CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213674Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA Multi-Disciplinary Review and Evaluation

Application Type	Original NDA
Application Number(s)	NDA 213674
Priority or Standard	Standard
Submit Date(s)	October 30, 2019
Received Date(s)	October 30, 2019
PDUFA Goal Date	August 30, 2020
Division/Office	DO1/OOD
Review Completion Date	July 22, 2020
Established/Proper Name	Enzalutamide
(Proposed) Trade Name	Xtandi
Pharmacologic Class	Androgen receptor inhibitor
Applicant	Astellas
Doseage form	oral
Applicant proposed Dosing Regimen	XTANDI 160 mg (two 80 mg tablets or four 40 mg tablets or four 40 mg capsules) administered orally once daily. Swallow capsules or tablets whole. XTANDI can be taken with or without food.
Applicant Proposed Indication(s)/Population(s)	XTANDI is an androgen receptor inhibitor indicated for the treatment of patients with: • castration-resistant prostate cancer. • metastatic castration-sensitive prostate cancer.
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	Malignant tumor of prostate (disorder) {399068003 , SNOMED-CT }
Recommendation on Regulatory Action	Regular approval
Recommended Indication(s)/Population(s) (if applicable)	XTANDI is an androgen receptor inhibitor indicated for the treatment of patients with: • castration-resistant prostate cancer. • metastatic castration-sensitive prostate cancer.
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Malignant tumor of prostate (disorder) {399068003 , SNOMED-CT }
Recommended Dosing Regimen	XTANDI 160 mg (two 80 mg tablets or four 40 mg tablets or four 40 mg capsules) administered orally once daily. Swallow capsules or tablets whole. XTANDI can be taken with or without food

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Reviewers of Multi-Disciplinary Review and Evaluation

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OPDP Reviewer	Lynn Panholzer
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DMPP Reviewer/Team Leader	Morgan Walker/Barbara Fuller

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Enzalutamide is an androgen receptor (AR) inhibitor that targets the AR signaling pathway and inhibits nuclear translocation of the AR and association of the AR with DNA in the setting of AR overexpression or resistance to antiandrogens.

Enzalutamide is currently indicated for the treatment of patients with:

- Castration-resistant prostate cancer.
- Metastatic castration-sensitive prostate cancer.

The Applicant has submitted this original NDA for a new dosage form (film-coated tablets) and new strength (80 mg) of enzalutamide for the treatment of castrate-resistant prostate cancer.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The application is based on the results of a pivotal clinical study to demonstrate bioequivalence between enzalutamide capsules and tablets under fasted and fed conditions, simulations of steady-state concentration-time profiles, and an exposure-response analysis to evaluate the relationship between exposure and clinical efficacy. (b) (4) No changes are proposed to the approved indications or dosing regimen of the currently approved XTANDI capsule formulation.

The results of the pivotal bioequivalence study demonstrated bioequivalence between enzalutamide currently approved capsules and the to-be-marketed (TBM) tablet for single-dose AUCs under fasted and fed conditions. Single-dose Cmax was approximately 28% (90% CI: 67-77) lower for the TBM; however, based on the pharmacokinetic properties of enzalutamide (long half-life and significant accumulation at steady state), differences in the single-dose Cmax is expected to be translated to smaller differences at steady state. Supplementary modeling analysis demonstrated that steady state enzalutamide Cmax after administration of the TBM tablet or capsule meet the bioequivalence criteria regardless of food condition (fasted or fed). Moreover, exposure-response analysis showed that differences in Cmax is unlikely to impact clinical outcomes.

Therefore, the TBM tablet and capsule can be used interchangeably without affecting enzalutamide effectiveness. These improvements in the drug product presentation are anticipated to increase treatment adherence over the long term and enhance health outcomes. The applicant provided adequate pharmacokinetic (PK) evidence from clinical studies in healthy volunteers to support the proposed tablet formulation.

1.3. Benefit-Risk Assessment

[Do not insert text here. Use the table]

Benefit-Risk Summary and Assessment

The results of the pivotal bioequivalence study demonstrated bioequivalence between enzalutamide currently approved capsules and the to-be-marketed (TBM) tablet for single-dose AUCs under fasted and fed conditions. (b) (4) (b) (4) No changes are proposed to the approved indications or dosing regimen of the currently approved enzalutamide capsule formulation. The overall risk/benefit calculus is favorable for this application.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Although 5-year survival rates are very high for men with locally or regionally confined prostate cancer, many men experience recurrences and progression of their prostate cancer, eventually developing castrate resistant disease. Once this disease is metastatic it is no longer curable.	**Castrate resistant prostate cancer is a serious and life-threatenening condition.**
Current Treatment Options	• Enzalutamide is approved for the treatment of castrate resistant prostate cancer and non-metastatic castrate sensitive prostate cancer. • The approved enzalutamide drug product is an immediate-release liquid-filled soft capsule containing 40 mg of enzalutamide. The recommended dose is 160 mg of enzalutamide (4 x 40 mg capsules) administered orally once daily, with or without food.	**Enzalutamide is approved to treat castrate resistant prostate cancer and non-metastatic castrate sensitive prostate cancer at a recommended dose of 160 mg of enzalutamide (4 x 40 mg capsules) administered orally once daily.**
Benefit	• The formulation submitted for review is an immediate-release, film-coated tablet of enzalutamide in 80 and 40 mg strengths. The application is based on the results of a pivotal clinical study to demonstrate bioequivalence between enzalutamide capsules and tablets under fasted and fed conditions, simulations of steady-state concentration-time profiles, and an exposure-response analysis to	**Bioequivalence has been demonstrated between enzalutamide currently approved capsules and the to-be-marketed (TBM) tablet for single-dose AUCs under fasted and fed conditions.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	evaluate the relationship between exposure and clinical efficacy. • The results of the pivotal bioequivalence study demonstrated bioequivalence between enzalutamide currently approved capsules and the to-be-marketed (TBM) tablet for single-dose AUCs under fasted and fed conditions.	
Risk and Risk Management	• The safety profile of enzalutamide including this formulation is acceptable in this indication.	**The safety profile of enzalutamide is acceptable in this indication.**

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable [e.g., Section 6.1 Study endpoints]
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	**Patient experience data was not submitted as part of this application.**			

X _____

Chana Weinstock

2 Therapeutic Context

2.1. Analysis of Condition

Prostate cancer is the second most common cancer in men in the United States after non-melanoma skin cancer.[1] It is also the second leading cause of cancer death among men in 2017 regardless of race or ethnicity per statistics provided by the Centers for Disease Control and Prevention. Early stage localized prostate cancer is usually managed with targeted definitive therapy which consists of some combination of prostatectomy, radiation to the prostate, prostate bed and/or regional lymph nodes, and androgen suppression therapy. Although 5-year survival rates are very high for men with locally or regionally confined prostate cancer, many men experience recurrences and progression of their prostate cancer eventually developing castrate resistant disease.[2]

The median age at diagnosis is 66 years old and the median age at death is 80 years old. With many patients being older adults with multiple comorbidities, management of prostate cancer involves treatment of disease while considering the barriers to care that can arise in an older patient population such as frailty, difficulty swallowing and polypharmacy. To address this issue, the sponsor proposes a new formulation of a smaller film-coated tablet in addition to a new dosage of 80 mg to decrease the daily required pill intake.

2.2. Analysis of Current Treatment Options

Typical first-line therapies for CRPC are prescribed based on extent of disease (nonmetastatic vs. metastatic) and consist of continuation of androgen deprivation with second generation androgen receptor inhibitors and/or chemotherapy. There has been significant growth in the treatment landscape for castrate-resistant prostate cancer.

