



## **Clinical trial results:**

**Title:** 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).

**Trial design:** This was a Phase 3, multi-national, randomised, open-label, parallel-group study to establish therapeutic equivalence between TAVT-45 and the currently marketed version of abiraterone acetate, Zytiga (R-AA) in patients with mCRPC and high-risk mCSPC. 108 patients (54 patients per prostate cancer population) were to be randomized (1:1) to either oral TAVT-45 or oral R-AA. Randomization was stratified by prostate cancer population (CRPC vs CSPC) and screening serum testosterone level (<10 vs ≥10 ng/dL). The study consisted of a 28-day screening period, an 84-day treatment period, and a 7-day follow-up period. 107 patients were randomised and 103 patients were treated (TAVT-45: 54; R-AA: 49).

Patients randomised to TAVT-45 were treated with 250 mg of TAVT-45 (reconstituted in water or fruit juice) twice daily (BID). Patients randomized to R-AA were treated with 2 x 500 mg tablets once daily (QD). Patients in both groups also took prednisone (5 mg once or twice daily, depending on prostate cancer population).

The median duration of treatment for all patients was 84.0 days (range: 1 to 87 days) and was similar for both treatment groups.

The primary endpoint was the comparison of the average of rounded-up serum testosterone levels on Days 9 and 10 between TAVT-45 and R-AA. TAVT-45 and R-AA were compared based on the equivalence approach of determining the 90% confidence interval (CI) of the test-to-reference geometric mean ratio (GMR) within the 80% to 125% equivalence limit when analyzed on a log scale (natural logarithms).

## Summary

EudraCT number	2020-005611-46
Trial protocol	FR SE HU ES
Global end of trial date	20 October 2022

## Results information

Result version number	v1 (current)
This version publication date	15 July 2023
First version publication date	15 July 2023

## Trial information

### Trial identification

Sponsor protocol code	TAVT45C02
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### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04887506
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Tavanta Therapeutics, Inc.
Sponsor organisation address	1000 First Avenue, Suite 405, King of Prussia, Upper Merion Township, United States, PA 19406
Public contact	Tavanta, Tavanta Therapeutics, Inc., +1 833776 8963, info@tavanta.com
Scientific contact	Tavanta, Tavanta Therapeutics, Inc., +1 833776 8963, info@tavanta.com

Notes:

### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

### Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 March 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 October 2022
Global end of trial reached?	Yes
Global end of trial date	20 October 2022
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Establish therapeutic equivalence between TAVT-45 granules and Zytiga tablets in patients with mCRPC or high-risk mCSPC.

Protection of trial subjects:

The trial was carried out in compliance with the protocol, in accordance with the principles of the Declaration of Helsinki, in accordance with GCP as described in ICH Guideline E6 (R2), and with all relevant laws and applicable regulatory requirements. An independent Data Monitoring Committee (DMC) was also established to review safety data collected during the conduct of the study and monitor the progress of the study.

Background therapy:

In addition to TAVT-45 or R-AA, all patients were to take oral prednisone: 5 mg BID for mCRPC patients, and 5 mg QD for mCSPC patients. This requirement for co-administration of prednisone (including the dose level and frequency) was consistent with the on-label dosing requirements for R-AA.

Evidence for comparator:

Zytiga is the currently approved and marketed version of abiraterone acetate. It decreases serum testosterone and other androgens to levels lower than those achieved by the use of GnRH analogues alone or by orchiectomy due to the selective inhibition of the CYP17 enzyme required for androgen biosynthesis.

Actual start date of recruitment	05 May 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 7
Country: Number of subjects enrolled	Spain: 38
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Hungary: 9
Country: Number of subjects enrolled	United States: 24
Worldwide total number of subjects	103
EEA total number of subjects	63

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	13
From 65 to 84 years	80
85 years and over	10

## Subject disposition

### Recruitment

Recruitment details:

Patients age  $\geq 18$  years, with pathologically-confirmed adenocarcinoma of the prostate, ongoing therapy with a GnRH agonist or antagonist (unless patient had already had a bilateral orchiectomy), and had either metastatic castration-resistant prostate cancer (mCRPC) or high-risk metastatic castration-sensitive prostate cancer (mCSPC) .

### Pre-assignment

Screening details:

Screening was up to 28 days before first dosing, when medical history, physical examination, serum testosterone, vital signs, and clinical laboratory data were collected. Upon meeting all inclusion/exclusion criteria set forth in the protocol, patients were randomized in a 1:1 fashion to receive TAVT-45 or R-AA.

### Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This was an open-label study.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	TAVT-45

Arm description:

Patients with mCRPC or high-risk mCSPC randomised and treated with at least one dose of TAVT-45. This was the TAVT-45 group of the mITT population.

Arm type	Experimental
Investigational medicinal product name	TAVT-45
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules for oral suspension
Routes of administration	Oral use

Dosage and administration details:

The dose in this study was 250 mg BID (total daily dose 500 mg). For each 250 mg dose, 1 granule sachet had to be reconstituted in tap water or specified juice (orange juice) and the resulting suspension immediately taken orally.

<b>Arm title</b>	R-AA
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Arm description:

Patients with mCRPC or high-risk mCSPC treated with at least one dose of reference abiraterone acetate (R-AA) (Zytiga). This was the R-AA group of the mITT population.

Arm type	Active comparator
Investigational medicinal product name	R-AA
Investigational medicinal product code	
Other name	Zytiga
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

The daily dose in this study was 1000 mg (2 x 500 mg tablets) administered QD (i.e., as a single daily dose).

<b>Number of subjects in period 1</b>	TAVT-45	R-AA
Started	54	49
Completed	48	45
Not completed	6	4
Adverse event, serious fatal	1	1
Consent withdrawn by subject	-	1
Adverse event, non-fatal	4	2
Other	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	TAVT-45
Reporting group description: Patients with mCRPC or high-risk mCSPC randomised and treated with at least one dose of TAVT-45. This was the TAVT-45 group of the mITT population.	
Reporting group title	R-AA
Reporting group description: Patients with mCRPC or high-risk mCSPC treated with at least one dose of reference abiraterone acetate (R-AA) (Zytiga). This was the R-AA group of the mITT population.	

Reporting group values	TAVT-45	R-AA	Total
Number of subjects	54	49	103
Age categorical Units: Subjects			
Adults (18-64 years)	7	6	13
Adults (>=65 years)	47	43	90
Age continuous Units: years			
arithmetic mean	74.5	74.9	
standard deviation	± 8.45	± 8.40	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	54	49	103
Gleason score Units: Subjects			
Low (<7)	3	7	10
Medium (7)	10	7	17
High (8-10)	38	35	73
Missing	3	0	3
ECOG score Units: Subjects			
Score 0	35	34	69
Score 1	18	14	32
Score 2	1	1	2
Screening testosterone level Units: Subjects			
<10 ng/dL	26	27	53
>=10 ng/dL	28	22	50

## End points

### End points reporting groups

Reporting group title	TAVT-45
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Reporting group description:

Patients with mCRPC or high-risk mCSPC randomised and treated with at least one dose of TAVT-45. This was the TAVT-45 group of the mITT population.

Reporting group title	R-AA
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Reporting group description:

Patients with mCRPC or high-risk mCSPC treated with at least one dose of reference abiraterone acetate (R-AA) (Zytiga). This was the R-AA group of the mITT population.

Subject analysis set title	TAVT-45 CR-ITT
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

The mCRPC Intention-to-treat (CR-ITT) population was defined as a subset of the mITT population and included all randomised patients who had mCRPC, and this reporting group included patients randomised to TAVT-45.

Subject analysis set title	TAVT-45 CS-ITT
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

The mCSPC Intention-to-treat (CS-ITT) population was defined as a subset of the mITT population and included all randomised patients who had mCSPC, and this reporting group included patients randomised to TAVT-45.

Subject analysis set title	R-AA CR-ITT
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

The mCRPC Intention-to-treat (CR-ITT) population was defined as a subset of the mITT population and included all randomised patients who had mCRPC, and this reporting group included patients randomised to R-AA.

Subject analysis set title	R-AA CS-ITT
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

The mCSPC Intention-to-treat (CS-ITT) population was defined as a subset of the mITT population and included all randomised patients who had mCSPC, and this reporting group included patients randomised to R-AA.

### Primary: Serum testosterone (ng/dL) Days 9 and 10 average (rounded-up), CR-ITT

End point title	Serum testosterone (ng/dL) Days 9 and 10 average (rounded-up), CR-ITT <sup>[1]</sup>
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End point description:

The primary endpoint was the between-group comparison of average (rounded-up) serum testosterone for the Days 9 and 10 for mCRPC patients treated with either TAVT-45 or R-AA.

