP)
11. To determine any associations between testosterone, change in body composition and cardiometabolic parameters: SBP and DBP, lipid panel (total cholesterol, LDL, triglycerides and HDL), HbA1c, fasting glucose and insulin, HOMA-IR and hs-CRP
12. To determine the change in bone mineral density (dual energy X-ray absorptiometry [DEXA] scan), bone turnover markers (C-terminal telopeptide [CTx1] and procollagen type 1 N-propeptide [P1NP], osteocalcin, bone alkaline phosphatase)
13. To explore the effects of BGS649 on bone biomarkers on subjects with and without 25 hydroxy vitamin D deficiency (vitamin D deficiency is defined as 25 hydroxy vitamin D < 20ng/ml)
14. To explore the relationship between BGS649 concentration and testosterone levels
15. To determine the effects of BGS649 on semen parameters (semen volume, sperm count, concentration, motility and morphology) and to measure BGS649 concentrations in seminal fluid in subjects that provide semen samples
16. To explore the relationship between LH/FSH change and improvement in semen analysis in subjects that provide semen samples.

Methodology:

This is a phase IIb, multicentre, double-blind, randomised, placebo-controlled parallel-group 36-week study evaluating safety and efficacy of BGS649 in male obese subjects with hypogonadotropic hypogonadism (HH). The study will have three phases:

1. A Screening Phase lasting up to 28 days, including Day -28 to Day -1
2. A Randomisation Phase including the Baseline visit (Day 1) and the treatment period Day 1 to Visit 8 (Week 24)
3. A Safety Follow-Up Phase to Visit 11 (Week 36, follow-up [FU]). Visits 9 and 10 are telephone assessments

Study participation will comprise up to 2 Screening Visits, 8 visits during the treatment period up to Week 24 (End of Treatment [EOT]), FU Visits 9, 10 (telephone assessments) and 11 (at Weeks 28, 32 and 36 respectively) for safety performed to 12 weeks after Visit 8 (EOT). PK in seminal fluid will be performed at Visits 8 (EOT). A minimum of 25 subjects per arm will be offered a 6 month extension study (Protocol MBGS206), starting at Visit 8 (EOT). Subjects participating in the 6-month extension will have their last study visit at Visit 8 (EOT). The end of the study will be the last visit of the last subject.

Eligible subjects will be randomised on Day 1 (Baseline) in a 1:1:1:1 ratio to one of the following treatment groups, consisting of three capsules per dose taken weekly:

- BGS649 [redacted]
- BGS649 [redacted]
- BGS649 [redacted]
- BGS649 matching placebo [redacted]

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Once approximately 100 of the overall planned enrolled subjects have completed the Week 4 visit, an interim analysis will be performed by an independent data monitoring committee (DMC) who will review unblinded data and determine whether the criteria for normalisation of testosterone (testosterone within or above normal reference range for healthy adult males according to the Food and Drug Administration [FDA] criteria) were met. The DMC will establish whether an individual arm has met the criteria of ≥ 75% of subjects reaching the normalisation of testosterone, or whether in the opinion of the DMC following unblinded review that when the arm is fully recruited it is expected to achieve a ≥ 75% response at Week 24. Dosing arms which meet either of these criteria will be deemed effective. For dosing arms deemed ineffective, dosing will be stopped and no further randomisation to that arm will be performed. Subjects assigned to the ineffective or unsafe arm(s), as determined per the DMC, will be discontinued from the treatment, will attend Visit 8 (EOT) and will be followed-up for an additional 12 weeks (FU, Visit 11).

The remainder of the randomisation will then continue in a 1:1:1 ratio of remaining active arms versus placebo to the following treatment groups:

- BGS649 [redacted]
- BGS649 matching placebo.

During the 24 week treatment period, subjects in the BGS649 groups and the matching placebo group will take the required dose weekly (± 1 day from the time schedule of regular planned dose) with water.

Seminal Fluid Evaluation:

Semen Quality

To evaluate the effect of BGS649 treatment on sperm quality, semen analysis (sperm count, semen volume, concentration, motility, and morphology) will be performed. Subjects will be expected to successfully provide semen samples on three occasions during the Randomisation Phase. It is understandable that some subjects will not be able to provide semen samples.

Semen PK

An additional semen sample will be required at Visit 8 (EOT) in order to assess PK in seminal fluid to evaluate the concentration of BGS649.

Any subjects who are vasectomised or have vasectomy planned during the study period, will be exempt from semen testing.

If discontinued from the study drug earlier, subjects will directly undergo Visit 8 (EOT) and will be followed-up for an additional 12 weeks (safety FU, to Visit 11).

Testosterone Monitoring:

To ensure adequate safety monitoring, serum total testosterone levels will be evaluated at each visit by an independent unblinded physician, and if subject meets discontinuation criteria (total testosterone is ≥ 1500 ng/dL (52 nmol/L) at any 2 consecutive time points during the study), the subject will be discontinued from treatment. In addition, if one of the active BGS649 study arms presents with ≥ 2 subjects meeting this discontinuation criterion at any time point within the first 24 randomized subjects to that arm or > 15% subjects meet this criterion at any time point ≥ 25 randomized subjects, then the arm will be evaluated by the independent DMC for potential dosing discontinuation based on FDA guidance (FDA Advisory Committee Industry Briefing Document Testosterone Replacement Therapy, Sept 2014). Subjects may be discontinued from the study arm and no further randomisation to that arm will be performed.

Efficacy assessments will include measurement of total and calculated bioavailable testosterone, LH, FSH, inhibins A and B, dihydrotestosterone (DHT) and total oestradiol, body composition measurement including waist and hip circumference and impedance, cardiometabolic parameters, PROs, physical activity and sleep pattern via the wearing of wrist monitors, grip strength via a dynamometer and semen analysis. Safety assessments will include vital signs, physical examination, electrocardiograms (ECGs), haematology, blood

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chemistry and urinalysis, bone turnover markers, DEXA, prostate-specific antigen (PSA), and recording of adverse events (AEs), serious AEs (SAEs), AEs of special interest (AESIs), and concomitant medications. Sparse plasma PK and semen PK will also be collected.

Number of Subjects:
It is planned to screen approximately 1000 subjects in order to enrol 268 subjects (67 subjects per arm).

Diagnosis and Main Criteria for Inclusion:

Inclusion

1. Adult male subject aged 18 to 65 years inclusive
2. BMI > 30 kg/m^2 and < 50 kg/m^2
3. Serum total testosterone concentration below the normal range (serum total testosterone < 300 ng/dL [< 10.4 nmol/L]) in both of two morning samples, taken before 11am, at least 3 days apart
4. LH levels below the upper limit of normal (ULN)
5. Oestradiol levels within or above the normal range of approved assay
6. At least two symptoms of androgen deficiency present for at least 2 months prior to the first Screening Visit, with at least one of these being a sexual dysfunction
7. Agreement on the part of the subjects to use double-barrier contraception for vaginal sexual intercourse with female partners of child bearing potential to prevent conception and theoretical fetal risk of BGS649 exposure from seminal fluid. To use single barrier protection (condom) to prevent semen exposure through non-vaginal sexual intercourse with female partners of child bearing potential and refrain from sperm donation for the duration of the study. All to be continued for at least 3 months following study drug discontinuation
8. Ability to understand and comply with the requirements of the protocol/study, including understanding and being able to give informed consent.

Exclusion

1. Evidence of clinically significant endocrinopathy at Screening that may interfere with the study assessments or mask/mimic symptoms of hypogonadism e.g., growth hormone deficiency, adrenal deficiency, untreated hypothyroidism (primary hypothyroidism on replacement with normal thyroid stimulating hormone [TSH] level is allowed), or that may interfere with the evaluation of efficacy/safety parameters
2. Other types of HH (e.g., Kallmann syndrome) or primary hypogonadism (e.g., cryptorchidism, or Klinefelter syndrome)
3. Any other pituitary or hypothalamic disease, as based on one of the following:
   - Current or past hypothalamic or pituitary tumour
   - Suspicion of pituitary or hypothalamic tumour based on a clinical or laboratory evidence, e.g., elevated prolactin or other pituitary hormone abnormality, symptoms/signs of tumour mass effect, very low testosterone and LH (unless there is documentation of a normal magnetic resonance imaging scan of pituitary and hypothalamus within 3 months before first Screening Visit)
   - Hypothalamic or pituitary conditions, which may contribute to hypogonadism e.g., pituitary sarcoidosis, histiocytosis or tuberculosis
4. Subject with prostate disease, as confirmed by the presence of one of the following:
   - History of prostate cancer
   - Elevated PSA levels ≥ 3 ng/mL at Screening
   - Subjects with a detectable prostate nodule or induration at Screening unless proven previously benign by a biopsy
   - Urologist confirmed symptomatic benign prostatic hyperplasia
5. History of type 1 diabetes mellitus
6. Current clinically symptomatic depression or current or past Bipolar disorder
7. Uncontrolled ype 2 diabetes mellitus (HbA1c > 10.5% at Screening) or significant diabetic neuropathy.

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Subjects with type 2 diabetes can be included when both of the following conditions are met:
- HbA1c ≤ 10.5 % at Screening, and:
- Anti-diabetic medication regimen (excluding insulin) has been stable for ≥ 8 weeks before the first Screening visit

8. Treatment with one or more of the following prescribed or over the counter medications in the six months prior to first Screening Visit:
   - Medications with known androgenic or estrogenic properties or known to affect production of sex hormones
   - Injectable testosterone enhancement therapy
   - Fertility drugs
   - Growth hormone
   - Anabolic steroids
   - Long acting opiates
9. Treatment with topical testosterone therapy in the two months prior to first Screening Visit
10. Treatment with one of the following medications for either ≥7 consecutive days in the three months prior to first Screening Visit OR any treatment within 3weeks of first Screening Visit:
    - Testosterone lowering drugs e.g., spironolactone, cimetidine, 5α-reductase inhibitors
    - Short acting opioids/opiates including methadone
    - Medications known to increase prolactin levels, e.g., antipsychotics
11. Treatment with the following medications:
    - Chronic systemic steroid treatment or systemic steroids for > 5 consecutive days for intercurrent illness within the 4 weeks prior to the first Screening visit (inhaled and topical steroids are allowed)
    - Clomid within 1 year before first Screening Visit
    - Bisphosphonates or other medication used to treat low bone density (denosumab, teriparatide) except calcium and vitamin D within 1 year before first Screening Visit
12. Weight loss or weight gain (gain or loss > 5% body weight) OR weight reduction surgery or procedure within the 3 months prior to first Screening Visit
13. Participation in any clinical trial using clinical investigational product intervention within 3 months before first Screening Visit or 5 half-lives of investigational product administration, whichever is longer
14. Any clinically significant 12-lead ECG abnormalities at Screening including corrected QT interval by Fridericia's correction method (QT_CF) > 450 ms
15. Medical history of Long QT syndrome
16. History of thromboembolic disease
17. Grade ≥3 lower extremity oedema
18. Use of cardiac pacemaker or other medical electronic devices that can be affected by bioimpedance assessment
19. Medical diagnosis of any of the following cardiovascular conditions within the 6 months prior to first Screening Visit:
    - Myocardial infarction or unstable angina
    - Coronary artery bypass surgery, balloon angioplasty, percutaneous coronary intervention or carotid revascularisation procedure
    - Uncontrolled hypertension within the 3 months prior to first Screening Visit
    - Significant cardiac arrhythmia (as determined by the investigator)
    - Endovascular procedure or surgical intervention for peripheral vascular disease within the 3 months prior to first Screening Visit
    - Advanced ischemic heart disease

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- Congestive heart failure (New York Heart Association [NYHA] III/IV)
- Stroke or transient ischemic attack

20. History of osteoporosis or fragility fractures or bone density below the expected range for age (for men < 50 years old [Z score ≤ -2]) based on The International Society for Clinical Densitometry definition
21. DEXA scan T-score less than -2.0 at Screening or within 6 months prior to first Screening Visit
22. Significant acute or chronic renal or hepatic dysfunction or disease or infection (as determined by the investigator), including chronic active hepatitis B and C, or human immunodeficiency virus positivity
23. Significant illness within the 2 weeks prior to the initial dose of study drug that could supress pituitary gonadal axis and decrease testosterone levels (as determined by the investigator)
24. Untreated sleep apnoea
25. Any of the following laboratory parameters at Screening:
    - Haematocrit above 50%
    - Abnormal prolactin (outside of reference range)
    - Abnormal TSH or free thyroxine (FT4) (outside of reference range)
    - Morning cortisol ≤ 5 mcg/dL
    - Fasting transferrin saturation > 50%
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 times the ULN or bilirubin ≥ 2 times the ULN (unless caused by Gilbert syndrome)
    - Estimated glomerular filtration rate (eGFR) < 60 mL/min (calculated using the Cockcroft-Gault formula)
26. History of cancer within last 5 years, with the exception of well treated basal cell or squamous cell carcinoma of the skin
27. Any history of breast cancer
28. Alcohol and/or drug abuse within the 12 months prior to the first Screening Visit
29. Current/previously reported allergy to the study drug or the class of drug under investigation
30. Documented history of significant psychiatric or medical disorder that would prevent the subject complying with the requirements of the protocol or would make it unsafe for the subject to participate in the study as per investigator judgment.

Test Product, Dose and Mode of Administration:

[redacted]

Reference Therapy, Dose and Duration of Administration:

Those subjects randomised to the placebo arm will be administered matching placebo capsules that are indistinguishable to the test product in appearance and taste but contain no active ingredient.

All doses should be taken orally by the subject, with water, on a weekly basis (± 1 day from the time schedule of regular planned dose) at approximately the same time of the day.

Duration of Treatment:

All subjects will be treated with BGS649 or matched placebo for a maximum of 24 weekly doses (which provides 24 weeks therapeutic coverage due to long half-life of BGS649). Some subjects who complete 24 weeks of treatment will be invited to participate in a 6-month blinded safety extension study (Protocol MBGS206). An interim analysis will be performed once approximately 100 of overall planned enrolled subjects have completed the Week 4 visit and any doses of BGS649 that did not lead to normalisation of testosterone or were considered unsafe will be identified and the dose arm terminated.

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Study endpoints

Primary

1. Normalisation of total testosterone levels in ≥ 75% of subjects at Week 24.

Secondary

1. Proportion of subjects that have normalisation of total testosterone at Week 24
2. Proportion of subjects that overshoot testosterone (total testosterone above 1000 ng/dL [35 nmol/L]) at Week 24
3. Normalisation of total testosterone in ≥ 90% subjects at Week 24
4. Change of LH and FSH at 24 weeks
5. Population PK analysis of plasma BGS649 concentrations
6. PK analysis of semen BGS649 concentrations.

Exploratory

1. Change in oestradiol, inhibins (A and B) levels and DHT
2. Change in testosterone/oestradiol ratio
3. Body composition changes at Week 12 and Week 24
4. Changes in markers of cardiometabolic disease: blood pressure, lipid profile, HbA1c, glucose and insulin, hs-CRP and HOMA-IR and association with change in body composition and testosterone level.
5. Change in markers of bone turnover in those with and without 25-hydroxy vitamin D deficiency
6. Change in total and domain scores on PRO measures (IIEF, PROMIS SexFS: to assess sexual function; BFI, PROMIS Fatigue Short Form, SF-36 - Vitality: to assess energy levels and fatigue; SF-36: to assess general quality of life (QoL); PGI-S: to assess the patients' impression of their current health status) over the 24-week period
7. Association of objective findings of improvement (e.g. testosterone, time in physical activity or sleep and grip strength) and domain scores on PROs
8. Change in physical activity, sleeping pattern and strength measured by wrist worn monitors and grip strength measurement at 12 and 24 weeks and association with body composition (as measured by BMI and waist circumference and impedance) and testosterone level.
9. PK/pharmacodynamic (PD) relationship between BGS649 concentrations and testosterone levels
10. For semen analysis: change in semen parameters throughout the study and association with LH/FSH level
11. Change in bioavailable testosterone
12. Time to first normal testosterone level.

