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Pharmacokinetics and Use-Testing of Apalutamide Prepared in Aqueous Food Vehicles for Alternative Administration

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Alex Yu[1], Maura Erba[2], and Anasuya Hazra[1]

Abstract

Patients may have difficulty swallowing a whole daily dose of 240 mg (4 × 60-mg tablets) of apalutamide. One of the unique properties of apalutamide tablets is easy disintegration and dispersion when mixed into aqueous vehicles, avoiding the need to crush/split the tablets. To evaluate whether this method of apalutamide tablet administration would be conducive in a patient setting, different variations in preparation were evaluated, and one preparation was tested in humans. In vitro compatibility studies evaluated purity, dose, or stability of different variations of apalutamide in applesauce/yogurt/orange juice/green tea. An open-label, randomized, crossover phase 1 study in healthy men determined the bioavailability of an apalutamide-applesauce mixture versus whole tablets based on maximum plasma analyte concentration (C_{max}), area under the plasma analyte concentration-time curve: $AUC_{0\text{-}72h}$ and $AUC_{0\text{-}168h}$. Different amounts of applesauce/yogurt/orange juice/green tea as well as durations (up to 6 hours) did not affect the total apalutamide content available. The phase 1 study (n = 12) showed increased total exposure of 5% and peak exposure of 27.6% when comparing the apalutamide-applesauce mixture with whole-tablet administration. Variations in preparation times and total content for applesauce/yogurt/orange juice/green tea did not affect the purity, dose, or stability of apalutamide. An apalutamide-applesauce mixture is a suitable alternative administration method to whole tablets.

Keywords

apalutamide, applesauce, food vehicles, swallowing, tea, water

Crushing or splitting tablets to take with water or food is often used as an alternative administration practice for patients with dysphagia or difficulty swallowing. However, the act of crushing/splitting often requires a specialized splitting tool or mortar and pestle, which can be inconvenient or difficult to use for the patient. Given that 1 in every 6 adults is estimated to have a degree of difficulty swallowing,[1] 28.9% of elderly patients reported swallowing issues with tablets,[2] and swallowing difficulties are more prevalent in the elderly (68% in elderly nursing homes and up to 38% of elderly who live independently),[3] a significant number of patients may benefit from an alternative oral administration method that is both easy to prepare and to ingest. In addition, swallowing disorders could result in nonadherence, especially when the tablet size is large.[4]

Apalutamide (ERLEADA, formerly JNJ-56021927 and ARN-509) is an androgen receptor inhibitor[5] currently approved for certain forms of prostate cancer[6–9] based on a dose of 240 mg once daily as 4 × 60-mg oral tablets with the current tablet dimensions of 16.7 × 8.7 mm. Apalutamide is primarily eliminated through metabolism via cytochrome P450 (CYP) 2C8 and CYP3A4 to form *N*-desmethyl-apalutamide.[10] The contribution of the 2 CYPs is estimated to be 58% and 13%, respectively, following a single dose, but

[1]Clinical Pharmacology & Pharmacometrics, Janssen Research & Development, Spring House, Pennsylvania, USA
[2]CMC Leadership SMPD, Janssen Research & Development, Latina, Italy

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Corresponding Author:
Alex Yu, PhD, Janssen Research & Development, 1400 McKean Road, Building 32–10476, Spring House, PA 19477
(e-mail: ayu19@its.jnj.com)

changes to 40% and 37%, respectively, as apalutamide induces CYP3A4 metabolism.[11] After oral administration, the pharmacokinetics (PK) of apalutamide are linear and dose proportional.[12] No differences in apalutamide PK are observed in patients with mild to moderate renal and hepatic dysfunction. Repeated once-daily oral administration of apalutamide under fasted conditions result in a 3- and 5-fold increase, respectively, of maximum plasma analyte concentration (C_{max}, 2.06 vs 5.95 μg/mL) and area under the plasma analyte concentration-time curve from time 0 to 24 hours (AUC_{24h}, 21.1 vs 100 μg·h/mL), respectively, compared with the first dose.[13] No major changes in the PK of apalutamide or pharmacologically active moieties is expected with strong CYP3A4/CYP2C8 inhibitors or inducers.[11] When coadministered with CYP3A4, CYP2C19, CYP2C9, P-glycoprotein, breast cancer resistance protein, or organic anion transporting polypeptide 1B1 substrates, apalutamide may reduce exposures of these drugs, potentially leading to loss of activity for these medications.[14]

