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Bioequivalence clinical trial simulation: a case study of apalutamide administered in applesauce versus whole tablets

Alex Yu[1*] and Oliver Ackaert[2]

Abstract

Patients who have difficulty swallowing apalutamide tablets may benefit from administration in a food vehicle that is easier to swallow. In a previous single-dose study conducted in healthy male volunteers ($n=12$) a larger peak exposure was observed (+27.6%) for apalutamide in applesauce compared with whole tablets, despite a comparable extent of exposure (+5%). However, because apalutamide is taken daily which results in a 3–5 fold accumulation ratio, the observed 27.6% difference in peak exposure with single-dose administration may be reduced with multiple doses. To evaluate the difference in peak exposure under daily administration of apalutamide, bioequivalence trial simulations assessing the probability of success in demonstrating bioequivalence between the two administration methods after repeat dose and single-dose administration were conducted. Simulated pharmacokinetic (PK) profiles for the reference treatment were based on an established population PK model for apalutamide. Simulated profiles for test treatment were based on the same model but with a treatment covariate fitted to the PK observations of the single-dose study. The present analysis found that >85% of simulated steady-state bioequivalence trials with 10 subjects or more comparing daily apalutamide administration in applesauce versus whole tablets met the 80–125% criteria for bioequivalence for both maximum concentration ($C_{max,ss}$) and area under the concentration curve at steady state ($AUC_{0-24\,h,ss}$). Results of these clinical trial simulations suggest that the daily administration of 240 mg apalutamide in applesauce is bioequivalent to whole tablet administration.

Keywords Antiandrogen, Applesauce, Bioequivalence, Food, Pharmacokinetics

Introduction

Apalutamide (ERLEADA®, also referred to as JNJ-56021927 and ARN-509) is an androgen receptor inhibitor currently approved by multiple health authorities for the treatment of metastatic castration-sensitive and non-metastatic castration-resistant prostate cancer based on a dose of 240 mg once daily as 4×60 mg oral tablets (FDA. 2019; FDA. 2018; Erleada and 2021; Erleada 2021).

A trending voice of customer analysis suggested that there is a need to provide an alternative dosing recommendation for patients who have swallowing difficulties due to the size of the apalutamide tablets (approximately 17×9 mm). This is a concern as patients with difficulty swallowing may delay or skip doses, which may subsequently impact treatment compliance and the therapeutic benefit of apalutamide. As apalutamide can rapidly disperse in aqueous media, patients, caretakers, and healthcare practitioners may seek to administer apalutamide with food vehicles to aid in ingestion, as is often done with solid oral dosage forms (Stegemann et al. 2012). However, administration of

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medication in food vehicles can potentially alter stability, potency, dissolution, and bioavailability (Carrier et al. 2004; Wells and Losin 2008; Yin et al. 2011).

To evaluate whether the administration in applesauce would be a suitable alternative to whole tablet administration, an exploratory 2-way crossover relative bioavailability study with 10 healthy volunteers was conducted (Yu et al. 2021). After administration of a single 240 mg dose of apalutamide-applesauce mixture, the area under the concentration curve from 0 to 168 h ($AUC_{0-168\ h}$) was found to have comparable bioavailability relative to whole tablets formulation (geometric mean ratio [GMR], 90% confidence interval [CI] of 105.22% [102.88–107.60%]) and had higher maximum concentration (C_{max}) (GMR [90% CI] 127.57% [113.76–143.05%]).

The criteria for bioequivalence are met when the 90% CI for C_{max} and AUC fall within 80.00–125.00%. As the GMR for C_{max} was 127.57%, this would suggest that administration in applesauce may not be bioequivalent to whole tablet administration. However, this may not be the case for apalutamide after repeated dosing due to its pharmacokinetic (PK) properties. Apalutamide is primarily eliminated through metabolism via cytochrome P450 (CYP) 2C8 and CYP3A4 to form N-desmethyl-apalutamide (Vries et al. 2019). While the PK of apalutamide are linear and dose proportional (Rathkopf et al. 2013), the contribution of the two CYPs is estimated to change from 58% and 13% following a single dose to 40% and 37% following repeat dosing as apalutamide induces CYP3A4 metabolism (Bergh et al. 2020). Repeat once-daily oral administration of apalutamide under fasted conditions results in an approximately 3- and fivefold increase of maximum plasma concentration (C_{max}, 2.06 vs 5.95 μg/mL) and area under the plasma concentration–time curve from time 0 to 24 h (AUC_{24h}, 21.1 vs 100 μg h/mL), respectively, when compared to the first dose (Belderbos et al. 2018). This can be attributed to the daily administration of a long mean effective half-life compound of 3 days at steady-state Erleada(R)2022. As such, accumulation at a steady state is theorized to result in a decrease in the apparent difference observed in C_{max} between the two administration methods for patients who are following the recommended daily dosing of apalutamide.