Safety

1. Treatment emergent AEs (TEAEs)/SAEs (from first dose of study drug until 90 days after last treatment dose)
2. Change in PSA during 24 week treatment duration
3. Change in haematocrit during 24 week treatment duration
4. Change in Bone Mineral Density (DEXA scan T-score and density in g/cm^2) from Screening and bone turnover biomarkers at 24-weeks from Baseline
5. Change in vital signs and clinical laboratory parameters, ECG
6. Change in physical examination (including general, prostate, breast and oedema of the lower extremities).

Statistical Methods:

The Primary Endpoint will be considered to have been met for a dose if ≥ 75% of subjects in the ITT population have normalisation of total testosterone levels at Week 24

Populations to be analysed:

The *intention to treat* (ITT) population includes all subjects who:

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1. Are randomised, and
2. Receive at least one dose of study medication, and
3. Provide a Baseline and at least one post-Baseline testosterone value.

The *per-protocol* (PP) population is a subset of the ITT population and includes all randomised subjects as randomised who have been treated according to the protocol and fulfil the following criteria:

1. All inclusion/exclusion criteria satisfied
2. Absence of relevant protocol violations with respect to factors likely to affect the efficacy of treatment where the nature of protocol violation will be defined before breaking the blind
3. Adequate study medication compliance
4. Adequate measurement of the primary variable.

The *safety* population includes all subjects who received at least one administration of the study medication.

For the nonlinear mixed effects modelling, all subjects who received at least one administration and have at least quantifiable concentration will be included in the *PK* population.

All primary and secondary efficacy endpoints will be analysed using the ITT population. The PP population will be used only for the analysis of the primary endpoint to examine the robustness of the primary analyses.

Safety and tolerability will be analysed using the safety population.

Sample Size and Power:

Sample size for the study is calculated using exact binomial methods for comparison of a single proportion to a performance goal of 75% normalisation. This assumes a one-sided test conducted at the 2.5% significance level, for which 67 subjects will be enrolled in each dose group of BGS649.

If the true normalisation rate in a dose group of BGS649 is 90% then the power of the study is 85%.

Version and Date of the Amended Protocol: 6.0, 10 March 2017

5 TABLE OF CONTENTS

5.1 List of Tables

5.2 List of Figures

5.3 List of Appendices and Supplements

6 LIST OF ABBREVIATIONS AND DEFINITONS OF TERMS

ACR	albumin:creatinine ratio
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BFI	Brief Fatigue Inventory
BMI	body mass index
CI	confidence interval
CRF	case report form
CSR	clinical study report
CTx1	C-terminal telopeptide
CYP	Cytochrome
CYP19	aromatase
D	Day
DBP	diastolic blood pressure
DEXA	dual energy X-ray absorptiometry
DHT	dihydrotestosterone
DMC	Data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ET	early termination
EOT	End of Treatment
EUDRACT	European Union Drug Regulatory Agency Clinical Trial
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
FT4	free thyroxine
FU	follow-up
GCP	Good Clinical Practice
H	hour
HbA1c	glycosylated haemoglobin
HDL	high density lipoprotein
HH	hypogonadotropic hypogonadism
HOMA-IR	homeostatic assessment of insulin resistance
hs-CRP	high sensitivity C-reactive protein
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration

ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IIEF	International Index of Erectile Function
INR	International Normalised Ratio
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intention to treat
LDL	low density lipoprotein
LH	luteinising hormone
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measure
MSAP	Modelling and Simulation Analysis Plan
NED	no-effect dose
NYHA	New York Heart Association
PGI-S	Patient Global Impression - Status
PCR	protein:creatinine ratio
PD	pharmacodynamics
P1NP	procollagen type 1 N-propeptide
PK	pharmacokinetics
PP	per-protocol
PRO	patient reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
PSA	prostate-specific antigen
QoL	quality of life
QT_C	corrected QT interval
QT_CF	QT_C by Fridericia's correction method
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SARM	selective androgen receptor modulator
SERM	selective oestrogen receptor modulator
SHBG	sex hormone binding globulin
SBP	systolic blood pressure
SD	standard deviation
SOP	standard operating procedure
TEAE	treatment emergent adverse event
T_{max}	time at which maximum serum concentration is reached
TSH	thyroid stimulating hormone
ULN	upper limit of normal

US	United States
W	week
WBC	white blood cell

7 INTRODUCTION

7.1 Background

Aromatase (CYP19) is highly expressed in adipose tissue, where it converts testosterone to oestradiol and androstenedione to oestrone. In human obesity, excess adipose tissue is associated with excess aromatase activity, which results in higher levels of oestradiol in men and women. In obese men, the relative excess of oestradiol can feed back to the hypothalamic pituitary axis, supressing gonadotropin secretion and thereby suppressing testicular testosterone production as well as spermatogenesis.

Severe obesity is associated with relative androgen deficiency in men and epidemiologic data support the hypothesis that excess adipose tissue contributes to the pathogenesis of hypogonadotropic hypogonadism (HH) in obese men. In one study in 160 men who were referred for medical or surgical treatment of obesity, HH was present in 36% subjects and the prevalence of HH rose linearly with increasing body mass index (BMI) (7.4% for a BMI of 30-35 kg/m^2 to 59.2% for a BMI > 50 kg/m^2) (Hofstra et al 2008). Given the prevalence of obesity (which is expected to continue to increase) it is estimated that up to 1.5 million men in the United States (US) and 1 million men in Europe may have androgen deficiency due to obesity.

There are many consequences of testosterone deficiency including decreased libido, erections and fertility, low bone mineral density, increased risk of fractures, decreased muscle mass and strength, fatigue, and impact on mood and cognition and loss of body hair (Bhasin et al 2006). Recent studies have also demonstrated that testosterone deficiency in older obese men is associated with metabolic abnormalities including insulin resistance, glucose intolerance and lipid abnormalities, contributing to an increased incidence of metabolic syndrome and likely increased risk of cardiovascular disease (Kapoor et al 2006).

BGS649 is a potent aromatase inhibitor and a derivative of the marketed drug letrozole (Femara). It was conceived as a long $T_{1/2}$ aromatase inhibitor for the treatment of refractory endometriosis and is being evaluated in obese men with HH. In vitro experiments with human placenta microsomal aromatase demonstrated a half maximal inhibitory concentration (IC_{50}) for BGS649 inhibition of 6 nM, which is 100 to 300 times more potent than aminoglutethimide and in the same range of potency as letrozole, for which an IC_{50} of 11.5 nM has been reported (Bhatnagar et al 1990).

[redacted]

[redacted]

[redacted]

To date, BGS649 has also been administered to 21 obese men with HH (8 subjects were assigned to placebo) and was found to be well tolerated without drug discontinuation or drug related serious adverse events (SAEs) (Study CBGS649A2204). This first-in-man study was a 2-part study over 12 weeks (11 treatments); Part 1 was an open-label dose finding study (weekly, individually titrated doses) and Part 2 used a fixed dose regimen (0.3 mg loading dose followed by 10 weekly fixed doses of 0.1 mg). Overall, BGS649 treatment (n=21) resulted in normalisation and maintenance of serum total testosterone, with no evidence of total testosterone peaks above the upper limit of normal (ULN). There were few SAEs reported (only during Part 2 and not considered related to the study drug) and the most commonly reported adverse events (AEs) included spontaneous penile erection and headache. Oestradiol levels were reduced by approximately 25-50% on average and gonadotropin levels (follicle stimulating hormone [FSH] and luteinising hormone [LH]) were increased in subjects treated with BGS649 (no effect observed for subjects on placebo). At the time of the interim analysis of Part 1, new data (Jones et al 2011) indicated that the variances of the homeostatic assessment of insulin resistance (HOMA-IR) were larger than assumed in the original sample size calculations and this (along with the discovery of dosing errors) contributed to the decision for early termination of Part 2 of the study.

A complete review of data obtained to date on BGS649 is presented in the most recent Investigator's Brochure (IB) and Food and Drug Administration (FDA) guidelines have been published on the use of testosterone replacement therapy (Testosterone Replacement Therapy, 2014).

This dose-ranging study aims to demonstrate the efficacy of BGS649 to normalise testosterone (to within normal lab-specific reference range i.e., total testosterone levels 300-1000 ng/dL [10.4-35 nmol/L]) in ≥ 75% of a population of obese male subjects with HH after 24 weeks of double-blind treatment compared to placebo. Study CBGS649A2204 demonstrated that testosterone levels normalised within 2 to 4 weeks of dosing. However, any impact of testosterone levels on the symptoms and signs of hypogonadism is expected to take longer. Therefore, this study evaluates the normalisation of testosterone levels as a primary endpoint, along with key secondary/exploratory endpoints of clinical efficacy after 24 weeks.

7.2 Rationale

This study will investigate the efficacy of different weekly oral doses of BGS649 [redacted] versus matching placebo in normalising testosterone levels in ≥ 75% of a population of obese men with HH over a 24-week period. Subjects will be randomised to three treatment arms with doses of [redacted] of BGS649 or matching placebo. If any of the three active treatment arms is found to be ineffective at the time of interim analysis and is predicted not to reach at week 24 therapeutic range in > 75% of subjects, or is considered unsafe per the data monitoring committee (DMC), dosing for the ineffective or unsafe arm(s) will be stopped for ethical reasons (see Section 13.6).

Doses and administration schedules were chosen based on data obtained from a previous study where weekly administration of BGS649 was investigated. This was a 2-part clinical study in obese men with HH over 12 weeks (11 treatments). Part 1 was an open-label, dose finding study [redacted] assessing normalisation of testosterone levels. Part 2 included a loading dose of [redacted] in the first week, followed by a maintenance dose of [redacted] weekly. The majority of subjects recruited had normalisation and maintenance of serum total testosterone levels with no evidence of total testosterone peaks above the ULN.

Oral androgen therapies are generally contraindicated because of the first pass hepatic effects which dramatically suppress high density lipoproteins (HDL), increase thrombogenic factors and often cause liver function abnormalities. These hepatic effects of androgens have so far limited the clinical utility of selective androgen receptor modulators (SARMs). Testosterone gels are currently widely used but require daily skin application and have a high potential for resulting in overshooting of testosterone levels above normal range and causing side effects such as elevated haematocrit and prostate-specific antigen (PSA), requiring dose titration. Thus, an oral therapy that normalises systemic testosterone, but does not significantly increase local hepatic exposure to androgens or require testosterone monitoring and dose titration is the therapeutic goal of testing BGS649 in men with HH.

This study will be conducted in compliance with the protocol and with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP).

8 STUDY OBJECTIVES

8.1 Primary Objectives

The primary objective is to demonstrate the efficacy of BGS649 to normalise total testosterone levels (300-1000 ng/dL [10.4-35 nmol/L]) in ≥ 75% of subjects after 24 weeks of treatment.

8.2 Secondary Objectives

1. To follow the time-course of normalisation in total testosterone levels
2. To demonstrate the efficacy of BGS649 to normalise total testosterone levels in ≥ 90% of subjects after 24 weeks of treatment
3. To evaluate the effect of BGS649 on LH and FSH
4. To further determine the pharmacokinetics (PK) of BGS649.

8.3 Safety Objectives

1. To evaluate safety and tolerability of BGS649.

8.4 Exploratory Objectives

1. To evaluate the effect of BGS649 on oestradiol, DHT and inhibins (A and B)
2. To evaluate the effect of BGS649 on testosterone/oestradiol ratio
3. To investigate the effect on patient reported outcomes (PROs) following treatment with BGS649. PRO measures will be:
   - International Index of Erectile Function (IIEF) and PROMIS Sexual Function and Satisfaction (PROMIS SexFS): to assess improvement in erectile function.
   - IIEF and PROMIS SexFS: to assess improvement in sexual desire and satisfaction with sex life.
   - 36-item Short Form Health Survey (SF-36): to assess general quality of life (QoL).
   - Brief Fatigue Inventory (BFI), PROMIS Fatigue Short Form and the SF-36 Vitality: to assess improvement in energy levels.
   - Patient Global Impression of Status items (PGI-S): to assess the patients' overall impression of their current health status.
4. To determine any change in physical activity and sleeping pattern via wrist worn monitor
5. To determine any change in grip strength, as measured by a dynamometer
6. To determine any associations between objective findings of improvement (e.g. testosterone, time in physical activity or sleep, and grip strength) and total and domain scores on PRO measures
7. To determine body composition change: waist circumference, BMI, body composition (as measured by impedance), and gynecomastia
8. To determine any associations between change in testosterone, body fat (as measured by BMI and waist circumference) and change in grip strength and wrist monitor data
9. To determine any associations between change in testosterone, body composition (as measured by impedance) and change in grip strength and wrist monitor data

10. To determine the effect of BGS649 on cardiometabolic parameters: systolic blood pressure (SBP) and diastolic blood pressure (DBP), lipid panel (total cholesterol, low density lipoprotein [LDL], triglycerides and HDL), glycosylated haemoglobin (HbA1c), fasting glucose and insulin, HOMA-IR and high sensitivity C-reactive protein (hs-CRP)
11. To determine any associations between testosterone, change in body composition and cardiometabolic parameters: SBP and DBP, lipid panel (total cholesterol, LDL, triglycerides and HDL), HbA1c, fasting glucose and insulin, HOMA-IR and hs-CRP
12. To determine the change in bone mineral density (dual energy X-ray absorptiometry [DEXA] scan), bone turnover markers (C-terminal telopeptide [CTx1] and procollagen type 1 N-propeptide [P1NP], osteocalcin, bone alkaline phosphatase)
13. To explore the effects of BGS649 on bone biomarkers on subjects with and without 25 hydroxy vitamin D deficiency (vitamin D deficiency is defined as 25 hydroxy vitamin D < 20ng/ml)
14. To explore the relationship between BGS649 concentration and testosterone levels
15. To determine the effects of BGS649 on semen parameters (semen volume, sperm count, concentration, motility and morphology) and to measure BGS649 concentrations in seminal fluid in subjects that provide semen samples
16. To explore the relationship between LH/FSH change and improvement in semen analysis in subjects that provide semen samples.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

9.1.1 Description

This is a phase IIb, multicentre, double-blind, randomised, placebo-controlled parallel-group 36-week study evaluating safety and efficacy of BGS649 in male obese subjects with HH. The study will have three phases:

1. A **Screening Phase** lasting up to 28 days (Screen Visit 1, Screen Visit 2), including Day -28 to Day -1
2. A **Randomisation Phase** including the Baseline visit (Day 1) and the treatment period Day 1 to Visit 8 (Week 24)
3. A **Safety Follow-Up Phase** to Visit 11 (Week 36, follow up [FU]). Visits 9 and 10 are telephone assesments.

Study participation will comprise up to 2 Screening Visits, 8 visits during the treatment period up to Week 24 (End of Treatment [EOT]), FU Visits 9, 10 (telephone assessment) and 11 (at Weeks 28, 32 and 36 respectively) for safety performed to 12 weeks after Visit 8 (EOT) (see schedule of assessments, Table 9–1). PK in seminal fluid will be performed at Visit 8. A minimum of 25 subjects per treatment arm will be invited to participate in a 6-month extension study (Protocol MBGS206), starting at Visit 8 (EOT). This transfer will be handled by the interactive response technology (IRT) and the blind will be maintained. Subjects participating in the 6-month extension will have their last study visit at Visit 8 (EOT) and will not participate in Visits 9, 10, and 11. The study design is summarised in Figure 9–1. The end of the study will be the last visit of the last subject.

