TAVT-45 (abiraterone acetate) Granules for Oral Suspension

Clinical Trial Protocol TAVT45C02

Phase 3 study investigating the efficacy and safety of TAVT-45 (abiraterone acetate) Granules for Oral Suspension (a novel abiraterone acetate formulation) relative to a reference abiraterone acetate formulation in patients with metastatic Castrate Sensitive Prostate Cancer (mCSPC) and metastatic Castrate Resistant Prostate Cancer (mCRPC)

Document Type:	Clinical Trial Protocol
Sponsor Study Number:	TAVT45C02
IND Number:	139118
EudraCT Number:	2020-005611-46
Version Number:	3.0
Clinical Trial Phase:	3
Date of Protocol:	26 Mar 2021
Sponsor:	Tavanta Therapeutics, Inc. [redacted]

Clinical Trial Protocol Version 3.0

Study Contacts

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Bioanalytical Laboratory:

Medical Monitor:

Pharmacovigilance:

[redacted]

Signatures for Investigators

CONFIDENTIALITY AND GCP COMPLIANCE STATEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other drug information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also protect the rights, safety, privacy, and well-being of study patients in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 7 of this protocol.

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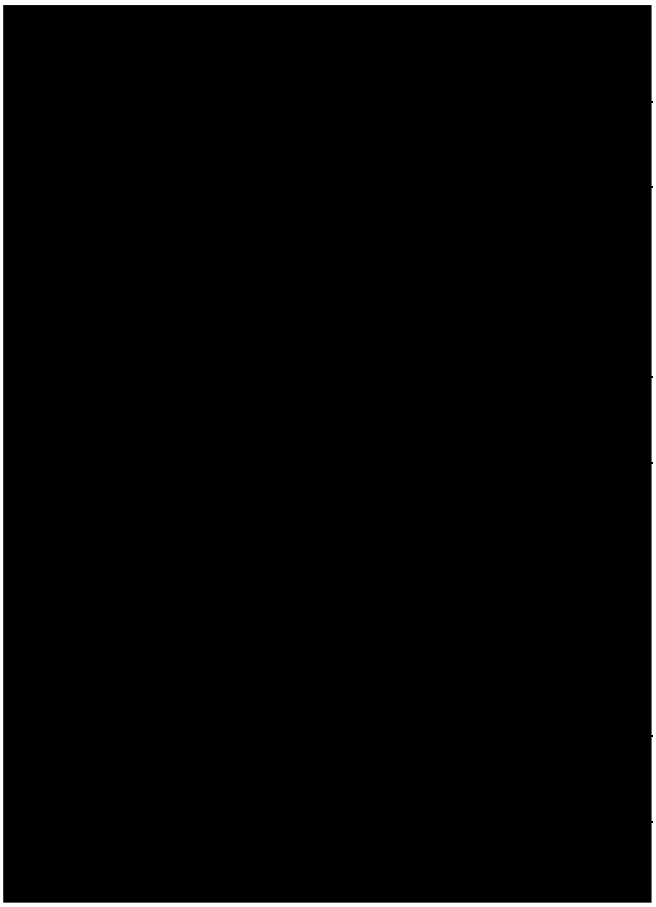

Summary of Revision History

Document Status	Version Date	Summary of Key Changes
Version 1.0 (final protocol)	01 Dec 2020	• Not applicable
Version 2.0 (amendment 1)	28 Jan 2021	• *Section 5.6.5 (Permitted dose adjustments and interruptions of study treatment):* added text to provide guidance on toxicity management during this study related to hepatotoxicity and Grade ≥ 3 toxicities, in alignment with Zytiga prescribing information • *Section 5.6.9 (Discontinuation of study treatment):* added text to clarify that ALT or AST rises above 5x ULN, or total bilirubin rises above 3x ULN, at any time during the study will result in permanent discontinuation of study medication • *Section 15 (References):* Added reference #20 for CTCAE version 5
Version 3.0 (amendment 2)	26 Mar 2021	• *Study Contacts:* Updated email address for [redacted] • *Synopsis and Section 4.1:* Updated Inclusion #10 to exclude herbal supplements only • *Synopsis and Section 4.2:* Revised definition of uncontrolled hypertension in Exclusion #13 and added new Exclusion #18 concerning post-trial treatment • *Sections 5.4, 5.8, and 6:* Added text to clarify timing of randomization, which is to occur before Day 1, but after confirming eligibility and receiving screening testosterone value due to just-in-time shipping of study medication • *Table 1:* Revised timing of randomization • *Section 5.6.7*: Added clarifications around other concomitant medication that should be used with caution during the study • *Section 5.6.8.2:* Added list of notable strong CYP3A4 inducers • *Section 5.10:* Added text to clarify the provision of post-trial treatment, including no post-trial access to study medication, and the definition of "End of Trial"

Document Status	Version Date	Summary of Key Changes, continued
Version 3.0 (amendment 2)	26 Mar 2021	• *Sections 7.1, 7.2.2, 7.2.3, 7.4 and 7.5:* Added/revised text to better describe timing and information needed for reporting AEs, SAEs, SUSARs and partner pregnancies • *Section 9.6*: Added text to note that additional patients may be randomized to ensure that a total of 108 patients are treated through Day 9 for collection of the primary endpoint data • *Section 9.7.1:* Clarified the definition of the Per Protocol population • *Section 10.3:* Added text to explicitly state source data should also be readily available upon any request from the authorities • *Section 13:* Added reference #21 for FDA source of strong CYP3A4 inducers

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List of abbreviations

ACTH	Adrenocorticotropic hormone
ADT	Androgen deprivation therapy
AE	Adverse Event
AJCC	American Joint Committee on Cancer
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
AST	Aspartate Aminotransferase
AUC	Area under the curve
AUC_{0-12}	Area under the concentration-time curve from time zero to 12 hours
AUC_{0-24}	Area under the concentration-time curve from time zero to 24 hours
AUC_{last}	Area under the concentration-time curve from time zero to the time of last sample with a quantifiable concentration
BID	Twice daily
CI	Confidence interval
C_{max}	Maximum plasma drug concentration
C_{min}	Minimum plasma drug concentration
CRF	Case Report Form
CR-ITT	Intent-to-treat population for the mCRPC patients
CRO	Contract Research Organization
CRPC	Castration-resistant prostate cancer
CSPC	Castration-sensitive prostate cancer
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DHEA	Dehydroepiandrosterone
dl	Deciliter
DMC	Data monitoring committee
ECOG	Eastern Cooperative Oncology Group
EMA/EMEA	European Medicines Agency
ET	Early Termination
FDA	(U.S.) Food and Drug Administration
GCP	Good Clinical Practice
GnRH	Gonadotropin-releasing hormone

HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMP	Investigational medicinal products
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-treat
LLOQ	Lower limit of quantification
LS	Least squares
mCRPC	Metastatic castration-resistant prostate cancer
mCSPC	Metastatic castration-sensitive prostate cancer
MedDRA	Medical dictionary for regulatory activities
mIU	Milli-International unit
mm Hg	Millimeter of mercury
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
ng	Nanogram
PFS	Progression-free survival
PiB	Powder-in-bottle
PSA	Prostate-specific antigen
R-AA	Reference abiraterone acetate (Zytiga®)
Rac	Accumulation index
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SE	Standard error
SmPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reactions
$t_{½}$	Effective half-life
TAVT	Tavanta Therapeutics, Inc.
TEAE	Treatment-Emergent Adverse Event
T_{max}	Time to maximum plasma concentration

TNM	Tumor, node, metastasis system of staging
ULN	Upper limit of normal
WHO	World Health Organization

Protocol synopsis

Name of Sponsor/Company: Tavanta Therapeutics, Inc. (Tavanta)	
Name of Finished Product: TAVT-45 (abiraterone acetate) Granules for Oral Suspension, hereafter referred to as TAVT-45 granules	
Name of Active Ingredients: Abiraterone acetate	
Title of Study:	Phase 3 study investigating the efficacy and safety of TAVT-45 (abiraterone acetate) Granules for Oral Suspension (a novel abiraterone acetate formulation) relative to a reference abiraterone acetate formulation in patients with metastatic Castrate Sensitive Prostate Cancer (mCSPC) and metastatic Castrate Resistant Prostate Cancer (mCRPC)
Principal Investigator:	Multi-center study
Study Center:	Multi-center study, including but not limited to, sites in US, Europe and other regions
Development Phase:	Phase 3

Primary Objectives:

To establish therapeutic equivalence between TAVT-45 granules and Zytiga® tablets in patients with metastatic castrate sensitive prostate cancer (mCSPC) and metastatic castrate resistant prostate cancer (mCRPC)

Secondary Objective:

To characterize the multiple-dose pharmacokinetic profile of TAVT-45 in a cohort of patients

Study Design:

This is a Phase 3 randomized, open-label study to evaluate the pharmacodynamic effect and safety profile of TAVT-45 compared to Zytiga (reference abiraterone acetate formulation, hereafter referred to as R-AA) in patients with mCSPC and mCRPC. Randomization will be stratified by prostate cancer population (CSPC vs CRPC) and baseline testosterone (<10 vs ≥ 10 ng/dL). Patients will be treated for 84 days and randomized into one of two groups in a 1:1 ratio:

- **TAVT-45:** Administered twice daily as 1 x sachet containing TAVT-45 (250 mg abiraterone acetate) + Prednisone (5 mg once or twice daily, depending on prostate cancer population)
- **R-AA:** Administered once daily as (2 x 500 mg Zytiga tablets) + Prednisone (5 mg once or twice daily, depending on prostate cancer population)

Methodology:

At Screening (up to 28 days prior to first dosing), all eligible patients will provide written informed consent to participate in the study before any protocol-specified procedures or assessments are initiated. Upon meeting all inclusion/exclusion criteria set forth in the protocol, patients will be randomized in a 1:1 fashion to receive either TAVT-45 (250 mg abiraterone acetate) twice daily (approximately every 12 hours) without respect to food or R-AA 1000 mg once daily either ≥ 1 hour before or ≥ 2 hours after a meal. All patients should also receive prednisone together with a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy. The mCSPC patients will receive prednisone 5 mg orally once daily, while the mCRPC patients will receive prednisone 5 mg orally twice daily. Randomization will be stratified by prostate cancer population (CSPC vs CRPC) and baseline testosterone (<10 vs ≥ 10 ng/dL).

Patients will return to the clinic in the morning on Days 9, 10, 28, 56 and 84 for assessments and evaluations of safety and efficacy, including testosterone, PSA, and abiraterone trough samples. Patients may return to the clinic or may visit a local laboratory for evaluation of liver function tests on Days 42 and 70. Blood samples for testosterone will be taken between the hours of 7:00-10:00 in the morning. A pharmacokinetic sub-study will be conducted in a cohort of up to 8 patients receiving TAVT-45 at select

site(s) only. Pharmacokinetic profiles over the dosing interval will be obtained on Day 1 (first dose) and on Day 9 (steady state). For all patients, a follow-up phone call will also be made approximately one week after the last dose for AE assessments.

Number of Planned Study Subjects:

Total patients planned to be enrolled: 108 (n=54 patients per prostate cancer population), randomized in a 1:1 ratio receiving either TAVT-45(n=27 mCRPC and n=27 mCSPC patients) or R-AA (n=27 mCRPC and n=27 mCSPC patients).

Inclusion Criteria:

1. Written informed consent obtained prior to any study-related procedure being performed
2. Male patients at least 18 years of age or older at time of consent
3. Pathologically confirmed adenocarcinoma of the prostate
4. Ongoing therapy with a gonadotropin releasing hormone (GnRH) agonist or antagonist (unless patient has already had a bilateral orchiectomy) AND serum testosterone level <50 ng/dL at screening
5. Have either metastatic CSPC or metastatic CRPC, as defined below:
    - CSPC: Using the American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) system, patients must have Stage T_{any} N_{any} M+ (distant metastases) disease AND two of the following:
        - Gleason score of 8 or greater
        - Three or more bone scan lesions
        - Measurable visceral metastases
    - CRPC: Patients must have metastatic* disease, and must also have disease progression according to the recommendations of the Prostate Cancer Working Group 3 by having at least one of the following criteria:
        - Two rises of PSA (taken a minimum of 1 week apart) from a baseline measurement of at least 1 ng/mL
        - Imaging progression (CT/MRI) by RECIST 1.1 criteria or PET/CT*
        - Nuclear scan progression by 2 or more new bone lesions.

    ** Note: Metastatic disease should be documented by MRI/CT, PET/CT (including, but not limited to, standard of care imaging using ^{18}F-fluciclovine, ^{11}C-choline, or PSMA where approved) or bone scan. Imaging obtained within 90 days prior to the start of study drug/reference product will be accepted.*
6. The following prior treatment and/or surgery for prostate cancer are allowed:
    - CSPC:
        - Up to 90 days of androgen deprivation therapy (ADT) with gonadotropin-releasing hormone (GnRH) agonists/antagonists or orchiectomy with or without concurrent anti-androgens prior to patients' randomization is permitted
        - Patients may have one course of palliative radiation or surgical therapy to treat symptoms resulting from metastatic disease (e.g., impending cord compression or obstructive symptoms) if administered prior to randomization
        - Radiation or surgical therapy that was not initiated 4 weeks after the start of ADT or orchiectomy
    - CRPC:
        - Previous chemotherapy with docetaxel for metastatic disease with treatment completed at least 1 year prior to Screening
7. Discontinuation of flutamide or nilutamide, and other anti-androgens prior to the start of study medication; discontinuation of bicalutamide prior to start of study medication.
8. Discontinuation of strong CYP3A4 inducers at least 4 weeks prior to start of study medication.

9. Discontinuation of radiotherapy prior to start of study medication
10. Discontinuation of herbal supplements at least 4 weeks prior to the first dose of study medication and for the duration of the trial.
11. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 at screening
12. Normal organ function with acceptable initial laboratory values within the screening period:

ANC	≥ 1,500/µl
Albumin	> 3.0g/dL
Hemoglobin	≥ 9g/dL
Platelet count	≥ 100,000/µl
Serum Creatinine	≤ 3.0 x the institutional upper limit of normal (ULN)
Potassium	≥ 3.5 mmol/L (within institutional normal range)
Bilirubin	≤ 1.5 ULN (unless documented Gilbert's disease)
SGOT (AST)	≤ 2.5 x ULN
SGPT (ALT)	≤ 2.5 x ULN

13. Life expectancy of at least 6 months at screening
14. Patients engaged in sex with women of child-bearing potential agree to use a condom plus another effective contraception method. Patients agree to use a condom when engaged in any sexual activity, including sex with a pregnant woman. These restrictions will apply from the time informed consent is provided until 3 weeks after the last dose of study medication is taken.
15. Patient is willing and able to comply with all protocol requirements assessments

Exclusion Criteria:

1. For mCSPC patients:
    - Any prior pharmacotherapy, radiation therapy, or surgery for metastatic prostate cancer not specified as allowable treatment in Inclusion Criterion 6. For example, prior therapy with apalutamide or enzalutamide is prohibited as well as therapy with an investigational agent as described in Exclusion Criterion 16.
2. For mCRPC patients:
    - Prior treatment with abiraterone or enzalutamide is prohibited
    - Previous chemotherapy is prohibited with exception of docetaxel treatment as specified in Inclusion Criterion 6.
3. Initiation of bisphosphonate or denosumab therapy within 4 weeks prior to the start of study drug/reference product. Patients who are on a stable dose of these medications for at least 4 weeks at the time of starting study drug/reference product will be eligible.
4. Therapy with estrogen within 4 weeks prior to the start of study drug
5. Use of systemic glucocorticoids equivalent to >10 mg prednisone daily. Patients who have discontinued or reduced dosing to the equivalent of ≤ 10 mg prednisone daily within 14 days prior to the start of study drug are eligible
6. Known, symptomatic metastases to the brain or central nervous system involvement (patients with asymptomatic and neurologically stable disease for the past 4 weeks will be permitted)
7. History of adrenal gland dysfunction defined as requiring treatment for adrenal insufficiency
8. History of other malignancy within the previous 2 years (no longer being actively treated), with the exceptions of basal cell carcinoma, non-muscle invasive bladder cancer that has been treated and is under surveillance, or other in-situ cancers with a low likelihood of recurrence
9. Major surgery within 4 weeks prior to the start of study drug
10. Known gastrointestinal disease or condition that could impair absorption inclusive of gastrocolic fistula, gastroenterostomy, biliary obstruction, cirrhosis, chronic pancreatitis or pancreatic cancer, cystic fibrosis, amyloidosis, celiac disease, Crohn's disease, radiation enteritis, intestinal resection, and history of bariatric surgery

11. Known history of human immunodeficiency virus or seropositive test for hepatitis C virus (HCV) or hepatitis B surface antigen (HBsAg) (note: HCV patients with undetectable viral load will be eligible)
12. Poorly controlled diabetes, defined as HbA1c > 8% within the past 12 months
13. Uncontrolled hypertension at screening
14. History of New York Heart Association class III or IV heart failure
15. Serious concurrent illness, including psychiatric illness, that could interfere with study participation
16. Receipt of another investigational agent within 4 weeks of treatment start or within 5 x the treatment half-life, whichever is longer.
17. Known hypersensitivity or allergy to abiraterone acetate, prednisone or any excipients in the study drugs
18. In the opinion of the investigator, participation in the trial would prevent the patient from receiving local standard-of-care treatment for metastatic prostate cancer, if clinically indicated, after completion of the trial
19. Other condition which, in the opinion of the Investigator, would preclude participation in this trial.

Test Product, Dose and Mode of Administration	
Test product:	TAVT-45 (250 mg abiraterone acetate)
Mode of administration:	Oral
Strength:	250 mg
Dose:	Administered twice daily as 1 x sachet TAVT-45 (250 mg abiraterone acetate) reconstituted in either water or juice, as specified in the medication preparation guide
Reference Product, Dose and Mode of Administration	
Reference product:	Reference abiraterone acetate (R-AA; Zytiga tablets)
Mode of administration:	Oral
Strength:	500 mg Zytiga tablets
Dose:	Administered once daily as 2 x 500 mg Zytiga tablets, swallowed whole with water
Additional Product, Dose and Mode of Administration	
Additional product:	Prednisone
Mode of administration:	Oral
Strength:	5 mg tablets
Dose:	mCRPC Patients: 5 mg twice daily mCSPC Patients: 5 mg once daily

Duration of Treatment:

For an individual patient, the duration of the clinical study will be up to approximately 17 weeks (including a Screening Phase up to 28 days, an 84-day treatment period, and a 1-week follow up period).

Efficacy Assessments:

Efficacy assessments will include:

- Serum testosterone
- Prostate specific antigen (PSA)
- Trough concentrations of abiraterone

Pharmacokinetic Assessments:

In a cohort of up to 8 patients randomized to TAVT-45, blood samples (approximately 4 mL each) for PK analysis will be collected at the following times on Day 1 and Day 9: pre-dose (time 0) and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 8, 10, and 12 hours post-dose and before the scheduled evening dose.

Safety Assessments:

Safety assessments will include:

- Vital signs
- Physical examinations
- Adverse events (AEs)
- Clinical laboratory assessments

Criteria for Evaluation:

Efficacy:

The primary efficacy endpoint is the comparison of the average of serum testosterone levels on days 9 and 10 between groups (TAVT-45 vs R-AA).

The key secondary efficacy endpoint is the PSA-50 response, defined as a decrease of ≥ 50% in PSA levels from baseline at any time over the 84-day post-treatment period.

Other secondary efficacy endpoints are as follows:

- Serum testosterone levels at Days 28, 56 and 84
- PSA-50 response at Days 28, 56 and 84
- PSA levels at Days 28, 56 and 84
- Trough concentrations of abiraterone at Days 9, 28, 56 and 84

Safety: Safety endpoints include incidence of treatment emergent adverse events (TEAE), and clinically relevant changes in vital signs and laboratory assessments.

Pharmacokinetics: For a cohort of up to 8 patients randomized to TAVT-45 and participating in the serial PK sampling on Day 1 and Day 9, the following PK parameters will be determined:

- Area under the concentration-time curve from time zero to 12 hours post dose (AUC_{0-12})
- Maximum measured plasma concentration (C_{max})
- Minimum measured plasma concentration (C_{min})
- Time to maximum measured concentration (t_{max})
- Accumulation ratio (Rac)
- Effective half-life ($t_{½}$)

Statistical Methods: The effects of TAVT-45 250 mg BID on serum testosterone will be compared to R-AA (1000 mg QD) based on the equivalence approach of 80% to 125% confidence interval (CI) of the test-to-reference geometric mean ratio. Under the assumptions of a coefficient of variation of 25%, a lower and upper limit of 80% to 125%, and an expected test-to-reference ratio of 1.05, 108 patients in total (54 patients in TAVT-45 and 54 patients in R-AA) will provide over 80% power (two one-sided t-tests at 0.05 level) to conclude therapeutic equivalence of TAVT-45 to R-AA.

The primary endpoint, the average serum testosterone levels on days 9 and 10, will be analyzed by an analysis of variance (ANOVA) model with treatment as a factor. The test-to-reference geometric mean ratio effect and its 90% confidence interval (CI) of TAVT-45 to R-AA will be compared to 80% to 125% limit [1,2] . The primary analysis will be performed on the mCRPC intent-to-treat (CR-ITT) population and repeated on the ITT and per-protocol populations. Primary analysis will also be repeated on CSPC patients. Different missing data imputation approaches will be used as sensitivity analyses based on the intent-to-treat population. If the equivalence of the average of serum testosterone levels on days 9 and 10 is achieved, then the key secondary endpoint (PSA-50 response) will be tested at 0.05 alpha level.

Safety will be assessed in all patients who received at least one dose of study drug. Treatment-emergent AEs, along with the number and percentage of patients with abnormal or potentially clinically significant clinical laboratory values and vital sign measurements, will be summarized by treatment. Hypothesis testing, unless otherwise indicated, will be performed at the 5% significance level.

1 INTRODUCTION

1.1 Background

Abiraterone acetate is rapidly converted in vivo to abiraterone, a selective, irreversible inhibitor of cytochrome P450 17α (17α-hydroxylase/C17-20 lyase; CYP17), an enzyme that is key in the production of androgens in all sites, including the testes and adrenal glands. CYP17 catalyses the conversion of pregnenolone and progesterone into testosterone precursors, dehydroepiandrosterone (DHEA) and androstenedione [3,4]. Inhibition of this biochemical process results in decreased proliferation of androgen sensitive castration-resistant prostate cancer (CRPC) cell lines and slower disease progression in patients.

Abiraterone acetate is indicated for the treatment of metastatic castration-resistant prostate cancer (mCRPC) and metastatic high-risk castration-sensitive prostate cancer (CSPC), in combination with prednisone in the US and in combination with either prednisone or prednisolone in Europe. Abiraterone acetate is currently marketed under the trade name Zytiga as film-coated tablets containing 500 mg abiraterone acetate and as uncoated tablets containing 250 mg. The recommended dose for Zytiga is 1000 mg orally once daily, together with prednisone/prednisolone (5 mg orally twice daily for mCRPC patients; and 5 mg orally once daily for high-risk CSPC patients). Patients receiving Zytiga should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy [3,4]. Abiraterone acetate has been shown to be safe and effective in both the CRPC and high-risk CSPC populations with distant metastases (M1, according to the American Joint Committee on Cancer [AJCC] tumor, node, metastasis [TMN] system). Of note, abiraterone acetate is also recommended as Category 1 evidence by the National Comprehensive Cancer Network (NCCN) as first-line treatments for both populations (i.e., nodal metastases [N+M0]).

Administration of Zytiga with food, compared with administration in a fasted state, results in up to a 10-fold (AUC) and up to a 17-fold (C_{max}) increase in mean systemic exposure of abiraterone, depending on the fat content of the meal. Given the normal variation in the content and composition of meals, taking Zytiga with meals has the potential to result in highly variable exposures. Therefore, Zytiga must not be taken with food. It should be taken at least two hours after eating and no food should be eaten for at least one hour after taking Zytiga. The 10-fold food effect observed also shows that the oral bioavailability of abiraterone is below 10% when Zytiga is administered in the fasted state. Inter-subject variability has been shown to be approximately 79% for C_{max} and 64% for AUC_{0-24} after multiple day dosing.

The objective of the TAVT-45 development program was to develop an abiraterone acetate formulation with improved oral bioavailability through enhanced solubility in the fasted state, thereby decreasing the food effect observed after the oral administration of Zytiga. This would eliminate the requirement of taking the drug on an empty stomach, would allow significant reduction of the dose, and would reduce the high variability of exposure. Additionally, and importantly, the oral suspension formulation of TAVT-45 addresses the unmet medical need of prostate cancer patients who have difficulty swallowing the currently approved 500 mg filmcoated tablet and the 250 mg uncoated tablet formulations of Zytiga. Both presentations require patients to swallow multiple, large tablets daily. This is of particular importance since dysphagia, defined as difficulty or discomfort in swallowing, has been reported to affect ~20% to 40% of cancer patients and can impact compliance to prescribed medications due to difficulty swallowing pills [5,6,7]. As an oral suspension, TAVT-45 provides an alternative formulation and choice for cancer patients with and without dysphagia and reduces the pill burden in these patients.