The equivalence ANCOVA model (using the natural logarithm scale) had treatment as an independent variable and the stratification factor, screening testosterone (<10 vs ≥10 ng/dL), as covariate. If the 90% CI fell within the recommended 0.800-1.250 limits of equivalence when analyzed on a natural log scale, then treatments were therapeutically equivalent based on rounded-up average Days 9 and 10 testosterone levels.

This primary analysis of therapeutic equivalence of TAVT-45 and R-AA resulted in a geometric mean ratio (GMR) of 1.000; the 90% CI of GMR was not evaluable.

End point type	Primary
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End point timeframe:

From baseline to Days 9 and 10.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Since the 90% CIs for GMR were not evaluable, these data could not be entered into the statistical analysis section.

End point values	TAVT-45 CR-ITT	R-AA CR-ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	33	30		
Units: ng/dL				
least squares mean (confidence interval 95%)	1.0000 (1.000 to 1.000)	1.0000 (1.000 to 1.000)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: PSA-50 response rate, mITT

End point title	PSA-50 response rate, mITT
End point description: A PSA-50 responder was defined as a patient with a decrease of $\geq 50\%$ in PSA levels from baseline at any time up to or on Day 84. The mITT population included mCRPC and mCSPC patients.	
End point type	Secondary
End point timeframe: From baseline to Day 84.	

End point values	TAVT-45	R-AA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	49		
Units: Subjects	47	39		

## Statistical analyses

Statistical analysis title	Odds ratio
Statistical analysis description: Odds ratio generated using the Wald method.	
Comparison groups	TAVT-45 v R-AA
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.3408
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.69



Confidence interval	
level	95 %
sides	2-sided
lower limit	0.574
upper limit	4.979

### Other pre-specified: Serum testosterone (ng/dL) Days 9 and 10 average (rounded-up), CS-ITT

End point title	Serum testosterone (ng/dL) Days 9 and 10 average (rounded-up), CS-ITT
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End point description:

This was a supplementary analysis of equivalence, with a between group comparison of serum testosterone for the Days 9 and 10 average (rounded-up) values for mCSPC patients treated with either TAVT-45 or R-AA.

End point type	Other pre-specified
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End point timeframe:

Baseline to Day 9 and 10.

End point values	TAVT-45 CS-ITT	R-AA CS-ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	19		
Units: ng/dL				
least squares mean (confidence interval 95%)	1.01179 (0.98533 to 1.03896)	1.03758 (1.00899 to 1.06697)		

### Statistical analyses

Statistical analysis title	Equivalence of TAVT 45 and R-AA - CS-ITT
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Statistical analysis description:

Equivalence ANCOVA model (using the natural logarithm scale) with treatment as an independent variable and the stratification factor, screening testosterone (<10 vs ≥10 ng/dL), as covariate.

Comparison groups	TAVT-45 CS-ITT v R-AA CS-ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence <sup>[2]</sup>
Method	ANCOVA
Parameter estimate	Geometric mean ratio
Point estimate	0.975
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.944
upper limit	1.007

Notes:

[2] - If the 90% CI fell within the recommended 0.800-1.250 limits of equivalence when analyzed on a natural log scale, then treatments were therapeutically equivalent based on rounded-up average Days 9 and 10 testosterone levels.

**Other pre-specified: Serum testosterone (ng/dL) Days 9 and 10 average (rounded-up), mITT**

End point title	Serum testosterone (ng/dL) Days 9 and 10 average (rounded-up), mITT
End point description: Supplementary analysis of equivalence of TAVT-45 and R-AA on Days 9 and 10 average (rounded-up) values in the mITT population (including mCRPC and mCSPC patients).	
End point type	Other pre-specified
End point timeframe: From baseline to Day 9 and 10.	

End point values	TAVT-45	R-AA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	49		
Units: ng/dL				
least squares mean (confidence interval 95%)	1.00410 (0.99406 to 1.01425)	1.01469 (1.00401 to 1.02548)		

**Statistical analyses**

Statistical analysis title	Equivalence of TAVT 45 and R-AA, mITT
Statistical analysis description: Equivalence ANCOVA model (using the natural logarithm scale) with treatment as an independent variable and the stratification factor, screening testosterone (<10 vs ≥10 ng/dL), as covariate.	
Comparison groups	TAVT-45 v R-AA
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	equivalence <sup>[3]</sup>
Method	ANCOVA
Parameter estimate	Geometric mean ratio
Point estimate	0.99
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.978
upper limit	1.002

Notes:

[3] - If the 90% CI fell within the recommended 0.800-1.250 limits of equivalence when analyzed on a natural log scale, then treatments were therapeutically equivalent based on rounded-up average Days 9 and 10 testosterone levels.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From baseline to end of treatment and follow-up period.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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### Reporting groups

Reporting group title	TAVT-45
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Reporting group description:

Patients with mCRPC and high-risk mCSPC treated with at least one dose of TAVT-45.

