1 TITLE PAGE

CLINICAL STUDY PROTOCOL

A 6 month, double-blind safety extension study of MBGS205 evaluating the effects of long term treatment with BGS649 on bone mineral density

Protocol No.: MBGS206	EUDRACT/IND No.: 2015-005760-42
Test Product:	BGS649
Indication:	Hypogonadotropic hypogonadism
Sponsor:	Mereo BioPharma 2 Ltd
Development Phase:	Phase IIb
Sponsor Signatory:	Dr. Alastair MacKinnon
Sponsor Medical Expert:	Dr. Jackie Parkin
Date of the Protocol:	28 March 2017
Version of the Protocol:	Final Version 2.0

SUMMARY AND JUSTIFICATION OF CHANGES

This amendment includes revisions to Protocol Version 1.0, dated 27 July 2016, summarized as follows

Change	Rationale
Change total number of doses from 23 to up to 24 throughout document	Clarification and correction
Change from AESI as exclusion criterion to AESI that meet MBGS205 discontinuation being the exclusion criterion	No safety reason to require AESIs that do not meet study drug discontinuation criterion to be exclusion for extension study MBGS206
Labelling section removal reference to placebo	No placebo in MBGS206
Clarification MBGS206 will be un blinded to sponsor and CRO when preceding study MBGS205 is un blinded.	As a result of un blinding MBGS205 the patient allocation for MBGS206 will be available to sponsor and CRO. MBGS206 will be fully recruited by this time and with quantitative endpoint the risk to the study conduct is considered acceptable. Site and subjects will remain blinded.
Increased technical guidance on DEXA scanning and requirement to utilise guidance within study DEXA imaging manual	To reduce the variability in DEXA results that had been observed in MBGS205
Removal of monoclonal antibodies as a prohibited medication	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 a prohibited medication.	To enable recruitment of representative target population of obese men with type 2 diabetes requiring insulin.
Removal of Cyp3A4 and Cyp2A6 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 worsening of lower limb oedema to exclude measurement artefacts and effects of restrictive clothing.	To prevent inappropriate drug interruption for artefactual worsening of leg oedema.

2 SPONSOR SIGNATURE PAGE

PROTOCOL TITLE: A 6 month, double-blind safety extension study of MBGS205 evaluating the effects of long term treatment with BGS649 on bone mineral density

PROTOCOL NUMBER: MBGS206

Mereo BioPharma 2 Limited

[redacted]

19th April 2017

Date (day/month/year)

[redacted]

19 April 2017

Date (day/month/year)

3 GENERAL INFORMATION

A 6 month, double-blind safety extension study of MBGS205 evaluating the effects of long term treatment with BGS649 on bone mineral density

Protocol No.:	MBGS206
Date of the Protocol:	27 July 2016
Date and Number of Amendment(s):	28 Mar 2017, Amendment 1
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
	[redacted]
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 6 month double-blind safety extension study of MBGS205 evaluating the effects of long term treatment with BGS649 on bone mineral density.</td></tr>
<tr><td colspan="3">Principal Investigator:
Professor Hugh Jones</td></tr>
<tr><td colspan="3">Study Centre(s):
Approximately 50 sites</td></tr>
<tr><td colspan="3">Publication(s):
None</td></tr>
<tr><td colspan="2">Planned Study Period:
Oct 2016 to Oct 2017</td><td>Development Phase:
Phase II</td></tr>
<tr><td colspan="3">Objectives:
<u>Primary Objective</u>
The primary objective is to evaluate the effect of 12 months treatment with BGS649 on bone mineral density (6 months treatment during Study MBGS205).
<u>Secondary Objectives</u>
Safety:
1. To evaluate the effect of BGS649 after 12 months period of treatment with active study drug (6 months treatment during Study MBGS205 and 6 months treatment during Study MBGS206) by dose group on:
o Bone turnover biomarkers
o Bone mineral density and bone biomarkers by vitamin D status (Baseline vitamin D from Study MBGS205)
o Oestradiol levels
o Testosterone outside upper limit of normal range
o Prostate specific antigen and haematocrit
o Blood pressure
o Adverse events (AEs)
2. To evaluate if there are associations between changes in bone mineral density after 12 months treatment with BGS649 with end of treatment testosterone and oestradiol levels
3. To collect safety data in subjects switching from placebo arm in Study MBGS205 and treated with 6 months active study drug in Study MBGS206.
Pharmacokinetic
The pharmacokinetic (PK) objective is to determine BGS649 concentration by dose in seminal fluid and relationship to plasma PK at the end of treatment
Efficacy
1. To follow the change of total testosterone, bioavailable testosterone, luteinising hormone (LH), and follicle stimulating hormone (FSH) over a total of 12 months administration of BGS649 in those on active treatment in Study MBGS205 and a total of 6 months administration of BGS649 on subjects that were switched from placebo treatment during Study MBGS205
2. Evaluation of percentage of subjects with normalised testosterone after 12 months treatment with BGS649 in those on active treatment in Study MBGS205 and total of 6 months administration of BGS649 on</td></tr>
</table>

Name of Sponsor/Company: Mereo BioPharma 2 Ltd	**Individual Study Table Referring to Part of the Dossier:**	**(For National Authority Use Only)**
Name of Product: BGS649		
Name of Active Ingredient: 4,4'-[fluoro-(1-H-1,2,4-triazol-1-yl)methylene]bisbenzonitrile	**Volume:** **Page:**	

subjects that were on placebo treatment during Study MBGS205

Exploratory Efficacy Objectives

1. To evaluate the effect of 12 months treatment with BGS649 (6 months treatment in Study MBGS205 and 6 months treatment in Study MBGS206) on:
   - Cardiometabolic parameters, body composition, physical activity, grip strength, and sleep pattern; and on sexual functioning, fatigue, and quality of life, assessed by patient reported outcomes (PROs)
   - The association between changes in PROs and changes in body composition, physical activity, grip strength, and sleep
   - The association between changes in testosterone and changes in cardiometabolic parameters, body composition, physical activity, grip strength, sleep, and PROs
2. To evaluate the 6 month efficacy data on subjects on placebo arm in Study MBGS205 treated with active study drug in Study MBGS206 (cardiometabolic parameters, body composition, physical activity, grip strength, sleep, and PROs).

Methodology:

This is a 6 months, active treatment, extension study, open to subjects who have completed full 24 weeks in Study MBGS205 (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 [HH]).

The main purpose of the study is to evaluate bone mineral density and other long term safety and efficacy parameters in subjects after 12 months exposure with BGS649, to better define the risk/benefit of BGS649 in the obese male HH patient. The study will also collect additional BGS649 safety and efficacy data on subjects that were randomised to placebo in Study MBGS205 and have 6 months active drug exposure in Study MBGS206.

Informed Consent will be taken prior to study procedures being performed. Study participation will comprise of an Extension Study Baseline visit (Week 24 of Study MBGS205), 7 visits during the treatment period up to Week 48 (End of Treatment [EOT]), and a Follow-Up (FU) visit for safety performed at Week 60, 12 weeks after the Week 48/EOT visit. The End of Study is defined as the last visit of the last global subject.

During the 24 week treatment period, subjects will take required dose weekly (± 1 day from the time schedule of regular planned dose) with water.

Safety assessments will include bone mineral density (by dual energy X-ray absorptiometry [DEXA] scan), vital signs, physical examination, electrocardiograms (ECGs), haematology, blood chemistry and urinalysis, bone turnover markers, prostate-specific antigen (PSA), oestradiol, and recording of AEs, serious AEs (SAEs), AEs of special interest (AESIs), and concomitant medications.

The safety of the study will also be periodically monitored through a data monitoring committee (DMC) and will include relevant subject data from Study MBGS205 and Study MBGS206.

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 ≥ 1500 ng/dL [52 nmol/L] at any 2 consecutive time points throughout both studies MBGS205 and MBGS206), the subject will be discontinued from the treatment.

Efficacy assessments will include measurement of total and calculated bioavailable testosterone, LH, FSH, body composition measurement including body mass index (BMI), waist and hip circumference and impedance, cardiometabolic parameters, physical activity and sleep pattern via the wearing of wrist monitors, and grip strength via a dynamometer, and sexual functioning and satisfaction, fatigue, and quality of life via PROs.

Pharmacokinetics of BGS649 in plasma and seminal fluid will also be evaluated at 12 months of study drug exposure. Seminal fluid PK will be assessed (excluding subjects that are vasectomised or have vasectomy planned during the study period) at the Baseline visit (Week 24 of Study MBGS205) and Week 48 (EOT Visit 7. Subjects that are discontinued early from the study drug will provide samples for seminal fluid PK at EOT Visit 7, unless they are not able to provide this sample. Concomitantly with semen PK, plasma PK will be assessed to estimate plasma to semen BGS649 transference.

Name of Sponsor/Company: Mereo BioPharma 2 Ltd	**Individual Study Table Referring to Part of the Dossier:**	**(For National Authority Use Only)**
Name of Product: BGS649		
Name of Active Ingredient: 4,4'-[fluoro-(1-H-1,2,4-triazol-1-yl)methylene]bisbenzonitrile	**Volume:** **Page:**	

Treatment allocation

Subjects receiving active doses of BGS649 in Study MBGS205 will continue with the same dose in Study MBGS206. Subjects receiving placebo in Study MBGS205 will be randomised, using interactive response technology (IRT), on a 1:1:1 basis to each of the following active treatment arms:

- BGS649 [redacted]
- BGS649 [redacted]
- BGS649 [redacted]

If one or more dosing arms are dropped during the conduct of Study MBGS205 these will not be progressed in Study MBGS206 and subjects switching from placebo will be randomly allocated to available dose arms.

