Abbreviated Title: Castration on Zolpidem PK
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Title: A Pilot Study to Evaluate the Effects of Castration on the Pharmacokinetics of Zolpidem After Single Dose Administration In Men with Prostate Cancer Undergoing Androgen Deprivation Therapy Compared to Normal Healthy Females

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Investigational Agent: None

Commercial Agent: Zolpidem

PRÉCIS

Background:

- Zolpidem is currently approved for the treatment of patients with insomnia.
- Women reported experiencing an increased incidence of adverse effects than men, resulting in a reduction of the recommended dose of zolpidem for women.
- Zolpidem metabolism is affected by both age and gender; the recommended dose for the elderly and female populations is 5mg daily.
- Subsequent studies have shown that women experience greater exposure to zolpidem than men, potentially due to androgen-driven differences in enzyme expression.
- A preclinical study showed that castrated male rats exhibited zolpidem pharmacokinetics similar to that of female rats, providing further evidence to suggest that zolpidem pharmacokinetics are androgen-driven.

Objectives:

- To evaluate the effect of castration on the pharmacokinetics of a single 5-mg dose of zolpidem in participants with prostate cancer undergoing androgen deprivation therapy (pre- vs. post-castration therapy) compared to normal healthy females.

Eligibility:

- Participants with prostate cancer (rising PSA and testosterone levels ≥ 100 ng/dL)
- Females in good health condition or without significant diseases
- After androgen deprivation therapy, castrate testosterone levels <50 ng/dL
- ECOG 0-1

Design:

- Comparative, single-dose pharmacokinetic study.
- Men with prostate cancer (pre-castration) and normal healthy females will receive treatment with a single dose of 5 mg tablet of zolpidem followed by 8-hour pharmacokinetic evaluation of zolpidem and its metabolites.
- Men will then undergo androgen deprivation therapy and when castrate testosterone levels <50 ng/dL (post-castration), they will receive another 5 mg single dose of zolpidem followed by 8-hour pharmacokinetic evaluation of zolpidem and its metabolites.
- Normal healthy females will receive treatment with a single dose of 5 mg tablet of zolpidem followed by 8-hour pharmacokinetic evaluation of zolpidem and its metabolites.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1. INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

- To evaluate the effect of castration on the pharmacokinetics of a single 5-mg dose of zolpidem by comparing the overall exposure of participants with prostate cancer before and after undergoing androgen deprivation therapy (pre- vs. post-castration therapy) and to the exposure of normal healthy females.

1.2 BACKGROUND AND RATIONALE

1.2.1 Zolpidem Background

Zolpidem is a nonbenzodiazepine imidazopyridine drug which functions as an agonist of the GABAA receptor to induce sleep. It displays high specificity for the benzodiazepine-1 receptor subtype over others. Receptor binding of zolpidem increases GABA activity and that of inhibitory synapses. It has a short clearance time making it beneficial for patients with difficulty falling asleep [1]. Insomnia is a common problem for many and recently zolpidem has been widely prescribed. However, some patients maintain the effects of the drug for long durations, mainly drowsiness upon waking the following morning. This can impair one's ability to perform necessary tasks or operate motor vehicles effectively [2]. With women and the elderly reporting higher incidences of insomnia, research has moved towards investigating the pharmacokinetic properties of zolpidem in differing populations [3, 4].

1.2.2 Sex Differences in Zopidem Pharmacokinetics

Women have reported a higher incidence of persisting adverse effects from zolpidem than men. Subsequent studies analyzed the pharmacokinetics properties of zolpidem in males and females.

In one study of healthy non-elderly individuals, females consistently experienced 40-50% higher AUC values (280 ng*h/mL vs 187 ng*h/mL) and a higher C_{MAX} (77 ng/mL vs 53 ng/mL) as seen in **Figure 1**[5]. This suggested slower clearance than males across several dosage levels. Such results led the FDA to decrease the recommended dose for female by half in 2013. The current FDA recommended dose is 5 mg for women and elderly or debilitated patients and either 5 or 10 mg for men. Despite acknowledgement of the sex-specific difference in zolpidem pharmacokinetics, the underlying mechanism has not been fully understood.

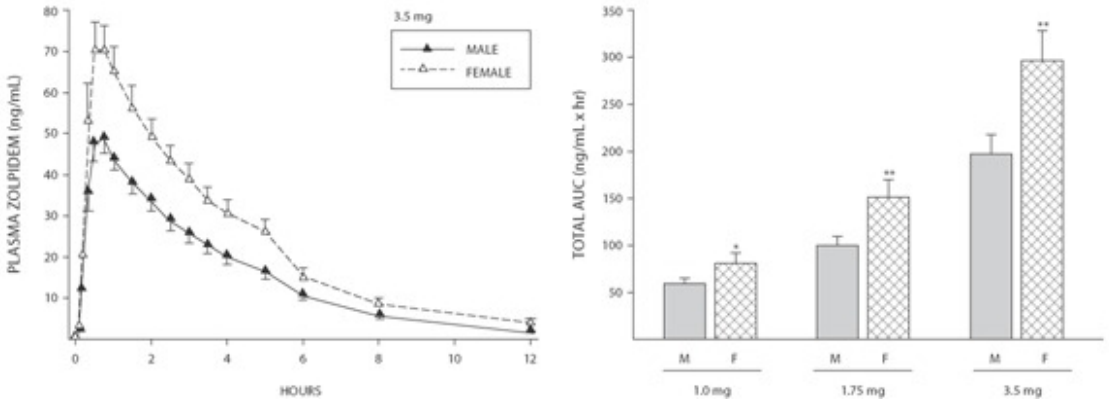

Figure 1. Mean (±SE) plasma zolpidem in male and female subjects after ZST doses of 3.5 mg. Mean (±SE) total area under the plasma zolpidem concentration curve (AUC) in male and female subjects after the three doses of ZST (1.0 mg, 1.75 mg, and 3.5 mg). Statisti Statistical comparisons of male and female groups using Student's t-test: *P = .05; **P < .05. SE, standard error; ZST, zolpidem sublingual tablet.

Sex-specific differences were thought to be attributed to differences in zolpidem metabolism. After administration zolpidem is initially metabolized by several cytochrome P450 enzymes. These enzymes hydrolyze the drug into one of three metabolites, contingent on the site of action. The most influential enzyme is CYP3A4, which is responsible for about 60% of CYP-mediated zolpidem metabolism. These metabolites are then converted to aldehydes by alcohol dehydrogenases (ADHs). The aldehyde is then converted to a carboxylic acid by aldehyde dehydrogenases (ALDHs). The two main zolpidem derived carboxylic acids are zolpidem phenyl 4-carboxylic acid (ZPCA) and zolpidem 6-carboxylic acid (ZCA) which constitute about 72-86% and 10% of the original dose, respectively [6]. Previously mentioned sex-specific differences could not be ascribed to CYP3A4, as females have greater CYP3A4 activity than men [7]. However, males express more ADH and ALDH in the gastrointestinal tract than females [8-12].