Reporting group title	R-AA
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Reporting group description:

Patients with mCRPC or high-risk mCSPC treated with at least one dose of reference abiraterone acetate (R-AA) (Zytiga).

Serious adverse events	TAVT-45	R-AA	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 54 (9.26%)	3 / 49 (6.12%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphoproliferative disorder			
subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 54 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injury, poisoning and procedural complications			
Cervical vertebral fracture			
subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Cardiac failure congestive			
subjects affected / exposed	0 / 54 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pyelonephritis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	1 / 54 (1.85%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

<b>Non-serious adverse events</b>	TAVT-45	R-AA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 54 (70.37%)	36 / 49 (73.47%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 54 (9.26%)	5 / 49 (10.20%)	
occurrences (all)	6	5	
Blood alkaline phosphatase increased			
subjects affected / exposed	4 / 54 (7.41%)	5 / 49 (10.20%)	
occurrences (all)	4	6	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 54 (5.56%)	3 / 49 (6.12%)	
occurrences (all)	4	3	
Vascular disorders			
Hypertension			
subjects affected / exposed	9 / 54 (16.67%)	7 / 49 (14.29%)	
occurrences (all)	11	10	
Hot flush			
subjects affected / exposed	5 / 54 (9.26%)	2 / 49 (4.08%)	
occurrences (all)	5	2	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 54 (5.56%)	4 / 49 (8.16%)	
occurrences (all)	3	6	
Oedema peripheral			
subjects affected / exposed	2 / 54 (3.70%)	5 / 49 (10.20%)	
occurrences (all)	2	5	
Fatigue			

subjects affected / exposed occurrences (all)	3 / 54 (5.56%) 3	3 / 49 (6.12%) 4	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1	3 / 49 (6.12%) 3	
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)  Diarrhoea subjects affected / exposed occurrences (all)  Nausea subjects affected / exposed occurrences (all)	4 / 54 (7.41%) 4  3 / 54 (5.56%) 4  3 / 54 (5.56%) 3	2 / 49 (4.08%) 2  3 / 49 (6.12%) 3  0 / 49 (0.00%) 0	
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)  Proteinuria subjects affected / exposed occurrences (all)	4 / 54 (7.41%) 4  3 / 54 (5.56%) 3	1 / 49 (2.04%) 1  0 / 49 (0.00%) 0	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	3 / 54 (5.56%) 3	3 / 49 (6.12%) 3	
Infections and infestations COVID-19 subjects affected / exposed occurrences (all)	6 / 54 (11.11%) 6	2 / 49 (4.08%) 2	
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)  Hypophosphataemia	0 / 54 (0.00%) 0	5 / 49 (10.20%) 5	

subjects affected / exposed	0 / 54 (0.00%)	4 / 49 (8.16%)	
occurrences (all)	0	5	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 January 2021	Amendment 1: Text was added to provide guidance on toxicity management during this study related to hepatotoxicity and CTCAE grade $\geq 3$ toxicities, in alignment with Zytiga prescribing information. Text was added to clarify that ALT or AST rises above 5x the upper limit of normal (ULN), or total bilirubin rises above 3x ULN, at any time during the study would result in permanent discontinuation of study medication.
26 March 2021	Amendment 2: Inclusion criterion #10 was updated to exclude herbal supplements only. Uncontrolled hypertension was defined for Exclusion criterion #13. A new exclusion criterion (#18) was added regarding post-trial treatment. Text was added to clarify timing of randomisation, which had to occur before Day 1, but after confirming eligibility and receiving screening testosterone values due to just-in-time shipping of study medication. Clarifications on concomitant medication that should be used with caution were added. Text was added to note that additional patients could be randomised to ensure that 108 patients were treated through Day 9 for collection of the primary endpoint data. The definition of the Per Protocol population was clarified. Added list of notable strong CYP3A4 inducers 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" Added/revised text to better describe timing and information needed for reporting AEs, SAEs, suspected unexpected serious adverse reactions (SUSARs) and partner pregnancies Added text to explicitly state source data should also be readily available upon any request from the authorities

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported