A novel abiraterone acetate oral suspension for patients with metastatic prostate cancer: An open-label phase 3 randomized trial

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Poster number: 146

Background

- Abiraterone acetate (AA) is an established first-line oral hormone therapy for metastatic prostate cancer (mPC)[1]
  - The currently licensed formulation is limited by large tablet size, requirement to take on an empty stomach, and pharmacokinetic variability[2]
- TAVT-45 is a novel formulation of AA granules for oral suspension
  - Offers improved oral bioavailability (allowing dose reduction) and decreased food effect[3] and may provide an option for the ~20–30% of patients with dysphagia[4,5]

Objectives

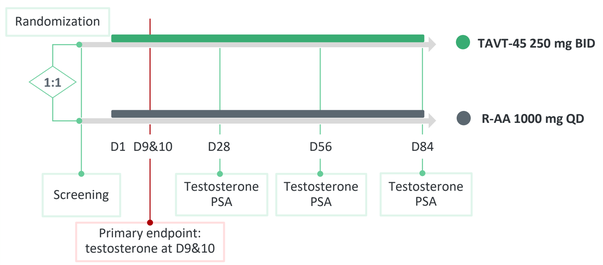
- To establish therapeutic equivalence between TAVT-45 granules and reference AA tablets (R-AA) in patients with castrate-resistant or high-risk castrate-sensitive mPC (mCRPC or mCSPC, respectively)

Methods

Design

- Phase 3, randomized, open-label, multisite trial (NCT04887506), stratified by mCRPC vs mCSPC and baseline testosterone level (<10 vs ≥10 ng/dL)
- Patients were randomized 1:1 to receive either TAVT-45 (1 sachet of AA granules [250 mg] in water or juice, twice daily with or without food) or R-AA tablets (2 × 500 mg once daily ≥1 h before or ≥2 h after food), plus prednisone (5 mg once daily for patients with mCSPC or twice daily for patients with mCRPC) for 84 days (**Figure 1**)

Figure 1: Study design



BID: twice daily; D: day; QD: once daily

Key eligibility

- Males ≥18 years of age with mPC
- Ongoing therapy with a gonadotropin-releasing hormone agonist or antagonist (or prior bilateral orchiectomy) AND serum testosterone level <50 ng/dL at screening
- Either mCSPC (high risk, with two of: Gleason score ≥8, ≥3 bone lesions, visceral metastases, prior androgen-deprivation therapy ≤90 days before randomization) or mCRPC (prostate serum antigen [PSA] rising or disease progression, ± prior docetaxel [completed >1 year previously])

Endpoints

- **Primary Efficacy:** Comparison of the average of serum testosterone levels on Days 9 and 10 between TAVT-45 vs R-AA
- **Key Secondary Efficacy:** PSA-50 response (decrease of ≥50% in PSA levels from baseline) at any time over the 84-day treatment period
- **Other Secondary Efficacy:** Serum testosterone, PSA, and PSA-50 response on Days 28, 56, and 84
- **Safety:** Treatment-emergent adverse events (TEAEs) and clinically relevant changes in vital signs and laboratory assessments recorded throughout

Statistical methods

Analysis populations

- **Efficacy:** primary analysis on patients with mCRPC, and also repeated on all patients (modified intent-to-treat [mITT]) and patients with mCSPC
- **Safety:** all randomized patients who received at least one dose of study medication

Analyses

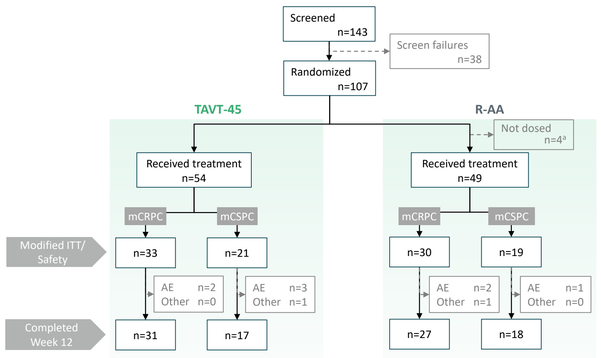
- **Primary endpoint** (average testosterone level on Days 9 and 10) analyzed using an analysis of covariance model, with geometric mean ratio (GMR) and 90% confidence interval (CI) compared with the 80% to 125% limits for equivalence
  - Absolute serum testosterone levels of <1 ng/dL were replaced with 1 ng/dL (rounded-up value); analysis using non-rounded values was performed post hoc for information only
- **Key secondary endpoint** (PSA-50 response over 84 days) analyzed by a logistic regression model

Results

Patients and baseline characteristics

- A total of 107 patients were randomized, and 103 were treated (**Figure 2**)
- Most randomized patients had mCRPC (n=63), and baseline characteristics were generally comparable between groups (**Table 1**)

Figure 2: Patient disposition



AE: adverse event; ITT: intent-to-treat
[a]Randomized but not dosed: n=2 withdrawal of consent; n=1 ineligible; n=1 AE

Table 1: Baseline characteristics (mITT population)