As an established population PK model for apalutamide accounts for changes in metabolism over time and can be used to evaluate differences between single vs repeat dosing, the present simulation study was conducted to assess whether administration of apalutamide in applesauce is bioequivalent to whole tablets under repeated once-daily conditions.

Materials and methods

Clinical study design, sample collection, and bioanalytical methods

This clinical study was a single-arm, phase 1, two-way crossover relative bioavailability study of apalutamide 240 mg administered orally as whole tablets and as a mixture in applesauce in healthy participants under fasting conditions ClinicalTrials.gov 2020. All plasma samples with quantifiable apalutamide concentrations, with available date and time as well as apalutamide dose administration, were included in the population PK analyses. Blood samples (2 mL each) for determination of apalutamide plasma concentrations were collected through a 168-h PK sampling period, including 11 samples on Day 1 (pre-dose, every 30 min until 2 h, followed by every hour until 6 h, and at 8 and 12 h), 2 samples on Day 2 (at 24 and 36 h), and single samples on Days 3–8 (at 48 h and every 24 h thereafter). The plasma concentration of apalutamide was determined using a validated LC–MS/MS assay developed at PRA Health Sciences (Assen, The Netherlands). Chromatography was performed with a Waters XBridge C18 column (50 × 2.1 mm, 3.5 μm) using a gradient solvent with 0.1% formic acid and acetonitrile. Multiple reaction monitoring transitions were from 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 trial was performed in accordance with the principles of the Declaration of Helsinki, Good Clinical Practices, and local regulatory requirements. The protocol was approved by the Institutional Ethics Committee and participants provided written informed consent.

Modeling approach

To characterize the effects of apalutamide in applesauce administration based on the study from the perspective of the overall population, an established population PK model for apalutamide was adapted (Pérez-Ruixo et al. 2020). A treatment covariate was added to the population PK model and the model was fitted to the previously reported PK observations from NCT03802682 ClinicalTrials.gov 2020. The parameters of the existing model were maintained when fitting the PK observations from this study; only covariates for the formulation were estimated. To describe the effect of the administration of apalutamide dispersed in food vehicles, three covariates were added:

- Lag time (ALAG; h) as administration in applesauce may result in an earlier median T_{max} (2 vs 3 h observed) which can be attributed to bypassing the

dispersion step by ex vivo by nature of food vehicle administration
- Estimated bioavailability (F) due to the minor but statistically significant increase in $AUC_{0-168\ h}$ between treatments (112 vs. 110 µg h/mL)
- First-order absorption rate constant (KA; $h.^{-1}$) marked by a statistically significant increase in C_{max} (2.35 vs. 1.91 µg/mL)

Additions of these formulation effects and respective interindividual variability were fitted using the established population PK model with the ADVAN library routines in NONMEM®. Only non-inducible clearance was considered when fitting the single-dose data.

Model assessment/qualification criteria

Given the goal of evaluating differences between treatments using an established population PK model, successful minimization, completion of the variance step, and obtaining reasonable values in empirical Bayesian estimates and numeric predictive checks were considered as criteria for the assessment of the model performance.

Clinical trial simulations

The established population PK model (primarily using whole tablets as the administration method) served as the reference treatment and the same model adapted with the fitted covariate parameters served as the test treatment.

A simulated population of 10,000 individuals with their associated PK parameters was used as a source for two simulation scenarios for bioequivalence trials ($n=1000$). In the single-dose scenario (SD) bioequivalence of the two administration methods was assessed using randomly sampled PK parameters (C_{max} and $AUC_{0-168\ h}$) for the test and reference treatments. This scenario assumed complete washout between single dose administrations for 10 individuals. In another scenario representing steady state (SS), bioequivalence between the two administration methods was assessed using randomly sampled PK parameters ($C_{max,ss}$ and $AUC_{0-24\ h,ss}$) for the test and reference treatments. Scenarios with 10, 20, 30, 40, 50, and 60 individuals per trial were investigated.

