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Oncologic Drugs Advisory Committee (ODAC) Meeting

April 30, 2026

New Drug Application (NDA)# 218197/Supplement 004

Drug name: capivasertib

Applicant: AstraZeneca UK Limited

Combined FDA and Applicant ODAC Briefing Document

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Applicant and the Food and Drug Administration (FDA) for the panel members of the advisory committee. We have brought the drug capivasertib (NDA# 218197/Supplement 004) to this advisory committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Advisory Committee Briefing Materials: Available for Public Release

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Glossary

Abbreviation/special term	Explanation
1L	first line
A/abi	abiraterone
ADT	androgen deprivation therapy
AE	adverse event
AKT	serine/threonine specific protein kinase
AR	androgen receptor
ARPI	androgen receptor pathway inhibitor
BFI	Brief Fatigue Inventory
BICR	blinded independent central review
BPI-SF	Brief Pain Inventory Short Form
BRCA2	breast cancer gene 2
C/capi	capivasertib
C+A/capi + abi	capivasertib + abiraterone + prednisone/prednisolone on a background of ADT
CI	confidence interval
COVID-19	coronavirus disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DCO	data cut-off
DKA	diabetic ketoacidosis
ECOG	Eastern Cooperative Oncology Group
FACT-P	Functional Assessment of Cancer Therapy – Prostate
FAS	Full Analysis Set
FDA	US Food and Drug Administration
FWB	functional well-being
HbA1c	glycosylated hemoglobin
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
HRR	homologous recombination repair
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IHC	immunohistochemistry
IQR	interquartile range
ITT	intention to treat
mCRPC	metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
mHSPC	metastatic hormone-sensitive prostate cancer
MTP	multiple testing procedure
n	number of patients
NA	not available
NC	non-calculable

Abbreviation/special term	Explanation
NDA	New Drug Application
NGS	next-generation sequencing
NR	not reported
OS	overall survival
P/plac	placebo
P+A/pbo + abi	placebo + abiraterone + prednisone/prednisolone on a background of ADT
PCWG3	Prostate Cancer Working Group 3
PD	progressive disease
PI3K	phosphoinositide 3-kinase
PIK3CA	gene encoding the phosphatidylinositol 3-kinase α catalytic subunit
PRO	patient-reported outcome
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
PS	performance status
PSA	prostate-specific antigen
PT	Preferred Term
PTEN	phosphatase and tensin homolog
PWB	physical well-being
Q	quarter
RECIST (v1.1)	Response Evaluation Criteria in Solid Tumors (version 1.1)
rPFS	radiographic progression-free survival
SAE	serious adverse event
SAS	Safety Analysis Set
SEER	Surveillance, Epidemiology, and End Results
sNDA	Supplemental New Drug Application
SOC	System Organ Class
SSE-FS	symptomatic skeletal event-free survival
TFSC	time to first subsequent chemotherapy
TFST	time to first subsequent anti-cancer therapy
TTCR	time to castration resistance
TTPP	time to pain progression
US	United States of America
USPI	United States Prescribing Information
WHO	World Health Organization

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1 Introduction

1.1 Proposed Indication

Capivasertib, in combination with abiraterone, is indicated for the treatment of adult patients with metastatic hormone-sensitive prostate cancer (mHSPC) that is phosphatase and tensin homolog (PTEN)-deficient as detected by an FDA-approved test.[1]

1.2 Purpose of the Meeting

The Applicant has submitted a supplemental New Drug Application (NDA) for capivasertib, an AKT kinase inhibitor intended for use in combination with abiraterone and prednisone in patients with mHSPC with PTEN deficiency. The U.S. Food and Drug Administration (FDA) is convening the Oncologic Drugs Advisory Committee (ODAC) to discuss whether:

- The magnitude of radiographic progression-free survival (rPFS) improvement observed in the CAPItello-281 trial represents a clinically meaningful treatment effect in the mHSPC population in the absence of an effect on OS.
- The overall benefit-risk of the investigational treatment is favorable.

The Applicant's CAPItello-281 trial is the primary source of evidence to support this sNDA. CAPItello-281 was a randomized, double-blind, placebo-controlled trial conducted in patients with PTEN-deficient mHSPC comparing either capivasertib or placebo added to abiraterone and prednisone. The trial met its primary endpoint of rPFS. The observed rPFS hazard ratio (HR) was 0.81 (95% CI: 0.66, 0.98; p=0.034) and sensitivity analyses of rPFS showed HR point estimates ranging from 0.77 to 0.89. No statistically significant OS benefit was observed at this interim analysis and OS results are immature (51% information fraction) with HR 0.90 (95% CI: 0.71, 1.15; p=0.401). Other secondary and exploratory endpoint analyses that the Applicant submitted to support the treatment effect were not formally tested and cannot be used to overcome concerns with the clinical meaningfulness of the rPFS results.

The FDA notes that the rPFS result is statistically significant and that there is no evidence for a detriment in OS. However, the rPFS benefit alone represents a smaller treatment effect in the context of previous approvals in mHSPC (Table 11). In the absence of a large improvement in rPFS, a statistically significant improvement in OS may be needed to support a clinically meaningful treatment effect. Additionally, the FDA has concerns regarding the clinical meaningfulness of the demonstrated treatment effect in the following clinical context:

- CAPItello-281 enrolled patients in an early metastatic disease setting, with time to progression of approximately 2-3 years. While the trial selected for patients with PTEN loss, which appears to be a biomarker for poor prognosis, the majority of enrolled patients had no or mild symptoms at baseline and less than 10% had progression of pain on trial, highlighting the early disease setting. The toxicity tolerance for this population

[1] Where the FDA-approved test is the Roche Diagnostics VENTANA PTEN (SP218) RxDx Assay, a qualitative immunohistochemistry (IHC) assay.

is different compared to patients with more advanced, symptomatic, and/or rapidly progressive disease.

- The risk for increased serious toxicities, including early fatal adverse reactions, increased healthcare utilization, and worse patient-reported diarrhea, skin symptoms, and overall side effect bother, in patients treated with capivasertib must be considered against the efficacy results.
- The addition of capivasertib to an effective and well-tolerated backbone therapy (abiraterone) creates a clinical challenge when making individual treatment decisions. The contribution of capivasertib cannot be distinguished from that of the backbone therapy for a given patient. While this challenge exists for any add-on therapy, it is of heightened concern for this combination regimen given: 1) the substantial added toxicity, and 2) the prolonged duration of treatment due to efficacy of the backbone. These factors converge to increase the risk that a patient may be exposed to the toxicities of capivasertib for an extended period without benefit.
- The activity of the control arm compared to other available therapies, i.e., triplet therapy with docetaxel, androgen receptor pathway inhibitor (ARPI), and androgen deprivation therapy (ADT), increases uncertainty that the rPFS effect demonstrated in CAPItello-281 is clinically meaningful.

1.3 Regulatory History

Capivasertib is a potent, selective oral inhibitor of all 3 serine/threonine specific protein kinase (AKT) isoforms (AKT1/2/3). On November 16, 2023, the FDA approved capivasertib in combination with fulvestrant for the treatment of adult patients with hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with one or more *PIK3CA/AKT1/PTEN*-alterations as detected by an FDA-approved test following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.[2] Capivasertib has since been approved in > 75 countries, with an estimated 12,000 patients having received the treatment, the majority of these being in the United States of America (US).

On August 18, 2025, the Applicant submitted a supplemental NDA (sNDA) to the FDA to seek approval of the proposed indication stated above. Prior to submission, on January 24 2025, a Type B (pre-sNDA) meeting was held between the FDA and the Applicant. High-level results from the primary analysis of the pivotal CAPItello-281 (D361BC00001) study were presented, demonstrating that the primary endpoint was met with statistical significance. Discussions addressed the ongoing unmet medical need in this patient population and focused on the interpretation of the efficacy and safety results. The FDA provided feedback and raised significant concerns regarding the magnitude of clinical benefit set against the increased toxicity observed versus control, stated the totality of data was unsupportive of a positive benefit-risk profile, and noted the immaturity of overall survival (OS) data.

[2] Where the FDA-approved test is the Foundation Medicine Inc FoundationOne® CDx (F1CDx) assay, a next-generation sequencing (NGS)-based in vitro diagnostic device.

Additional details for the pre-sNDA meeting are summarized in Appendix 1, in addition to those for the end-of-Phase 2 meeting with the FDA.

1.3.1 FDA – Regulatory History

The FDA's Position:

The FDA generally agrees with the Applicant's summary of regulatory history. At the January 2025 pre-sNDA meeting, the FDA strongly recommended not submitting an sNDA based on CAPItello-281 results.

At the end-of-Phase 2 meeting in 2020, the FDA emphasized that while rPFS is an acceptable regulatory primary endpoint, a large magnitude of effect, with consistency across other endpoints, would be needed to demonstrate clinical benefit. The FDA stated that in the absence of a large magnitude of improvement in rPFS, an improvement in overall survival may be needed.

2 Efficacy

2.1 Description of Clinical Setting

The Applicant's Position:

2.1.1 Disease Setting

mHSPC is incurable [1], having spread beyond the prostate, and is naive to or expected to respond to anti-hormonal therapy. The most common locations for metastatic spread are lymph nodes and bones, with a minority of patients having visceral metastases.

Despite treatment with anti-hormonal therapies, mHSPC will inevitably progress to a castration-resistant disease state [2]. This loss of disease control of mHSPC, such as through prostate-specific antigen (PSA) progression, worsening of existing metastatic lesions, or new lesions identified on imaging, signals transition to the castration-resistant setting [3]. Metastatic castration-resistant prostate cancer (mCRPC) is an important biologic inflection point of disease progression, signaling increased risk for disease morbidity and lethality [4]. A shorter time course from mHSPC diagnosis to castration resistance has been associated with worse OS [5].

mCRPC is associated with significant morbidity that frequently leads to troublesome clinical sequelae, notably pathological fractures, spinal cord compression from vertebral collapse or metastatic deposit encroaching on the spinal cord, and significant bone pain requiring radiotherapy for local control of the pain and metastasis [6]. These skeletal events are associated with complications such as impairment in mobility and the potential loss of the ability to perform normal daily activities.

The primary treatment goal for mHSPC is to maintain the hormone-sensitive state in order to prolong survival and prevent tumor growth/spread and disease-related symptoms (such as lower urinary tract symptoms, bone pain, and skeletal events), while maintaining quality of life through minimization or prevention of both cancer-related complications as well as treatment adverse events (AEs). PSA is typically used in routine clinical practice as a marker of treatment

response and tumor control. Imaging is also employed, but on a less regular and less standardized basis. To update recommendations for designing and conducting clinical trials in prostate cancer and help improve standardization, an international expert committee of prostate cancer clinical investigators (Prostate Cancer Working Group 3 [PCWG3]) was convened. The criteria developed by this group have been widely adopted in clinical trials in prostate cancer.

Prognosis of mHSPC is variable and depends upon a range of risk factors. Established risk factors associated with the highest risk of progression are high metastatic volume, Gleason scores of 8 or above[3], a diagnosis of metastatic prostate cancer at the time of the first prostate cancer diagnosis (synchronous metastatic disease), and presence of visceral metastases, particularly liver metastases [2,7,8]. These factors are typically combined to yield composite risk categorizations for patients (eg, low-, intermediate-, or high-risk disease) [2]. Clinical trial data for patients with high-risk mHSPC, ie, for those with the highest risk phenotype per traditional risk factors, treated with current standard of care options have shown a median time to progression of ~33 months [9] and a median OS of ~53 months [10].

PTEN deficiency is identified in approximately 25% of mHSPC [11,12,13,14,15] and is a widely recognized biomarker that has emerged as an additional risk factor of clinical significance. PTEN protein is a natural tumor suppressor. Loss of PTEN function leads to uncontrolled tumor proliferation that arises from AKT pathway activation [16] that is independent of proliferation driven by the androgen receptor (AR) (Section 2.1.3). Loss of PTEN function (PTEN deficiency) can be identified in clinical tumor specimen by immunohistochemistry (IHC) detecting absence of PTEN protein expression, or by next-generation sequencing (NGS) for genetic alterations in the *PTEN* gene (*PTEN*-altered).

Clinically, PTEN deficiency is associated with poor outcomes regardless of stage of diagnosis (Appendix 2). In localized disease, PTEN deficiency is associated with higher Gleason grades, higher rates of clinical recurrence, shorter recurrence-free survival, and prostate cancer death [11,12,13,14,16,17,18]. For PTEN-deficient mCRPC, clinical and real-world data show shorter time to radiographic progression and shorter OS compared with men without this biomarker [19,20,21]. Within the mHSPC setting, real-world analyses across a variety of databases demonstrate consistently worse clinical outcomes for men with PTEN-deficient disease than for those with PTEN-proficient disease (Table 1). These data indicate that men with PTEN-deficient mHSPC are underserved by current prostate cancer therapies.

[3] Gleason grading is a well-established system of grading (historically graded from 1 to 5) prostate cancer specimens based on glandular architecture and microscopic appearances. Lower numbers indicate more differentiation, with pattern 5 being the least differentiated. Gleason score is the sum of the 2 most prevalent Gleason grades: primary and secondary, in the tumor specimen. Gleason score can range from 2 to 10 where 10 represents the most aggressive cancer. Gleason score has been shown to predict outcome in prostate cancer.

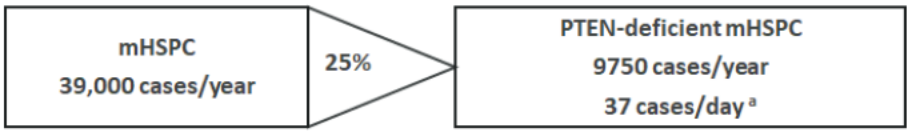
Table 1 Real-world Evidence of the Impact of PTEN Deficiency on Outcomes in mHSPC

Identifier	Treatment	N	*PTEN*-altered, n (%) [a]	Endpoint	*PTEN*-altered median (months)	Non-*PTEN*-altered median (months)	HR (95% CI) [b]
TEMPUS (data on file)	1L abiraterone + ADT	230 [c]	44 (19%)	Real-world PFS	14.7 (7.6, 24.7)	28.7 (19.5, NC)	2.27 (1.31, 3.90)
TEMPUS (data on file)	1L abiraterone + ADT	243	46 (19%)	Real-world OS	49.3 (35.4, NC)	NC	2.05 (1.17, 3.58)
Flatiron (data on file)	1L ARPI + ADT	267	86 (32%)	Real-world OS	35.8 (22.5, NC)	68.9 (52.7, NC)	1.48 (1.07, 2.05)
Flatiron (data on file)	1L docetaxel + ADT	144	52 (36%)	Real-world OS	31.9 (22.0, 50.3)	38.3 (31.7, 47.0)	1.22 (0.89, 1.68)
Flatiron (data on file)	1L ADT	521	160 (31%)	Real-world OS	29.2 (23.1, 39.6)	38.0 (32.5, 44.1)	1.20 (1.00, 1.43)
PROMISE [22]	ARPI + ADT	299	66 (22%)	Real-world PFS	21.8 (9.2, 34.7)	29.6 (19.4, 41.8)	NR
PROMISE [22]	Any systemic therapy (ADT +/- ARPI or docetaxel)	1036	212 (20%)	Real-world PFS	31.0 (26.0, 43.4)	37.5 (31.5, 45.6)	1.25 (1.04, 1.52)
PROMISE [22]	Any systemic therapy (ADT +/- ARPI or docetaxel)	1036	212 (20%)	Real-world OS	48.7 (45.3, 57.5)	65.4 (60.0, 72.6)	1.37 (1.11, 1.69)

a *PTEN*-altered: genetic alterations in the *PTEN* gene identified using NGS.
b HR > 1 favors shorter outcomes in PTEN-altered population. In some cases, the HR and 95% CI have been manually calculated from the reciprocal values reported in the source data.
c 13 patients were excluded from the analysis due to having a progression or censoring event within 14 days of the index date.
1L, first line; ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; CI, confidence interval; HR, hazard ratio; NC, not calculable; NR, not reported; PFS, progression-free survival.

In 2027 in the US, an estimated 37 men per day will be diagnosed with mHSPC with PTEN deficiency (Figure 1).

Figure 1 Estimated Rates of Diagnosis in the US in 2027



a Calculated based on PTEN deficiency (defined as ≥ 90% of viable malignant cells with no specific cytoplasmic staining) having a prevalence of 25% in mHSPC, and 260 days per year on which diagnosis can be made in the clinic.
Source: Oracle Life Sciences – CancerMPact

2.1.2 FDA – Disease Setting

The FDA acknowledges that patients with advanced cancer generally all have unmet need, that mHSPC is incurable and that PTEN deficiency appears to be associated with worse outcomes. However, several considerations limit the interpretation and applicability of the presented data to the population enrolled in CAPItello-281:

- According to the available data in mHSPC presented in Table 1, the biomarker definition used in the literature is different. The reported studies defined PTEN loss by NGS, while CAPItello-281 defined PTEN loss by IHC.
- The real-world data provided do not appear to include triplet therapy, which may be a more active therapy for most of the patients enrolled in CAPItello-281 (see Section 2.2.4, discussion of Control Arm Considerations).
- This real-world data analysis result may be biased by confounding effects from non-randomized treatment assignment, inconsistent imaging schedules, and baseline differences between two biomarker subgroups.

2.1.3 Current Therapy Options and Unmet Need

Currently, PTEN deficiency is recognized in emerging prostate cancer guidelines as being associated with aggressive disease [23]. However, treatment options remain the same as those for a biomarker agnostic population, with no approved targeted agents.