Table 1: Summary of Medical Armamentarium Relevant to Castrate Resistant Prostate Cancer

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments [Combine by Pharmacologic Class, if relevant]						
Enzalutamide	mCRPC	2012	160 mg daily by mouth	**AFFIRM** (prior chemo) mOS HR 0.63 (0.53, 0.75)	Significant adverse events for drugs in this class include: - bone fracture	

	nmCRPC	2018		**PREVAIL** (no prior chemo) mrPFS HR 0.17 (0.14, 0.21) **TERRAIN** (no prior chemo) mrPFS HR 0.60 (0.43, 0.83) **PROSPER** MFS HR 0.29 (0.24, 0.35)	- fall - fatigue/asthenic conditions - weight decreased - cardiovascular disorders - hypertension - vasodilatation and flushing - diabetes mellitus and hyperglycemia - mental impairment disorders - depressed mood disorders - breast disorders/gynecomastia	
Abiraterone Acetate	mCRPC	2011	1000 mg twice daily by mouth	**COU-AA-301** (prior chemo) mOS HR 0.646 (0.543, 0.768) **COU-AA-302** (no prior chemo) mOS HR 0.81 (0.70, 0.93)		
Apalutamide	nmCRPC	2018	240 mg daily by mouth	**SPARTAN** MFS HR 0.28 (0.23, 0.35)		
Darolutamide	nmCRPC	2019	600 mg twice daily by mouth	**ARAMIS** MFS HR 0.41 (0.34, 0.50)		Noted to have improved AE profile and fewer neurological AEs
Other Treatments – [Combine by Pharmacologic Class, if relevant]						
Docetaxel	CRPC	2004	75 mg/m^2 every 3 weeks with 5 mg prednisone twice daily	mOS HR 0.761 (0.619, 0.936)	Hepatotoxicity, neutropenia, hypersensitivity reactions, fluid retention, peripheral neuropathy	
Cabazitaxel	CRPC	2010	25 mg/m^2 every 3 weeks with 10 mg prednisone daily	mOS HR 0.70 (0.59, 0.83)	Neutropenic deaths, severe hypersensitivity	

CRPC – castrate-resistant prostate cancer, nmCRPC – non-metastatic prostate cancer, mOS – median overall survival, MFS – metastasis free survival, HR – hazard ratio

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Enzalutamide was initially approved in 2012 for the treatment of patients with castrate-resistant prostate cancer who have previsouly received docetaxel. The indication of enzalutamide has since been expanded to include the treatment of castrate-resistant prostate cancer and non-metastatic castrate-sensitive prostate cancer .

3.2. Summary of Presubmission/Submission Regulatory Activity

Activity	Date	Comment
Approval for treatment of patients with castrate-resistant prostate cancer who have previously received docetaxel under NDA 203415	August 31, 2012	
Type B, Pre-NDA	October 28, 2015	Meeting discussion of proposed registrational package for new formulation
[redacted]		(b) (4)
Approval for the treatment of non-metastatic castrate-resistant prostate cancer under NDA 203415	July 13, 2018	
Type B, Pre-NDA	April 26, 2019	WRO

Approval for treatment of non-metastatic castrate-sensitive prostate cancer under NDA 203415	December 16, 2019	
Submission of original NDA 213674 for tablet reformulation and new dosage	October 30, 2019	

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The drug product for this application is commercially available and there were no clinical studies conducted for this NDA. No clinical site inspections were performed.

4.2. Product Quality

As noted in the review by Dr. Xiao Hong Chen (Technical Lead), the application is based on the results of a pivotal clinical study to demonstrate bioequivalence between Enzalutamide Capsules and Tablets for single-dose AUC under fasted and fed conditions. The drug substance is sourced from the same supplier as that for NDA #203415. (b) (4)

The product quality team's reviews of drug substance, drug product, manufacturing and facility, and biopharmaceutics found all to be adequate.

Product quality review team recommends approval of NDA 213674 based on the adequate CMC information submitted in the NDA and acceptable facilities status.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not Applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The Applicant did not submit any new nonclinical pharmacology/toxicology study reports in support of this NDA submission. Access to nonclinical data for enzalutamide was provided by cross-reference to previously submitted nonclinical study reports submitted in support of NDA 203415 for Xtandi (enzalutamide) capsules. The data were considered adequate to support this NDA submission for the film-coated tablet formulation of Xtandi.

This NDA for Xtandi (enzalutamide) tablets is recommended for approval from the perspective of the Pharmacology/Toxicology discipline.

5.2. Referenced NDAs, BLAs, DMFs

NDA 203415

X	X
Haw-Jyh Chiu	Tiffany Ricks
Primary Reviewer	Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

Enzalutamide (XTANDI®) is an approved androgen receptor (AR) inhibitor for the treatment of patients with metastatic and nonmetastatic castration-resistant prostate cancer (CRPC). The approved enzalutamide drug product is an immediate-release liquid-filled soft capsule containing 40 mg of enzalutamide. The recommended dose is 160 mg of enzalutamide (4 x 40 mg capsules) administered orally once daily, with or without food.

In the current submission, the applicant seeks the full approval of a newly developed immediate-release, film-coated tablet of enzalutamide in 80 and 40 mg strengths to the approved liquid-filled 40 mg soft capsule for oral use in the currently marketed indications. No changes are proposed to the approved indications or dosing regimen of the currently approved XTANDI capsule formulation. The application is based on the results of a pivotal clinical study to demonstrate bioequivalence between enzalutamide capsules and tablets under fasted and fed conditions, simulations of steady-state concentration-time profiles, and an exposure-response analysis to evaluate the relationship between exposure and clinical efficacy.

The results of the pivotal bioequivalence study demonstrated bioequivalence between enzalutamide currently approved capsules and the to-be-marketed (TBM) tablet for single-dose AUCs under fasted and fed conditions. Single-dose C_{max} was approximately 28% (90% CI: 67-77) lower for the TBM; however, based on the pharmacokinetic properties of enzalutamide (long half-life and significant accumulation at steady state), differences in the single-dose C_{max} is expected to be translated to smaller differences at steady state. Supplementary modeling analysis demonstrated that steady state enzalutamide C_{max} after administration of the TBM tablet or capsule meet the bioequivalence criteria regardless of food condition (fasted or fed). Moreover, exposure-response analysis showed that differences in C_{max} is unlikely to impact clinical outcomes. Therefore, the TBM tablet and capsule can be used interchangeably without affecting enzalutamide effectiveness.

These improvements in the drug product presentation are anticipated to increase treatment adherence over the long term and enhance health outcomes. The applicant provided adequate pharmacokinetic (PK) evidence from clinical studies in health volunteers to support the proposed tablet formulation.

6.1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 213674 submission. This NDA is approvable from a clinical pharmacology perspective.
The key review issues with specific recommendations and comments are summarized below:

Review Issue	Recommendations and Comments
Evidence of PK bioequivalence (BE) between the commercial capsules and the proposed commercial tablets.	Phase 1 trial, Study 9785-CL-0014, demonstrated bioequivalence between enzalutamide currently approved capsules and TBM tablet for single-dose AUCs under fasted and fed conditions. Single-dose C_{max} was approximately 28% (90% CI: 67-77) lower for the TBM tablet than the capsule under fasted conditions and approximately 10% (90% CI: 80-101) lower under fed conditions.
Simulations of steady-state concentration-time profiles and an exposure-response analysis.	Based on simulations of steady-state concentration-time profiles of data from Study 9785-CL-0014, geometric mean ratios of simulated steady state C_{max} was approximately 9% (90% CI: 87-95) lower for the TBM tablet than the capsule under fasted conditions and approximately 8% (90% CI: 84-102) lower under fed conditions. Exposure-response analysis shows that differences in C_{max} is unlikely to impact clinical outcomes.
Evidence of the proposed commercial tablets can be taken with or without food.	A Phase 1 trial (Study 9785-CL-0014) demonstrated no clinically significant food effect for the proposed TBM tablets.