Since the approval of apalutamide, the manufacturer has received a number of inquiries from patients and health care professionals for alternative drug administration routes. This is consistent with the recognition that patients with difficulties swallowing solid oral drug products is a major concern, that there is limited understanding of how these patients manage oral medication at home, and that alteration or manipulation of dose forms is a risky practice that may cause serious concerns about safety and efficacy and raise questions about the lawfulness of this practice.[15] The variety of food vehicles used in these practices could be of additional concern, as facilitation of administration via food vehicles has ranged from sprinkling on meals or toast to mixing with jam, blended fruit, custard, yogurt, honey, chocolate milk, and thickened pear juice.[16]

One of the unique properties of the apalutamide tablet is the ability to disintegrate and disperse with relative ease when mixed into various aqueous vehicles. Not only does this avoid the difficulty and need for specialized equipment to crush/split the tablets, it also provides a convenient medium that can help with swallowing. However, the hypothetical feasibility of preparation does not guarantee potency or clinical equivalence, as it is well acknowledged that administration of medication in food vehicles can alter stability, potency, dissolution, and bioavailability.[17–19]

To better assess whether this method of apalutamide tablet administration would be conducive in a patient setting, applesauce, yogurt, green tea, and orange juice were evaluated for feasibility and intervehicle comparability (via dose accuracy and in-use stability) as commonly available aqueous food products. A phase 1 study was conducted in healthy volunteers to ensure that such an administration method would be clinically equivalent in terms of PK exposure of apalutamide.

Methods

Feasibility of Mixing Apalutamide Tablets in Aqueous Food Vehicles

The feasibility of mixing apalutamide tablets (240 mg as 4 × 60-mg) with selected food vehicles of applesauce, yogurt, orange juice, and green tea was evaluated. For semisolid vehicles, yogurt and applesauce, 2 different brands, were randomly selected to introduce variation in thickness. In addition, for yogurt, low- and high-fat brands were selected, without fruit flavors. The applesauce study was conducted in Belgium, whereas the studies for the other 3 vehicles were conducted in India; hence, the commonly used brands available in those countries were chosen. For orange juice and green tea, only 1 common brand was used because these are liquids; however, an in-use study was performed using duplicate measurements for each brand to assess analytical variation.

A specified amount of vehicle—50 or 200 g of applesauce (correlating with 48 to 190 mL, considering an average applesauce density of 1.05 g/mL), 50 or 200 g of yogurt, and 50 or 200 mL of orange juice (after the container was shaken well) or green tea extract—was measured into a high-density polyethylene container. Four tablets were added to the vehicle, and the content was gently mixed with a spatula for about 10 seconds and repeated after 15 minutes and subsequently after an additional 15 minutes (30 minutes from the start) until a uniform mixture was formed. To ensure that the full content was transferred and analyzed, after emptying the food-tablet mixture into a volumetric flask, the container was rinsed twice with water and added to the volumetric flask before adding the dilution solvent as a part of sample preparation for the high-performance liquid chromatography (HPLC) analyses.

Accuracy and Stability of Apalutamide Tablets Mixed in Aqueous Food Vehicles

To evaluate the impact of mixing or storage on the total dose of apalutamide in aqueous food vehicles, triplicate dose accuracy, in-use stability testing, and chromatographic purity assessments were conducted. The validated chromatography assay and purity method of apalutamide tablets were used. Separation between apalutamide and potential degradation compounds was achieved by ultra-HPLC on a reversed-phase

C18 column (150 × 2.1 mm, 1.7-μm particles) using a mixture of 10 mmol/L ammonium acetate solution (with 0.1% trifluoroacetic acid), acetonitrile (90:10) as mobile phase A, and acetonitrile as mobile phase B. The flow rate was 0.45 mL/min, the column temperature was 55°C and the detection wavelength was 268 nm. A representative placebo for each vehicle was prepared to determine if chromatography peaks were product-related or related to the vehicle. Placebo peak correction was applied if interference was observed at the peak of interest in the sample injections. For yogurt, coelution was observed, and the calculation to determine apalutamide and its impurities was corrected for this.

For in-use stability testing, the sample mixtures were tested over a period (after 3 and 6 hours) at room temperature to verify the chemical stability of the product in contact with food vehicle and evaluate situations in which a dose was prepared far in advance of administration.