In the mHSPC setting, multiple treatment options exist based upon clinical trials conducted in non-biomarker selected patients. Androgen deprivation therapy (ADT) with combination treatment intensification is recommended for patients with mHSPC, including [3]:

- ADT + androgen receptor pathway inhibitor (ARPI) (abiraterone, apalutamide, darolutamide, or enzalutamide).
- ADT + docetaxel + ARPI.[4]
- ADT + niraparib + abiraterone for breast cancer gene 2 (BRCA2)-mutated tumors.
- ADT + external beam radiation therapy to the primary tumor (with or without docetaxel, abiraterone, apalutamide, or enzalutamide) for low-metastatic burden.

The standard of care treatments for mHSPC (ADTs, ARPIs, docetaxel) are available globally, with US and European treatment guidance being closely aligned on the use of these agents in the treatment of patients with mHSPC.

Until the CAPItello-281 study, none of these standard therapies had been studied specifically in patients with PTEN-deficient mHSPC. Data for the PTEN-deficient subset of previous studies are not typically reported. Recent real-world evidence discussed in Section 2.1.1 suggests that patients with PTEN-deficient disease are underserved by current treatment options and have a high unmet need.

2.1.4 FDA – Current Therapy Options

<u>The FDA's Position:</u>

The Applicant states that "patients with PTEN-deficient disease are underserved by current

[4] Some of these recommendations are supported by limited data and are based on the premise that the 4 ARPIs are generally interchangeable.

treatment options and have a high unmet need." The FDA notes that the degree of unmet need is best reflected in the control arm outcomes in CAPItello-281. Regardless of the prognostic implications of PTEN loss, regulatory standards remain consistent. Ultimately, in both a biomarker-selected population or an all-comers population, for an add-on trial design, the magnitude of the treatment effect needs to be considered in the context of the added toxicity. The clinical meaningfulness of delaying progression must be weighed against the toxicity burden in an early metastatic population where the majority of patients have few or no symptoms and where median OS is measured in years. The benefit-risk consideration for this population differs from the clinical context of symptomatic, rapidly progressive disease.

2.1.5 Rationale to Develop Capivasertib for this Indication

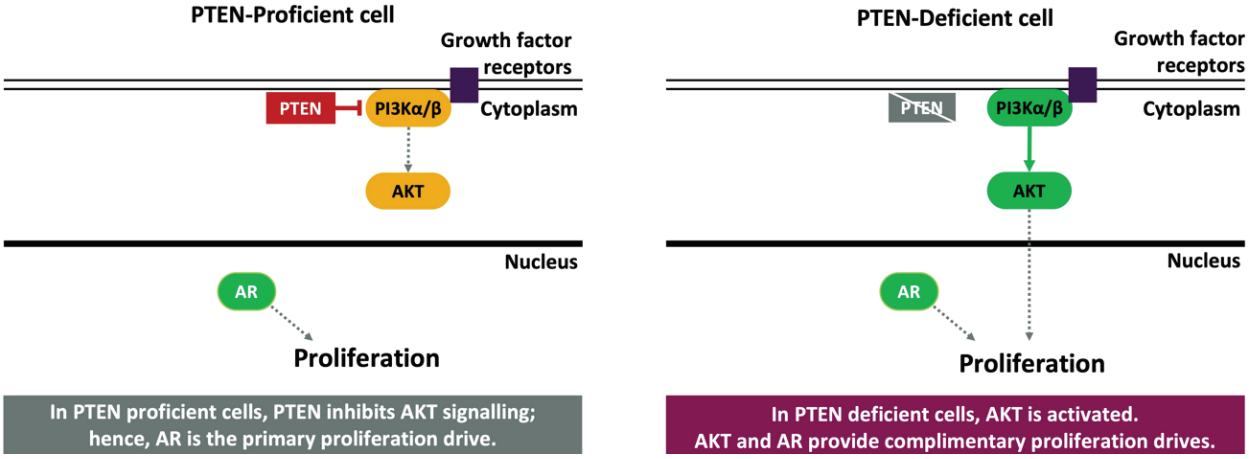
The Applicant's Position:

The hypothesis for the CAPItello-281 study was that in PTEN-deficient prostate cancer the combined inhibition of the AKT pathway and the AR axis would lead to greater disease control than could be achieved by targeting either pathway alone. The choice of mHSPC rather than mCRPC as the target study population was driven by the observation that PTEN deficiency tends to occur early and maintenance of the hormone-sensitive disease state is an important goal for prostate cancer management [5].

In mHSPC disease, AR signaling is a key driver of proliferation [24]. In PTEN-proficient tumor cells, the PTEN tumor suppressor acts as the natural antagonist of the AKT pathway. Loss of this PTEN antagonist function in PTEN-deficient prostate tumor cells increases AKT signaling, which in turn acts as an additional driver of proliferation (Figure 2).

Numerous non-clinical studies have demonstrated that PTEN deficiency accelerates early disease [25,26] and increases the rate of metastatic progression [27,28]. As PTEN deficiency enables the tumor cell to access an alternative survival mechanism conferred by AKT pathway activation [29,30], efficacy of therapy inhibiting tumor drive through the AR axis alone (ADT + ARPI) is insufficient to control the disease.

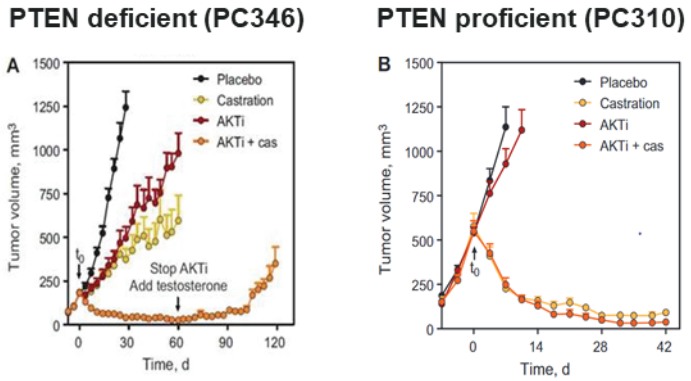
Figure 2 Drivers of Proliferation in PTEN-proficient versus PTEN-deficient Cells



PI3K, phosphoinositide 3-kinase; RTK, receptor tyrosine kinase.

In non-clinical prostate tumor models with absence of PTEN expression, capivasertib plus AR pathway suppression (via castration, abiraterone, or enzalutamide) resulted in greater tumor growth inhibition than AR-axis inhibition alone [31,32,33,34] (Figure 3). Capivasertib monotherapy suppressed growth in PTEN-deficient—but not PTEN-expressing—cell lines and showed greater activity in PTEN-deficient xenografts, indicating AKT dependence in PTEN-deficient tumors. In HSPC-like models with AR signaling abrogated, adding capivasertib increased anti-tumor response and/or duration of benefit. Collectively, these data extensively validate the combination in non-clinical PTEN-deficient prostate cancer models.

Figure 3 Anti-tumor Effects of Capivasertib in a PTEN-deficient Prostate Cancer Tumor Model Following Castration



Capivasertib is denoted by 'AKTi'. PTEN-deficient (PC346) and PTEN-proficient (PC310) cells were grown subcutaneously in male mice. Following castration to abrogate androgen signaling, PTEN-proficient tumors regressed, while in PTEN-deficient tumors only slowing of growth was achieved. Addition of capivasertib (100mg/kg once daily) resulted in regression of the PTEN-deficient tumors. Mean tumor volume +/- SEM are shown.
SEM, standard error of the mean.
Source: Marques et al 2015 [32].

2.1.5.1 Clinical Proof of Concept

The non-clinical hypothesis was supported by the results of the Phase II ASTON MARTIN trial conducted independently of the Applicant. ASTON MARTIN demonstrated the activity of anti-hormonal therapy in combination with AKT inhibition in PTEN-deficient mCRPC. The study compared ipatasertib, an AKT inhibitor with a mechanism of action similar to capivasertib, in combination with abiraterone to placebo + abiraterone. The study population was patients with mCRPC previously treated with docetaxel-based therapy and progressing after ≥ 1 hormonal therapy. Co-primary efficacy endpoints were radiographic progression-free survival (rPFS) in the intention to treat (ITT) population and in patients with PTEN-deficient tumors. PTEN deficiency was defined as near complete absence of PTEN protein expression by IHC, with absence in ≥ 90% of cancer cells (H-score ≤ 10). The addition of ipatasertib to abiraterone showed greater rPFS improvement in patients with PTEN-deficient tumors (hazard ratio [HR]: 0.39; 90% confidence interval [CI]: 0.22, 0.70) than in the unselected study population (HR: 0.75; 95% CI: 0.54, 1.05) [35].

2.1.6 FDA – Rationale to Develop Capivasertib

The FDA's Position:

The FDA acknowledges the preclinical data supporting a rationale to develop capivasertib in PTEN-deficient prostate cancer. However, in the current stage of development that includes clinical data from a large, randomized trial, the pre-clinical rationale for use of capivasertib in patients with PTEN-deficient mHSPC is less relevant.

Clinical Proof of Concept

The FDA acknowledges that the Phase 2 ASTON MARTIN trial provided a clinical proof-of-concept for evaluating the combined inhibition of the AKT pathway and the AR axis. However, this was a hypothesis-generating trial exploring the safety and efficacy of ipatasertib plus abiraterone vs placebo plus abiraterone in mCRPC. Note PTEN-deficient (IHC cutoff at 90%) was a post-hoc subgroup with very small sample size (n=46), which greatly limits the interpretation and generalizability of the observed preliminary rPFS result.

The proof-of-concept Phase 2 trial led to a Phase 3 randomized trial, IPATential150, with 1101 patients, to confirm the efficacy and safety of the combination therapy of ipatasertib plus abiraterone versus placebo plus abiraterone in patients with mCRPC. The dual-primary endpoints were rPFS in ITT and rPFS in PTEN-deficient population (defined by no detectable PTEN IHC staining in >=50%). The study demonstrated a statistically significant improvement of rPFS in the PTEN-deficient population, with HR 0.77 (95% CI: 0.61, 0.98; p=0.034), estimated median rPFS 18.5 and 16.5, and OS HR 0.94 (95% CI: 0.76, 1.17). Although the study met the dual-primary endpoint of rPFS in the PTEN-deficient population, the FDA would not have considered this efficacy result to be clinically meaningful. Ipatasertib is not currently approved for an indication in prostate or other cancers and these data suggest that the class of AKT inhibitors may have limited activity in patients with prostate cancer with PTEN deficiency as defined in these studies.

Table 2. FDA – Summary of Efficacy Results: IPATential150 (PTEN-Deficient by IHC Cutoff at 50%; N=521)

	Median: Ipatasertib, Placebo Months (95% CI)	HR (95%CI)
rPFS by INV DCO 03/16/2020	18.5 (16.3, 22.1), 16.5 (13.9, 17.0)	0.77 (0.61, 0.98); p=0.034[1]
Final OS DCO 12/31/2022	36.8 (31.4, 42.1), 35.8 (30.8, 39.6)	0.94 (0.76,1.17); p=0.57

[1], significant at alpha =0.04

References: Sweeney 2021 [Applicant's reference 38], deBono 2025 [Applicant's reference 20].

2.2 Summary of Clinical Trials Supporting Efficacy: CAPItello-281

The Applicant's Position:

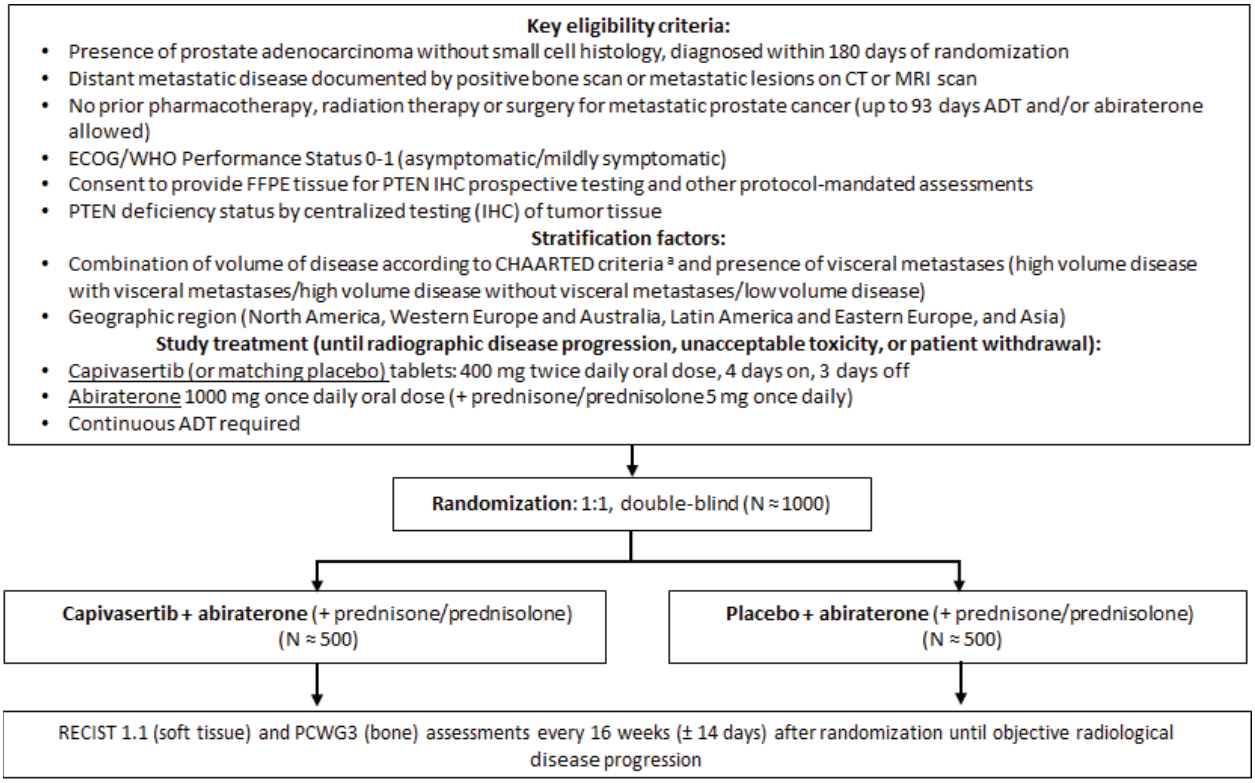
Data demonstrating the efficacy of capivasertib in combination with abiraterone in patients

with PTEN-deficient mHSPC are provided by the pivotal CAPItello-281 study.

2.2.1 Study Design

CAPItello-281 is the first pivotal Phase III study conducted specifically in patients with PTEN-deficient mHSPC. This double-blind, randomized, placebo-controlled, parallel-group, global study was designed to evaluate the efficacy and safety of capivasertib versus placebo when added to abiraterone (+ prednisone/prednisolone) (Figure 4).

Figure 4 CAPItello-281 Study Design



a High volume is defined as the presence of visceral metastases or ≥ 4 bone lesions with ≥ 1 beyond the vertebral bodies and pelvis [36].
CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; FFPE, formalin-fixed paraffin-embedded; MRI, magnetic resonance imaging; PCWG, Prostate Cancer Working Group; WHO, World Health Organization.

All patients eligible for randomization to treatment in CAPItello-281 had been prospectively identified as having PTEN-deficient tumors using central testing with the VENTANA PTEN (SP218) IHC assay, and then completed screening for other entry criteria. IHC was selected for determination of PTEN status. IHC is an inexpensive and analytically validated assay, easily implemented into pathologist diagnostic work-up in clinical practice, with quick turnaround times, limited tissue requirements, and very high test success rates. Importantly, IHC enables detection of absence of PTEN protein expression that is caused by genomic as well as non-genomic mechanisms such as microRNA and epigenetic silencing [37].

PTEN status was centrally tested and determined by pathologists who assigned a percentage score (0% to 100%) of viable malignant cells with no specific cytoplasmic staining. PTEN deficiency was defined as ≥ 90% of viable malignant cells with no specific cytoplasmic staining.

This cut-off was pre-specified prior to study initiation, supported by the following considerations.

- A cut-off with near complete absence of PTEN protein expression was considered likely to select patients with disease that would have a clinically meaningful response to AKT inhibition when combined with AR-axis blockade based on the understanding of the disease biology (Section 2.1.5).
- Data from the co-primary analysis of the Phase II ASTON MARTIN study of the AKT inhibitor ipatasertib (Section 2.1.5) showed a greater treatment benefit in PTEN-deficient tumors using a cut-off of ≥ 90% PTEN negative tumor cells (H-score ≤ 10) (HR: 0.39; 90% CI: 0.22, 0.70) compared to an exploratory analysis applying a lower (≥ 50%) cut-off (HR: 0.50; 90% CI: 0.29, 0.87). The ≥ 90% cut-off used in the co-primary analysis selected a population for which the observed HR was not only more favorable but also more clearly differentiated from the remaining PTEN-proficient population than was the case for the ≥ 50% cut-off [35,38,39].
- The Applicant, in conjunction with diagnostic partner Roche Diagnostics, demonstrated in a cohort of prostate cancer samples with varying percentages of PTEN IHC staining that the ≥ 90% cut-off captures the vast majority of *PTEN* loss of function alterations identified by NGS. This was later verified in a separate cohort of 83 prostate cancer samples, including mHSPC.

Placebo with abiraterone + prednisone/prednisolone on a background of ADT (P+A) was considered suitable as the control arm for the study. ADT intensification with abiraterone was and remains recommended in treatment guidelines for mHSPC (Section 2.1.). This choice of control arm allowed for robust assessment of the contribution of capivasertib in the combination regimen under study. Other ARPIs such as enzalutamide and apalutamide, which were available at the time of study initiation, were ruled out as options for the control arm as they are strong cytochrome P450 (CYP)3A4 inducers, a feature which is known to decrease capivasertib exposure upon concomitant use. In the externally sponsored Phase I/II RE-AKT (NCT02525068) study, co-administration of enzalutamide reduced capivasertib exposure by approximately 40% to 50%.