Number of Subjects:

Enrolment will continue until 30 subjects from each of the previous active treatment arms in Study MBGS205 have entered this study aiming for approximately 25 subjects completing each dose level with 48 weeks total exposure. Assuming about 17% dropout rate in the extension study. Subjects previously treated with placebo will be enrolled until target subject population is met in all active arms.

Diagnosis and Main Criteria for Inclusion:

Inclusion

1. Participating in Study MBGS205 and completion of the 24 week treatment period without meeting any discontinuation criteria of Study MBGS205
2. 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 foetal 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
3. Ability to understand and comply with the requirements of the protocol/study, including understanding and being able to give informed consent
4. In opinion of the investigator has been compliant with the requirements of the Study MBGS205 protocol.

Exclusion

1. Development of clinically significant medical or psychiatric condition during Study MBGS205 that may interfere with the study assessments or mask/mimic symptoms of hypogonadism, 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
2. Development of hypothalamic or pituitary tumour (or inflammatory condition) or 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 (unless there is documentation of a normal magnetic resonance imaging scan of pituitary and hypothalamus within 3 months before Baseline)
3. Meeting any of the discontinuation criteria of initial Study MBGS205
4. Evidence of new significant prostatic disease in Study MBGS205
5. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 times the upper limit of normal (ULN) or bilirubin ≥ 2 times the ULN (unless caused by Gilbert syndrome)
6. Fragility fracture or bone mineral density T-score < -2.0
7. Use of cardiac pacemaker or other medical electronic devices that can be affected by bio-impedance assessment
8. Planned treatment with prohibited medications (including self-prescribed)
9. 12-lead ECG abnormalities at Baseline including QT_C by Fridericia's correction method (QT_CF) interval > 450 ms
10. Intention to take part in study of other investigational product during the next 36 weeks.

Name of Sponsor/Company: Mereo BioPharma 2 Ltd	**Individual Study Table Referring to Part of the Dossier:**	**(For National Authority Use Only)**
Name of Product: BGS649		
Name of Active Ingredient: 4,4'-[fluoro-(1-H-1,2,4-triazol-1-yl)methylene]bisbenzonitrile	**Volume:** **Page:**	

Test Product, Dose and Mode of Administration:
BGS649 is prepared [redacted] Subjects will receive [redacted]

Reference Therapy, Dose and Duration of Administration:
None.

Duration of Treatment in Study MBG206:
Subjects will be treated for maximum of 24 weeks with BGS649, with a 12 week follow-up period after completion

Study endpoints

Primary

1. Percentage change in lumbar bone mineral density measured by DEXA (g/cm^2) from Baseline in Study MBGS205 to Week 48 in Study MBGS206 by dose group in subjects randomised to active treatment in Study MBGS205.

Secondary

Safety

1. In subjects that were randomised to active treatment in Study MBGS205 by dose group:
   - Percentage change in hip bone mineral density measured by DEXA (g/cm^2) from Baseline in Study MBGS205 to Week 48 in Study MBGS206
   - Percentage change in bone turnover markers (C-terminal telopeptide [CTx1], osteocalcin, bone alkaline phosphatase, and procollagen type 1 N-propeptide [P1NP]) from Baseline in Study MBGS205 to Week 48 in Study MBGS206
   - Proportion of subjects with T-scores ≤ -2.5 at Week 48
   - Percentage change in bone density and bone biomarkers adjusted for vitamin D deficiency from Baseline in Study MBGS205 to Week 48 in Study MBGS206
   - Change of oestradiol (absolute and percentage) from Baseline in Study MBGS205 to Week 48
   - Proportion of subjects that overshoot testosterone (total testosterone above 1000 ng/dl [35 nmol/L], from first dose of study drug in Study MBGS205 until study completion)
   - Change in PSA from Baseline in Study MBGS205 to Week 48 in Study MBGS206
   - Change in haematocrit from Baseline in Study MBGS205 to Week 48 in Study MBGS206
   - Change in blood pressure (systolic and diastolic) Baseline in Study MBGS205 to Week 48 in Study MBGS206
   - Treatment emerged AE, SAE, and AESI (from first dose of study drug in Study MBGS205 until study completion)
   - Relationship between change in bone mineral density from Baseline in Study MBGS205 to Week 48 in Study MBGS206 and absolute levels of oestradiol and total testosterone at Week 48 in MBGS206
2. In subjects that were randomised to placebo in Study MBGS205 by dose group:
   - Percentage change in hip bone mineral density measured by DEXA (g/cm^2) from Baseline in Study MBGS206 to Week 48
   - Percentage change in bone turnover markers (CTx1, osteocalcin, bone alkaline phosphatase, and P1NP) from Baseline in Study MBGS206 to Week 48
   - Change of oestradiol (absolute and percentage) from Baseline in Study MBGS206 to Week 48
   - Proportion of subjects with T-scores ≤ -2.5 at Week 48 of Study MBGS206

Name of Sponsor/Company: Mereo BioPharma 2 Ltd	**Individual Study Table Referring to Part of the Dossier:**	**(For National Authority Use Only)**
Name of Product: BGS649		
Name of Active Ingredient: 4,4'-[fluoro-(1-H-1,2,4-triazol-1-yl)methylene]bisbenzonitrile	**Volume:** **Page:**	

- Proportion of subjects that overshoot testosterone (total testosterone above 1000 ng/dl [35 nmol/L] from first dose of study drug in Study MBGS206 until study completion)
- Change in PSA from Baseline in Study MBGS206 to Week 48
- Change in haematocrit from Baseline in Study MBGS206 to Week 48
- Change in blood pressure (systolic and diastolic) Baseline in Study MBGS206 to Week 48
- Treatment emerged AE, SAE, and AESI (from first dose of study drug in Study MBGS206 until study completion).

Efficacy

1. In subjects that were randomised to active treatment in Study MBGS205 by dose group:
   - Percentage of subjects that have normalisation of total testosterone at Week 48 in Study MBGS206
   - Change in total and bioavailable testosterone from Baseline in Study MBGS205 to Week 48 in Study MBGS206
   - Change of LH and FSH from Baseline in Study MBGS205 to Week 48 in Study MBGS206
2. In subjects that were randomised to placebo in Study MBGS205 by dose group:
   - Percentage of subjects that have normalisation of total testosterone at Week 48 of Study MBGS206
   - Change in total and bioavailable testosterone from Extension Study Baseline to Week 48 in Study MBGS206
   - Change of LH and FSH from Extension Study Baseline to Week 48. in Study MBGS206

Pharmacokinetics

1. EOT plasma and semen concentration of BGS649 by dose group.

Exploratory

1. In subjects that were randomised to active treatment in Study MBGS205:
   - Change in exploratory parameters from Baseline in Study MBGS205 to Week 48 in Study MBGS206 by dose group
     - Body composition (weight, BMI, waist and hip circumference, and parameters measured by bio-impedance)
     - Markers of cardiometabolic disease (blood pressure, lipid profile, HbA1c, glucose and insulin, hs-CRP, and homeostatic assessment of insulin resistance [HOMA-IR])
     - Physical activity, sleeping pattern, and strength (measured by wrist worn monitors and grip strength measurement)
     - Total and domain scores on PRO measures (Sexual function (IIEF, PROMIS SexSF), Energy/fatigue (BFI, PROMIS Fatigue), SF-36
   - The relationship between changes in PROs and changes in body composition, physical activity, grip strength, and sleep
   - The relationship between changes in testosterone and changes in cardiometabolic parameters, body composition, physical activity, grip strength, sleep, and PROs.
2. In subjects that were randomised to placebo in Study MBGS205:
   - Change in exploratory parameters from Baseline in Study MBGS206 to Week 48 in Study MBGS206 by dose group
     - Body composition (weight, BMI, waist and hip circumference, and parameters measured by bio-impedance)
     - Markers of cardiometabolic disease (blood pressure, lipid profile, HbA1c, glucose and insulin, hs-CRP, and HOMA-IR)
     - Physical activity, sleeping pattern, and strength (measured by wrist worn monitors and grip strength measurement)
     - Total and domain scores on PRO measures (Sexual function (IIEF, PROMIS SexSF),

Name of Sponsor/Company: Mereo BioPharma 2 Ltd	**Individual Study Table Referring to Part of the Dossier:**	**(For National Authority Use Only)**
Name of Product: BGS649		
Name of Active Ingredient: 4,4'-[fluoro-(1-H-1,2,4-triazol-1-yl)methylene]bisbenzonitrile	**Volume:** **Page:**	

Energy/fatigue (BFI, PROMIS Fatigue), SF-36

Statistical Methods:

Populations to be analysed:

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

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

The safety population includes all subjects who received at least 1 administration of the study medication.

For the summary of semen concentration of BGS649, all subjects who received at least 1 administration of the study medication and have at least 1 quantifiable concentration will be included in the PK population.

All safety endpoints will be analysed using the safety population. All efficacy endpoints will be analysed using the ITT population.

Further safety and tolerability will be analysed using the safety population.

Primary Statistical Hypothesis: The percentage decrease from Baseline in lumbar bone mineral density measured in g/cm^2 by DEXA [redacted]

H0: $\leq 3\%$

H1: $> 3\%$

The null hypothesis will be rejected for a dose group and the endpoint considered met if the lower bound of the 2-sided 95% confidence interval for the percentage decrease from Baseline in lumber spine is greater than 3%.

Assuming a 2-sided test at [redacted] significant level and a standard deviation of [redacted] to achieve 90% power N=25 subjects in each dose group would be needed to detect a [redacted] decrease from Baseline in bone mineral density at 48 weeks.