6.1.2 Post-Marketing Requirements and Commitments

None.

6.2. Comprehensive Clinical Pharmacology Review

6.2.1 General Dosing

The recommended dose is 160 mg of enzalutamide (4 x 40 mg capsules) administered orally once daily, with or without food, with the possibility of dose reduction to 120 or 80 mg should toxicity or intolerable side effects occur. If a patient experiences a ≥ grade 3 toxicity or an intolerable side effect, dosing may be withheld for 1 week or until symptoms improve to ≤ grade 2, after which dosing may resume at the same (160 mg) or a reduced (120 or 80 mg) dose, if warranted. No changes are proposed to the approved indications or dosing regimen of the currently approved XTANDI capsule formulation.

6.2.2 Clinical Pharmacokinetics

Following oral administration of enzalutamide at 160 mg in CRPC patients, the median T_{max} is 1 hour (range 0.5 to 3 hours) and the mean $T_{1/2}$ is ~ 6 days (range 2.8 to 10.2 days). With daily dosing regimen, enzalutamide steady state is achieved by Day 28, and enzalutamide

accumulates ~ 8.3-fold relative to a single dose. Daily fluctuations in enzalutamide plasma concentrations are low (mean peak-to-trough ratio of 1.25). At steady state, enzalutamide shows approximately dose proportional pharmacokinetics over the daily dose range of 30 to 360 mg.

The human mass balance trial showed that enzalutamide is primarily eliminated by hepatic metabolism. *In vitro*, enzalutamide is metabolized by CYP2C8 and CYP3A4. Enzalutamide has two major metabolites in human, N-desmethyl enzalutamide (M2; active, similar potency to enzalutamide) and a carboxylic acid metabolite (inactive). *In vivo*, the sum of enzalutamide and M2 exposure was increased by 2.2-fold and 1.3-fold when it was co-administered with gemfibrozil (strong CYP2C8 inhibitor) or itraconazole (strong CYP3A4 inhibitor), respectively. A dose reduction is not needed in patients with mild or moderate renal impairment, or mild or moderate hepatic impairment.

6.2.3 BE/BA evaluation between the commercial capsules and the proposed tablets

A total of 5 clinical biopharmaceutic studies support this marketing application and provide data on 5 development tablets (Tablets A, B, C, E and F), as well as the to-be-marketed (TBM) tablet. The TBM tablet had the same composition as Tablet E (b) (4) These studies assessed the pharmacokinetics of enzalutamide after a single 160 mg dose or after multiple-dose administration at 160 mg/day. All bioanalytical methods supporting the clinical studies in this marketing application were previously summarized in NDA 203415.

6.2.3.1 Study 9785-CL-0014

An open-label, 2-period, crossover bioequivalence study that compared the capsule and the TBM tablet following a single 160 mg dose under fasted and fed conditions in healthy male subjects (Figure 1). The results from this study showed that, the 90% confidence interval (CI) for $AUC_{0\text{-}72h}$, AUC_{last} and AUC_{inf} were within the bioequivalence criteria limits (80%-125%), and the 90% CI for C_{max} were below the lower boundary for bioequivalence (Table 1 and Figure 2). Under fasted conditions, the median T_{max} occurred 1 hour later with the tablet than with the capsule (2 vs. 1 hours). Under fed conditions, the median T_{max} of the tablet was the same as that of the capsule (3 vs. 2.99 hours). Exploratory assessment suggested that the exposure of N-desmethyl enzalutamide (M2) (AUC_{last}, AUC_{inf} and C_{max}) appears not to be affected by formulation or food condition.

The TBM tablet contains 2 dose strengths of 40 mg and 80 mg. (b) (4) There are no clinical study results for the proposed 40 mg tablets in this submission. To support a biowaiver for the TBM 40 mg tablet, dissolution profiles of the 80 and 40 mg tablets were compared at pH (b) (4). Please refer to the Biopharmaceutics review on the in vitro assessment.

Figure 1. 9785-CL-0014 Study schematic

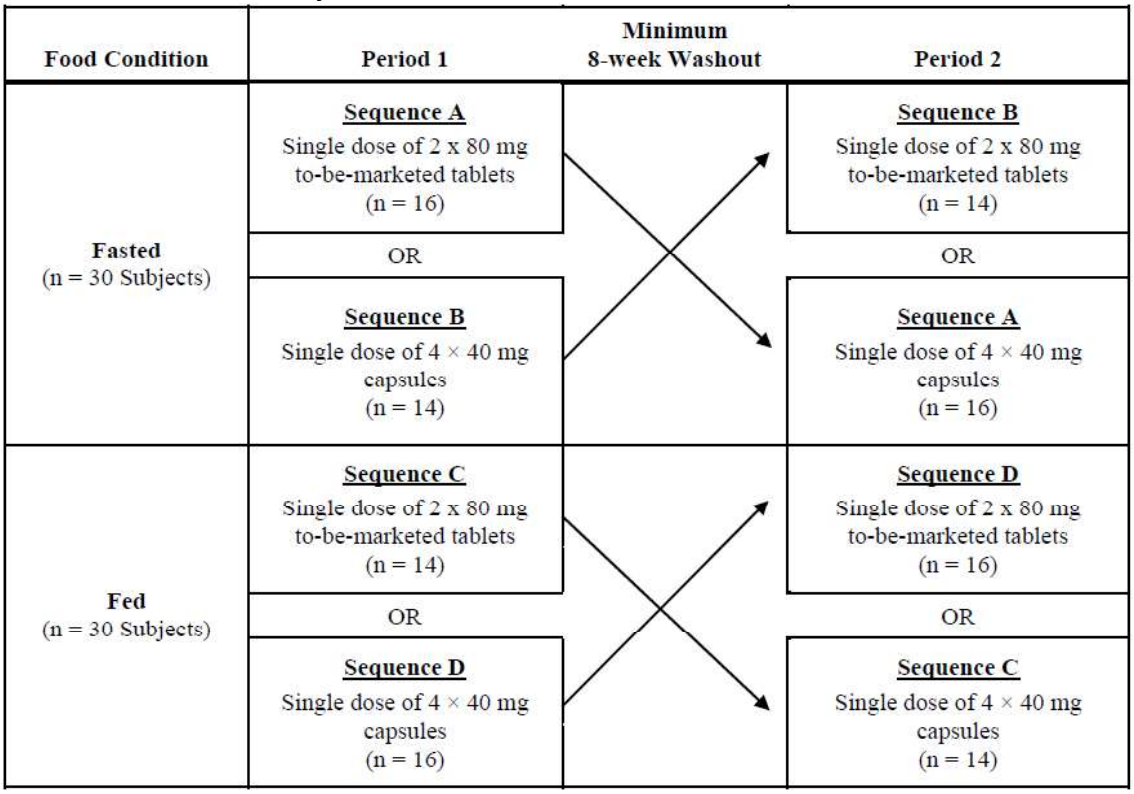
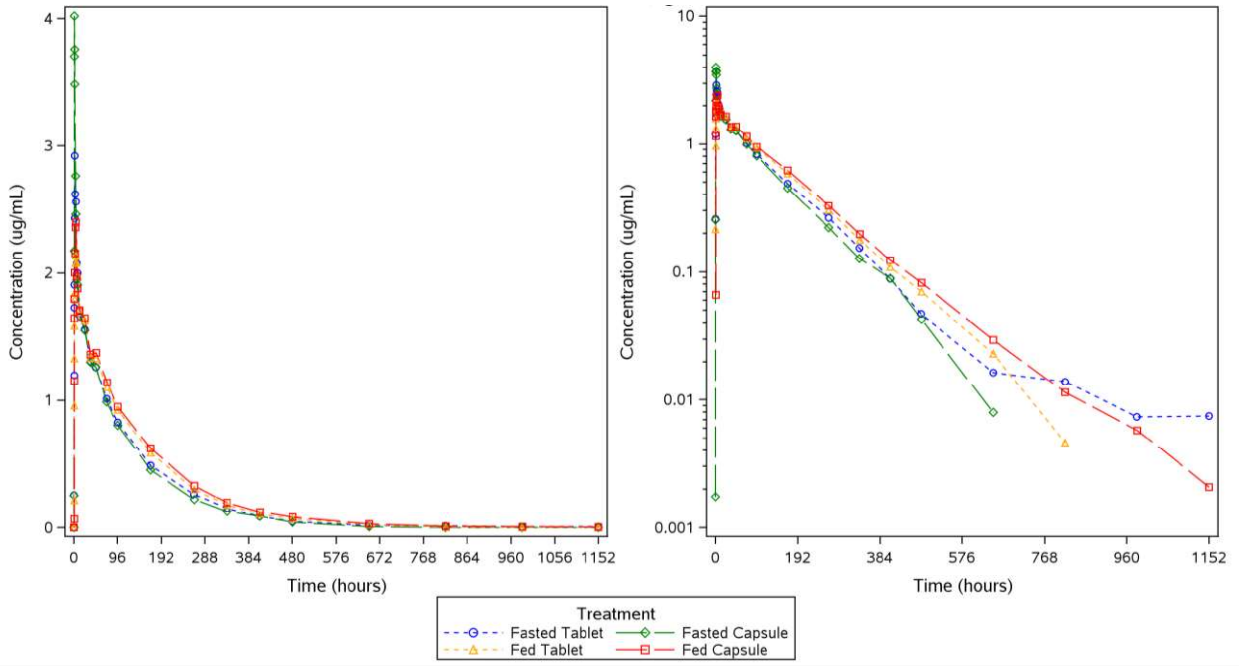