The selected dose of capivasertib of 400 mg BD 4 days on, 3 days off in combination with abiraterone was found to be well tolerated in patients with pre-treated mCRPC in the Phase I dose-finding study (D3618C00002).

PCWG3 guidelines were followed in CAPItello-281 for assessing bone metastases. These recommend specific rules for assessing the radionuclide bone scans used to assess bone metastases. These include rules to differentiate tumor flare from true progression to ensure consistency of assessing progression. They require that at least 2 new bone metastatic lesions must appear for progression to be called on the basis of a radionuclide bone scan. PCWG3 also integrates Response Evaluation Criteria in Solid Tumors (RECIST 1.1) for soft tissue lesions into the assessments. This approach was applied in CAPItello-281.

rPFS was chosen as the primary endpoint of the study as it provides a well-controlled assessment of treatment benefit of an experimental agent and, unlike OS, is not influenced by the impact of post-progression therapy. Accordingly, rPFS has been accepted as the primary endpoint for prior prostate cancer approvals. Prior approvals have included niraparib + abiraterone for BRCA2-mutated mHSPC [40] and talazoparib + enzalutamide for homologous recombination repair (HRR) gene-mutated mCRPC [41].

Other efficacy endpoints such as symptomatic skeletal event-free survival (SSE-FS), time to PSA progression, and time to castration resistance (TTCR) were selected to characterize the impact of treatment on clinically important outcomes and on the patient's experience of their disease course. The TTCR endpoint was in line with the definition of progression to castration resistance in prostate cancer guidelines [3].

Major and relevant amendments to the protocol for the study are summarized in Appendix 4.

2.2.2 Statistical Methods

2.2.2.1 Endpoints

Type	Endpoint	Acronym	Definition
Primary	Radiographic progression-free survival	rPFS	Time from randomization to: 1) radiographic progression, as assessed by the investigator per RECIST v1.1 (soft tissue) and/or PCWG3 criteria (bone), or 2) death due to any cause.
Key secondary	Overall survival	OS	Time from randomization until the date of death due to any cause.
Key secondary	Time to first subsequent therapy	TFST	Time from randomization to the earlier of: the start date of the first subsequent anti-cancer therapy after discontinuation of randomized treatment, or death due to any cause.
Key secondary	Symptomatic skeletal event-free survival	SSE-FS	Time from randomization until any of the following: • Use of radiation therapy to prevent or relieve skeletal symptoms. • Occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral). Radiologic documentation is required. A pathological fracture, as determined by investigator, is defined as associated with low or no trauma and deemed to have occurred at a site of bone metastasis. • Occurrence of spinal cord compression. Radiologic documentation is required. • Orthopedic surgical intervention for bone metastasis. • Death due to any cause.
Key secondary	Time to pain progression	TTPP	Time from randomization to clinically meaningful pain progression based on a 2-point increase from baseline in the Brief Pain Inventory Short Form (BPI-SF) Item 3 "worst pain in 24 hours" score and/or initiation of/increase in opiate analgesic use.
Secondary	Time to castration resistance	TTCR	Time from randomization to the first castration-resistant event (radiographic disease progression including death, PSA progression, or symptomatic skeletal event), whichever occurs first, with castrate levels of testosterone (below 50 ng/dL).
Secondary	Time to PSA progression	None	Time from randomization to PSA progression, as determined by PCWG3 criteria.

Type	Endpoint	Acronym	Definition
Exploratory	Time to first subsequent chemotherapy	TFSC	Time from randomization to the earlier of start date of subsequent chemotherapy after discontinuation of randomized treatment, or death due to any cause.

2.2.2.2 Statistical Testing

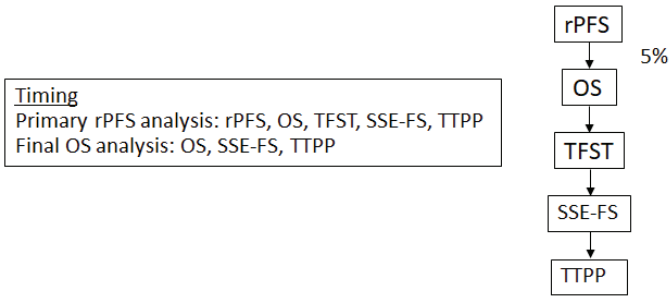
The primary population for reporting efficacy data was the Full Analysis Set (FAS), comprising all patients randomized into the study and analyzed according to randomized treatment regardless of the treatment received (ITT principle).

For the primary endpoint of rPFS, the effect of capivasertib versus placebo was tested using a log-rank test stratified by the randomization stratification factors (geographic location, and combination of volume of disease according to CHAARTED criteria[5] and presence of visceral metastases). From the stratified Cox proportional hazards model with ties = Efron, the HR for capivasertib + abiraterone + prednisone/prednisolone on a background of ADT (C+A) versus placebo + abiraterone + prednisone/prednisolone on a background of ADT (P+A) was calculated, together with its corresponding 95% CI, using a profile likelihood approach. An HR less than 1 would favor C+A.

Analysis of time to first subsequent anti-cancer therapy (TFST), time to castration resistance (TTCR), and time to first subsequent chemotherapy (TFSC) used the same methodology as for the primary endpoint, while the log-rank tests and Cox models for overall survival (OS), symptomatic skeletal event-free survival (SSE-FS), time to pain progression (TTPP), and time to PSA progression were stratified only by combination of volume of disease according to CHAARTED criteria and presence of visceral metastases.

A multiple testing procedure (MTP) was used in the study, in which testing of the primary endpoint and key secondary endpoints followed a simple hierarchy (rPFS, OS, etc) (Figure 5). Further details are provided in Appendix 5.

Figure 5 CAPItello-281: MTP



2.2.2.3 Statistical Assumptions

The study was powered to show a statistically significant difference in rPFS between treatment arms. In the original study design, the assumed performance (median rPFS) of the control (P+A)

[5] High volume is defined as the presence of visceral metastases or ≥ 4 bone lesions with ≥ 1 beyond the vertebral bodies and pelvis.

arm was an estimate of 43 months. This was based on clinical trial data for mHSPC and with reference to outcomes that would be expected based on the proportion of patients with high- and low-risk disease and Gleason scoring. These estimates made no provision for any negative prognostic impact of PTEN deficiency due to the limited data available on this for mHSPC at the time. For an assumed HR of 0.70, this would have translated to an approximate 18-month improvement in median rPFS for the experimental (C+A) arm.

At a time when ~80% of patients had been randomized in the study, independent data emerged indicating the negative impact of PTEN deficiency on outcomes in metastatic prostate cancer (Appendix 2). From these data, it was estimated that median rPFS in the P+A arm was likely to lie in a range of 25 to 33 months. A new estimate of 33 months was selected for an updated study protocol. For an assumed HR of 0.70, as per the original protocol, this revised assumption for the P+A arm led to an estimated 14-month improvement in rPFS for the C+A arm. In addition, the number of events required to trigger the planned analyses for the study was increased, providing 94% power to show a statistically significant difference in rPFS at the 2-sided 5% alpha level.

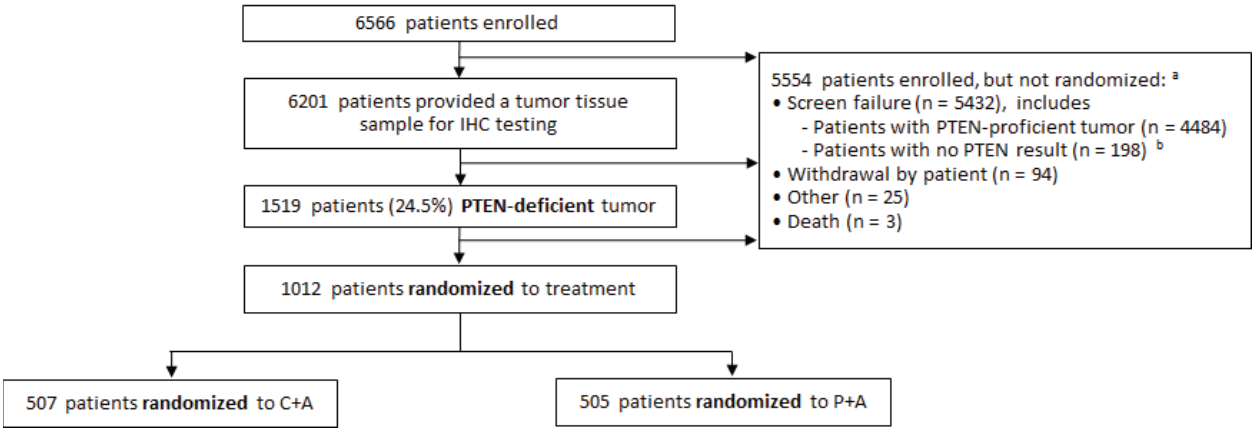
2.2.2.4 Analysis Timepoints

The sNDA under discussion is based on the primary rPFS analysis of the study, which was planned to take place after 386 rPFS events (38.6% maturity) had occurred. This included an interim OS analysis. The final OS analysis is planned to take place once 522 deaths (52.2% maturity) have been observed. This is estimated to occur in Q4 2027/Q1 2028.

2.2.3 Study Patients

The majority of patients enrolled in the study provided a tumor tissue sample for determination of PTEN status by a qualified pathologist experienced in IHC procedures. A valid PTEN test result was reported for 96.8% of patients who provided sample, with PTEN deficiency identified in ~1 in 4 patients (Figure 6 and Figure 7). A more extensive consort diagram showing patient disposition throughout the study is presented in Appendix 6.

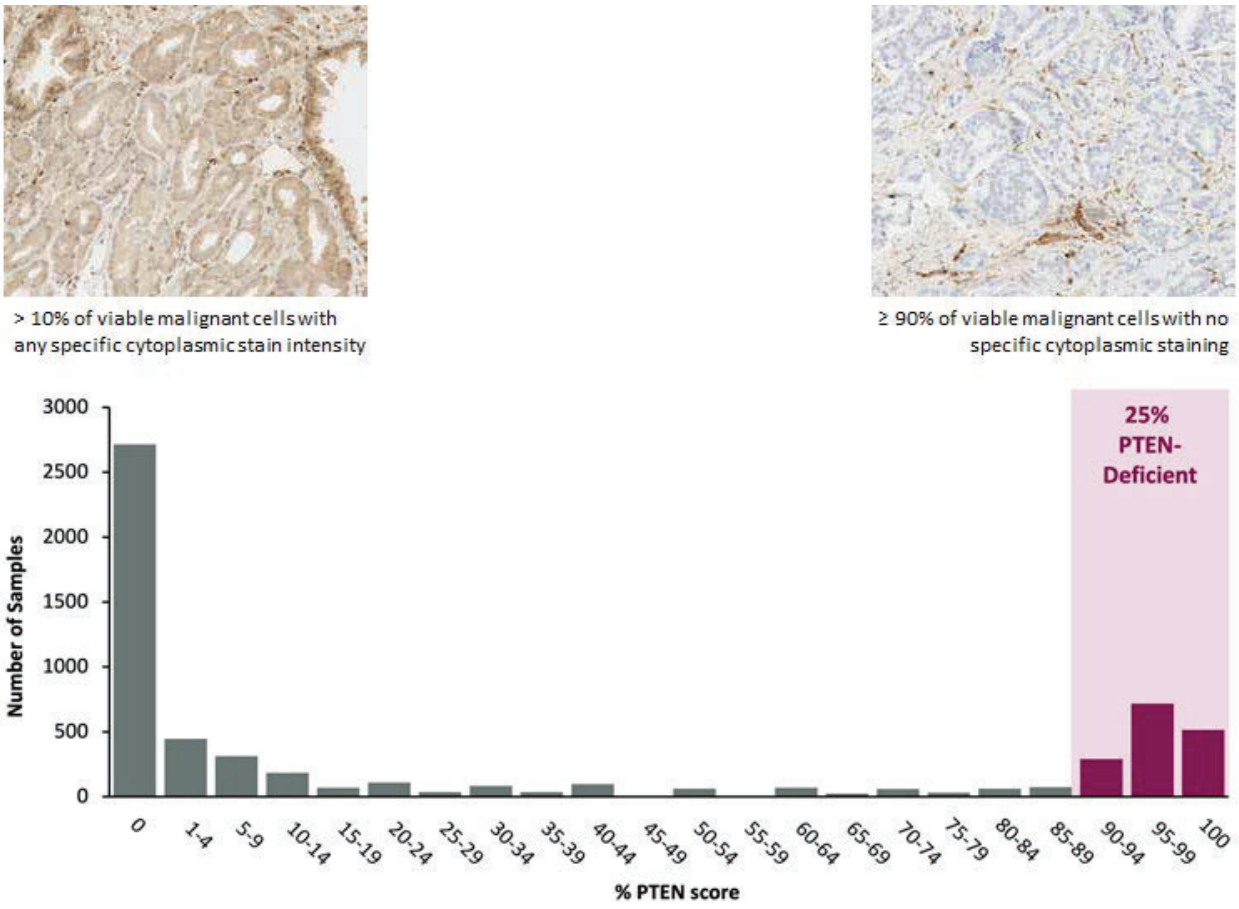
Figure 6 CAPItello-281: Patient Disposition Through Screening (All Patients)



a Patients may have had more than one reason for being enrolled but not randomized.

a No PTEN result was reported for 3.2% of patients who provided a sample, due to insufficient viable mHSPC tumor cells on hematoxylin and eosin slide (0.8%) or other sample failure (2.4%) such as unacceptable controls or tissue folding/wash off.

Figure 7 CAPItello-281: PTEN Percentage Score Histogram (Screened Patients)



Sources: staining patterns - VENTANA PTEN (SP218) RxDx Assay Interpretation Guide for Prostate Adenocarcinoma; histogram - IEMT581.

Patients were randomized to treatment in the study across 259 centers in 32 countries. In the US, 19 patients were randomized across 16 centers. These were in urban locations and were predominantly community centers (13) with a small number of academic centers (3).

As expected in a study of mHSPC specifically in men with PTEN-deficient tumors, the majority of patients had disease characteristics suggesting aggressive disease. Importantly, however, patients with low volume (25.4%) and low-risk disease (34.4%) were also identified and recruited, confirming that PTEN deficiency can exist independent of traditional prostate cancer risk factors. Visceral disease was present in 19.1% of patients. Overall, demographic and disease characteristics were balanced between treatment arms. Further details of baseline characteristics are presented in Appendix 7, with characteristics of the subgroup of patients in the US shown in Appendix 3.

2.2.4 FDA – Study Design

The FDA's Position:

The FDA notes the following important study design and statistical analysis plan considerations:

- OS Analysis Plan: The FDA stated, in a formal meeting with the Applicant in 2020 (see Appendix 1), that an improvement in OS or other clinically meaningful endpoints may be needed to demonstrate clinical benefit in the absence of a large magnitude of improvement in rPFS. The FDA recommended including OS as a primary endpoint. The Applicant proposed OS as a key secondary endpoint in the SAP. The Applicant's proposal was acceptable to FDA; however, the FDA noted that a large magnitude benefit in rPFS and no detriment in OS should be observed. In the SAP, no formal power calculation was provided for the OS analysis.
- Sample Size Adjustment: As the Applicant stated above, at the time when ~80% patients had been randomized and in SAP version 2.0, the Applicant adjusted the final rPFS analysis from 331 events to 386 events, resulting in a study power of 94% to detect target HR of 0.70. The minimum detectable difference (MDD) to declare statistical significance was a HR of 0.82, which translated to about 7-month median rPFS improvement. The FDA acknowledges that this sample size change was made prior to interim analysis and is procedurally acceptable. However, the study was overpowered (able to detect a small, statistically significant rPFS improvement) for the primary rPFS analysis. A small but statistically significant improvement in rPFS may not be considered clinically relevant.
- Control Arm Considerations: While the control arm (abiraterone + prednisone + ADT) was an acceptable treatment at the time of the design of the trial, and this therapy remains an option, it currently does not appear to reflect the most active or preferred therapy for the enrolled population. CAPItello-281 enrolled patients with metastatic disease at the first diagnosis of prostate cancer and approximately three quarters of enrolled patients had high-volume disease, defined as presence of either visceral metastases or at least 4 bone metastases with at least 1 beyond the vertebral bodies and pelvis. High-volume prostate cancer that is metastatic at initial diagnosis, also referred to as *de novo* or synchronous metastatic disease, is associated with aggressive biology and a poor prognosis.
    - Guidelines and expert consensus encourage triplet therapy for patients who are fit for chemotherapy and have synchronous high-volume mHSPC (NCCN 2026; Gillessen 2023). Triplet therapy consists of an ARPI such as abiraterone, docetaxel, and ADT. These guidelines are supported by meta-analyses in mHSPC suggesting a potential PFS benefit for triplet therapy with abiraterone and docetaxel compared to doublet, such as the control arm therapy in CAPItello-281. Furthermore, in patients with synchronous high-volume disease, meta-analyses suggest potential OS benefit of triplet compared to doublet.

- Patient Selection and Generalizability: The exclusion criteria requiring HbA1c <8% and no insulin requirement at baseline, while appropriate for safety given concerns around hyperglycemia based on prior experience with capivasertib, may limit generalizability to real-world populations. These criteria were necessary but the enrolled population of CAPItello-281 represents a selected population that may not fully represent a real-world

population in whom the potential risks of capivasertib may be greater than in the trial setting.