Date of the Protocol: Amended Version 2.0, 28 Mar 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

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
CTx1	C-terminal telopeptide
CYP	Cytochrome
CYP19	aromatase
D	Day
DBP	diastolic blood pressure
DEXA	dual energy X-ray absorptiometry
DMC	Data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOT	End of Treatment
EUDRACT	European Union Drug Regulatory Agency Clinical Trial
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
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
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
P1NP	procollagen type 1 N-propeptide
PGI-S	Patient Global Impression of Status
PK	pharmacokinetics
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
SexFS	Sexual Function and Satisfaction
SF-36	36-item Short Form Health Survey
SHBG	sex hormone binding globulin
SBP	systolic blood pressure
SD	standard deviation
$T_{1/2}$	half-life
TEAE	treatment emergent adverse event
T_{max}	time at which maximum serum concentration is reached
ULN	upper limit of normal
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, resulting 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 and 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 (Hofstra et al 2008).

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 half-life ($T_{1/2}$) aromatase inhibitor for the treatment of refractory endometriosis and is being evaluated in obese men with HH.

The safety and efficacy (in terms of normalisation of serum testosterone levels) of BGS649 in male obese subjects with HH is currently being evaluated in the ongoing Study MBGS205.

Use of aromatase inhibitors in women with breast cancer have been associated with reduction in bone mineral density and risk of fracture. This is attributed to the oestrogen lowering effects in post-menopausal women. The potential for BGS649 to affect bone in obese males with hypogonadism is expected to be less as oestrogen levels are similar to those in pre-menopausal women and only 25% oestradiol reduction was observed after 12 weeks of BGS649 0.3 mg loading dose and 0.1 mg weekly. There may be other factors that reduce sensitivity to aromatase inhibition on bone in this population as bone mineral density increases with increasing BMI, and bone anabolic effects are expected with the normalisation of testosterone.

Understanding any potential effect is a critical element to the risk/benefit profile of BGS649. Bone turnover biomarkers and bone mineral density are being assessed in MBGS205, however 6 months is too short duration to assess bone mineral density. Study MBGS206 will be a 6 month extension of Study MBGS205 to measure the effects of 12 months treatment with BGS649 on bone mineral density.

7.1.1 Aromatase Inhibitors and Bone

In the adult skeleton, bone remodelling is controlled by regulating the balance between the resorptive activity of osteoclasts and the bone-forming action of osteoblasts (Perez and Weilbaecher 2006). Normal bone turnover is maintained by a complex regulatory system involving both systemic and local factors. Oestrogen has suppressive, antiresorptive effects on osteoclasts during the process of bone remodelling; these effects are pleiotropic and largely indirect. Aromatase inhibitors block the peripheral conversion (aromatisation) of oestrogen from androgen precursors, thereby lowering tissue and circulating oestrogen levels. Treatment with aromatase inhibitors can decrease oestrogen levels and lead to excessive bone resorption. It has been associated with bone loss, decreased bone mineral density, and an increase in osteoporotic fractures. However, these effects have generally been observed in woman treated for breast cancer with high relative doses and long duration of treatment of the aromatase inhibitor and in post-menopausal women with low oestrogen levels (Mincey et al 2006).

Testosterone and oestradiol are critical for normal bone development and maintenance in men (Sinnesael et al 2011). However, there are limited data on aromatase inhibition in this population and none in the obesity-related HH population which is the target for BGS649 or with the lower levels of aromatase inhibition that is being developed within this dose-ranging study.

Bone mineral density was investigated in two studies in older men with low testosterone levels (Dias et al 2015, Burnett-Bowie et al 2009). The effects of a transdermal testosterone gel, anastrozole (an aromatase inhibitor) 1 mg daily, or placebo on body composition, bone mass, muscle strength, and gait speed were evaluated for 12 months in 43 older men with low testosterone levels (Dias et al 2015). Both transdermal testosterone and anastrozole increased serum testosterone levels (>500 ng/dL, $p < 0.05$) compared with baseline, and testosterone levels remained stable throughout the study. At 12 months, the primary outcome of lumbar spine bone mineral density increased compared with baseline in the transdermal testosterone and placebo groups ($p < 0.01$), and remained stable in the anastrozole group. The reason for the increase in bone mineral density in the placebo group was unclear and expected to have driven the statistical significance of the change in bone mineral density of anastrozole which was assessed relative to placebo. The effects of anastrozole 1 mg daily or placebo on bone mineral density and bone turnover were evaluated in a 1-year study in 69 older men with borderline or low testosterone levels and hypogonadal symptoms (Burnett-Bowie et al 2009). The aromatase inhibitor increased testosterone levels and moderately decreased oestradiol levels. Posterior-anterior spine bone mineral density decreased in the anastrozole group compared with the placebo group ($p = 0.0014$); there were no significant effects on bone mineral density at other anatomical sites. Bone turnover markers were not affected by anastrozole therapy. Therefore, aromatisation of testosterone may play a role in bone mineral density in older men with low testosterone levels.

Further understanding on the gonadal steroid-dependent effects on bone turnover and bone mineral density has come through investigation in healthy adult men aged 20-50 years (Finkelstein et al 2016). All volunteers were given goserelin acetate to suppress endogenous

gonadal steroid production. One cohort (198 men) were randomised to treatment with increasing concentrations of testosterone gel daily for 16 weeks. A second cohort (202 men) were randomised to receive these treatments together with anastrazole. A control group (37 men) were given placebo. The study supports other studies that a balance between oestrogen and testosterone is important. Although oestrogen may primarily regulate bone metabolism in adult men, in order to affect bone development, testosterone and oestradiol levels must decline substantially. Oestradiol levels above 10 pg/mL and testosterone levels above 200 ng/dL were generally sufficient to prevent increases in bone resorption and decreases in bone mineral density in men in this study, suggesting that in hypogonadism the elevation of testosterone in association with oestradiol above a threshold may enable maintenance or improvement of bone density.

7.1.2 Clinical Experience with BGS649

To date, 54 post-menopausal and 52 pre-menopausal women of non-childbearing potential have been exposed to single doses of BGS649 up to 20 mg. BGS649 showed a dose-dependent suppression of oestrone, which was maximal at 0.1 mg, and oestrone inhibition was sustained for more than 3 weeks after a single dose. There was no effect of BGS649 on cortisol metabolism, aldosterone synthesis, progesterone levels, androgen levels, urinary 17-keto, or 17-hydroxysteroids. However, BGS649 at the highest single doses of 10 and 20mg showed small but clinically significant decrease in bone density limited to the lumbar spine at 6 months.

To date, BGS649 has also been administered to 21 obese men with HH (8 subjects were assigned to placebo) (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 [redacted]. 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). Oestradiol levels were reduced by approximately 25-50%. There was no change in femoral neck bone mineral density and bone turnover markers after first or second part of the study. However, the second part of the study was underpowered and result not interpretable.

Study MBGS205 is an ongoing Phase IIb multicentre, double-blind, dose-ranging, randomised, placebo-controlled study evaluating the safety and efficacy of BGS649 in male obese subjects with HH. The primary objective of the study is 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 $\geq$ 75% of a population of obese male subjects with HH after 24 weeks of double-blind treatment compared to placebo. As a part of safety objectives, study will evaluate effect of BGS649 on bone mineral density and bone turnover markers.

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).

7.2 Rationale/Discussion

7.2.1 Rationale for bone density safety study.

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 HH. However, the effects of long-term treatment with BGS649 in male obese subjects with HH have not been investigated.

Men with hypogonadism have low testosterone that is associated with a decrease in bone mineral density. However, men with obesity related HH may have oestrogen levels similar to the levels in pre-menopausal women. In addition, obesity has protective effect on the bone mineral density so the risk associated with aromatase inhibitor treatment may be attenuated (Zhao et al 2007).

Study MBGS206 will investigate the effect of BGS649 on bone mineral density after a 12 month period of treatment with active study drug (6 months treatment during Study MBGS205). The overall 12 months exposure with BGS649 in the obese male HH patient should be an adequate duration of the aromatase inhibitor therapy to detect a change in bone mineral density to better define the risk/benefit of BGS649 in the obese male HH patient (Dias et al 2015; Burnett-Bowie et al 2009). The study is powered to detect a 3% decrease from Baseline in lumbar bone mineral density measured in g/cm^2 by dual energy X-ray absorptiometry (DEXA) at 48 weeks (Kacker et al 2014).

Rational for other study considerations:

The doses of BGS649 [redacted] and dosing schedule [redacted] selected for use in Study MBGS205 were 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). To assure 12 months each dose arm study drug exposure, subjects will continue with the same active study drug assignment from Study MBGS205 to the Study MBGS206. To keep the study blinded and offer subjects receiving placebo the benefit of active arm treatment, the placebo subjects in Study MBGS205 will be randomised to one of the active treatment arms. If one or more dosing arms are dropped during the conduct of Study MBGS205, these will not be progressed in Study MBGS206.

Aromatase inhibitors decrease oestrogen synthesis and increase pituitary luteinising hormone (LH) and follicle stimulating hormone (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: effect on insulin resistance, on body composition, strength and sexual and overall well-being. Therefore, additional safety, efficacy, and pharmacokinetic (PK) will be collected in subjects who completed the full 24 week treatment period in Study MBGS205. It is conceivable that up to 12 month exposure may be needed to demonstrate full treatment benefit in regards to positive effect on cardiometabolic parameters (Haider et al 2010). In addition, the improvement in body composition may be also shown consistently only after 12 months treatment (Emmelot-Vonk et al 2008).

Testosterone increase may lead to worsening certain parameters e.g. prostate-specific antigen (PSA), haematocrit. To ensure adequate safety monitoring, these parameters together with testosterone level will be monitored in the same way as in MBGS205 study (see Section 9.1.1 for a detailed description)

BGS649 has been shown to be present in semen. PK assessment of seminal fluid and plasma will be performed to determine the plasma/semen relationship to enable modelling of BGS649 semen concentration by dose in order to determine the potential transference of BGS649 to sexual partners.

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 Objective

The primary objective is to evaluate the effect of 12 months treatment with BGS649 on bone mineral density (6 months treatment during Study MBGS205).

