SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Investigational Product	JNJ-56021927 (apalutamide)

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Status: Approved

Date: 13 November 2019

Prepared by: Janssen Research & Development, LLC

Protocol No.: 56021927PCR1024

Title of Study: A Randomized, Open-label, Two-way, Crossover Study to Evaluate the Relative Bioavailability of Apalutamide Administered Orally as Whole Tablets and as a Mixture in Applesauce in Healthy Subjects

EudraCT Number: 2018-003774-27

NCT No.: NCT03802682

Clinical Registry No.: CR108562

Principal Investigator(s): Annemie Deiteren, MD

Study Center: Clinical Pharmacology Unit of Johnson & Johnson Pharmaceutical Research & Development, PPD, Belgium

Publication (Reference): None

Study Period: 14 January 2019 (Date first subject signed informed consent) to 29 April 2019 (Date of last observation for last subject recorded)

Phase of Development: Phase 1

Objectives:

Primary Objective

The primary objective was to determine the bioavailability of apalutamide tablets administered orally as dispersed tablets mixed in applesauce relative to whole tablets under fasting conditions in healthy male subjects.

Secondary Objective

The secondary objective was to assess the safety profile of apalutamide following single dose administration as whole tablets and as dispersed tablets mixed in applesauce.

Exploratory Objective

The exploratory objective was to evaluate the palatability of apalutamide-applesauce mixture.

Hypothesis

This was an exploratory study to provide point estimation and no formal hypothesis was tested.

Methodology:

This was a randomized, open-label, balanced, single dose, two-treatment, two-period, two sequence, crossover relative bioavailability study. Healthy male subjects were administered a single dose of apalutamide 240 mg on 2 separate occasions either as whole tablets or as dispersed tablets in applesauce.

Number of Subjects (planned and analyzed):

As planned, 12 subjects were enrolled in this study. All subjects were included in the safety analysis and the pharmacokinetics (PK) data analysis set.

Diagnosis and Main Criteria for Inclusion:

Healthy men between 18 and 55 years of age (inclusive), who had a body mass index (BMI) between 18 and 30 kg/m² (inclusive) and body weight of not less than 50 kg, were eligible for enrollment into the study. Subjects were required to have normal blood pressure and a 12-lead electrocardiogram (ECG) consistent with normal cardiac conduction and function at screening. Subjects with clinically significant abnormal values for hematology, clinical chemistry, serum testosterone level of <200 ng/dL, and thyroid stimulating hormone (TSH) level > upper limit of normal at screening were excluded from the study.

Test Product, Dose and Mode of Administration, Batch No.:

Apalutamide supplied for this study was formulated as a 60 mg tablet (Batch number 18BG4473X). The 60 mg apalutamide tablet (G023) for all treatments contains 60 mg of apalutamide CCI [redacted] This oral coated tablet also contained the following inactive ingredients: colloidal anhydrous silica, croscarmellose sodium, microcrystalline cellulose, silicified microcrystalline cellulose, magnesium stearate and coating powder green OPADRY II. CCI [redacted]

All study drug was taken in the morning of Day 1 of each treatment period under fasting conditions with 240 mL of noncarbonated water (Treatment A, whole tablets) or mixed with an approximate volume of 4 oz or 120 mL of applesauce supplemented by a container rinse of 120 mL of noncarbonated water (Treatment B, dispersed tablets mixed in applesauce). An additional 50 mL water for either treatments was allowed if necessary. Subjects continued fasting until 4 hours after study drug administration. A standard lunch was served for all subjects after collection of the 4-hour PK blood sample.

Reference Therapy, Dose and Mode of Administration, Batch No.:

Not applicable.

Duration of Treatment:

The study consisted of the screening phase (within 21 days before study drug administration in the first period); an open-label treatment phase consisting of 2 single-dose treatment periods; an end of study or early withdrawal assessments done upon completion of the 168-hour PK sampling on Day 8 of period 2 or upon early withdrawal. The duration of participation in the study for an individual subject was approximately 84 days (including screening).