- Isolation of Contribution of Effect: CAPItello-281 was appropriately designed to demonstrate the added benefit of capivasertib across the trial population. However, the FDA notes a clinical challenge: for any individual patient receiving the combination, it is not possible to determine whether the observed clinical benefit is due to capivasertib or to the effective backbone therapy of abiraterone and prednisone (AAP). For example, if a patient remains progression-free for 2 years on the combination, the physician and patient cannot know whether this benefit would have occurred with AAP alone or whether capivasertib contributed. In the context of an early metastatic population, in which patients may do well on standard therapy for years, this leads to the potential for a patient to be exposed to capivasertib toxicity for a prolonged period regardless without deriving benefit from it. This differs from monotherapy, where efficacy of a single agent in a given patient can be more directly assessed. AAP is an effective therapy, generally well-tolerated with long duration of treatment. Persuasive rPFS and/or OS results may be needed to demonstrate that the benefits outweigh the risks for an add-on therapy in this context.

2.3 Efficacy Summary: CAPItello-281

The Applicant's Position:

At the primary rPFS analysis (data cut-off [DCO]: October 07, 2024), the CAPItello-281 study met its primary endpoint, demonstrating a statistically significant reduction in the risk of radiographic progression, and a clinically meaningful improvement in median rPFS for patients treated with C+A compared to P+A (33.2 vs 25.7 months) (Section 2.3.1). The performance of the P+A arm was worse than the assumed 33 months (Section 2.2.2), augmenting existing data showing that disease progression on standard therapies for mHSPC is accelerated in patients with PTEN-deficient tumors (Appendix 2).

This was supported by other measures of efficacy which collectively showed that the addition of capivasertib to abiraterone provided clinical benefit to patients with PTEN-deficient mHSPC (Table 3):

- Improvements were observed in endpoints that relate directly to the patient clinical experience and the way in which the disease course is managed in the clinic: symptomatic skeletal event free survival (SSE-FS), time to PSA progression, time to castration resistance (TTCR), and time to first subsequent chemotherapy (TFSC). While time to pain progression (TTPP) is also a direct measure of burden to the patient, the low maturity of this endpoint (8.6%) precluded its interpretation.

- Interim results for OS at 26.4% maturity were formally tested but did not show statistical significance. The analysis indicated no survival detriment for patients receiving C+A. Data from the Day 120 safety update (DCO: July 04, 2025), capturing an additional 9-month period since the primary rPFS analysis, included 77 additional deaths, of which 50 were in the P+A arm.

Table 3 CAPItello-281: Summary of Clinically Meaningful Efficacy Endpoints (FAS)

Type of endpoint	Endpoint	Events (%) C+A (N = 507)	Events (%) P+A (N = 505)	Median C+A (months)	Median P+A (months)	HR	95% CI	2-sided p-value
Primary	rPFS	183 (36.1)	215 (42.6)	33.2	25.7	0.81	0.66, 0.98	0.034
Key Secondary	OS	129 (25.4)	138 (27.3)	NC	NC	0.90	0.71, 1.15	0.401
Key Secondary	SSE-FS	150 (29.6)	176 (34.9)	42.5	37.3	0.82	0.66, 1.02	0.079 [a]
Secondary	Time to PSA progression	60 (11.8)	82 (16.2)	NC	NC	0.73	0.52, 1.01	0.060 [a]
Secondary	TTCR	185 (36.5)	231 (45.7)	29.5	22.0	0.77	0.63, 0.94	0.009 [a]
Exploratory	TFSC	159 (31.4)	192 (38.0)	46.8	32.9	0.79	0.64, 0.97	0.026 [a]

a Nominal p-value.
NC, not calculable
Source: Table 14.2.1.1, Table 14.2.2.1, Table 14.2.4.1, Table 14.2.6.1, Table 14.2.7.1, IEMT620.1 CAPItello-281 Clinical Study Report.

Results for these endpoints are discussed in the following sections. Further efficacy endpoints of the study are summarized in Appendix 8.

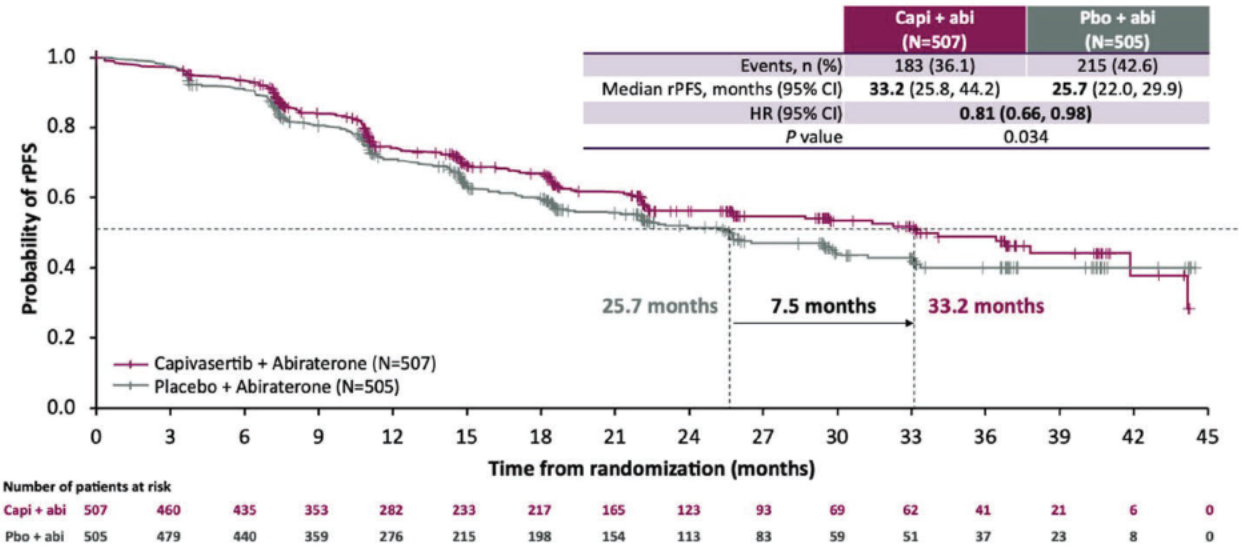
2.3.1 Radiographic Progression-free Survival

2.3.1.1 Primary Analysis

At the primary rPFS analysis, rPFS events by investigator assessment had been reported for 398 patients (39.3%). The analysis took place ~48 months after randomization of the first patient and ~7.5 months after randomization of the last patient in the study.

Treatment with C+A resulted in a statistically significant reduction in the risk of investigator-assessed radiographic progression compared with P+A (HR: 0.81; 95% CI: 0.66, 0.98; p = 0.034), showing a clinically meaningful improvement in median rPFS (33.2 vs 25.7 months) (Figure 8).

Figure 8 CAPItello-281: Kaplan-Meier Plot of rPFS by Investigator Assessment (FAS)



Patients who had not progressed or died at the time of analysis are censored at their last evaluable RECIST v1.1/ PCWG3 assessment.
Patients who had progressed or died immediately after 2 or more consecutive missed visits are censored at the latest evaluable assessment prior to the 2 missed visits.

Patients without any evaluable visits or baseline data are censored at Day 1 unless they died within 2 visits of baseline in which case they have been treated as an event with date of death as the event date.
Vertical lines represent censored observations. 2-sided p-value.
Capi + abi, capivasertib + abiraterone + prednisone/prednisolone on a background of ADT; FAS, Full Analysis Set; Pbo + abi, placebo + abiraterone + prednisone/prednisolone on a background of ADT.
Source: Figure 14.2.1.2, CAPItello-281 Clinical Study report.

In both arms, most progression events identified by either type of imaging assessment were new lesions, and rPFS results were not driven by small increases in target lesion size (Table 4):

- Most RECIST v1.1 progressions were new lesions (C+A vs P+A: 11.0% vs 18.4%), with visceral metastases being the most frequently reported new soft tissue lesion (6.3% vs 8.5%).
- Bone scan progressions (14.6% vs 16.0%) were defined as 2 or more new metastatic bone lesions, in line with PCWG3 recommendations.

New soft tissue or bone lesions for rPFS were required to be unequivocally metastatic lesions and not due to differences in scanning technique or findings due to non-malignant causes. Furthermore, the development of visceral metastases is associated with poor clinical outcomes. As such, the decreased risk of progression in patients treated with C+A was clinically meaningful.

Table 4 CAPItello-281: rPFS by Investigator Assessment Events by Category (FAS)

Treatment arm	C+A	P+A
Total number of patients in treatment arm, N	**507**	**505**
Total events, n (%) [a, b]	183 (36.1)	215 (42.6)
RECIST v1.1 progression	71 (14.0)	113 (22.4)
Target lesion progression	16 (3.2)	21 (4.2)
Non-target lesion progression	20 (3.9)	37 (7.3)
New lesion	56 (11.0)	93 (18.4)
Lymph node	17 (3.4)	29 (5.7)
Visceral metastases	32 (6.3)	43 (8.5)
Other soft tissue metastases	14 (2.8)	32 (6.3)
Missing	3 (0.6)	4 (0.8)
Bone scan PCWG3 progression	74 (14.6)	81 (16.0)
RECIST and bone scan PCWG3 progression [c]	9 (1.8)	18 (3.6)
Death in the absence of progression	47 (9.3)	39 (7.7)

a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
b Only includes progression events that occur within 2 missed visits of the previous evaluable assessment. Progression, as assessed by investigator, defined by RECIST v1.1 and/or PCWG3 or death by any cause.
c Defined as RECIST and PCWG3 progression at the same visit.
Source: IEMT645.1, CAPItello-281 Clinical Study Report.

2.3.1.2 Sensitivity Analyses

Pre-specified sensitivity analysis conducted to assess the robustness of rPFS by investigator assessment showed results consistent with the primary analysis (Table 5).

Table 5 CAPItello-281: Pre-specified rPFS Sensitivity Analyses (FAS)

Sensitivity analysis	Arm	N	Events (%)	Median rPFS / months	Median rPFS 95% CI	HR	HR 95% CI
Ascertainment bias [a]	C+A	507	149 (29.4)	37.8	29.5, NC	0.86	0.69, 1.07
Ascertainment bias [a]	P+A	505	168 (33.3)	29.8	22.7, NC		
Evaluation -time bias [b]	C+A	507	183 (36.1)	35.0	27.1, NC	0.81	0.67, 0.99
Evaluation -time bias [b]	P+A	505	215 (42.6)	24.0	20.5, 31.2		
Attrition bias [c]	C+A	507	164 (32.3)	36.4	29.7, 44.2	0.78	0.63, 0.96
Attrition bias [c]	P+A	505	202 (40.0)	25.8	22.1, 33.1		

a Analysis performed based on the assessment of imaging data by BICR.
b Analysis performed using mid-point between time of progression and previous evaluable assessment (RECIST v1.1 or PCWG3). For patients whose death was used as the rPFS event, the date of death was used.
c Analysis performed using the actual rPFS event times, rather than the censored times, for patients who progressed or died (in the absence of progression) following 2 or more missed visits. In addition, patients who took subsequent therapy prior to progression or death are censored at their last evaluable assessment prior to taking subsequent therapy.
BICR, blinded independent central review; NC, not calculable.
Source: Table 14.2.1.4 and Table 14.2.1.6, CAPItello-281 Clinical Study Report.

The sensitivity analysis of rPFS by blinded independent central review (BICR) to assess ascertainment bias showed increased censoring compared to the primary rPFS analysis, further details of which are provided in Appendix 9.

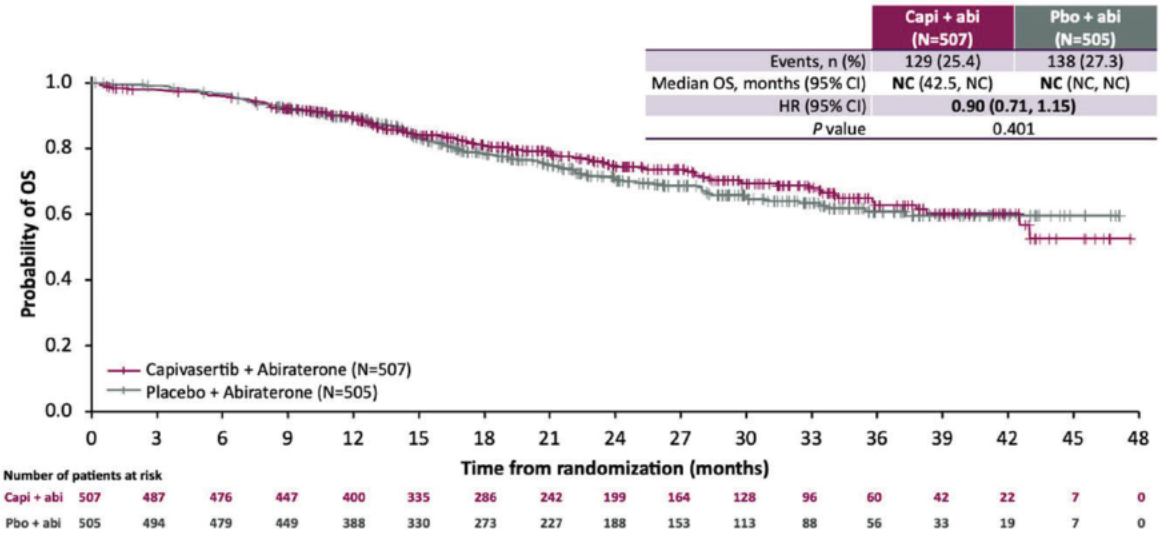
2.3.1.3 Subgroup Analysis

Pre-specified subgroup analyses of rPFS were conducted to assess the consistency of the point estimate (HR) of the treatment effect across potential or expected prognostic factors. The study was not powered for these analyses and therefore, given small number of events in some subgroups, wide confidence limits may apply. The rPFS HR for the majority of subgroups lies within the 95% CI of the primary rPFS analysis and therefore consistency was observed (Appendix 8).

2.3.2 Overall Survival

At the time of the primary rPFS analysis, 267 deaths had been reported (26.4%). Interim OS results numerically favored the C+A arm compared to the P+A arm (HR: 0.90; 95% CI: 0.71, 1.15; p = 0.401) (Figure 9). Use of post-discontinuation disease-related anti-cancer therapies are considered unlikely to explain the observed treatment effect for OS (Table 6).

Figure 9 CAPItello-281: Kaplan-Meier Plot of OS (FAS)



Patients not known to have died at the time of analysis are censored at the last recorded date on which the patient was last known to be alive. Vertical lines represent censored observations. 2 sided p-value.
Source: Figure 14.2.2.2, CAPItello-281 Clinical Study Report.

Table 6 CAPItello-281: Post-discontinuation Disease-related Anti-cancer Therapy (FAS)

Treatment arm	C+A	P+A	Total
Total number of patients in treatment arm, N	**507**	**505**	**1012**
Patients with any post-discontinuation anti-cancer therapy, n (%) [a]	131 (25.8)	151 (29.9)	282 (27.9)
Cytotoxic chemotherapy	87 (17.2)	121 (24.0)	208 (20.6)
Immunotherapy	6 (1.2)	2 (0.4)	8 (0.8)
ARPIs	53 (10.5)	34 (6.7)	87 (8.6)
Other hormonal agents	4 (0.8)	6 (1.2)	10 (1.0)
PARP inhibitors	4 (0.8)	4 (0.8)	8 (0.8)
Radiopharmaceuticals	6 (1.2)	9 (1.8)	15 (1.5)
Other	6 (1.2)	12 (2.4)	18 (1.8)

a Therapies post-discontinuation of study therapy (post discontinuation of capivasertib/placebo and abiraterone).
Patients can be counted in more than one anti-cancer therapy. Corticosteroids, ADT, and medications indicated for the prevention of cancer-related bone problems are not included in this table.
PARP, poly(ADP-ribose) polymerase.
Source: Table 14.1.14, CAPItello-281 Clinical Study Report.

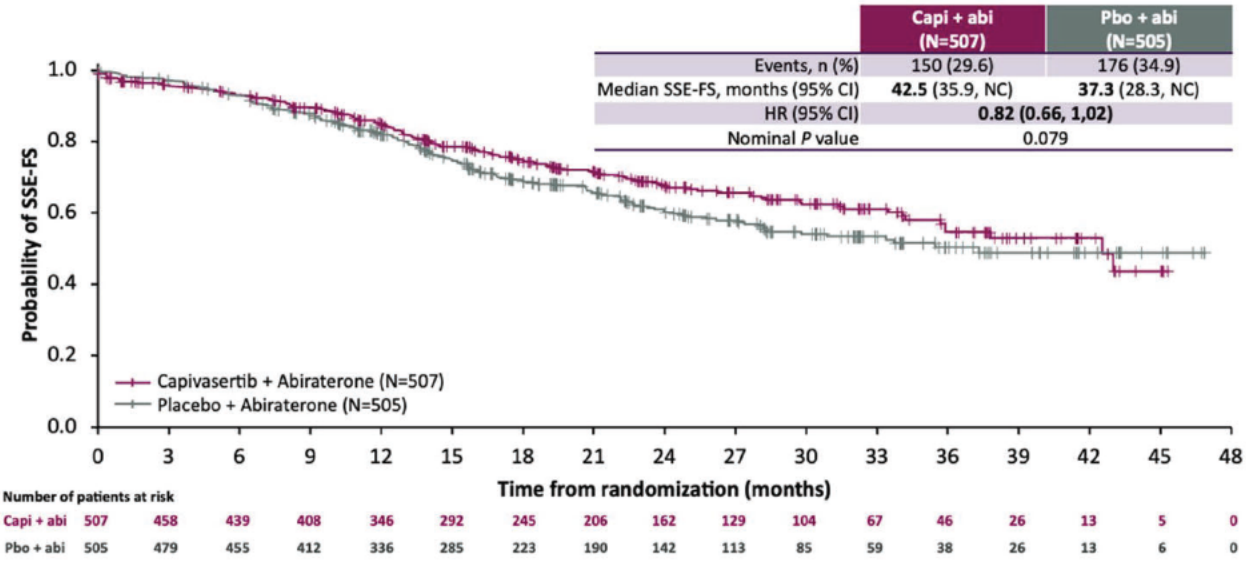
2.3.3 Symptomatic Skeletal Event-free Survival

Bone metastases are common in prostate cancer and drive substantial morbidity. Skeletal complications—pathologic fractures, spinal cord compression from vertebral collapse or epidural tumor, and severe bone pain often requiring radiotherapy or surgery—impair mobility and activities of daily living. These skeletal-related events reduce quality of life (pain, fatigue, diminished physical/emotional/functional well-being), increase healthcare utilization (hospitalizations, procedures), and are associated with higher mortality [42,43,44].