A comparison of elderly and young men revealed drastic changes in pharmacokinetics. Compared to young men, elderly men recorded vastly decreased oral clearance (276 mL/min vs 820 mL/min) as well as higher C_{MAX} (93 ng/mL vs 40 ng/mL), AUC (400 ng*h/mL vs 110 ng*h/mL), and a longer half-life (2.7 h vs 1.5 h). The same analysis in women also revealed an increased AUC (398 ng*h/mL vs 249 ng*h/mL) and decreased clearance (209 mL/min vs 376 mL/min) with age but to a far lesser degree. Further analysis showed that elderly men posted values closer to that of women than younger men. This might be explained by free serum testosterone concentrations, which were found to be lower in elderly than younger men (10.5 pg/mL vs 19.0 pg/mL). When compared to

zolpidem pharmacokinetics, free serum testosterone concentrations were correlated with both zolpidem AUC ($r^2 = 0.43$) and oral clearance ($r^2 = 0.46$) [13]. These results suggested that sex-specific differences in zolpidem pharmacokinetics could be androgen driven. One caveat is that clearance is often calculated as dividing oral dose by AUC_{INF}, and increased bioavailability (F) can increase AUC_{INF} without affecting clearance.

Androgens have been shown to cause sexual differences in ADH and ALDH expression. To explore the impact of androgens on zolpidem pharmacokinetics, a preclinical study was conducted in female, uncastrated male and castrated male rats given a human equivalent dose. Female rats presented higher C_{MAX} (112 ng/mL vs 68.1 ng/mL) and AUC (538 ng*h/mL vs 232 ng*h/mL) values than male, consistent with previous studies. Castrated males showed increased C_{MAX} (1.6 fold), AUC values (1.5 fold) and half-life (5.9 h vs 3.3 h) over uncastrated males. Castrated male C_{MAX} and AUC values were also similar to corresponding female values. These findings are shown in **Figure 2** and **Figure 3**. Additionally, treatment with the ALDH inhibitor disulfiram showed similar results to castration [14]. These results provide strong evidence that sex-specific differences in zolpidem pharmacokinetics is due to androgen-driven ADH and ALDH expression differences.

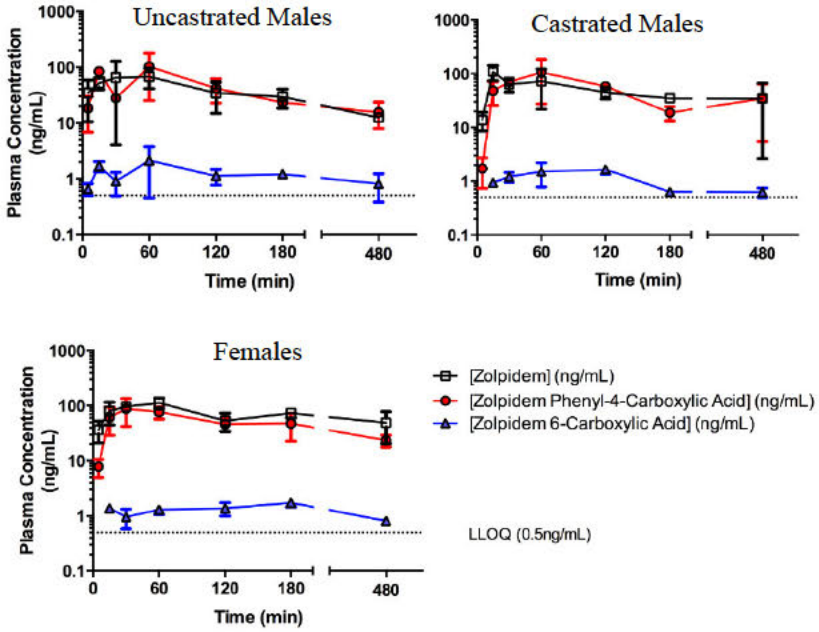

Figure 2. Zolpidem plasma concentration vs time profiles in A) Group 1: uncastrated males + vehicle (1% CMC, i.p.), B) Group 2: castrated males + vehicle, C) Group 3: females + vehicle. Zolpidem (open squares), the major metabolite zolpidem phenyl 4-carboxylic acid (red circles), and the minor metabolite zolpidem 6-carboxylic acid (blue triangles) were measured in rat plasma at varying time points post oral gavage of 2.6 mg/kg either with its vehicle (CMC).

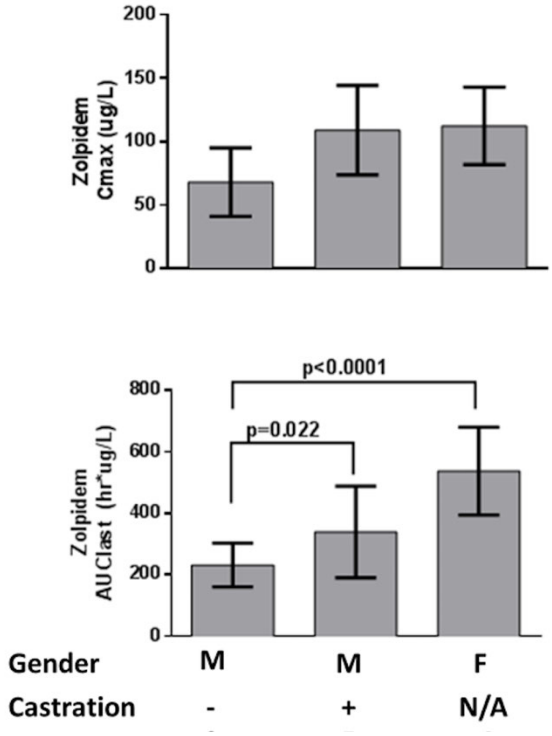

Figure 3. Zolpidem plasma (A) Cmax and (B) AUClast by sex and castration status. Data are represented by bar graphs depicting the mean ± the standard error of the mean (SEM), and p-values were determined by Bailer's Z-test.

1.2.3 Rationale

Previous studies have revealed sex differences affecting zolpidem pharmacokinetic properties. Females were found to experience greater exposure to the drug resulting in an increased incidence of adverse effects. One study attributed these differences to a discrepancy in zolpidem clearance between sexes [5]. This led to a revision to dosing protocols where females and elderly receive half the dose of males. However, a subsequent preclinical study suggested that these differences may be androgen-driven and be caused by a difference in absorption [14]. This clinical study will provide a unique opportunity to observe the effects of castration on zolpidem pharmacokinetics in humans. The findings could lend more evidence that sex differences in zolpidem pharmacokinetics are driven by androgens that affect first-pass metabolism and absorption more than clearance.

Subjects of Asian descent often have a lack of alcohol dehydrogenase isoenzyme activity in the stomach tissue [15, 16], express atypical ADH2*2 that rapidly converts alcohols into aldehydes [17], and harbor the E487K polymorphism in ALDH2 that inactivates the conversion of aldehydes into carboxylates [18]. Thus, these individuals often have altered alcohol disposition as compared to other world populations. Since we observed that ADH and ALDH affect zolpidem disposition in animals as a function of plasma androgen, Asians will be excluded from this study.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria – for male cohort

2.1.1.1 Participants must have histologically or cytologically confirmed prostate cancer. Note: If histologic documentation is unavailable, a clinical course consistent with prostate cancer is acceptable.

2.1.1.2 Participants must be eligible for and must be planning to undergo androgen deprivation therapy

2.1.1.3 Testosterone levels ≥ 100 ng/dL

2.1.1.4 Participants must have progressive prostate cancer as indicated by either PSA progression (PSA progression is defined as two consecutively rising PSAs above the nadir post-definitive therapy and an absolute value greater than 1.0 ng/mL separated by at least 2 weeks) or radiographic progression based on RECIST v1.1 or Prostate Cancer Working Group 3 (PCWG3).