Criteria for Evaluation:

Pharmacokinetics

Serial PK samples were collected predose and at various timepoints postdose up to Day 8 (168-hour postdose). Plasma samples were analyzed to determine concentrations of apalutamide using a validated, specific, and sensitive liquid chromatography/mass spectrometry/mass spectrometry (LC-MS/MS) method by or under the supervision of the sponsor's Department of Bioanalysis. The following PK parameters were derived for apalutamide in all groups: maximum observed plasma analyte concentration (C_{max}), the actual time to reach the maximum observed plasma analyte concentration (t_{max}), area under the plasma analyte concentration versus (vs) time curve from time 0 to 72 hours (AUC_{72h}), and area under the plasma analyte concentration vs time curve from time 0 to 168 hours (AUC_{168h}).

Safety

Safety was evaluated throughout the study by means of adverse events (AEs), physical examination, vital signs, ECG, and laboratory safety (including hematology and serum chemistry).

Taste

Feedback regarding palatability of the apalutamide dispersed in applesauce (Treatment B) was collected via a taste questionnaire conducted within 30 min after intake of Treatment B. The questionnaire consisted of a visual analogue scale to rate 3 items (sweetness, bitterness, and smell) as well as overall acceptability (not acceptable or acceptable).

Statistical Methods:

Most recent studies with similar study designs (clinical study report [CSR] 56021927PCR1015 [2015] and CSR 56021927PCR1017 [2016]) indicated the intra-subject coefficient of variation (CV) for C_{max} and AUCs of apalutamide ranged 11-12% and 4-7%, respectively.

Applying a conservative assumption for intra-subject CV of 12% for C_{max} and 7% for AUCs respectively, a sample size of 10 subjects in the current study was deemed to be sufficient for the point estimates of the geometric mean ratios of C_{max} and AUCs to fall within (91%, 110%) and (95%, 105%) of the true value respectively, with 90% confidence.

Assuming a dropout rate of 17%, approximately 12 subjects were randomized to ensure at least 10 PK evaluable (a PK evaluable subject was defined by having sufficient and interpretable PK assessments to calculate at least 1 noncompartmental PK parameter) subjects completed the study. If the number of PK evaluable subjects who completed the study dropped to less than 10, additional subjects could have been enrolled for replacement by assigning them to the same treatment sequence as the subjects being replaced. Replacement subjects started with Period 1. Subjects who were prematurely discontinued from the study due to drug related AEs or AEs which occurred in relation to study procedures were not replaced.

Pharmacokinetics

For each treatment, descriptive statistics were calculated for plasma concentrations of apalutamide, as applicable, at each applicable time point specified, and for the derived plasma PK parameters. Statistics included sample size (n), mean, standard deviation (SD), %CV, geometric mean, median, minimum, and maximum.

The primary objective of the statistical analysis was to determine the relative bioavailability of Treatment B with respect to the reference Treatment A. The primary parameters of interest for the statistical analysis were C_{max}, $AUC_{0\text{-}72h}$ and $AUC_{0\text{-}168h}$. If one of the PK parameters could not be determined for a given subject in 1 or more periods, the subject's data was not included in the statistical analysis of that particular PK parameter. The analysis was performed on log-transformed PK parameters.

A mixed effect model that included treatment, period, and treatment sequence as fixed effects, and subject as a random effect, was used to estimate the least squares means and intrasubject variance. Using these estimated least squares means and intrasubject variance, the point estimate and 90% confidence intervals (CIs) for the difference in means on a log scale between test and reference were constructed. The limits of the CIs were retransformed using antilogarithms to obtain 90% CIs for the geometric mean ratios of C_{max} and AUC_{0-168h} of the test to reference formulation. A similar analysis was conducted for AUC_{0-72h} for supplemental purpose.

Safety

Baseline for all laboratory evaluations, 12-lead ECG measurements and vital signs were defined as the last evaluation done before study drug administration. Safety was evaluated by examining the incidence and type of AEs, and changes in clinical laboratory test values, physical examination results, 12-lead ECGs, and vital signs measurements from the screening phase through study completion, including the end-of-study visit.

Taste

Questionaire data (sweetness, bitterness, smell, and overall acceptability) was summarized using descriptive statistics.