Table 1. Statistical summary of single-dose formulation comparison (TBM Tablet versus Capsule) under fasted and fed conditions

Fasted Conditions					
Enzalutamide Pharmacokinetic Parameters (Units)	Geometric Means		Ratio (Test/Reference) (%)	90% CI for Ratio (%)	
	To-be-marketed Tablet (Test)	Capsule (Reference)		Lower	Upper
n	29	27	--	--	--
AUC_{0-72h} (µg·h/mL)	102	105	97.26	95.13	99.43
AUC_{last} (µg·h/mL)	225	223	100.94	96.26	105.84
AUC_{inf} (µg·h/mL)	235	232	101.17	96.77	105.77
C_{max} (µg/mL)	3.39	4.71	71.82	66.75	77.28
t_{max} (h)†	2.00 [0.50–6.02]	1.00 [0.50–3.02]	--	--	--
Fed Conditions					
Enzalutamide Pharmacokinetic Parameters (Units)	Geometric Means		Ratio (Test/Reference) (%)	90% CI for Ratio (%)	
	To-be-marketed Tablet (Test)	Capsule (Reference)		Lower	Upper
n	28	28	--	--	--
AUC_{0-72h} (µg·h/mL)	102	106	95.56	88.35	103.35
AUC_{last} (µg·h/mL)	250	267	93.56	84.34	103.78
AUC_{inf} (µg·h/mL)	259	276	93.75	85.25	103.11
C_{max} (µg/mL)	2.68	2.97	90.01	79.94	101.36
t_{max} (h)†	3.00 [0.50–8.03]	2.99 [0.50–8.00]	--	--	--

Figure 2. Mean concentration-time profiles of enzalutamide by formulation and food condition



6.2.3.2 Study MDV3100-05

A phase 1, single-center, open-label, randomized, 2-period relative bioavailability and food-effect study following a single 160 mg dose of enzalutamide (Tablet A or the capsule) in healthy male subjects. The formulation comparison of Tablet A versus capsule under both fasted and fed conditions showed that the 90% CI for AUC_{last} and AUC_{inf} were within the bioequivalence criteria limits, and the 90% CI for C_{max} were below the lower boundary for bioequivalence (Table 2).

6.2.3.3 Study 9785-CL-0003

A phase 1, multicenter, open-label, randomized, 1-period relative bioavailability and food-effect study of enzalutamide 160 mg/day (Tablet A or the capsule) in male patients with CRPC. The comparison of Tablet A versus the capsule under both fasted and fed conditions showed that the 90% CI for AUC_{tau} and C_{min} were within the bioequivalence criteria limits and the 90% CI for C_{max} were below these limits (Table 2). Exploratory assessment to determine whether Tablet A differs from the capsules with regard to steady-state exposure to M2 metabolite showed that AUC_{tau}, C_{max} and C_{min} of metabolite were within the bioequivalence criteria limits under both fasted and fed conditions.

6.2.3.4 Study 9785-CL-0010

A phase 1, single-center, open-label, randomized, parallel group, relative bioavailability study following a single 160 mg dose of enzalutamide in healthy male subjects. The objectives were to compare Tablet B and Tablet C to the capsule under fasted conditions. The comparison of

Tablet B versus the capsule showed that the 90% CI for AUC_{last} and AUC_{inf} were within the bioequivalence criteria limits, and the 90% CI for Cmax was below the lower boundary for bioequivalence (Table 2). The comparison of Tablet C versus capsule showed that the 90% CI for AUC_{last} and AUC_{inf} extended slightly above the upper boundary for bioequivalence criteria limits, and the 90% CI for C_{max} extended below the lower boundary for bioequivalence (Table 2).

6.2.3.5 Study MDV3100-19

A phase 1, single-center, open-label, randomized, parallel group, relative bioavailability study following a single 160 mg dose of enzalutamide in healthy male subjects. The objectives were to compare Tablet E and Tablet F to the capsule under fasted conditions. The comparisons of both Tablet E and Tablet F versus the capsule showed that the 90% CI for AUC_{last} and AUC_{inf} were within the bioequivalence criteria limits, and the 90% CI for C_{max} extended below the lower boundary for bioequivalence (Table 2).