2.1.1.5 ECOG performance status 0 to 1 (see **APPENDIX A**)

2.1.1.6 Participants must have normal organ and marrow function as defined below:

– Hemoglobin	≥ 9 g/dL
– leukocytes	≥ 3,000/mcL
– absolute neutrophil count	≥ 1,500/mcL
– platelets	≥ 150,000/mcL
– total bilirubin	within normal institutional limits
– AST(SGOT)/ALT(SGPT)	≤ institutional upper limit of normal
– creatinine	within normal institutional limits
	OR
– creatinine clearance	≥ 60 mL/min/1.73 m^2 for participants with creatinine levels above institutional normal (calculated via Cockcroft-Gault equation)

2.1.1.7 Participants must not have other concurrent malignancies (within the past 2 years with the exception of non-melanoma skin cancer and Rai Stage 0 chronic lymphocytic leukemia), in situ carcinoma of any site, or life threatening illnesses, including untreated

infection (must be at least 1 week off intravenous antibiotic therapy before beginning zolpidem).

2.1.1.8 Ability of subject to understand and the willingness to sign a written informed consent document.

2.1.1.9 Ability to swallow study medication.

2.1.1.10 Willingness to travel to NIH for follow-up visits.

2.1.1.11 Men age ≥ 18 years of age. Children are excluded because prostate cancer is not common in pediatric populations.

2.1.2 Inclusion Criteria - for normal healthy female cohort

2.1.2.1 Females age ≥ 18 years of age

2.1.2.2 Good health conditions or without significant diseases, according to best medical judgement.

2.1.2.3 If breastfeeding, must be willing to discard breastmilk for 24 hours following zolpidem.

2.1.2.4 Ability of subject to understand and the willingness to sign a written informed consent

2.1.2.5 Ability to swallow study medication.

2.1.3 Exclusion Criteria - for male cohort

2.1.3.1 Participants who are receiving any other investigational agents (in the past 28 days) or herbal medications (within 1 day).

2.1.3.2 Participants who have received systemic chemotherapy for prostate cancer will not be eligible.

2.1.3.3 Known hypersensitivity to Zolpidem or chemically related compounds; history of serious adverse reactions or hypersensitivity to any drug.

2.1.3.4 Clinically significant cardiac disease, e.g. New York Heart Association (NYHA) classes III-IV; uncontrolled angina, uncontrolled arrhythmia or uncontrolled hypertension, myocardial infarction in the previous 6 months as confirmed by an electrocardiogram (ECG).

2.1.3.5 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection,symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

2.1.3.6 HIV-positive participants on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with zolpidem. Appropriate studies will be undertaken in participants receiving combination antiretroviral therapy when indicated.

2.1.3.7 Participants with known active treatment for Hepatitis B and C infections.

2.1.3.8 Participants who are taking medications that may alter the metabolism of zolpidem. This includes strong CYP3A4 inhibitors or inducers or CYP3A4 substrates with a

narrow therapeutic index. For a current table of Substrates, Inhibitors and Inducers please access the following website: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

2.1.3.9 History or presence of hepatic or gastrointestinal diseases, or other condition that interferes with drug absorption, distribution, excretion or metabolism.

2.1.3.10 Participants currently taking other sedative hypnotic medications

2.1.3.11 Participants with a known history of psychiatric issues

2.1.3.12 Participants at risk for fall or who have had recent fractures

2.1.3.13 Participants of Asian descent

2.1.4 Exclusion Criteria - for normal healthy female cohort

2.1.4.1 Chronic therapy with any drugs, except contraceptives

2.1.4.2 History of hepatic, kidney, lungs, gastrointestinal, epileptic, hematologic or psychiatric disease; hypotension or hypertension, of any etiology, that requires pharmacological treatment; history of myocardial infarction, angina and/or heart failure.

2.1.4.3 Use of regular medications within 2 weeks prior study enrollment or use of any medications within one week prior to study enrollment, except contraceptives or cases which, based on drug's or metabolite's half-life, complete elimination can be assumed.

2.1.4.4 Hospitalization for any reason up to 8 weeks before enrollment.

2.1.4.5 Any condition, according to investigator's best judgement, that prevents the subject to participate in the trial

2.1.4.6 Pregnancy, labor or miscarriage within 12 weeks before admission predicted date.

2.1.4.7 Known hypersensitivity to zolpidem or chemically related compounds; history of serious adverse reactions or hypersensitivity to any drug.

2.1.4.8 Females of Asian descent

2.1.4.9 History of taking estrogen derivatives, androgens, or similar hormonal replacement or supplementation products. Past and current use of hormonal contraceptives is allowed.

2.1.5 Recruitment Strategies

This study will be listed on available websites (www.clinicaltrials.gov, https://ccr.cancer.gov/clinical-trials/patients) and participants will be recruited from the current participant population at NIH. This study will be posted on NIH websites and on NIH social media forums. Recruitement flyers may be used to advertise this study in future.

Healthy women volunteers may be self-referred or recruited through the healthy volunteer office and may include NIH employees. Recruitment, enrollment and compensation of NIH employee subjects will be consistent with NIH policy 2300-630-3, Leave Policy for NIH Employees Participating in Medical Research Studies (see Section **9.6**).

2.2 SCREENING EVALUATION

2.2.1 Screening activities performed prior to obtaining informed consent

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Email, written, in person or telephone communications with prospective subjects.
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images.
- Review of existing photographs or videos.
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes.

A waiver of consent for these activities has been requested in Section **9.7.1**.

2.2.2 Screening activities performed after a consent for screening has been signed

The following activities will be performed only after the subject has signed the consent for this study for screening. Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once a participant has signed the consent.

2.2.2.1 For men

- **Pathological confirmation: P**articipants must have histopathological documentation of prostate cancer prior to enrollment. Note: If no pathologic documentation is available, a clinical course consistent with prostate cancer is acceptable.
- **Within 8 weeks** of study entry:
    - CT scan reports (only required if confirmation of radiographic progression is necessary; both scans performed on another protocol at NIH and scans outside NIH are acceptable)
    - ECG
    - Laboratory tests: CBC with differential, Creatinine, ALT, AST, total bilirubin, PT/PTT, serum PSA, testosterone level,
    - Focused history, physical examination with documentation of weight and ECOG performance status.

2.2.2.2 For women

- **Pregnancy test** (serum or urine) within 3 days before study entry.
- **Within 8 weeks** of study entry:
    - ECG
    - Laboratory tests: CBC with differential, Creatinine, ALT, AST, total bilirubin, PT/PTT,
    - Focused history, physical examination with documentation of weight.

2.3 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found here.

2.3.1 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

2.3.2 Treatment Assignment Procedures

Cohorts

Number	Name	Description
1	Prostate cancer cohort	Participants with prostate cancer undergoing androgen deprivation therapy (pre- vs. post-castration therapy)
2	Healthy females cohort	Normal healthy females

Arms

Number	Name	Description
1	Zolpidem pre and post castration	5 mg oral dose of zolpidem prior to undergoing ADT followed by 5 mg oral dose of zolpidem after ADT and testosterone reaches castrate levels
2	One time zolpidem	Single 5 mg oral dose of zolpidem

Arm Assignment

Participants in Cohort 1 will be directly assigned to Arm 1.