Subjects that agree to participate in the trial (informed consent form [ICF] process completed; subject has signed and dated ICF) will be screened (Screening Phase) and assessed against inclusion/exclusion criteria. Symptoms of androgen deficiency will be assessed based on the questionnaire provided (see Section 12.8) and all positive symptoms will be entered in the electronic case report form (eCRF).

Testosterone levels to be taken before 11 am. If there is evidence that screening was failed due to a sample inadvertently being taken after this time, technical error (for example due to failure to meet storage conditions defined in laboratory manual) or clinically discrepant results (>100ng/dl difference between tests with one test being ≤200ng/dl), a retest is allowed in discussion with the Medical Monitor.

Due to the potential for dehydration to affect Haematocrit, subjects should be fully hydrated at the time of screening and during the trial when the haematocrit is tested, to ensure a reliable result both for study eligibility assessment and the ongoing monitoring (with respect to the haematocrit stopping criterion).

Eligible subjects will be randomised on Day 1 (Baseline) in a 1:1:1:1 ratio to one of the following treatment groups, consisting of three capsules per dose taken weekly:

[redacted]

- [redacted]

Once approximately 100 of the overall planned enrolled subjects have completed the Week 4 visit, an interim analysis will be performed by an independent DMC who will review unblinded data and determine whether the criteria for normalisation of testosterone (testosterone within or above normal reference range for healthy adult males according to FDA criteria) were met. The DMC will establish whether an individual arm has met the criteria of ≥ 75% of subjects reaching the normalisation of testosterone, or whether in the opinion of the DMC following unblinded review that when the arm is fully recruited it is expected to achieve a ≥ 75% response at Week 24 (see Section 13.6). Dosing arms which meet either of these criteria will be deemed effective. For dosing arms deemed to be ineffective, dosing will be stopped and no further randomisation to that arm will be performed. Subjects assigned to ineffective or unsafe arm(s), as determined per the DMC, will be discontinued from the study, will attend Visit 8 (EOT) and will be followed-up for an additional 12 weeks (FU, Visit 11) and will not be eligible for MBGS206 extension study. Recruitment will continue while the interim analysis is ongoing.

The remainder of the randomisation will then continue in a 1:1:1 ratio of remaining active arms versus placebo to the following treatment groups:

[redacted]

During the 24-week treatment period, subjects in the BGS649 groups and the matching placebo group will take the required dose weekly (± 1 day from the time schedule of regular planned dose). The treatment period consists of 24 weekly doses providing therapeutic coverage to week 24 due to long half-life of BGS649. The capsule will be taken orally by the subject with water.

Seminal Fluid Evaluation:

Semen Quality

To evaluate the effect of BGS649 treatment on semen quality, semen analysis (semen volume, sperm count, concentration, motility and morphology) will be performed. Subjects will be expected to successfully provide semen samples on three occasions during the Randomisation Phase. It is understandable that some subjects will not be able to provide semen samples.

Semen samples will be collected after a minimum of 48 hours of sexual abstinence, therefore no sexual activity should be performed in this time period and no spermicidal cream used to avoid interference with semen evaluation.

Semen PK

Additional semen samples will be required at EOT in order to assess PK in seminal fluid to evaluate the concentration of BGS649 at steady state. Seminal fluid PK will be assessed at Visit 8 (EOT) (Section 11.3.7). For subjects that are discontinued early from the study drug, an EOT sample will be obtained.

Any subjects who are vasectomised or have vasectomy planned during the study period, will be exempt.

Semen samples at baseline be taken up to 48 hours before or after the Baseline Visit. During Randomisation Phase semen samples may be provided up to 48 hours before or after the Assessment visit.

Testosterone Monitoring:

To ensure adequate safety monitoring, serum total testosterone levels will be evaluated at each visit by an independent unblinded physician (see Section 9.3.6 and Section 16.3) and if subject meets discontinuation criteria (total testosterone is ≥ 1500 ng/dL (52 nmol/L) at any 2 consecutive time points during the study), the subject will be discontinued from treatment. In addition, if one of the active BGS649 study arms presents with ≥ 2 subjects meeting this discontinuation criterion at any time point within the first 24 randomized subjects to that arm or > 15% subjects meet this criterion at any time point ≥ 25 randomized subjects, then the arm will be evaluated by the independent DMC for potential dosing discontinuation based on FDA guidance (FDA Advisory Committee Industry Briefing Document Testosterone Replacement Therapy, Sept 2014). Subjects may be discontinued from the study arm and no further randomisation to that arm will be performed.

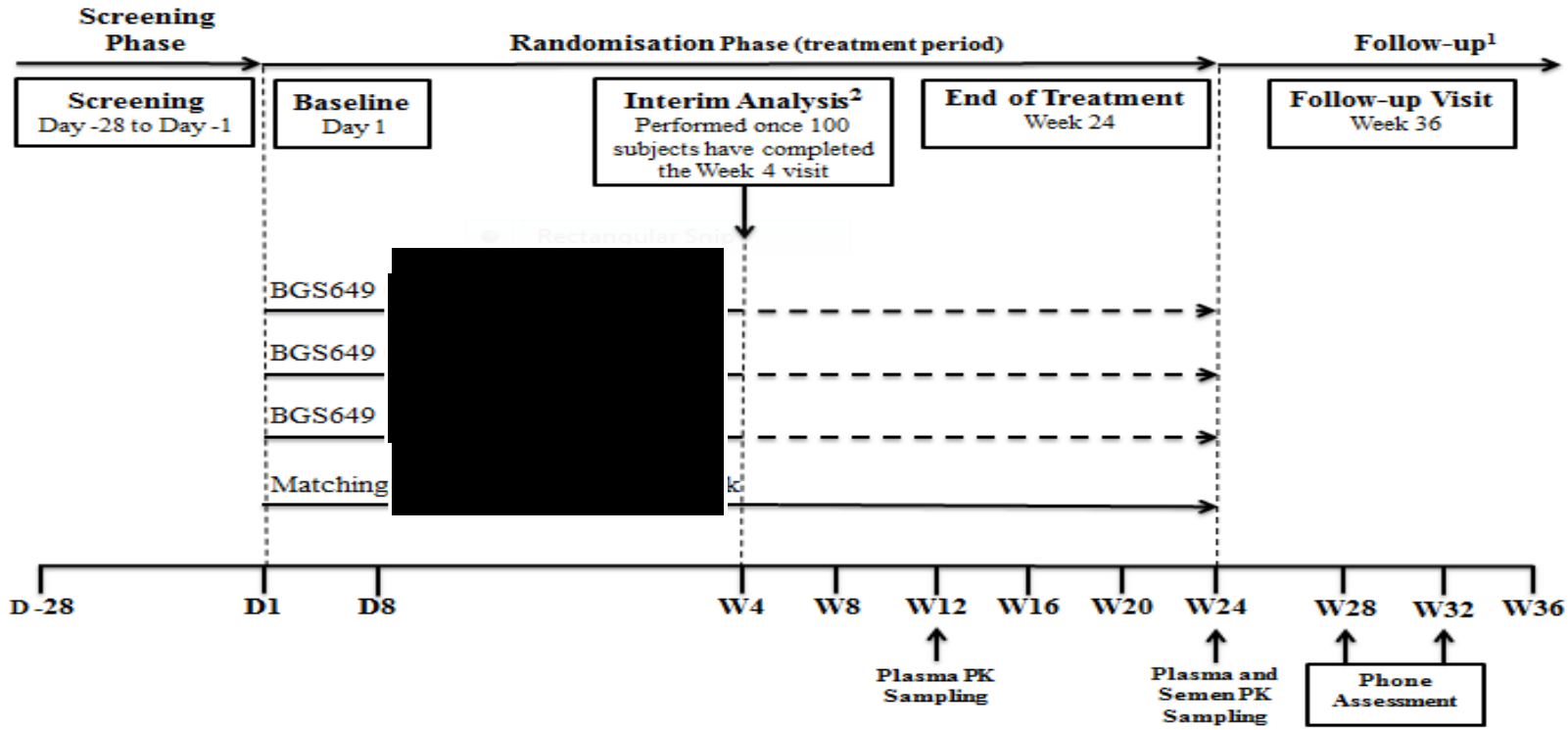
Efficacy and safety variables will be assessed according to the schedule of assessments in Table 9–1. Efficacy assessments will include measurement of total and calculated bioavailable testosterone, LH, FSH, inhibins A and B, dihydrotestosterone (DHT), and total oestradiol, body composition measurement including waist and hip circumference and impedance, cardiometabolic parameters, PROs, physical activity and sleep pattern via the wearing of wrist monitors, grip strength via a dynamometer and semen analysis. Safety assessments will include vital signs, physical examination, electrocardiograms (ECGs), haematology, blood chemistry and urinalysis, bone turnover markers, DEXA scan, PSA, and recording of AEs, SAEs, AEs of special interest (AESIs) and concomitant medications.

Pharmacokinetic samples will be collected as follows (see Table 9–1):

1. Plasma PK samples will be taken pre-dose and 1h post-dose at Visit 5. At Visit 8 (EOT; Week 24) it will be taken only once.
2. Semen samples for seminal fluid PK will be taken at Visit 8 (EOT)

The primary efficacy endpoint is the normalisation of total testosterone in ≥ 75% of subjects at Week 24. Secondary and exploratory efficacy endpoints are presented in Section 11.2, and safety endpoints in Section 12.2.

Figure 9–1 Study Design



D=day; DMC=Data Monitoring Committee; EOT= End of Treatment; IRT=interactive response technology; PK, pharmacokinetic; W=week

1 A minimum of 25 subjects per treatment arm will be invited to participate in a 6-month extension study (Protocol MBGS206), starting at Visit 8 (Week 24 EOT). This transfer will be handled by the IRT and the blind will be maintained. Subjects participating in the 6-month extension will have their last study visit at Visit 8 (Week 24 EOT)

2 If one of the BGS649 study arms at Visit 3 (Week 4) fulfils discontinuation criteria as determined per DMC, the dosing for the ineffective or unsafe arm(s) will be stopped and no further randomisation to that arm will be performed.

9.1.2 Schedule of Assessments

The schedule of assessments is presented in Table 9–1.

Table 9–1 Schedule of Assessments

	Screening Phase		Randomisation Phase (Treatment Period)								Follow-Up[1]		
Visit	**Screening (D -28 to D -1)**		**1 (Baseline)**	**2**	**3**	**4**	**5**	**6**	**7**	**8 (EOT)**	**9**	**10**	**11 (FU)**
Week/Day	**Screen Visit 1**	**Screen Visit 2 (Visit 1 + 3-7 days)**	**D 1**	**D 8 (±1 D)**	**W4 (±2 D)**	**W8 (±2 D)**	**W12 (±2 D)**	**W16 (±2D)**	**W20 (±2 D)**	**W24 (±2 D)**	**W28[2] (±2 D)**	**W32[2] (±2 D)**	**W36 (±2 D)**
Written informed consent	X												
Demographics	X												
Medical/surgical history	X												
Inclusion/exclusion criteria	X												
Androgen deficiency symptom checklist	X												
Randomisation			X										
Full general physical exam and prostate exam and breast exam	X						X			X			
Limited physical exam[3]			X	X	X	X		X	X				X
Vital signs[4]; height (Visit 1 only)	X		X	X	X	X	X	X	X	X			X
12-Lead ECG	X		X		X	X	X			X			
Specialised chemistry: morning cortisol, TSH, FT4, prolactin, iron, transferrin[5]	X												
25 hydroxy vitamin D			X										
Clinical laboratory tests: haematology, blood chemistry, eGFR by Cockcroft-Gault formula, dipstick urinalysis[6] and PSA[7]	X		X	X	X	X	X	X	X	X			X
Cardiometabolic parameters 1:HbA1c, fasting lipids (total cholesterol, LDL, HDL, triglycerides)[7]	X				X		X			X			X
Cardiometabolic parameters 2: Fasting glucose and insulin, hs-CRP, HOMA-IR **Bone turnover markers**[7,8]			X				X			X			X
Sex hormones 1: testosterone (total), oestradiol (total), LH	X[9, 11]	X[9,10, 11]	X[11]	X[11]	X[11]	X[11]	X[11]	X[11]	X[11]	X[11]			X
Bioavailable testosterone, SHBG			X[11]	X[11]	X[11]	X[11]	X[11]	X[11]	X[11]	X[11]			X
Sex hormones 2: FSH			X	X	X	X	X	X	X	X			X
DHT, inhibin A and B			X				X			X			X
Semen quality analysis[12]			X				X		X				
Semen PK samples[13]										X			
Plasma PK samples[14]							X			X			
Hip and waist measurement			X				X			X			

	Screening Phase		Randomisation Phase (Treatment Period)								Follow-Up[1]		
Visit	**Screening (D -28 to D -1)**		**1 (Baseline)**	**2**	**3**	**4**	**5**	**6**	**7**	**8 (EOT)**	**9**	**10**	**11 (FU)**
Week/Day	**Screen Visit 1**	**Screen Visit 2 (Visit 1 + 3-7 days)**	**D 1**	**D 8 (±1 D)**	**W4 (±2 D)**	**W8 (±2 D)**	**W12 (±2 D)**	**W16 (±2D)**	**W20 (±2 D)**	**W24 (±2 D)**	**W28[2] (±2 D)**	**W32[2] (±2 D)**	**W36 (±2 D)**
Body composition using bioimpedance[15] (by impedance)			X				X			X			
Actigraphy[16]			X				X			X			X
Grip strength			X		X	X	X			X			X
PROs: IIEF, BFI, PROMIS SexFS, PROMIS Fatigue Short Form, PGI-S		X[17]	X		X	X	X			X			X
PROs: SF-36			X				X			X			X
DEXA	X[18]									X[18]			
Study treatment			X	Once weekly[19]									
Study drug dispensation			X		X	X	X	X	X				
Study drug accountability				X	X	X	X	X	X	X			
AE assessment[20]		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X		X	X	X	X	X	X	X	X	X	X	X

1 A minimum of 25 subjects per treatment arm will be invited to participate in a 6-month extension study (Protocol MBGS206), starting at Visit 8 (EOT). Subjects participating in the 6-month extension will have their last study visit at Visit 8 (EOT)

2 Telephone Assessment Visit only

3 Limited physical examination (cardiovascular system and lower extremities oedema)

4 Vital signs assessment will include the measurement of SBP, DBP, pulse, oral temperature and body weight

5 Fasting transferrin

6 A microscopic examination including RBC and WBC will be performed only when dipstick evaluation is positive for WBC and/or blood or protein

7 All blood samples are to be collected after 8 hours fasting, after ECG and vital sign measurements

8 Bone turnover markers include CTx1, osteocalcin, bone alkaline phosphatase and P1NP

9 At Screening serum total testosterone concentration must be < 300 ng/dL (10.4 nmol/L) based on two morning samples, taken before 11 am at least 3 days apart. Laboratory parameters from screening visit 1 do not need to be received before screening visit 2 is take place

10 Oestradiol and LH will not be measured at this visit

11 Samples to be collected in the morning before 11 am pre-dose

12 Semen quality analysis will include semen volume, sperm count, concentration, motility and morphology. Sample collection is not required to be the same day as the assessment visit. Therefore sample collection is allowed within +/-48 hours the scheduled visit for Baseline and attendance Visits during the treatment phase

13 Semen samples for seminal fluid PK is not required to be the same day as the assessment visit. Therefore semen PK collection is allowed +/- 48 hours around the attendance visits

14 Samples will be taken at pre-dose and 1h post-dose for sparse plasma PK sampling at Visit 5 (week 12). Investigators should ensure that Visit 5 where plasma PK is measured coincides with the study drug dosing day. At EOT Visit 8 (Week 24), PK will be taken only once together with other laboratory assessments taken at that visit.

