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Clinical Trial Results

Study to Compare Capsule and Liquid Formulations of Enzalutamide After Single-Dose Administration Under Fasting Conditions in Prostate Cancer

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Key Words. Prostate cancer • Enzalutamide • Liquid formulation • Bioequivalence • Pharmacokinetics

Trial Information

- **ClinicalTrials.gov Identifier**: NCT03478904
- **Sponsor**: National Cancer Institute
- **Principal Investigator**: William Douglas Figg
- **IRB Approved**: Yes

Lessons Learned

- Limited evidence suggests an acceptable pharmacokinetic profile when enzalutamide is administered via a liquid formulation extracted from the commercially available liquid-filled soft-gelatin capsules.
- Tolerability may limit use in clinical practice.

Abstract

Background. Enzalutamide is an established standard-of-care treatment for advanced prostate cancer with a commercially available formulation that may be inconvenient for some patients. We proposed a study to evaluate the bioequivalence of a liquid formulation to provide an alternative method of administration.

Methods. This was a single-dose, randomized, open-label, two-way crossover pilot bioequivalence study to compare two oral formulations of enzalutamide: four enzalutamide 40 mg liquid-filled soft-gelatin capsules (commercially available) administered whole versus enzalutamide 160 mg liquid (extracted from capsules) administered via oral syringe. To assess bioequivalence, patients were randomized to receive a single dose of one formulation, then cross over to receive the alternative formulation following a 42-day washout period; serial plasma samples were collected over the course of 24 hours, followed by collections at 3, 8, and 42 days after the dose for both formulations. Bioequivalence of the formulations was assessed via comparisons of area under the plasma concentration–time curve (AUC) calculations per U.S. Food and Drug Administration (FDA) guidance. The study also assessed the safety and tolerability of the formulations.

Results. The study failed to meet proposed accrual, with only one patient enrolled, thus limiting the bioequivalence evaluation. Based on the data from a single patient, the drug exposure (measured by AUC) of enzalutamide and *N*-desmethyl enzalutamide (primary active metabolite) for the liquid formulation was 112% and 117%, respectively, compared with the capsule formulation. Although both formulations appeared well tolerated with no adverse events reported, the tolerability assessment questionnaire revealed an unpleasant taste of the liquid formulation.

Conclusion. Preliminary evidence suggests a similar pharmacokinetic profile when administering liquid extracted from enzalutamide soft-gelatin capsules compared with intact capsules in patients with prostate cancer. ***The Oncologist*** 2021;26:729–e1493

Discussion

This study sought to evaluate enzalutamide administration in patients with prostate cancer using an alternative formulation to that of the standard liquid-filled capsules. We first established the stability of the liquid extracted from the

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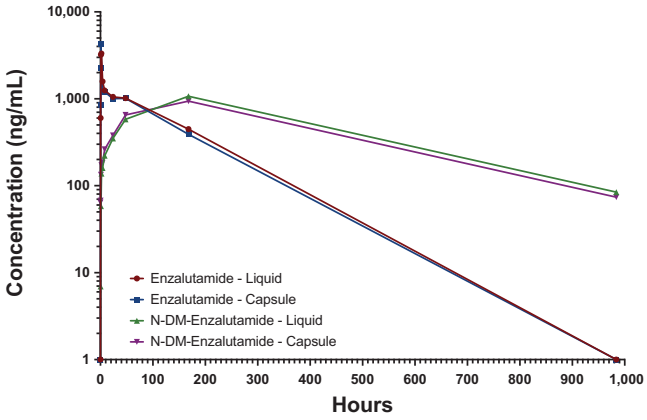

Figure 1. Comparisons of enzalutamide and *N*-desmethyl enzalutamide plasma concentration over time between liquid and capsule formulation. Enzalutamide and *N*-desmethyl enzalutamide plasma concentrations in patient samples were quantitated using a validated ultra-high-performance liquid chromatography–tandem mass spectrometry analytical method (developed based on prior literature [24]).
Abbreviation: N-DM-enzalutamide, *N*-desmethyl enzalutamide.