Participants in Cohort 2 will be directly assigned to Arm 2.

2.4 BASELINE EVALUATION

Tests performed during screening do not need to be repeated if performed within 17 days prior to the first administration of zolpidem.

2.4.1 For men, and women

- History and physical examination.

- Laboratory and urine studies: **CBC with differential**, **PT/PTT**, and **Acute care panel** (Serum sodium, Potassium test, Serum chloride, CO2, Creatinine, Glucose test, BUN); **Mineral panel** (Albumin, Calcium, Magnesium, Phosphorous – serum); **Hepatic Panel** (Alkaline phosphatase, ALT, AST, direct and total bilirubin); Gamma-GT, LDH, total cholesterol, total protein, Serum PSA (only for men), uric acid, urinalysis; androstenedione level, dihydrotestosterone level, estradiol level
- ECG
- Vital signs including weight
- Height (if not previously recorded at any time)

2.4.2 For women, additionally following test will be done:

- Pregnancy Test (serum or urine) must be repeated within 3 days of receiving zolpidem.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is single-dose, comparative trial evaluating the effect of castration on the pharmacokinetics of a single 5-mg dose of zolpidem in participants with prostate cancer (cohort 1, arm 1) undergoing androgen deprivation therapy (pre- vs. post-castration therapy) compared to normal healthy females (cohort 2, arm 2). In men with prostate cancer, males (pre-castration, n=10) will receive oral zolpidem in the form of a 5 mg tablet. Blood samples will be collected for pharmacokinetic analysis at pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, and 8-hours post-dose. This cohort of men will then undergo androgen deprivation therapy until castrate testosterone levels reach <50 ng/dL. When castrate testosterone levels reach <50 ng/dL (post-castration), they will receive another 5 mg single dose of zolpidem followed by 8-hr PK evaluation (as described above for pre-castrate men) of zolpidem and its metabolites.

Normal healthy females (n=10) will receive a single dose of 5 mg tablet of zolpidem followed by 8-hr PK evaluation of zolpidem and its metabolites. Blood samples will be collected for PK analysis at pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, and 8-hours post-dose.

3.2 DRUG ADMINISTRATION

The rate and extent of absorption of zolpidem is influenced by dosage coincident with food. For orally administered immediate-release and controlled- release zolpidem, coadministration with a standard high-fat meal slows the rate of absorption and reduces the extent of absorption. These findings are described in the product label, but are not published in the literature. The effect of zolpidem may be slowed by ingestion with or immediately after a meal. In a food effect study on the rate and extent of absorption of zolpidem from a standard 3.5 mg dose of the buffered zolpidem sublingual tablet, zolpidem plasma levels were lower in the fed state compared to the fasting state from 20 minutes to 3 hour post-dose. Beyond 4 hour post-dose, zolpidem levels in the fed state exceeded the fasting levels, but net total AUC was not significantly different between the conditions [19]. Therefore, we recommend that participants should fast (no caloric intake) for at least 4 hours prior to being administered the dose of the study medication.

Subjects are admitted to the Clinical Center on Day 1 in the evening (for the first 8-hours of PK sampling) and will take a single 5 mg dose of an oral zolpidem tablet. Participants will be advised to have an early dinner (~18:00) and must have fasted for at least 4 hours prior to taking the study medication. The clinical research personnel or designee will administer the study medication at approximately 23:00 hours with ambient temperature water to a total volume of about 240 mL. Subjects are required to swallow the study medication whole and not chew the medication prior to swallowing. The subjects are required to refrain from drinking beverages other than water during the first 4 hours after dosing. Water is allowed except 1 hour pre and post dose.

Subjects may be discharged the following day when the blood draws have completed. One day following discharge, a study coordinator will contact the subject via phone to query for any adverse events.

This will be repeated for the men who receive a second dose of zolpidem when their castrate testosterone levels reach <50 ng/dL (post-castration). Baseline tests as described in Section **2.4.1** will be obtained when the subject is admitted to the hospital for the second dose of zolpidem.

3.3 STUDY CALENDAR

3.3.1 Cohort 1 (Prostate Cancer)

Procedure	Screening	Baseline[1]	Period 1		Period 2	
			Day 1	Day 3	Day 1	Day 3
Confirmation of diagnosis	X					
History and PE	X	X	X		X	
Vital signs (including weight)	X	X	X		X	
Height[4]		X				
Performance Score	X				X	
Labs	X[2]	X[3]	X[3]		X[3]	
ECG	X	X				
PKs			X		X	
Adverse Events			X	X	X	X
Concomitant Medications			X		X	
Follow up phone call				X		X

1. Baseline and day 1 assessments already performed at screening do not need to be repeated if peformed within 17 days prior to the first administration of zolpidem.
2. CBC with differential, creatinine, ALT, AST, total bilirubin, PT/PTT, serum PSA, serum testoterone
3. CBC with differential, PT/PTT, and Acute care panel (Serum sodium, Potassium test, Serum chloride, CO2, Creatinine, Glucose test, BUN); Mineral panel (Albumin, Calcium, Magnesium, Phosphorous – serum); Hepatic Panel (Alkaline phosphatase, ALT, AST, direct and total bilirubin); Gamma-GT, LDH, total cholesterol, total protein, serum PSA, uric acid, urinalysis; androstenedione level, dihydrotestosterone level, estradiol level
4. If not previously recorded at any time.

3.3.2 Cohort 2 (Healthy Females)

Procedure	Screening	Baseline[1]	Period 1	
			Day 1[1]	Day 3
History and PE	X	X	X	
Vital sign (including weight)	X	X	X	
Height[4]		X		
Performance Score	X			
Urine or serum hCG	X		X	
Labs	X[2]	X[3]	X[3]	
Androstendione, dihydrotestosterone and estradiol levels		X		
ECG	X	X		
PK			X	
Adverse Events			X	X
Concomitant Medications			X	
Follow up phone call				X

1. Except for pregnancy test, baseline and day 1 assessments already performed at screening do not need to be repeated if peformed within 17 days prior to zolpidem administration. Pregnancy test must be repeated within 3 days prior to receiving zolpidem.
2. Please refer to Section **2.2** for details.
3. Please refer to Section **2.4** for details.
4. If not previously recorded at any time

3.4 COST AND COMPENSATION

3.4.1 Costs

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. If some tests and procedures are performed outside the NIH Clinical Center, participants may have to pay for these costs if they are not covered by insurance company. Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.

3.4.2 Compensation

All study participants will be compensated for each blood sample collected for PK analysis as follows:

- $20 for the 1st pre-dose PK sample
- $20 for the 2nd (0.25 hours) PK sample
- $20 for the 3rd (0.5 hours) PK sample
- $20 for the 4th (1 hour) PK sample
- $20 for the 5th (1.5 hours) PK sample
- $20 for the 6th (2 hours) PK sample
- $20 for the 7th (3 hours) PK sample
- $20 for the 8th (4 hours) PK sample
- $20 for the 9th (8 hours post dose) PK sample

All remuneration will be directed to be paid to the participant via check through standard compensation procedures. These funds are intended to compensate for time away from work that is required to participate in this study. As we intend to recruit from the local metropolitan region, we will not provide remuneration for meals, lodging or transportation. If a participant withdraws from study, no future compensation will be made, but prior compensation will not be revoked.