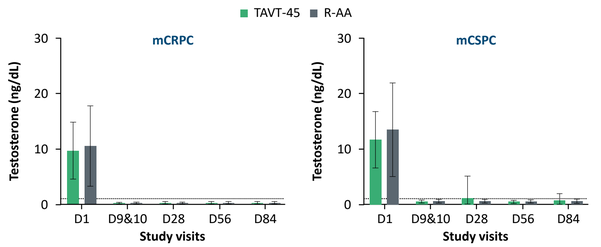
	TAVT-45 (N=54)		R-AA (N=49)	
Age (years)				
Mean (SD)	74.5 (8.45)		74.9 (8.40)	
Range	(47–91)		(53–91)	
Race, n (%)				
White	51 (94.4)		44 (89.8)	
Geographic location, n (%)				
US	8 (14.8)		16 (32.7)	
Europe	46 (85.2)		33 (67.3)	
Prostate cancer type, n (%)	mCRPC 33 (61.1)	mCSPC 21 (38.9)	mCRPC 30 (61.2)	mCSPC 19 (38.8)
Duration of mPC (months)				
Mean (SD)	42.42 (40.7)	2.38 (1.0)	19.63 (26.4)	2.30 (1.1)
Range	(1.4–139.4)	(0.8–4.2)	(0.8–125.1)	(0.8–5.5)
Treatment duration (days)				
Mean (SD)	79.5 (18.11)	69.3 (32.02)	73.6 (25.79)	79.3 (18.97)
Range	(9–86)	(1–87)	(9–85)	(1–84)

SD: standard deviation

Efficacy

- Mean serum testosterone concentrations fell rapidly from baseline in both arms, and were <1 ng/dL in all patients with mCRPC by Day 9 (**Figure 3**)
- Therapeutic equivalence, based on testosterone concentrations on Days 9 and 10, was demonstrated (**Table 2**)
- PSA-50 response on or before Day 84 was not statistically different between arms (**Figure 4**)

Figure 3. Mean (±SD) serum testosterone concentration over time



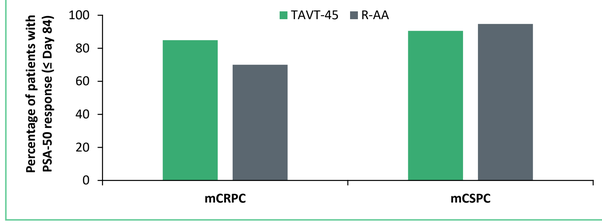
D: day; SD: standard deviation; D9&10: average observed values on Days 9 and 10
Dashed line represents testosterone level of 1 ng/dL

Table 2: Analysis of equivalence

Analysis population	Geometric LS mean testosterone level (95% CI), ng/dL[a]		Equivalence analysis[b]	
	TAVT-45	R-AA	GMR	90% CI of GMR
Patients with mCRPC	(n=32) 1.00 (NE, NE)	(n=29) 1.00 (NE, NE)	1.000	NE, NE
mITT population	(n=52) 1.00 (0.994, 1.014)	(n=47) 1.01 (1.004, 1.026)	0.990	0.978, 1.002
Patients with mCSPC	(n=20) 1.01 (0.985, 1.039)	(n=18) 1.04 (1.009, 1.067)	0.975	0.944, 1.007

LS: least squares; NE: not evaluable
[a]Rounded-up analysis: values of <1 ng/dL were rounded up to 1 ng/dL. [b]Equivalence analysis of covariance model (using the natural logarithm scale) with treatment as an independent variable and the stratification factor, screening testosterone (<10 vs ≥10 ng/dL), and the prostate cancer type (for the mITT analysis), as covariate(s)

Figure 4. PSA-50 response at any time up to Day 84



Safety

- Safety observations were balanced between groups and consistent with known safety profile of abiraterone (**Table 3**)
- TEAE frequency was similar between groups and the majority were mild or moderate in intensity
- No serious TEAEs were considered to be related to study treatment
- There were two deaths in treated patients due to cardiorespiratory arrest (TAVT-45) and prostate cancer (R-AA); neither was considered related to study drugs

Table 3: Treatment-emergent AEs (safety population)

	TAVT-45 (N=54)		R-AA (N=49)	
	No. of events	No. of patients (%)	No. of events	No. of patients (%)
Any AE	126	38 (70.4)	133	36 (73.5)
Treatment-related AE	35	21 (38.9)	48	21 (42.9)
Most frequent AEs (occurring in ≥5 patients in either treatment group)				
Hypertension		9 (16.7)		7 (14.3)
Hot flush		5 (9.3)		2 (4.1)
Alanine aminotransferase increased		5 (9.3)		5 (10.2)
Blood alkaline phosphatase increased		4 (7.4)		5 (10.2)
Edema peripheral		2 (3.7)		5 (10.2)
COVID-19		6 (11.1)		2 (4.1)
Hypokalemia		0		5 (10.2)
AEs of special interest[a]	2	2 (3.7)	4	3 (6.1)
Serious AEs	8	5 (9.3)	3	3 (6.1)
AEs leading to study withdrawal	N/A	5 (9.3)	N/A	3 (6.1)
Deaths	N/A	1 (1.9)	N/A	1 (2.0)

AE: adverse event; N/A: not applicable
[a]Hepatotoxicity; symptomatic adrenocortical insufficiency; hypertension, hypokalemia, and/or edema appearing together, suggestive of mineralocorticoid excess; hypoglycemia

Conclusions

- This Phase 3 study demonstrates that TAVT-45, administered without regard to food, yields similar testosterone/PSA responses and a similar safety profile compared with the currently approved AA formulation
- As an oral suspension, TAVT-45 may be a suitable alternative for patients with mPC who have dysphagia

This study was funded by Tavanta Therapeutics

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