Supporting Information

Introduction

Minimum Anticipated Biological Effect Level (MABEL)

In a 28-day orchiectomized rat model, 0.001, 0.003, 0.01, 0.03, 0.1, and 0.3 mg/kg GSK2881078 demonstrated dose-dependent anabolic stimulation of the *levator ani* muscle. A dose of 0.003 mg/kg provided minimal evidence for activity and thus represented the minimal effect level for anabolic effects in the *levator ani* muscle. Based on proportional scaling from a 0.5 mg/kg dose, the 0.003 mg/kg dose corresponded to an estimated AUC of 6.3 ng•h/mL. This estimated AUC was the best estimate for the MABEL (unpublished data on file, GlaxoSmithKline, 709 Swedeland Road, King of Prussia, PA, USA 19406).

Methods

Inclusion/Exclusion Criteria

Inclusion Criteria

A subject was eligible for inclusion only if all of the following criteria applied:

1. Part A (Cohort 1): Males between 18 and 50 years of age (inclusive) at the time of signing the informed consent form.

Part B (Cohort 2): Males between 18 and 50 years of age (inclusive) at the time of signing the informed consent form.

Part B (Cohorts 3, 4, and 5): Males between 18 and 70 years of age (inclusive) at the time of signing the informed consent form.

Part B (Cohort 6): Females, postmenopausal, between 50 and 70 years of age (inclusive) at the time of signing the informed consent form.

- Postmenopausal is defined as 12 months of spontaneous amenorrhea and, in questionable cases, a blood sample with simultaneous follicle-stimulating hormone (FSH) >40 mIU/mL and estradiol <40 pg/mL (<147 pmol/L) is confirmatory, depending on local laboratory ranges.

2. Body weight ≥50 kg and body mass index (BMI) within the range 19–32 kg/m^2 (inclusive), where BMI = (weight in kg) (height in meters)^2

3. Healthy as determined by an experienced physician based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring. A subject with a clinical abnormality or laboratory parameters outside the reference range for the population being studied may be included only if the Investigator and the GlaxoSmithKline (GSK) Medical Monitor agree that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.

4. Male subjects with female partners of child-bearing potential must agree to use one of the contraception methods listed in the Lifestyle Section of the protocol. This criterion must be followed through the completion of the follow-up visit.

5. Average QTcF <450 msec; or QTcF <480 msec in subjects with bundle branch block.

6. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form.

Exclusion Criteria

A subject was not eligible for inclusion if any of the following criteria applied:

Criteria Based Upon Medical Histories

1. Subjects with a history of clinically significant endocrine, gastrointestinal, hepatic, cardiovascular, neurological, haematological, immunological, renal, respiratory or genitourinary abnormalities or diseases.

2. Postmenopausal women who have taken hormone replacement therapy (HRT) within 6 months of the first dose of study drug.

3. Subjects with a history of coronary artery disease, congestive heart failure, angina, myocardial infarction, any cardiac surgery, valvular heart disease, clinically significant arrhythmia, dyspnea, pulmonary edema, stroke or transient ischemic attack.

- ECG exclusion criteria:
    - Heart rate <40 and >100 beats per minute

- PR interval <120 and >200 msec
- QRS duration <70 and >120 msec

- Echocardiography with 2-D Doppler exclusion criteria:
  - Ejection fraction <55% as assessed by reproducible method of measurement and not by visual estimate only
  - Left ventricular wall thickness >1.1 cm
  - Left ventricular septal thickness >1.1 cm
  - Wall motion: Any wall motion abnormalities

- Regurgitant valvular lesions exclusion criteria:
  - Aortic and mitral valves: anything greater than trace regurgitation
  - Tricuspid and pulmonary: anything greater than mild regurgitation
  - Stenotic valvular lesions: any lesion(s)

4. Subjects with a history of malignancy that is not in complete remission for at least 5 years or 1 year for non-melanoma skin carcinoma.

5. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).

6. History of drug or alcohol abuse within 5 years prior to the Screening Period.

7. History of regular alcohol consumption within 6 months of the study defined as an average weekly intake of >14 drinks for males or >7 drinks for females. One drink is equivalent to 12 g of alcohol: 12 ounces (360 mL) of beer, 5 ounces (150 mL) of wine or 1.5 ounces (45 mL) of 80 proof distilled spirits.

8. History of sensitivity to any of the study medications or components thereof or a history of drug or other allergy that, in the opinion of the Investigator or GSK Medical Monitor contraindicates the subject's participation.

9. Subjects with a family history of early onset prostate cancer or multiple members with prostate cancer.

Criteria Based Upon Diagnostic Assessments

10. A positive pre-study drug or alcohol screen.

11. Cotinine levels indicative of smoking or history or regular use of tobacco- or nicotine-containing products within 30 days prior to screening.

12. Subjects with values outside the specified ranges for the following Key Clinical Laboratory Tests must be excluded from the study:

- Liver function tests – ALT, direct bilirubin or albumin more than 10% outside the normal reference range (<0.9 x the lower limit of normal [LLN] or >1.1 x ULN), unless

discussed with the GSK Medical Monitor (e.g., the lower limits of the assay range may be taken into consideration).

- Renal function
- Men (Part A & B) aged <50 y – Creatinine >1.6 mg/dL with an age-appropriate GFR <90 (mL/min/1.73 m2)
- Postmenopausal women, and men ≥50 y (Part B) – Creatinine >1.6 mg/dL with an age-appropriate GFR ≤60 (mL/min/1.73 m^2)
- Electrolytes – Sodium more than ± 5 mEq/L outside the normal reference range, potassium or calcium more than 10% outside the normal reference range (<0.9 x LLN or >1.1 x ULN)
- Metabolic – Glucose more than 10% outside the normal reference range (<0.9 x LLN or >1.1 x ULN) and total cholesterol >240 mg/dL
- Muscle – Creatine phosphokinase >2.0 x ULN
- Hematology – Hemoglobin, WBC, neutrophils or platelets more than 10% outside the normal reference range (<0.9 x LLN or >1.1 x ULN)
- Prostate specific antigen (PSA) > than the upper limit of the normal range for the assay for the age group

13. A positive test for HIV antibody.

14. A positive pre-study hepatitis B surface antigen or positive hepatitis C antibody result within 3 months of screening.

Other Criteria

15. Exposure to more than four new chemical entities within 12 months prior to the first dosing day.

16. Unable to refrain from prescription or non-prescription drugs, including vitamins, herbal and dietary supplements (including St John's Wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication and throughout the study, unless in the opinion of the Investigator and GSK Medical Monitor the medication will not interfere with the study procedures or compromise subject safety.

17. The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).

18. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within a 56-day period.

19. Unable to refrain from consumption of red wine, seville oranges, grapefruit or grapefruit juice and/or pummelos, exotic citrus fruits, grapefruit hybrids or fruit juices from 7 days prior to the first dose of study medication.