15 Subjects should come well hydrated, drinking water the night before and the morning before the impedance measurements

16 Activity wrist monitors will be worn by subjects for 7 continuous days after Baseline visit and visit 5 and 7 continuous days before Visits 8 and 11, so that the monitors can be collected at Visit 8 from subjects transferring to the extension study and at Visit 11 from subjects completing FU visit.

17 Screening PRO's should be performed no more than 7 days before dosing and may be performed outside of the Screen Visit 2 to meet this timing if required

18 Screening DEXA scan will be performed during screening and up to Day 8 after randomisatio. The End of treatment DEXA will be performed only in a case patient reached minimum visit 5(w12) and it can be performed within 14 days before EOT to accommodate scheduling

19 The administration of the study drug (BGS649/placebo) will be performed at the study site on Week 12 to allow measurement of PK at pre-dose and 1h post-dose

20 SAEs collected from signature of informed consent and AEs, AESIs collected from randomization.

9.2 Discussion of Study Design

This phase IIb, randomised, multi-centre, double-blind, parallel group, placebo-controlled 24-week study design is considered suitable for the assessment of normalisation of serum testosterone levels, the effect on clinical symptoms and signs, and safety and tolerability in adult obese male subjects with HH.

The assessment methods used to demonstrate the efficacy of BGS649 in normalising testosterone levels in ≥ 75% of subjects after 24 weeks of double-blind treatment are considered appropriate. For the primary efficacy endpoint, a clinically significant treatment effect is considered to be 75% of subjects attaining total testosterone levels within normal therapeutic range. This is in line with the current regulatory efficacy endpoint (FDA), where 75% subjects with testosterone in the therapeutic range was the recommended target for clinical trials with hypogonadism (Testosterone Replacement Therapy, 2014).

The doses of BGS649 selected for use in this study [redacted]) are chosen based on results obtained in a previous study in obese male subjects with HH, which suggested that these doses were well tolerated and may normalise testosterone levels (Study CBGS649A2204). However, to attempt to define a no-effect dose (NED), there will be an interim analysis conducted once approximately 100 of overall planned enrolled subjects have completed the Week 4 visit (see Section 13.6). If any of the initial three active treatment arms is found to be ineffective or unsafe, dosing for the ineffective or unsafe arm(s) will be stopped for ethical reasons.

The selected dosing schedule (1 intake per week) was chosen based on the PK properties of BGS649, which indicate rapid absorption (time at which the maximum serum concentration is reached [T_{max}] of 1h), extensive distribution and a prolonged elimination phase (elimination half-life of 21 days) (Study CBGS649A2204). Previous studies also indicated that a once weekly or monthly administration of BGS649 should provide continuous, stable levels of aromatase inhibition (Study CBGS649A2101). The treatment period of 24 weeks is considered to be a suitable length to allow demonstration of the primary objective on dose-finding for testosterone normalisation and clinical effects.

Aromatase inhibitors decrease oestrogen synthesis and increase pituitary LH and FSH with a consequent stimulation of testosterone production (de Boer et al 2005; Loves et al 2008). This increase in testosterone has multiple clinical effects, including:

1. Effect on insulin resistance with an improvement observed specifically in subjects with Baseline high insulin resistance (Cai et al 2014; Traish et al 2014). Therefore multiple cardiovascular risk markers and HOMA-IR as a marker for insulin resistance will be evaluated during this study.
2. Effect on body composition leading to an increase in lean body mass and a decrease in total fat mass (Wang et al 2000). Therefore change in body composition will be evaluated.

3. Effect on sleep pattern, (Barrett-Connor et al.,2008) increase in strength and stamina and physical activity Therefore, sleep quality and duration, strength, stamina and physical activity will be evaluated
4. Effect on sexual well-being leading to substantial improvements in erectile dysfunction and libido/sexual desire (Pexman-Fieth et al., 2014). Therefore, sexual functioning, including erectile function, will be evaluated via the International Index of Erectile Function (IIEF) PRO and via the Patient-Reported Outcomes Measurement Information System(®) Sexual Function and Satisfaction (PROMIS(®) SexFS) PRO (Flynn et al., 2013)
5. Effect on fatigue leading to substantial improvements in fatigue (Pexman-Fieth et al., 2014). Therefore, levels of fatigue will be evaluated via the PROMIS Fatigue Short Form and Brief Fatigue Inventory (BFI) (Mendoza et al., 1999) and levels of vitality via the Short Form 36 (SF-36) Vitality domain
6. Effect on overall well-being and health status is inconsistent, with open label but not randomised studies finding an improvement in mood and well-being (Spitzer et al, 2013). Therefore quality of life will be evaluated via the Short Form 36 (SF-36) (McHorney et al., 1994) and via Patient Global Impression of Status items (PGI-S)
7. Total and domain scores on PRO measures will then be compared to objective measurement of functionality via actigraphy evaluating the time spent in sedentary, moderate and vigorous physical activity and sleep, and assessment of muscle strength by assessing grip strength.

Bone density decrease is a class effect of aromatase inhibitors via a mechanism of decreased oestrogenic production. BGS649 has been shown to decrease oestrogen by 25-50%, potentially affecting the bone formation process and leading to osteoporosis (Study CBGS649A2204). In a single dose study in post-menopausal women, BGS649 at the highest doses of 10 and 20 mg showed a small but clinically significant decrease in bone density limited to the lumbar spine at 6 months. In clinical studies to date there has been no consistent effect of BGS649 on bone resorption biomarkers and no effects of BGS649 on bone density were demonstrated at 12 weeks in the previous study in males with hypogonadotropic hypogonadism. The planned study may be too short to detect a significant effect on bone density, as evaluated by DEXA scan, but bone formation and resorption markers will be monitored. However, there will be an extension study planned that will evaluate bone density by DEXA.

An increase of LH and FSH stimulates spermatogenesis and in this way may improve fertility. However excessive testosterone exposure could lead to testicular atrophy and therefore this study will monitor semen parameters (Crosnoe et al 2013). It will be accepted that not all subject will be able to provide semen sample on all visits. Vasectomised subjects or those who have vasectomy planned during the study period will be exempt from this assessment.

BGS649 has been shown to be present in semen in a previous study (Study CBGS649A2204). PK assessment of seminal fluid will be performed to further monitor the levels of BGS649 present in the semen at the three doses used in this study.

Aromatase inhibitors, such as BGS649 could theoretically cause androgens to rise above normal ranges, potentially leading to elevation of haematocrit, spermatogenesis suppression and worsening of other parameters. Such effects have not been observed in the previous human BGS649 study (Study CBGS649A2204) or other aromatase inhibitor studies (Saylam et al 2011) and therefore the likelihood of these effects being observed in this study is low due to a functioning feedback loop. However, to ensure adequate safety monitoring, testosterone levels will be monitored throughout the study by an unblinded independent physician. In the event of subjects presenting with total testosterone $\geq$ 1500 ng/dL (52 nmol/L) at any 2 consecutive time points, treatment will be discontinued (see Section 9.1.1).

9.2.1 Risk/Benefit and Ethical Assessment

BGS649 is a highly specific and potent aromatase inhibitor, which is structurally related to letrozole (Femara), a currently marketed aromatase inhibitor.

Oestrogens in men, together with testosterone, contribute to the regulation of LH and FSH levels and therefore an aromatase inhibitor such as BGS649 is expected to increase gonadotrophins and lead to an increase in androgen levels. This is both the on-target pharmacology of aromatase inhibitors, and a clinical risk, as pharmacologic suppression of aromatase in men can cause androgens to rise above normal ranges (Loves et al 2008). Acute consequences of elevated androgens are rare; however chronic testosterone elevation can lead to testicular atrophy via suppression of gonadotrophins, and suppression of spermatogenesis. Other effects of high testosterone include elevation of haematocrit, effect on prostate and elevation of PSA and cardiovascular effects. The measures which will be used in this study to monitor/avoid these risks are described in Section 9.2.

Administration of BGS649 therefore presents a theoretical risk of impaired spermatogenesis and infertility, although this is regarded as generally reversible based on clinical experience with androgens and aromatase inhibitors, and on pre-clinical studies in dogs dosed with BGS649 (Study 1070172 and Study 1170689). The emerging pre-clinical profile of BGS649 predicts multiple beneficial effects on the pathophysiology of HH. Administration of BGS649 in men has not led to significantly elevated levels of testosterone. It is expected that the benefits of BGS649 will be similar to those of testosterone (standard of care treatment), including improvement in serum testosterone levels and hypogonadal signs and symptoms. It may also potentially improve fertility via restoration of LH and FSH feedback loops (see Section 9.2 for further details).

Decrease in oestrogen is a risk factor for osteoporosis development in a postmenopausal woman. Administration of BGS649 in man leading to reduction of estradiol levels may therefore represent a risk potentially leading to decrease in bone density and development of osteoporosis.

BGS649 does not exhibit genotoxicity, and is not a substrate or inducer of major Cytochrome (CYP) 450 enzymes. It has shown 100-fold selectivity for CYP19 inhibition compared to other CYPs and has also shown minimal inhibition of CYP2A6, which is considered to be unlikely to be relevant at therapeutic drug concentrations. In addition, BGS649 is metabolised very slowly by CYPs. Therefore, the potential of BGS649 drug-drug interactions from a PK perspective is considered to be low.

The most common side effects associated with BGS649 include headache, sweats, increased incidence of morning erections, nasal congestion, sore throat, cough, diarrhoea, musculoskeletal pain, insomnia and abnormal hair growth. Based on safety pharmacology studies in animals, BGS649 is not anticipated to cause cardiovascular, central nervous system or respiratory AEs. No significant corrected QT interval (QT_C) or QT_C by Fridericia's correction method (QT_CF) prolongation was observed in subjects across a wide range of doses up to [redacted]). Therefore a large therapeutic index is expected in humans.

Based on the benefit/risk profile of BGS649 in obese male subjects with HH, BGS649 is expected to normalise testosterone levels with very few adverse effects. This study compares the effect of different doses of BGS649 [redacted] with a matched placebo in the normalisation of testosterone levels in obese male subjects with HH.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

1. Adult male subject aged 18 to 65 years inclusive
2. BMI > 30 kg/m^2 and < 50 kg/m^2
3. Serum total testosterone concentration below the normal range (serum total testosterone < 300 ng/dL [< 10.4 nmol/L]) in both of two morning samples, taken before 11am, at least 3 days apart
4. LH levels below the ULN
5. Oestradiol levels within or above the normal range of approved assay
6. At least two symptoms of androgen deficiency present for at least 2 months prior to the first Screening Visit, with at least one of these being a sexual dysfunction (a full list is provided in Appendix II)
7. Agreement on the part of the subjects to use double-barrier contraception for vaginal sexual intercourse with female partners of child bearing potential to prevent conception and theoretical fetal risk of BGS649 exposure from seminal fluid. To use single barrier protection (condom) to prevent semen exposure through non-vaginal sexual intercourse with female partners of child bearing potential and refrain from sperm donation for the duration of the study. All to be continued for at least 3 months following study drug discontinuation
8. Ability to understand and comply with the requirements of the protocol/study, including understanding and being able to give informed consent.

9.3.2 Exclusion Criteria

1. Evidence of clinically significant endocrinopathy at Screening that may interfere with the study assessments or mask/mimic symptoms of hypogonadism e.g., growth hormone deficiency, adrenal deficiency, untreated hypothyroidism (primary hypothyroidism on

replacement with normal thyroid stimulating hormone [TSH] level is allowed), or that may interfere with the evaluation of efficacy/safety parameters

2. Other types of HH (e.g., Kallmann syndrome) or primary hypogonadism (e.g., cryptorchidism, or Klinefelter syndrome)
3. Any other pituitary or hypothalamic disease, as based on one of the following:
   - Current or past hypothalamic or pituitary tumour
   - Suspicion of pituitary or hypothalamic tumour based on a clinical or laboratory evidence, e.g., elevated prolactin or other pituitary hormone abnormality, symptoms/signs of tumour mass effect, very low testosterone and LH (unless there is documentation of a normal magnetic resonance imaging scan of pituitary and hypothalamus within 3 months before first Screening Visit)
   - Hypothalamic or pituitary conditions, which may contribute to hypogonadism e.g., pituitary sarcoidosis, histiocytosis or tuberculosis
4. Subject with prostate disease, as confirmed by the presence of one of the following:
   - History of prostate cancer
   - Elevated PSA levels ≥ 3 ng/mL at Screening
   - Subjects with a detectable prostate nodule or induration at Screening unless proven previously benign by a biopsy
   - Urologist confirmed symptomatic benign prostatic hyperplasia
5. History of type 1 diabetes mellitus
6. Current clinically symptomatic depression or current or past Bipolar disorder
7. Uncontrolled type 2 diabetes mellitus (HbA1c > 10.5% at Screening) or significant diabetic neuropathy. Subjects with type 2 diabetes can be included when both of the following conditions are met:
   - HbA1c ≤ 10.5% at Screening, and:
   - Anti-diabetic medication regimen has been stable for ≥ 8 weeks before the first Screening visit
8. Treatment with one or more of the following prescribed or over the counter medications in the six months prior to first Screening Visit:
   - Medications with known androgenic or estrogenic properties or known to affect production of sex hormones
   - Injectable testosterone enhancement therapy
   - Fertility drugs
   - Growth hormone
   - Anabolic steroids
   - Long acting opiates

9. Treatment with topical testosterone therapy in the two months prior to first Screening visit

10. Treatment with one of the following medications for either >7 consecutive days in the three months prior to first Screening Visit OR any treatment within 3 weeks of first Screening Visit:
    - Testosterone lowering drugs e.g., spironolactone, cimetidine, 5α-reductase inhibitors
    - Short acting opiates/opioids including methadone
    - Medications known to increase prolactin levels, e.g., antipsychotics
11. Treatment with the following medications:
    - Chronic systemic steroid treatment or systemic steroids for > 5 consecutive days for intercurrent illness within the 4 weeks prior to the first Screening visit (inhaled and topical steroids are allowed)
    - Clomid within 1 year before first Screening Visit
    - Bisphosphonates or other medication used to treat low bone density (denosumab, teriparatide) except calcium and vitamin D within 1 year before first Screening Visit
12. Weight loss or weight gain (gain or loss > 5% body weight) OR weight loss surgery or procedures within the 3 months prior to first Screening Visit
13. Participation in any clinical trial using clinical investigational product intervention within 3 months before first Screening Visit or 5 half-lives of investigational product administration, whichever is longer
14. Any clinically significant 12-lead ECG abnormalities at Screening including QT_CF interval > 450 ms
15. Medical history of Long QT syndrome
16. History of thromboembolic disease
17. Grade ≥3 lower extremity oedema
18. Use of cardiac pacemaker or other medical electronic devices that can be affected by bioimpedance assessment
19. Medical diagnosis of any of the following cardiovascular conditions within the 6 months prior to first Screening Visit:
    - Myocardial infarction or unstable angina
    - Coronary artery bypass surgery, balloon angioplasty, percutaneous coronary intervention or carotid revascularisation procedure
    - Uncontrolled hypertension within the 3 months prior to first Screening Visit
    - Significant cardiac arrhythmia (as determined by the investigator)
    - Endovascular procedure or surgical intervention for peripheral vascular disease within the 3 months prior to first Screening Visit
    - Advanced ischemic heart disease
    - Congestive heart failure (New York Heart Association [NYHA] III/IV)

- Stroke or transient ischemic attack

20. History of osteoporosis or fragility fractures or bone density below the expected range for age (for men < 50 years old (Z score ≤ -2) based on The International Society for Clinical Densitometry definition
21. DEXA scan T-Score less than -2.0 at Screening or within 6 months prior to first Screening Visit
22. Significant acute and chronic renal or hepatic dysfunction or disease or infection (as determined by the investigator), including chronic active hepatitis B and C, or human immunodeficiency virus positivity
23. Significant illness within the 2 weeks prior to the initial dose of study drug that could supress pituitary gonadal axis and decrease testosterone levels (as determined by the investigator)
24. Untreated sleep apnoea
25. Any of the following laboratory parameters at Screening:
    - Haematocrit above 50%
    - Abnormal prolactin (outside of reference range)
    - Abnormal TSH or free thyroxine (FT4) (outside of reference range)
    - Morning cortisol ≤ 5 mcg/dL
    - Fasting transferrin saturation > 50%
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 times the ULN or bilirubin ≥ 2 times the ULN (unless caused by Gilbert syndrome)
    - Estimated glomerular filtration rate (eGFR) < 60 mL/min (calculated using the Cockcroft-Gault formula)
26. History of cancer within last 5 years, with the exception of well treated basal cell or squamous cell carcinoma of the skin
27. Any history of breast cancer
28. Alcohol and/or drug abuse within the 12 months prior to the first Screening Visit
29. Current/previously reported allergy to the study drug or the class of drug under investigation
30. Documented history of significant psychiatric or medical disorder that would prevent the subject complying with the requirements of the protocol or would make it unsafe for the subject to participate in the study as per investigator judgment.