RESULTS:

STUDY POPULATION:

Overall, 12 white male subjects were enrolled in this study. The median age was 49 years (range: 21 to 55 years). The median BMI was 24.2 kg/m^2 (range: 22.6 to 28.6 kg/m^2). In total, 12 subjects were randomized to receive Treatment A and Treatment B in a crossover (2 periods) manner, of which 10 (83.3%) subjects completed the study. Two subjects discontinued from the study for the following reasons: 1 (8.3%) subject withdrew due to personal reasons after Treatment A in Period 1 and 1 (8.3%) subject discontinued the study due to the AE gynecomastia after Treatment B in Period 1.

PHARMACOKINETIC RESULTS:

Apalutamide median t_{max} was reached 1 hour sooner after Treatment B (median t_{max} of 2 hours) than after Treatment A (median t_{max} of 3 hours).

The administration of apalutamide either as a dispersed mixture in applesauce (Treatment B) or as standard oral administration (Treatment A) showed comparable exposures as shown by the 90% CI of the geometric mean ratio for AUC0-168h values contained within the 80%-125% limit. C_{max} was increased by 27.6% when apalutamide was administered as a dispersed mixture in applesauce compared to standard oral administration of tablets.

SAFETY RESULTS:

Across both treatment sequences, 5 (41.7%) subjects reported at least 1 treatment-emergent AE (TEAE), including 3 (27.3%) subjects after Treatment A (240 mg apalutamide, swallowed whole fasted) and 5 (45.5%) subjects after Treatment B (240 mg apalutamide, tablets dispersed mixture in applesauce, fasted). All TEAEs were of Grade 1 (33.3% of subjects) in severity except for 1 (8.3%) subject who reported a Grade 2 TEAE of bursitis after treatment A, which was considered not drug-related by the investigator. Drug-related TEAEs were reported by 3 (27.3%) subjects after Treatment A and 4 (36.4%) subjects after Treatment B. The most common TEAE was gynecomastia reported in 3 (25.0%) subjects; all other TEAEs were reported in at most 1 subject. Two subjects spontaneously reported the TEAE gynecomastia after study completion (one subject reported the TEAE 17 days following Treatment B [Period 2] and one subject 45 days following Treatment A [Period 2]). Both TEAEs were of severity Grade 1, considered drug-related to Treatment A and B by the investigator and

ongoing at time of database lock. One subject was reported with gynecomastia after 29 days following the first dose of apalutamide (Treatment B). The TEAE was of Grade 1 in severity, considered drug-related and ongoing at time of database lock. Further follow-up demonstrated that all gynecomastia TEAEs were resolved 90 to 125 days after the start of the event. No other sexual side effects were reported.

There were no deaths or serious TEAEs reported. Overall, there were no clinically meaningful changes or abnormalities observed compared to baseline in vital signs, ECG parameters, and safety laboratory parameters.

PALATABILITY:

The overall acceptability of Treatment B ranged from "maybe bad maybe good" in 1 (9.1%) subject to "super good" in 3 (27.3%) subjects. Most of the subjects (90.9%) did not find it annoying to swallow the substance and the taste of the applesauce mixture was "sweet" or "pleasant". The bitterness and the smell ranged from "good" to "super good". All subjects reported that it was acceptable for long period use.

STUDY LIMITATIONS:

No notable study limitations were identified by the Sponsor.

CONCLUSION(S):

The intake of 240 mg of apalutamide administered as whole tablets and as dispersed tablets mixed in applesauce was safe and generally well tolerated. A higher incidence of TEAE gynecomastia has been observed (25% of the subjects) in this study, which has not been reported in prior clinical studies with single dose administration of 240 mg apalutamide in healthy volunteers. Otherwise the AE profile was as expected and no new safety signals were noted.

Administration of apalutamide either as a dispersed mixture in applesauce (Treatment B) or as standard oral administration (Treatment A) showed comparable exposures as shown by the 90% CI of the geometric mean ratio for $AUC_{0\text{-}168h}$ values contained within the 80%-125% limit. Administration as a dispersed mixture of apalutamide in applesauce resulted in higher C_{max} (27.6%) and shorter t_{max} (by 1 hour) compared to standard oral administration of tablets. Both $AUC_{0\text{-}168h}$ and C_{max} values were within the similar range of previously reported results from earlier studies.

Thus, administration of apalutamide using applesauce as a food vehicle is expected to be similar to standard oral administration for patients taking apalutamide daily.

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