8.2 Secondary Objectives

8.2.1 Safety Objectives

1. To evaluate the effect of BGS649 after 12 months period of treatment with active study drug (6 months treatment during Study MBGS205 and 6 months treatment during Study MBGS206) by dose group on:
    - Bone turnover biomarkers
    - Bone mineral density and bone biomarkers by vitamin D status (Baseline vitamin D from Study MBGS205)
    - Oestradiol levels
    - Testosterone outside upper limit of normal range
    - Prostate specific antigen and haematocrit
    - Blood pressure
    - Adverse events (AEs)
2. To evaluate if any association between changes in bone mineral density after 12 months treatment with BGS649 with end of treatment testosterone and oestradiol levels
3. To collect safety data in subjects switching from placebo arm in Study MBGS205 and treated with 6 months active study drug in Study MBGS206.

8.2.2 Pharmacokinetic Objective

The PK objective is to determine BGS649 concentration by dose in seminal fluid and relationship to plasma PK at the end of treatment.

8.2.3 Efficacy Objectives

1. To follow the change of total testosterone, bioavailable testosterone, LH, and FSH over a total of 12 months administration of BGS649 in those on active treatment in Study MBGS205 and a total of 6 months administration of BGS649 on subjects that were switched from placebo treatment during Study MBGS205
2. Evaluation of percentage of subjects with normalised testosterone after 12 months treatment with BGS649 in those on active treatment in Study MBGS205 and total of 6 months administration of BGS649 on subjects that were on placebo treatment during Study MBGS205

8.2.4 Exploratory Efficacy Objectives

1. To evaluate the effect of 12 months treatment with BGS649 (6 months treatment in Study MBGS205 and 6 months treatment in Study MBGS206) on:
    - Cardiometabolic parameters, body composition, physical activity, grip strength, and sleep pattern; and on sexual functioning, fatigue, and quality of life, assessed by patient reported outcomes (PROs)
    - The association between changes in PROs and changes in body composition, physical activity, grip strength, and sleep
    - The association between changes in testosterone and changes in cardiometabolic parameters, body composition, physical activity, grip strength, sleep, and PROs
2. To evaluate the 6 month efficacy data on subjects on placebo arm in Study MBGS205 treated with active study drug in Study MBGS206 (cardiometabolic parameters, body composition, physical activity, grip strength, sleep, and PROs).

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

9.1.1 Description

This is a 6 month, active treatment, extension study, open to subjects who have completed the full 24 week treatment period in Study MBGS205 (a Phase IIb multicentre, double-blind, dose-ranging, randomised, placebo-controlled study evaluating safety and efficacy of BGS649 in male obese subjects with HH).

The main purpose of this study is to evaluate bone mineral density in subjects after 12 months exposure with BGS649. The study will also collect additional BGS649 safety and efficacy data on subjects that were randomised to placebo in Study MBGS205 and have 6 months active drug exposure in Study MBGS206. The study design and schedule of assessments are summarised in Figure 9–1 and Table 9–1, respectively.

Subjects that completed full 24 weeks treatment period of Study MBGS205 will be invited to participate. Informed consent will be taken prior to study procedures being performed. Study participation will comprise of the Extension Study Baseline visit (Week 24 of Study MBGS205), 7 visits during the treatment period up to Week 48 (End of Treatment [EOT]), and a Follow-Up (FU) visit for safety performed at Week 60, 12 weeks after the Week 48/EOT visit. The End of Study is defined as the last visit of the last global subject.

Extension Study Baseline assessment:

The Extension Study Baseline assessment will be performed on a same day as the EOT visit of Study MBGS205. As applicable, EOT assessments of Study MBGS205 will be used for Baseline assessments of Study MBGS206 and do not need to be repeated. The results of liver biochemistry, PSA, haematocrit, and electrocardiogram (ECG) assessments performed at the Baseline visit (EOT of MBGS205) may not be available for eligibility assessment, therefore results of these parameters from last valid visit of Study MBGS205 will be used to enable recruitment and dosing. This includes any of the parameters from last scheduled or unscheduled visit, measured not longer than 1 month before Baseline visit/EOT of MBGS205. Bone density from EOT assessment of MBGS205 will be used for eligibility evaluation for MBGS206.

If results of liver biochemistry, renal function, PSA, haematocrit and ECG measured at Extension Study Baseline visit/EOT of MBGS205 are subsequently found to meet any study discontinuation criteria, the subject will be withdrawn.

During the 24 week treatment period, subjects will take the required dose weekly (± 1 day from the time schedule of regular planned dose), starting with the first dose being taken at the baseline visit. The treatment period will consist of up to 24 weekly doses of BGS649. The capsule will be taken orally by the subject with water. Subjects receiving active doses of BGS649 in Study MBGS205 will continue with the same dose in Study MBGS206; this transfer will be handled by the interactive response technology (IRT) and the blind will be

maintained. Subjects receiving placebo in Study MBGS205 will be re-randomised, using IRT, on a 1:1:1 basis to each of the active treatment arms:

- BGS649 [redacted] capsules)
- BGS649 [redacted]
- BGS649 [redacted].

If one or more dosing arms are dropped during the conduct of Study MBGS205 these will not be progressed in Study MBGS206 and subjects switching from placebo will be randomly allocated to available dose arms.

Details of the safety assessments to be performed are provided in Section 12.

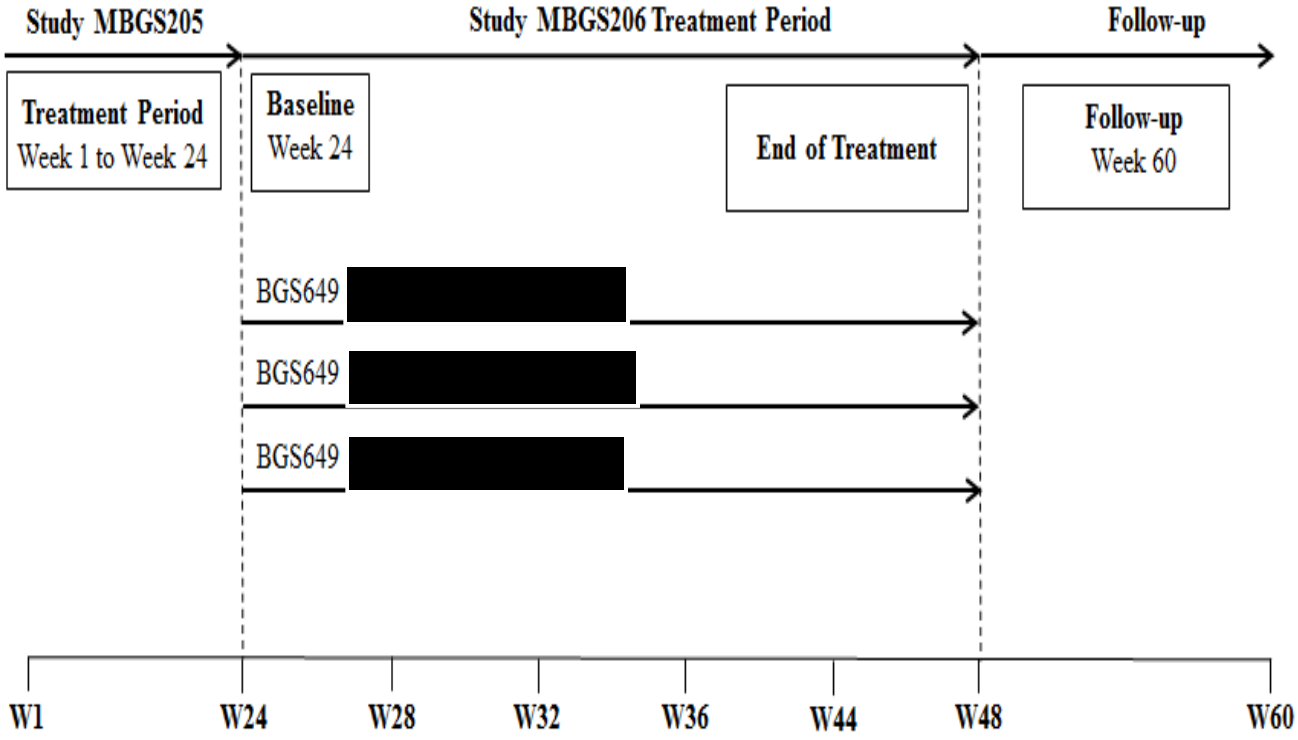
The safety of the study will also be periodically monitored through a data monitoring committee (DMC) and will include relevant subject data from Study MBGS205 and Study MBGS206.

To ensure adequate safety monitoring, serum total testosterone levels will be evaluated at each visit by an independent unblinded physician (see Section 9.3.4 and Section 16.3), and if a subject meets the discontinuation criteria (total testosterone ≥ 1500 ng/dL [52 nmol/L] at any 2 consecutive time points throughout both studies the subject will be discontinued from the treatment. This would also include situation when first testosterone value that meets this threshold of ≥ 1500 ng/dL [52 nmol/L] was measured during MBGS205 and consecutive testosterone during study MBGS206.

Details of the efficacy assessments to be performed are provided in Section 11.

PK of BGS649 in seminal fluid will also be evaluated after 12 months of study drug exposure. Seminal fluid PK will be assessed (excluding subjects that are vasectomised or have vasectomy planned during the study period) at the Baseline visit (Week 24 of Study MBGS205) and End of Treatment (Visit 7). Subjects that are discontinued early from the study drug will provide samples for seminal fluid PK at the time of the End of Treatment visit, unless they are not able to provide this sample. Simultaneously with semen PK, plasma PK will be assessed to estimate plasma to semen BGS649 transference.