Clinical Study Comparing Apalutamide Swallow Whole Versus Apalutamide Mixed in Applesauce

Phase I Study. In this open-label, randomized crossover study, healthy men were assigned to 1 of the 2 treatment sequences (whole tablets followed by an apalutamide-applesauce mixture, or the reverse sequence).

The study comprised a screening phase (≤21 days before study drug administration in period 1); an open-label treatment phase consisting of 2 single-dose treatment periods; and end-of-study or early withdrawal assessments done on completion of the 168-hour PK sampling on day 8 of period 2 or on early withdrawal. The 2 treatment periods were separated by a 42- to 56-day washout. The duration of study participation for an individual subject was approximately 84 days (including screening).

The study was conducted in accordance with principles for human experimentation as defined in the Declaration of Helsinki and was consistent with Good Clinical Practices and applicable regulatory requirements. The study was carried out at Clinical Pharmacology Unit of Johnson & Johnson Pharmaceutical Research & Development, Merksem, Belgium, and was approved by the Human Investigational Review Board/Independent Ethics Committee, UZ Antwerp Wilrijkstraat, Edegem, Belgium (approval no. 18/47/537). Informed consent was obtained before enrollment from each subject after being informed about the investigational nature of the study and the risks/benefits of the treatment.

Study Population. Healthy men aged 18 to 55 years, with body mass index 18 to 30 kg/m^2 (inclusive) with a body weight ≥ 50 kg were eligible for enrollment. Subjects were required to have normal blood pressure and a 12-lead electrocardiogram (ECG) consistent with normal cardiac function at screening. Subjects with clinically significant abnormal values for hematology, clinical chemistry, serum testosterone < 200 ng/dL, and thyroid stimulating hormone level > the upper limit of normal at screening were excluded.

Study Drug Administration. Before each study drug administration in each treatment period, study participants were asked to remain fasting for at least 10 hours. Noncarbonated water was allowed up to 1 hour before study drug administration.

All study drugs were taken in the morning on day 1 of each treatment period, with 240 mL of noncarbonated water accompanying the whole tablets or with a 120-mL container rinse of noncarbonated water accompanying the 120 mL of applesauce mixed with apalutamide tablets. The study drug-applesauce mixture was prepared by a pharmaceutical technician or pharmacist. An additional 50 mL of water for either treatment was allowed if necessary. The applesauce mixture had to be ingested within 5 minutes. For the standard administration, the apalutamide tablets were swallowed whole. For each subject, all doses were administered at approximately the same time of day. Subjects continued fasting until 4 hours postdose.

Approximately 1 hour postdose, all subjects drank 1 glass (approximately 240 mL) of water, with drinking of water allowed from then onward. A standardized lunch was served on day 1 of each period for all subjects after collection of the 4-hour PK sample.

Pharmacokinetics. In each treatment period, subjects stayed at the study center until after the collection of the 72-hour PK sample on day 4 and returned daily to the study center for PK sampling from day 5 to day 8. Blood samples (2 mL each) for determination of apalutamide plasma concentrations were collected through a 168-hour PK sampling period, including 11 samples on day 1 (predose, every 30 minutes until 2 hours, followed by every hour until 6 hours, and at 8 and 12 hours), 2 samples on day 2 (at 24 and 36 hours), and single samples on days 3 to 8 (at 48 hours and every 24 hours thereafter). On days with multiple PK sampling (eg, day 1), a catheter was used for blood sample collection. Plasma apalutamide concentrations were analyzed using a validated liquid chromatography-tandem mass spectrometry method. Chromatography was performed with a Waters XBridge C18 column (50×2.1 mm, 3.5 μm) using a gradient with 0.1% formic acid and acetonitrile. Multiple reaction monitoring transitions were *m/z* 476.1 to 419.1 and 479.1 to 419.1 for apalutamide and the internal standard, respectively. The quantification range was 0.0250–25.0 μg/mL. The recorded values met the acceptance criteria.