All subjects will not receive direct benefit from their study participation in this protocol.

All subjects will only be compensated if samples are collected solely for research purposes.

3.4.3 Reimbursement

The NCI will cover the costs of some expenses associated with protocol participation. Some of these costs may be paid directly by the NIH and some may be reimbursed to the participant/guardian as appropriate. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy.

If subjects return to clinic solely for any clinical/non-research reasons, subjects will not be reimbursed.

3.5 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from study, effort must be made to have all subjects complete a safety phone call one day following discharge.

3.5.1 Criteria for removal from protocol therapy

- Screen failure

- Completion of protocol therapy/interventions
- Participant requests to be withdrawn from active therapy/interventions
- Unacceptable Toxicity (defined as any adverse event attributable to zolpidem that is Grade 3 or higher as per CTCAE v4.0)
- Investigator discretion
- Permanent loss of capacity to give consent

3.5.2 Off-Study Criteria

- Completed study follow-up period
- Participant requests to be withdrawn from study
- Permanent loss of capacity to give consent
- Death

4 CONCOMITANT MEDICATIONS/MEASURES

Participants may be on concomitant drugs to prevent bone loss, including calcium, vitamin D, bisphosphonates and denosumab.

Other supportive care with blood components, antibiotics, analgesics, general medical therapy, etc., will be delivered as required.

4.1 GENERAL GUIDELINES

All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) taken within 28 days before starting study treatment through the final follow up phone call should be reported on the CRF.

While participants are on protocol treatment, all medications required for the health of the participant are allowed with the following exceptions**:**

- Concurrent chemotherapy
- Concurrent radiation therapy
- Concurrent immunotherapy
- Concurrent anti-cancer radionuclides
- Concurrent systemic corticosteroid use (daily or every other day for continued use > 14 days)
- Concomitant use of secondary hormonal treatments
- Concomitant use of herbal supplements
- Concomitant use of medications mentioned in Sections **2.1.3.8** and **2.1.4.3**.

4.2 CNS DEPRESSANTS

- Co-administration of zolpidem with other CNS depressants increases the risk of CNS depression. Concomitant use of zolpidem with these drugs may increase drowsiness and psychomotor impairment, including impaired driving ability. Zolpidem tartrate was

evaluated in healthy volunteers in single-dose interaction studies for several CNS drugs.

- Imipramine in combination with zolpidem produced no pharmacokinetic interaction other than a 20% decrease in peak levels of imipramine, but there was an additive effect of decreased alertness. Similarly, chlorpromazine in combination with zolpidem produced no pharmacokinetic interaction, but there was an additive effect of decreased alertness and psychomotor performance.
- An additive adverse effect on psychomotor performance between alcohol and oral zolpidem was demonstrated.
- Concomitant administration of zolpidem and sertraline increases exposure to zolpidem and should be avoided.
- After multiple doses of zolpidem tartrate and fluoxetine an increase in the zolpidem half-life (17%) was observed and should be avoided. There was no evidence of an additive effect in psychomotor performance.

4.3 DRUGS AFFECTING CYTOCHROME P450

- Some compounds known to induce or inhibit CYP3A may affect exposure to zolpidem. The effect of drugs that induce or inhibit other P450 enzymes on the exposure to zolpidem is not known.
- Rifampin, a CYP3A4 inducer, significantly reduced the exposure to and the pharmacodynamic effects of zolpidem. Use of CYP3A4 inducers in combination with zolpidem may decrease the efficacy of zolpidem. Co-administration of zolpidem with strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine) may decrease the plasma exposure of zolpidem and are not allow while on study. Selection of a concomitant medication with no or minimal CYP3A4 induction potential is recommended.
- Ketoconazole, a potent CYP3A4 inhibitor, increased the exposure to zolpidem and is not allowed while on study.
- Concomitant use of zolpidem with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), should be avoided, as zolpidem may decrease their exposure.
- Moderate CYP3A4 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) and St. John's Wort may also reduce the plasma exposure of zolpidem and should be avoided if possible.
- Grapefruit, Seville oranges, and starfruit affect P450 and PgP activity. Concomitant use should be avoided.

5 CORRELATIVE STUDIES FOR RESEARCH/PHARMACOKINETIC STUDIES

5.1 BIOSPECIMEN COLLECTION

Male participants will be administered a 5 mg dose of zolpidem before and after castration. Post-castration dose will be given when castrate testosterone levels reach <50 ng/dL followed by 8-hr PK evaluation. Normal healthy females will be administered a single dose of 5 mg tablet of zolpidem followed by 8-hr PK evaluation of zolpidem and its metabolites.

Pharmacokinetic blood samples will be collected with sodium heparin as the anticoagulant. Venous blood samples for plasma will be collected at the following times: pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, and 8-hours post-dose. The Clinical Pharmacology Program will quantitatively measure zolpidem, zolpidem phenyl 4-carboxylic acid, and zolpidem 6-carboxylic acid using a validated uHPLC-MS/MS assay with a lower limit of quantitation of 0.5 ng/mL. Immediately place specimens on wet ice and refrigerate. The date and exact time of each blood draw should be recorded on the sample tube and the PK sheet.

5.2 SAMPLE PROCESSING

All samples will be sent to and stored in [redacted] Lab [redacted]. Place all samples on ice (4ºC).

Please e-mail [redacted] at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page [redacted]

For immediate help, call [redacted] (main blood processing core number) or, if no answer, [redacted] (main clinical pharmacology lab number).

For questions regarding sample processing, contact [redacted]
Noncompartmental pharmacokinetic (PK) parameters will be calculated using Phoenix WinNonlin v6.3 (Certara, Cary, NC), including $AUC_{0\text{-}24hr}$, AUC_{INF}, apparent oral clearance (dose/AUC_{INF}), terminal elimination rate (k_{el}), half-life (ln2/k_{el}), apparent oral volume of distribution. The maximum plasma concentration (C_{MAX}) and time to C_{MAX} (T_{MAX}) will be recorded as observed values. PK parameters will be used to identify differences based on sex, androgen levels, age, etc.

5.3 SAMPLE STORAGE, TRACKING AND DISPOSITION

Samples will be ordered in CRIS and tracked through a [redacted]. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without appropriate approvals and/or agreements, if required.

Any transfer of materials to other NIH or non-NIH investigators will occur following NIH Intramural Research Program guidelines. If the subject withdraws consent the participants' data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

Upon arrival in the [redacted] blood samples will be centrifuged and the plasma transferred into cryovials for storage at -80° C until the time of analysis.

All PK samples will be barcoded, with data entered and stored in the Labmatrix utilized by the CPP. This is a secure program, with access to Labmatrix limited to defined CPP personnel, who are issued individual user accounts. Installation of Labmatrix is limited to computers specified by [redacted]. These computers all have a password restricted login screen. The program creates a unique barcode ID for every sample and sample box, which cannot be traced back to participants with Labmatrix access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer locations. Participant demographics associated with the clinical center participant number

are provided in the system. For each sample, there are notes associated with the processing method (e.g., delay in sample processing, storage conditions on the ward, etc.).

Barcoded samples are stored in barcoded boxes in locked freezers at either -20 C or -80 C according to stability requirements. These freezers are located onsite in the [redacted] and offsite at [redacted] Samples will be stored until requested by a researcher named on the protocol.

All requests are monitored and tracked in Labmatrix. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per IRB approved protocol) and that any unused samples must be returned to the CPP.

- Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.
- If, at any time, a participant withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed.

The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of Section 7.2

Sample barcodes are linked to participant demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the Labmatrix. It is critical that the sample remains linked to participant information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate pharmacokinetic data with these variables.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into two data capture systems (C3D, a 21 CFR Part 11-compliant data capture system, and Labmatrix) provided by the NCI CCR and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event.

Document AEs from the first study intervention, Study Day 1, through 3 days after removal from study treatment. Beyond 3 days after the last intervention, only adverse events which are serious and related to the study intervention need to be recorded.

An abnormal laboratory value will be recorded in the database as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms

- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the participant's outcome.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in Section **7.2.1**.

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

What data will be shared?

I will share human data generated in this research for future research as follows:

- Coded, linked data in an NIH-funded or approved public repository.
- Coded, linked data in BTRIS

How and where will the data be shared?

Data will be shared through:

- An NIH-funded or approved public repository. Insert name or names: ClinicalTrials.gov.
- BTRIS
- Publication and/or public presentations.

When will the data be shared?

- Before publication.
- At the time of publication or shortly thereafter.

6.3 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each participant while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

7 NIH REPORTING REQUIREMENTS / DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found here.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found here.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found here.

7.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reported to the OHSRP in iRIS will also be reported to the NCI Clinical Director. A separate submission is not necessary as reports in iRIS will be available to the Clinical Director.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention should be reported via email to the Clinical Director unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to [redacted] at [redacted] within one business day of learning of the death

7.4 NIH REQUIRED DATA AND SAFETY MONITORING PLAN

7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis (at least weekly) when participants are being actively treated on the trial to discuss each participant. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior participant.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in Section **7.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each participant to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 STATISTICAL CONSIDERATIONS

8.1 STATISTICAL HYPOTHESES

Primary efficacy endpoints:

In male participants, AUC after completing androgen deprivation therapy compared to AUC prior to receiving androgen deprivation therapy.

Secondary Efficacy endpoints:

AUC in females compared to males after receiving androgen deprivation therapy, to establish the approximate equivalence of the two groups with respect to this endpoint.

8.2 SAMPLE SIZE DETERMINATION

Ten males will receive Zolpedim and have an AUC determined based on the initial administration of the agent. Then following androgen deprivation therapy, they will receive a second administration of the agent and have the AUC determined. With 10 evaluable participants, there would be 80% power to detect the difference in the two measurements with an effect size of 1.0 (1.0 SD of the difference between the two AUC values for each male subject) using a paired t-test with a 0.05 two-sided significance level.

Ten female normal volunteers will receive Zolpedim and have an AUC determined based on this single administration of the agent. The AUC for females will be compared to the AUC in males after receiving androgen deprivation therapy, to establish the approximate equivalence of the two groups with respect to this endpoint. Assuming AUC values on the order of 200 ug*h/mL, it is considered that if AUC for post-ADT males is not less than 30-40 ug*h/mL below that of females, that this would be bioequivalent. When there are 10 females and 10 post-ADT males, a two group 0.10 one-sided t-test will have 81% power to reject the null hypothesis that the AUCs from males and females are not equivalent (the difference in means, $m_{male} - m_{female}$, is 40 or farther from zero, assuming that the female values would be higher) in favor of the alternative hypothesis that the means of the two groups are equivalent, if the expected difference in means is 10 ug*h/mL and the common standard deviation is 30 ug*h/mL.

Evaluable subject is defined as the one who completes all parts of the study. Subjects who drop out of the study will be replaced. To account for possible dropouts and screen failures, the accrual ceiling for each arm will be set at 15 for a total accrual ceiling of 30 participants.

8.3 POPULATIONS FOR ANALYSIS

Modified intention to treat. Only participants who receive full dose administrations of the agents (two doses for males; one dose for females) will be included.

8.4 STATISTICAL ANALYSES

8.4.1 General Approach

AUC values will be obtained for pre-ADT males, post-ADT males, and healthy female volunteers. The AUC values will be compared between the time points for males to see if the AUC increases significantly, and the AUC values will be compared between those of post-ADT males and healthy females to see if they are at least approximately equivalent.

8.4.2 Analysis of the Primary Efficacy Endpoints

The AUCs in pre-ADT males will be subtracted from the paired values in males once they are post-ADT and tested for a difference using a paired t-test with a two-sided 0.05 significance level, or a Wilcoxon signed rank test if the paired differences are not normally distributed. The mean or median of the differences and a 95% confidence interval on the difference will be reported.

8.4.3 Analysis of the Secondary Endpoints

The AUC values will be compared between those of post-ADT males and healthy females to see if they are at least approximately equivalent. A one-sided 90% confidence interval on the difference between the mean of the values of post-ADT males and healthy females will be constructed and interpreted in order to assess whether the two groups have approximately equivalent AUC values.

8.4.4 Safety Analyses

None will be performed.

8.4.5 Baseline Descriptive Statistics

None will be provided.

8.4.6 Planned Interim Analyses

None will be performed.

8.4.7 Subgroup Analyses

Descriptive evaluations of parameters in the groups based on gender will be undertaken and reported on the basis of gender.

8.4.8 Tabulation of Individual Participant Data

No individual participant data will be tabulated.

8.4.9 Exploratory Analyses

Estimation of the pharmacokinetic parameters obtained and estimates of sample statistics such as means, standard deviations, medians, interquartile ranges, etc. may be determined. PK parameters may be compared between the males and females using Wilcoxon rank sum tests. Other tests to evaluate the trends or differences in values obtained may be undertaken for exploratory purposes.

9 HUMAN SUBJECTS PROTECTIONS

9.1 RATIONALE FOR SUBJECT SELECTION

9.1.1 Selection Based on Ethnicity, and Race

Subjects from all racial/ethnic groups, except Asians (see Section **1.2.3** for exclusion rationale), are eligible for this study if they meet the eligibility criteria. Efforts will be made to extend accrual to a representative population, but in this preliminary study, a balance must be struck between participant safety considerations and limitations on the number of individuals exposed to potentially toxic and/or ineffective treatments on one hand and the need to explore ethnic aspects of clinical research on the other hand. If differences in outcome that correlate with ethnic identity are noted, accrual may be expanded or a follow-up study may be written to investigate those differences more fully. Women are eligible for this protocol as participants in the healthy female cohort.

9.2 PARTICIPATION OF CHILDREN

Because no dosing or adverse event data are currently available on the use zolpidem in participants <18 years of age and because prostate cancer is uncommon in pediatric populations, children are excluded from this study, but may be eligible for future pediatric trials.

9.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. Adults who become incapacitated or cognitively impaired during the course of the study will be removed from the study as the study involves no direct benefit.

9.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

9.4.1 Alternative Approaches or Treatments

Participants will be consented verbally and in writing regarding the risks and benefits of this trial, the treatment requirements, and alternative approaches to entering on this trial.

9.4.2 Procedure for Protecting Against or Minimizing any Potential Risks

All care will be taken to minimize side effects, but they can be unpredictable in nature and severity. This study may involve risks to participants, which are currently unforeseeable. All participants will have blood tests, examinations and scans as described in the protocol evaluation (Section **3.3** Study Calendar). Participants will also be required to have a local physician to provide long-term care and to monitor for complications. If participants suffer any physical injury as a result of the participation in this study, immediate medical treatment is available at the Clinical Center, National Cancer Institute, Bethesda, Maryland. Any injury will be evaluated and treated in keeping with the benefits or care to which participants are entitled under applicable regulations.

9.4.3 Provisions for Monitoring Data Collection to Ensure Safety of Subjects

As information is gathered from this trial, clinical results will be shared with participants as they become available. Laboratory and clinical data will be frequently gathered and any new

significant finding(s) found during the course of the research, which may affect a participant's willingness to participate further, will be explained. Confidentiality of information concerning participants will be maintained, including in all publications and presentations results from this study. Names of participants and/or material identifying participants will not be released without permission, except as such release is required by law. Records at the National Cancer Institute are maintained according to current legal requirements, and are made available for review, as required by the Food and Drug Administration or other authorized users, only under the guidelines established by the Federal Privacy Act.

9.5 RISKS/BENEFITS ANALYSIS

The risks of blood draw are relatively small. In addition, the drug (5 mg of zolpidem) being used in this study has been approved by the FDA for the short-term treatment of insomnia characterized by difficulties with sleep initiation.

9.6 NIH HEALTHY VOLUNTEERS

NIH staff and family members of study team members may be enrolled in this study as this population meets the study entry criteria. Neither participation nor refusal to participate as a subject in the research will have an effect, either beneficial or adverse, on the participant's employment or position at NIH. Staff will be expected to comply with policy 2300-630-3, Leave Policy for NIH Employees Participating in Medical Research Studies.

Every effort will be made to protect participant information, but such information may be available in medical records and may be available to authorized users outside of the study team in both an identifiable an unidentifiable manner.

The NIH FAQs for NIH Staff Who are Considering Participation in NIH Research found in policy 404 – Research Involving NIH Staff will be made available. Please see Section **9.7.2** for consent of NIH Staff.

9.7 CONSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided as a physical or electronic document to the participant for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the participant/consent designee(s). Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant/consent designee, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant/consent designee will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to participant) or as described below, with a manual (non-electronic) signature on the electronic document. When required, witness signature will be obtained similarly as described for the investigator and participant.

Manual (non-electronic) signature on electronic document:

When a manual signature on an electronic document is used for the documentation of consent at the NIH Clinical Center, this study will use the following to obtain the required signatures:

- Adobe platform (which is not 21 CFR Part 11 compliant); or,
- iMedConsent platform (which is 21 CFR Part 11 compliant)

During the consent process, participants and investigators will view individual copies of the approved consent document on screens at their respective locations (if remote consent); the same screen may be used when in the same location but is not required.

Both the investigator and the participant will sign the document using a finger, stylus or mouse.

Note: Refer to the CCR SOP PM-2, Obtaining and Documenting the Informed Consent Process for additional information (e.g., verification of participant identity when obtaining consent remotely) found here.

9.7.1 Request for Waiver of Consent for Screening Activities

Prior to the subject signing the consent for this study pre-screening activities listed in Section **2.2.1** may be performed.

We request a waiver of consent for these activities as they involve only minimal risk to the subjects. A waiver will not adversely affect the rights and welfare of the subjects given that the activities are only intended to determine suitability for screening for participation in research protocols. These activities could not practicably be carried out without the wavier as central recruiting services, utilized in the NIH Clinical Center, perform pre-screening activities for multiple studies and obtaining consent for each one is beyond their resources. The subjects will be provided with additional pertinent information after participation as they will be informed whether or not they are eligible to sign a consent for additional screening.

9.7.2 Consent for NIH Staff

Consent for NIH staff will be obtained as detailed in Section **9.6** with following additional protections:

Consent from staff members will be obtained by an individual independent of the staff member's team whenever possible. In addition, if the participant is in a subordinate relationship with an investigator on the research team or is part of the work unit where the research is taking place, the consent procedure will be independently monitored by the CC Department of Bioethics Consultation Service in order to minimize the risk of undue pressure on the staff member.

10 REGULATORY AND OPERATIONAL CONSIDERATIONS

10.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants and the Institutional Review Board (IRB) and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants;
- Insufficient compliance to protocol requirements;
- Data that are not sufficiently complete and/or evaluable; and/or,
- Determination that the primary endpoint has been met.

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB.

10.2 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing and inspection by local and regulatory authorities.

10.3 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the National Cancer Institute has

established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.4 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators and their staff. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

All research activities will be conducted in as private a setting as possible.

The study monitor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB or Institutional policies and requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored at the NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site and by NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NIH.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

11 PHARMACEUTICAL INFORMATION

11.1 ZOLPIDEM

11.1.1 Source

Zolpidem will be obtained from commercial sources and dispensed by the Clinical Center pharmacy.

11.1.2 Toxicity

11.1.2.1 CNS Depressant Effects and Next-Day Impairment

Zolpidem, like other sedative-hypnotic drugs, has central nervous system (CNS) depressant effects. Co-administration with other CNS depressants (e.g., benzodiazepines, opioids, tricyclic antidepressants, alcohol) increases the risk of CNS depression. Dosage adjustments of zolpidem and of other concomitant CNS depressants may be necessary when zolpidem is administered with such agents because of the potentially additive effects. The use of zolpidem with other sedative-hypnotics (including other zolpidem products) at bedtime or the middle of the night is not recommended.

The risk of next-day psychomotor impairment, including impaired driving, is increased if zolpidem is taken with less than a full night of sleep remaining (7 to 8 hours); if a higher than the recommended dose is taken; if co-administered with other CNS depressants or alcohol; or if co-administered with other drugs that increase the blood levels of zolpidem. Participants should be warned against driving and other activities requiring complete mental alertness if zolpidem is taken in these circumstances.

Vehicle drivers and machine operators should be warned that, as with other hypnotics, there may be a possible risk of adverse reactions including drowsiness, prolonged reaction time, dizziness, sleepiness, blurred/double vision, reduced alertness and impaired driving the morning after therapy. In order to minimize this risk a full night of sleep (7-8 hours) is recommended.

11.1.2.2 Severe Anaphylactic and Anaphylactoid Reactions

Cases of angioedema involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses of sedative-hypnotics, including zolpidem. Some patients have had additional symptoms such as dyspnea, throat closing or nausea and vomiting that suggest anaphylaxis. Some patients have required medical therapy in the emergency department. If angioedema involves the throat, glottis or larynx, airway obstruction may occur and be fatal. Participants who develop angioedema after treatment with zolpidem should not be rechallenged with the drug.

11.1.2.3 Abnormal Thinking and Behavioral Changes

Abnormal thinking and behavior changes have been reported in patients treated with sedative/hypnotics, including zolpidem. Some of these changes included decreased inhibition (e.g., aggressiveness and extroversion that seemed out of character), bizarre behavior, agitation and depersonalization. Visual and auditory hallucinations have been reported.

In controlled trials of zolpidem 10 mg taken at bedtime < 1% of adults with insomnia reported hallucinations. In a clinical trial, 7% of pediatric patients treated with zolpidem 0.25 mg/kg taken at bedtime reported hallucinations versus 0% treated with placebo.