Per the study protocol, only the first symptomatic skeletal event experienced by a patient was required to be reported. At the time of the primary rPFS analysis, 326 skeletal events (including

death) had been reported (32.2%). A clinically meaningful improvement in SSE-FS was observed in patients treated with C+A (Figure 10).

Figure 10 CAPItello-281: Kaplan-Meier Plot of SSE-FS (FAS)



Patients who did not experience an SSE or died at the time of analysis are censored at the time of the last SSE assessment.
Vertical lines represent censored observations. 2-sided p-value.
Source: Figure 14.2.4.2, CAPItello-281 Clinical Study Report.

In contrast to the skeletal-related event endpoint used in many previous trials, the SSE-FS endpoint used here requires that the events are of clear clinical significance (spinal cord compression, radiation or surgical intervention needed) and, in particular, pathological fracture has to be associated with symptoms and not just radiological findings of limited clinical consequence. More than half of patients with a symptomatic skeletal event had multiple events concurrently at their first skeletal event presentation (33/55 in the C+A arm and 46/87 in the P+A arm). The incidence of new symptomatic pathological bone fractures and spinal cord compressions, both of which have serious implications for the patient, was reduced in patients treated with C+A (Table 7).

Table 7 CAPItello-281: Symptomatic Skeletal Event-Free Survival Events by Category (FAS)

Treatment arm	C+A	P+A
Total number of patients in treatment arm, N	**507**	**505**
Total events, n (%) [a]	150 (29.6)	176 (34.9)
Symptomatic skeletal event [b]	55 (10.8)	87 (17.2)
Use of radiation therapy	41 (8.1)	66 (13.1)
Occurrence of new symptomatic pathological bone fractures	37 (7.3)	48 (9.5)
Occurrence of spinal cord compression	34 (6.7)	48 (9.5)
Orthopedic surgical intervention	28 (5.5)	30 (5.9)
Death in the absence of symptomatic skeletal event	95 (18.7)	89 (17.6)

a Includes patients who experienced an SSE, or death due to any cause. Patients not known to have died or experienced an SSE at the time of analysis are censored at the time of the last SSE assessment.

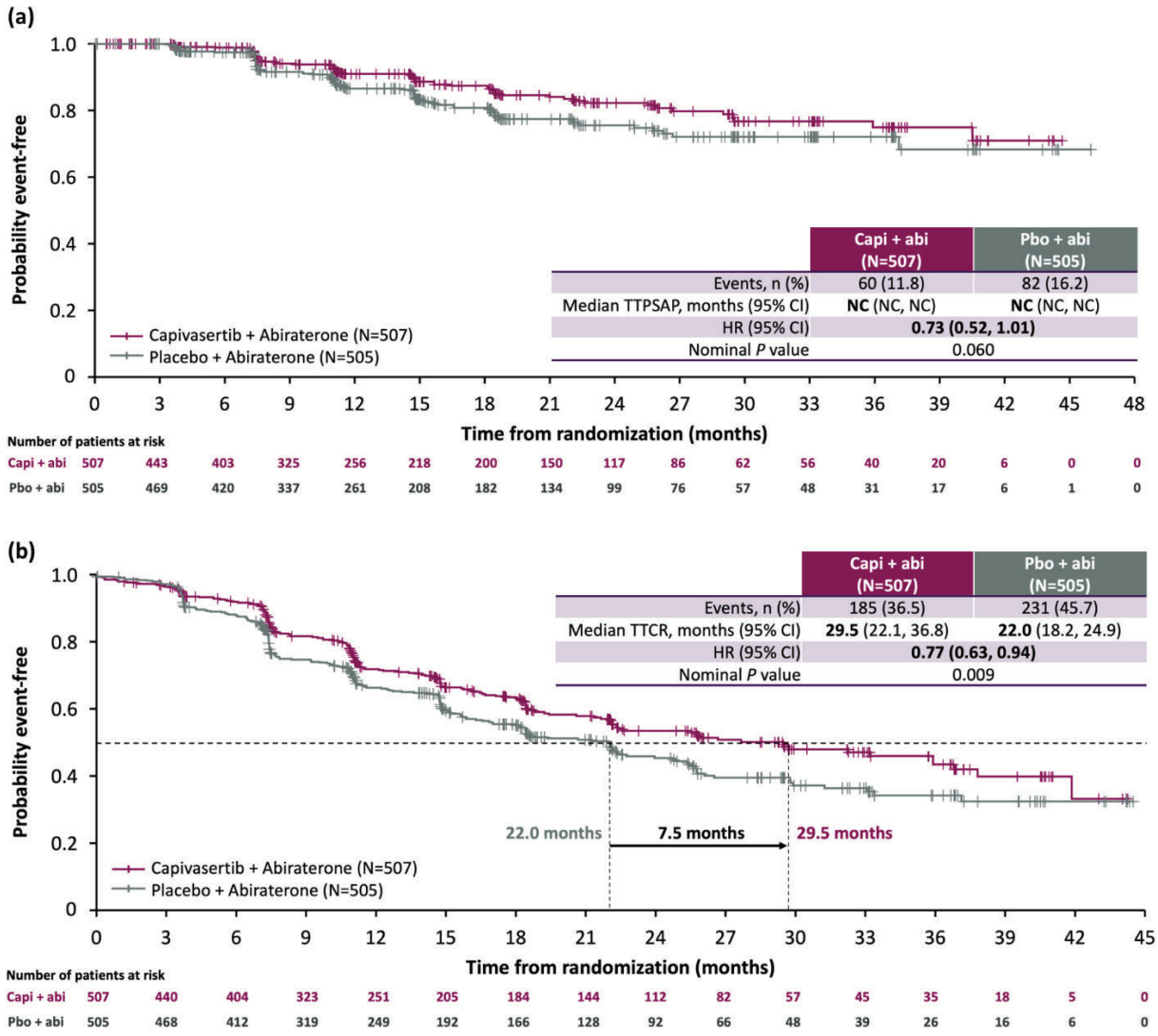
b Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

Source: IEMT645.2.

2.3.4 Time to PSA Progression and Time to Castration Resistance (TTCR)

Progression of mHSPC to castration-resistant disease can be biochemical, radiographic, or symptomatic in nature. While time to PSA progression was used as a specific measure of biochemical progression in the study, TTCR captured progression irrespective of its nature (radiographic disease progression including death, PSA progression, or symptomatic skeletal events). Results for TTCR are considered impactful in clinical practice, as the development of castration resistance often necessitates a change in therapeutic approach, such as requiring the application of a chemotherapeutic, and is associated with poorer response to further therapy and treatment outcomes.

Figure 11 CAPItello-281: Kaplan-Meier Plot of (a) Time to PSA Progression, (b) TTCR (FAS)



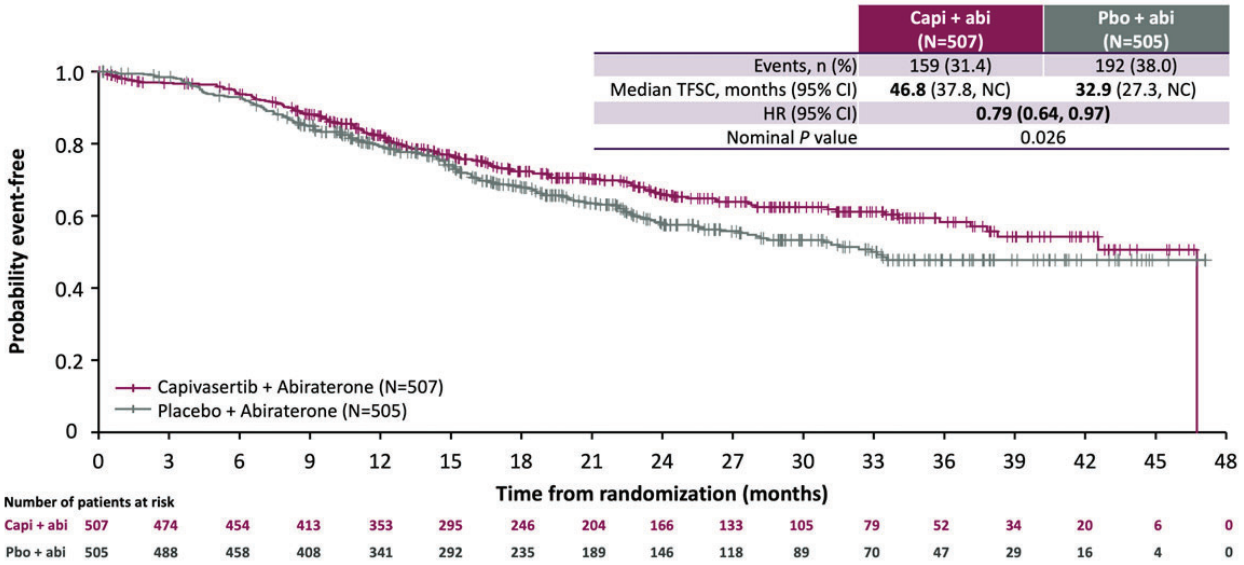
Patients who had not experienced PSA progression at the time of analysis (before receiving subsequent anti-cancer therapy) are censored at last known assessment that showed an absence of PSA progression.
Patients who had not experienced a castration-resistant event at the time of analysis (before receiving subsequent anti-cancer therapy) are censored at last known time not having had a castration-resistant event.
Vertical lines represent censored observations. 2-sided p-value.
Source: Figure 14.2.6.2 and Figure 14.2.7.2, CAPItello-281 Clinical Study Report.

At the time of the primary rPFS analysis, 142 PSA progression events (14.0%) and 416 TTCR events had been reported (41.1%), indicating that most patients progressed to castration resistance in the absence of biochemical progression. TTCR events by category are summarized in Appendix 8. Both time to PSA progression and TTCR were prolonged in the C+A arm compared with the P+A arm (Figure 11).

2.3.5 Time to First Subsequent Chemotherapy (TFSC)

Capivasertib did not appear to impair the use of subsequent chemotherapy. The use of post-discontinuation cytotoxic chemotherapy was balanced between arms in patients who received subsequent therapy after discontinuing study treatment due to radiographic disease progression (C+A vs P+A: 60 of 74 patients [81.1%] vs 96 of 116 patients [82.1%]). Overall, TFSC was improved in patients receiving C+A (median: 46.8 vs 32.9 months; HR: 0.79; 95% CI: 0.64, 0.97; median:), showing a meaningful 13-month delay to the start of chemotherapy and associated risks (Figure 12).

Figure 12 CAPItello-281: Kaplan-Meier Plot of TFSC (FAS)



Patients who had not had subsequent chemotherapy or died at the time of the analysis are censored at their last known time to have not received subsequent chemotherapy.
Vertical lines represent censored observations. 2 sided p-value.
Source: IEMT620.2, CAPItello-281 Clinical Study Report.

2.3.6 Post-Hoc Analysis of the Impact of Extent of PTEN Deficiency on Study Endpoints

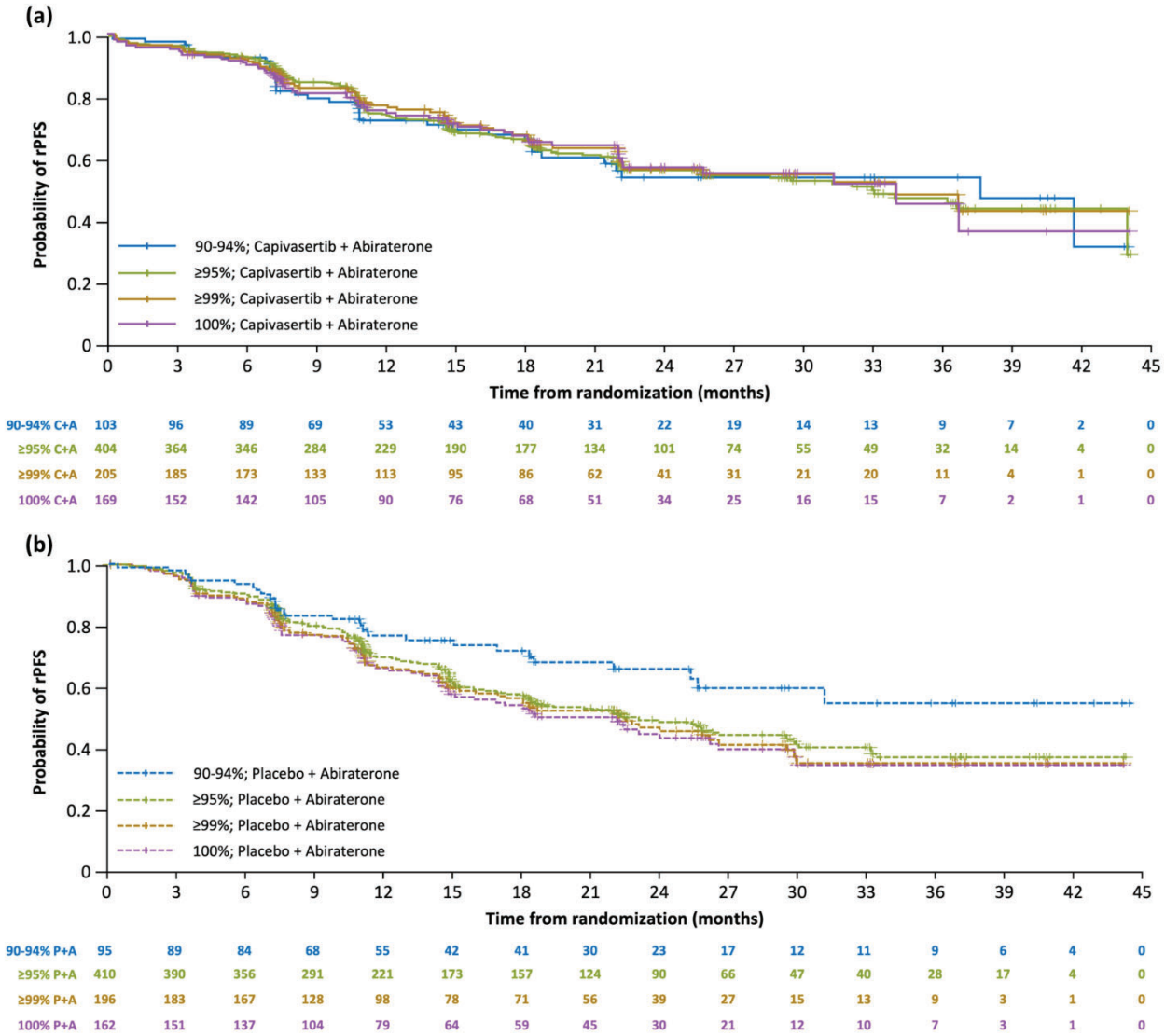
During the course of CAPItello-281, clinical data emerged from IPATential150, a Phase III study independent of the Applicant, confirming efficacy of the AKT inhibitor ipatasertib in combination with abiraterone + ADT in PTEN-deficient mCRPC. A post-hoc analysis of IPATential150 revealed a gradient for worsening performance of the ARPI + ADT control arm and increasing treatment effect with increasing extent of PTEN deficiency (Appendix 10). This is in line with findings from non-clinical data showing an increased dependency on the PI3K/AKT pathway in PTEN-deficient cells (Section 2.1.5).

These observations led to the hypothesis that a similar gradient effect would be observed in the

mHSPC setting. To explore potential differences in treatment effect across varying levels of PTEN deficiency in the CAPItello-281 study, post-hoc exploratory analyses were conducted. The overall study population had PTEN-deficient tumors defined as ≥ 90% of viable malignant cells with no specific cytoplasmic staining. Four subgroups defined by PTEN scores of 90% to 94%, ≥ 95%, ≥ 99%, and 100% of viable malignant cells with no specific cytoplasmic staining were investigated.

Acknowledging the exploratory and retrospective nature of the post-hoc analyses, the rPFS performance of the C+A arm remained consistent across the range of exploratory PTEN scores/ranges that were examined (Figure 13a). By contrast, rPFS in the P+A arm showed evidence of worsening performance with increasing PTEN score (Figure 13b).

Figure 13 CAPItello-281: rPFS by Investigator Assessment by Increasing PTEN Score in (a) the C+A Arm and (b) the P+A arm (FAS)



The analyses were conducted using the same methodology as for the rPFS primary analysis, as described in Appendix 5.
Source: IEMT706.20.km, IEMT706.32, IEMT706.11, Table 14.2.2.1, IEMT706.21, IEMT706.31, IEMT706.8.

The FDA's Position:
The FDA acknowledges that CAPItello-281 met its primary endpoint with statistical significance. However, the FDA is uncertain about the clinical meaningfulness of the results in the context of the issues outlined below.

2.3.7 FDA – Primary Endpoint – Magnitude of rPFS Benefit:

The FDA agrees with the Applicant's reported results for rPFS, including a HR of 0.81 (95% CI: 0.66, 0.98) and estimated median rPFS improvement of approximately 7.5 months (33.2 vs. 25.7). The FDA also acknowledges that the majority of events in the control arm included measurable disease progression (RECIST v1.1 progression, with or without bone scan progression). Nevertheless, the magnitude of effect in the clinical context has unclear clinical meaningfulness (Refer to Sections 2.1.6, 2.3.9, and 3.3.1).

Median rPFS estimates based on the rPFS Kaplan-Meier curves alone do not adequately characterize the treatment effect of rPFS over time. The FDA notes that the medians occur at a point in the Kaplan-Meier curves where the difference between arms appears largest, but where there are substantially fewer patients at risk. Exposure to protocol therapy is similar between arms (Table 18), due to a high rate of discontinuations because of toxicity in the investigational arm, discussed further below. Additionally, landmark analyses are presented below, illustrating the modest absolute effects at various time points. For example, the difference in the Kaplan-Meier estimated proportion of patients who were progression-free and alive 6 and 12 months are 2-3%, and 5% at 24 months (Table 8). In general, the FDA interprets landmark analyses with caution considering the analyses depend on arbitrarily chosen time points and are impacted by censoring. Overall, the Kaplan-Meier curves provide a more comprehensive summary of rPFS results than landmark time points.

Table 8. FDA – CAPItello-281: Landmark Analyses of rPFS by Investigator

Landmark timepoint	rPFS (%, 95% CI) C + AAP	rPFS (%, 95% CI) P + AAP	Difference (%)
6 months	93.2 (90.5, 95.2)	90.8 (87.9, 93.1)	2.4
12 months	74.2 (69.8, 78.1)	70.9 (66.5, 74.8)	3.3
18 months	66.9 (62.0, 71.2)	59.8 (54.9, 64.4)	7.1
24 months	56.2 (50.8, 61.3)	51.5 (46.2, 56.5)	4.7

Abbreviations: BICR: blinded independent central review; C+AAP: capivasertib + abiraterone acetate + prednisone; CI: confidence interval; HR: hazard ratio; P+AAP: placebo + abiraterone acetate + prednisone; rPFS: radiographic progression-free survival

In addition to the pre-specified sensitivity analysis presented by the Applicant in Table 5, sensitivity and supplementary analyses were conducted by the Applicant at the request of the

FDA to further evaluate the robustness of the primary rPFS results. Overall, the results of the sensitivity and supplementary analyses were consistent with the primary analysis, though the clinical meaningfulness of the findings remain uncertain. The analyses showed a range of HR point estimates from 0.77 to 0.89 (Table 9).

Table 9. FDA – CAPItello-281: Sensitivity and Supplementary Analyses of rPFS by Investigator

	rPFS analytic approach	HR (95% CI)
Primary analysis	rPFS not censored for receiving a new anti-cancer therapy[1]	0.81 (0.66, 0.98)
rPFS by BICR	Same with above	0.86 (0.69, 1.07)
Stratification factors	Stratified analysis based on case report form stratification factor data	0.82 (0.68, 1.01)
	Unstratified analysis	0.84 (0.69, 1.02)
New anti-cancer therapy	rPFS censored for receiving a new anti-cancer therapy[1]	0.77 (0.62, 0.95)
	rPFS event for receiving a new anti-cancer therapy[2]	0.89 (0.74, 1.08)

[1] rPFS censored for progression or death after missing 2 or more consecutive tumor assessments
[2] rPFS not censored for progression or death after missing 2 or more consecutive tumor assessments
Abbreviations: BICR: blinded independent central review; CI: confidence interval; HR: hazard ratio; rPFS: radiographic progression-free survival

Investigating the Impact of Treatment Discontinuation on rPFS by INV:
The FDA noted that the capivasertib arm had a higher percentage of patients who discontinued treatment relative to the placebo arm. A higher proportion of patients discontinued both study treatments in the absence of PD in the capivasertib arm compared to the placebo arm (25% vs 18%). Similarly, a higher proportion of patients discontinued capivasertib and abiraterone individually due to reasons other than PD (Applicant's disposition figure in Appendix 6; 18% discontinued capivasertib and 9% discontinued abiraterone due to AE in the capivasertib arm; 5% discontinued placebo and 5% discontinued abiraterone due to AE in the placebo arm).

Capivasertib is not considered a curative treatment or a therapy to have prolonged pharmacodynamic effects after exposure to the drug is stopped. Thus, after capivasertib is discontinued, capivasertib may no longer continue to exert its intended therapeutic effect. Supplementary analyses of rPFS showed a HR of 0.95 (95% CI: 0.80, 1.13) when including treatment discontinuation of both capivasertib/placebo and AAP due to any reason as an rPFS event, and a HR of 0.88 (95% CI: 0.73, 1.06) when including treatment discontinuation due to clinical progression or AE as an rPFS event in both arms (Table 35 in Appendix 13). The FDA acknowledges that these analyses are considered exploratory only and reflect a more conservative approach that treats treatment discontinuation as having the same clinical meaningfulness as PD or death.

Investigating the Impact of Study Discontinuation with Prior AE on rPFS by INV:
A total of 55 patients terminated study due to "withdrawal by patient" or "other," i.e., 30 patients in the capivasertib arm and 25 in the placebo arm (Applicant's disposition figure, Appendix 6). Further evaluation showed that more patients in the capivasertib arm discontinued study in the setting of a Grade 3-4 toxicity when compared to the placebo arm (20

vs 5 patients).

Patients who withdraw from a study due to AE may experience an rPFS event earlier than those who remain on the study, due to worse performance status or medical comorbidities, which can bias the treatment effect of the primary rPFS analysis. To further investigate the potential impact of informative censoring, supplementary analyses of rPFS showed a HR of 0.87 (95% CI: 0.71, 1.05) when including study discontinuation with Grade 3-4 AE as an rPFS event in both arms. This exploratory rPFS analysis showed a more modest effect when accounting for patients who withdrew study consent in the setting of Grade 3-4 AE.

The numbers of patients discontinuing one or both drugs in the absence of PD or who withdrew from the study entirely are key findings. When viewed alongside the overall increased incidence of Grade 3-4 AEs in the capivasertib arm detailed in the Safety section (3.3.1), they raise concerns about the overall benefit:risk profile demonstrated in CAPItello-281.

In summary, while multiple exploratory analyses were consistent with the hazard ratio of 0.81 (95% CI: 0.66, 0.98) from the primary rPFS analyses, the FDA is concerned that the magnitude of the rPFS treatment effect is not sufficient to be clinically meaningful in the context of increased risk of toxicity in this early metastatic disease setting.

2.3.8 FDA – Lack of Supportive Evidence from Other Efficacy Endpoints:

Secondary Endpoints Included in the Formal Testing Plan

No statistically significant OS benefit was observed at this interim analysis and OS results are immature at 51% information fraction (HR 0.90; 95% CI: 0.71, 1.15; p=0.401). The final OS analysis is predicted to occur between Q4 2027 and Q2 2028. As of this interim analysis, the FDA agrees that there is no evidence for a detriment in OS. However, in the absence of a large improvement in rPFS, a statistically significant improvement in OS may be needed to support a clinically meaningful treatment effect.

Since OS was not statistically significant, all other key secondary endpoints included in the testing hierarchy were not formally tested and their results were considered exploratory. The efficacy results of all key secondary endpoints are shown in Table 10 with corresponding KM curves in Appendix 13, Figure 24.

Table 10. FDA – CAPItello-281: Summary of Key Secondary Endpoints in the Statistical Testing Plan

Endpoint	Events (%) C+AAP (N = 507)	Events (%) P+AAP (N = 505)	Median (95% CI) C+AAP (months)	Median (95% CI) P+AAP (months)	HR (95% CI)
Overall survival (OS)	129 (25.4)	138 (27.3)	NC (42.5, NC)	NC (NC, NC)	0.90 (0.71, 1.15)
Time to first	192 (37.9)	206 (40.8)	37.0 (28.0, NC)	28.5 (23.7, NC)	0.91 (0.75, 1.11)

Endpoint	Events (%) C+AAP (N = 507)	Events (%) P+AAP (N = 505)	Median (95% CI) C+AAP (months)	Median (95% CI) P+AAP (months)	HR (95% CI)
subsequent therapy (TFST)					
Symptomatic skeletal event-free survival (SSE-FS)	150 (29.6)	176 (34.9)	42.5 (35.9, NC)	37.3 (28.3, NC)	0.82 (0.66, 1.02)
Time to pain progression (TTPP)	46 (9.1)	41 (8.1)	NC (NC, NC)	NC (NC, NC)	1.14 (0.75, 1.75)

Abbreviations: C+AAP: capivasertib + abiraterone + prednisone; CI: confidence interval; HR: hazard ratio; P+AAP: placebo + abiraterone + prednisone; rPFS: radiographic progression-free survival; NC, not calculable.

Time to first subsequent therapy (TFST) measures how long patients remained on their assigned treatment regimen before requiring additional anticancer therapy. The most common subsequent therapy received in both arms was chemotherapy. The challenges from a regulatory perspective regarding the use of endpoints evaluating the subjective decisions involved in a change in therapy are discussed in further detail below. Furthermore, TFST may be unsuitable for evaluating clinical benefit because it incorporates a clinical decision rather than a direct assessment of disease status or patient benefit.

For Symptomatic Skeletal Event-Free Survival (SSE-FS), the paucity of pain progression events and lack of a numerical trend for an improvement with capivasertib in pain progression does not appear consistent with a clinically meaningful improvement in symptomatic skeletal events and further complicates interpretation of this endpoint.

Time to Pain progression (TTPP) provides little interpretable information due to the very small number of events observed. See Section 4 for more details on PROs.

Exploratory Endpoints

The FDA notes that the Applicant's above reported efficacy results represent selected endpoints, some of which were not included in the formal testing plan.

For time to first subsequent chemotherapy (TFSC) or death, the Applicant reports that "Capivasertib did not appear to impair the use of subsequent chemotherapy. The use of post discontinuation cytotoxic chemotherapy was balanced between arms in patients who received subsequent therapy after discontinuing study treatment due to radiographic disease progression (C+A vs P+A: 60 of 74 patients [81.1%] vs 96 of 116 patients [82.1%])." However, this analysis does not account for patients who discontinued study treatment due to adverse events prior to radiographic disease progression. Whether use of capivasertib impaired the use of subsequent chemotherapy for these patients who discontinued treatment due to AEs or other reasons is uncertain.

While the transition to chemotherapy may be clinically important in an individual patient's disease course, the FDA does not consider TFSC suitable for evaluating clinical benefit. The decision to initiate chemotherapy reflects a clinical decision rather than a direct assessment of disease status or patient benefit. This decision may vary based on drug availability, patient/clinician preference, performance/medical status of the patient, and is therefore inherently subjective, capturing heterogeneous effects. To highlight this issue, the FDA notes that some of the toxicities associated with capivasertib such as diarrhea, infections, anemia, and lymphopenia, may themselves delay or compromise subsequent chemotherapy delivery. Patients who develop these complications may be unable to receive timely, effective chemotherapy, potentially worsening long-term outcomes. Thus, whether delay of chemotherapy would represent an efficacy measure or a potential safety concern is challenging to ascertain in this context. Additionally, capivasertib-related toxicities can impact quality of life, which raises the question of the clinical meaningfulness of delaying a subsequent therapy with safety or tolerability concerns.

The clinical relevance of time to PSA progression and time to castration resistance is limited from a regulatory perspective. The Time to Castration Resistance endpoint is driven by a composite of rPFS events and PSA progression events. PSA progression does not always necessitate a change in therapy or additional therapies per current clinical guidelines. Radiographic progression events have been considered more meaningful than PSA progression. Therefore, the FDA does not consider the endpoints of Time to PSA progression and Time to Castration Resistance to provide additional clinically useful information beyond the rPFS results.

For the exploratory endpoint of ORR, the ORR difference between two arms was 4.7% (95% CI: -4.9%, 14.2%) with an ORR of 66.5% in the capivasertib arm and 61.8% in the placebo arm; the clinical meaningfulness of this difference is unclear as it does not appear to be large.

In summary, the results of these secondary and exploratory endpoints do not overcome concerns with the uncertain clinical meaningfulness of rPFS, particularly without statistical significance in OS in this early metastatic disease setting.

2.3.9 FDA – Clinical Context: Control Arm Therapy:

Guidelines and expert consensus encourage triplet therapy for patients who are chemotherapy-fit and have synchronous high-volume mHSPC (see Section 2.2.4). Triplet therapy includes an ARPI and docetaxel. Thus, if the control arm patients had received triplet therapy, it is plausible that the rPFS benefit over the triplet, if observed, might have been even smaller. In the absence of an improvement in OS and with the added toxicity of capivasertib, the activity of the control arm compared to other available therapies needs to be considered to interpret the clinical meaningfulness of the magnitude of the improvement in rPFS.

2.3.10 FDA – Historical Context

The CAPItello-281 results represent a smaller treatment effect than all previous approvals in

mHSPC (Table 11). All prior approvals were supported by either rPFS benefits with large magnitudes of effect, OS benefits, or both.

Table 11. FDA – Historical Context: Approvals in mHSPC

Trial	Treatment Arm vs. Control Arm	Basis of Approval HR (95% Confidence Interval)	Supportive secondary endpoints[2]
TITAN	Apalutamide + ADT vs Placebo + ADT	rPFS HR 0.48 (0.39, 0.60); OS HR 0.67 (0.51, 0.89)	Initiation of subsequent therapies
ARCHES	Enzalutamide + ADT vs Placebo + ADT	rPFS HR 0.39 (0.30, 0.50)[2]; OS HR 0.66 (0.53, 0.81)	Time to cytotoxic chemotherapies
ARANOTE	Darolutamide + ADT vs Placebo + ADT	rPFS HR 0.54 (0.41, 0.71); OS HR 0.78 (0.58, 1.05)[3]	Time to subsequent antineoplastic therapy
AMPLITUDE	Niraparib + AAP + ADT vs. Placebo + AAP + ADT	(*BRCA2* only) rPFS HR 0.46 (0.32, 0.66)[3]; OS events 22% [niraparib] vs. 34% [placebo]	Time to pain progression
LATITUDE	AAP + ADT vs Placebo + ADT	OS HR 0.62 (0.51, 0.76)	None
ARASENS	Darolutamide + Docetaxel + ADT vs. Placebo + Docetaxel + ADT	OS HR 0.68 (0.57, 0.80)	Time to symptomatic progression

[1]Supportive secondary endpoints are secondary endpoints that were statistically significant and included in product labeling.
[2]OS not mature at time of approval
[3]Not significant
Abbreviations: AAP: abiraterone acetate + prednisone; CI: confidence interval; HR: hazard ratio; OS: overall survival; rPFS: radiographic progression-free survival

The trials that included rPFS as a primary endpoint were TITAN, ARCHES, ARANOTE, and AMPLITUDE. While the approvals of apalutamide, enzalutamide, and darolutamide, all in combination with androgen deprivation therapy (ADT), were supported by trials that randomized patients to doublet therapy versus ADT alone, the most contemporary trial was AMPLITUDE, which randomized patients to niraparib + AAP + ADT versus AAP + ADT, the same control arm as CAPItello-281. This trial demonstrated a clinically meaningful rPFS HR of 0.46 (95% CI: 0.32, 0.66) in the indicated population of patients with *BRCA2*-mutated mHSPC, supported by numerically favorable while immature overall survival results.

The other approvals that FDA has granted for mHSPC, supported by the LATITUDE and ARASENS trials, were approved based on OS as a primary endpoint, with OS HRs of 0.62 (95% CI: 0.51, 0.76) and 0.68 (95% CI: 0.57, 0.80), respectively. The approval of darolutamide with docetaxel and ADT was based on a trial with a control arm therapy of docetaxel with ADT, which is a more effective therapy than ADT alone.

The FDA evaluates each application individually based on the totality of evidence, including the magnitude of treatment effect, toxicity, and meaningfulness in the clinical context. The historical context provided above illustrates that past FDA approvals for therapies in mHSPC

have been supported by improvements in OS and/or large improvements in rPFS. Standard of care therapy has evolved over time in mHSPC, which is reflected in the control arm therapies. While ADT was considered standard in mHSPC in trials conducted more than 10 years ago, the more recent approvals were based on clinically meaningful treatment effects over doublet control arm therapies. This historical context informs the assessment of the clinical meaningfulness of the treatment effect observed in CAPItello-281, while not establishing a threshold treatment effect for approval.

2.3.11 FDA – Lack of Supportive Evidence From Other Trials

The FDA considers CAPItello-281 to be the primary source of evidence to support the sNDA. However, the FDA also considered additional clinical data regarding the efficacy of AKT pathway inhibitors in patients with PTEN-deficient prostate cancer. The FDA identified two Phase 3 trials that addressed this question. IPATential150 is described in Section 2.1.6 ("Clinical Proof of Concept"). In summary, IPATential demonstrated a statistically significant rPFS HR of 0.77 (95% CI: 0.61, 0.98; p=0.034) with a 2-month improvement of median rPFS and no OS benefit with HR of 0.94 (95% CI: 0.76, 1.17), with the addition of ipatasertib to abiraterone, prednisone, and ADT in patients with PTEN-deficient first-line mCRPC. While ipatasertib is a different drug than capivasertib, the trial was conducted in patients with mCRPC rather than mHSPC, and there were differences in the definition of PTEN deficiency, these results do not appear to support inhibition of the AKT pathway as a clearly effective mechanism for providing a clinically meaningful benefit in patients with PTEN-deficient prostate cancer.

The Applicant states that IPATential150 led to the hypothesis that a gradient effect would be observed across levels of PTEN deficiency. The FDA acknowledges the Applicant's exploratory rPFS analysis of CAPItello-281 with subgroups defined by PTEN deficiency scores of 90% to 94%, ≥ 95%, ≥ 99%, and 100% suggested possible increased efficacy with increasing PTEN score cutoffs (2.3.6, Figure 13). Further analyses are provided in Appendix 10 and Table 36 in Appendix 13, including results of the complementary subgroups. However, PTEN loss category was not a stratification factor in CAPItello-281. Thus, baseline covariates may have been imbalanced, limiting interpretability of these post-hoc analyses. The FDA considers these analyses to be hypothesis-generating only and does not agree that they identify a population for whom the addition of capivasertib has a clear favorable benefit-risk assessment than demonstrated for the overall population enrolled in CAPItello-281.

The other Phase 3 trial that evaluated the potential benefit of AKT pathway inhibition in patients with PTEN-deficient prostate cancer was CAPItello-280. CAPItello-280 was conducted by the Applicant and randomized patients with mCRPC who had received prior ARPI but were chemotherapy-naïve to docetaxel and ADT with or without the addition of capivasertib. In contrast to CAPItello-281, patients in CAPItello-280 were unselected for PTEN status, due to the rationale that docetaxel activates the AKT pathway. The dual primary endpoints were OS and rPFS. The OS and rPFS in the two subgroups (PTEN-proficient and PTEN-deficient) were key

secondary endpoints. PTEN status was determined by retrospective central testing of tumor tissue. IHC ≥90% cutoff, the same PTEN-loss cutoff used in CAPItello-281, was used to define PTEN-deficient subgroup.

The trial was deemed futile for efficacy with the dual primary endpoints of OS and rPFS. The HR for OS was 1.22 (95% CI: 1.00, 1.49) and HR for rPFS was 0.98 (95% CI: 0.84, 1.15). CAPItello-280 was terminated in April 2025 following IDMC recommendation for futility and safety concerns given the increased number of deaths in the capivasertib arm.

In addition, the pre-specified exploratory analysis did not suggest more favorable OS or rPFS treatment effects for subgroups with PTEN deficiency. See Appendix Table 38 for topline efficacy results of CAPItello-280.

Despite the differences between CAPItello-280 and CAPItello-281, the demonstration of futility in this trial increases the FDA's concern regarding the efficacy and safety of capivasertib in patients with metastatic prostate cancer.

3 Safety

The Applicant's Position:

The addition of capivasertib to background therapy of abiraterone + prednisone/prednisolone + ADT in CAPItello-281 was associated with increased toxicity that is considered to be predictable, monitorable, and reversible using management measures established in routine oncology practice. When toxicities arose, these were managed with dose interruptions in the first instance; or dose reductions; or, when warranted, dose discontinuations.

The overall incidence of AEs was higher in CAPItello-281 than in breast cancer studies, consistent with an older, metastatic prostate cancer population receiving abiraterone, corticosteroid, and ADT. The overall safety profile is consistent, with no new safety signals.

Furthermore, despite toxicity associated with capivasertib as an add-on therapy in CAPItello-281, patient-reported data did not show a clinically meaningful reduction in quality of life during study treatment (Section 4).

3.1 Exposure to Capivasertib in Clinical Trials and the Post-marketing Setting

As an approved treatment for hormone receptor-positive, HER2-negative advanced breast cancer, capivasertib has a well-characterized safety profile based on extensive clinical data and post-marketing experience:

- As of November 15, 2025, ~3275 patients and 73 healthy volunteers have received capivasertib in ongoing and completed studies in the clinical development program.

- Between launch and October 31, 2025, the cumulative global post-marketing patient exposure to capivasertib is estimated at ~4900 patient-years for 200 mg tablets and ~1150 patient-years for 160 mg tablets.

3.2 Safety Summary as of the Primary rPFS Analysis for CAPItello-281

3.2.1 Exposure

3.2.1.1 Exposure to Capivasertib

In CAPItello-281, a total of 503 patients with PTEN-deficient mHSPC were treated with C+A.

At the primary rPFS analysis (DCO: October 07, 2024), the median treatment duration of capivasertib was 1.1 years, ranging up to nearly 4 years. Importantly, treatment with capivasertib did not compromise exposure to abiraterone overall.

Median total treatment duration for capivasertib was shorter than for placebo (Table 12), with fewer patients continuing to receive capivasertib (43.5%) than placebo (49.1%) at the time of the DCO. This reflects the higher rate of AEs leading to discontinuation of capivasertib compared to placebo during the first 3 months of therapy, which was balanced between arms thereafter (Figure 14).

Overall dose intensity of capivasertib remained high, indicating successful dose management over the treatment period; noting that median actual treatment duration of capivasertib, calculated as the total treatment duration minus the length of time of treatment interruptions, was shorter than total median treatment duration (Table 12). This was in line with management of the add-on therapy by dose modification.

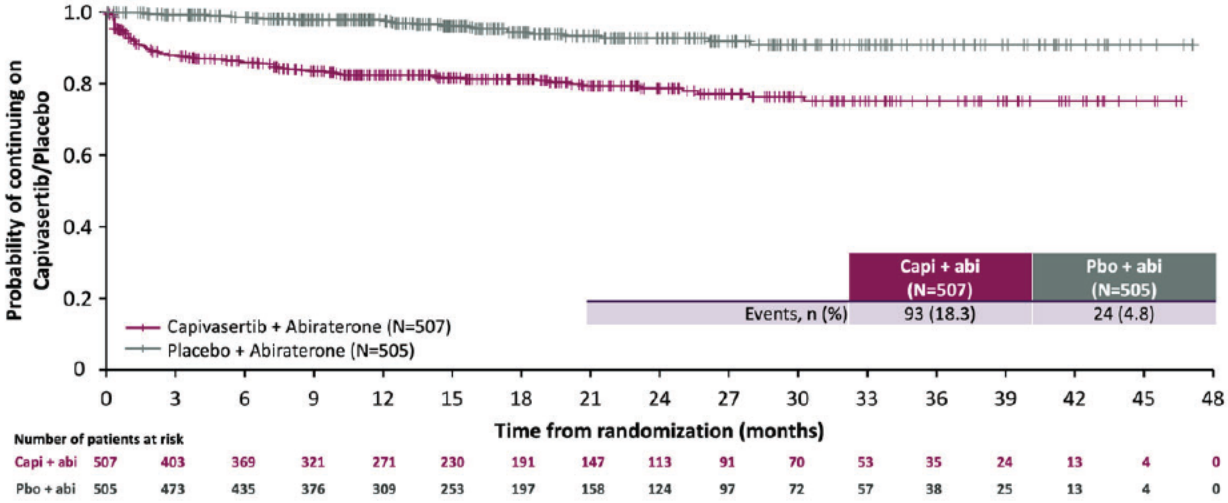
Table 12 CAPItello-281: Duration of Exposure and Dose Intensity for Capivasertib/Placebo (SAS)

Treatment arm	C+A	P+A
Total number of patients in treatment arm, N	**503**	**503**
Total treatment duration (months), median (range) [a]	13.6 (0.1, 46.6)	14.9 (0.1, 47.1)
Actual treatment duration (months), median (range) [b]	12.1 (0.1, 46.4)	14.7 (0.1, 47.1)
Relative dose intensity (%), median (IQR) [c]	96.3 (78.6, 100.0)	99.9 (98.0, 100.0)
Percentage intended dose (%), median (IQR) [d]	87.0 (53.8, 98.7)	98.9 (95.2, 99.8)

a Total treatment duration = number of days from first dose to last dose of study treatment.
b Actual treatment duration = total treatment duration minus the total duration of dose interruptions and minus any forgotten to take dose days.
c Relative dose intensity is the percentage of the actual dose delivered relative to the intended dose through to treatment discontinuation.
d Percentage intended dose is the percentage of the actual dose delivered relative to the intended dose through to radiological progression. In the Clinical Study Report, percentage intended dose was erroneously calculated through to treatment discontinuation.

IQR, interquartile range; SAS, Safety Analysis Set.
Source: Table 14.3.1.1, Table 14.3.1.2 CAPItello-281 Clinical Study Report; IEMT911 Table 1.

Figure 14 CAPItello-281: Kaplan-Meier Plot of Time from Randomization to Discontinuation of Capivasertib/Placebo due to AEs (FAS)



Patients not known to have discontinued capivasertib/placebo due to AEs are censored at the earliest of the following: death date, end of study date, DCO date, and when discontinuation of capivasertib/placebo was not due to AEs.
Circles represent censored observations.
Source: IEMT559.2, CAPItello-281 Clinical Study Report.

3.2.1.2 Impact of Capivasertib on Abiraterone Administration

The co-administration of capivasertib did not negatively impact the use of standard of care abiraterone with ADT. Median treatment duration and percentage intended dose for abiraterone were similar in both arms (Table 13). Dose interruptions of abiraterone were more common in the C+A arm, but with minimal impact on overall exposure (percentage intended dose) (Table 13).

Table 13 CAPItello-281: Abiraterone Duration of Exposure, Dose Intensity, and AEs Leading to Discontinuation/Dose Modification of Abiraterone (SAS)

Treatment arm	C+A	P+A
Total number of patients in treatment arm, N	**503**	**503**
Total abiraterone treatment duration (months), median (range) [a]	14.9 (0.1, 46.6)	14.9 (0.1, 47.1)
Actual abiraterone treatment duration (months), median (range) [b]	14.5 (0.1, 46.5)	14.7 (0.1, 47.1)
Relative abiraterone dose intensity (%), median (IQR) [c]	99.7 (95.4, 100.0)	100.0 (98.8, 100.0)
Abiraterone percentage intended dose (%), median (IQR) [d]	97.5 (84.6, 99.7)	99.3 (95.1, 99.8)
AE, n (%) [e]	497 (98.8)	463 (92.0)
AE leading to dose interruption of abiraterone, n (%) [e]	238 (47.3)	127 (25.2)
AE leading to dose reduction of abiraterone, n (%) [e]	49 (9.7)	27 (5.4)
AE leading to discontinuation of abiraterone, n (%) [e]	48 (9.5)	27 (5.4)

a Total treatment duration = number of days from first dose to last dose of study treatment.
b Actual treatment duration = total treatment duration minus the total duration of dose interruptions and minus any forgotten to take dose days.
c Relative dose intensity is the percentage of the actual dose delivered relative to the intended dose through to treatment discontinuation.
d Percentage intended dose is the percentage of the actual dose delivered relative to the intended dose through to radiological progression. In the Clinical Study Report, percentage intended dose was erroneously calculated through to treatment discontinuation.

e Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
IQR, interquartile range; SAS, Safety Analysis Set.
Note: AEs with an onset date on/after date of the first dose and AEs with onset date prior to the first dose but worsen after the first dose are reported, up to 30 days (+7 days) following the date of last dose.
Source: Table 14.3.1.1, Table 14.3.1.2, Table 14.3.2.1, CAPItello-281 Clinical Study Report; IEMT911 Table 1.

3.2.2 Adverse Events

3.2.2.1 Adverse Events by Category

Patients in the C+A arm had a higher incidence of reported AEs overall in the study, including Grade ≥ 3 AEs and serious adverse events (SAEs) than patients in the P+A arm (Table 14). Deaths and SAEs are discussed below.

AEs were managed primarily with interruptions (in 62.8% of patients in the C+A arm), with 29.0% patients in the C+A arm having a dose reduction due to an AE. For both dose interruptions and dose reductions, the most common AEs were diarrhea, rash, and hyperglycemia.

A total of 18.3% of patients discontinued capivasertib due to an AE. The majority (58/92) of discontinuations were within the first 3 months. The most common AEs leading to discontinuation of capivasertib were Rash maculo-papular (3.8%), Erythema multiforme (1.2%), Diabetes mellitus (1.0%), Diarrhea (1.0%), and Hyperglycemia (1.0%). These AEs are consistent with the known safety profile of capivasertib, discussed below.

Table 14 CAPItello-281: AEs by Category (SAS)

Treatment arm	C+A	P+A
Total number of patients in treatment arm, N	**503**	**503**
AE, n (%) [a]	497 (98.8)	463 (92.0)
AE of Grade ≥ 3, n (%) [a, b]	337 (67.0)	203 (40.4)
SAE (including AEs leading to death), n (%) [a]	214 (42.5)	131 (26.0)
AE leading to death, n (%) [a]	36 (7.2)	26 (5.2)
AE leading to discontinuation of capivasertib/placebo, n (%) [a]	92 (18.3)	24 (4.8)
AE leading to dose interruption of capivasertib/placebo, n (%) [a]	316 (62.8)	135 (26.8)
AE leading to dose reduction of capivasertib/placebo, n (%) [a]	146 (29.0)	18 (3.6)

a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
b Grading per CTCAE Version 5.0.
Note: AEs with an onset date on/after date of the first dose and AEs with onset date prior to the first dose but worsen after the first dose are reported, up to 30 days (+7 days) following the date of last dose.
CTCAE, Common Terminology Criteria for Adverse Events; SAS, Safety Analysis Set.
Source: Table 14.3.2.1, CAPItello-281Clinical Study Report.

3.2.2.2 Deaths

The total number of deaths was greater in the P+A arm (138) compared to the C+A arm (129) (Section 2.3.2).

There were 25 deaths in the C+A arm that were reported as an AE leading to death (vs 23 on the P+A arm). A further 11 deaths on the C+A arm (vs 3 on the P+A arm) were attributed to the disease under investigation as well as an AE, underscoring the challenges in establishing causes of death in a population with considerable morbidity and mortality due to their underlying disease (Table 15).

The AEs leading to death were distributed over several System Organ Classes (SOCs), with no clustering or patterns of Preferred Terms (PTs) to suggest common or leading causes of death. Furthermore, most of the AEs leading to death were assessed as not causally related to capivasertib (30/36 in C+A arm; 25/26 on P+A arm). Of the 6 events assessed as possibly causally related to capivasertib on the C+A arm, 5 were assessed as possibly related to capivasertib and abiraterone, and 1 to capivasertib only. A summary of AEs leading to death by SOC and a listing of AEs leading to death by PT are presented in Appendix 12.

Table 15 CAPItello-281: Summary of Deaths (FAS)

Treatment arm	C+A	P+A
Total number of patients in treatment arm, N	**503**	**503**
AE leading to death, n (%)	36 (7.2)	26 (5.2)
AE leading to death only, n (%) [a]	25 (4.9) [b]	23 (4.6)
Death attributed to disease under investigation and AE(s), n (%) [a, c]	11 (2.2)	3 (0.6)

a AEs with an onset date on/after date of first dose; AEs with onset date prior to the first dose which worsened after the first dose; AEs occurring up to 30 days (+ 7 days) following date of last dose.
b In 4 of these 25 patients, AEs with outcome of death only occurred more than 30 (+7 days) after the last dose of capivasertib.
c Death related to disease under investigation as determined by the investigator.
Source: Table 14.3.2.1 and Table 14.3.5.1, CAPItello-281 Clinical Study Report; IEMT877.

The cumulative incidence of AEs leading to death at the Day 120 safety update, capturing an additional ~9 months of follow-up after the primary rPFS analysis, are reported in Section 3.3.

3.2.2.3 Serious Adverse Events

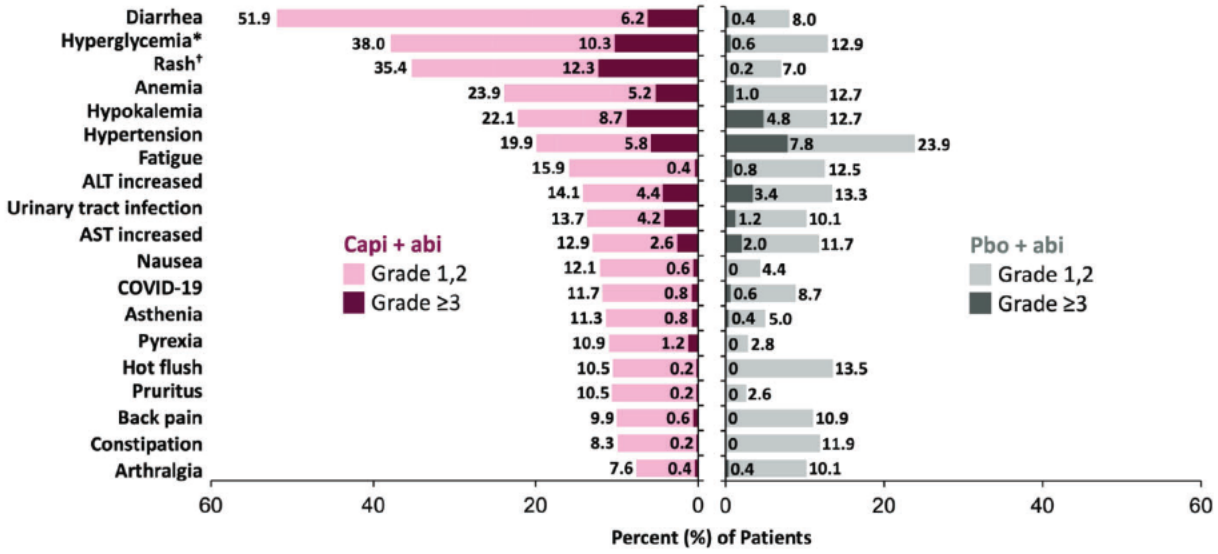
SAEs were more common in the C+A arm than in the P+A arm (42.5% vs 26.0%). The most common SAEs in the C+A arm were Pneumonia (3.8% vs 2.4%), Hyperglycemia (3.6% vs 0%), and urinary tract infection (3.0% vs 0.8%). Additionally, SAEs were reported for known adverse drug reactions (ADRs) of capivasertib (eg, diarrhea, rash, and cutaneous events, diabetic ketoacidosis [DKA], hypokalemia, diabetes). Other lower-frequency SAEs had no clear pattern and were generally reported in few (< 2%) patients.

3.2.2.4 Most Common Adverse Events

Overall, the observed pattern of PTs reported for patients receiving the combination of C+A in CAPItello-281 was generally predictable based on the established safety profiles of capivasertib and background therapy (abiraterone + corticosteroid + ADT) and the underlying comorbidity burden in this population (Figure 15).