9.3.3 Rescreening

There are three categories of subjects that may be considered for rescreening:

1.Subjects who met inclusion criteria 3 to 6 at Screening Visits 1, but who were not randomised or received study drug, may be rescreened at a later date.

2.Subjects who failed screening due to an inclusion/exclusion criterion or other study requirement that has been changed through a protocol amendment may also be rescreened at a later date

3. Subjects who failed inclusion criteria 3 to 6 at screening ≥ 6 months previously, and where the clinical situation has changed so that in the investigators judgement they may now meet the criteria may also be rescreened. To include where there was screen failure on total testosterone inclusion criterion through clinically discrepant results (>100ng/dl difference between tests with one test being ≤200ng/dl).

Prior to rescreening, every case has to be discussed and approved by Medical Monitor. Rescreening is allowed only one time per screened subject. Rescreened subjects will receive a new Screening number. Previous Screening numbers will not be reused. Rescreened subjects will need to repeat complete Screening assessment (except bone mineral density measured by DEXA if it still falls within 6 months of rescreening visit) starting with signing the ICF.

9.3.4 Retesting of laboratory parameters

Retesting of individual laboratory procedures may be permitted in the following circumstances

- When there is obvious methodological issue (hemolysed sample, dilution or calculation error) or sampling error documented at the site (sampling time is outside the window, incorrect procedure followed)
- When a data point is considered aberrant, including where there was screen failure on total testosterone inclusion criterion through clinically discrepant results (>100ng/dl difference between tests with one test being ≤200ng/dl). Also where the value reported would be incompatible with life or in a range clearly discrepant with current medical status of the subject.

In either of these instances, the investigator should get approval to repeat laboratory parameters from the medical monitor. The reason for re-test should be recorded by the Investigator in the patient's source documentation.

9.3.5 Early Termination

The study may be terminated at any time by the sponsor if serious side effects should occur, or per the DMC decision. In the event of an early termination of the study, the sponsor will inform the study investigators, institutions and all regulatory authorities.

9.3.6 Withdrawal of Subjects from the Study

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs when a subject does not want to participate in the study anymore and does not want to attend any further visits or assessments, have further study-related contact, or allow analysis of already obtained biologic material.

If a subject withdraws consent, the investigator must make every effort to determine the primary reason for this decision and record this information. Investigational treatments must be discontinued and no further assessments conducted. All biological material that has not been analysed at the time of withdrawal may be used, unless consent for its use is withdrawn in writing. Further attempts to contact the subject are not allowed unless safety findings require communication or follow-up.

Under the following circumstances the subject MUST be withdrawn from the study:

1. Withdrawal of informed consent
2. Any safety reasons, clinical AE, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator or sponsor indicates that continued participation in the study is not in the best interest of the subject
3. Exogenous testosterone use or additional monitoring of testosterone levels that inadvertently unblinds the subject's study arm allocation
4. Severe non-compliance to the protocol, as judged by the investigator and/or sponsor
5. Treatment code or unblinding prematurely broken by the investigator
6. Termination of the study by the sponsor
7. Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

9.3.7 Study Drug Interruption and Discontinuation

Subjects may voluntarily discontinue investigational treatment for any reason at any time.

At the time of study drug discontinuation, the subject should have (as soon as possible) an EOT visit with the assessments that are normally done at the Week 24 visit (this should take place within 7 days of discontinuation of study drug). In addition subjects who discontinue the study drug are expected to complete the 12 week follow-up period (Visits 9, 10 and 11) to collect safety data. Subjects who have discontinue before Week 12 (Visit 5) are not required to have EOT DEXA scan measured The subjects will in addition provide semen sample for PK analysis at Visits 8 (EOT) , unless they are not able to provide the samples. This applies also to a subject discontinued because of elevated testosterone as determined by an unblinded physician and if the whole treatment arm is discontinued because of elevated testosterone level as determined by DMC. The investigator and study staff must discuss with the subject, the subject's continued participation in the study and request subjects to continue attending follow-up visits according to the study visit schedule. A study arm may be discontinued from the treatment at the Week 4 visit as decided by DMC during interim analysis (see Section 9.1). Discontinued subjects will not be replaced. Those subjects will attend only Visit 8 (EOT) and will be followed at FU-Visit s 9, 10 and 11 (to 12 weeks after EOT).

The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If the subject cannot, or is unwilling to attend the follow-up visits, the site staff should request maintenance of regular phone contact with the subject, or with a person pre-designated by the subject. This phone contact should preferably be performed according to the study visit schedule. Data concerning the subject's health status, including information regarding new/concomitant treatments, AEs, AESIs, i.e., rash and vital status will continue to be collected.

If the subject decides to completely withdraw from the study (refuses any further study participation or contact) all study participation for that subject will cease and data to be collected at subsequent visits will be considered missing.

The investigator must also contact the IRT to register the subject's discontinuation from investigational treatment.

If study drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

If the subject temporarily discontinue study drug because of AE or SAE or other relevant issue, investigator may restart if considered medically safe and in discussion with the Medical Monitor.

Investigational treatment MAY be permanently discontinued under the following circumstances:

1. Significant worsening of lower extremity oedema (demonstrated by use of the same technique of evaluation for comparison over time and which is not due to local pressure /venostasis effects such as may be caused by socks or other clothing).
2. Significant worsening of obstructive urinary symptoms

Investigational treatment MUST be permanently discontinued under the following circumstances:

3. Total testosterone ≥ 1500ng/dL (52 nmol/L) at any two consecutive scheduled visits during the study
4. Liver laboratory values of:
   - ALT or AST >5 times the ULN

     If the increase in ALT or AST, is associated with normal bilirubin and ALP, the medical evaluation of withdrawing a patient can be made on a repeat AST/ALT test taken within 48 hours. (Repeated parameters should include: ALT, AST, Alkaline phosphatase and total bilirubin). The subject should interrupt study drug until the repeat liver enzymes are available. If repeat liver parameters are all within the normal range, dosing may be continued. If not normalised the subject should be permanently discontinued.

     or

   - ALT or AST >3 times the ULN and bilirubin total >2 times ULN or International Normalised Ratio (INR) >1.5 or the appearance of worsening fatigue, nausea, vomiting, right upper quadrant pain/tenderness, fever, rash, or eosinophilia.
   - A hepatic event leading to subject discontinuation should be followed up until event resolution, or becomes not clinically significant
5. Any of the following laboratory abnormalities:
   - Renal function values that require discontinuation:

- Discontinue investigational treatment for a subject if individual serum creatinine increases ≥50% compared to Baseline (and is considered clinically significant), or in the event of treatment emergent proteinuria (albumin:creatinine ratio [ACR] >300 mg/g or >30 mg/mmol; protein:creatinine ratio [PCR] ≥500 mg/g or >50 mg/mmol). (Creatinine can be repeated once within 7 days of initial alert. Study drug administration should be suspended during this time and resumed only if repeat creatinine is back to pre-alert level)
- A renal event leading to subject discontinuation should be followed up until event resolution (serum creatinine within 10% of Baseline, protein-creatinine ratio within 50% of Baseline), stabilises or becomes not clinically significant, or is assessed as being chronic.

6. Subject missed 4 or more consecutive study drug dosing.
7. Development of prostate cancer or PSA increase more than 1.4 ng/ml above Screening level. It is recommended that in these cases subjects undergo urologic consultation.
8. Haematocrit >54% (Hematocrit can be repeated once within 7 days of initial alert. Study drug administration should be suspended during this time and resumed only if repeat hematocrit is under 54%)
9. Development of sleep apnoea.
10. Development of cardiovascular event (significant arrhythmia acute myocardial infarction, brain stroke, transient ischemic attack, unstable angina, congestive heart failure).
11. Emergence of the following adverse events:
    - Absolute QTcF >500 msec, or a rise of QTcF of ≥ 60 msec above baseline confirmed by triplicate ECG measurements.
12. Pregnancy in female sexual partner of the male study subject, occurring after the start of study treatment.
13. Fragility bone fracture.
14. Breast cancer.

Procedures for handling patients incorrectly enrolled or randomized

Subjects who fail to meet the inclusion/exclusion criteria must not be enrolled or randomized. If a subject not meeting the study criteria is randomized in error, a discussion must occur between the Medical Monitor and the investigator regarding whether to continue or discontinue the subject from the study. If agreement is reached, the subject should complete the study unless there are safety concerns or if the subject withdraws the consent.

9.3.8 Lost to Follow-up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorised by the subject. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes or emails, as well as a lack of response by the subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that

the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If the investigator's use of a third-party representative to assist in the Follow-Up Phase of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the Follow-Up Phase of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigators should be reported and documented in the subject's medical records.

10 TREATMENT OF SUBJECTS

10.1 Identity of Study Treatment(s)

Details of the study treatments are presented in Table 10–1.

Table 10–1 Study Treatments

Drug Name	BGS649	BGS649 matched placebo
Active ingredient	BGS649	Not applicable
Strength(s)	[redacted]	Not applicable
Dosage Form	[redacted]	c [redacted]
Route of administration	Oral	Oral
Mode of administration	With water	With water
Dose	[redacted]	[redacted]

10.1.1 Administration of Study Treatment(s)

[redacted]

10.2 Study Treatment Packaging and Labelling

10.2.1 Packaging

[redacted]

A unique medication number is printed on the label of each pack which corresponds to one of the treatment regimens. Investigator staff will identify the investigational treatment to dispense to the subject by contacting the IRT and obtaining the medication number(s). Records of subjects assigned medication numbers will be recorded in source documentation.

10.2.2 Labelling

Labels will comply with the legal requirements of each country and be printed in the local language. They will supply no information about the subjects.

10.2.3 Storage

[redacted]

10.2.4 Blinding and Randomisation of Study Treatment(s)

At Visit 1 (Baseline) all eligible subjects will be randomised via the IRT to one of the four treatment regimens [redacted] in a 1:1:1:1 ratio. After the interim analysis (see Section 13.6), if one or more of the BGS649 study arms is discontinued by the DMC, the dosing for that arm(s) will be stopped and no further randomisation to that arm will be performed. The remaining subjects will be randomised in a 1:1:1 ratio into remaining active arms: [redacted] The investigator or his/her delegate will contact the IRT after confirming that the subject fulfils all the inclusion/exclusion criteria. The IRT will assign a medication number to the subject, which will be used to link the subject to a treatment regimen and will specify a unique medication number on the label of investigational treatment to be dispensed to the subject. The randomisation number will not be communicated to the caller.

The randomisation numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A subject randomisation list will be produced by ICON Biostatistics using a validated system that automates the random assignment of subject numbers to randomisation numbers. These randomisation numbers are linked to the different treatment regimens, which in turn are linked to medication numbers. A separate medication list will be produced using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug.

Subjects, investigational staff, persons performing the assessments and data analysts (other than those described below) will remain blind to the identity of the treatments [redacted] from the time of randomisation until database lock. In order to maintain the blind described above, testosterone measurements will be blinded to site and sponsor staff and monitoring will be performed by an independent unblinded physician. The interim analysis will be performed by an independent unblinded committee (see Section 16.3).

The blind will be maintained using the following methods:

1. Randomisation data will be kept strictly confidential until the time of blinding, and will not be accessible to anyone involved in the study

2. The identity of the treatments will be concealed by the use of investigational treatment that is identical in packaging, labelling, schedule of administration and appearance.

Should a situation arise where unblinding is required, the investigator at that site may perform immediate unblinding without the need for communication with the sponsor (see Section 10.3).

10.3 Procedure for Breaking the Randomisation Code

Emergency treatment code breaks should only be undertaken when it is essential to treat the subject safely and efficaciously. Most often, investigational treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the ICON site monitor, the medical monitor, and the ICON Project Manager that the code has been broken, but no treatment assignment will be communicated.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT in case of emergency. The investigator will inform the subject how to contact his/her backup in cases of emergency when he/she is unavailable. The investigator will provide the protocol number, investigational treatment name if available, subject number, and instructions for contacting the local entity which has responsibility for emergency code breaks to the subject in case an emergency treatment code break is required at a time when the investigator and backup are unavailable.

10.4 Subject Compliance

Each time study medication is dispensed subjects will be informed about compliance. When study medication is returned, compliance will be assessed based on the subject's interview and a count of the tablets. The investigator (or designee) will record the amount of study medication dispensed and returned at each visit, as well as document the reasons for non-compliance in the source document. The investigator will record the date and time of the study drug intake to the EDC. The subject should be re-educated regarding treatment compliance and/or recording dose. A significant noncompliance with protocol or study drug will be communicated to the sponsor.

10.5 Study Treatment Accountability

Records shall be maintained of the delivery of study treatments to the study centres, the inventory at the study centres, the use of each subject and the return to the sponsor.

These records shall include dates, quantities, batch numbers, expiry dates and the unique code numbers assigned to the study medication and to the study subjects.

The investigator shall be responsible for ensuring that the records adequately document that the subjects were provided the doses specified in the protocol and that all study medication

received from the sponsor is reconciled. All study medication must be returned to the sponsor at the end of the study.

10.6 Contraception

Semen samples will be collected after a minimum of 48 hours of sexual abstinence, therefore no sexual activity should be performed in this time period and no spermicidal cream used to avoid interference with semen evaluation.