1.2 Investigational medical product

The following investigational medicinal products (IMPs) will be used in this clinical study:

- **TAVT-45:** Administered twice daily as 1 x sachet containing TAVT-45 (250 mg abiraterone acetate). Each sachet is reconstituted in water or specified fruit juice.
- **Reference abiraterone acetate (R-AA):** Administered once daily as (2 x 500 mg Zytiga tablets). Tablets are administered with water.

1.3 Previous study findings

Three novel formulations of abiraterone acetate have been used to support the clinical development. Initial formulations were identified as DRGT-45, while the final formulation to be evaluated in this study is identified as TAVT-45.

[redacted] The granule formulation of TAVT-45 will be used in this study.

1.3.1 Nonclinical studies

The non-clinical aspects of abiraterone acetate are well documented [3,4]. [redacted]

Full details of nonclinical assessments may be found in the TAVT-45 Investigator Brochure [8].

1.3.2 Clinical studies

Abiraterone acetate has been investigated extensively as Zytiga in healthy volunteers and patients [3, 4]; further clinical study results are available in the Investigator's Brochure [8], and are discussed below.

[redacted]

1.3.2.1 Zytiga pharmacokinetics and metabolism

Following administration of Zytiga, the PK of abiraterone and abiraterone acetate have been studied in healthy subjects, patients with metastatic advanced prostate cancer and subjects without cancer with hepatic or renal impairment. Abiraterone acetate is rapidly converted in vivo to abiraterone, an androgen biosynthesis inhibitor.

Following oral administration of abiraterone acetate in the fasting state, the time to reach maximum plasma abiraterone concentration is approximately 2 hours. No major deviation from dose proportionality was observed in the dose range of 250 to 1000 mg. Steady state is achieved within eight days following once-daily dosing of 1000 mg, with approximately 2-fold higher exposure at steady state (steady state AUC) compared to when the same dose is administered as a single dose. Inter-subject variability has been shown to be approximately 79% for C_{max} and 64% for AUC_{0-24} after multiple day dosing.

Following oral administration of ^{14}C-abiraterone acetate as capsules, abiraterone acetate is hydrolysed to abiraterone, which then undergoes metabolism including sulphation, hydroxylation and oxidation primarily in the liver. The majority of circulating radioactivity (approximately 92%) is found in the form of metabolites of abiraterone. Approximately 88% of the radioactive dose is recovered in faeces and approximately 5% in urine.

Administration of abiraterone acetate with food, compared with administration in a fasted state, results in up to a 10-fold (AUC) and up to a 17-fold (C_{max}) increase in mean systemic exposure of abiraterone, depending on the fat content of the meal. Given the normal variation in the content and composition of meals, taking Zytiga with meals has the potential to result in highly variable exposures. The mean half-life of abiraterone in plasma is approximately 15 h based on data from healthy subjects.

The plasma protein binding of ^{14}C-abiraterone in human plasma is 99.8%. The apparent volume of distribution is approximately 5630 L suggesting that abiraterone extensively distributes to peripheral tissues [4].

1.3.2.2 Zytiga clinical efficacy and safety

Zytiga decreases serum testosterone and other androgens to levels lower than those achieved by the use of gonadotropin-releasing hormone (GnRH) analogues alone or by orchiectomy. This results from the selective inhibition of the CYP17 enzyme required for androgen biosynthesis.

The key studies with Zytiga include two randomized placebo-controlled, multicenter Phase 3 trials in patients with metastatic CRPC (COU-AA-301 and COU-AA-302) and one randomized placebo-controlled, multicenter Phase 3 trial (LATITUDE) in patients who had metastatic high-risk CSPC [9,10,11]. In these trials, Zytiga was administered orally at a dose of 1,000 mg daily in combination with prednisone 5 mg (twice daily for mCRPC patients and once daily for high-risk CSPC), and added to standard androgen deprivation therapy (ADT), consisting of either a gonadotropin-releasing hormone (GnRH) analog or prior orchiectomy. In the mCRPC patients,

overall survival was prolonged in the Zytiga–prednisone group compared to the placebo–prednisone group in both patients who previously received chemotherapy [9] and those who were chemotherapy naïve [10]. Similarly, in patients with metastatic high-risk CSPC, addition of Zytiga-prednisone to ADT significantly increased overall survival and radiographic progression-free survival in men with newly diagnosed, metastatic, CSPC [11]. These studies also demonstrated that Zytiga was well tolerated. Most toxic effects were predominantly grade 1 or 2, with a low rate of drug discontinuation or dose reduction and were largely mechanism-based and secondary to mineralocorticoid excess resulting from blockade of CYP17. The common adverse events (≥1%) resulting in discontinuation of Zytiga-prednisone were hepatotoxicity and cardiac disorder.

The current NCCN guidelines for treatment of prostate cancer also recommends Zytiga usage in high-risk CSPC patients with nodal metastases (N+ M0). This is based, in part, on the findings from the STAMPEDE trial, which demonstrated that adding abiraterone leads to an increased life expectancy and improvement in disease control in newly diagnosed metastatic or node-positive disease [12].

An additional observational study showed that abiraterone trough concentration correlates with PSA response and progression-free survival (PFS). Moreover, a cut-off value for plasmatic concentration (8.4 ng/mL) was determined for PSA response [13]. These data show that there is a relationship between steady state abiraterone trough concentrations, primary treatment resistance, and efficacy response (PSA and PFS). Of note, since Zytiga exhibits highly variable PK, low plasma abiraterone concentrations are not infrequent. This highlights a major limitation for Zytiga.

1.3.2.3 TAVT-45 clinical experience

[redacted]

1.4 Clinical rationale

The low bioavailability, significant food effect and the highly variable nature of abiraterone PK after dosing with Zytiga results in known efficacy and potential safety issues. As noted above, it has been shown that patients who exhibited primary resistance to 1,000 mg Zytiga had lower plasma abiraterone concentrations when compared to responders [13]. Therefore, TAVT-45 is being developed to have an abiraterone acetate formulation with improved oral bioavailability, and thus the highly variable nature of abiraterone exposure seen after Zytiga dosing is expected to be reduced with TAVT-45 dosing. This may result in a greater proportion of patients having abiraterone trough concentrations exceeding the 8.4 ng/mL threshold after TAVT-45 treatment compared to Zytiga. Moreover, through enhanced solubility in the fasted state, it is expected that TAVT-45 would decrease the positive food effect observed after the oral administration of Zytiga, eliminating the requirement of taking the drug on an empty stomach. The improved bioavailability of TAVT-45 would also allow significant reduction of the dose compared to Zytiga. Finally, TAVT-45 would be the first and only anti-androgen therapy that does not increase patient pill-burden in that it is dosed as a suspension in water or fruit juice. The oral suspension formulation of TAVT-45 also addresses the unmet medical need of prostate cancer patients who have difficulty swallowing the currently approved 500 mg film-coated tablet and the 250 mg uncoated tablet formulations of Zytiga. This is of particular importance since dysphagia, defined as difficulty or discomfort in swallowing, has been reported to affect ~20% to 40% of cancer patients and can impact compliance to prescribed medications due to difficulty swallowing pills [5,6,7].

1.5 Purpose

This study aims to establish therapeutic equivalence of clinical efficacy and safety between TAVT-45 and Zytiga in patients with mCSPC (distant metastases) and mCRPC.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary objective

The primary objective of this study is to establish therapeutic equivalence between TAVT-45 granules and Zytiga tablets, hereafter referred to as reference abiraterone acetate (R-AA), in patients with mCSPC and mCRPC.

2.2 Secondary objective

The secondary objective of this study is to characterize the multiple-dose pharmacokinetic profile of TAVT-45 in a cohort of patients.

2.3 Endpoints

Efficacy:

The primary efficacy endpoint is the comparison of the average of serum testosterone levels on days 9 and 10 between groups (TAVT-45 vs R-AA).

The key secondary efficacy endpoint is the PSA-50 response, defined as a decrease of ≥ 50% in PSA levels from baseline at any time over the 84-day post-treatment period.

Other secondary efficacy endpoints are as follows:

- Serum testosterone levels at Days 28, 56 and 84
- PSA-50 response at Days 28, 56 and 84
- PSA levels at Days 28, 56 and 84
- Trough concentrations of abiraterone at Days 9, 28, 56 and 84

Safety:

Safety endpoints include incidence of treatment emergent adverse events (TEAE), and clinically relevant changes in vital signs and laboratory assessments.

For more details on study endpoints, see Section 9.

Pharmacokinetics:

For a cohort of up to 8 patients randomized to TAVT-45 and participating in the serial PK sampling on Day 1 and Day 9, the following PK parameters will be determined:

- Area under the concentration-time curve from time zero to 12 hours post dose (AUC_{0-12})
- Maximum measured plasma concentration (C_{max})
- Minimum measured plasma concentration (C_{min})
- Time to maximum measured concentration (t_{max})
- Accumulation ratio (Rac)
- Effective half-life ($t_{½}$)

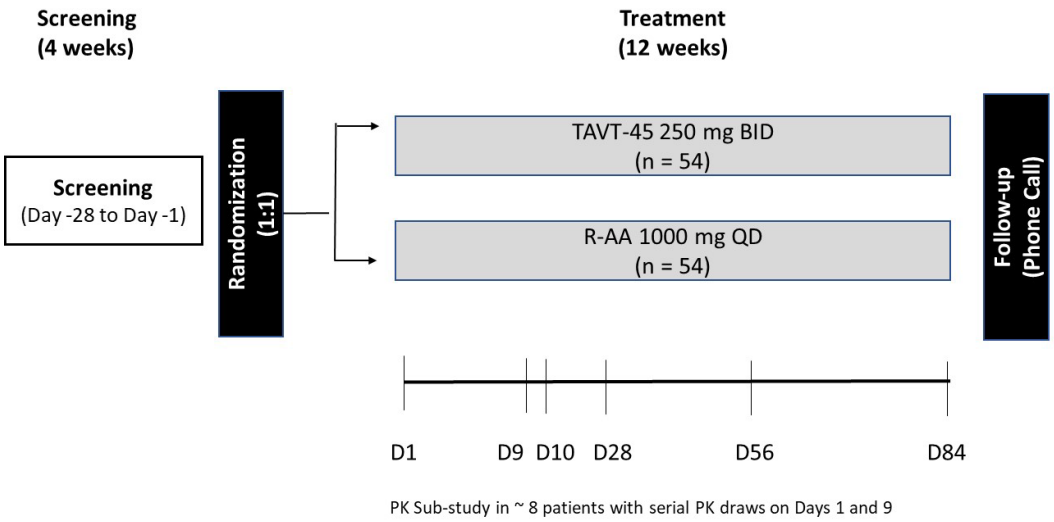
3 INVESTIGATIONAL PLAN

3.1 Study design

This is a Phase 3 randomized, open-label study to evaluate the pharmacodynamic effect of TAVT-45 compared to Zytiga (reference abiraterone acetate formulation, hereafter referred to as R-AA) in patients with mCSPC (distant metastases) and mCRPC. Randomization will be stratified by prostate cancer population (CSPC vs CRPC) and baseline testosterone (< 10 vs ≥ 10 ng/dL). Patients will be treated for 84 days and randomized into one of two groups in a 1:1 ratio:

- **TAVT-45:** Administered twice daily as 1 x sachet TAVT-45(250 mg abiraterone acetate) + Prednisone (5 mg once or twice daily, depending on prostate cancer population)
- **R-AA:** Administered once daily as 2 x 500 mg Zytiga tablets + Prednisone (5 mg once or twice daily, depending on prostate cancer population)

Figure 1 Study schema



It is planned to enroll 108 patients in this study (n=54 patients per prostate cancer population), randomized in a 1:1 ratio receiving either TAVT-45 (n=27 mCRPC and n=27 mCSPC patients) or R-AA (n=27 mCRPC and n=27 mCSPC patients).

3.2 Rationale for study design

Because this study will administer TAVT-45 at 250 mg BID, while maintaining the standard approved dosing of once daily R-AA (i.e., 1000 mg QD), as discussed below, it is not possible to directly compare the PK profile between these two agents using a traditional bioequivalence of C_{max} and AUC. Therefore, this study aims to establish therapeutic equivalence of clinical efficacy and safety.

This study will evaluate serum testosterone levels after treatment with TAVT-45 compared to R-AA as the primary efficacy endpoint to show equivalent pharmacodynamic effects. Testosterone suppression has been recognized by the FDA as an appropriate efficacy endpoint for establishing efficacy of GnRH agonists and antagonists that are approved after the

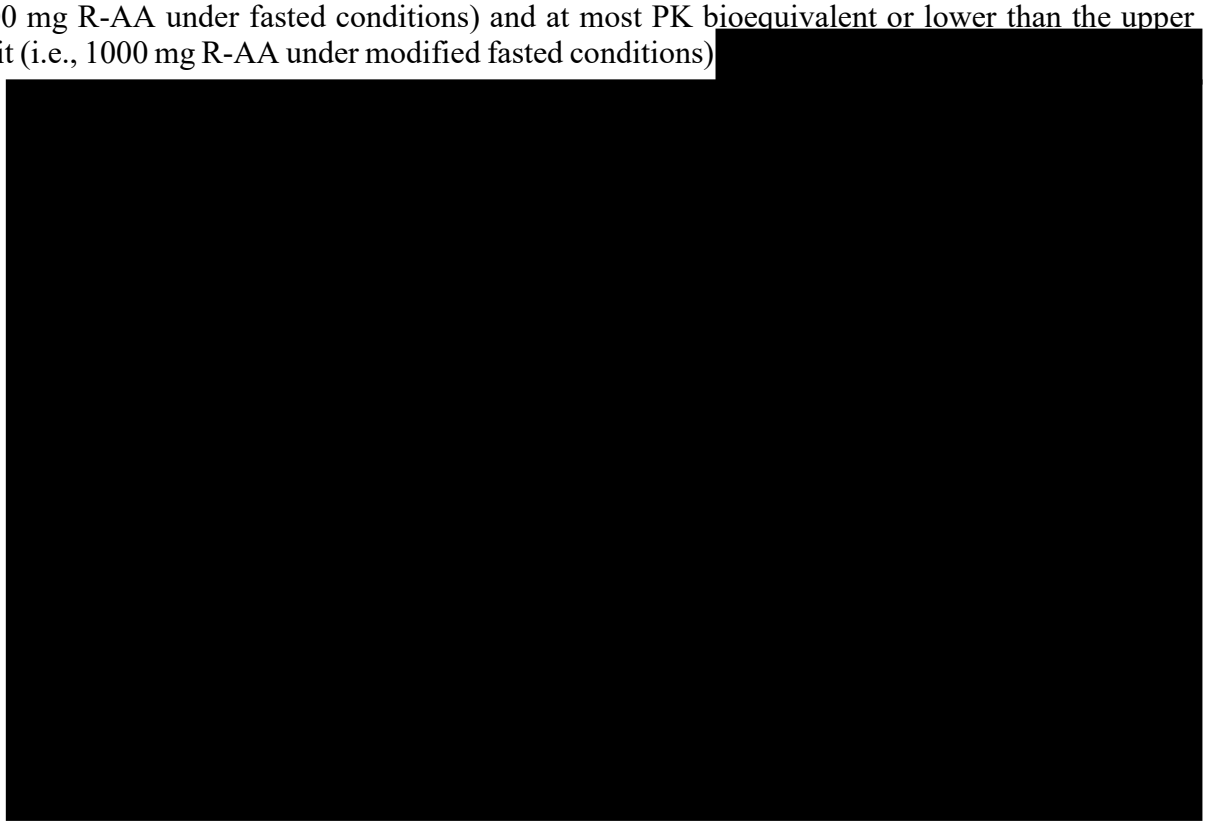
originator/prototype agents. Using serum testosterone as the primary endpoint for clinical equivalence is also consistent with the study design used in the STAAR study, which was a randomized phase 2 therapeutic equivalence study of abiraterone acetate fine particle formulation (Yonsa®) vs. originator abiraterone acetate (Zytiga) in patients with mCRPC [15]. Like the STAAR study, this study will also assess serum testosterone on Days 9 and 10 of treatment, which aligns with the expected attainment of steady state abiraterone plasma concentrations. The safety and tolerability profiles will also be examined, together with other measures of efficacy, including PSA, which is the key secondary efficacy endpoint that will provide further supportive evidence of the clinical similarity between TAVT-45 and R-AA.

The two study populations, mCRPC and mCSPC, will be randomized in a 1:1 ratio to ensure balance of the populations across the two treatment groups. Likewise, randomization will be stratified by baseline testosterone levels (< 10 and ≥ 10 ng/dL) to ensure balance in each treatment arm. The testosterone stratification threshold of 10 ng/dL was selected considering the baseline levels reported in the STAAR study for the patients with mCRPC [15] as well as average testosterone values observed following bilateral orchiectomy [16].

3.3 Rationale for dose/regimen, route of administration and duration of treatment

The dose level of R-AA for this study is 1000 mg once daily, which is the standard approved dose level [3].

The dose level of TAVT-45 will be 250 mg BID, which corresponds to a total daily dose of 500 mg. Selection of this dosing regimen is supported by single dose data from the Phase 1 PK study DRGT45C03 (see also Section 1.3.2.3 for details). One of the aims of Part 2 of this study was to have an in-study comparison between DRGT-45 and R-AA for PK bioequivalence assessments after single doses. Of specific interest was to evaluate whether abiraterone exposure after 250 mg DRGT-45 dosing was at least PK bioequivalent or higher than the lower limit (i.e, 1000 mg R-AA under fasted conditions) and at most PK bioequivalent or lower than the upper limit (i.e., 1000 mg R-AA under modified fasted conditions)



In the study described herein, R-AA will be administered orally either ≥ 1 hour before or ≥ 2 hours after a meal. TAVT-45 will be administered without respect to food with the exception of dose administration in the pharmacokinetic sub-study. Patients participating in the serial blood draws on Days 1 and 9 will administer TAVT-45 in the fasted state (minimum of 8 h fast) on these days and may resume normal meal schedules 2 h after administration of the TAVT-45.

The duration of treatment in this study will be 84 days (12 weeks). This is equivalent to three 28-day cycles, and consistent with the STAAR study that also compared a novel abiraterone formulation to R-AA [15]. Moreover, 12 weeks is a time point that is historically used in many metastatic CRPC studies as a landmark for measuring response to therapy; for example, PSA responses at 12 weeks was a statistically significant factor associated with survival in a multivariate analysis using a prognostic model applied to multiple clinical trials [17,18].

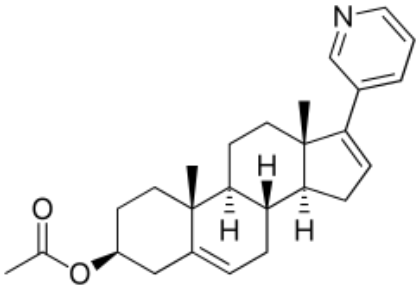
For the dose selection and timing of the concomitant prednisone, see Section 3.5.

3.4 Formulation to be used

This study will use TAVT-45 and R-AA (which is the reference abiraterone acetate currently marketed under the trade name Zytiga).

Abiraterone acetate is the acetyl ester of abiraterone, which is an inhibitor of CYP17. The chemical designation is 3β-acetoxy-17-(3-pyridyl)-androsta-5,16-diene. It is a white to off-white powder practically insoluble in aqueous media (pH range 2.0 to 12.9), very slightly soluble in 0.1N HCl solution and soluble to freely soluble in organic solvents. Abiraterone acetate is classified as Class IV compound (low solubility low permeability) according to the biopharmaceutical classification system (BCS). Its empirical formula is $C_{26}H_{33}NO_2$. The structural formula is shown in Figure 2.

Figure 2 **Structural formula of the study drug (abiraterone acetate)**



R-AA tablets are available as film-coated tablets containing 500 mg abiraterone acetate and as uncoated tablets containing 250 mg. The excipients used in the formulation of Zytiga are lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate, magnesium stearate and colloidal silicon dioxide.

TAVT-45 granules contain [redacted]

3.5 Rationale for choice of additional treatment

In addition to the TAVT-45 or R-AA treatments, all patients in this study will also receive prednisone during the treatment period. Specifically, 5 mg prednisone will be administered orally twice daily for mCRPC patients, and 5 mg prednisone orally once daily will be administered for mCSPC patients.

This requirement for co-adminstration of prednisone (including the dose level and frequency for mCRPC and mCSPC patients) is consistent with the on-label dosing requirements on R-AA. Abiraterone is a CYP17A1 inhibitor, and one of the side effects of CYP17A1 inhibition is a decrease in cortisol levels. This leads to a compensatory increase in adrenocorticotropic hormone (ACTH), and an accumulation of steroids with mineralocorticoid properties. Glucocorticoids, such as prednisone, can suppress ACTH secretion from the anterior pituitary and thus prevent mineralocorticoid-related side effects (e.g., hypokalemia, hypertension, and fluid retention).

As part of the standard ADT background, all patients in this study must also be receiving a GnRH analog concurrently if they have not had a bilateral orchiectomy. ADT background will be recorded in the CRF. Patients receiving a GnRH analog will record administration in a diary to allow assessment of compliance with ADT therapy.

3.6 Purpose and timing of interim analyses/design adaptations

Not applicable as there are no plans for conducting an interim analysis.

3.7 Risks and benefits

Since R-AA is already approved by the FDA for both mCRPC and mCSPC with distant metastases, and TAVT-45 contains the same active ingredient (abiraterone acetate), it is expected that patients will benefit from these treatments. Additional potential benefits of TAVT-45 over R-AA are described in Section 1.4, and may include less variability of exposure, no requirement to take the drug on an empty stomach, and an alternative choice for patients with dysphagia or aversion to swallowing large pills.

There is considerable data available on the adverse effects associated with abiraterone acetate from placebo-controlled clinical trials (comprising over 2000 patients from the Zytiga clinical program); full details are available in the Zytiga SmPC [4].

Based on pooled safety analyses of multiple clinical trials [3,4], the most common adverse reactions (≥10%) that occurred more commonly (>2%) in Zytiga treatment arm compared to placebo were fatigue, arthralgia, hypertension, nausea, edema, hypokalemia, hot flush, diarrhea, vomiting, upper respiratory infection, cough, and headache. The most common laboratory abnormalities (>20%) that occurred more commonly (≥2%) in the Zytiga arm were anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, and hypokalemia. Grades 3-4 adverse events were reported for 53% of patients in the Zytiga arm and 46% of patients in the placebo arm. Treatment discontinuation was reported in 14% of patients in the Zytiga arm and 13% of patients in the placebo arm. The common adverse events (≥1%) resulting in discontinuation of Zytiga and prednisone were hepatotoxicity and cardiac disorder.

Since TAVT-45 also contains abiraterone acetate as the active ingredient, any adverse reactions and their incidences are expected to be similar to those reported for Zytiga.

[redacted]

General Risks

During cannulation, more than one attempt may be needed to insert the cannula in a vein of a patient, and it is possible that bruising and/or inflammation may be experienced at the site of cannulation.

COVID-19 Related Risks

The following risks and risk mitigating measures apply to this study which may be impacted by the ongoing SARS-CoV-2 (COVID-19) global pandemic:

- Test Product Related Risk:
  - Based on a review of both nonclinical and clinical data, neither Zytiga nor TAVT-45 have immunomodulatory effects that would confer an increased risk to participants enrolled in the study either contracting or experiencing a more serious disease if infected with COVID-19.
- General COVID-19 Related-Risk Mitigation Measures:
  - Tavanta and [redacted] will work with clinical sites to document site-level procedures regarding COVID-related precautions for patients and staff (such as personal protective devices of face coverings, masks, shields, temperature screening, and social distancing procedures). The study visit schedule has also been carefully reviewed to minimize unnecessary visits and patient exposure.
  - Tavanta and [redacted] will continue to assess risk during the course of the clinical study due to COVID-19 impact. This includes risk assessment for the overall study, as well as at the country/regional levels since changes/adaptations may be needed at a local level depending on the local COVID-19 situation. This may include impacts on visit schedules, assessments performed in-person or virtually, and alternative options for IMP re-supply for patients. Tavanta and [redacted] will also communicate as needed with IRB/IEC and Data Monitoring Committee (DMC) staff. The risk mitigation measures, where applicable, will be amended based on emerging government guidances.

4 STUDY POPULATION

The study population will consist of mCSPC and mCRPC patients.

The study population will be comprised of the patients who have passed screening assessments and who comply with eligibility criteria. Screening procedures can be repeated once to confirm out of range values prior to excluding a patient from participating in the study. Patients can be re-screened only once, and no study related re-screening procedures should be performed before re-consent by the patient. Mis-randomized patients will not be re-screened.

4.1 Inclusion Criteria

1. Written informed consent obtained prior to any study-related procedure being performed
2. Male patients at least 18 years of age or older at time of consent
3. Pathologically confirmed adenocarcinoma of the prostate
4. Ongoing therapy with a gonadotropin releasing hormone (GnRH) agonist or antagonist (unless patient has already had a bilateral orchiectomy) AND serum testosterone level <50 ng/dL at screening

5. Have either metastatic CSPC or metastatic CRPC, as defined below:
    - CSPC: Using the American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) system, patients must have T_{any} N_{any} M+ (distant metastases) disease AND two of the following:
        - Gleason score of 8 or greater
        - Three or more bone scan lesions
        - Measurable visceral metastases
    - CRPC: Patients must have metastatic* disease, and must also have disease progression according to the recommendations of the Prostate Cancer Working Group 3 by having at least one of the following criteria:
        - Two rises of PSA (taken a minimum of 1 week apart) from a baseline measurement of at least 1 ng/mL
        - Imaging progression (CT/MRI) by RECIST 1.1 criteria or PET/CT*
        - Nuclear scan progression by 2 or more new bone lesions.

      ** Note: Metastatic disease should be documented by MRI/CT, PET/CT (including, but not limited to, standard of care imaging using ^{18}F-fluciclovine, ^{11}C-choline, or PSMA where approved) or bone scan. Imaging obtained within 90 days prior to the start of study drug/reference product will be accepted.*
6. The following prior treatment and / or surgery for prostate cancer are allowed:
    - CSPC:
        - Up to 90 days of androgen deprivation therapy (ADT) with gonadotropin-releasing hormone (GnRH) agonists/antagonists or orchiectomy with or without concurrent anti-androgens prior to patients' randomization is permitted
        - Patients may have one course of palliative radiation or surgical therapy to treat symptoms resulting from metastatic disease (e.g., impending cord compression or obstructive symptoms) if administered prior to randomization
        - Radiation or surgical therapy that was not initiated 4 weeks after the start of ADT or orchiectomy
    - CRPC:
        - Previous chemotherapy with docetaxel for metastatic disease with treatment completed at least 1 year prior to Screening
7. Discontinuation of flutamide or nilutamide, and other anti-androgens prior to the start of study medication; discontinuation of bicalutamide prior to start of study medication
8. Discontinuation of strong CYP3A4 inducers at least 4 weeks prior to start of study medication
9. Discontinuation of radiotherapy prior to start of study medication
10. Discontinuation of herbal supplements at least 4 weeks prior to the first dose of study medication and for the duration of the trial.
11. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 at screening

12. Normal organ function with acceptable initial laboratory values within the screening period:

ANC	≥ 1,500/µl
Albumin Hemoglobin	≥ 3.0g/dL ≥ 9g/dL
Platelet count	≥ 100,000/µl
Serum Creatinine	≤ 3.0 x the institutional upper limit of normal (ULN)
Potassium	≥ 3.5 mmol/L (within institutional normal range)
Bilirubin	≤ 1.5 ULN (unless documented Gilbert's disease)
SGOT (AST)	≤ 2.5 x ULN
SGPT (ALT)	≤ 2.5 x ULN

13. Life expectancy of at least 6 months at screening
14. Patients engaged in sex with women of child-bearing potential agree to use a condom plus another effective contraception method. Patients agree to use a condom when engaged in any sexual activity, including sex with a pregnant woman. These restrictions will apply from the time informed consent is provided until 3 weeks after the last dose of study medication is taken.
15. Patient is willing and able to comply with all protocol requirements assessments

4.2 Exclusion criteria

1. For mCSPC patients:
    - Any prior pharmacotherapy, radiation therapy, or surgery for metastatic prostate cancer not specified as allowable treatment in Inclusion Criterion 6. For example, prior therapy with apalutamide or enzalutamide is prohibited as well as therapy with an investigational agent as described in Exclusion Criterion 16.
2. For mCRPC patients:
    - Prior treatment with abiraterone or enzalutamide is prohibited
    - Previous chemotherapy is prohibited with exception of docetaxel treatment as specified in Inclusion Criterion 6.
3. Initiation of bisphosphonate or denosumab therapy within 4 weeks prior to the start of study drug/reference product. Patients who are on a stable dose of these medications for at least 4 weeks at the time of starting study drug/reference product will be eligible.
4. Therapy with estrogen within 4 weeks prior to the start of study drug
5. Use of systemic glucocorticoids equivalent to >10 mg prednisone daily. Patients who have discontinued or reduced dosing to the equivalent of ≤ 10 mg prednisone daily within 14 days prior to the start of study drug are eligible
6. Known, symptomatic metastases to the brain or central nervous system involvement (patients with asymptomatic and neurologically stable disease for the past 4 weeks will be permitted)
7. History of adrenal gland dysfunction defined as requiring treatment for adrenal insufficiency
8. History of other malignancy within the previous 2 years (no longer being actively treated), with the exceptions of basal cell carcinoma, non-muscle invasive bladder cancer that has been treated and is under surveillance, or other in-situ cancers with a low likelihood of recurrence
9. Major surgery within 4 weeks prior to the start of study drug

10. Known gastrointestinal disease or condition that could impair absorption inclusive of gastrocolic fistula, gastroenterostomy, biliary obstruction, cirrhosis, chronic pancreatitis or pancreatic cancer, cystic fibrosis, lactate deficiency, amyloidosis, celiac disease, Crohn's disease, radiation enteritis, intestinal resection, and history of bariatric surgery
11. Known history of human immunodeficiency virus or seropositive test for hepatitis C virus (HCV) or hepatitis B surface antigen (HBsAg) (note: HCV patients with undetectable viral load will be eligible)
12. Poorly controlled diabetes, defined as HbA1c > 8% within the past 12 months
13. Uncontrolled hypertension at screening
14. History of New York Heart Association class III or IV heart failure
15. Serious concurrent illness, including psychiatric illness, that could interfere with study participation
16. Receipt of another investigational agent within 4 weeks or 5 x the treatment half-life, whichever is longer, of treatment start.
17. Known hypersensitivity or allergy to abiraterone acetate, prednisone or any excipients in the study drugs
18. In the opinion of the investigator, participation in the trial would prevent the patient from receiving local standard-of-care treatment for metastatic prostate cancer, if clinically indicated, after completion of the trial
19. Other condition which, in the opinion of the Investigator, would preclude participation in this trial.

5 TREATMENT

5.1 Study treatment: investigational and control drugs

Tavanta will supply the following study drug:

Investigational treatment

- TAVT-45 (250 mg abiraterone acetate) - Granules for Oral Suspension

Tavanta will supply the reference treatment which will be centrally sourced and supplied.

Reference treatment

- R-AA (reference abiraterone acetate [Zytiga]) 500 mg tablets

5.2 Additional treatments

In addition to the study drugs described above in Section 5.1, Tavanta or designee will also supply prednisone (5 mg tablets). Specifically, 5 mg prednisone will be administered orally twice daily for mCRPC patients, and 5 mg prednisone orally once daily will be administered for mCSPC patients.

All patients must also be receiving a GnRH analog concurrently if they have not had a bilateral orchiectomy. GnRH analogs will not be provided by Tavanta and will be sourced locally through the patient's current prescription.

5.3 Treatment arms

In this study, patients will be randomized 1:1 to one of two groups and treated for 84 days:

- **TAVT-45:** Administered twice daily as 1 x sachet containing TAVT-45 granules (250 mg abiraterone acetate) + Prednisone (5 mg once or twice daily, depending on prostate cancer population)
- **R-AA once daily:** Administered once daily as (2 x 500 mg Zytiga tablets) + Prednisone (5 mg once or twice daily, depending on prostate cancer population)

5.4 Treatment assignment and randomization

All eligible patients will be randomized 1:1 to one of the two treatment arms. Randomization will be stratified by prostate cancer population (CSPC vs CRPC; n=54 per cancer population) and baseline testosterone (<10 vs ≥ 10 ng/dL).

Patients will be assigned a Subject Number upon screening. Eligible patients will be randomized via an Interactive Response Technology (IRT) system. Sites will contact the IRT system only after confirming all eligibility criteria and receiving the screening testosterone value that is needed for stratification (see Table 1). The IRT will assign the patient to the appropriate treatment arm and provide a medication number that will be linked to the different treatments. A separate medication list will be produced by or under the responsibility of Tavanta using a validated system that automates the random assignment of medication numbers to packs containing the study drug(s).

5.5 Treatment blinding

This study is open label.

5.6 Treating the subject

5.6.1 Subject numbering

Each patient is uniquely identified by a Subject Number. Once assigned to a patient, the Subject Number will not be reused. Patients may be re-screened once. In this case, the IRT can be used to request the initial Subject Number in order to link the re-screening to the original screen of that patient. Patients who are mis-randomized cannot be re-screened.

5.6.2 Dispensing the investigational treatment

Each study site will be supplied by Tavanta or designee with sachets containing TAVT-45 and R-AA tablets. A unique medication number is printed on each part of the label which corresponds to test or reference treatment.

5.6.3 Handling of study treatment

Study Investigational treatment must be received by a designated staff member at the study site, handled and stored safely and properly, and kept in a secured location. Upon receipt, all investigational treatment should be stored according to the instructions specified on the labels. TAVT-45 granules should be stored at room temperature in the aluminum foil sachet. R-AA tablets should be stored at 20°C to 25°C (68°F to 77°F); excursions permitted in the range from 15°C to 30°C (59°F to 86°F). Clinical supplies are to be dispensed only in accordance with the protocol. Any excursions or lack of compliance should be reported to Tavanta or designee.

Medication labels will include storage conditions for the study treatment and the medication number and will be compliant with labeling regulations.

The qualified site personnel must maintain an accurate record of the shipment and dispensing of study treatment. Monitoring of drug accountability will be performed by a field monitor during site visits and at the completion of the trial. At the conclusion of the study and as appropriate during the study, all investigational treatments will be reconciled at the site and depot level. Instructions for the final disposition of all unused study medication will be provided to each site in advance of site closure.

5.6.4 Instructions for prescribing and taking study treatment

Study treatments TAVT-45 and R-AA [Zytiga] tablets) will be administered orally each day from Day 1 to Day 84.

TAVT-45 will be taken twice daily (approximately every 12 hours) and may be taken without respect to meals. An exception applies to those patients included in the serial pharmacokinetic cohort. Patients participating in the serial blood draws on Days 1 and 9 will administer TAVT-45 in the fasted state (minimum of 8 h overnight fast) on these days and may resume normal meal schedules 2 h after administration of the TAVT-45 on these days.

Each TAVT-45 sachet contains 250 mg abiraterone acetate, and excipients that ensure abiraterone acetate disperses instantaneously in water or specified juice. For a 250 mg dose, 1 granule sachet should be reconstituted in tap water or specified juice and the resulting suspension immediately administered orally. Reconstitution of the granules can be obtained by stirring the suspension with a spoon for 3 minutes. The reconstituted suspension should be taken immediately after reconstitution. Patients will receive training and a medication preparation guide to ensure correct preparation and administration. At visits when trough abiraterone samples are obtained (see Table 1), the reconstitution fluid (water or juice) used for the last dose will be recorded in the eCRF.

For R-AA, tablets should be taken once daily, either ≥ 1 hour before or ≥ 2 hours after a meal, and swallowed whole with water. For a 1000 mg dose, 2 tablets (containing 500 mg abiraterone acetate) should be taken together.

Patients will be instructed to record administration of study medications in a dosing diary. This is inclusive of TAVT-45, R-AA, prednisone and GnRH analog, if applicable. The patient will record the date and time of each administration of each medication. For TAVT-45, the patient will also record the fluid (water or specified juice) used for reconstitution.

The investigator should promote compliance by instructing the patient to attend the study visits as scheduled and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if he is unable for any reason to attend a study visit as scheduled.

5.6.5 Permitted dose adjustments and interruptions of study treatment

There will not be any planned permitted adjustments of dose strength and frequency. Patients should take TAVT-45 and R-AA as per protocol.

However, if needed due to adverse events, study medication may be temporarily or permanently discontinued at the discretion of the Investigator based on the toxicity management guidance described below related to hepatotoxicity and Grade ≥ 3 toxicities, which aligns with Zytiga prescribing information [3, 4]. Investigators should consult with the Medical Monitor for questions/clarifications as needed.

- *Hepatotoxicity:* If at any time during the trial, the ALT or AST rises above 5x ULN, or total bilirubin rises above 3x ULN, treatment with TAVT-45 or R-AA should be discontinued immediately and the patient should be discontinued from the study. As noted

above, dose reductions are not applicable for this clinical trial, as only one strength of each study medication (TAVT-45 and R-AA) are supplied to patients. Liver function should be closely monitored as part of adverse event monitoring.

- *Grade ≥ 3 toxicities of hypertension, hypokalaemia, oedema and other non-mineralocorticoid toxicities:* If at any time during the trial, a patient experiences Grade ≥ 3 hypertension, hypokalaemia, oedema or other non-mineralocorticoid toxicities (according to the National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE], Version 5.0 [20]), treatment should be withheld and appropriate medical management should be instituted. Treatment with TAVT-45 or R-AA should not be reinitiated until symptoms of the toxicity have resolved to Grade 1 or baseline.

All actions with respect to study drug dosing in relation to an AE must be documented appropriately within the CRF.

5.6.6 Rescue medication

Not applicable.

5.6.7 Concomitant medication

In addition to the TAVT-45 or R-AA treatments, all patients in this study will also receive prednisone during the treatment period. Specifically, 5 mg prednisone will be administered orally twice daily for mCRPC patients and 5 mg prednisone orally once daily will be administered for mCSPC patients.

Per protocol, all patients in this study should also be taking a GnRH analog concurrently or should have had bilateral orchiectomy.

Bisphosphonate usage is allowed only if patients are on the medication at a stable dose and regimen for 4 weeks prior to Study Day 1 (see Exclusion Criterion #3).

The investigator should instruct the patient to notify the study site about any new medications over-the-counter drugs, supplements, and vitamins administered after the patient is enrolled into the study. All medications (other than study treatment), procedures and significant non-drug therapies (including physical therapy and blood transfusions) must be recorded on the CRF. The reason, name of the drug, procedure or non-drug therapy should be listed.

Since androgen deprivation treatment may prolong the QT interval, caution is advised when administering abiraterone acetate with medicinal products known to prolong the QT interval or medicinal products able to induce torsades de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc.

Use of spironolactone with abiraterone acetate is not recommended, since spironolactone binds to the androgen receptor and may increase PSA levels.

5.6.8 Prohibited medication (interaction with other medicinal products and other forms of interaction)

Refer to the Inclusion and Exclusion Criteria regarding medications that are prohibited, or must be discontinued, prior to the start of study drug and throughout the study (see Sections 4.1 and 4.2).

Concomitant use of a strong CYP3A4 inducer should be avoided (see Section 5.6.8.2) and caution should be exercised if a CYP2D6 substrate with a narrow therapeutic index cannot be avoided (see Section 5.6.8.3).

5.6.8.1 Abiraterone acetate contraindications

Abiraterone acetate can cause fetal harm and potential loss of pregnancy based on animal studies. However, it is not indicated for use in women.

5.6.8.2 Effects of other medicinal products on abiraterone acetate

Cytochrome P450 inhibitor

In a dedicated drug interaction trial, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone.

Cytochrome P450 inducers

In a dedicated drug interaction trial, co-administration of rifampin, a strong CYP3A4 inducer, decreased exposure of abiraterone by 55%. This reduced exposure can be anticipated to decrease the efficacy of abiraterone. Thus, concomitant strong CYP3A4 inducers should be avoided during abiraterone treatment. Notable examples of strong CYP3A4 inducers are apalutamide, carbamazepine, enzalutamide, mitotane, phenobarbital, phenytoin, rifabutin, rifampicin, rifapentine and St John's wort [4,21].

5.6.8.3 Effects of abiraterone acetate on other medicinal products

CYP2D6 Substrate

Abiraterone is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. In a CYP2D6 drug-drug interaction trial, the C_{max} and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1,000 mg daily and prednisone 5 mg twice daily. Avoid co-administration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, consider a dose reduction of the concomitant CYP2D6 substrate drug.

CYP2C8 Substrate

Abiraterone is an inhibitor of the hepatic drug-metabolizing enzyme CYP2C8. In a CYP2C8 drug-drug interaction trial, the AUC of pioglitazone (CYP2C8 substrate) was increased by 46% when pioglitazone was given together with a single dose of 1,000 mg abiraterone acetate. Therefore, patients should be monitored closely for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with abiraterone. Investigators may consult with the Medical Monitor for identification of CYP2C8 substrates with narrow therapeutic index.

5.6.9 Discontinuation of study treatment

Patients may voluntarily discontinue study treatment or the study for any reason at any time. The investigator should discontinue study treatment for a patient if, on balance, he/she believes that continuation would be detrimental to that patient's well-being. Study treatment must be discontinued under the following circumstances:

- Withdrawal of informed consent
- Patient's request to terminate treatment (in this case, the patient may choose to discontinue study treatment, but remain in the study to be followed for safety and undergo study procedures through the follow-up period)

- Any AE, clinically relevant change(s) in a safety parameter, or other medical condition or situation that occurs such that continued participation in the study would not be in the participant's best interest. This includes ALT or AST rises above 5x ULN, or total bilirubin rises above 3x ULN, at any time during the study as described in Section 5.6.5.
- Use of prohibited treatment without approval from the Medical Monitor
- Any other protocol deviation that results in a significant risk to the patient's safety
- Study is terminated by the Sponsor or local health authority, IRB, or IEC

For patients who discontinue study treatment, a CRF should be completed, giving the date and primary reason for stopping study treatment. In the event that the decision is made to permanently discontinue the study treatment, the patient will be withdrawn, and the ET visit should be conducted. Reasonable efforts should be made to have the patient return for this follow-up visit.

5.7 Withdrawal of consent

Patients may be considered discontinued if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

If premature discontinuation occurs for any reason, the investigator must make every effort to determine the primary reason for a patient's premature discontinuation from the study and record this information on the CRF. Patients may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs when a patient does not want to participate in the study anymore, that is, the patient does not want any further visits, assessments, or study-related contact and does not allow analysis of already obtained biologic material. Study treatment must be discontinued, and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up. The data collected on the patient to the point of withdrawal remains part of the study database and may not be removed.

5.8 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be formally considered lost to follow-up until his scheduled End-of-Study visit would have occurred.

5.9 Emergency breaking of assigned treatment code

Not applicable as the study is open label.

5.10 Study completion and post-study treatment

End of study is defined as the date of the last patient last visit (i.e., the Visit 10 follow-up phone call for patients completing the trial as planned, or the Early Termination Visit for patients who are treated but discontinue prior to completing the Day 84 visit [see Table 1 below]).

Information on the patient's completion of dosing during the Treatment Period, or premature discontinuation and the reason for discontinuation will be recorded on the appropriate form of CRF. In any case, the investigator or site staff must contact as soon as possible to record the patient's study completion and/or discontinuation.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study or must refer them for appropriate ongoing care. This care may include initiating another treatment outside of the study as deemed appropriate by the investigator.

There is no post-trial access to study medication after patients complete this trial; instead investigators will prescribe the local standard-of-care treatment for metastatic prostate cancer, if clinically indicated.

5.11 Early study termination

The study can be terminated at any time for any reason by Tavanta. Should this be necessary, the patient must be seen as soon as possible and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board (IRBs) or Independent Ethics Committee (IECs) of the early termination of the trial.

6 VISIT SCHEDULE AND ASSESSMENTS

Table 1 lists all of the assessments and indicates with an "X" when the assessments should be performed at the designated time points. Patients should be seen for all visits on the designated day or as closely as possible to the original planned visit schedule. Missed or rescheduled visits should not lead to automatic discontinuation.

If patients refuse to return for these assessments or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine the reason. Attempts to contact the patient should be recorded in the source documentation.

Screening will be flexible in duration of up to 28 days before first dosing, during which time the patient will sign the informed consent form (ICF) to participate in the study before any protocol-specified procedures or assessments are initiated. Patients evaluated at screening for eligibility should not be screen failed on the basis of a medication requiring washout, unless the patient will be unable to complete the washout in the appropriate time frame before randomization. Upon meeting all inclusion/exclusion criteria set forth in the protocol, patients will be randomized in a 1:1 fashion to receive either TAVT-45 250 mg twice daily (approximately every 12 hours) or R-AA 1000 mg once daily either ≥ 1 hour before or ≥ 2 hours after a meal. All patients should also receive prednisone together with a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy. The mCSPC patients will receive prednisone 5 mg orally once daily, while the mCRPC patients will receive prednisone 5 mg orally twice daily. Randomization will be stratified by prostate cancer population (CSPC vs CRPC) and baseline testosterone (<10 vs ≥ 10 ng/dL). All patients will be treated for 84 days (12 weeks). Patients will return to their clinics on Days 9, 10, 28, 56 and 84 for assessments and evaluations of safety and efficacy, including testosterone, PSA, and abiraterone trough concentrations. Patients may return to the clinic or may visit a local laboratory for evaluation of liver function tests on Days 42 and 70. Blood samples for testosterone will be taken between the hours of 7-10 in the morning. A pharmacokinetic sub-study will be conducted in a cohort of up to 8 patients receiving TAVT-45. Pharmacokinetic profiles over the dosing interval will be obtained on Day 1 (first dose) and on Day 9 (steady state). For all patients, a follow-up phone call will also be made approximately one week after the last dose for AE assessments.

Table 1 Assessment schedule

	Screening (Day -28 to -1)	**Day 1**	**Day 9 (+2)**	**Day 10 (+2)**	**Day 28 (+/-1)**	**Day 42 (+/- 3)**	**Day 56 (+/-1)**	**Day 70 (+/- 3)**	**Day 84 (+/-1)**	**Follow-up Visit[1] (Day 91 (+/-4)**	**Early Termination (ET) Visit[2]**
Visit number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**ET**
Informed consent	[redacted]										
Inclusion/Exclusion criteria											
Demography											
Medical history/diagnosis											
Physical examination[3]											
ECOG											
12-lead ECG[4]											
Vital signs											
Body weight and height[5]											
Clinical laboratory tests[6]											
Hepatotoxicity Monitoring[7]											
Serum testosterone[8]											
PSA[8]											
Serial Pharmacokinetic Sampling[9]											
Abiraterone trough concentrations[10]											
Prior/concomitant medication											
Adverse Events/SAEs[11]											
Randomization											
Drug dispensation											
Drug return/compliance/diary review											

1. For the follow-up visit, a phone call should be made approximately one week after the last dose for AE assessments
2. If patients are randomized and treated, but discontinue prior to completing the Day 84 visit, then an early termination visit should be scheduled.
3. Physical examination at screening includes examination of general appearance, skin, lungs, heart, abdomen, lymph nodes, extremities and vascular system. Abbreviated examinations thereafter to include targeted assessment(s) of the body systems or organs, as indicated by patient symptoms, AEs, or other findings.
4. ECG to be completed after the patient has been in the supine position for a minimum of 5 minutes. ECG to be conducted before vital signs or blood draws if scheduled at the same visit.
5. Height without shoes is measured at the screening visit only.
6. Laboratory safety tests include panels for haematology, clinical chemistry, and urinalysis. At screening only, patients will also be tested for HCV and HBsAg.
7. Transaminases (ALT and AST) along with bilirubin will be obtained to monitor liver function. These assessments may be completed by a local laboratory and reported to the clinical site, if necessary.
8. Testosterone and PSA blood samples are to be collected between 7 and 10 in the morning.
9. Completed only in a cohort of up to 8 patients randomized to TAVT-45 at select site(s) only. Patients are to take their TAVT-45 morning dose in the fasted state (following an overnight fast of at least 8 h) on Days 1 and 9 and will continue to fast for 2 h after morning dose administration after which a normal meal schedule can be resumed. The morning dose administered on Days 1 and 9 will be reconstituted with water. Allowable windows for PK sample collection are provided in Section 6.6.
10. All patients will have pre-dose blood samples collected. However, a separate sample on Day 9 is not needed if this Day 9 pre-dose sample is already being collected as part of the serial PK sampling cohort. Reconstitution fluid used for the previous dose (water or specified juice) will be recorded in the eCRF on days of trough sampling.
11. All AEs /SAEs occurring after the patient has provided informed consent must be reported.
12. This randomization step will be the last activity to occur during the Screening window. Sites will contact the IRT system only after confirming all eligibility criteria and receiving the screening testosterone value that is needed for stratification.

6.1 Information to be collected on screen failures

Patients may discontinue from the study prior to randomization. These patients are considered screen failures. If a patient discontinues before entering the treatment period at baseline, the reason for not being randomized will be entered on the CRF.

All patients who have signed informed consent and are randomized into the Treatment Period of the study will have all AEs occurring after informed consent is signed recorded on the Adverse Event CRF.

6.2 Subject demographics/other baseline characteristics

Patient demographic, baseline characteristic, and medical history data must be collected on all patients and recorded in the CRF. Also, medical history relevant to prostate cancer (such as date of diagnosis and Gleason score) should also be recorded. Whenever possible, diagnoses and not symptoms will be recorded. Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment.

6.3 Treatment exposure and compliance

All dates of study treatment dispensing will be recorded on the appropriate CRF. Drugs administered prior to start of treatment and other drugs/procedures continuing or started during the study treatment period will be entered in the Prior/Concomitant medications CRF.

Compliance (adherence) is expected to be 100%. During each Treatment Period, the number of granule sachets or tablets dispensed and returned will be counted to determine compliance with dosing regimen for TAVT-45, R-AA and prednisone. Compliance (adherence) will also be assessed by a study monitor using information provided by the authorized site personnel.

6.4 Contraception

All sexually active patients must use a condom. Male patients who are sexually active with a female partner of child-bearing potential* must use, with their partner, a condom plus an approved method of highly effective contraception from the time of informed consent until 3 weeks after the last dose of study medication.