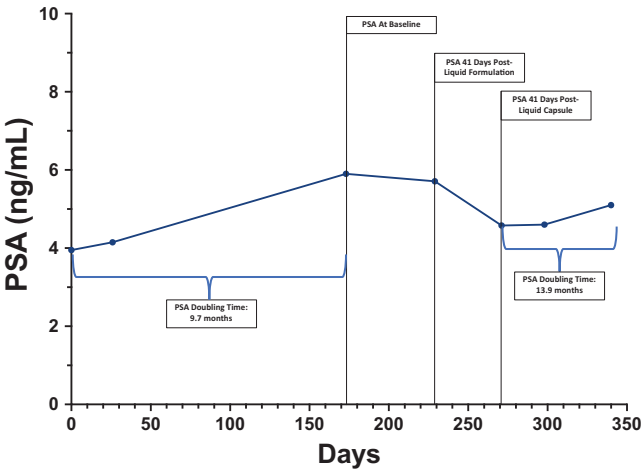

Figure 2. Trend of PSA measurements of a single patient during the course of the study.
Abbreviation: PSA, prostate-specific antigen.

capsule and found a sustained drug concentration for 28 days in an oral syringe using an ultra-high-performance liquid chromatography–tandem mass spectrometry–based analytical method. To evaluate the direct administration of the liquid formulation, we planned to implement a two-way crossover study design to assess bioequivalence to the standard liquid-filled capsule via comparison of plasma pharmacokinetics in a total of 12–14 patients. Ultimately, our study enrollment was limited to one patient because of unforeseen patient restrictions associated with the coronavirus disease 2019 (COVID-19) pandemic and the eventual introduction of a tablet formulation of enzalutamide. Nonetheless, we herein report our clinically relevant findings pertaining to this single patient. First, we report the feasibility and tolerability of administering enzalutamide directly as a liquid. Despite an unpleasant taste of the enzalutamide, likely related to the diluent Labrasol, no adverse events were reported following administration of the liquid formulation, including nausea or vomiting. Second, our findings suggested bioequivalence of the liquid formulation to the capsule formulation, as the AUC comparisons of plasma exposure of both enzalutamide and the active metabolite, *N*-desmethyl enzalutamide, were within 80%–125% SE per FDA guidance; further assessment in a larger cohort of patients would be necessary to formally establish bioequivalence of this formulation (Fig. 1). Lastly, we report a prostate-specific antigen (PSA) decline following the administration of two doses of enzalutamide (42-day interval between doses) to our single patient with a slowly rising PSA prior to study enrollment (a decline of 1.32 ng/mL from a PSA of 5.90 ng/mL at baseline) (Fig. 2). The reduction in PSA in a patient with castration-sensitive prostate cancer following minimally dosed enzalutamide is noteworthy, with possible attribution to sustained exposure to *N*-desmethyl enzalutamide despite a 42-day washout as well as corroboration with published literature. Further studies would be necessary to validate the routine administration of the extracted liquid formulation of enzalutamide and potential regimens that may incorporate reduced dosing of enzalutamide.

Trial Information	
Disease	Prostate cancer
Stage of Disease/Treatment	Any
Prior Therapy	Non-applicable
Type of Study	Phase I, single-dose, randomized, open-label, two-way crossover pilot bioequivalence study
Primary Endpoint	To evaluate the bioequivalence of two oral formulations of enzalutamide following a single 160 mg dose in male subjects with prostate cancer.
Secondary Endpoint	To evaluate the safety and tolerability of two oral formulations of enzalutamide following a single 160 mg dose in male subjects with prostate cancer
Investigator's Analysis	Limited study suggests bioequivalence of an oral liquid formulation of enzalutamide.

Drug Information: Enzalutamide	
Generic Name	Enzalutamide
Trade Name	Xtandi
Company Name	Astellas
Drug Type	Small molecule
Drug Class	Androgen receptor
Dose	160 milligrams (mg) per flat dose
Route	Oral (p.o.)
Schedule of Administration	One-time dose of one formulation (liquid or capsule) followed by a 42-day washout period; then a one-time dose of the alternative formulation.