Safety. Adverse events (AEs) were either reported by the subject voluntarily or obtained by interviewing subjects in a nondirected manner at study visits. AEs were coded using the MedDRA version 21.1[20] and graded as per NCI-CTCAE version 5.0. ECGs were recorded at screening or at admission to the study center and at study completion, including the end-of-study visit. Clinical laboratory tests (hematology and serum chemistry) and vital signs (blood pressure, pulse, respiratory rate, and body temperature) were evaluated at screening, on day −1, on day 2, and at study completion, including the end-of-study visit. All randomized subjects who received ≥1 dose of the study drug (240 mg apalutamide, either as whole tablets or dispersed in applesauce) were included in the safety analysis.

PK Analysis. Noncompartmental PK and statistical analysis were done using Phoenix WinNonlin (version 8.0; Certara LP, Princeton, New Jersey). Descriptive statistics were calculated for plasma concentrations of apalutamide, as applicable, at each specified time and for the derived plasma PK parameters. Concentrations below the lower limit of quantification were treated as zero in the summary statistics and for the calculation of PK parameters. The primary objective of the analysis was to determine the relative bioavailability of the applesauce mixture with respect to the reference whole tablets, and primary parameters of interest were C_{max}, AUC from time zero to 72 hours ($AUC_{0\text{-}72h}$), and $AUC_{0\text{-}168h}$. If one of the PK parameters could not be determined for a given subject in one or both treatment periods, the subject's data were not included in the respective statistical analysis. The analysis was performed on log-transformed PK parameters. A mixed-effects 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, the point estimate and 90% confidence intervals (CIs) for the difference in means on a log scale between test and reference were constructed. The CI limits were retransformed using antilogarithms to obtain 90%CIs for the geometric mean ratios of C_{max} and $AUC_{0\text{-}168h}$ of the test to reference formulation. A similar analysis was conducted for $AUC_{0\text{-}72h}$ for supplemental purpose.

Taste Assessment. To assess the palatability of the apalutamide dispersed in applesauce, a questionnaire was provided to each subject within 30 minutes of administration of the apalutamide-applesauce mixture. The questionnaire consisted of a visual analog scale to rate 3 items (sweetness, bitterness, and smell) as well as overall acceptability (not acceptable/acceptable). Each question had 7 possible responses, ranging from "superbad" to "supergood" (Figure S1).

Results

Compatibility of Drug Product and Food Vehicle

Appearance of Mixture. No notable changes were observed during the in-use period of the applesauce, yogurt, orange juice, and green tea mixtures. The colors of the applesauce, orange juice, and green tea were found to be lighter for the mixtures, changing from orange for the applesauce and orange juice and yellowish-brown for the green tea (placebo) to yellowish (mixture). Similarly, the yogurt appearance changed from white (placebo) to slightly yellowish (mixture); see Table S1.

Assay of Apalutamide. Dose-accuracy testing found results for all food vehicles to be within the 85.0% to 115.0% criterion (applesauce, 98.3% to 104.5%; yogurt, 95.1% to 101.3%; orange juice, 97.5% to 102.0%; green tea, 99.7% to 101.5%; Table S2). As such, the tested food vehicles do not appear to impact the availability of apalutamide.

Chromatographic Purity. No significant changes were observed during the in-use study of the applesauce, yogurt, orange juice, or green tea mixtures, and all the samples met the specification limit of 85% to 115%. In addition, none of the impurities showed an increasing trend during the tested in-use period of 6 hours (Table S2).

Phase 1 Study

Study Population. A total of 12 men, all white, with a mean age of 45.3 ± 10.4 years and a body mass index of 25.1 ± 2.4 kg/m^2 were randomized to receive whole tablets or the applesauce mixture (Table 1), of whom 10 (83.3%) completed the study. Two subjects discontinued the study in period 1 for personal reasons after receiving the whole tablets or grade 1 gynecomastia after receiving the applesauce mixture (n = 1 each).

Pharmacokinetics. Mean plasma concentration-time profiles showed that apalutamide plasma concentrations reached a maximum 3 hours (range, 2-8 hours) after administration of whole tablets and 2 hours (range, 1-4 hours) after administration of the applesauce mixture (Figure 1; Table 2). On average, apalutamide plasma levels were higher with the applesauce mixture than the whole tablets until about 4 hours postdose. Thereafter, the plasma concentrations were comparable for both treatments. Apalutamide plasma concentrations decreased in a multiphasic manner and were still quantifiable at the last PK sample (168 hours postdose) for both treatments and for all subjects.

Results of statistical analysis (relative bioavailability of the applesauce mixture with respect to whole tablets) for the ln-transformed apalutamide PK parameters are summarized in Table 3. The administration of apalutamide as either an applesauce mixture or whole tablets

Table 1. Demographic and Baseline Characteristics (Safety Analysis Set)

	Whole Tablets → Applesauce Mixture (n = 6)	Applesauce Mixture → Whole Tablets (n = 6)	Total (n = 12)
Age (y), mean (SD)	49.3 (3.8)	41.2 (13.5)	45.3 (10.4)
Weight (kg), mean (SD)	75.6 (10.9)	76.1 (11.7)	75.8 (10.8)
Height (cm), mean (SD)	173.3 (7.1)	173.9 (7.5)	173.6 (7.0)
Body mass index (kg/m^2), mean (SD)	25.1 (2.5)	25.1 (2.5)	25.1 (2.4)

SD, standard deviation.

showed comparable exposures, as shown by the 90%CI of the geometric mean ratio for $AUC_{0\text{-}168h}$ contained within the 80% to 125% limit. C_{max} was increased by 27.6% when apalutamide was administered as an applesauce mixture relative to whole tablets. Intrasubject variability in the apalutamide PK parameters was low for C_{max}, $AUC_{0\text{-}72h}$, and $AUC_{0\text{-}168h}$, with intrasubject coefficient of variation ranging from 2.7% to 13.8%.

Safety. Across both treatment sequences, 5 subjects (41.7%) reported ≥1 AE, including 3 subjects receiving whole tablets (27.3%) and 5 receiving the applesauce mixture (45.5%); see Table 4. Most AEs were grade 1 (33.3%). One subject (8.3%) experienced a grade 2 AE (bursitis), which was not considered drug related by the investigator, and no subjects experienced grade 3 or 4 AEs. The most common AE was gynecomastia, reported in 3 subjects (25.0%); all other AEs were reported in at most 1 subject (8.3%).

Three subjects receiving whole tablets (27.3%) reported drug-related grade 1 AEs: hot flush, vesicular rash, and gynecomastia (n = 1 each). Four subjects receiving the applesauce mixture (36.4%) developed drug-related grade 1 gynecomastia (n = 2), generalized rash (n = 1), or vesicular rash (n = 1).

Sexual side effects were reported in 3 subjects (25.0%); all were grade 1 gynecomastia. Two subjects spontaneously reported gynecomastia after study completion (one 17 days following the applesauce mixture [period 2] and one 45 days following whole tablets [period 2]). Both cases were considered drug related by the investigator. One subject receiving the applesauce mixture reported drug-related gynecomastia 29 days following the first dose of apalutamide. All 3 events were ongoing during database lock; however, further follow-up showed that all AEs of gynecomastia were resolved 90 to 125 days postevent.

No clinically meaningful changes in laboratory parameters, vital signs, or ECG abnormalities were reported.

Palatability. The overall acceptability of the applesauce mixture ranged from "maybe bad, maybe good" in 1 subject (9.1%) to "supergood" in 3 subjects (27.3%). Most subjects (90.9%) did not find it annoying to swallow the applesauce mixture, and the taste was reported to be "sweet" or "pleasant." Bitterness and smell ranged from "good" to "supergood." Most subjects did not experience bitterness (81.8%); the remaining subjects experienced bitterness 1 or 2 minutes postdose. Bitterness did not last for >5 minutes in any of the subjects. All subjects reported that it was acceptable for long-term use. A summary of the taste questionnaire results is provided in Table S3.

Discussion

For an oncology drug product such as apalutamide, loss of pharmacodynamic effect from poor medication adherence can lead to a risk of poor outcome. As 69% of patients have admitted not taking a tablet or capsule because of difficulty in swallowing the drug product,[21] it is understandable that health care professionals, patients, and caregivers may choose to modify administration of tablet or capsule by crushing or administering with food so that the patient receives the necessary medication.[16] However, doing so may alter stability, potency, dissolution, and bioavailability, and as such, in vitro and in vivo tests were conducted with apalutamide.

When exploring which food vehicle would be suitable to test with apalutamide, it was noted that apalutamide tablets disperse when added to an aqueous medium. Although this limits potential food vehicles for alternative administration of apalutamide, there is also the benefit of convenience, as patients would not need to split or crush the tablet. Based on these criteria, applesauce, yogurt, tea, and orange juice, which are readily available around the world, were selected for testing.

As preferences may differ between patients for quantity of food vehicle administered, apalutamide was tested with approximately 50 and 200 mg/mL for each food vehicle. For situations in which the food vehicles are chilled (eg, refrigerated applesauce), an informal test confirmed that the tablet does disintegrate, albeit at a reduced pace (data not presented). Although colder temperatures likely will not impact the content of apalutamide, it should be noted that all compatibility experiments were conducted at room temperature. Higher

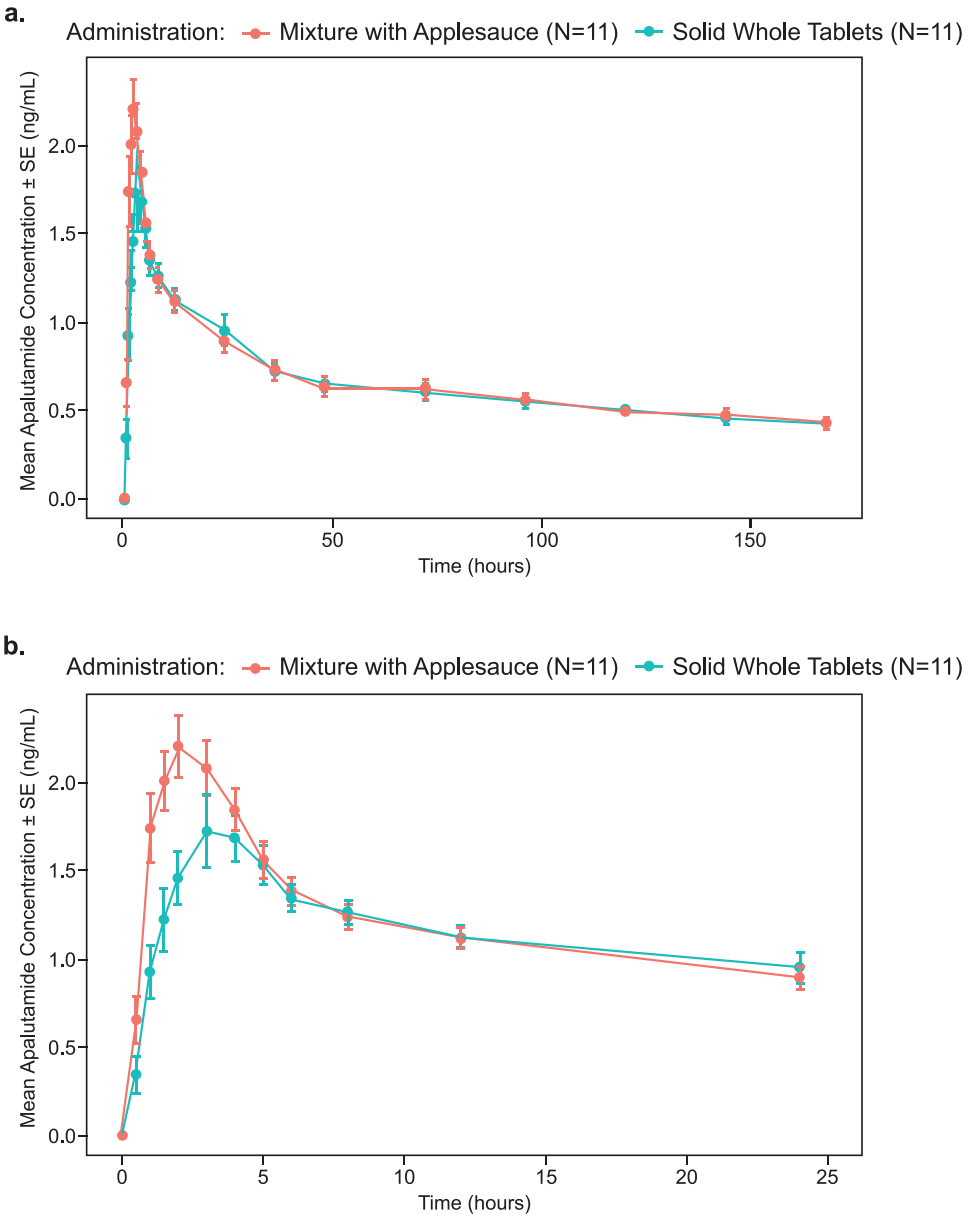

Figure 1. Mean plasma concentration-time profile of apalutamide. (a) 0-168 hours; (b) 0-24 hours. SE, standard error.

Table 2. Pharmacokinetic Parameters of Apalutamide After Single Oral Administration of 240 mg Apalutamide (Pharmacokinetic Data Analysis Set)

	Whole Tablets (Reference)	Applesauce Mixture (Test)
n	11	11
C_{max} (μg/mL), mean (SD)	1.91 (0.521)	2.35 (0.560)
t_{max} (h), median (range)	3.00 (2.00-8.00)	2.00 (1.00-4.00)
$AUC_{0\text{-}72h}$ (μg·h/mL), mean (SD)	61.3 (12.8)	62.5 (13.0)
$AUC_{0\text{-}168h}$ (μg·h/mL), mean (SD)	110 (20.9)	112 (21.1)

$AUC_{0\text{-}72h}$, area under the plasma analyte concentration-versus-time curve from time 0 to 72 hours; $AUC_{0\text{-}168h}$, area under the plasma analyte concentration-versus-time curve from time 0 to 168 hours; C_{max}, maximum observed plasma analyte concentration; SD, standard deviation; t_{max}, time to maximum concentration.

Table 3. Statistical Analysis of the Pharmacokinetic Parameters of Apalutamide (Pharmacokinetic Data Statistical Analysis Set)

		Geometric Means		Applesauce Mixture Versus Whole Tablets			
Parameter	n	Whole Tablets (Reference)	Applesauce Mixture (Test)	Geometric Mean Ratio (%)	Lower Limit 90%CI (%)	Upper Limit 90%CI (%)	Intrasubject CV (%)
C_{max} (μg/mL)	10	1.80	2.30	127.57	113.76	143.05	13.8
$AUC_{0\text{-}72h}$ (μg·h/mL)	10	58.6	61.5	105.02	101.87	108.27	3.7
$AUC_{0\text{-}168h}$ (μg·h/mL)	10	106	111	105.22	102.88	107.60	2.7

$AUC_{0\text{-}72h}$, area under the plasma analyte concentration-versus-time curve from time 0 to 72 hours; $AUC_{0\text{-}168h}$, area under the plasma analyte concentration-versus-time curve from time 0 to 168 hours; C_{max}, maximum observed plasma analyte concentration; CI, confidence interval; CV, coefficient of variance; PK, pharmacokinetic.
Only data from subjects who completed both treatments were considered in the PK inferential statistical analysis (comparative statistics). Two subjects did not complete the study; therefore, only 10 subjects were included in the pharmacokinetics data statistical analysis set.

Table 4. Treatment-Emergent Adverse Events (Safety Analysis Set)

	Whole Tablets → Apalutamide-Applesauce Mixture			Apalutamide-Applesauce Mixture → Whole Tablets		
	Total	Grade 1 (Mild)	Grade 2 (Moderate)	Total	Grade 1 (Mild)	Grade 2 (Moderate)
Subjects treated, n	11			11		
Subjects with ≥1 TEAE, n (%)	3 (27.3)	2 (18.2)	1 (9.1)	5 (45.5)	5 (45.5)	0
Gastrointestinal disorders, n (%)	0	0	0	1 (9.1)	1 (9.1)	0
Diarrhea	0	0	0	1 (9.1)	1 (9.1)	0
Infections and infestations, n (%)	0	0	0	2 (18.2)	2 (18.2)	0
Fungal infection	0	0	0	1 (9.1)	1 (9.1)	0
Viral pharyngitis	0	0	0	1 (9.1)	1 (9.1)	0
Musculoskeletal and connective tissue disorders, n (%)	1 (9.1)	0	1 (9.1)	0	0	0
Bursitis	1 (9.1)	0	1 (9.1)	0	0	0
Musculoskeletal stiffness	1 (9.1)	1 (9.1)	0	0	0	0
Reproductive system and breast disorders, n (%)	1 (9.1)	1 (9.1)	0	2 (18.2)	2 (18.2)	0
Gynecomastia	1 (9.1)	1 (9.1)	0	2 (18.2)	2 (18.2)	0
Skin and subcutaneous tissue disorders, n (%)	1 (9.1)	1 (9.1)	0	2 (18.2)	2 (18.2)	0
Rash, generalized	0	0	0	1 (9.1)	1 (9.1)	0
Rash, vesicular	1 (9.1)	1 (9.1)	0	1 (9.1)	1 (9.1)	0
Vascular disorders, n (%)	1 (9.1)	1 (9.1)	0	0	0	0
Hot flush	1 (9.1)	1 (9.1)	0	0	0	0

TEAE, treatment-emergent adverse event.
Subjects who had a TEAE more than once and with different severity grades is only counted once in the highest toxicity grade. There were no grade 3 (severe) or 4 (life-threatening) events. Adverse events are coded using MedDRA v21.1.

temperatures were not evaluated, as there is a potential for drug degradation.