A highly effective method of contraception is defined as one that has no higher than a 1% failure rate. In this study, the only highly effective methods of contraception are:

- Partner’s use of combined (oestrogen and progestogen-containing) hormonal contraception:
  - Oral
  - Intravaginal
  - Transdermal
- Partner’s use of progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable/implantable
  - Intrauterine hormone-releasing system
- Partner’s use of implantable intrauterine device

- Surgical sterilization (for example, vasectomy or partner's bilateral tubal occlusion, provided that partner is the sole sexual partner of a study patient of child-bearing potential and that the vasectomized partner has received medical assessment of the surgical success)

Alternatively, true abstinence is acceptable when it is in line with the patient's preferred and usual lifestyle. Periodic abstinence (eg, calendar, ovulation, symptothermal, post ovulation methods for the female partner) and withdrawal are not acceptable methods of contraception. If a patient is usually not sexually active but becomes active, they, with their partner, they must comply with the contraceptive requirements detailed above.

*For clarification, a women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥12 consecutive months; or women on hormone replacement therapy with documented serum follicle-stimulating hormone level ≥35 mIU/mL).

6.4.1 Exposure to Partners During the Study

There is a significant risk of drug exposure through the ejaculate (which also applies to vasectomized males) that might be harmful to the sexual partners (both male and female), including pregnant partners of male patients. Therefore, a condom should be used by all male subjects from the time of informed consent until three weeks after the last dose of study medication.

6.4.2 Sperm Donation

Male patients should not donate sperm from the time of informed consent until three weeks after the last dose of study medication.

6.5 Efficacy assessments

6.5.1 Serum testosterone

Samples for serum testosterone during the Screening period will be taken between 7 am and 10 am. The result of this serum testosterone will be used to qualify the patient for participation in the trial and to randomize eligible patients with stratification by testosterone level.

Samples for serum testosterone assessment points during the treatment period as specified in Table 1 should be taken between 7 and 10 in the morning and be analyzed using a validated and ultrasensitive testosterone assay at a central laboratory with a lower limit of quantification (LLOQ) of 0.1 ng/dL. The serum testosterone obtained pre-dose on Day 1 will be the baseline value for any testosterone change from baseline comparisons during the treatment period.

6.5.2 Prostate-specific antigen

Samples for PSA will be collected as specified in Table 1 should be taken between 7 and 10 in the morning and analyzed using a validated and ultrasensitive PSA assay at a central reference laboratory.

6.5.3 Abiraterone trough concentrations

Blood samples for abiraterone trough concentrations will be collected on Days 9, 28, 56 and 84 (taken before dosing) for all patients. Study staff will remind patients to withhold their morning study medication administration on these visit days. The reconstitution fluid (water or specified juice) used for administration of the previous dose will be recorded in the eCRF on days of trough sampling.

Abiraterone trough concentrations will be analyzed using a validated bioanalytical method.

6.6 Pharmacokinetics

For a cohort of up to 8 patients randomized to TAVT-45 granules and participating in the serial PK sampling on Day 1 and Day 9, blood samples (approximately 4 mL) will be collected at the following times:

- Day 1: at pre-dose (± 30 min), and 0.25 (± 5 min), 0.5 (± 5 min), 0.75 (± 5 min), 1 (± 5 min), 1.5 (± 10 min), 2 (± 10 min), 3 (± 10 min), 4 (± 30 min), 8 (± 30 min), 10 (± 30 min), and 12 (± 30 min) hours post-dose and before the scheduled evening dose
- Day 9: at pre-dose (± 30 min), and 0.25 (± 5 min), 0.5 (± 5 min), 0.75 (± 5 min), 1 (± 5 min), 1.5 (± 10 min), 2 (± 10 min), 3 (± 10 min), 4 (± 30 min), 8 (± 30 min), 10 (± 30 min), and 12 (± 30 min) hours post-dose and before the scheduled evening dose

Patients will be in the fasted state (overnight fast of at least 8 h) at the time of morning TAVT-45 administration and will remain fasted for 2 hours after morning dose administration after which time the normal meal schedule may be resumed. The morning dose of TAVT-45 granules will be reconstituted with water on Days 1 and 9. Abiraterone concentrations in these serial samples will be analyzed using a validated bioanalytical method.

6.7 Safety

All safety assessments should be done prior to study treatment administration. Appropriate safety assessments should be repeated after the dose is administered as per Table 1.

Safety assessments will include:

- Clinical chemistry and hematology
- Vital signs
- Electrocardiograms
- Physical examination
- AEs

6.7.1 Clinical laboratory assessments

At Screening only, patients will be tested for HCV and HBsAg to determine eligibility.

At Screening and during the study, laboratory safety tests will also be performed according to the time schedule presented in Table 1. The following parameters will be collected:

- Haematology: Haemoglobin, Platelet Count, White Blood Cells, including absolute neutrophil count (ANC)
- Clinical Chemistry: Alanine Aminotransferase (ALT), Albumin, Alkaline Phosphatase (ALP), Aspartate Aminotransferase (AST), Bilirubin (Total), Bilirubin (Direct) (only if Total is elevated), Creatine Kinase, Creatinine, Gamma Glutamyl Transferase, Glucose (Fasting), Lactate Dehydrogenase, Potassium, Phosphate (Inorganic), Protein (Total), Sodium, Urea
- Urinalysis: Bilirubin, Blood, Glucose, Ketones, Leukocytes, Nitrites, pH, Protein, Specific gravity, Urobilinogen

In cases where laboratory findings are outside the normal range and the investigator believes that the results may be of clinical significance, repeat sampling may be requested as clinically indicated. If the abnormal finding is clinically significant, appropriate actions will be taken e.g.,

the patient may not be entered into the study or the patient may be withdrawn from the study. The patient will be referred to their general practitioner or other appropriate provider for further care.

Any clinically significant abnormality, including changes from baseline, must be reported as an AE.

Additional blood and/or urine samples may be taken for safety tests. Furthermore, additional assays outside those specified in the protocol may be performed for safety reasons as requested by the investigator.

6.7.2 Vital signs

Vital signs will be performed according to the time schedule presented in Table 1. Vital sign assessments will include blood pressure, heart rate, respiratory rate and body temperature; body weight will also be measured according to the time schedule presented in Table 1, with the patient lightly clothed and without shoes. Patient height (without shoes) will be measured at Screening only.

If a patient shows an abnormal assessment at any stage, repeat measurements may be made and the abnormality followed to resolution if required. Additional measurements may be taken as deemed necessary by the investigator

Any clinically significant abnormality, including changes from baseline, must be reported as an AE.

6.7.3 Electrocardiograms

Twelve-lead ECGs will be conducted at Screening, after the patient has been in the supine position for a minimum of 5 min. If possible, it is preferred that ECGs be conducted prior to vital sign assessments or blood draws if scheduled for the same visit.

6.7.4 Physical examination

The physical examination will include the examination of general appearance, skin, lungs, heart, abdomen, lymph nodes, extremities and vascular system. Patients will have a full physical examination at Screening, and then abbreviated exams during each subsequent visit that will be targeted assessment(s) of the body systems or organs, as indicated by patient symptoms, AEs, or other findings.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present before signing the ICF must be included in the relevant medical history CRF. Significant findings made after signing the ICF which meet the definition of an AE must be recorded in the Adverse Event CRF.

7 SAFETY MONITORING

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign, including clinically significant abnormal laboratory findings, symptom or disease) in a clinical investigation patient after providing informed consent for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

An adverse reaction is any untoward and unintended responses to study treatment related to any dose administered.

An unexpected adverse reaction is an adverse reaction in which the nature or severity is not consistent with the Reference Safety Information (RSI) outlined in the IB (for TAVT-45) or SmPC (for R-AA).

All AEs spontaneously reported by the patient or reported in response to the open-ended and non-leading verbal questioning from the study personnel (e.g., "How are you feeling?" "Have you had any health problems since the previous visit/you were last asked?"), or revealed by observation will be collected and recorded in the CRF.

Abnormal laboratory values or test results constitute AEs only if they are clinically significant, which is defined as fulfilling at least one of the following criteria:

- they induce clinical signs or symptoms,
- they fulfil any of the criteria for a serious adverse event,
- they require therapy
- they cause a dose reduction, or interruption or discontinuation of a medication
- they cause study withdrawal
- they require additional investigation

Adverse events must be recorded in the Adverse Events CRF, accompanied by the following information:

- the severity (intensity) grades according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 or higher that has unique clinical descriptions of severity for each adverse event, but follows the following guidelines:
  - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
  - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL) (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc).
  - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
  - Grade 4: Life-threatening consequences; urgent intervention indicated.
  - Grade 5: Death related to AE.
- its relationship to the study treatment (TAVT-45 or R-AA). See NOTE below
  - Related: There is a reasonable possibility that the event may have been caused by the study treatment.
  - Not related: The adverse event can be readily explained by other plausible factors such as medical history; lack of efficacy / worsening of the treated condition; concomitant medication, or no obvious temporal relationship exists between the study medication and the adverse event.
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported
- outcome

- whether it constitutes a serious adverse event and which seriousness criteria have been met
- action taken regarding investigational treatment.

NOTE: Causality (relationship between each AE and study treatment) must be carefully considered to answer a question: Is there a reasonable possibility that the AE or SAE may have been caused by the study treatment? The investigator must endeavor to obtain sufficient information to support the causality of the AE and give their opinion of the causal relationship between each AE and study treatment considering the following (list not exhaustive): time latency, concurrent conditions (including disease under study), concomitant medications, dechallenge (even resolves or improves after interruption of study treatment) or rechallenge (event reappears or worsens when dosing is resumed) and pharmacological activity of study treatment.

Once an AE is detected, it must be followed until its resolution, until it is judged to be permanent, or it becomes unlikely that any additional information can be obtained. Assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Whenever possible, diagnoses should be given when signs and symptoms are due to a given etiology. In such cases, the diagnosis should be documented as the adverse event. Associated signs or symptoms not generally attributed to a given diagnosis should be recorded separately.

If deterioration in a laboratory value, vital sign, ECG or other safety assessment is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or other finding will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (e.g, anaemia versus low haemoglobin value). In the absence of clinical signs and symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of eg. laboratory value or other safety assessment that is unequivocally due to disease progression should not be reported as an AE.

To ensure patient safety, every AE, regardless of causality, occurring after the patient has provided informed consent and until the Follow-up Visit must be captured via the eCRF as soon as possible on learning of its occurrence. AE follow up information will be collected as required until either the event is considered as resolved, agreed as not possible to resolve or until the patient is lost to follow up.

7.2 Serious adverse events

7.2.1 Definition of SAE

An AE or suspected adverse reaction is considered serious (SAE) if, in the view of either the investigator or sponsor, it meets any one of the following criteria:

- Death.
- Life-threatening. Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- In-patient hospitalization or prolongation of existing hospitalization. Note: an emergency room or urgent care visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or

planned before signing of informed consent, or elective treatment of a pre-existing condition that did not worsen from baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits, respite care) will not be considered serious.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect.
- Important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse. All malignant neoplasms will be assessed as a medically important event if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction. All AEs (serious and non-serious) are captured on the eCRF.

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until the Follow-up Visit must be reported to Tavanta or designee within 24 hours of learning of its occurrence (see Safety contact information below).

Any SAEs experienced after this period should only be reported to Tavanta or designee if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. At a minimum, the following information should be provided:

- Sponsor study number
- Subject number
- Valid reporter (reporter and PI signature)
- Event term (Diagnosis if available, symptoms if not)
- Suspected study medications (IMPs)
- Causality assessment

Safety Contact Information:

[redacted]

7.2.3 Expedited Reporting

The sponsor/designee will report all relevant information about suspected unexpected serious adverse reactions (SUSARs) that are fatal or life-threatening as soon as possible to the FDA, applicable regulatory authorities in all the concerned countries, and to the Central Ethics Committee(s), and in any case no later than seven days after knowledge by the sponsor/designee of such a case.

All other serious cases and any significant new information on an already reported case received by the sponsor meeting SUSAR criteria will be reported to the FDA, applicable regulatory authorities concerned and to the Central Ethics Committee(s) concerned as soon as possible but within a maximum of 15 days of first knowledge by the sponsor/designee.

The sponsor/designee will also report any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The sponsor/designee will also inform all investigators as required per local regulation.

The requirements above refer to the requirements relating to the investigational medicinal product. Expedited reporting of suspected unexpected serious adverse reactions related to R-AA is also required in line with the requirements above.

Expedited reporting of suspected unexpected serious adverse reactions related to prednisone (and any other non-investigational medical products) is not required.

7.3 Adverse Events of Special Interest

The following will be considered adverse events of special interest (AESI):

- Hepatotoxicity
- Symptomatic adrenocortical insufficiency
- Hypertension, hypokalemia and/or edema appearing together, suggestive of mineralocorticoid excess
- Hypoglycemia

Regardless of seriousness, the Investigator shall provide detailed initial information and follow-up using the same reporting process as for SAE reporting (see details in Section 7.2.2) within 24 hours of awareness.