Patient Characteristics	
Number of Patients, Male	1
Age, Years	78.2
Stage	Stage T3a prostate cancer; Gleason score of 8
Prior Treatment	Radical prostatectomy followed by salvage radiation
Performance Status: ECOG	0
Baseline PSA	5.90 ng/mL

Primary Assessment Method		
	160 mg enzalutamide liquid	**4 × 40 mg enzalutamide capsule**
Number of patients	1	1
Enzalutamide AUC_{inf}	329.14 μg*hour/mL	295.03 μg*hour/mL
N-desmethyl enzalutamide AUC_{inf}	617.52 μg*hour/mL	529.18 μg*hour/mL

Adverse Events							
Cycle 1							
Name	**NC/NA**	**1**	**2**	**3**	**4**	**5**	**All grades**
Nausea	100%	0%	0%	0%	0%	0%	0%
Vomiting	100%	0%	0%	0%	0%	0%	0%

Adverse Events Legend
Adverse events of interest were nausea and vomiting. No adverse events were observed.
Abbreviation: NC/NA, no change from baseline/no adverse event.

Pharmacokinetics/Pharmacodynamics				
Dose level	**Dose of drug: enzalutamide**	**Number enrolled**	**Enzalutamide AUC_{inf}**	***N*-desmethyl enzalutamide AUC_{inf}**
Liquid	160 mg	1	329.14 μg*hour/mL	617.52 μg*hour/mL
Capsule	4 × 40 mg	1	295.03 μg*hour/mL	529.18 μg*hour/mL

Assessment, Analysis, and Discussion	
Completion	Competing agents; study terminated before completion
Investigator's Assessment	Limited study suggests bioequivalence of an oral liquid formulation of enzalutamide.

In 2021, it is estimated that 248,530 men will be diagnosed with prostate cancer, with 34,130 estimated deaths [1]. Although definitive treatment for localized disease is possible for some men, many will develop castration-resistant prostate cancer (CRPC) and ultimately succumb to the disease [2, 3]. Numerous therapies have been developed for the treatment of metastatic CRPC (mCRPC), notably androgen receptor (AR) pathway targeting treatments like

abiraterone acetate and enzalutamide. Enzalutamide, a second-generation androgen receptor antagonist (ARA), is currently available worldwide for the treatment of mCRPC [4]. Improving on prior ARAs (e.g., bicalutamide, flutamide), enzalutamide not only has higher affinity for the ligand binding domain of the AR, but also blocks AR translocation to the nucleus and inhibits the interaction of the AR with DNA [5]. The efficacy and safety of enzalutamide was assessed in two randomized, placebo-controlled, multicenter phase III clinical trials, AFFIRM and PREVAIL, both before and after chemotherapy [6, 7]. Subsequent trials, such as ENZAMET and PROSPER, expanded the indication of enzalutamide to patients with metastatic castration-sensitive prostate cancer and nonmetastatic CRPC, respectively [8, 9].

Until August 2020, enzalutamide was only available commercially as a 40 mg liquid-filled capsule formulation, with four capsules constituting the U.S. Food and Drug Administration (FDA)–approved 160 mg daily oral dose. Enzalutamide, a Biopharmaceutics Classification System class 2 drug (low solubility, high permeability) [10], is optimally delivered in lipid-based formulations. Contained within the soft-gelatin capsule, 40 mg of enzalutamide is dissolved in approximately 0.96 mL of caprylocaproyl polyoxylglycerides (Labrasol) [11, 12]. The four-capsule regimen is inconvenient because of the number of capsules needed per dose and the size of the capsules; many patients have regimens comprising multiple drugs and/or have difficulty with swallowing [13]. Our aim was to evaluate an alternative formulation derived from the direct oral administration of the liquid component of the formulation extracted from the soft-gelatin capsule.

The proposed alternative formulation was prepared via the extraction of liquid from the soft-gelatin capsule by National Institutes of Health pharmacy personnel in a biological safety cabinet. The volume of extracted liquid equivalent to 160 mg (3.84 mL) was dispensed in 10 mL amber syringes for oral administration. The stability of enzalutamide in the extracted liquid formulation was evaluated for up to 28 days. In comparison with freshly extracted liquid (day 0), no significant differences in enzalutamide concentration were observed following storage of extracted liquid in amber syringes at room temperature for 28 days (Fig. 3), confirming stability of the proposed alternative formulation.

The purpose of our single-dose, randomized, open-label, two-way crossover study was to evaluate the bioequivalence of the extracted liquid formulation to that of the reference formulation (commercially available liquid-filled soft-gelatin capsules). Prior studies have used single-dose pharmacokinetics to address the role of drug-drug interaction, food effect, and hepatic impairment on enzalutamide plasma exposure, as measured by area under the plasma concentration–time curve (AUC) [14, 15]. Per FDA guidance, bioequivalence of an investigational formulation to a reference formulation (i.e., soft-gelatin capsule) can be declared if the AUC_{inf} calculation is within 80%–125% of SE; AUC_{inf} is calculated using the linear-log trapezoidal method with concentrations beyond the last observed concentration extrapolated out to zero based on the patient-specific terminal clearance estimate [16]. The crossover design was implemented to enable intrapatient evaluation of both formulations and to reduce patient sample size, with randomization to determine which patients received either liquid or capsule first ($n = 6$–7 per arm; Fig. 4). Important to the study design, a 42-day washout period was required prior to each dose because of the long half-life of enzalutamide (∼5.8 days) and the primary active metabolite, *N*-desmethyl enzalutamide (∼8 days) [12]. For each dose, pharmacokinetic samples were collected before the dose, 0.5, 1, 2, 4, 8, 24, 48, and 168 hours after the dose, and 42 days after the dose. AUC_{inf} was calculated for both enzalutamide and *N*-desmethyl enzalutamide and compared between the liquid and capsule formulations to assess bioequivalence. The secondary endpoint of the study was to evaluate the safety and tolerability of the liquid formulation in comparison with the capsule formulation.

Eligible patients over the age of 18 had histologically or cytologically confirmed prostate cancer, Eastern Cooperative Oncology Group performance status 0–2, adequate organ and bone marrow function, no prior history of seizures, no significant cardiac disease, and no uncontrolled intercurrent illness. Patients were excluded if they received enzalutamide within 42 days of study treatment initiation, primarily because of the aforementioned long half-life of enzalutamide, or if they had received investigational agents within 28 days or herbal medications within 7 days. At the time of study inception, apalutamide and darolutamide, two alternative second-generation ARAs, were not approved by the FDA, thus eligibility criteria did not reference these agents; investigators were aware of this during screening procedures. Restrictions were also implemented on co-administered drugs that were inducers, inhibitors, and/or substrates of CYP2C8, CYP2C9, CYP2C19, or CYP3A4 to prevent potential drug-drug interactions [12].

The study ultimately only enrolled one patient, who was assigned to receive the liquid formulation followed by the capsule formulation (arm B) from August to November 2020. Plasma concentration–time curves are depicted in Figure 1, and AUC calculations are summarized in the Primary Assessment Method table. In comparison with the capsule formulation, AUC_{inf} of the liquid formulation differed by 112% and 117% for enzalutamide and *N*-desmethyl enzalutamide, respectively. Although the enzalutamide plasma concentration was 0 ng/mL prior to the second dose, we detected a *N*-desmethyl enzalutamide concentration of 64.15 ng/mL at this time point; thus we implemented use of an "AUC_{tau}" calculation for *N*-desmethyl enzalutamide following the second dose (AUC_{tau} incorporates dosing interval [42 days] and associated residual drug accumulation into the AUC_{inf} measurement). Nonetheless, although our calculations suggest bioequivalence, more patients were needed to confirm the finding. No adverse events were reported on study for this patient, including our primary adverse events of interest, nausea and vomiting, which were mainly related to direct oral administration of Labrasol, the diluent of enzalutamide. However, the tolerability assessment questionnaire completed by the patient revealed an overall unpleasant taste of the liquid enzalutamide formulation that was "bitter" and "irritating" and lasted approximately 30 minutes after

administration; a prior study assessing a nasal formulation using Labrasol similarly reported three patients who described a "bitter or acid taste of mild intensity" following administration [17]. Other commonly reported adverse events of enzalutamide (e.g., fatigue, hypertension) were not expected nor reported, as such adverse events typically present following continuous daily administration.

Unexpectedly, we found minimal, but potentially clinically significant, decreases in prostate-specific antigen (PSA) for our single patient on study. The patient was initially diagnosed with localized high-risk prostate cancer in 2009, underwent radical prostatectomy in February 2010 that confirmed stage T3a disease, and completed salvage radiation in March 2011 in response to PSA elevation. The PSA was reported to be 0.54 ng/mL in 2013, and standard conventional imaging (^{99}Tc bone scan) did not show disease progression in 2015. The patient was castration-sensitive at the time of study enrollment and had not received prior androgen deprivation therapy. The patient's PSA was 4.15 and 5.90 ng/mL at 23 and 2 weeks prior to study enrollment, respectively. Following the two doses of enzalutamide and both subsequent 42-day periods after the doses, the patient's PSA declined by 1.32 ng/mL and stabilized for an additional 4 weeks (Fig. 2). Although such findings are limited to one patient and PSA data collection is incomplete (e.g., between the first and second doses), the PSA impact of minimal enzalutamide dosing appeared noteworthy. It is possible to suggest that the prolonged exposure of *N*-desmethyl enzalutamide over the entire study time frame may have contributed to the decline in PSA. A recent study of enzalutamide without androgen deprivation therapy in nonmetastatic castration-sensitive prostate cancer was associated with PSA control for nearly a year [18]. Another retrospective study in elderly, symptomatic patients with mCRPC reported a similar median progression-free survival in patients receiving ≤80 mg of enzalutamide daily versus those receiving the standard 160 mg dose (11.2 [$n = 16$] vs. 11.9 months [$n = 43$], respectively; $p = .612$) [19]. Additional studies have not found a significant correlation between enzalutamide and *N*-desmethyl enzalutamide exposure and response (efficacy or toxicity) [20–22], further suggesting the potential effectiveness of enzalutamide at reduced doses.

The study failed to accrue the proposed full study population because of unexpected constraints brought about from the coronavirus disease 2019 (COVID-19) pandemic and the recent FDA approval of the enzalutamide tablet formulation. Beginning in March 2020, in response to COVID-19, our patient visits were limited to patients requiring immediate anticancer treatment, thus restricting resources for enrolling patients on studies with pharmacokinetics-driven endpoints; in fact, our single patient was planned to start the study in March 2020 but was postponed to August 2020 because of the pandemic. In August 2020, patient accrual was further limited by the introduction of a tablet formulation that resolved the primary issues our study planned to address. Two new tablet strengths of 40 and 80 mg significantly reduced the dimensions of the delivery vehicle in comparison with the capsule, as well as pill burden to those receiving 80 mg tablets [23]. In response to these factors, it was decided to close the study in late 2020.

Despite early termination of this study, our efforts highlighted the feasibility of administering liquid extracted from the capsule formulation of enzalutamide but also accentuated the potentially unpleasant taste when the liquid is administered orally. Additionally, evidence of the extracted liquid formulation's bioequivalence was suggested by our single patient, information that may be useful to clinicians in the future. Further studies evaluating alternate routes of administration (e.g., feeding tubes) of the liquid formulation are warranted, as it is strongly advised to not crush tablets in the updated prescribing recommendations [12]. Lastly, our data suggest the potential efficacy of minimally dosed enzalutamide in patients with castration-sensitive prostate cancer, possibly explained via prolonged exposure to *N*-desmethyl enzalutamide. Further studies are needed prior to the routine clinical use of the extracted liquid formulation of enzalutamide in patients with prostate cancer.

Disclosures

The authors indicated no financial relationships.

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Figures

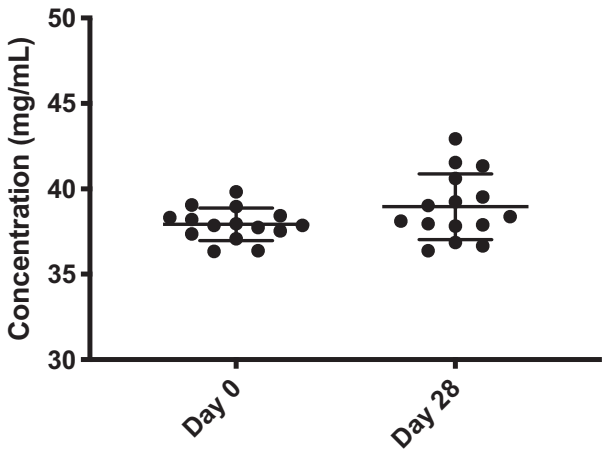

Figure 3. The stability of enzalutamide was assessed 28 days following the extraction of the liquid component from the soft-gelatin capsules and storage in amber syringes at room temperature (day 28) and compared with freshly extracted liquid (day 0). Fifteen separate samples for each group were prepared and quantitated using a validated ultra-high-performance liquid chromatography–tandem mass spectrometry analytical method (developed based on previous literature [24]). Statistical assessment using a Mann-Whitney test demonstrated no significant difference between the enzalutamide concentrations in the liquid formulation at day 0 versus day 28 ($p = .137$), confirming stability of the proposed alternative formulation.

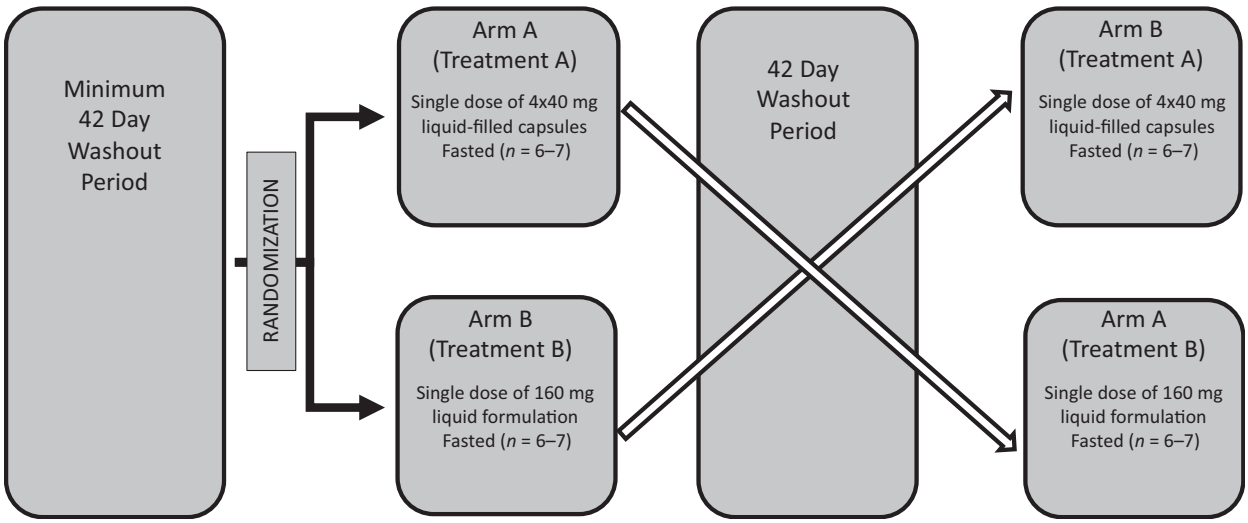

Figure 4. Study schema.