Figure 9–1 Study Design



DMC=data monitoring committee; W=week

During the 24 week treatment period, [redacted] to total of up to 24 doses. The capsule will be taken orally by the subject with water. Subjects receiving active doses of BGS649 in Study MBGS205 will continue with the same dose in Study MBGS206 and the blind will be maintained at randomisation. Subjects receiving placebo in Study MBGS205 will be randomised on a 1:1:1 basis to each of the active treatment arms. If one or more dosing arms are dropped during the conduct of Study MBGS205 these will not be progressed in Study MBGS206 and subjects switching from placebo will be randomly allocated to available dose arms. The safety of the study will be monitored through a DMC and will include relevant subject data from Study MBGS205 and Study MBGS206.

9.1.2 Schedule of Assessments

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

Table 9–1 Schedule of Assessments

			Treatment Period						
Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7 (EOT)**	**8 (FU)**
Week	**Assessments transferred from MBGS205**	**MBGS206 Baseline[1] W24**	**W28 (±2 D)**	**W32 (±2 D)**	**W36 (±2 D)**	**W40 (±2 D)**	**W44 (±2 D)**	**W48 (±2 D)**	**W60 (±2 D)**
Confirmation of written informed consent		X							
Medical/surgical history	X								
Inclusion/exclusion criteria		X							
Treatment allocation[2]		X							
Full physical exam: general, prostate and breast exam	X				X			X	
Limited physical exam			X	X		X	X		X
Blood pressure (SBP, DBP) and heart rate	X		X	X	X	X	X	X	X
12-Lead ECG	X				X			X	
Clinical laboratory tests[3]: haematology, blood chemistry, and dipstick urinalysis[4], eGFR by Cockcroft-Gault formula, PSA	X		X	X	X	X	X	X	X
Cardiometabolic parameters[3]: HbA1c, fasting lipids (total cholesterol, LDL, HDL, triglycerides), fasting glucose and insulin, hs-CRP, HOMA-IR	X							X	
Bone turnover markers[5]	X				X			X	
Testosterone total[6]	X		X	X	X	X	X	X	X
Testosterone bioavailable, oestradiol (total), SHBG, FSH, LH[6]	X							X	
Semen PK[7]	X							X	
Plasma PK[7]	X							X	
Weight, BMI hip and waist measurement	X				X			X	
Body composition using bioimpedance[8]	X				X			X	
Actigraphy[9]	X							X	
Grip strength	X				X			X	
PROs: IIEF, BFI, SF-36 QoL PROMIS: SexFS, Fatigue Short Form PGI-S[10]	X				X			X	
DEXA[11]	X							X	
Study drug dispensation		X	X	X	X	X	X		
Study drug administration[12]		[redacted]							
Study drug accountability		X							

			Treatment Period						
Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7 (EOT)**	**8 (FU)**
Week	**Assessments transferred from MBGS205**	**MBGS206 Baseline[1] W24**	**W28 (±2 D)**	**W32 (±2 D)**	**W36 (±2 D)**	**W40 (±2 D)**	**W44 (±2 D)**	**W48 (±2 D)**	**W60 (±2 D)**
AE assessment[13]	X		X	X	X	X	X	X	X
Concomitant medication	X		X	X	X	X	X	X	X

1 Baseline assessment will be performed on a same day as the EOT visit of Study MBGS205. As applicable, EOT assessments of Study MBGS205 will be used for Baseline assessments of Study MBGS206 and do not need to be repeated. The results of liver enzymes, PSA, haematocrit, and ECG assessments performed at the Baseline visit will not be available for eligibility assessment, therefore results of these parameters from last valid visit of Study MBGS205 will be used. This includes any of these parameters from last scheduled or unscheduled visit measure but no longer than 1 month before Baseline visit/EOT of MBGS205.

2 Only subjects receiving placebo in Study MBGS205 to be randomised. Subjects already on active in Study MBGS205 will maintain their treatment allocation

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

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

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

6 Has to be collected before 11 am. If the sample was inadvertently taken after this time, a retest is allowed after a discussion with the Medical Monitor.

7 All subjects that are not vasectomised will be asked to provide a semen sample. Subjects that provided semen sample for PK will also have plasma for PK drawn at the assessment visit Semen sample collection is not required to be the same day as the assessment visit. Therefore, semen PK collection is allowed ± 48 hours around the plasma PK attendance visits.

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

9 Activity wrist monitors will be collected from subjects at EOT visit of the Study MBGS205. If the activity wrist monitor was not performed before EOT of Study MBGS205 and collected at EOT Study MBGS205, it can be applied at the Baseline visit of current study and worn for 7 c consecutive days and collected at Visit 2. An activity wrist monitor will also be worn for 7 continuous days after Visit 7 (EOT) and collected at Visit 8 (FU)

10 Some questionnaires will be new for some subjects and completed first time at the Baseline visit

11 For subjects that discontinued early, EOT DEXA scan will be performed only if they reached minimum Week 36 (Visit 4) active treatment period. In order to accommodate scheduling, EOT DEXA can be performed within 5 days before the EOT visit or 5 days after the EOT Visit

12 [redacted]

13 AEs, SAEs, and AESIs collected from signature of informed consent

9.2 Discussion of Study Design

9.2.1 Risk/Benefit and Ethical Assessment

Refer to the most recent Investigator's Brochure (IB) for a benefit/risk assessment of BGS649.

Aromatase inhibitors decrease oestrogens, normalising LH, FSH, restoring physiologic hypothalamic, pituitary axis leading to normalisation in androgen levels. This is on-target pharmacology of aromatase inhibitors leading to benefit of treating symptoms of hypogonadism but also a clinical risk, as pharmacologic suppression of aromatase in men can cause androgens to rise above normal ranges (Loves et al 2008).

The emerging pre-clinical profile of BGS649 predicts multiple beneficial effects on the pathophysiology of HH. 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 7.1 for further details).

Acute consequences of elevated androgens are rare; however chronic testosterone elevation can lead to elevation of haematocrit, effect on prostate and elevation of PSA and cardiovascular effects. Chronic suppression of oestrogens can also lead to worsening of bone mineral density. The study examines all potential adverse effects by evaluating bone density and other safety parameters on subjects exposed for 12 months and 6 months to BGS649.

Current study design allows 12 months benefit of study drug exposure (6 months from MBGS205 and 6 months from current study). To keep the study blinded and offer subjects receiving placebo the benefit of active arm treatment, the placebo subjects in Study MBGS205 will be randomised to one of the active treatment arms.

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 20 mg (see the IB). 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 leading to all benefits of testosterone normalisation. BGS649 is also expected to decrease oestradiol with the potential risk of a reduction in bone mineral density and increased risk of fracture in subjects (see Section 7). Therefore, subjects will not be enrolled in the study if they have history of fragility fracture. In order to prevent potential premature withdrawals because of bone density deterioration, subjects with T score in pre-osteoporotic range and lower (T-score < -2.0) will not be allowed to participate. In addition, subjects will be monitored throughout the study and must be permanently withdrawn from study treatment if they develop fragility fracture (see

Section 9.3.5). An independent, unblinded external DMC will periodically review accumulating safety data (see Section 16.3).

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

1. Participating in Study MBGS205 and completion of the 24 week treatment period without meeting any discontinuation criteria of Study MBGS205
2. 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 foetal 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
3. Ability to understand and comply with the requirements of the protocol/study, including understanding and being able to give informed consent
4. In opinion of the investigator has been compliant with the requirements of the Study MBGS205 protocol.

9.3.2 Exclusion Criteria

1. Development of clinically significant medical or psychiatric condition during Study MBGS205 that may interfere with the study assessments or mask/mimic symptoms of hypogonadism, 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
2. Development of hypothalamic or pituitary tumour (or inflammatory condition) or 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 (unless there is documentation of a normal magnetic resonance imaging scan of pituitary and hypothalamus within 3 months before Baseline)
3. Meeting any of the discontinuation criteria of initial Study MBGS205
4. Evidence of new significant prostatic disease in Study MBGS205
5. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 times the ULN or bilirubin ≥ 2 times the ULN (unless caused by Gilbert syndrome)
6. Fragility fracture or bone mineral density T-score < -2.0
7. Use of cardiac pacemaker or other medical electronic devices that can be affected by bio-impedance assessment
8. Planned treatment with prohibited medications (including self-prescribed)
9. 12-lead ECG abnormalities at Baseline including QT_CF interval > 450 ms
10. Intention to take part in study of other investigational product during the next 36 weeks.

9.3.3 Rescreening

Not applicable.

9.3.4 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 48 visit (EOT, Visit 7). This should take place within 7 days after discontinuation of study drug. The reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate electronic case report form (eCRF) page. All subjects who discontinue the study drug should enter the FU phase and attend the final follow up visit 12 weeks after EOT (FU, Visit 8).

Subjects will in addition be asked to provide a plasma and semen sample for PK at EOT (Visit 7), unless they are not able to provide this sample. This applies also to a subject discontinued because of elevated testosterone as determined by an unblinded physician. The investigator and study staff must discuss with the subject, the subject's continued participation in the study and request subjects to continue attending FU visits according to the study visit schedule.

If the subject cannot, or is unwilling to attend the FU 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.

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

If the subject temporarily discontinues study drug because of AE or SAE or other relevant issue, the investigator should attempt to restart it as soon as possible after circumstances allow and in agreement with the Medical Monitor.

Investigational treatment MAY be permanently discontinued under the following circumstances:

1. Significant worsening of lower extremity oedema
2. Significant worsening of obstructive urinary symptoms

Investigational treatment MUST be permanently discontinued under the following circumstances:

3. If subject develops fragility fracture.
4. Total testosterone ≥ 1500 ng/dL (52 nmol/L) at any 2 consecutive scheduled visits during and in between the both studies MBGS205 and MBGS206. This would also include situation when first testosterone value that meets this threshold of ≥ 1500 ng/dL

[52 nmol/L] was measured during MBGS205 and consecutive testosterone during Study MBGS206.