Table 2. Summary of pharmacokinetic results in biopharmaceutic studies comparing tablets and capsules

Summary of AUC_{inf} (µg·h/mL) Geometric Mean Values					
Tablet	**Food Condition**	**Tablet**	**Capsule**	**Tablet/Capsule Ratio (%)**	**Equivalent†**
Tablet A	Fasted	262 (n = 26)	280 (n = 26)	93.65	Yes
Tablet A	Fed	271 (n = 30)	276 (n = 30)	98.26	Yes
Tablet B	Fasted	232 (n = 18)	236 (n = 18)	98.43	Yes
Tablet C	Fasted	260 (n = 18)	236 (n = 18)	110.12	No
Tablet E	Fasted	275 (n = 15)	298 (n = 14)	92.44	Yes
Tablet F	Fasted	294 (n = 15)	298 (n = 14)	98.66	Yes
Summary of C_{max} (µg/mL) Geometric Mean Values					
Tablet	**Food Condition**	**Tablet**	**Capsule**	**Tablet/Capsule Ratio (%)**	**Equivalent†**
Tablet A	Fasted	2.94 (n = 26)	5.15 (n = 26)	57.23	No
Tablet A	Fed	2.83 (n = 30)	3.61 (n = 30)	78.20	No
Tablet B	Fasted	2.48 (n = 18)	4.63 (n = 19)	53.60	No
Tablet C	Fasted	3.78 (n = 18)	4.63 (n = 19)	81.55	No
Tablet E	Fasted	4.41 (n = 16)	5.42 (n = 14)	81.34	No
Tablet F	Fasted	4.51 (n = 15)	5.42 (n = 14)	83.19	No
Summary of t_{max} (h) Median Values					
Tablet	**Food Condition**	**Tablet**	**Capsule**	**Tablet - Capsule (h)**	
Tablet A	Fasted	4.00 (n = 27)	1.02 (n = 27)	2.98	
Tablet A	Fed	4.00 (n = 30)	2.00 (n = 30)	2.00	
Tablet B	Fasted	1.00 (n = 18)	1.02 (n = 19)	-0.02	
Tablet C	Fasted	1.25 (n = 18)	1.02 (n = 19)	0.23	
Tablet E	Fasted	2.52 (n = 16)	1.50 (n = 14)	1.02	
Tablet F	Fasted	2.00 (n = 15)	1.50 (n = 14)	0.50	

The results of the single-dose relative bioavailability studies were consistent in showing that the tablet formulations were comparable to the capsule in the extent of absorption (AUC) and had lower rates of absorption (C_{max} was lower and T_{max} tended to occur later) (Table 2). These findings could be explained by the fact that the commercially available capsule is a liquid-filled soft capsule that releases fully dissolved enzalutamide into the gastrointestinal tract, thereby eliminating the need for dissolution prior to absorption and promoting high oral bioavailability. Enzalutamide exhibits limited aqueous solubility and high permeability across Caco-2 monolayers, so dissolution of the drug substance is considered the rate-limiting step for

absorption. Across all of bioavailability studies, inter-subject variability (expressed as coefficient of variation [%CV]) for AUC_{last}, AUC_{inf} and C_{max} was similar for Tablet formulations (Tablet A, B, C, E, F and TBM) and the capsule formulations, with values generally below approximately 30% under fasted and fed conditions. Thus, variability of the primary pharmacokinetic parameters was low and did not appear to be affected by formulation or food.

6.2.4 Food Effect

Food-effect comparisons of the TBM tablet and capsule were nested within the study 9785-CL-0014 design (Figure 1). For fasted conditions, study drug was administered with 240 mL water after an overnight fast (no caloric intake) of at least 10 hours; no fluid intake was allowed for at least 1 hour before the dose. For fed conditions, subjects underwent an overnight fast (no caloric intake) of at least 10 hours and then received a standard high-fat, high-calorie breakfast; the meal had to be consumed within 30 minutes and study drug was administered with 240 mL water 30 minutes after the start of the meal. For both fasted and fed conditions, no fluid intake was allowed for at least 1 hour after dose administration. In addition, no food was allowed until 4 hours after dose administration, when subjects received a standardized lunch/meal.

The food-effect comparison (fed versus fasted conditions) for the TBM tablet showed that the GMR and 90% CI for AUC_{last}, AUC_{inf} and C_{max} were 111% (90% CI: 96.8%, 127.3%), 110.6% (90% CI: 96.6%, 126.7%) and 79.2% (90% CI: 68.6%, 91.4%), respectively. The 90% CI for AUC_{last} and AUC_{inf} extended slightly above the upper boundary of the bioequivalence criteria limits, the 90% CI for C_{max} extended below the lower boundary (Table 3). The median T_{max} occurred 1 hour later with fed conditions than with fasted conditions (3 vs. 2 hours).

Similar food effect on AUC_{last}, AUC_{inf} and C_{max} was observed for the capsule formulation (Table 3). Notably, the GMR values for the tablets were closer to 100%; therefore, the extent of food effect was smaller for the TBM tablets than for the capsules.

Table 3. Statistical summary of single-dose food-effect comparison for To-be-marketed tablet and capsule

Enzalutamide Pharmacokinetic Parameters (Units)	Geometric Means		Ratio (Test/Reference) (%)	90% CI for Ratio (%)	
	To-be-marketed Tablet - Fed (Test)	To-be-marketed Tablet - Fasted (Reference)		Lower	Upper
n	28	28	--	--	--
AUC_{0-72h} (µg·h/mL)	102	102	99.24	88.91	110.76
AUC_{last} (µg·h/mL)	250	225	111.01	96.78	127.33
AUC_{inf} (µg·h/mL)	259	234	110.64	96.59	126.74
C_{max} (µg/mL)	2.68	3.38	79.18	68.58	91.43
t_{max} (h)†	3.00 [0.50–8.03]	2.00 [0.500–6.02]	--	--	--
Enzalutamide Pharmacokinetic Parameters (Units)	**Geometric Means**		**Ratio (Test/Reference) (%)**	**90% CI for Ratio (%)**	
	Capsule - Fed (Test)	**Capsule - Fasted (Reference)**		**Lower**	**Upper**
n	28	27	--	--	--
AUC_{0-72h} (µg·h/mL)	106	104	102.63	94.79	111.12
AUC_{last} (µg·h/mL)	267	220	121.44	108.15	136.36
AUC_{inf} (µg·h/mL)	276	226	122.08	108.35	137.54
C_{max} (µg/mL)	2.97	4.70	63.34	56.76	70.69
t_{max} (h)†	NC	NC	NC	NC	NC

The results of food effect analysis from pivotal BE study 9785-CL-0014 were consistent with the findings from previous food effect study included in original NDA submission (Study MDV3100-05). Study MDV3100-05 (section 2.1.2) showed that a high fat meal reduces the rate of enzalutamide absorption (30% reduction in C_{max}), but the extent of absorption (AUC) is not changed, this effect was considered to be not clinically meaningful.

The current labeling recommendation for capsule administration is to administered enzalutamide capsule with or without food. This recommendation based on the findings of study MDV3100-05 and the phase 3 clinical protocols that allowed the administration of enzalutamide capsule without regards to food. Overall, these results support the dosing recommendation of enzalutamide TBM tablets with or without food.

6.2.5 Simulation of the Steady State Pharmacokinetics

In the pivotal BE study 9785-CL-0014, the observed single-dose C_{max} did not meet bioequivalence criteria. However, due to rapid absorption and a long $T_{1/2}$ (~ 6 days in patients), difference in enzalutamide C_{max} after a single dose is expected to translate to a smaller difference in C_{max} after once-daily dosing to steady state. Moreover, analyses based on steady-state exposure parameters are appropriate for enzalutamide because of its mechanism of action and clinical use that targets long-term endpoints such as overall survival (OS).

In the current submission, supplemental pharmacokinetic modeling and simulation analyses were performed to show that the TBM tablet is bioequivalent to the capsule at steady state (after multiple dosing of 160 mg/day). Nonparametric superposition was applied to single-dose data from the pivotal bioequivalence study (9785-CL-0014) to predict steady state pharmacokinetic profiles of enzalutamide for the tablet and capsule formulations. Steady-state PK profiles were simulated for after once-daily administration from Day 1 to Day 56 under fasted and fed conditions using the nonparametric superposition (Figure 3). A summary of the simulated multiple-dose pharmacokinetic parameters for the TBM tablet and the capsule under fasted and fed is provided in Table 4. While the observed single-dose data showed equivalence of AUC but not C_{max}, the simulated multiple-dose data showed that the TBM tablet is predicted to be bioequivalent to the capsule for both AUC and C_{max} with once daily dosing to steady state under fasted and fed conditions.

