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A Phase IIa Study of BGS649, an Oral Aromatase Inhibitor for the Treatment of Men with Obesity-Associated Secondary Hypogonadotropic Hypogonadism

Mohamed Bidair[1], Jackie Parkin[2], Alastair MacKinnon[2]

[1]San Diego Clinical Trials, San Diego, CA, USA; [2]Mereo BioPharma Group plc, London, UK

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Background

- Aromatase is highly expressed in adipose tissue, where it converts testosterone to estradiol[1]
  - Excess adipose tissue is associated with excess aromatase activity in obese patients; this results in high estradiol levels[2]
  - Excess estradiol can feed back to the hypothalamic pituitary axis (HPA), suppressing gonadotropin secretion, testicular testosterone production and spermatogenesis in obese men[2]
- Thus, severe obesity in men is associated with symptomatic androgen deficiency, a condition known as obesity-associated hypogonadotropic hypogonadism (OHH)
- Current treatment options for OHH are limited:
  - Testosterone replacement therapies carry risks of supra-physiological testosterone levels, infertility as a result of follicle stimulating hormone (FSH)/ luteinizing hormone (LH) suppression
  - Topical administration of testosterone can cause transference to partners and children
- BGS649 is an oral, once-weekly aromatase inhibitor, which is under investigation as a treatment for OHH:
  - Designed to be used in low-dose regimens suitable for endocrine indications with a long half-life enabling convenience of once-weekly dosing
  - Mechanism of action anticipated to restore testosterone whilst maintaining HPA feedback, thereby avoiding risks of supra-physiological testosterone levels while maintaining gonadotrophins and testicular function

Study objective

- This was a proof-of-concept, dose-finding, two-part study of efficacy and safety/tolerability of BGS649 for the treatment of men with obesity-associated secondary OHH:
  - Specifically to determine doses of BGS649 that increase and maintain total testosterone levels within the normal range (Part 1)
  - To assess the impact of BGS649 normalization of testosterone on metabolic clinical endpoints (Part 2)
  - To explore the safety and tolerability of BGS649 in the OHH population, including in a randomized, placebo-controlled study (Part 2)

Methods

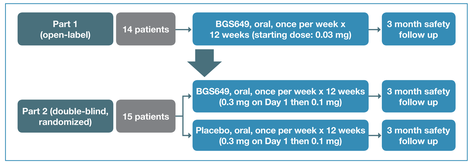
Study design

- This Phase II study comprised two separate parts:
  - Part 1: a 12-week, non-randomized, open-label, BGS649 dose-finding study
  - Part 2: a 12-week, randomized, double-blind study of BGS649 versus placebo
- ClinicalTrials.gov: NCT01200862

Patients

- Adult males with body mass index (BMI) ≥30 kg/m^2
- Morning testosterone levels (<300 ng/dL) on ≥2 separate occasions
- Estradiol levels within or above normal range
- Inappropriately low gonadotropins consistent with secondary hypogonadism
  - LH levels below normal range
  - FSH levels below normal range
- No underlying endocrinopathy/pituitary disease

Figure 1: Study design



Treatment

- Part 1: starting dose was 0.03 mg BGS649, titrated weekly until total and free testosterone were within normal levels (maximum allowable single dose 5.0 mg)
- Part 2: BGS649 dosing was determined by Part-1 pharmacokinetic (PK) / pharmacodynamic (PD) analyses and was 0.3 mg Day 1 and 0.1 mg at all subsequent visits (total of 11 weekly doses)

Primary endpoint:

- **Part 1:** total testosterone levels
- **Part 2*:** insulin sensitivity by:
  - Homeostatic Model Assessment of Insulin Resistance (HOMA-IR)
  - Quantitative Insulin-sensitivity Check Index (QUICKI)

Secondary endpoints (both parts):

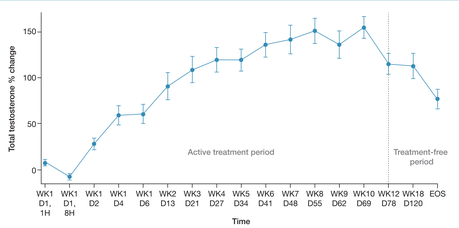
- Testosterone normalization
- Gonadotropins FSH and LH
- Estradiol
- Metabolic parameters: glycated hemoglobin (HbA1c), glucose tolerance, lipids, insulin sensitivity
- Safety/tolerability: adverse events (AEs); hematology, chemistry and urinalysis; semen parameters; bone turnover biomarkers and bone mineral density (BMD)

**Part 2 was stopped early when proof of concept for testosterone normalization was observed and re-evaluation of the sample size showed the study was underpowered for insulin sensitivity analyses; this (along with the discovery of dosing errors in the placebo arm) contributed to the decision for early termination of Part 2 of the study*

Patient demographics

- **Part 1:** 14 patients were enrolled and 13 completed the study (1 patient was lost to follow-up)
- **Part 2:** 15 patients were enrolled, but not all completed the study due to early study termination outlined above:
  - 7 patients received BGS649
    - 5 patients completed 12 weeks' treatment
    - 1 patient completed 8 weeks' dosing and 1 patient completed 6 weeks' dosing
  - 8 patients received placebo
    - 3 patients completing 12 weeks' treatment
    - 2 patients completed to Week 10, 1 patient to Week 7, 1 patient to Week 6 and 1 patient to Week 2
- Baseline characteristics were similar in the two parts of the study:
  - **Part 1:** Male patients with a mean age of 50.3 years, and mean BMI of 33.952 kg/m^2; 12 (86%) patients were Caucasian and 2 (14%) were Black
  - **Part 2:** Male patients with mean age of 50.3 years, and mean BMI of 37.868 kg/m; 13 (86%) patients were Caucasian, 1 (7%) was Black and 1 (7%) was Native American

Figure 2: Primary endpoint Part 1: Mean (±SE) profiles of percent change from baseline for total testosterone



BAS, baseline, EOS, end of study; SCR, screening; SE, standard error

Efficacy results: Part 1

Total testosterone levels (primary endpoint)

- Dose titration with BGS649 increased total testosterone levels from baseline to Week 12 to within normal levels (mean ± SD: 239 ± 52 to 514 ± 188 ng/dL [n=14])
- Increases in testosterone were rapid, seen at Week 1, with all 14 patients reaching normal levels by Week 4, and 13/13 patients maintaining normal levels through Week 12 (one patient was lost to follow-up)
- There was no testosterone elevation above the normal range

Other sex hormones (estradiol, FSH and LH)

- FSH increased by 135% and LH increased by 100% from baseline to Week 12 consistent with the increases in testosterone levels with BGS649
- There was a 30% reduction from baseline to Week 12 in estradiol levels with BGS649 treatment reflecting the mechanism of action

Table 1: Hormone levels at baseline and Week 12

Parameter, mean ± SD	N	Baseline	N	Week 12
Total testosterone, ng/mL	14	239 ± 52	14	514 ± 188
Estradiol, ng/mL	11	26.2 ± 7.2	11	18.2 ± 9.6
FSH, IU/L	14	4.06 ± 1.62	14	9.56 ± 6.03
LH, IU/L	14	6.05 ± 2.59	14	12.12 ± 4.77

FSH, follicle stimulating hormone; IU, international unit; LH, luteinizing hormone; SD, standard deviation

Efficacy results: Part 2

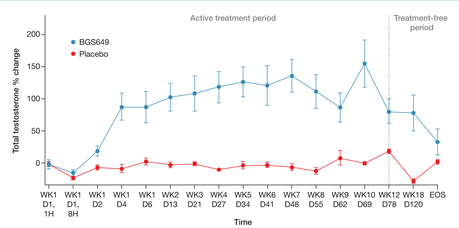
Testosterone normalization

- Treatment with BGS649 resulted in normalization of baseline testosterone levels from baseline to Week 12 to within normal levels in all patients; levels returned towards baseline by EOS (mean ± SD: 273 ± 142 to 423 ± 70 ng/dL [n=5])
- Increases in testosterone levels occurred quickly and were seen as early as Week 1
- Placebo did not show an elevation in testosterone levels from baseline to Week 12 (mean: 309 to 366 ng/dL [n=1])
- There was no testosterone elevation above the normal range

Insulin sensitivity (primary endpoint)

- Based on Part-1 PK/PD analyses, BGS649 was dosed in Part 2 at 0.3 mg (Week 1), then 0.1 mg (Weeks 2–11) to maintain drug plasma levels above the IC90 for aromatase inhibition
- Data for insulin sensitivity were therefore deemed insufficient to allow meaningful interpretation. BGS649 had no effect on other metabolic parameters (HbA1c, glucose tolerance, or lipids)
- Testosterone normalization was further confirmed versus placebo following 12 weeks of treatment (Part 2)

Figure 3: Part 2: Mean (±SE) profiles of percent change from baseline for total testosterone



BAS, baseline, EOS, end of study; SCR, screening; SE, standard error

Total testosterone levels

- Normal testosterone levels were sustained with BGS649 from baseline to Week 12, but not with placebo
- Increases in testosterone levels were seen as early as Week 1 and normalized by EOS
- There was no testosterone elevation above the normal range

Other sex hormones (estradiol, FSH and LH)

- Estradiol levels in patients receiving BGS649 were reduced compared with those in patients receiving placebo over the treatment period
- FSH and LH levels increased in patients treated with BGS649 compared with those in patients receiving to placebo over 12 weeks

Table 2: Hormone levels at baseline, Week 10 and Week 12 for BGS649 and placebo (per-protocol)

Parameter, mean ± SD	BGS649						Placebo					
	N	Baseline	N	Week 10	N	Week 12	N	Baseline	N	Week 10	N	Week 12
Total testosterone, ng/dL	5	273 ± 142	5	569 ± 129	5	423 ± 70	3	256 ± 51	3	257 ± 63	1	366
Estradiol, ng/dL	5	31.0 ± 15.4	5	26.4 ± 14.0	5	14.0 ± 2.1	3	17.3 ± 4.2	3	28.7 ± 12.9	1	46.0
FSH, IU/L	3	6.70 ± 4.03	3	9.07 ± 4.30	3	9.40 ± 4.21	2	6.75 ± 3.89	2	6.80 ± 2.69	1	2.60
LH, IU/L	3	5.97 ± 4.20	3	5.70 ± 2.70	3	9.52 ± 4.40	2	3.05 ± 0.35	2	6.20 ± 2.40	1	4.50

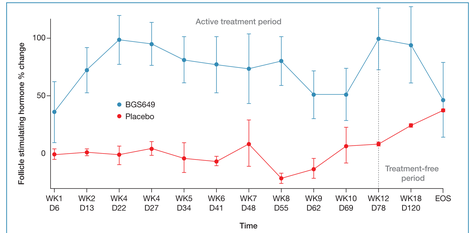
FSH, follicle stimulating hormone; IU, international unit; LH, luteinizing hormone; SD, standard deviation

Safety/Tolerability results (Part 1 and Part 2)

Adverse events

- There were no deaths in the study, no discontinuations due to AEs related to study drug, and no SAEs on BGS649 treatment
- **Part 1:** 11 patients had a total of 59 AEs, the most common of which were: spontaneous penile erection, headache, oropharyngeal pain, nasal congestion, diarrhoea, arthralgia, cough, dizziness, frequent bowel movements, and abnormal hair growth
- **Part 2:** 5 patients from the BGS649 group had a total of 16 AEs and 7 patients from the placebo group had a total of 25 AEs, the most common of which were: headache, asthenia, increased appetite, nasal congestion, somnolence, and spontaneous penile erection
- All AEs in BGS649 arms were mild or moderate, transient and resolved without intervention

Figure 4: Part 2: Mean ± profiles of percent change from baseline in FSH



EOS, end of study; SCR, screening; BAS, baseline

Table 3: Most common treatment-emergent adverse events (those in 2 patients or more in either treatment or placebo groups)

AE, n (%)	Part 1	Part 2	
	BGS649 (n=14)	BGS649 (n=7)	Placebo (n=8)
Any AE	11 (78.6)	5 (71.4)	7 (87.5)
Headache	4 (28.6)	2 (28.6)	1 (12.5)
Spontaneous penile erection	4 (28.6)	1 (14.3)	1 (12.5)
Diarrhoea	3 (21.4)	0 (0)	0 (0)
Nasal congestion	3 (21.4)	1 (14.3)	1 (12.5)
Oropharyngeal pain	3 (21.4)	1 (14.3)	0 (0)
Arthralgia	2 (14.3)	0 (0)	0 (0)
Cough	2 (14.3)	1 (14.3)	0 (0)
Dizziness	2 (14.3)	0 (0)	0 (0)
Frequent bowel movements	2 (14.3)	0 (0)	0 (0)
Abnormal hair growth	2 (14.3)	0 (0)	0 (0)
Asthenia	0 (0)	0 (0)	2 (25.0)
Somnolence	0 (0)	0 (0)	2 (25.0)

Data are for adverse events in treatment period only, and exclude treatment free follow-up period

Laboratory parameters

- There were no clinically significant hematology, urinalysis or clinical chemistry abnormalities, outside of a single case of elevated triglycerides and no changes in semen parameters
- In particular, there were no significant changes in hemoglobin, hematocrit and prostate specific antigen
- There was no effect on bone turnover biomarkers (BSAP, CTx, P1NP and osteocalcin) or bone mineral density

Conclusions

- BGS649 is an oral aromatase inhibitor specifically designed for low-dose, once-weekly use and in development for the treatment of men with OHH
- Once-weekly BGS649 restored normal physiological testosterone levels maintained over 12 weeks in men with OHH, the effects being observed as early as 1 week with no testosterone overshoot
- Increases in both FSH and LH were seen with BGS649 across the 12 weeks consistent with its mechanism of action; these positive effects support the potential for BGS649 to maintain or improve testicular function
- Decreases in estradiol were observed consistent with BGS649 mode of action
- BGS649 was generally safe and well-tolerated with no severe AEs or drug-related study discontinuations during the entire study period
- To further evaluate the testosterone normalization, clinical benefit and safety of BGS649, a larger 6-month dose-ranging Phase IIb study of BGS649 in men with OHH is ongoing (NCT02730169) with a 12-month extension study (NCT02908074)

References

1. Stocco C. *Steroids* 2012;77:27-35.
2. Pitteloud N et al. *J Clin Endocrinol Metab* 2008;93:2686-2692.

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Disclosures

Mohamed Bidair has no disclosures

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