10.7 Prohibited Therapy

The following classes of medication listed below are not permitted to be taken during the conduct of the study starting from Screening (for details of Screening criteria concerning medications, see Section 9.3.1 and Section 9.3.2):

1. Over the counter or ordered via the internet or prescribed medications that are known to influence production or efficacy of sex hormones, or with oestrogen/androgen-like or antioestrogen/antiandrogen-like properties e.g.,
    - Opiates/Opioids including methadone for > 7 consecutive days during study duration
    - Chronic systemic steroid treatment or systemic steroids for > 5 consecutive days for intercurrent illness (inhaled and topical steroids are allowed)
    - Medications known to increase prolactin levels, e.g., antipsychotics
    - 5-α-reductase inhibitors, e.g., Finasteride
    - Spironolactone
    - Cimetidine
    - Growth hormone
    - Testosterone, known testosterone enhancers, anabolic steroids, known active Fertility drugs and Oestrogens or selective oestrogen receptor modulators (SERMS)

- Clomid
- Bisphosphonates, Teriparatide, Denosumab (treatment with calcium and vitamin D for bone health is allowed at the discretion of the investigator)

11 ASSESSMENT OF EFFICACY

11.1 Efficacy and Pharmacokinetic Variables

1. Total and bioavailable testosterone, LH, FSH, inhibins (A and B), oestradiol (total)
2. Testosterone/oestradiol ratio
3. Body composition:
   - Body weight and BMI
   - Waist circumference, hip circumference and waist to hip ratio
   - Gynecomastia
   - Fat and muscle percentage (by impedance)
4. Cardiometabolic parameters
   - Blood pressure (DBP and SBP)
   - Fasting lipid panel (total cholesterol, LDL, HDL, triglycerides)
   - HbA1c
   - Fasting glucose and insulin
   - hs-CRP
   - HOMA-IR (see Section 11.3.3 for details)
5. PRO measures
   - International Index of Erectile Function (IIEF) and PROMIS Sexual Function and Satisfaction (PROMIS SexFS): to assess improvement in erectile function.
   - IIEF and PROMIS SexFS: to assess improvement in sexual desire and satisfaction with sex life.
   - 36-item Short Form Health Survey (SF-36): to assess general quality of life (QoL)).
   - Brief Fatigue Inventory (BFI), PROMIS Fatigue Short Form and the SF-36 Vitality: to assess improvement in energy levels.
   - Patient Global Impression of Status items (PGI-S): to assess the patients' overall impression of their current health status.
6. Actigraphy derived activity and sleep parameters
   - Counts of sedentary, moderate and vigorous activity
   - Sleep quality and duration
7. Dynometry derived grip strength assessment
8. Semen analysis
   - Sperm count
   - Sperm concentration
   - Volume of semen

- Sperm motility
- Sperm morphology

9. PK plasma analysis and PK semen analysis.

Detail of assessment of the efficacy and PK variables are presented in Section 11.3 and Section 11.4, respectively.

11.2 Efficacy and Pharmacokinetic Endpoints

Primary

1. Normalisation of total testosterone levels in ≥ 75% of subjects at Week 24.

Secondary

1. Proportion of subjects that have normalisation of total testosterone to Week 24
2. Proportion of subjects that overshoot testosterone (total testosterone above 1000 ng/dL [35 nmol/L]) to Week 24
3. Normalisation of total testosterone in ≥ 90% subjects at Week 24
4. Change of LH and FSH to 24 weeks
5. Population PK analysis of plasma BGS649 concentrations
6. PK analysis of semen BGS649 concentrations.

Exploratory

1. Change in oestradiol, inhibins (A and B) levels and DHT
2. Change in testosterone/oestradiol ratio
3. Body composition changes at Week 12 and Week 24
4. Changes in markers of cardiometabolic disease: blood pressure, lipid profile, HbA1c, glucose and insulin, hs-CRP and HOMA-IR and association with change in body composition and testosterone level.
5. Change in markers of bone turnover in those with and without 25-hydroxy vitamin D deficiency
6. Change in total and domain scores on PRO measures (IIEF, PROMIS SexFS: to assess sexual function; BFI, PROMIS Fatigue Short Form, SF-36 - Vitality: to assess energy levels and fatigue; SF-36: to assess general quality of life (QoL); PGI-S: to assess the patients' impression of their current health status) over the 24-week period
7. Association of objective findings of improvement (e.g. testosterone, time in physical activity or sleep and grip strength) and domain scores on PROs
8. Change in physical activity, sleeping pattern and strength measured by wrist worn monitors and grip strength measurement at 12 and 24 weeks and association with body composition (as measured by BMI and waist circumference and impedance) and testosterone level.
9. PK/pharmacodynamic (PD) relationship between BGS649 concentrations and testosterone levels
10. For semen analysis: change in semen parameters throughout the study and association with LH/FSH level
11. Change in bioavailable testosterone
12. Time to first normal testosterone level.

11.3 Efficacy Assessments

All efficacy assessments will be performed according to the schedule of assessments (Table 9–1).

11.3.1 Male Hormonal Parameters

Testosterone

Serum total testosterone and sex hormone binding globulin (SHBG) levels will be measured. Bioavailable testosterone will be calculated.

All serum total testosterone and SHBG laboratory parameters are to be taken before 11 am.

Samples are to be separated within an hour of being taking to prevent artificial increases in testosterone levels, and further stored and transported as described in the laboratory manual.

If total testosterone is ≥ 1500ng/dL (52 nmol/L) at any 2 consecutive measurements (time points) during the study, the subject will be discontinued from treatment (see Section 9.3.6).

Testosterone monitoring will be blinded to the subject, sponsor and investigators and a decision about discontinuing BGS649/placebo will be made by an independent unblinded physician on a one to one basis after detailed evaluation of the subject (Section 10.2.4 and Section 16.3). It is important that investigators do not monitor testosterone independently of the study protocol as this will have the potential to inadvertently unblind the protocol. A subject may be withdrawn from the study if there was unblinded testosterone monitoring in addition what is described in the protocol.

Other Parameters

LH, FSH, Inhibins A and B, total oestradiol and DHT will be assessed.

11.3.2 Body Composition

Body weight will be measured as part of the vital signs assessment (Section 12.6).

BMI

Body weight will be measured at the same time of day (± 30 minutes) at each assessment, before eating. Subjects should be instructed to wear similar clothing at each visit where weight will be measured. Shoes and heavy accessories should be removed prior to measurement. Study staff should ensure that the same scale is used for the same subject at each assessment, and that the scales have been properly calibrated.

Height will be measured at Screening to enable BMI determination.

BMI is to be calculated from the height obtained at Screening. The BMI is calculated by dividing the measured subject weight by the square of the measured subject height, and is expressed in kg/m^2.

Waist Circumference/Hip Circumference

Measurements will be taken to the nearest 0.1 cm.

The **waist measurement** (in cm) will be taken by measuring the circumference distance around the waist at the mid-point between the lowest rib and the top of the hip bone (iliac crest). The **hip measurement** (in cm) will be taken by measuring the distance around the largest extension of the buttocks and at the level of the bony prominences felt in the front of the hips.

The **waist to hip ratio** will be calculated by dividing the waist girth by the hip girth.

Measurements will preferably be performed using a flexible tape measure (provided for the study) and a non-permanent pen for marking the skin. If a plastic or cloth tape is used, it should be regularly checked against a metal tape to ensure that it has not stretched with prolonged use. Measurements should be made with the measuring tape placed firmly against the skin, but not so tight that it is compressing the skin. The tape should be placed so that it is lying flat and horizontal on the skin, parallel to the floor. Subjects should be asked to relax and exhale before the measurements are read.

Gynecomastia

Breast examination will be performed by palpation by an investigator. The subject will be in a supine position with hands behind their head. Investigators will perform a thorough examination of the breasts, noting their size and consistency, presence of any nipple discharge or axillary lymphadenopathy. The purpose is to look for or monitor enlargement or irregularities of glandular breast tissue. The investigator will then document the findings and, if gynecomastia is present, will document size of glandular breast tissue in centimetres/inches.

Body composition by bioimpedance

Bioelectrical impedance analysis estimates body composition. Measuring electrical impedance or opposition to the flow of an electric current through body tissues will be used to estimate and calculate subcutaneous and visceral body fat and proportion of muscle during the study.

The evaluation takes a few minutes. Subjects should be well hydrated (drinking water the night before and morning before assessment) and rested prior to the measurements as impedance is influenced by hydration and exercise.

11.3.3 Cardiometabolic Parameters

Blood pressure (SBP and DBP) will be measured as part of the vital signs analysis (Section 12.6).

All blood samples are to be collected after 8 hours fasting, after ECG and vital sign measurements

HbA1c, fasting lipids (total cholesterol, LDL, HDL, triglycerides), fasting glucose and insulin and hs-CRP will be measured. In addition HOMA-IR will be calculated to estimate insulin resistance using the following formula:

HOMA-IR = [glucose (nmol/L) * insulin (μU/mL)/22.5], where glucose and insulin must be fasting (Matthews et al 1985).

Insulin use will be documented within the concomitant medications to enable the analysis of insulin and HOMA-IR to be appropriately performed to exclude the confounding effects of exogenous insulin use.

11.3.4 Patient Reported Outcomes

The impact of BGS649 on various aspects of subject's health-related quality of life will be assessed using the following questionnaires. Ideally, PROs are to be evaluated before any other study activity is performed

International Index of Erectile Function

The IIEF is a 15-item self-administered questionnaire, providing a quantitative index of erectile dysfunction severity by examining the following five relevant areas of sexual function (Rosen et al., 1997; Cappelleri et al., 2000):

1. Erectile function
2. Orgasmic function
3. Sexual desire
4. Intercourse satisfaction
5. Overall satisfaction.

Patient-Reported Outcomes Measurement Information System(®) Sexual Function and Satisfaction (PROMIS(®) SexFS)

The PROMIS SexFS PRO measure is an up to 19 item self-administered questionnaire compiled from relevant items in the PROMIS Sexual Function and Satisfaction domains (Flynn et al., 2013). The measure assesses global satisfaction with sex life (up to 7 items), erectile function (up to 6 items), interest in sexual activity (up to 4 items), and interfering factors (up to 2 items) in the last 30 days.

PROMIS(®) Fatigue Short Form

The PROMIS Fatigue Short Form measure is an 7-item self-administered questionnaire assessing the extent of fatigue and its impact on work and functioning in the last 7 days.

Brief Fatigue Inventory

The BFI is a 99-item self-administered questionnaire, providing an assessment of the severity of fatigue and its impact on the subject's ability to function at present and in the previous 24 hours (Mendoza et al., 1999).

36-Item Short Form Health Survey

The SF-36 QoL questionnaire is a multidimensional instrument that evaluates quality of life. It consists of questions assigned to the following categories (McHorney et al., 1994):

1. Vitality
2. Physical functioning
3. Bodily pain
4. General health perceptions
5. Physical role functioning

6. Emotional role functioning
7. Social role functioning
8. Mental health.

Patient Global Impression of Status items (PGI-S)

Three patient global impression items will be included to assess the patients' overall impression of their current health status and thus to evaluate the performance of the other PROs in this patient population.

1) Overall, how much does your hypogonadotropic hypogonadism affect your **physical function**? Typical effects include low energy levels and difficulties in performing physical activities.
    a. Not at all
    b. A little bit
    c. Somewhat
    d. Quite a bit
    e. Very much

2) Overall, how much does your hypogonadotropic hypogonadism affect your **mental function**? Typical effects include feelings of tiredness and problems with sleep, mood and thoughts.
    a. Not at all
    b. A little bit
    c. Somewhat
    d. Quite a bit
    e. Very much

3) Overall, how much does your hypogonadotropic hypogonadism affect your **sex life**? Typical effects include lack of sexual desire and erectile dysfunction.
    a. Not at all
    b. A little bit
    c. Somewhat
    d. Quite a bit
    e. Very much

11.3.5 Actigraphy Derived Activity and Sleep Parameters

The Autograph Link is a portable device that measures gross motor movements featuring a validated 3-axis accelerometer and data filtering technology that captures and records continuous, high resolution physical activity and sleep/wake information. It is a large, water-resistant wrist watch worn on the non-dominant hand.

Subjects will wear the monitor for 7 days consecutively starting with the day of the scheduled Visit 1, and 5 and 7 days consecutively before Visits 8 and 11, so that the monitors can be collected at Visit 8 from subjects transferring to the extension study and at Visit 11 from subject completing FU visit, as described in the schedule of assessments (Table 9–1).

Activity parameters

Moderate and vigorous physical activity, sedentary bouts and activity counts will be measured. Software algorithms will be used to differentiate the amount of time spent at each of these activity levels. The cut-offs selected will be chosen to reflect the sedentary lifestyle of the subjects.

Sleep parameters

Time spent in sleep will be measured to enable assessment of sleep quality and duration.

11.3.6 Grip Strength Measurement

Grip strength assessment using a hand held dynamometer will be used as a surrogate measure of muscle strength. During this assessment, the subject will squeeze the device three times with each hand. An average of three measurements for each hand will be calculated and recorded.

11.3.7 Semen Analysis

Subjects who are vasectomised or have vasectomy planned during the study period will be exempt from the semen analysis.

Semen Quality

Semen samples will be collected after a minimum of 48 hours of sexual abstinence based on WHO laboratory manual for the examination and processing of human semen. Condoms will not be used for collection as they may contain spermicide affecting quality of the specimen. The analysis will be performed at the study sites for the assessment of semen volume, sperm count, concentration, motility and morphology. Samples may be repeated up to two times at a scheduled time point due to individual variability in semen parameters.

Semen PK

Seminal fluid PK will also be performed at EOT to assess the concentration of BGS649 at steady state (see Section 11.4). .

11.4 Pharmacokinetic Assessments

Sparse Plasma Pharmacokinetic Sampling

PK sampling for BGS649 will be performed at the following time points, as defined in the schedule of assessments (Table 9–1):

Visit 5 (Week 12). Pre-dose and 1h post-dose. The investigator should ensure that the site visit when PK is taken coincides with the scheduled dosing visit.

Visit 8 (EOT;Week 24) PK will be taken only once together with other laboratory assessments taken at that visit.

It is important that the time that the last dose of study drug was taken prior to PK testing is recorded when PK is performed.

Semen Pharmacokinetic Sampling

PK sampling for BGS649 will be performed as defined in the schedule of assessments (Table 9–1) at Visit 8 (EOT).

Semen samples for PK analysis will be centrifuged (1000 g x 10 minutes) and the separated seminal plasma will be stored at -20°C until samples are used.

12 ASSESSMENT OF SAFETY

The timing and frequency of safety assessments provided in Table 9–1.

12.1 Adverse Events

12.1.1 Definitions

The definitions for AEs and SAEs are given below. It is of the utmost importance that all staff involved in the study are familiar with the content of this section. The principal investigator is responsible for ensuring this.

Adverse Event

An AE is defined as any untoward medical occurrence in a subject, or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign, symptom or disease temporally associated with the use of a medicinal (investigation) product, whether or not related to the medicinal (investigational) product.

Any relevant observations made at the Screening Visit (prior to signing the ICF) are to be recorded as pre-existing conditions. AE will only be recorded if there is a worsening of the pre-existing condition during study conduct with regard to nature, severity or frequency .

Only SAEs will be collected during Screening Period (the time between signing the ICF and randomisation). From randomisation to Day 90 after last study drug administration all AEs will be reported.

An adverse drug reaction is an “untoward and unintended response to an investigational medicinal product related to any dose administered”.

All AEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse drug reactions. The expression of “reasonable causal relationship” means to convey in general that there are facts or arguments which suggest a causal relationship.

Serious Adverse Event

An SAE is defined as, but is not limited to, one that:

1. Results in death

   Death is not an AE in itself, but an outcome. The cause of the death is the AE which resulted in death.

2. Is life-threatening

   Life-threatening means that the subject was at immediate risk of death at the time of the SAE; it does not refer to an SAE that hypothetically might have caused death if it had been more severe.

3. Requires in-subject hospitalisation or prolongs existing hospitalisation

Hospitalisation is defined as at least one overnight formal admission into hospital, usually in order to perform additional tests, provide treatment which it is not possible to provide at home and/or due to an unstable medical condition which requires specific monitoring of the subject. Pre-planned hospitalisations (known already prior to signing the ICF) will not be considered an SAE, unless any of the above criteria are fulfilled over the course of the hospitalisation due to unplanned complications. "Social" hospitalisation whereby it is administratively impossible to release the subject home is not necessarily an SAE. Complications that occur during hospitalisations are AEs. If the complication delays subject release from hospital then the AE becomes an SAE.