Figure 3. Predicted enzalutamide PK profiles for capsule and TBM tablet 160 mg/day for 56 days

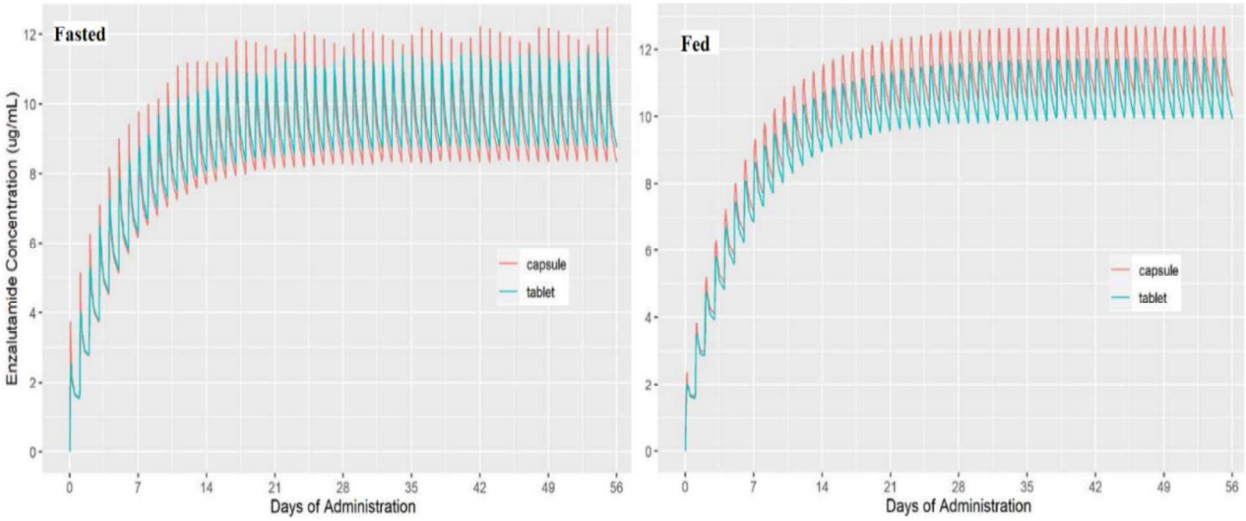


Table 4. Statistical comparison of the TBM tablet versus capsule based on observed single-dose and simulated multiple-dose data

AUC† (µg·h/mL) Geometric Means					
Regimen	**Food Condition**	**Tablet (Test)**	**Capsule (Reference)**	**Ratio (Test/Reference) (%)**	**90% CI for Ratio (%)**
Single-dose	Fasted	235 (n = 29)	232 (n = 27)	101.17	96.77–105.77
Single-dose	Fed	259 (n = 28)	276 (n = 28)	93.75	85.25–103.11
Multiple-dose	Fasted	235 (n =29)	232 (n = 27)	101.19	96.75–105.83
Multiple-dose	Fed	259 (n=28)	276 (n = 28)	93.70	85.13–103.12
C_{max} (µg/mL) Geometric Means					
Regimen	**Food Condition**	**Tablet (Test)**	**Capsule (Reference)**	**Ratio (Test/Reference) (%)**	**90% CI for Ratio (%)**
Single-dose	Fasted	3.39 (n = 29)	4.71 (n = 27)	71.82	66.75–77.28
Single-dose	Fed	2.68 (n = 28)	2.97 (n = 28)	90.01	79.94–101.36
Multiple-dose	Fasted	12.09 (n = 29)	13.29 (n = 27)	90.94	87.06–95.00
Multiple-dose	Fed	12.43 (n = 28)	13.47 (n = 28)	92.30	83.92–101.51

To assess the validity of nonparametric superposition analysis, a study compared the observed and predicted values for AUC_{tau}, C_{max} and C_{min} for development Tablet A, a tablet formulation that had been compared to the capsule in a single-dose relative bioavailability study (MDV3100-05), as well as a multiple-dose relative bioavailability study (9785-CL-0003). The results of the validation study showed that nonparametric superposition accurately predicts the steady-state pharmacokinetics of enzalutamide from single-dose relative bioavailability data (Table 5).

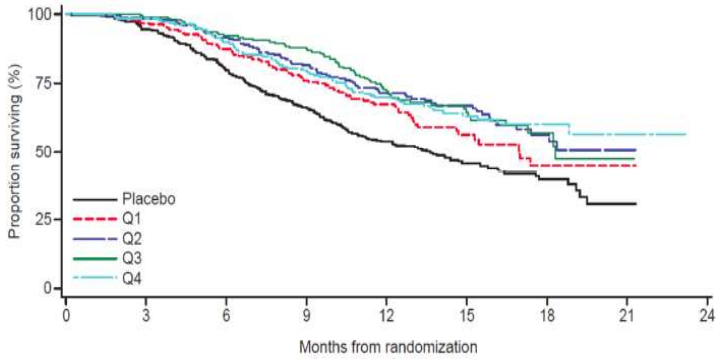
Table 5. Summary of observed and predicted multiple-dose parameters for tablet A and capsule under fasted conditions

Enzalutamide Pharmacokinetic Parameters (Units)	Geometric Means		Ratio (Test/Reference) (%)	90% CI for Ratio (%)	
	Tablet A (Test)	Capsule (Reference)		Lower	Upper
Observed in Multiple-dose Study 9785-CL-0003					
AUC_{tau} (µg.h/mL)	290	318	91.19	82.63	100.63
C_{max} (µg/mL)	13.9	16.9	82.48	74.28	91.60
C_{min} (µg/mL)	12.4	12.8	97.04	85.55	110.07
Predicted from Single-dose Data in Study MDV3100-05					
AUC_{tau} (µg.h/mL)	262	279	94.03	81.97	107.86
C_{max} (µg/mL)	12.7	15.4	82.81	73.53	93.28
C_{min} (µg/mL)	9.9	10.3	96.53	83.39	111.75

6.2.6 Exposure Response Relationship

The original marketing application 9 NDA 203415 included exposure-response analyses of data from the phase 3 study CRPC2, in which a total of 1199 patients with mCRPC were randomized 2:1 to 160 mg/day enzalutamide (n = 800) or placebo (n = 399). The analysis of exposure-response between enzalutamide C_{min} values and efficacy showed a clinically meaningful and statistically significant prolongation of survival in enzalutamide arm, as reflected in the 37% decrease in the risk of death for patients receiving enzalutamide compared with those receiving placebo (Figure 4). However, pairwise tests showed no difference in the risk of events among active treatment C_{min} quartiles. Thus, the active treatment C_{min} quartile groups were uniformly beneficial relative to placebo.