7.4 Overdose and dosing errors

Special situations may require expedited reporting and/or safety evaluation. This may include:

- Overdose of a study treatment
- Suspected abuse/misuse of study treatment
- Inadvertent or accidental exposure to study treatment

- Medication error involving study treatment

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol. Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

A study treatment overdose is the accidental or intentional use of study treatment in an amount higher than the dose being studied.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded in the relevant sections of clinical database irrespective of whether or not associated with an AE/SAE. Should a treatment error be associated with an SAE, then this would need to be reported to safety within 24 hours of awareness as per the guidance on SAE reporting in Section 7.2.2.

7.5 Pregnancy reporting

To ensure patient safety, each pregnancy of a female partner of a male patient on study treatment, must be reported to Tavanta or designee within 24 hours of learning of its occurrence. Following consent from the female partner (non-trial participant), the pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to Tavanta or designee using the same safety contact information as used for SAE reporting (see details in Section 7.2.2). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

8 DATA REVIEW AND DATABASE MANAGEMENT

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Tavanta representative or designee will review the protocol and data capture requirements (i.e. CRFs) with the investigators and their staff. During the study, Tavanta employs several methods of ensuring protocol and Good Clinical Practice (GCP) compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of data capture / data entry, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Continuous monitoring of each site's data may be performed by a CRO.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, and the results of any other tests or assessments. All information on CRFs must be

traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or CRF entries. Tavanta monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

8.2 Data collection

The Investigator must certify that the data entered into the CRF are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

CRO/Tavanta staff will review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries can be asked to the investigational site. Designated investigator site staff is required to respond to the query and confirm or correct the data. All queries and responses are subject to an audit trail.

Concomitant medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Randomization codes and data about all study drug(s) dispensed to the patient and all dosage changes will be tracked. Each occurrence of a code break will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Tavanta.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked, and the treatment codes will be made available for data analysis.

8.4 Data Monitoring Committee

An independent data monitoring committee (DMC) will be established to review the safety data collected during the conduct of the study and monitor the progress of the study.

Details of the composition, roles, and responsibilities, and processes of the DMC will be documented in a separate DMC Charter. The DMC will review safety data at specified intervals and can make recommendations to the Sponsor to stop or amend the study on the basis of safety findings. The frequency of these reviews, as well as the data to be reviewed, will be agreed with the DMC and outlined in the Charter, with DMC review meetings being held in a blinded manner to the Sponsor. Outcomes of the DMC review meetings will be shared by Tavanta or designee with the Investigators.

9 DATA ANALYSIS

9.1 Study design

This is a Phase 3 randomized, open-label study to evaluate the pharmacodynamic effect of TAVT-45 compared to Zytiga (reference abiraterone acetate formulation, hereafter referred to as R-AA) in patients with mCSPC (distant metastases) and mCRPC. Randomization will be stratified by prostate cancer population (CSPC vs CRPC) and baseline testosterone (<10 vs ≥ 10 ng/dL). Patients will be treated for 84 days and randomized into one of two groups in a 1:1 ratio:

- **TAVT-45:** Administered twice daily as 1 x sachet containing TAVT-45 (250 mg abiraterone acetate) + Prednisone (5 mg once or twice daily, depending on prostate cancer population)
- **R-AA once daily:** Administered once daily as (2 x 500 mg Zytiga tablets) + Prednisone (5 mg once or twice daily, depending on prostate cancer population)

It is planned to enroll 108 patients in this study (n=54 patients per prostate cancer population), randomized in a 1:1 ratio receiving either TAVT-45 (n=27 mCRPC and n=27 mCSPC patients) or R-AA (n=27 mCRPC and n=27 mCSPC patients).

9.2 Efficacy endpoints

The primary efficacy endpoint is the comparison of the average of serum testosterone levels on days 9 and 10 between groups (TAVT-45 vs R-AA).

The key secondary efficacy endpoint is the PSA-50 response, defined as a decrease of ≥ 50% in PSA levels from baseline at any time over the 84-day post-treatment period.

Other secondary efficacy endpoints are as follows:

- Serum testosterone levels at Days 28, 56 and 84
- PSA-50 response at Days 28, 56 and 84
- PSA levels at Days 28, 56 and 84
- Trough concentrations of abiraterone at Days 9, 28, 56 and 84

9.3 Safety endpoints

The following safety endpoints will also be assessed:

- Incidence of treatment-emergent adverse events (TEAEs)
- Physical examination findings
- Clinical laboratory assessments, including potentially clinically significant changes
- Vital signs measurements, including potentially clinically significant changes

Safety variables will be summarized descriptively. The number and percentage of patients with abnormal or potentially clinically significant clinical laboratory values and vital sign measurements will be summarized by treatment.

9.4 Pharmacokinetic endpoints

For a cohort of up to 8 patients randomized to TAVT-45 and participating in the serial PK sampling on Day 1 and Day 9, the following PK parameters will be determined:

- Area under the concentration-time curve from time zero to 12 hours post dose (AUC_{0-12})
- Maximum measured plasma concentration (C_{max})
- Minimum measured plasma concentration (C_{min})

- Time to maximum measured concentration (t_{max})
- Accumulation ratio (Rac)
- Effective half-life ($t_{½}$)

9.5 Other endpoints

Other exploratory endpoints may be described within the study SAP.

9.6 Sample size

In this study, the effects of TAVT-45 250 mg BID on serum testosterone will be compared to R-AA (given at 1000 mg QD) based on the equivalence approach of determining the 90% confidence interval (CI) of the test-to-reference geometric mean ratio within the 80 to 125% equivalence limit [1,2].

Under the assumptions of a coefficient of variation of 25%, a lower and upper limit of 80% to 125%, and an expected test-to-reference ratio of 1.05, 108 patients in total (54 patients in TAVT-45 and 54 patients in R-AA) will provide approximately 80% power (two one-sided t-tests at 0.05 level) to conclude therapeutic equivalence of TAVT-45 to R-AA.

Among the total 108 patients planned for this study, at least 54 mCRPC patients must be enrolled (n=27 in each treatment arm), which will provide at least 80% power for mCRPC patients. This sample size for each cancer population is also consistent with a similarly designed trial evaluating the therapeutic equivalence of R-AA and an abiraterone acetate fine particle formulation [15].

To ensure an adequate number of patients are enrolled given the above sample size considerations, additional patients may be randomized to ensure that a total of 108 patients are treated up through Day 9 for collection of the primary efficacy endpoint data.

9.7 Data analysis

This section presents a summary of the planned statistical analyses. Before database lock, a final Statistical Analysis Plan (SAP) will be prepared that will contain full details of all planned analyses. Any deviations from the planned analyses will be described and justified in the clinical study report.

9.7.1 General analyses

Statistical analysis will be performed on the following populations:

- **mCRPC Intent-to-treat population (CR-ITT):** All randomized patients who have mCRPC
- **Intent-to-treat population (ITT):** All randomized patients inclusive of both mCRPC and mCSPC
- **Safety population:** All randomized patients who receive at least one dose of study medication, including those who do not complete the study.
- **Per-protocol population:** All randomized patients who do not have a major protocol deviation that could potentially impact efficacy.

All original and derived parameters as well as demographic data will be listed and described using summary statistics. Frequency counts (number of patients and percentages) will be made for each qualitative variable. Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be calculated for each quantitative variable (unless otherwise stated) and will be presented by treatment (if applicable).

If not otherwise specified, 'baseline' refers to the last non-missing observation before study medication administration. All statistical tests will be two-sided and performed at the 5% level of significance, unless otherwise stated.

For changes from baseline, only changes subsequent to the defined baseline will be shown in the listings and tabulations; in the listings any repeat/unscheduled measurements will be included in chronological order with the scheduled measurements, no unscheduled and/or repeated measurements (unless used as the baseline measurement) will be included in the tables.

Handling of Missing and Incomplete Data

If any baseline value is missing, the screening value will be used. Post baseline missing values will be kept as missing. For efficacy data analyses, different missing data imputation methods may be explored to test the robustness of the primary efficacy analysis method and will be defined within the SAP.

9.7.2 Efficacy data analyses

The primary endpoint, the average serum testosterone levels on days 9 and 10, will be analyzed by an analysis of variance (ANOVA) model with treatment as a factor. The test-to-reference geometric mean ratio effect and its 90% confidence interval (CI) of TAVT-45 to R-AA will be compared to 80% to 125% limit.

The primary analysis will be performed based on the CR-ITT and repeated on the ITT and per-protocol populations.

Different missing data imputation approaches will be used as sensitivity analyses based on the intent-to-treat population and will be defined within the SAP.

PSA-50 response at any time over the 84-day post-treatment period will be analyzed by a logistic model with treatment as a factor. Odds ratio, 95% CI using modified Wilson score method of TAVT-45 to R-AA will be presented.

Serum testosterone levels at Days 28, 56 and 84 will be analyzed as the same manner as the primary endpoint.

PSA-50 response at Days 28, 56 and 84 will be analyzed by a logistic model with treatment as a factor. Odds ratio, 95% CI and p-value will be presented.

Trough concentrations of abiraterone at Days 9, 28, 56 and 84 will be summarized descriptively. The number of patients with trough concentrations abiraterone above and below 8.4 ng/mL at Days 9, 28, and 56 will also be summarized.

Regarding subgroup analysis, both the primary and key secondary efficacy endpoints will also be repeated on the CSPC patients.

9.7.3 Multiplicity and testing strategy

In order to control the family-wise type I error, a sequential testing procedure will be implemented. The primary endpoint, the average of serum testosterone levels on days 9 and 10, will be tested using two one-sided t-tests at 0.05 alpha [1,2].

If the equivalence of the average of serum testosterone levels on days 9 and 10 is achieved, then the key secondary endpoint (PSA-50 response, defined as a decrease of ≥50% in PSA levels from baseline at any time over the 84-day post-treatment period) will be tested at 0.05 alpha level.

The primary and key secondary efficacy endpoints will be tested for mCRPC population using CR-ITT population first. If rejected, the same primary and key secondary efficacy endpoints will also be tested for the overall population using the ITT population.

9.7.4 Safety data analyses

Treatment-emergent AEs (TEAEs) are defined as adverse events that started after the first dose of study drug (reference or test) or events present prior to the first dose of study treatment but increased in severity based on preferred term) will be summarized. Non-treatment-emergent AEs will be presented in a listing but not summarized by treatment group.

TEAEs will be summarized by treatment group; the number and percentage of patients having any AE, having an AE in each primary system organ class and having each individual AE will be presented. Summaries will also be presented for AEs by severity and for study treatment related AEs. If a patient reported more than one AE with the same preferred term, the AE with the greatest severity will be presented. If a patient reported more than one AE within the same primary system organ class, the patient will be counted only once with the greatest severity at the system organ class level, where applicable. SAEs will also be summarized. Separate summaries will be provided for death, SAE, other TEAEs leading to study treatment interruption or study treatment discontinuation.

The number and percentage of patients with abnormal or potentially clinically significant clinical laboratory values and vital sign measurements will be summarized by treatment. These thresholds will be pre-defined within the SAP.

9.7.5 Pharmacokinetic data analyses

Plasma samples will be analyzed using a validated assay; the samples from all evaluable patients will be analyzed. PK parameters for abiraterone will be calculated using a non-compartmental analysis.

Patients who are dosed and who have sufficient concentration-time data to report at least one PK parameter will be included in the PK analysis. PK calculations will be performed using Phoenix™ WinNonlin® (Version 8.0 or higher, Pharsight Corporation) and/or SAS® (Version 9.4 or higher, SAS Institute Inc.). Additional details regarding the PK analysis will be included within the SAP.

Abiraterone concentration-time data and PK parameters will be summarized by treatment group using descriptive statistics (n, mean, SD, min, median, max, and CV%). Procedures for accounting for missing, unused, or spurious data, specific to the PK analyses, will be outlined separately in the SAP.

9.7.6 Other analyses

Additional analyses, including other subgroup analyses and other exploratory analyses, will be described in the SAP.

10 ETHICAL CONSIDERATIONS

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing the approved Informed Consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate assent by personally signing and dating the Informed Consent document or a separate assent form. Informed Consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Tavanta will provide to investigators in a separate document a proposed Informed Consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study.

10.3 Responsibilities of the investigator

Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol.

If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Tavanta immediately that this request has been made.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

10.4 Publication of study protocol and results

Tavanta assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

11 PROTOCOL ADHERENCE

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Tavanta, it cannot be implemented. All significant protocol deviations will be recorded and reported in the clinical study report.

12 PROTOCOL AMENDMENTS

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Tavanta, Health Authorities prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients/subjects may be implemented immediately provided the Health Authorities are subsequently notified by protocol amendment. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol.

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