Safety, Pharmacokinetic, and Pharmacodynamic Evaluation After Single and Multiple Ascending Doses of a Novel Selective Androgen Receptor Modulator in Healthy Subjects

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ABSTRACT

Purpose: Tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) properties of single ascending doses (SADs) and multiple ascending doses (MADs) of PF-06260414, a novel selective androgen receptor modulator, were assessed after oral administration in healthy subjects.

Methods: Range of SAD and MAD levels tested were 1 to 400 mg and 3 to 100 mg BID, respectively (n = 8 per cohort). In addition, a 60-mg once-daily (n = 8) cohort and a Japanese cohort receiving 30 mg BID (n = 7) also received PF-06260414. Plasma was collected to study PK properties and hypothalamic-pituitary-gonadal (HPG) axis hormones. Tolerability was evaluated from adverse events (AEs), physical examinations, vital signs, ECGs, and clinical laboratory results.

Findings: PF-06260414 was well tolerated with no serious AEs. The most frequently reported AEs were increase in alanine aminotransferase and headache, which were reported by 7 and 3 subjects, respectively. PF-06260414 had fast absorption (median T_{max}, approximately 1–2 hours), a mean $t_{½}$ of approximately 6.9 to 12.8 hours, time-independent PK properties and dose proportionality. C_{max} and AUC_{τ} geometric means in Japanese subjects were 98.6% and 79.5% higher than in Western subjects, respectively, but had similar HPG axis modulation. Changes in HPG axis hormones monitored in SADs were similar to placebo. Maximum placebo-corrected modulations were observed for total testosterone and sex hormone–binding globulin in the MAD 100-mg BID regimen.

Implications: This study was the first to compare a number of different factors of PF-06260414, including tolerability, PK and PD properties, and ethnic differences between Japanese and Western healthy subjects. PF-06260414 had favorable PK properties and found that sex hormone–binding globulin, total testosterone, and HDL were most sensitive to modulation. ClinicalTrials.gov identifier: NCT02070939. (*Clin Ther.* 2016;▮:▮▮▮–▮▮▮) © 2016 Elsevier HS Journals, Inc. All rights reserved.

Key words: first in human, hypothalamic-pituitary-gonadal axis hormones, pharmacokinetic properties, pharmacodynamic properties, selective androgen receptor modulator.

INTRODUCTION

Selective androgen receptor modulators (SARMs) are a diverse class of synthetic ligands that selectively bind to and stimulate or inhibit androgen receptor (AR) activity in various target tissues. Therefore, SARMs may be designed to act as agonists or antagonists in target tissues.[1] Importantly, several classes of agonistic SARMs have been found in preclinical studies to provide anabolic benefit in muscle and bone with a reduced tendency to induce unwanted androgenic adverse events (AEs) compared with the naturally occurring endogenous steroidal AR ligands, testosterone and dihydroxytestosterone (DHT), which induce both anabolic and androgenic effects.[2–4] Therefore, SARMs may provide an improved safety profile over steroidal AR ligands. As evidence of this, recently completed clinical studies found that a nonsteroidal SARM, enobosarm (GTx-024), did not induce AEs related to androgenic activity, such as

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prostate hypertrophy in men and virilization effects in women.[5] In this Phase II study, enobosarm improved lean body mass and physical function in healthy elderly men and postmenopausal women after 12 weeks of treatment. Together with the reduced androgenic effects, this finding suggests that enobosarm activity was tissue selective and may therefore provide a treatment option for patients with symptoms of muscle wasting, which is safer than the use of testosterone. Another Phase II study with enobosarm in patients with cancer cachexia found similar benefits on lean body mass and physical function.[6] However, the recently completed Phase III studies with enobosarm, Prevention and Treatment of Muscle Wasting in Patients with Cancer (POWER) 1 and POWER-2 studies, in patients with non–small cell lung cancer failed to meet the co-primary end points (significant increases in lean body mass and improved physical function) at day 84.[7]

Basaria et al[8] also found the beneficial effects of another SARM (LGD-4033) on lean body mass and physical function in a Phase I study in healthy young males. Overall, nonsteroidal SARMs, such as enobosarm and LGD-4033, appear to be well tolerated in healthy young men, healthy elderly men, and postmenopausal women.

PF-06260414 is a nonsteroidal SARM that exhibits selective AR agonist activity in vitro and in vivo. PF-06260414 had potent AR agonist activity in a cell-based transcriptional reporter assay, with a concentration of a drug that gives half-maximal response of approximately 0.3 nM (79% efficacy vs DHT). PF-06260414 had no antagonist activity in the presence of DHT. Together, these data suggest that PF-06260414 is a partial AR agonist. PF-06260414 was screened for selectivity against several other steroidal nuclear hormone receptors in cell-based competitive binding assays. The binding of PF-06260414 to progesterone (PR), estrogen (ER), and mineralocorticoid (MR) receptors in the presence of positive control ligands was quantified. PF-06260414 had potent AR binding (concentration of an inhibitor where the response is reduced by half, approximately 2 nM in the presence of DHT) but did not bind ER or MR in the presence of ER and spironolactone, respectively. PF-06260414 had weak binding to PR in the presence of PR (concentration of an inhibitor where the response is reduced by half, approximately 75 nM), suggesting that this compound is >30-fold selective for the AR over the PR.

In nonclinical in vivo studies, PF-06260414 induced an increase in the tissue weight of the levator ani bulbocavernosus muscle in rats with limited hypertrophic effects on androgenic tissues, such as the prostate, similar to that seen with enobosarm. The rodent levator ani bulbocavernosus muscle is a skeletal muscle that is hyperresponsive to androgens, and the anabolic effects induced by SARMs in this muscle translate to increased lean body mass and improved muscle function in clinical studies with SARMs.[5,8] Hypertrophic effects on the prostate in this animal model are used as a surrogate for overall androgenic activity in humans (eg, prostate enlargement in men and virilization effects in women). It is hypothesized that patients with muscle wasting disease, who are responsive to anabolic stimuli, such as exercise or testosterone augmentation therapy, will respond to SARM treatment with increased lean body mass and improved muscle function.[9]

The primary objective of this first-in-human (FIH) study was to determine the safety and tolerability of escalating single ascending dose (SAD) and multiple ascending dose (MAD) of PF-06260414. The secondary objective was to characterize the pharmacokinetic (PK) properties and biomarker modulation (pharmacodynamic [PD] properties) after administration of different doses of PF-06260414 in healthy adult men.

METHODS

Study Design

The study protocol was approved by the institutional review board at the investigational center participating in the study, and written informed consent was obtained from all subjects enrolled in the study. This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good clinical Practice guidelines.

This study was a Phase I combination, within cohort, randomized, double-blind, placebo-controlled, single- and multiple-dose escalation, parallel-group study in healthy adult men, including men of Japanese descent. Subjects enrolled in this study were required to be willing and able to comply with study