5. 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 subject 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

6. 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 > 300 mg/g or > 30 mg/mmol; protein: creatinine ratio ≥ 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

7. Subject missed 4 or more consecutive study drug dosing
8. Development of prostate cancer or PSA increase more than 1.4 ng/mL above Baseline level in study MBGS205. It is recommended that in these cases subjects undergo urologic consultation
9. Haematocrit > 54% (Haematocrit can be repeated once within 7 days of initial alert. Study drug administration should be suspended during this time and resumed only if repeat haematocrit is under 54%)
10. Development of sleep apnoea

11. Development of cardiovascular event (significant arrhythmia acute myocardial infarction, brain stroke, transient ischemic attack, unstable angina, congestive heart failure)
12. Emergence of the following AEs:
    - Absolute $QT_CF > 500$ msec, or a rise of QT_CF of ≥ 60 msec above Baseline confirmed by triplicate ECG measurements
13. Pregnancy in female sexual partner of the male study subject, occurring after the start of study treatment
14. Breast cancer.

9.3.5 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 study participation for that subject will cease and data to be collected at subsequent visits will be considered missing.

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.

9.3.6 Procedures for handling subjects incorrectly enrolled or randomised

Subjects who fail to meet the inclusion/exclusion criteria must not be enrolled or randomised. If a subject not meeting the study criteria is randomised 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.

9.3.7 Discontinuation of Study Sites

Study site participation may be discontinued if Mereo BioPharma or designee, the investigator or Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

9.3.8 Discontinuation of Study

The study may be discontinued if Mereo BioPharma or designee, including through DMC recommendation, judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulation, and GCP.

9.3.9 Lost to Follow-up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. There should be three documented attempts to contact the subject. 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 3 documented phone calls, faxes or emails, as well as a lack of response by the subject to 1 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 FU visit 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 FU visit 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]	[redacted]
Route of administration	Oral	Oral
Mode of administration	With water	With water
Dose	[redacted] Possible doses are: [redacted] OR [redacted] OR [redacted]	

10.1.1 Administration of Study Treatment(s)

Subjects receiving active doses of BGS649 in Study MBGS205 will continue with the same dose in Study MBGS206 and the blind will be maintained. Subjects receiving placebo in Study MBGS205 will be randomised to receive BGS649 [redacted] If one or more dosing arms are dropped during the conduct of Study MBGS205 these will not be progressed in Study MBGS206 and subjects switching from placebo will be randomly allocated to available dose arms. All doses should be taken orally by the subject, with water, on a [redacted] at approximately the same time. Treatment may be self-administered except at the Baseline visit of Study MBGS206 (Week 24 of Study MBGS205), when it must be taken by the subject at the study site.

10.2 Study Treatment Packaging and Labelling

10.2.1 Packaging

Each study site will be supplied with investigational treatment [redacted] and matching placebo, indistinguishable in appearance and taste) in three pack types [redacted] with packaging of identical appearance, consistent with Table 10–1.

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. Packs are labelled for both MBGS205 and MBGS206. However, the IRT will not allow allocation of placebo packs to subjects in MBGS206.

10.2.3 Storage

Based on available stability data, BGS649 [redacted] packaged in Aclar blisters, should be stored below 25°C. The storage conditions for the study drug will be described on the medication label. Until dispensed to the subjects, the study drug will be stored in a securely locked area, accessible to authorised personnel only.

10.2.4 Blinding and Randomisation of Study Treatment(s)

Subjects receiving active doses of BGS649 in Study MBGS205 will continue with the same dose in Study MBGS206; this transfer will be handled by the IRT and the blind will be maintained.

Subjects receiving placebo in Study MBGS205 will be re-randomised at the Baseline visit to receive one of the 3 treatment regimens [redacted] in a 1:1:1 ratio. If one or more dosing arms are dropped during the conduct of Study MBGS205 these will not be progressed in Study MBGS206 and subjects switching from placebo will only be randomly allocated to available dose arms.

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 after database lock. The Sponsor and CRO personnel may be unblinded at the time of unblinding the MBGS205 study, in order to make development decisions. At this time, enrolment of MBGS206 will be completed and the opportunity to introduce a bias, minimal. In order to maintain the blind described above, testosterone, LH, FSH and oestradiol measurements will

be blinded to site and sponsor staff and monitoring will be performed by an independent unblinded physician.

The blind will be maintained using the following methods:

1. Randomisation data will be kept strictly confidential until the time of unblinding, 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 capsules. 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 electronic data capture (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

There is potential to transfer BGS649 to a female partner through seminal fluid, with resulting theoretical risk to embryo-foetal development. Therefore, sexually active study subjects must use a double barrier method during vaginal sexual intercourse with women of child bearing potential while taking the study drug and for 3 months after completing the study treatment, even if the female partner is using a highly effective contraception, and should not father a child in this period. Single barrier (condom) should be used for non-vaginal penetrative intercourse with women of child bearing potential to prevent exposure of the partner to BGS649 through the semen and theoretical risk to an unborn child. This to be continued while taking the study drug and for 3 months after completing the study treatment. The subject should also not perform sperm donation while taking the study drug and for 3 months after completing the study treatment. A condom, together with a spermicide cream is required to be used in order to reduce risk of conception and to prevent delivery of the drug via the seminal fluid.

Seminal fluid 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 seminal fluid 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 Baseline. 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, SHBG, FSH, LH
2. Body composition
   - Body weight and BMI
   - Waist circumference, hip circumference, and waist to hip ratio
   - Gynecomastia
   - Fat and muscle percentage (by impedance)
3. Cardiometabolic parameters
   - Blood pressure (diastolic blood pressure [DBP] and systolic blood pressure [SBP]) and heart rate
   - Fasting lipid panel (total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL], triglycerides)
   - Glycosylated haemoglobin (HbA1c)
   - Fasting glucose and insulin
   - High sensitivity C-reactive protein (hs-CRP)
   - Homeostatic assessment of insulin resistance (HOMA-IR) (see Section 11.2.3 for details)
4. PRO measures
   - International Index of Erectile Function (IIEF) and Patient-Reported Outcomes Measurement Information System® (PROMIS®) Sexual Function and Satisfaction (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 (PGI-S) items: to assess the subjects' overall impression of their current health status.

5. Actigraphy derived activity and sleep parameters
   - Counts of sedentary, moderate, and vigorous activity
   - Sleep quality and duration
6. Dynometry derived grip strength assessment
7. PK semen analysis. Concomitantly with semen PK, plasma PK will be assessed to estimate plasma to semen BGS649 transference.

Detail of assessment of the efficacy and PK variables are presented in Section 11.2 and Section 11.3, respectively.

11.2 Efficacy Assessments

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

11.2.1 Male Hormonal Parameters

Testosterone

Serum total testosterone and SHBG levels will be measured. Bioavailable testosterone will be calculated.

Serum total testosterone and SHBG laboratory parameters have to be taken before 11 am. If there is evidence that a sample has been inadvertently taken after this time, a retest is allowed after discussion with medical monitor.

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 9.3.4 and Section 16.3). The subject may be discontinued if meeting testosterone discontinuation criteria as per section 9.3.4. 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, and FSH will be assessed. In order not to unblind treatment assignment, these parameters will be blinded.

11.2.2 Body Composition

Body weight will be measured as part of the vital signs assessment (Section 12.8).

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 was measured at Screening in Study MBGS205 to enable BMI determination.

BMI is to be calculated from the height obtained at Screening in Study MBGS205. 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 performed to the nearest 0.1 cm.

The **waist measurement** (in cm) will be taken by measuring the distance around the narrowest part of the waist or, if this is not apparent, by measuring 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 bio-impedance

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.

11.2.3 Cardiometabolic Parameters

Blood pressure (SBP and DBP) will be measured as part of the vital signs analysis (Section 12.8).

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).

11.2.4 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 5 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 a 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 9-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

Three patient global impression items (physical function, mental function, and sex life) will be included to assess the subjects' overall impression of their current health status and thus to evaluate the performance of the other PROs in this patient population. For full details of this assessment see Appendix II.

11.2.5 Actigraphy Derived Activity and Sleep Parameters

The Actigraph 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 after Visit 7, 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.

11.2.6 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 3 times with each hand. An average of 3 measurements for each hand will be calculated and recorded.

11.3 Pharmacokinetic Assessments

Semen Pharmacokinetic sampling

Semen PK sampling for BGS649 will be performed at the following time points (excluding subjects that are vasectomised or have vasectomy planned during the study period), as defined in the schedule of assessments (Table 9–1): Baseline visit (Week 24 of Study MBGS205) and EOT (Visit 7).

Subjects that are discontinued early from the study drug will provide samples for seminal fluid PK at EOT (Visit 7) unless they are not able to provide this sample.

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

Plasma Pharmacokinetic Sampling

Plasma PK sampling for BGS649 will be performed at the Baseline visit (Week 24 of Study MBGS205) and EOT (Visit 7) to estimate plasma to semen BGS649 transference.

12 ASSESSMENT OF SAFETY

The timing and frequency of safety assessments provided in Table 9–1. For the primary and secondary safety endpoints see Section 13.4.1 and Section 13.4.2, respectively.

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.

AEs/SAEs that resolve in Study MBGS205 will be recorded as a pre-existing condition/past medical or surgical history.

AEs will be recorded if there is a worsening of the pre-existing condition during study conduct with regard to nature, severity, or frequency or when there is new relevant occurrence. AEs ongoing from Study MBGS205 will be captured as AEs and followed accordingly.

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 1 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 administered during the study MBGS206

Adverse Events of Special Interest

Refer to Section 12.1.7.

12.1.2 Recording of Adverse Events

For the purposes of this study, any detrimental change in the subject's condition, after signing the ICF and any unresolved AEs from MBGS205 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 signing of the informed consent. 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

Outcome:

Each single AE must be rated by choosing 1 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 1 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. A repeat measurement is in that situation may be recommended.

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 above 20mg as single dose or 2 or more doses

above 5mg/dose. 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. Polycythaemia as measured by a haematocrit > 54%
5. Fragility fracture
6. Development of sleep apnoea
7. Development of osteoporosis as per DEXA measurement (T score ≤ -2.5)
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 dose of study drug, AESI from the time of randomisation until 90 days after last dose of study drug 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:

[redacted]

If the report is sent via email, then the completed and signed SAE/AESI or Pregnancy report form must be attached to the email. A notification email of the event describing it in the email text is not sufficient.

Alternatively, the following fax number can be used for completed SAE/AESI reporting forms.

[redacted]

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

12.3 Laboratory Assessments

Laboratory measurements for blood chemistry, PSA, haematology, urinalysis, and 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, prothrombin time/INR, total bilirubin, total protein, calcium, lipid panel (total cholesterol, LDL, HDL, triglycerides), and PSA will be measured.

Estimated glomerular filtration rate (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.

Due to the potential for dehydration to affect haematocrit, subjects should come fully hydrated during the trial when the haematocrit is tested to ensure reliable results.

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.

12.4 DEXA Scan

Bone density will be evaluated with standard procedure described in study imaging manual. All evaluations during the study for particular subject should, where possible, be performed on the same machine with particular attention to ensuring consistency in positioning patients.

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. 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 values will be evaluated for safety.

EOT DEXA scan: If the subject is discontinued from the treatment early, DEXA will be performed only if they reached minimum Week 36 (Visit 4) active treatment period. In order to accommodate scheduling, EOT DEXA can be performed within 5 days before the EOT visit

12.5 Bone Turnover Markers

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

12.6 Hormonal Parameters

Total oestradiol. In order not to unblind treatment assignment, total oestradiol will be blinded.

12.7 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. In a case an abnormality on prostate examination is detected, or subject develops significant worsening of obstructive urinary symptoms, it is recommended to have full urologic evaluation
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 2 mm depression, immediate rebound; +2 - a 4 mm deep oedema, few seconds to rebound; +3 – 6 mm deep oedema, 10-12 seconds to rebound; or + 4 – 8 mm deep oedema, > 20 seconds to rebound; and recorded in the eCRF.

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.

12.8 Vital Signs

Blood pressure (SBP and DBP) and heart rate will be measured at all visits.

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.

12.9 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 eCRFs 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.

12.10 24/7 Medical Emergency Coverage

In a study related emergency situation, when assigned Medical Monitors for a study cannot be reached by a caller, an on-call Physician can be reached 24 hours per day, 7 days per week via an ICON Call Centre:

[redacted]

(Chargeable telephone number allowing a global reach from both landlines and mobile phones)

- https://icophone.iconplc.com

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

Primary Statistical Hypothesis: The percentage decrease from Baseline in lumbar bone mineral density measured in g/cm^2 by DEXA within a dose group is greater than [redacted]

H0: $\leq 3\%$

H1: $> 3\%$

The null hypothesis will be rejected for a dose group and the endpoint considered met if the lower bound of the 2-sided 95% confidence interval (CI) for the percentage decrease from Baseline in lumber spine is greater than [redacted].

Assuming a 2-sided test at 5% significant level and a standard deviation (SD) of 0.0439 g/cm^2, to achieve 90% power N=25 subjects in each dose group would be needed to detect a [redacted]decrease from Baseline in bone mineral density at 48 weeks.

Enrolment will continue until 30 subjects from each of the previous active treatment arms in Study MBGS205 have entered this study. Subjects previously treated with placebo will be enrolled until target subject population is met in all active arms.

13.2 Randomisation

Subjects that received active doses of BGS649 in Study MBGS205 will continue with the same dose in Study MBGS206. ICON Biostatistics will prepare the randomisation list, based on a randomisation scheme blocked by site. Each subject that received placebo in Study MBGS205 will be re-randomised to one of the 3 active doses defined in Section 9.1 in a 1:1:1 ratio.

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

13.3 Analysis Sets

All safety endpoints will be analysed using the safety population. All efficacy endpoints will be analysed using the intention to treat (ITT) population.

Further safety and tolerability data will be analysed using the safety population.

PK data will be analysed using the PK population.

13.3.1 Intention to Treat

The ITT population includes all subjects who:

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

13.3.2 Safety Population

The safety population includes all subjects who received at least 1 administration of the study medication.

13.3.3 PK Population

For the summary of semen concentration of BGS649, all subjects who received at least 1 administration of the study medication and have at least 1 quantifiable concentration will be included in the PK population.

13.4 Endpoints

13.4.1 Primary Endpoint

The primary endpoint is percentage change in lumbar bone mineral density measured by DEXA (g/cm^2) from Baseline in Study MBGS205 to Week 48 in Study MBGS206 by dose group in subjects randomised to active treatment in Study MBGS205.

The primary endpoint will be assessed using the safety population.

13.4.2 Secondary Endpoints

13.4.2.1 Secondary Safety Endpoints

1. In subjects that were randomised to active treatment in Study MBGS205 by dose group:
    - Percentage change in hip bone mineral density measured by DEXA (g/cm^2) from Baseline in Study MBGS205 to Week 48 in Study MBGS206
    - Percentage change in bone turnover markers (C-terminal telopeptide [CTx1], osteocalcin, bone alkaline phosphatase, and procollagen type 1 N-propeptide [P1NP]) from Baseline in Study MBGS205 to Week 48 in Study MBGS206
    - Proportion of subjects with T-scores $\leq$ -2.5 at Week 48
    - Percentage change in bone density and bone biomarkers adjusted for vitamin D deficiency from Baseline in Study MBGS205 to Week 48 in Study MBGS206
    - Change of oestradiol (absolute and percentage) to Week 48
    - Proportion of subjects that overshoot testosterone (total testosterone above 1000 ng/dl [35 nmol/L], from first dose of study drug in Study MBGS205 until study completion)
    - Change in PSA from Baseline in Study MBGS205 to Week 48 in Study MBGS206
    - Change in haematocrit from Baseline in Study MBGS205 to Week 48 in Study MBGS206
    - Change in blood pressure (systolic and diastolic) Baseline in Study MBGS205 to Week 48 in Study MBGS206
    - Treatment emerged AE, SAE, and AESI (from first dose of study drug in Study MBGS205 until study completion)

- Relationship between change in bone mineral density from Baseline in Study MBGS205 to Week 48 in Study MBGS206 and absolute levels of oestradiol and total testosterone at Week 48 in MBGS206

2. In subjects that were randomised to placebo in Study MBGS205 by dose group:
   - Percentage change in hip bone mineral density measured by DEXA (g/cm^2) from Baseline in Study MBGS206 to Week 48
   - Percentage change in bone turnover markers (CTx1, osteocalcin, bone alkaline phosphatase, and P1NP) from Baseline in Study MBGS206 to Week 48
   - Change of oestradiol (absolute and percentage) from Baseline in Study MBGS206 to Week 48
   - Proportion of subjects with T-scores ≤ -2.5 at Week 48 of Study MBGS206
   - Proportion of subjects that overshoot testosterone (total testosterone above 1000 ng/dl [35 nmol/L] from first dose of study drug in Study MBGS206 until study completion)
   - Change in PSA from Baseline in Study MBGS206 to Week 48
   - Change in haematocrit from Baseline in Study MBGS206 to Week 48
   - Change in blood pressure (systolic and diastolic) Baseline in Study MBGS206 to Week 48
   - Treatment emerged AE, SAE, and AESI (from first dose of study drug in Study MBGS206 until study completion).

13.4.2.2 Secondary Efficacy Endpoints

1. In subjects that were randomised to active treatment in Study MBGS205 by dose group:
   - Percentage of subjects that have normalisation of total testosterone at Week 48 in Study MBGS206
   - Change in total and bioavailable testosterone from Baseline in Study MBGS205 to Week 48 in Study MBGS206
   - Change of LH and FSH from Baseline in Study MBGS205 to Week 48 in Study MBGS206
2. In subjects that were randomised to placebo in Study MBGS205 by dose group:
   - Percentage of subjects that have normalisation of total testosterone at Week 48 of Study MBGS206
   - Change in total and bioavailable testosterone from Baseline to Week 48 in Study MBGS206
   - Change of LH and FSH from Baseline to Week 48 in Study MBGS206

13.4.2.3 Secondary Pharmacokinetic Endpoint

1. EOT plasma and semen concentration of BGS649 by dose group.

13.4.2.4 Exploratory Endpoints

1. In subjects that were randomised to active treatment in Study MBGS205:
    - Change in exploratory parameters from Baseline in Study MBGS205 to Week 48 in Study MBGS206 by dose group
        - Body composition (weight, BMI, waist and hip circumference, and parameters measured by bio-impedance)
        - Markers of cardiometabolic disease (blood pressure, lipid profile, HbA1c, glucose and insulin, hs-CRP, and HOMA-IR)
        - Physical activity, sleeping pattern, and strength (measured by wrist worn monitors and grip strength measurement)
        - Total and domain scores on PRO measures (Sexual function (IIEF, PROMIS SexSF), Energy/fatigue (BFI, PROMIS Fatigue), SF-36
    - The relationship between changes in PROs and changes in body composition, physical activity, grip strength, and sleep
    - The relationship between changes in testosterone and changes in cardiometabolic parameters, body composition, physical activity, grip strength, sleep, and PROs.
2. In subjects that were randomised to placebo in Study MBGS205:
    - Change in exploratory parameters from Baseline in Study MBGS206 to Week 48 in Study MBGS206 by dose group
        - Body composition (weight, BMI, waist and hip circumference, and parameters measured by bio-impedance)
        - Markers of cardiometabolic disease (blood pressure, lipid profile, HbA1c, glucose and insulin, hs-CRP, and HOMA-IR)
        - Physical activity, sleeping pattern, and strength (measured by wrist worn monitors and grip strength measurement)
        - Total and domain scores on PRO measures (Sexual function (IIEF, PROMIS SexSF), Energy/fatigue (BFI, PROMIS Fatigue), SF-36

13.5 Description of Statistical Analyses

13.5.1 General Considerations

All analysis will be considered as exploratory analysis.