Figure 4. Comparison of Kaplan-Meier exposure-response analysis based on C_{min} for enzalutamide versus OS with the capsule formulation in Study CRPC2



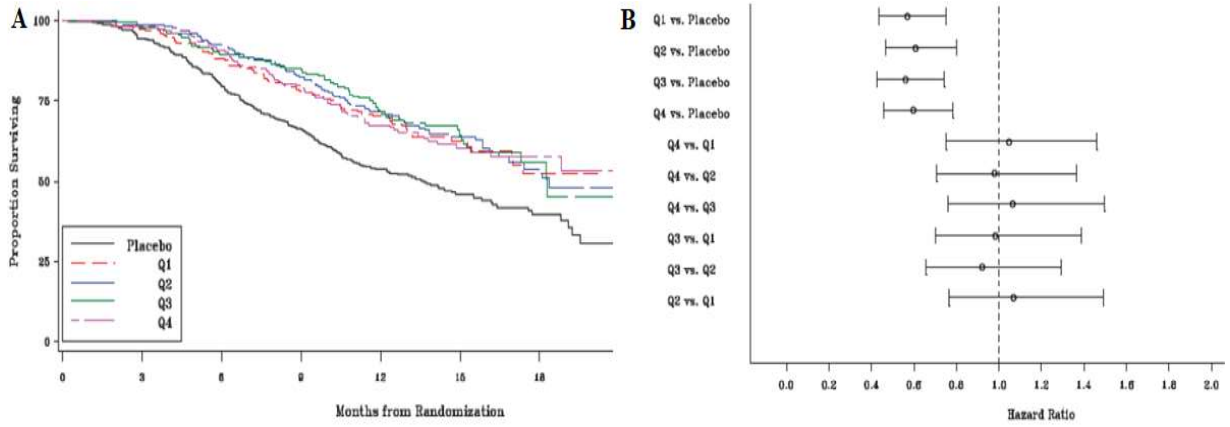
To further the understanding of whether C_{max} differences between the TBM tablet and capsule formulations may have an impact on enzalutamide effectiveness, an exposure-response analysis was conducted for steady-state C_{max}. The methods were identical to those of the analysis based on C_{min} that have been submitted and reviewed in the original NDA application. C_{max} values in individual patients were estimated by population pharmacokinetic modeling previously established in the original NDA application. The predicted C_{max} values at steady state for enzalutamide were within the range of C_{max} values observed in clinical studies (Table 6). These findings indicate that the population PK model was able to predict acceptable estimates fo enzalutamide steady state C_{max} values that could be used for exposure response analysis.

Table 6. Comparison of steady state C_{max} values for capsules versus the TBM tablet.

	Steady-State C_{max} (µg/mL) in Patients			
	Observed			Generated by PK Modeling and Simulation
Study[a]	S-3100-1-01[b]	9785-CL-0003[c]	9785-CL-0007	CRPC2
n	23	24	14	756
Minimum	7.35	13.60	11.80	5.21
25% Quartile	13.65	14.45	14.10	12.28
Median	15.79	15.95	15.55	13.74
75% Quartile	17.60	17.35	18.00	15.24
Maximum	23.47	22.10	28.00	23.07
Mean	15.43	16.35	16.59	13.88
95% CI of Mean	13.91 - 16.94	15.42 – 17.29	14.38 - 18.79	13.70 - 14.06

The predicted C_{max} values were use in the exposure response analysis for enzalutamide efficacy using the previously used model for the C_{min}. Kaplan-Meier plots show a clear separation in the placebo group from all curves associated with enzalutamide C_{max} groups (Figure 5A). However, similar to C_{min}, there were no significant differences in rates of survival among the active treatment C_{max} quartiles when compared to each other (Figure 5B).

Figure 5. (A) Comparison of Kaplan-Meier ER analysis based on C_{max} versus OS in Study CRPC2. (B) Cox proportional hazard model ER analysis based on C_{max} versus OS in Study CRPC2.



The similarity in the findings between using the C_{min} versus C_{max} as exposure metric for the exposure response analysis could be explained by the mean peak-to-trough ratio for enzalutamide of 1.25, so the steady-state C_{max} concentrations are only slightly higher than C_{min}. The lack of clear exposure response relationship between different predicted C_{max} quartiles and enzalutamide efficacy supports the premise that small changes in steady state enzalutamide C_{max} between the TBM tablet and capsule formulations will not have effect on enzalutamide efficacy. In addition, preliminary PK/PD cell-growth model included in in the original NDA 203415 submission, had estimated EC_{50} value for inhibition of PSA response to be < 100 ng/mL, a value that is lesser by at least an order of magnitude than the lowest observed enzalutamide concentration at steady state with 160 mg/day dose. This PK/PD analysis give additional evidence that enzalutamide pharmacological activity as represented by inhibition of PSA response is at maximum at C_{max} values observed with dose of 160 mg/day dose.

6.3 Outstanding Issues

None.

6.4 Summary of Labeling Recommendations

The applicant proposed clinical pharmacology related labeling changes are in the left column and the FDA proposed revisions are in the right column. FDA proposed labeling changes were conveyed to the applicant on May 2020. The applicant agreed with all the changes.

The Applicant's Proposed Labeling Changes	FDA Proposed Labeling Changes
12.3 Pharmacokinetics **……** **Absorption** Following oral administration of XTANDI capsules (160 mg daily) in patients with metastatic CRPC, the median time to reach maximum plasma enzalutamide concentrations (C_{max}) is 1 hour (range 0.5 to 3 hours). At steady-state, the plasma mean C_{max} values for enzalutamide and N-desmethyl enzalutamide are 16.6 µg/mL (23% CV) and 12.7 µg/mL (30% CV), respectively, and the plasma mean predose trough values are 11.4 µg/mL (26% CV) and 13.0 µg/mL (30% CV), respectively. (b) (4) [redacted] With the daily dosing regimen, enzalutamide steady-state is achieved by Day 28, and enzalutamide accumulates approximately 8.3-fold relative to a single dose. Daily fluctuations in enzalutamide plasma concentrations are low (mean peak-to-trough ratio of 1.25). At steady-state, enzalutamide showed approximately dose proportional pharmacokinetics over the daily dose range of 30 to 360 mg. A single 160 mg oral dose of XTANDI was administered to healthy volunteers with a high-fat meal or in the fasted condition. A high-fat meal did not alter the AUC to enzalutamide or N-desmethyl enzalutamide.	**12.3 Pharmacokinetics** **……** **Absorption** Following oral administration of XTANDI capsules (160 mg daily) in patients with metastatic CRPC, the median time to reach maximum plasma enzalutamide concentrations (C_{max}) is 1 hour (range 0.5 to 3 hours). At steady-state, the plasma mean C_{max} values for enzalutamide and N-desmethyl enzalutamide are 16.6 µg/mL (23% CV) and 12.7 µg/mL (30% CV), respectively, and the plasma mean predose trough values are 11.4 µg/mL (26% CV) and 13.0 µg/mL (30% CV), respectively. Following a single dose administration of 160 mg enzalutamide in healthy male volunteers, enzalutamide extent of absorption (AUC) was comparable between XTANDI tablet and XTANDI capsule, but the mean C_{max} was 10%-28% lower than that of XTANDI capsules. The steady-state pharmacokinetic profiles (AUC and C_{max}) of enzalutamide and N-desmethyl enzalutamide are similar for XTANDI tablet and XTANDI capsule. With the daily dosing regimen, enzalutamide steady-state is achieved by Day 28, and enzalutamide accumulates approximately 8.3-fold relative to a single dose. Daily fluctuations in enzalutamide plasma concentrations are low (mean peak-to-trough ratio of 1.25). At steady-state, enzalutamide showed approximately dose proportional pharmacokinetics over the daily dose range of 30 to 360 mg. A single 160 mg oral dose of XTANDI was administered to healthy volunteers with a high-fat meal or in the fasted condition. A high-fat meal did not alter the AUC to enzalutamide or N-desmethyl enzalutamide.

Primary Reviewer
Hisham Qosa, PhD.

Team Leaders
Pengfei Song, PhD.
Jingyu (Jerry) Yu, PhD.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

No clinical studies of efficacy or safety of enzalutamde were submitted with this NDA.

7.2.Review Strategy

Not applicable.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

The Applicant did not submit any new clinical efficacy data to support this NDA. Studies of efficacy were submitted in the original marketing application and subsequent submissions. Efficacy of enzalutamide in the treatment of CRPC has been sufficiently demonstrated and considered adequate to support this NDA submission for the film-coated tablet formuatiol of enzalutamide.

8.2. Review of Safety

Data from five biopharmaceutical studies with various development tablets (Tablets A, B, C, E and F) and the TBM tablet were submitted. Data from these studies consisted of 219 healthy male volunteers that were enrolled to a single-dose study and 27 male patients with CRPC that were enrolled in a multiple-dose study. There were no deaths or treatment discontinuations due to treatment emergent adverse events in any of the five biopharmaceutical studies. Due to the small number of patients with CRPC that received multiple doses of enzalutamide in a tablet formulation that is not the TBM form, no definitive conclusions regarding safety can be made from these biopharmaceutical studies. However, studies of safety were submitted in the original marketing application and subsequent submissions. The safety of enzalutamide in the treatment of CRPC has been sufficiently demonstrated and considered adequate to support this NDA submission for the film-coated tablet formuation.

During this review, incidence data for seizure, hypersensitivity, ischemic heart disease, and falls and fracures was updated in product labeling.

8.3. Conclusions and Recommendations

The Applicant has submitted this original new drug application for a new dosage form (immediate-release, film-coated tablets) and new strength (80 mg) of enzalutamide for the treatment of castrate-resistant prostate cancer. The data to support review of this application comes from the pivotal clinical study evaluating bioequivalence of enzalutamide capsules and tablets under fasted and fed conditions, simulations of steady-state concentration-time profiles, and an exposure-response analysis to evaluate the relationship between exposure and clinical efficacy. Limited data of safety was included in this application from five biopharmaceutical studies and no definitive conclusions on safety can be made from this data due to small sample size and no multiple-dose studies with the TBM tablet. However, the Applicant was able to demonstrate bioequivalene between the currently approved enzalutamide tablets and the TBM tablet for single-dose AUCs under fasted and fed conditions.

Safety of enzalutamide has been sufficienty characterized in the cross-referenced NDA and considered adequate to support the approval of this NDA submission for the film-coated tablet formulation. In addition, studies of efficacy submitted with the original cross-referenced NDA and in subsequent submissions has demonstrated the efficacy of enzalutamide in the treatment of CRPC.

This new dosage and formulation of enzalutamide reduces the size and number of dosage units required and will provide an alternative in the management of CRPC in a patient population that tends to be elderly and at risk for dysphagia and adverse events associated with polypharmacy. In addition, the availability of both 40mg and 80mg dosage strengths tablets allows for easier dose reductions. The clinical team has reviewed the information in NDA 213674 and recommend approval of enzalutamide for the proposed indication. All disciplines agree that the new formulation of enzalutamide has a favorable risk-benefit profile and do not identify any issues that would preclude approval.

X

Jamie Brewer
Primary Clinical Reviewer

X

Chana Weinstock
Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

Not applicable.

10 Pediatrics

Not applicable.

11 Labeling Recommendations

11.2 Prescription Drug Labeling

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Proposed Labeling**	**Approved Labeling**
Dosing Information	Added new information regarding administration of tablets according to daily dosing recommendations.	Same
Warnings and Precautions	Incidence data for seizure, hypersensitivity, ischemic heart disease, and falls and fracures was updated.	Same
Pharmacokinetics	Information regarding absorption of film-coated tablets added to label.	Same

12 Risk Evaluation and Mitigation Strategies (REMS)

No REMS will be required.

13 Postmarketing Requirements and Commitment

No postmarketing requirements or commitment will be required.

14 Division Director (DHOT)

X

15 Division Director (OCP)

X

16 Division Director (OB) Comments

X

17 Division Director (Clinical) Comments

X

18 Office Director (or designated signatory authority) Comments

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

19 Appendices

19.2 References

1. U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on 2019 submission data (1999-2017): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; www.cdc.gov/cancer/dataviz, released in June 2020.

2. Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2017, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2017/, based on November 2019 SEER data submission, posted to the SEER web site, April 2020.

19.3 Financial Disclosure

The Aplicant submitted a Form FDA 3454 for the clinical investigator conducting Study 9785-CL-0014 stating that as the sponsor of the submitted clinial studies they have not entered into any financial arrangement with the listed clinical investigator in which the value of compensation to the investigator could be affected by the outcome of the study. The clinical investigator did not disclose any proprietary interest in this product or significant equity in the sponsor. The clinical investigator was not the recipient of significant payments or other sorts.

Covered Clinical Study (Name and/or Number): Study 9785-CL-0014

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): NA		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____		

Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Hisham Qosa	CDER/OTS/OCP/DCP II	Section: 6 (Clinical Pharmacology)	**Select one:** _X_ Authored _X_ Approved
	Signature: Hisham Qosa -S (Affiliate) Digitally signed by Hisham Qosa -S (Affiliate) DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001883898, cn=Hisham Qosa -S (Affiliate) Date: 2020.08.04 10:55:48 -04'00'			
Clinical Pharmacology Team Leader	Pengfei Song	CDER/OTS/OCP/DCP II	Section: 6 (Clinical Pharmacology)	**Select one:** ___ Authored _X_ Approved
	Signature: Pengfei Song -S Digitally signed by Pengfei Song -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Pengfei Song -S, 0.9.2342.19200300.100.1.1=2000464900 Date: 2020.08.04 11:10:15 -04'00'			
Nonclinical Reviewer	Haw-Jyh Chiu	CDER/OND/OOD/DHOT	Section: 5	**Select one:** _x_ Authored ___ Approved
	Signature: Haw-jyh Chiu -S Digitally signed by Haw-jyh Chiu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Haw-jyh Chiu -S, 0.9.2342.19200300.100.1.1=2000207498 Date: 2020.08.04 11:05:13 -04'00'			
Nonclinical Team Leader	Tiffany Ricks	CDER/OND/OOD/DHOT	Section: 5	**Select one:** ___ Authored _x_ Approved
	Signature: Tiffany K. Ricks -S Digitally signed by Tiffany K. Ricks -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000497170, cn=Tiffany K. Ricks -S Date: 2020.08.04 11:37:28 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Jamie Brewer	CDER/OOD/DO1	Section: 1.1, 2.1, 2.2, 3.1, 3.2, 4.1, 4.2, 7.1, 8.1, 8.2, 11.2, 19.3	**Select one:** X Authored ___ Approved
	Signature: Jamie R. Brewer -S Digitally signed by Jamie R. Brewer -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002614013, cn=Jamie R. Brewer -S Date: 2020.08.04 10:52:03 -04'00'			
Associate Director for Labeling (ADL)	William Pierce	CDER/OOD	Section: Labeling Recommendations, Prescribing Information	**Select one:** ___ Authored X Approved
	Signature: William F. Pierce -S5 Digitally signed by William F. Pierce -S5 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300235575, cn=William F. Pierce -S5 Date: 2020.08.04 11:41:39 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Chana Weinstock	CDER/OOD/DO1	Section: All	**Select one:** x Authored x Approved
	Signature: Chana Weinstock -S Digitally signed by Chana Weinstock -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001659606, cn=Chana Weinstock -S Date: 2020.08.04 14:08:08 -04'00'			
Division Deputy Director (Clinical)	Amna Ibrahim	CDER/OOD/DO1	Section: All	**Select one:** x Authored x Approved
	Signature: Amna Ibrahim -S Digitally signed by Amna Ibrahim -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Amna Ibrahim -S, 0.9.2342.19200300.100.1.1=1300150984 Date: 2020.08.04 12:50:35 -04'00'			

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/s/

ALICE A LEE
08/04/2020 02:17:48 PM

CHANA WEINSTOCK
08/04/2020 02:22:42 PM

AMNA IBRAHIM
08/04/2020 02:28:07 PM