Complex behaviors such as “sleep-driving” (i.e., driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event) have been reported in sedative-hypnotic-naive as well as in sedative-hypnotic-experienced persons. Although behaviors such as “sleep-driving” have occurred with zolpidem alone at therapeutic doses, the co-administration of zolpidem with alcohol and other CNS depressants increases the risk of such behaviors, as does the use of zolpidem at doses exceeding the maximum recommended dose. Due to the risk to the participant

and the community, discontinuation of zolpidem should be strongly considered for participants who report a "sleep-driving" episode.

Other complex behaviors (e.g., preparing and eating food, making phone calls, or having sex) have been reported in patients who are not fully awake after taking a sedative-hypnotic. As with "sleep-driving", patients usually do not remember these events. Amnesia, anxiety and other neuro-psychiatric symptoms may also occur.

It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above is drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

11.1.2.4 Withdrawal Effects

There have been reports of withdrawal signs and symptoms following the rapid dose decrease or abrupt discontinuation of zolpidem. Monitor participants for tolerance, abuse, and dependence

11.1.2.5 Other Adverse Effects

Approximately 4% of 1,701 patients who received zolpidem at all doses (1.25 to 90 mg) in U.S. premarketing clinical trials discontinued treatment because of an adverse reaction. Reactions most commonly associated with discontinuation from U.S. trials were daytime drowsiness (0.5%), dizziness (0.4%), headache (0.5%), nausea (0.6%), and vomiting (0.5%).

Approximately 4% of 1,959 patients who received zolpidem at all doses (1 to 50 mg) in similar foreign trials discontinued treatment because of an adverse reaction. Reactions most commonly associated with discontinuation from these trials were daytime drowsiness (1.1%), dizziness/vertigo (0.8%), amnesia (0.5%), nausea (0.5%), headache (0.4%), and falls (0.4%).

Data from a clinical study in which selective serotonin reuptake inhibitor (SSRI)-treated patients were given zolpidem revealed that four of the seven discontinuations during double-blind treatment with zolpidem (n=95) were associated with impaired concentration, continuing or aggravated depression, and manic reaction; one patient treated with placebo (n =97) was discontinued after an attempted suicide.

11.1.3 Formulation and Preparation

Zolpidem tartrate is a gamma-aminobutyric acid (GABA) A agonist of the imidazopyridine class and is available in 5 mg and 10 mg strength tablets for oral administration. Chemically, zolpidem is N,N,6-trimethyl-2-p-tolylimidazo[1,2-a] pyridine-3-acetamide L-(+)-tartrate (2:1).

Zolpidem tartrate is a white to off-white crystalline powder that is sparingly soluble in water, alcohol, and propylene glycol. It has a molecular weight of 764.88.Each zolpidem tablet includes the following inactive ingredients: hydroxypropyl methylcellulose, lactose, magnesium stearate, micro-crystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide. The 5 mg tablet also contains FD&C Red No. 40, iron oxide colorant, and polysorbate 80.

Zolpidem is available in 5 mg strength (generic) tablets for oral administration. Tablets are not scored.

11.1.4 Stability and Storage

Store zolpidem tablets at controlled room temperature 20°–25°C (68°–77°F) in a dry place and keep the container tightly closed.

The company providing the drug will also provide the expiration date for each lot allocated to this study.

11.1.5 Administration Procedures

The effect of zolpidem may be slowed by ingestion with or immediately after a meal. Therefore, zolpidem will be administered under fasting conditions (no caloric intake for at least 4 hours before dosing). Participants will swallow tablets whole.

12 REFERENCES

1. Pichard, L., et al., *Oxidative metabolism of zolpidem by human liver cytochrome P450S.* Drug Metab Dispos, 1995. **23**(11): p. 1253-62.
2. Gunja, N., *In the Zzz zone: the effects of Z-drugs on human performance and driving.* J Med Toxicol, 2013. **9**(2): p. 163-71.
3. Zhang, B. and Y.K. Wing, *Sex differences in insomnia: a meta-analysis.* Sleep, 2006. **29**(1): p. 85-93.
4. Kamel, N.S. and J.K. Gammack, *Insomnia in the elderly: cause, approach, and treatment.* Am J Med, 2006. **119**(6): p. 463-9.
5. Greenblatt, D.J., et al., *Gender differences in pharmacokinetics and pharmacodynamics of zolpidem following sublingual administration.* J Clin Pharmacol, 2014. **54**(3): p. 282-90.
6. Von Moltke, L.L., et al., *Zolpidem metabolism in vitro: responsible cytochromes, chemical inhibitors, and in vivo correlations.* Br J Clin Pharmacol, 1999. **48**(1): p. 89-97.
7. Wolbold, R., et al., *Sex is a major determinant of CYP3A4 expression in human liver.* Hepatology, 2003. **38**(4): p. 978-88.
8. Estonius, M., et al., *Distribution of alcohol and sorbitol dehydrogenases. Assessment of mRNA species in mammalian tissues.* Eur J Biochem, 1993. **215**(2): p. 497-503.
9. Aasmoe, L. and J. Aarbakke, *Sex-dependent induction of alcohol dehydrogenase activity in rats.* Biochem Pharmacol, 1999. **57**(9): p. 1067-72.
10. Westerlund, M., et al., *High and complementary expression patterns of alcohol and aldehyde dehydrogenases in the gastrointestinal tract: implications for Parkinson's disease.* FEBS J, 2007. **274**(5): p. 1212-23.
11. Quertemont, E., *Genetic polymorphism in ethanol metabolism: acetaldehyde contribution to alcohol abuse and alcoholism.* Mol Psychiatry, 2004. **9**(6): p. 570-81.
12. Koppaka, V., et al., *Aldehyde dehydrogenase inhibitors: a comprehensive review of the pharmacology, mechanism of action, substrate specificity, and clinical application.* Pharmacol Rev, 2012. **64**(3): p. 520-39.
13. Olubodun, J.O., et al., *Pharmacokinetic properties of zolpidem in elderly and young adults: possible modulation by testosterone in men.* Br J Clin Pharmacol, 2003. **56**(3): p. 297-304.
14. Peer, C.J., et al., *Alcohol and Aldehyde Dehydrogenases Contribute to Sex-Related Differences in Clearance of Zolpidem in Rats.* Front Pharmacol, 2016. **7**: p. 260.
15. Baraona, E., et al., *Lack of alcohol dehydrogenase isoenzyme activities in the stomach of Japanese subjects.* Life Sci, 1991. **49**(25): p. 1929-34.
16. Dohmen, K., et al., *Ethnic differences in gastric sigma-alcohol dehydrogenase activity and ethanol first-pass metabolism.* Alcohol Clin Exp Res, 1996. **20**(9): p. 1569-76.
17. Bjorn, M.K. and H.T. Northen, *Effects of 2,4-Dichlorophenoxyacetic Acid on Chicks.* Science, 1948. **108**(2809): p. 479-80.

18. Yoshida, A., I.Y. Huang, and M. Ikawa, *Molecular abnormality of an inactive aldehyde dehydrogenase variant commonly found in Orientals.* Proc Natl Acad Sci U S A, 1984. **81**(1): p. 258-61.

19. Greenblatt, D.J., et al., *Influence of food on pharmacokinetics of zolpidem from fast dissolving sublingual zolpidem tartrate tablets.* J Clin Pharmacol, 2013. **53**(11): p. 1194-8.

13 APPENDIX A - PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.