At the time of unblinding of the MBGS205 study, ICON will also be unblinded to MBGS206 treatment assignment. At this time analysis maybe conducted to support MBGS205 reporting. As all analysis will be considered exploratory there will be no adjustment for multiplicity.

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, 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, for subjects randomised to active treatment in Study MBGS205, change in the extension study MBGS206 will be measured against their Baseline assessments in Study MBGS205 for subjects randomised to placebo in Study MBGS205, unless stated otherwise, Baseline will be the last value prior to first dose of study medication in Study MBGS206.

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

The analysis of the primary safety endpoint will be 1-sided test conducted at the 2.5% significance level. Unless stated otherwise, all other statistical tests will be 2-sided and conducted at the 5% level, and all quoted CIs will be 2-sided 95% CIs. All 3 treatment arms will be assessed by pairwise comparisons made.

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

13.5.2 Analysis of Primary Endpoint

The percentage change from Baseline in lumbar bone mineral density measured in g/cm^2 by DEXA will be summarised by dose group and visit. A single sample 1-sided t-test conducted at the 2.5% significance level will be used to analyse percentage change from Baseline (MBGS205) at Week 48 (MBGS206) in each treatment arm to test the null hypothesis that the percentage decrease from Baseline is $\leq 3\%$. Only subjects that have a post-Baseline DEXA assessment in MBGS206 will be included in this analysis.

The primary analysis will be performed using the safety population.

13.5.3 Analysis of Secondary Endpoints

13.5.3.1 Safety

The analysis of secondary safety endpoints will be performed using the safety population.

The percentage change from Baseline in hip bone mineral density measured in g/cm^2 by DEXA will be summarised by treatment arm and visit. A single sample 1-sided t-test conducted at the 2.5% significance level will be used to analysis percentage change from Baseline (MBGS205) at Week 48 (MBGS206) in each treatment arm to test the null hypothesis that the percentage decrease from Baseline is $\leq 3\%$. Only subjects that have a post-Baseline DEXA assessment in MBGS206 will be included in this analysis.

The percentage change from Baseline in bone turnover markers, bone density, bone biomarkers and oestradiol (absolute and percentage) will be summarised by treatment arm and visit. A 95% CI will be presented for the mean change at each visit.

The proportion of subject with a T-score ≤ -2.5 at Week 48 will be summarised by treatment arm and visit. A 95% CI will be presented for the proportion of subjects with a T-score ≤ -2.5.

The proportion of subjects with testosterone ≤ 1000 ng/dl (35 nmol/L) and > 1000 ng/dl (35 nmol/L) will be summarised by treatment arm and visit.

TEAEs will be summarised per Section 13.5.5. For subjects randomised to active treatment in Study MBGS205 first dose is considered as the first dose in Study MBGS205. For subjects randomised to placebo in Study MBGS205 first dose is considered as the first dose in Study MBGS206.

A more detailed description will be presented in the SAP.

13.5.3.2 Efficacy

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

The proportion of subjects that have normalisation of testosterone at Week 48 will be summarised by treatment arm and visit. For each treatment arm an exact 2-sided binomial test conducted at the 5% significance level will be performed to test the null hypothesis that the proportion of normalised subjects is ≤ 75%. An alternative way of expressing this is that the null hypothesis will be rejected for a treatment group and the endpoint considered met if the lower bound of the 2-sided 95% CI for the proportion of subjects with testosterone normalisation is greater than 75%.

The change from Baseline in total and bioavailable testosterone, LH, and FSH will be summarised by treatment arm and visit. A single sample 2-sided t-test conducted at the 5% significance level will be used to analyse the percentage change from Baseline at Week 48 within each treatment arm.

For subjects randomised to placebo in Study MBGS205, unless otherwise stated, the Extension Study Baseline (Week 24) will be used for analysis of efficacy endpoints to Week 48.

A more detailed description will be presented in the SAP.

13.5.3.3 Pharmacokinetics

EOT and FU semen concentration of BGS649 will be summarised by dose group.

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 arm and visit.

For each continuous parameter, the change from Baseline will be summarised by treatment arm and visit. A single sample 2-sided t-test conducted at the 5% significance level will be

used to analyse the change from Baseline at Week 48 within each treatment arm. In addition, the change from Baseline will be assessed with a mixed model repeated measure analysis, with treatment dose as a factor and the Baseline value as a covariate. The adjusted mean difference between treatment doses 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.

Associations between changes in PROs and changes in body composition, physical activity, sleep, and grip strength will be assessed with correlation coefficients and with separate linear regression models in which changes in PRO measure total or subscale scores will be taken as the predictor variable, and Baseline score as a covariate. The associations between changes in testosterone and changes in PROs, body composition, physical activity, grip strength, and sleep will be assessed in the same way. Correlation coefficients, Beta coefficients, standard errors, and 95% CIs will be presented.

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. Further details of this will be provided in a SAP. 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 1 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.

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 in Study MBGS205 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 arm.

14 DIRECT ACCESS TO SOURCE DATA/NOTES

The investigator/institution shall provide direct access to source data/documents for study-related monitoring, audits, IEC/ 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 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.

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 from MBGS205 and MBGS206. 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 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 eCRFs (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 clinical study report 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

Bhatnagar AS, Häusler A, Schieweck K, et al (1990). Highly selective inhibition of estrogen biosynthesis by CGS 20267, a new non-steroidal aromatase inhibitor. J Steroid Biochem Molec Biol 37:1021–27.

Burnett-Bowie SAM, McKay EA, Lee H, and Leder BZ (2009). Effects of Aromatase Inhibition on Bone Mineral Density and Bone Turnover in Older Men with Low Testosterone Levels. J Clin Endocrinol Metab, 94(12): 4785–4792.

Cappelleri JC, Siegel RL, Osterloh IH, et al (2000). Relationship between patient self-assessment or erectile function and the erectile function domain of the International Index of Erectile Function. Urology, 56:477–481.

de Boer H, Verschoor L, Ruinemans-Koerts J, et al (2005). Letrozole normalizes serum testosterone in severely obese men with hypogonadotropic hypogonadism. Diabetes Obes Metab, 7:211–215.

Dias JP, Melvin D, Simonsick EM, et al (2016). Effects of aromatase inhibition vs. testosterone in older men with low testosterone: randomized-controlled trial. Andrology, 4(1):33–40.

Emmelot-Vonk MH, Verhaar HJ, Nakhai Pour HR, et al (2008). Effect of testosterone supplementation on functional mobility, cognition, and other parameters in older men: a randomized controlled trial. JAMA, 299(1):39–52.

Finkelstein JS, Lee H, Leder BZ, et al (2016). Gonadal steroid-dependent effects on bone turnover and bone mineral density in men. J Clin Invest, 126(3):1114–11125.

Flynn KE, Lin L, Cyranowski JM, et al (2013). Development of the NIH PROMIS ® Sexual Function and Satisfaction measures in patients with cancer. J Sex Med, 10(Suppl 1):43–52.

Haider A, Gooren LJ, Padungtod P, and Saad F. Improvement of the metabolic syndrome and of non-alcoholic liver steatosis upon treatment of hypogonadal elderly men with parenteral testosterone undecanoate. Exp Clin Endocrinol Diabetes, 118(3):167–171.

Hofstra J, Loves S, van Wageningen B, et al (2008). High prevalence of hypogonadotropic hypogonadism in men referred for obesity treatment. Neth J Med, 66:103–109.

Investigator's Brochure (IB).

Kacker R, Conners W, Zade J, and Morgentaler A (2014). Bone mineral density and response to treatment in men younger than 50 years with testosterone deficiency and sexual dysfunction or infertility. J Urol, 191(4):1072–1076.

Kapoor D, Aldred H, Clark S, et al (2006). Clinical and Biochemical Assessment of Hypogonadism in Men With Type 2 Diabetes. Diabetes Care, 30:911–917.

Loves S, Ruinemans-Koerts J, and de Boer H (2008). Letrozole once a week normalizes serum testosterone in obesity-related male hypogonadism. Eur J Endocrinol, 158:741–747.

Matthews DR, Hosker JP, Rudenski AS, et al (1985). Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentration in man. Diabetologia, 28:412–429.

McHorney CA, Ware JE, Lu JFR, and Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36®): III. tests of data quality, scaling assumptions and reliability across diverse patient groups. Med Care1994, 32(4):40–66.

Mendoza TR, Wang XS, Cleeland CS, et al (1999). The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. Cancer, 85(5):1186–1196.

Mincey BA, Duh MS, Thomas SK, et al (2006). Risk of cancer treatment-associated bone loss and fractures among women with breast cancer receiving aromatase inhibitors. Clin Breast Cancer, 7(2):127–132.

Perez EA and Weilbaecher K (2006). Aromatase inhibitors and bone loss. Oncology (Williston Park), 20(9):1029-139.

Rosen RC, Riley A, Wagner G, et al (1997). The International Index of Erectile Function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology, 49:822–830.

Sinnesael M, Boonen S, Claessens F, et al (2011). Testosterone and the male skeleton: a dual mode of action. J Osteoporos, 2011:240328.

Study CBGS649A2204 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.

Testosterone Replacement Therapy, 2014. Advisory Committee Industry Briefing Document. Bone, Reproductive and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee.

Zhao LJ, Liu YJ, Liu PY, et al (2007). Relationship between obesity and osteoporosis. J Clin Endocrinol Metab, 92(5):1640–1646.

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: Patient Global Impression of Status items

Three patient global impression items (physical function, mental function, and sex life) will be included to assess the subjects' 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 HH 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 HH 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 HH 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