Statistical analysis of pharmacokinetic parameters in simulated bioequivalence trials

For each simulated bioequivalence trial, a mixed effect model that included treatment, period, and treatment sequence as fixed effects and the individual as a random effect was used to estimate the least squares means and intraindividual variance. Using these estimated values, the point estimate and 90% confidence intervals (CIs) for the difference in mean PK parameters on a log scale between the test (tablets dispersed in applesauce) and reference (tablets) formulations were constructed. The limits of the CIs were retransformed using antilogarithms to obtain 90% CIs for the GMRs of C_{max} and AUC of the test to the reference formulation. Administration in applesauce was considered bioequivalent with tablet administration if the 90% CI for the test vs. reference ratio of the geometric mean C_{max} and AUC fell within 80.00% to 125.00%. The percentage of trials by the number of individuals per trial passing bioequivalence was reported.

Software

Non-linear mixed effect modeling was carried out by extended least-squares regression using the first-order conditional estimation with interaction method using NONMEM® version 7.4.0 or higher (ICON plc, Ellicott City, MD) and Intel® Fortran 64 Compiler Professional, Version 11.1. Post-processing of NONMEM® analysis results, non-compartmental analysis (NCA), and trial simulations was carried out in R version 3.4.1 or higher (Comprehensive R Network, http://cran.r-project.org/) (Elkoshi et al. n.d.). The R-package mrgsolve was used to simulate both single-dose and steady-state scenarios.

Results

Exploratory analysis

Plots of the observed concentrations of apalutamide on a linear scale as a function of time following single-dose administration are shown in Fig. 1. Following an increase in concentration, a biphasic decline in apalutamide concentration was observed.

Final model

Parameter estimates for the covariates of formulation on the model parameters F, KA, and ALAG from the final model are given in Table 1. All structural model parameters were estimated with reasonable precision based on relative standard error (RSE). Standard goodness-of-fit plots are shown in Fig. 2. Additional measures of the goodness of fit including individual predicted concentrations and observed concentrations vs. time are provided in Fig. 3, and a visual predictive check is provided in Fig. 4.

Model evaluation

Comparison of model-derived PK parameters versus study PK parameters is shown in Table 2. The geometric mean ratio based on the empirical Bayes estimates (EBE) is slightly higher than based on the observed data. Nonetheless, the 90% CI largely overlaps. In addition, the numeric predictive check of the apalutamide administration in applesauce versus whole tablets (Fig. 5) demonstrated that the model can adequately capture the

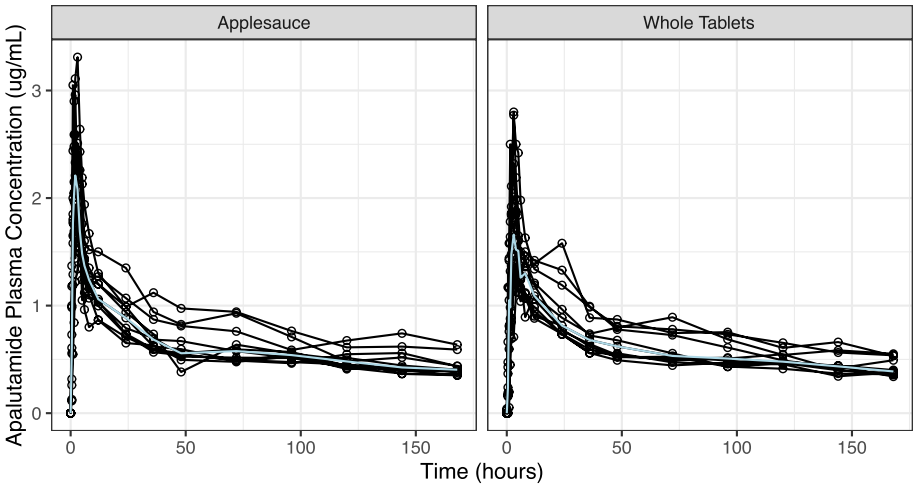

Fig. 1 Apalutamide concentration versus time in NCT03802682. Black symbols represent observed data and blue lines indicate medians. All data refer to hour since the last dose

Table 1 Population pharmacokinetic parameter estimates for applesauce covariates added

Parameter[a]	Structural model parameters		Interindividual variability (CV%)	
	Estimate	RSE%	Estimate	RSE%
$COV_{applesauce}$ on F	0.0254	54.3	100.6	35.0
$COV_{applesauce}$ on KA	0.406	26.6	155.5	0.144
$COV_{applesauce}$ on ALAG	−0.0352	18.3	185.0	0.07

ALAG Absorption lag time, *COV* Covariate, *CV* Coefficient of variation, *F* Oral bioavailability, *KA* Absorption rate constant, *RSE* Relative standard error

[a] Parameters defined as $Parameter_{applesauce} = Parameter_{reference}*(1 + COV_{applesauce}*exp(IIV_{COV,applesuace})$

observed geometric mean ratio of C_{max} and $AUC_{0-168\ h}$ after a single dose in study NCT03802682.

Bioequivalence simulations

Summary statistics of GMRs for C_{max} and AUC derived from analysis of variance (ANOVA) of simulated data are provided in Table 3. It can be observed that at steady state, $AUC_{0-24\ h,ss}$ is comparable with $AUC_{0-168\ h}$ and C_{max} decreased by approximately 19% compared to a single dose.

The probability of success in demonstrating bioequivalence (i.e., 90% CIs within 80–125% for both

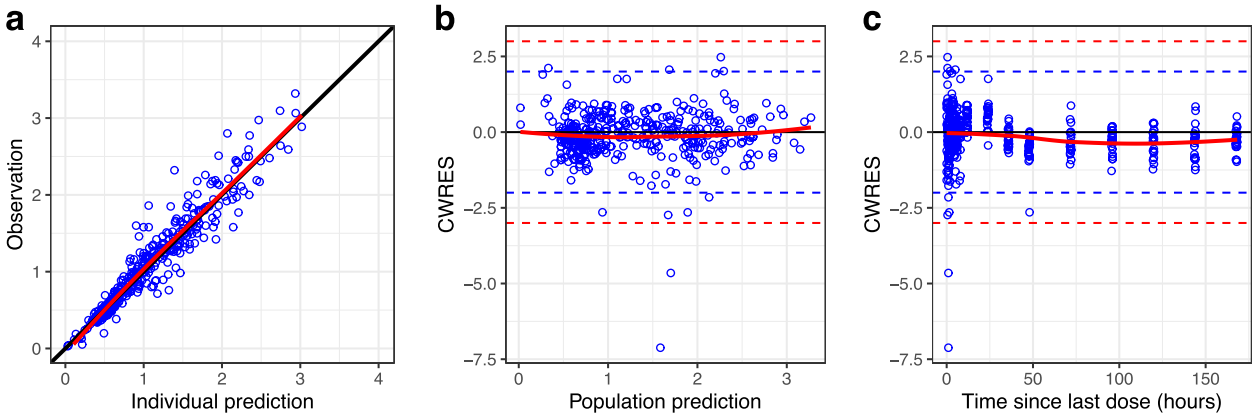

Fig. 2 Goodness-of-fit plots for **a** observation (DV) versus individual prediction (IPRED), **b** conditional weighted residue (CWRES) versus population prediction (PRED), and **c** conditional weighted residue (CWRES) versus time since the last dose. The solid red line represents LOWESS regression line, the solid black line the line of identity (**a**) or the zero line (**b** and **c**), and the area between dashed blue and red lines the 95th and 99th percentile interval, respectively (**b** and **c**)

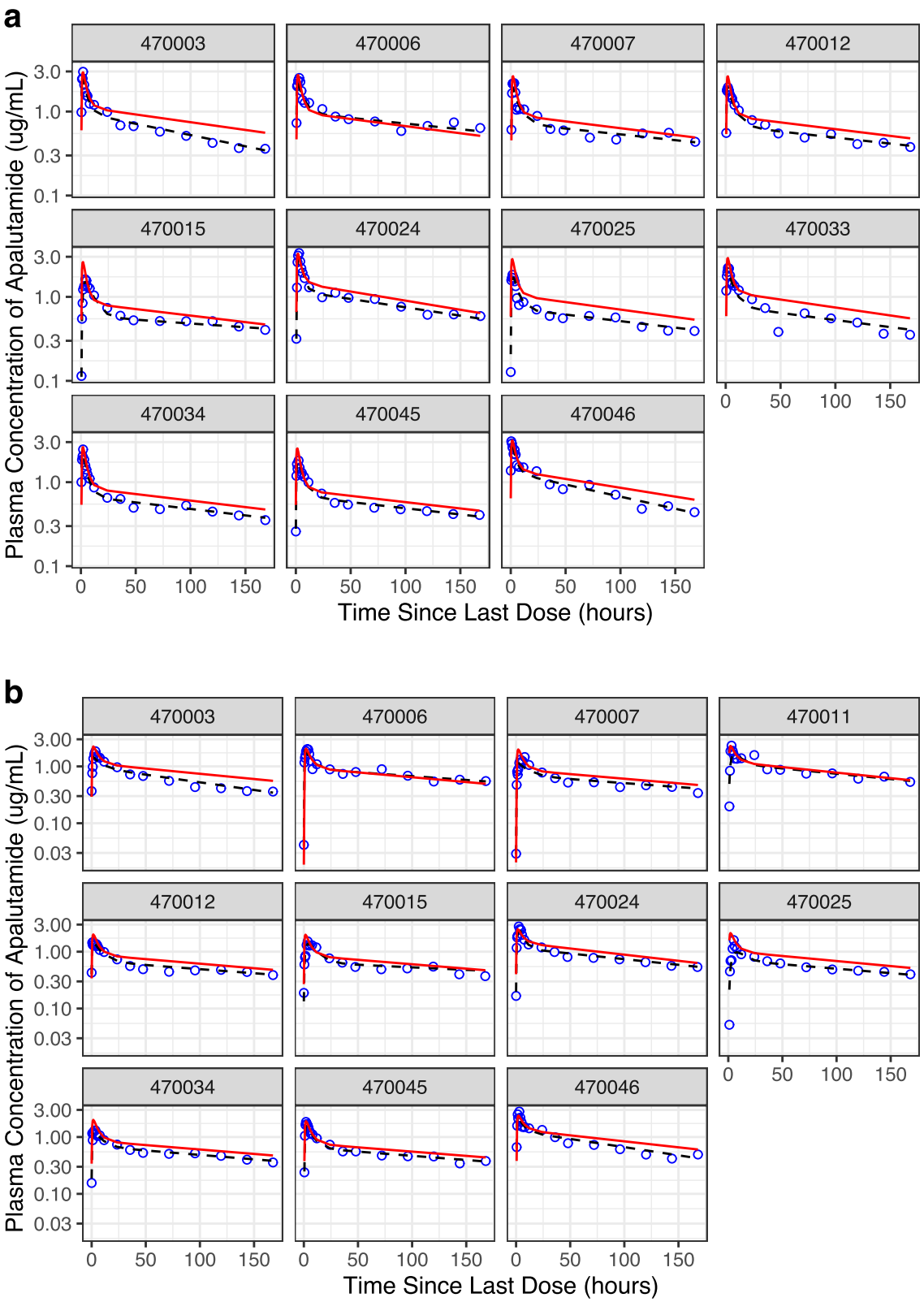

Fig. 3 Individual goodness-of-fit plots for apalutamide **a** whole tablets (log-linear) and **b** in applesauce (log-linear)

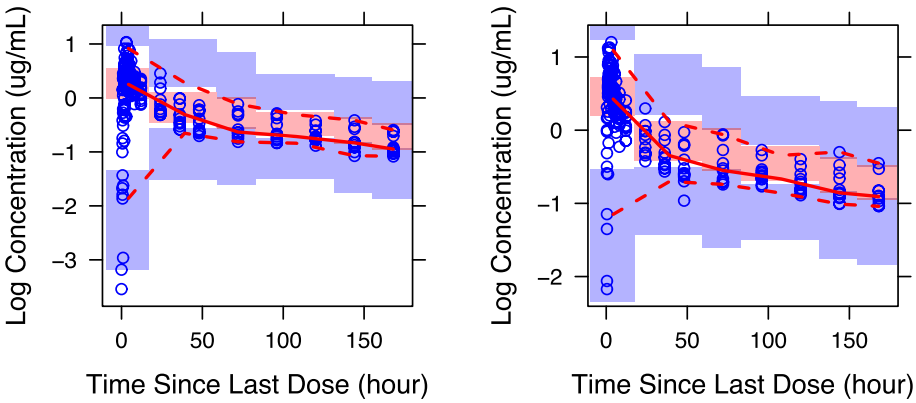

Fig. 4 Visual predictive check of observations versus time since the last dose for apalutamide administration as whole tablets or applesauce. Whole tablets (left) and applesauce (right). The 2 dashed red lines represent the 5th and 95th percentiles of the observed apalutamide concentrations, while solid red line represents the 50th percentile of the observed apalutamide concentrations. The solid blue, gray, and blue shaded areas represent the 95% CI for the corresponding model-based predicted 5th, 50th, and 95th percentiles computed for each bin across time and replicates, respectively. The blue shaded circles represent apalutamide observed plasma concentrations and the vertical lines at the top represent the time at where the bins were performed

Table 2 Numeric predictive check of statistical analysis of pharmacokinetic parameters comparison of statistical analysis of pharmacokinetic parameters derived from empirical Bayesian estimates versus pharmacokinetic parameters from study NCT03802682

PK parameter	Source	*n*	Geometric means		Applesauce versus whole tablet		
			Whole tablet	Mixed in applesauce	Geometric mean ratio (%)	Lower limit 90% CI	Upper limit 90% CI
C_{max} (μg/mL)	Study[a]	10	1.80	2.30	127.57	113.76	143.05
	EBE	10	1.54	2.14	138.95	124.60	154.96
$AUC_{0-168\,h}$	Study[a]	10	106	111	105.22	102.88	107.60
	EBE	10	107	111	103.12	100.50	105.80

AUC Area under the concentration–time curve, C_{max} Maximum plasma concentration, *CI* Confidence interval, *EBE* Empirical Bayes estimates, *PK* Pharmacokinetics

[a] Refers to NCT03802682

C_{max} and AUC) is shown in Table 4. The simulations illustrate that administration in applesauce versus whole tablets will meet bioequivalence criteria following repeated doses to a steady state with > 85% likelihood when the number of individuals per trial is equal to or greater than 10. When the number of individuals was increased to 40, the likelihood was 100% (1000 out of 1000 studies). Single-dose administrations are unlikely to meet bioequivalence criteria (1.1% and 0% when $N = 10$ and 40, respectively).

Discussion

At the initiation of the present clinical study, it was hypothesized that the use of a food vehicle would not increase exposure to apalutamide tablets. This was based on results from NCT02160756, where a decrease of 16.05% and 3.27% was observed for C_{max} and AUC$_{last}$ respectively when the apalutamide tablets were co-administered with a high-fat meal. Due to the recommendation for a single-dose study and the assumption that a multiple-dose study is inherently less sensitive in detecting differences in C_{max} EMA 2010, NCT03802682 was designed as a single-dose study to follow up on the previous food effect study. The limited number of evaluable participants ($N = 10$) was based on the expectation that this sample size would be sufficient to characterize the differences if intraindividual variability was low and the true ratio was close to 1 (Wang and Zhou 1999). The results, however, differed from previous observations of single-dose apalutamide PK under fasting or fed conditions.

Given that an increase in C_{max} after a single dose was identified in the healthy subjects, interpretation of PK after multiple dosing in prostate cancer patients

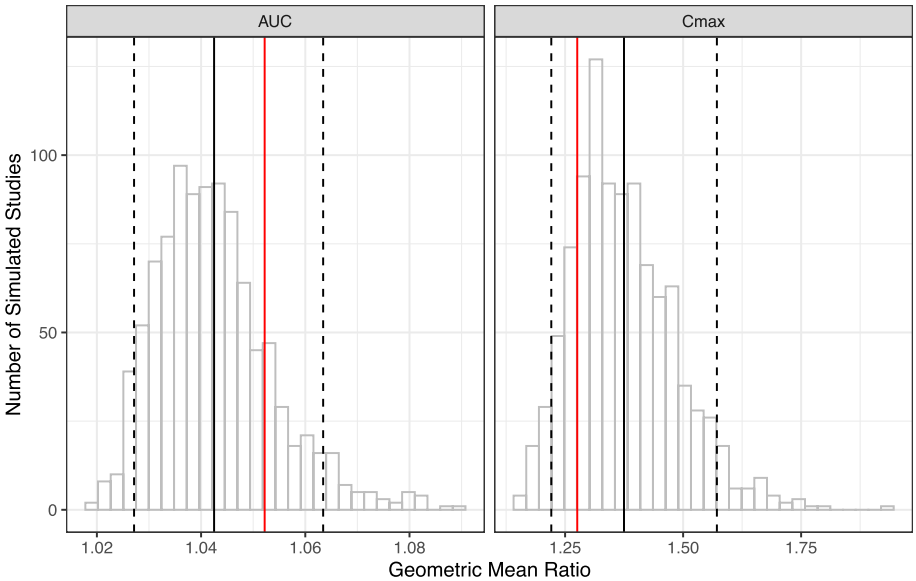

Fig. 5 Numeric predictive check showing the predictive performance of the applesauce covariates for central tendency of relative apalutamide C_{max} and $AUC_{0-168\ h}$. The histogram represents the distribution of the geometric mean ratios across the 1000 simulated studies. The solid black lines (dashed black lines) represent the mean ratio (5 and 95% percentile) across the simulated studies. The solid red vertical line indicates the observed GMR from the statistical analysis of study NCT03802682 PK parameters

Table 3 Summary statistics of geometric mean ratios derived from ANOVA of simulated data

	Predicted parameter	*N* per trial	No. of simulation	Mean	Std Dev	5th percentile	95th percentile
SD	$AUC_{0-168\ h}$	10	1000	104.25	1.13	104.14	106.34
	C_{max}	10	1000	137.47	11.0	135.99	157.15
SS	$AUC_{0-24\ h,ss}$	10	1000	103.53	1.07	103.45	105.58
	$C_{max,ss}$	10	1000	111.30	3.56	110.69	118.10

AUC Area under the concentration–time curve, C_{max} Maximum plasma concentration, *SD* Single dose, *SS* Steady state

Table 4 Simulation of 1000 bioequivalence trials

No. of subjects per BE trial (*N*)	Single dose		Multiple dose (steady state)	
	No. of trials met BE (out of 1000)	POS (%)	No. of trials met BE (out of 1000)	POS (%)
10	11	1.1	860	86.0
20	2	0.2	977	97.7
30	1	0.1	995	99.5
40	0	0	1000	100

AUC Area under the concentration–time curve, *BE* Bioequivalence, C_{max} Maximum plasma concentration, *POS* Probability of success in demonstrating bioequivalence for both C_{max} and AUC in 1000 simulated trials

is critical, particularly if the observed differences may be further increased in multiple-dose settings (Elkoshi et al. n.d.). Considering the limited solubility of apalutamide, the difference in exposure was hypothesized to be due to the ex vivo dispersion process and applesauce being primarily an aqueous medium with limited caloric content. Rather than conduct an analogous study under steady-state conditions in patients, clinical trial simulations offer an ethically sound and scientifically reasonable approach to bridging the gap between single-dose and multi-dose PK. Modeling and simulation have previously been used to demonstrate that confidence intervals will narrow at steady state vs. single dose for drugs with high accumulation indices and a large difference in absorption rate constants (KA) between test and reference formulations (El-Tahtawy et al. 1994).

Given that extensive PK data in healthy subjects and patients with prostate cancer (richly and sparsely sampled data) for apalutamide exist and have been incorporated in a population PK model (Pérez-Ruixo et al. 2020), fitting the established population PK model for apalutamide to the relative bioavailability study

results to quantify treatment covariates for alternative administration was carried out, while the structural parameters were kept the same as estimated previously (Perez-Ruixo et al. 2020). This allowed for the characterization of administration effects while providing consideration for the broader patient population when running simulated bioequivalence studies. Because apalutamide disperses rapidly upon introduction into an aqueous environment and a homogenous mixture can be attained following standardized food vehicle preparation steps, it was hypothesized that any change in PK, especially on absorption and bioavailability, could be attributed to the ex vivo preparation of apalutamide. Thus, the effect of the formulation was quantified on observed bioavailability, absorption rate constant, and absorption lag time.

The effect on administration captured by the fitted model parameters appears to reproduce the differences observed in the study. As applesauce is primarily water, the slight decrease in absorption lag time and increase in absorption rate constant are consistent with the oral intake of an ex vivo preparation. Coupled with the small increase of applesauce on oral bioavailability, which is estimated to be around 2.54%, compared to tablet formulation, the parameters appear consistent with an increase in observed F, increased C_{max}, and decreased T_{max} previously reported (Vries et al. 2019).

In determining whether the model-fitted parameters were acceptable, the visual predictive check suggested an acceptable characterization of the central tendency and the variability. The predicted geometric mean AUC was comparable to the observed, while the GMR of the C_{max} was slightly overpredicted (124.60% estimated vs 113.76% observed). Since the 90% CI of the GMR of the observed and the model predicted largely overlapped and the NPC showed that the model could adequately predict the observed GMR, the model-based approach was considered adequate. In addition, the model-derived GMR of C_{max} is slightly larger than the observed GMR, the developed model was considered a conservative approach as this would increase the likelihood of failure to demonstrate bioequivalence for any simulation based on these fitted parameters.

For simulated bioequivalence trials to evaluate the difference between a single dose and steady state, the same number of individuals statistically tested in the trial ($N=10$) were simulated over 1000 bioequivalence studies. This was done to better reproduce the variability due to the sample size in the study and to serve as a point of comparison. For a single dose, the probability of simulated studies meeting the criteria for bioequivalence dropped from 1.1 to 0% with the number of subjects increasing from 10 to 40, respectively. This is attributed to the increased precision of the estimate with an increasing number of subjects. In contrast, the probability of multiple dose studies meeting the criteria for bioequivalence increased from 86 to 100% with the number of subjects increasing from 10 to 40, respectively. Given that the minimum required power for a pivotal bioequivalence study is 80%, this suggests that a steady-state study with 10 individuals is reasonably powered to demonstrate bioequivalence.

It is acknowledged that a level of uncertainty in the simulation can be attributed to the limited number of subjects in NCT03802682. However, using a model-based approach allows to take into account historical knowledge of apalutamide PK (Pérez-Ruixo et al. 2020) in healthy subjects and patients with prostate cancer. Simulations demonstrated that the 95th percentile of the predicted geometric mean ratio following a single dose is 157.15% and reduces to 118.10% at a steady state. The upper limit of the 90% prediction interval of the steady state C_{max} GMR of 118.10% is within 80–125% BE criteria, the simulation suggests the administration method to be bioequivalent to whole tablet administration even if the limited number of subjects led to an overestimation of the GMR or C_{max}.

Conclusions

While simulated bioequivalence trials indicated that a single dose study is unlikely to demonstrate bioequivalence (0%), the present analysis found that > 85% of simulated steady-state bioequivalence trials with 10 subjects or more comparing daily apalutamide administration in applesauce versus whole tablets met the 80–125% criteria for bioequivalence for both maximum concentration ($C_{max,ss}$) and area under the concentration curve at steady state ($AUC_{0-24\ h,ss}$). The results of this clinical trial simulation suggest that the daily administration of 240 mg apalutamide in applesauce is bioequivalent to whole tablet administration.

Abbreviations

ALAG	Lag time
ANOVA	Analysis of variance
AUC	Area under the curve
AUC_{last}	Area under the curve up to the last measurable concentration
AUC_{24h}	Area under the plasma concentration–time curve from time 0 to 24 h
$AUC_{0-24h,ss}$	Area under the plasma concentration–time curve from time 0 to 24 h at steady state
AUC_{0-168h}	Area under the concentration curve from 0 to 168 h
CI	Confidence interval
C_{max}	Maximum concentration
$C_{max,ss}$	Steady-state maximum concentration
CYP	Cytochrome
EBE	Empirical Bayes estimates
F	Estimated bioavailability
GMR	Geometric mean ratio
KA	Absorption rate constants

NCA	Non-compartmental analysis
PK	Pharmacokinetic
RSE	Relative standard error
SD	Single-dose
SS	Steady state

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Authors' contributions
Alex Yu conceived the study. Alex Yu and Oliver Ackaert designed the analysis and interpreted the results. Alex Yu wrote the manuscript. All authors provided final review and approval.

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Availability of data and materials
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.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
Alex Yu and Oliver Ackaert are employees of Janssen Research & Development and may own stock/stock options in Johnson & Johnson.

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