Although apalutamide was compatible with each food vehicle as well as comparable in regard to purity and stability, dissolution testing was not conducted, as the amount of food vehicle was found to affect the pH of the dissolution apparatus and resulting dissolution profile (data not presented). As other similar studies observed similar changes to the dissolution profile because of the addition of a food vehicle,[17,22] it is likely that differences in dissolution results may not reflect in vivo drug product performance. As it was not feasible to demonstrate comparability via dissolution profiles, an in vivo study was conducted to determine clinical comparability. Applesauce was selected for the clinical study because of the natural sweetness, which can help to mask the taste in case the dispersed apalutamide tablets have an unpleasant taste.

One of the concerns with administering ex vivo dispersion or disintegration of a solid oral drug product is the bypassing of in vivo disintegration of tablets, which may alter the PK profile. This effect is partially observed in this phase 1 study. Although the PK of whole tablets is consistent with prior knowledge of PK[13] and the population PK model for apalutamide,[23] and the extent of absorption via $AUC_{0\text{-}168h}$ between apalutamide-applesauce and standard oral administration is highly comparable (5% difference with 90%CI within the 80% to 125% criterion for bioequivalence), the observed C_{max} for applesauce mixture was 27.6% higher than the C_{max} for the whole tablets. Similar increases in C_{max} have been observed in an applesauce study with poorly soluble compounds such as nilotinib (31%)[19] and tizanidine (17%),[24] whereas a highly soluble and permeable compound such as amlodipine had a decrease in C_{max} (6.5%).[25] As apalutamide is poorly soluble, bypassing in vivo disintegration of tablets with ex vivo preparation in applesauce may result in earlier and faster systemic absorption.

Although the C_{max} after a single dose of the apalutamide-applesauce mixture is higher compared with tablets, the concentration at 24 hours and the $AUC_{0\text{-}24h}$ were comparable (0.96 vs 0.90 μg/mL and 27.9 vs 29.5 μg·h/mL, respectively). As such, it is anticipated that the accumulation of apalutamide will be comparable between whole tablets and the apalutamide-applesauce mixture. Considering the high accumulation ratio of apalutamide at approximately 5-fold, the difference in C_{max} after administration of four 60-mg apalutamide tablets dispersed in applesauce is anticipated to decrease significantly and is therefore not considered clinically relevant. This is consistent with previous modeling and simulation exercise for apalutamide that demonstrated that differences in peak exposures at a single dose are minimized at steady state.[26]

In addition, study participants found that the apalutamide-applesauce mixture was palatable, with few individuals reporting bitterness. Overall, acceptability of the apalutamide-applesauce mixture was high, with no subjects responding that they would not be able to take apalutamide-applesauce mixture every day.

Conclusion

Administration of 240 mg apalutamide as a mixture in applesauce is a suitable alternative to whole tablets, as it provides equivalent systemic drug exposure based on comparable $AUC_{0\text{-}168h}$. Apalutamide will disperse on introduction into aqueous food vehicles (eg, applesauce, yogurt, orange juice, and green tea) without the need to crush/split the tablet. Mixing of tablets in each of the tested aqueous food vehicles did not affect the purity, dose accuracy, or stability of apalutamide in the resulting mixture.

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Conflicts of Interest

Alex Yu, Maura Erba, and Anasuya Hazra are employees of Janssen Research and Development (a subsidiary of Johnson & Johnson) and own Johnson & Johnson stock or stock options.

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Data-Sharing Statement

The data-sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through the Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

Author Contributions

A.Y. and M.E. were involved in the conception and design of the study. A.Y. was involved in study methodology. A.Y. and A.H. were involved in data analysis and interpretation. A.Y. and M.E. were also involved in project administration. All authors were involved in manuscript writing and review

and editing. All authors have approved the final manuscript for submission.

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