4. Results in persistent or significant disability/incapacity

   The term significant disability refers to any condition that impairs physical/physiological well-being to the extent that the subject is unable to function normally. Physical disability may include, but is not limited to, permanent disability of locomotion or motility, but also systemic permanent dysfunction including heart failure, liver insufficiency or pulmonary fibrosis.

5. Is a congenital anomaly/birth defect

6. Is an important medical event

   Important medical events that may not result in death, be life-threatening or require hospitalisation may be considered as an SAE when, based on appropriate medical judgement, they may jeopardise the subject or the subject may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Treatment Emergent Adverse Event

Treatment emergent AEs (TEAEs) are defined as any AE occurring or worsening on or after the first dose of study medication.

Adverse Events of Special Interest

Refer to Section 12.1.7.

12.1.2 Recording of Adverse Events

For the purposes of this study, only SAEs will be collected during Screening Period (the time between signing the ICF and randomisation).

Any detrimental change in the subject's condition, after randomisation and up to 90 days after the last administration of study drug should be considered an AE.

The following variables will be recorded for each AE: verbatim/AE description and date for AE start and stop, severity, seriousness, causality rating, whether or not the AE caused the subject to discontinue, and the outcome. If the severity of the AE changes, a new AE must be recorded.

SAEs and AEs will be recorded after randomisation. SAEs only will be reported during the screening period (from signing of the informed consent to randomisation). All AEs/SAEs

have to be reported, whether or not considered causally related to the investigational product or to the study procedure(s).

All ongoing AEs/SAEs should be followed up until resolution or stabilisation or the last visit if in the investigator's opinion, the AE is unlikely to resolve due to the subject's underlying disease.

At any time after the FU visit, if an investigator learns of an SAE that can be reasonably related to study drug, he/she should promptly notify the sponsor.

Intensity

The investigator will assess the intensity of AEs based on the following definitions:

1. Mild (awareness of sign or symptom, but easily tolerated)
2. Moderate (discomfort sufficient to cause interference with normal activities)
3. Severe (incapacitating, with inability to perform normal activities).

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 12.1.8.

An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

For an AE to be a suspected drug-related event there should be at least a reasonable possibility of a causal relationship between the study drug and the AE.

12.1.3 Causal Assessment

The following “binary” decision choice will be used by the investigator to describe the causality assessment:

- Reasonable possibility of relatedness
- No reasonable possibility of relatedness

The term “reasonable possibility of relatedness” is meant to convey, in general, that there is enough evidence or argument to suggest a causal relationship. The investigator should consider the following, before reaching a decision on causality assessment:

- Time relationship between study drug intake and event’s onset
- Dechallenge
- Rechallenge
- Medical history
- Study treatment
- Mechanism of action of study drug
- Class effect

- Concomitant treatments in use
- Withdrawal of study treatment
- Lack of efficacy/worsening of existing condition
- Erroneous treatment with study medication or concomitant medication
- Protocol-related process.

Action taken with study drug due to the AE:

- None
- Drug permanently discontinued
- Drug temporarily discontinued
- Unknown/not applicable.

Other action taken:

- Specific therapy/medication
- Surgical medical procedure
- (Prolonged) hospitalisation.

Each single AE must be rated by choosing one of the following:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered with sequelae/resolved with sequelae
- Fatal
- Unknown.

12.1.4 Abnormal Laboratory Values/Vital Signs/Electrocardiograms

Laboratory/vital signs/ECG abnormalities should be reported as AE/SAEs if any one of the following criteria is met:

1. The result is clinically significant or associated with signs/symptoms
2. Requires additional diagnostic testing and/or interventions
3. Leads to a change in dose, discontinuation or interruption of the study drug.

Results of an abnormal test results without any of the above criteria do not constitute an AE. Any test result determined to be an error is not required to be reported as an AE.

12.1.5 Overdose

A drug overdose is defined as the accidental or intentional use of a drug or medicine or an administration error in drug administration in an amount that is higher than is normally used.

Every overdose must be reported to ICON Pharmacovigilance and Safety Services within 24 hours of awareness, irrespective of whether the overdose was associated with an AE/SAE.

12.1.6 Partner Pregnancies

Pregnancy outcomes must be collected for the female partners of the subjects who took study treatment in this study. Pregnancy itself is not regarded as an AE unless there is suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. If a pregnancy is reported for a subject's partner, study drug will be immediately discontinued. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented. Follow up should be performed up to delivery and examination of the new-born, after which a follow-up report should be sent with any new information regarding the pregnancy and the outcome of the birth. After study drug discontinuation, the subject should continue with all study schedule assessments, except study drug administration. The male study subject has to continue to wear a condom for at least 3 months after the last medication intake. Unprotected intercourse with his pregnant partner presents a risk of toxicity to the unborn child.

All congenital abnormalities/birth defects should be classified as SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as SAEs, but should be reported as AEs.

Pregnancies must be reported to ICON Pharmacovigilance and Safety Services using the reporting details and timelines provided in Section 12.1.8 within 24 hours of awareness.

12.1.7 Adverse Events of Special Interest

Some AEs, despite their severity or outcome, will be expedited due to the relevance for subject safety or study drug safety profile. These AESIs should be reported as expedited within 24 hours of awareness to ICON Pharmacovigilance and Safety Services:

1. Cardiovascular event (acute myocardial infarction, brain stroke, transient ischemic attack, unstable angina, congestive heart failure)
2. Prostate cancer
3. Lower extremity oedema ≥ Grade 3 (which is not due to local pressure /venostasis effects such as may be caused by socks or other clothing).
4. Polycythemia as measured by a haematocrit > 54%
5. Fragility fracture
6. Development of sleep apnoea
7. Development of osteoporosis or low mineral density as per DEXA measurement (T score ≤ -2.5 for men ≥ 50 years or Z score ≤ -2 for men < 50 years of age)
8. Breast cancer.

12.1.8 Reporting of Serious Adverse Events and Adverse Events of Special Interest

Investigators and other site personnel must inform ICON Pharmacovigilance and Safety Services of any SAE/AESI that occurs during the course of the study whether or not considered causally related to the investigational product or to the study procedure(s): SAE: from the time of informed consent until the 90 days after last study drug dose, AESI from the time of randomisation until 90 days after last study drug dose and within 24 hours of when he or she becomes aware of it.

Follow-up information on SAEs/AESIs must also be reported by the investigator within the same time frames.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to ICON within 24 hours as described above.

All SAEs/AESIs will also be recorded in the eCRF. The investigator is responsible for informing the Ethics Committee of the SAE/AESI as per local requirements.

Paper SAE/AESI forms should be completed at the site and faxed/emailed to the relevant ICON Pharmacovigilance and Safety Services or e-mailed to the global email distribution list within 24 hrs of awareness of the event.

SAE/AESI reports should be sent to:

There may be situations when an SAE/AESI has occurred and the investigator has minimal information to include in the initial SAE/AESI report. However, it is very important that the investigator always makes an assessment of causality for every event prior to transmission of the SAE/AESI report form. Minimum criteria are identifiable subject (number), a suspect product (i.e. study drug or concomitant medication), an identifiable reporting source (investigator/study site identification), and an event or outcome that can be identified as serious or as an AESI. The investigator may change his/her opinion of causality in the light of follow-up information, amending the SAE/AESI report form accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements for SAEs.

12.2 Safety Endpoints

1. TEAEs/SAEs (from first dose of study drug until 90 days after last treatment dose)
2. Change in PSA during 24 week treatment duration
3. Change in haematocrit during 24 week treatment duration

4. Change in Bone Mineral Density (DEXA scan T-score and density in g/cm^2) from Screening and bone turnover biomarkers at 24-weeks from Baseline
5. Change in vital signs and clinical laboratory parameters, ECG
6. Change in physical examination (including general, prostate, breast and oedema of the lower extremities).

12.3 Laboratory Assessments

Laboratory measurements for blood chemistry, PSA, haematology, urinalysis and specialised chemistry will be performed according to the schedule of assessments (Table 9–1). Specific details not mentioned in this section (including shipping requirements) are included in the laboratory manual.

All blood samples are to be collected after 8 hours fasting, after ECG and vital sign measurements.

12.3.1 Clinical Laboratory Tests

Blood Chemistry

Sodium, potassium, chloride, bicarbonate/CO_2, blood urea nitrogen, creatinine, fasting glucose, albumin, alkaline phosphatase, AST, ALT, PT/INR, total bilirubin, total protein, calcium, lipid panel (total cholesterol, LDL, HDL, triglycerides) and PSA will be measured.

eGFR will be calculated based on Cockcroft-Gault formula:

$$eGFR = ((140 - Age) / (SerumCreat)) * (Weight / 72)$$

Haematology

Haemoglobin, white blood cell (WBC) count with differentials (monocytes, eosinophils, basophils, neutrophils, lymphocytes) as an absolute value, red blood cell (RBC) count and platelet count will be measured.

Urinalysis

Specific gravity, pH, semi-quantitative “dipstick” evaluation of glucose, protein, bilirubin, ketones, leukocytes and blood will be measured.

A microscopic examination including RBC and WBC will be performed only when dipstick evaluation is positive for WBC and/or blood or protein. A midstream urine sample (about 30 mL) will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments.

12.3.2 Specialised Chemistry

The following laboratory parameters will be measured at Screening only, for assessment of exclusion criteria (see Section 9.3.2):

1. Morning cortisol
2. TSH
3. FT4

4. Prolactin
5. 25-hydroxy vitamin D (no exclusion criteria related to this parameter)
6. Fasting transferrin saturation reported in % and calculated according to the formula:
   - Transferrin saturation = [Iron / (Transferrin × 1.4)] × 100

12.3.3 Bone Turnover Markers

CTx1, osteocalcin, bone alkaline phosphatase and P1NP will be measured.

12.4 DEXA Scan

Bone density will be evaluated with standard procedure. An overview is provided here. The study imaging manual contains more detailed guidance which should be followed. All evaluations during the study for particular subject will be performed on the same machine, wherever possible by the same technician. It is important that the same subject positioning is followed for each scan. Primary scan results need to be stored for central overread when required.

To assess the spine, the subject will be in supine position with legs supported on a padded box to flatten the pelvis and lower (lumbar) spine. To assess the hip, the foot is placed in a brace that rotates the hip inward. Both femoral neck and total hip results will be reported.. The detector will be slowly passed over the area separately for spine and hip, generating images. The duration of examination will be up to 30 minutes. DEXA T-Score will be calculated based on actual measured bone density value. Both density and T-score values will be evaluated for safety.

12.5 Physical Examination

The following examinations will be performed:

1. Full evaluation and physical examination (general appearance, skin and body hair, neck [including thyroid]), eyes, ears, nose, throat, lungs, heart, abdomen, testicular examination, lymph nodes, lower extremities examination for oedema and basic nervous system evaluation)
2. Digital prostate examination
3. Limited physical examination (cardiovascular system and lower extremities oedema) at all visits where a full physical examination is not scheduled. For lower extremities examination, subject will be sitting with their lower extremities in the dependent position. Lower extremities will be inspected and palpated to look for pitting oedema.

The lower extremities examination findings will be graded as per standard medical practice on a 5-point scale: 0 - no oedema, +1- barely detectable 2mm depression. Immediate rebound, +2- a 4mm deep oedema, few seconds to rebound, +3 - 6mm deep oedema. 10-12 seconds to rebound to + 4- 8mm deep oedema, >20 seconds to rebound and recorded in the eCRF. Use of bony prominence such as the malleoli may reduce the artefactual pitting oedema that may occur above sites of constriction such as tight socks.

Information about the physical examination must be present in the source documentation at the study site. Significant findings that are present prior to the start of the study drug treatment must be included in the relevant medical history/current medical conditions section of the CRF. Significant findings made after the start of study drug treatment, which meet the definition of an AE must be recorded in the AE CRF summary page.

12.6 Vital Signs

Vital signs include measurement of oral temperature, SBP, DBP, pulse and weight. Height will also be measured at Screening only, to enable BMI determination (Section 11.3.2).

Details on body weight measurement are provided in Section 11.3.2. Body weight taken at Baseline will be utilised for all PK calculations.

Blood pressure (SBP and DBP, see Section 11.3.2) and pulse rate will be assessed after the subject has rested quietly in the supine position for at least 5 minutes. Three consecutive recordings will be taken and the average value will be noted in the eCRF. Blood pressure will be assessed using the same arm each time.

12.7 12-Lead ECG

The subject number and initials or date of birth, the date and actual time of the tracing, and the study code must appear on each page of the tracing. The ECGs should be performed at approximately the same time of day at each of the ECG assessments, after subject has been in supine position for 10 min. Tracings will be dated and signed by the person who interprets the ECG.

The CRFs will contain:

1. Date and time of the ECG
2. Heart rate
3. PR interval
4. QT interval (QT_CF)
5. QRS duration.
6. RR interval

The overall interpretation will be collected with a yes/no statement to confirm if any clinically significant abnormalities are present, which need to be detailed further and reported as AE/SAE if appropriate. Original ECG tracings, appropriately signed, will be archived at the study site.

12.8 Androgen Deficiency Guidance

All subjects will be assessed by an investigator at Screening for symptoms of androgen deficiency based on an androgen deficiency guidance document that will list all androgen deficiency symptoms (see Appendix II). All positive symptoms will be entered into the eCRF.

12.9 24/7 Medical Emergency Coverage

On this internet page, a list of country-specific toll-free telephone numbers is provided. It should be noted that not all countries globally have access to toll-free numbers as indicated on the "24/7 Medical Helpdesk" index. Countries without toll-free numbers need to dial the chargeable number as indicated above. Furthermore, toll-free numbers are not available from mobile phones.

13 STATISTICAL EVALUATION

13.1 Sample Size and Power

Statistical Hypothesis:

[redacted]

ICON Biostatistics will prepare the randomisation list, based on a randomisation scheme blocked by site. Until the outcome of the interim analysis is known, each subject will be assigned to one of four dosing regimens defined in Section 9.1 in a 1:1:1:1 ratio. This will be adjusted as per Section 9.1 depending on the outcome of the interim analysis.

See Section 10.2.4 for further details of the Randomisation procedures to be applied.

13.3 Analysis Sets

All primary and secondary efficacy endpoints will be analysed using the intention to treat (ITT) population. The per-protocol (PP) population will be used only for the analysis of the primary endpoint to examine the robustness of the primary analyses.

Safety and tolerability will be analysed using the safety population.

Pharmacokinetic data will be analysed using the PK population.

13.3.1 Intention to Treat (ITT) (Full Analysis Set)

The ITT population includes all subjects who:

1. Are randomised, and
2. Receive at least one dose of study medication, and
3. Provide a Baseline and at least one post-Baseline testosterone value.

13.3.2 Per Protocol

The PP population is a subset of the ITT population and includes all randomised subjects as randomised who have been treated according to the protocol and fulfil the following criteria (to be further described in the statistical analysis plan [SAP]):

1. All inclusion/exclusion criteria satisfied

2. Absence of relevant protocol violations with respect to factors likely to affect the efficacy of treatment where the nature of protocol violation will be defined before breaking the blind
3. Adequate study medication compliance
4. Adequate measurement of the primary variable.

13.3.3 Safety Population

The safety population includes all subjects who received at least one administration of the study medication.

13.3.4 PK Population

For the nonlinear mixed effects modelling, all subjects who received at least one administration and have at least quantifiable concentration will be included.

13.4 Endpoints

13.4.1 Primary Efficacy Endpoint(s)

The primary efficacy endpoint is the normalisation of total testosterone levels in ≥ 75% of subjects at Week 24.

13.4.2 Secondary Efficacy Endpoint(s)

Efficacy will be further assessed based on the secondary endpoints, as defined in Section 11.2.

Further details and the time points for collection are given in Section 11.3 and in the Schedule of assessments (Table 9–1). A complete list of efficacy endpoints is given in Section 11.2.

These secondary efficacy parameters will be assessed using the ITT population.

13.4.3 Pharmacokinetics

Nonlinear mixed effects PK/PD models evaluating the relationship between BGS649 exposure and testosterone levels.

13.4.4 Exploratory Endpoints(s)

Exploratory endpoints are defined in Section 11.2.

13.4.5 Safety Endpoint(s)

The following data will be collected for assessment of safety:

1. AEs including SAEs and AESIs
2. Vital signs and clinical laboratory parameters
3. ECG
4. Physical examination (including general, prostate, breast and oedema of the lower extremities)
5. DEXA scan T-Score and density in g/cm^2.

These safety parameters will be assessed using the safety population. A list of safety endpoints is given in Section 12.2.

13.5 Description of Statistical Analyses

13.5.1 General Considerations

The statistical evaluation will be performed by ICON using SAS®, Version 9.3 or later. Data will be analysed by either enumeration of subjects displaying distinctive characteristics within each treatment regimen or by descriptive statistical summaries such as means, standard deviations (SD), medians, and ranges for continuous measures. Categorical variables will be presented by the number of observations and absolute and relative (%) frequency.

For efficacy data summary statistics (N, mean, SD, median minimum and maximum for continuous data, and N [%] for categorical data) will be presented at each visit.

Similarly, changes from Baseline (or percentage change from Baseline if appropriate) will be summarised in a similar manner.

The main population for efficacy analysis will be the ITT population.

Unless stated otherwise the Baseline value for a variable will be latest value take prior to first dose of study medication.

Data in summary tables will generally be presented on an Observed Cases basis.

Unless stated otherwise, all statistical tests will be two-sided and conducted at the 5% level, and all quoted CIs will be two-sided 95% CIs. All four treatment regimens will be assessed by pairwise comparisons, no adjustment for multiplicity will be made and all analyses will be considered as exploratory analyses.

Full details of the statistical analysis will be given in a SAP.

13.5.2 Analysis of Primary Endpoint

The Primary Endpoint will be considered to have been met for a dose if ≥ 75% of subjects in the ITT population have normalisation of total testosterone levels at Week 24

The proportion of subjects with normal testosterone levels will be summarised by treatment regimen and visit.

The primary analysis of efficacy will be performed with the ITT population. Additionally for exploring the robustness of the intent-to-treat results, a supportive analysis using the PP population will be carried out.

As per section 13.7 the primary analysis will be conducted once all data up to Visit 8 has been collected.

13.5.3 Analysis of Secondary Endpoints

The analysis of secondary efficacy endpoints will be performed on the ITT population.

For the secondary efficacy endpoints data will be summarised by treatment regimen and visit.

For each continuous parameter, change from Baseline will be assessed with a mixed model repeated measure (MMRM) analysis, with treatment regimen as a factor and the Baseline value as a covariate. The adjusted mean difference between treatments will be presented along with a 95% CI for the time-points of interest.

For binary outcomes the proportion of subjects with a response will be summarised and compared between treatment regimens using Fisher's Exact Test.

A more detailed description will be presented in the SAP.

13.5.4 Analysis of Exploratory Endpoints

The analysis of exploratory endpoints will be performed on the ITT population.

Data will be summarised by treatment regimen and visit.

For each continuous parameter, change from Baseline will be assessed with a MMRM analysis, with treatment regimen as a factor and the Baseline value as a covariate. The adjusted mean difference between treatments will be presented along with a 95% CI for the time-points of interest.

For binary outcomes the proportion of subjects with a response will be summarised and compared between treatment regimens using Fisher's Exact Test.

A more detailed description will be presented in the SAP.

13.5.5 Safety Analyses

The analysis of safety parameters will be based on the safety population. In general, missing safety data will not be replaced. A more detailed description will be presented in the SAP.

Adverse Events

AEs will be coded using the most recent version available of the Medical Dictionary for Regulatory Activities (MedDRA). Summaries will be by system organ class and preferred term. TEAEs are defined as any AE occurring or worsening on or after the first dose of study medication. If a subject experiences the same preferred term multiple times then the event will be counted only once and by the greatest severity.

The frequency and incidence of TEAEs will be presented by system organ class and preferred term for each treatment regimen (number and percentage of subjects experiencing at least one AE per preferred term as well as the number of observed events per preferred term). Separate tables will be presented by severity and by relationship. All AEs will be presented in full in a comprehensive listing including subject number, treatment regimen, severity, seriousness, action taken, outcome, relationship to treatment, onset/stop and duration. Details of SAEs and AEs leading to withdrawal will be listed separately.

Concomitant Medication

Concomitant medication will be tabulated and summarised by treatment regimen.

Physical Examination

Physical examination results will be listed by subject and body system.

Vital Signs

Vital signs will be summarised as actual values and change from Baseline by treatment regimen and visit.

ECG

The overall ECG interpretation will be summarised by presenting the number and percentage of subjects with "Normal" "Abnormal, not clinically significant" and "Abnormal, clinically significant".

ECG parameter values (e.g., QT_CF) will be summarised as actual values and change from Baseline by treatment regimen and visit to end of treatment.

Clinical Laboratory

Descriptive statistics will be presented for quantitative laboratory parameters for each treatment regimen and time-point. Similarly, changes from Baseline will be summarised.

Values outside the normal range will be categorised as H (above the normal range) or L (below the normal range) based on the laboratory's reference range and these will be flagged in the listings of individual subject data.

DEXA Scan

DEXA scan T-Score and density in g/cm^2 will be summarised as actual values and change from Screening at Week 24 and by treatment regimen.

Withdrawals

Subjects who withdraw from the study will be summarised by treatment regimen according to their reason for withdrawal.

13.5.6 Analysis of Further Endpoints

Demographic data and subjects' characteristics at Screening will be listed and summarised using descriptive statistics. Formal statistical analysis will not be performed on Baseline demographic data.

Medical history will be coded using MedDRA. An incidence table by body system and preferred term will be presented by treatment regimen.

Compliance with study medication will be summarised descriptively by treatment regimen.

13.6 Interim Analysis

An interim analysis will be conducted once approximately 100 of overall planned subjects have completed the Week 4 visit. The analysis will be performed by an independent DMC who will review un-blinded data to identify:

1. Any safety signals across the dose groups which would preclude further continuation of dosing

2. Whether an individual arm has met the criteria of ≥ 75% of subjects reaching the normalisation of testosterone (testosterone within or above normal reference range for healthy adult males according to the FDA)
3. Whether in the opinion of the DMC following unblinded review that when the arm is fully recruited it is expected to achieve a ≥ 75% response at Week 24.

Dosing arms which meet either criterion 2 or 3 will be deemed effective. For arms that are determined to be ineffective or unsafe, dosing will be stopped and no further randomisation to that arm will be performed.

Subjects assigned to the ineffective or unsafe arm(s) will be discontinued from the treatment, will attend an EOT visit and will be followed-up for an additional 12 weeks (FU, Visit 11). While the interim analysis is being performed, dosing and recruitment of study subjects will continue.

13.7 Interim Clinical Study Report

The primary efficacy analysis and study unblinding will be performed when all data up to Visit 8 (Week 24) has been collected. Given the study has been powered at Week 24 and there will not be multiple comparisons, there is no requirement to adjust the Type I error rate.

An interim Clinical Study report (CSR) will be prepared based upon the results of this analysis.

The safety data collected during the off treatment 12 week follow-up will be separately analysed and published in the full CSR.

13.8 Population Pharmacokinetic/Pharmacodynamic Modelling

Nonlinear mixed effects modelling will be utilised to develop a population PK model for plasma BGS649 concentrations and to develop a PK/PD model linking BGS649 concentrations to changes in testosterone levels.

A separate Modelling and Simulation Analysis Plan (MSAP) will be prepared and results from the PK and PK/PD modelling will be reported separately from the clinical study report (CSR).

14 DIRECT ACCESS TO SOURCE DATA/NOTES

The investigator/institution shall provide direct access to source data/documents for study-related monitoring, audits, Independent Ethics Committee (IEC)/Institutional Review Board (IRB) review and regulatory inspection.

15 QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Conduct of the Study

ICON shall implement and maintain quality control and quality assurance procedures with written standard operating procedures (SOPs) to ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, ICH GCP and applicable regulatory requirements.

This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 1996) and all revisions thereof (See Appendix I:), and in accordance with FDA regulations (CFR, Sections 312.50 and 312.56) and with ICH GCP (CPMP 135/95).

The investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IEC/IRB, except when necessary to eliminate immediate hazards to the subject or when the change(s) involve(s) only logistical or administrative aspects of the study. Any deviations may result in the subject having to be withdrawn from the study and render that subject non-evaluable.

15.2 Study Monitoring

The investigator shall permit the ICON Site Monitor to review study data as frequently as deemed necessary to ensure that data are being recorded in an adequate manner and that protocol adherence is satisfactory.

The investigator will provide access to medical records for the Monitor in order that entries in the eCRF may be verified. The investigator, as part of his/her responsibilities, is expected to co-operate with ICON in ensuring that the study adheres to GCP requirements.

The investigator may not recruit subjects into the study until such time that a visit, or with the agreement of the sponsor, attendance at the investigator meeting, has been made by a sponsor/ICON monitor to conduct a detailed review of the protocol and eCRF.

16 ETHICS

16.1 Independent Ethics Committee/Institutional Review Board

Prior to the start of the study, the investigator is responsible for ensuring that the protocol and consent form have been reviewed and approved by a relevant IEC/IRB. The IEC/IRB shall be appropriately constituted and perform its functions in accordance with FDA ICH GCP and local requirements as applicable.

The IEC/IRB shall approve all protocol amendments (except for logistical or administrative changes), written informed consent documents and document updates, subject recruitment procedures (e.g., advertisements), written information to be provided to the subjects, IB, available safety information, information about payment and compensation available to subjects, the investigator's curriculum vitae and/or other evidence of qualifications and any other documents requested by the IEC/IRB and Regulatory Authority (Competent Authority) as applicable.

16.2 Written Informed Consent

The nature and purpose of the study shall be fully explained to each subject (or their legally responsible guardian).

Written informed consent must be obtained from each subject (or guardian) prior to any study procedures being performed. The process of obtaining informed consent must be documented in the subject source documents.

The consent documents to be used for the study shall include all the elements of informed consent in accordance with FDA, ICH GCP and local requirements as applicable and be reviewed and approved by the appropriate IEC/IRB prior to use.

16.3 Data Monitoring Committee

An independent, unblinded external DMC will periodically review accumulating safety data. T[redacted]. The DMC will in addition perform the interim analysis in order to determine any doses of BGS649 that did not lead to normalisation of testosterone (not reaching therapeutic range of testosterone > 300ng/dL). Full details of composition, operational aspects, and data to be reviewed and recommendation of the DMC will be provided in a separate DMC charter.

17 DATA HANDLING AND RECORD KEEPING

17.1 Case Report Forms/Source Data Handling

All required study data must be entered in the eCRF created for the study. This data collection tool is a validated electronic data capture (EDC) system that contains a system generated audit trail. Data required according to this protocol are recorded by investigational site personnel via data entry into the internet based EDC software system. The investigator shall ensure that all data from subject visits are promptly entered into the eCRFs in accordance with the specific instructions given. The investigator must sign each eCRF to verify the integrity of the data recorded. All internal ICON and external investigational site personnel seeking access to the eCRF are to do so according to the FDA guidance for industry on electronic source data in clinical investigations. At the end of the study all data captured electronically will be provided to the investigator on CD-ROM for archiving at the investigational site.

A list of the normal ranges for all laboratory tests to be undertaken forms part of the documentation to be collated prior to study start. If a central laboratory has been selected to conduct any or all tests, it is essential that all samples be analysed at that laboratory.

The investigator must maintain source documents, such as laboratory reports, X-rays, ECGs, consultation reports, and complete medical history and physical examination reports. All information in the eCRF must be traceable to the source documents in the subject's file.

Data to be recorded directly on the CRFs (i.e., no prior written or electronic record of data) and considered to be source data must be identified in the protocol.

17.2 Retention of Essential Documents

The investigator/institution should maintain the study documents as specified in the ICH guidelines on GCP and as required by the applicable regulatory requirements. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

18 FINANCING AND INSURANCE

The sponsor shall carry an insurance policy to cover compensation of subjects' health injuries arising from the study. If a subject incurs a study-related injury, the subject may be treated (and other necessary measures taken) at the study site and/or another medical institution. If it is necessary to compensate for the treatment, the sponsor will cover the cost. The sponsor shall not impose on the subject the burden of proving the causal relation between the study and the injury.

If any of the following is confirmed, the sponsor may refuse or restrict the payment of the compensation:

1. A serious GCP or protocol deviation by the investigator or sub-investigator (except deviation medically necessary to avoid an immediate hazard to the study subjects)
2. Intentional act or negligence on the part of the investigator or sub-investigator or malpractice thereby
3. Injury caused by unlawful act or delinquency of a third party
4. Injury caused by intentional act or negligence of the subject.

If compensation becomes necessary for a study-related injury, the site will promptly notify the sponsor and will co-operate with the sponsor and its insurer (or their legal representatives) in their handling thereof.

19 PUBLICATION POLICY

The sponsor shall retain the ownership of all data. When the study is complete the sponsor shall arrange the analysis and tabulation of data. A CSR shall then be prepared, which may be used for publication, presentation at scientific meetings or submission to regulatory authorities. All proposed publications based on this study must be subject to the sponsor's approval requirements.

The sponsor assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalisation of the study report, the results of this trial will be submitted for publication and/or posted in a publicly accessible database of clinical trial results.

20 SIGNATURE OF INVESTIGATOR

I agree to conduct the study outlined above in accordance with the terms and conditions of the protocol, ICH guidelines on GCP and with applicable regulatory requirements. All information pertaining to the study shall be treated in a confidential manner.

_____ _____

Date (day/month/year)

21 REFERENCE LIST

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Study CBGS649A2101 A randomised, double-blind, placebo-controlled, parallel group, adaptive design, ascending single dose first-in-human study to explore the safety, tolerability, pharmacokinetics and pharmacodynamics of oral BGS649 in healthy premenopausal and postmenopausal female volunteers without childbearing potential.

Study CBGS639A2204 An open label dose finding study (part 1) followed by a parallel group, randomised, double blind study to evaluate the safety, tolerability and pharmacodynamics of 12 week BGS649 treatment (part 2) in obese, hypogonadotropic hypogonadal (OHH) men.

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22 APPENDICES

Appendix I: World Medical Association Declaration of Helsinki, 2013

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy

volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

Appendix II: Symptoms and Signs Suggestive of Androgen Deficiency

The following list is symptoms and signs that are suggestive of androgen deficiency:

- Reduced sexual desire (libido) and sexual activity
- Decreased spontaneous erections
- Reduced intensity of orgasm
- Gynecomastia
- Loss of body (axillary and pubic) hair (can be measured by reduced shaving)frequency
- Very small (especially _5 ml) or shrinking testes
- Infertility or documented oligospermia or azoospermia
- Hot flushes
- Decreased energy, motivation, initiative, and self-confidence
- Feeling depressed
- Mood swings
- Poor concentration and memory
- Sleep disturbance, increased sleepiness
- Mild anemia (normochromic, normocytic, in the female range)
- Reduced muscle bulk and strength
- Increased body fat, body mass index
- Diminished physical or work performance