The most common Grade ≥ 3 AEs observed in the C+A arm of CAPItello-281 are known ADRs for capivasertib and/or abiraterone, monitorable as part of standard clinical practice (standard physical examination and routine clinical chemistries), and are clinically manageable with dose modifications or supportive therapy. Diarrhea, rash, and hyperglycemia are assessed below.

Figure 15 CAPItello-281: AEs by PT (Incidence ≥ 10% in Either Arm) (SAS)



*Grouped term (includes the PTs of Blood glucose increased, Hyperglycemia).
†Grouped term (includes the PTs of Erythema, Rash, Rash erythematous, Rash macular, Rash maculo-papular, Rash popular, Rash pruritic).
% of patients with AEs. Patients with multiple events in the same PT are counted only once in that PT. Patients with events in more than one PT are counted once in each of those.
Note: AEs with an onset date on/after date of the first dose and AEs with onset date prior to the first dose but worsen after the first dose are reported, up to 30 days (+7 days) following the date of last dose.
MedDRA Version: 27.0.
abi, abiraterone; ALT, alanine aminotransferase; AST, aspartate aminotransferase; capi, capivasertib; COVID-19, coronavirus disease 2019; MedDRA, Medical Dictionary for Regulatory Activities; SAS, Safety Analysis Set;.
Source: Module 5.3.5.3 Pooled Safety Outputs, IEMT777 Table 4; Module 2.7.4 Section 2.1.8; ZYTIGA® United States Prescribing Information (USPI) 2024 [45].

3.2.2.5 Key Adverse Events (Diarrhea, Hyperglycemia and Rash)

The most common events in the C+A arm (diarrhea, hyperglycemia, and rash) are known on-target toxicities for capivasertib and are associated with inhibition of the PI3K/AKT/PTEN signaling pathway. Consistent with this mechanism of action, these events are likely to occur early in treatment. Most events were Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or 2 in severity and non-serious, monitorable with basic laboratory and routine clinical assessments, and successfully managed with supportive treatments and/or capivasertib dose modification (Table 16).

Table 16 CAPItello-281: Characterization of Diarrhea, Hyperglycemia, and Rash (Grouped Terms) (SAS)

Toxicity grouped term	Diarrhea [a]	Diarrhea [a]	Hyper-glycemia [b]	Hyper-glycemia [b]	Rash [c]	Rash [c]
Treatment arm	**C+A**	**P+A**	**C+A**	**P+A**	**C+A**	**P+A**
Total number of patients in treatment arm, N	**503**	**503**	**503**	**503**	**503**	**503**
Any grade AE, n (%)	261 (51.9)	40 (8.0)	232 (46.1)	72 (14.3)	178 (35.4)	35 (7.0)
SAEs, n(%)	6 (1.2)	1 (0.2)	24 (4.8)	0	16 (3.2)	0
Grade 1, n(%) [d]	158 (31.4)	28 (5.6)	62 (12.3)	40 (8.0)	51 (10.1)	27 (5.4)
Grade 2, n (%) [d]	72 (14.3)	10 (2.0)	100 (19.9)	29 (5.8)	65 (12.9)	7 (1.4)
Grade 3, n (%) [d]	30 (6.0)	2 (0.4)	68 (13.5)	3 (0.6)	62 (12.3)	1 (0.2)

Toxicity grouped term	Diarrhea [a]	Diarrhea [a]	Hyper-glycemia [b]	Hyper-glycemia [b]	Rash [c]	Rash [c]
Treatment arm	C+A	P+A	C+A	P+A	C+A	P+A
Grade 4, n (%) [d]	1 (0.2)	0	1 (0.2)	0	0	0
Grade 5, n (%) [d]	0	0	1 (0.2)	0	0	0
Median time to onset, days (IQR)	12.0 (3.0, 43.0)	141.5 (27.5, 339.0)	57.0 (15.0, 124.0)	126.0 (77.0, 335.0)	13.0 (11.0, 43.0)	78.0 (37.0, 195.0)
AE leading to dose reduction of capivasertib/placebo, n (%) [e]	22 (4.4)	0	40 (8.0)	1 (0.2)	43 (8.5)	2 (0.4)
AE leading to dose interruption of capivasertib/placebo, n (%) [e]	63 (12.5)	1 (0.2)	71 (14.1)	4 (0.8)	85 (16.9)	3 (0.6)
AE leading to discontinuation of capivasertib/placebo, n (%) [e]	5 (1.0)	0	11 (2.2)	0	24 (4.8)	0
Recovered/recovering, n/patients with events (%) [f]	216/261 (82.8%)	36/40 (90.0%)	136/232 (58.6%)	40/72 (55.6%)	154/178 (86.5%)	27/35 (77.1%)
Not reported as recovered, n/patients with events (%)	45/261 (17.2%)	4/40 (10.0%)	96/232 (41.4%) [g]	32/72 (44.4%)	24/178 (13.5%)	8/35 (22.9%)

a Diarrhea is a medical concept including the following PTs: Diarrhea, Frequent bowel movements, and Gastrointestinal hypermotility.
b Hyperglycemia is a medical concept composed of the PTs: Blood glucose increased, Hyperglycemia, Diabetes mellitus and Type 2 diabetes mellitus
c Rash is a medical concept composed of the PTs: Rash, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic, Rash erythematous, and Erythema.
d Patients with more than one AE are counted with the maximum CTCAE grade reported.
e In case of multiple events, each patient was only counted once per category but can be counted in more than one category.
f Includes terms of recovered, recovered with sequelae, and recovering.
g Includes one additional patient with hyperglycemia had a fatal outcome.
CTCAE Version: 5.0.
MedDRA Version: 27.0 (CAPItello-281).
IQR, interquartile range; MedDRA, Medical Dictionary for Regulatory Activities; SAS, Safety Analysis Set.
Source: Table 14.3.3.12, CAPItello-281 Clinical Study Report; IEMT579 Table 2 IEMT928.1, IEMT928.2, IEMT928.3; IEMT800, Pooled Safety Outputs.

Data discussed below are for patients treated on the C+A arm of CAPItello-281.

3.2.2.6 Diarrhea

Diarrhea was reported in 261 patients (51.9%, total of 599 events reported) and generally occurred early (median time to onset 12 days), allowing for prompt identification and management. The majority of patients had low maximum grade diarrhea reported (CTCAE Grade 1 [31.4%] and Grade 2 [14.3%]), with fewer Grade 3 (6.0%) and one Grade 4 (0.2%).

Overall, over two-thirds of diarrhea events were reported as intermittent, and over two-thirds reported that diarrhea occurred on capivasertib dosing days only. These AE data are also consistent with the patient experience data, reported in Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), with patients experiencing diarrhea reporting that it occurred rarely or occasionally (Section 4).

There were 33 events (in 31 patients) with a maximum Grade 3 to 4 reported, of which 6 were SAEs. Events with a maximum Grade 3 to 4 had a median duration of 4.5 days (range: 1, 11). All Grade 3 to 4 events were reported as recovered, one with sequelae.

Most patients with diarrhea of any grade did not require dose modifications. Where needed, capivasertib was interrupted (12.5%) or dose reduced (4.4%), and infrequently discontinued (1.0%).

Diarrhea was also managed using standard antidiarrheal measures as needed, eg, loperamide used in 131/261 (50.2%) of patients with diarrhea AEs. Diarrhea was reported as recovered/recovering in most (216/261 [82.8%]) patients at end of treatment or at the time of the DCO.

3.2.2.7 Rash

Rash is represented by a grouped term of events considered typical of PI3K/AKT rash. Rash occurred early (median time to onset 12 days) and was most commonly reported as maculopapular rash, with severity spread across CTCAE Grades 1, 2, and 3, and was serious in 3.2% of patients. Capivasertib was discontinued due to rash in 4.8% of patients.

Rash AEs were also managed with routine supportive care (e.g., antihistamines, topical corticosteroids, or systemic corticosteroids). A high proportion of patients' rash had a reported outcome of recovered or recovering at last assessment.

In addition to the common AKT inhibitor rash phenotype captured above, other clinically important cutaneous events were reported, such as Erythema multiforme (2.6%, Grade 2 to 3), Dermatitis exfoliative (0.2%, Grade 3), Dermatitis exfoliative generalized (0.8%, Grade 2 to 4) and Drug eruption (0.8%, Grade 3). Three events of Stevens-Johnson Syndrome (SJS) (Grade 3 to 4) were reported in 2 patients (0.4%). In one patient, one SJS event was assessed as possibly related to capivasertib by the investigator and unlikely related to abiraterone, and both study drugs were interrupted. The patient continued therapy with non-study drug abiraterone and had a second event of SJS reported, which was classified as possibly related to abiraterone by the investigator. In the other patient, the event of SJS was assessed as possibly related to capivasertib by the investigator. However, the description (target lesions without blisters or evidence of skin peeling) was not consistent with SJS, and concurrent bacteremia may have been an alternative cause for rash. Overall, these cutaneous events were infrequent, but when serious, often prompted dose modifications and treatment including corticosteroids.

3.2.2.8 Hyperglycemia

Hyperglycemia AEs (including Hyperglycemia, Blood glucose increased, Type 2 diabetes mellitus and Diabetes mellitus) were reported early (median time to onset of 57 days). The maximum grade of hyperglycemia reported in the majority of patients was 1 to 2 (32.2%), with Grade ≥ 3 events reported in fewer patients (13.9%). Approximately half of the patients with hyperglycemia had dose modifications: dose interruptions in 14.1% of patients, dose reductions in 8.0% of patients, and discontinuation in 2.2% of patients overall.

Management of hyperglycemia included standard antihyperglycemic therapy, most commonly metformin (121/232 patients [52.2%]) or other antidiabetic drugs[6] (91/232 patients [39.2%]), and less commonly with insulin (67/232 patients [28.9%]).

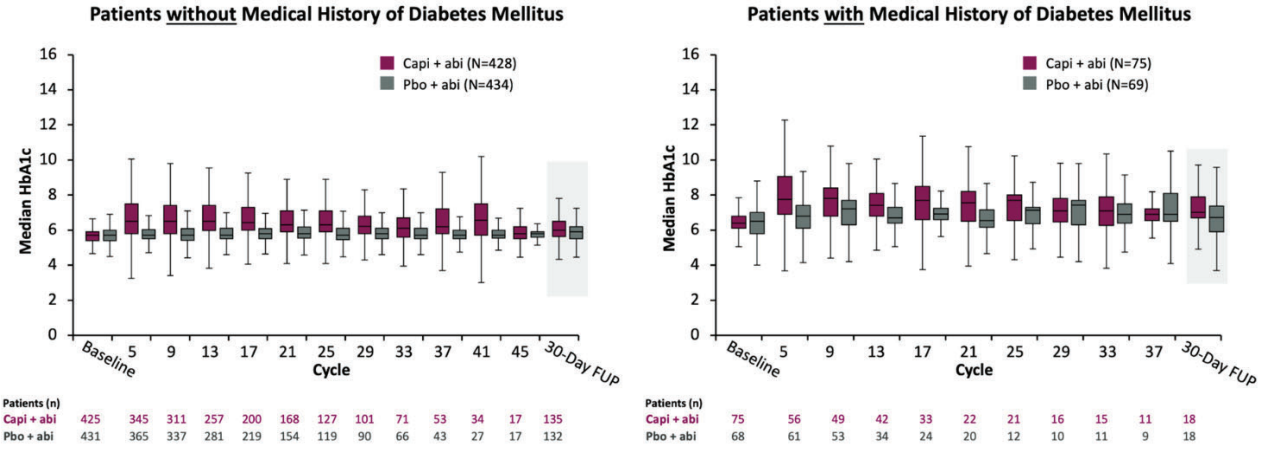
[6] Does not include patients who received metformin or insulin as well as other antidiabetic drugs.

Hyperglycemia AEs had a reported outcome of recovered or recovering at last assessment in the majority of patients (58.6%), indicating that events of hyperglycemia and diabetes were generally reversible.

An early increase in HbA1c was noted on the C+A arm, with the median HbA1c rising by 0.9% to a median of 6.6% at Cycle 5 (first timepoint assessed). This then showed a trend of steady decrease (improvement) over the course of subsequent cycles, and reversibility following capivasertib discontinuation, including at the 30-day post-discontinuation follow-up (Figure 16), with the greatest improvement observed ≥ 56 days post-discontinuation in patients with available data (median: 5.8%).

Note: for most adults with diabetes, the American Diabetes Association recommends an HbA1c goal of < 7.0%; however, for older adults with complex health status or higher risk from treatment, American Diabetes Association guidance suggests less stringent goals (eg, < 8.0%), with targets individualized based on medication benefit-risk balance and patient preference [46].

Figure 16 HbA1C Over Time (SAS)



Bars depict median HbA1C (IQR), error bars depict 1.5 times IQR.
Source: IEMT572 Table 1 and IEMT572 Table 2.

Patients with a medical history of diabetes and/or baseline HbA1c ≥ 6.5% had greater increases in HbA1c throughout the study compared to those without these baseline risk factors (Figure 16) and may require closer monitoring and earlier initiation/ intensification of anti-hyperglycemic therapy. In common with the existing indication for breast cancer, the US prescribing information (USPI) will include toxicity management guidance specific to hyperglycemia.

Events of DKA, an acute complication of hyperglycemia, were reported in 6 patients (1.2%) in the C+A arm (all reported as Grade ≥ 3 SAEs), with a median time to onset of 265 days. These all occurred in a setting of one or more comorbidities, treatments and concurrent events (eg, infections, increasing HbA1c with no treatment with antidiabetic medications, etc), which most likely contributed to the events. All 6 patients received insulin for the treatment of diabetic ketoacidosis, and all resulted in discontinuation of capivasertib. The reported outcome was

fatal in one patient, reported as recovered/recovering in 4 patients, and not reported as recovered in one patient (who died due to concurrent septic shock).

The proposed USPI includes measures intended to prevent uncontrolled hyperglycemia and DKA, including optimizing glycemic control prior to initiating therapy, blood glucose monitoring, and guidance on dose reductions and/or supportive therapies based on fasting plasma glucose thresholds.

3.3 Day 120 Safety Update for CAPItello-281 AEs

Safety results based on a DCO of July 04, 2025 include ~9 additional months of follow-up compared to the primary rPFS analysis. At the DCO, 35% of patients in the C+A arm and 39% of patients in the P+A arm were continuing to receive capivasertib or placebo, respectively. The updated safety data showed few additional AEs compared to the primary rPFS analysis, supporting that most AEs occurred early after commencing treatment (Table 17). No new safety signals were identified.

Of 77 deaths of any cause reported since the primary rPFS analysis, 50 occurred in patients receiving placebo. Most of the new deaths were attributed to the underlying disease only (C+A: 21 deaths, P+A: 36 deaths). The cumulative incidence of AEs leading to death at the Day 120 safety update was 7.8% (39 patients) in the C+A arm and 6.4% (32 patients) in the P+A arm. The 3 AEs leading to death in the C+A arm that were reported since the primary rPFS analysis were assessed as not causally related to study treatment.

Table 17 CAPItello-281 Day 120 Safety Update: AEs by Category (SAS)

Analysis	Primary rPFS analysis	Primary rPFS analysis	Day 120	Day 120
Treatment arm	**C+A**	**P+A**	**C+A**	**P+A**
Total number of patients in treatment arm, N	**503**	**503**	**503**	**503**
Variable	**n (%) [a]**	**n (%) [a]**	**n (%) [a]**	**n (%) [a]**
AE	497 (98.8)	463 (92.0)	499 (99.2)	469 (93.2)
AE of Grade ≥ 3	337 (67.0)	203 (40.4)	357 (71.0)	224 (44.5)
SAE (including AEs leading to death)	214 (42.5)	131 (26.0)	234 (46.5)	152 (30.2)
AE leading to death	36 (7.2)	26 (5.2)	39 (7.8)	32 (6.4)
AE leading to discontinuation of capivasertib/placebo	92 (18.3)	24 (4.8)	100 (19.9)	28 (5.6)
AE leading to dose interruption of capivasertib/placebo	316 (62.8)	135 (26.8)	328 (65.2)	148 (29.4)
AE leading to dose reduction of capivasertib/placebo	146 (29.0)	18 (3.6)	159 (31.6)	19 (3.8)

a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
Note: AEs with an onset date on/after date of the first dose and AEs with onset date prior to the first dose but worsen after the first dose are reported, up to 30 days (+7 days) following the date of last dose.
MedDRA version 27.0.
MedDRA, Medical Dictionary for Regulatory Activities; SAS, Safety Analysis Set.
Source: Table 14.3.2.1, Day 120 Safety Update.

Overall, the addition of capivasertib to background therapy of abiraterone + prednisone/ prednisolone + ADT in this metastatic prostate cancer population was associated with increased toxicity, with a pattern of AEs that was consistent with the known safety profile of capivasertib

and was manageable and reversible using established routine oncology practice measures.

3.3.1 FDA – Safety

The FDA's Position:

Exposure

Given the long exposure of therapy, the FDA's safety review focused on the Day 120 Safety update (Applicant's Table 17), which would more closely reflect the anticipated clinical experience of capivasertib in combination with abiraterone and prednisone in patients with PTEN-deficient mHSPC.

Based on this data cut, median duration of exposure to capivasertib on the experimental arm was 16.8 months and, for placebo, was 18.6 months on the control arm (Table 18). Exposure to abiraterone was similar in both arms. These data reflect longer exposures compared to the Applicant's presented exposures in Table 12 and Table 13, based on an earlier data cut. The FDA agrees that the shorter duration of exposure to capivasertib vs placebo appears to be due to the higher rate of AEs leading to discontinuation of capivasertib. While the FDA agrees with the Applicant that treatment with capivasertib did not compromise exposure to abiraterone overall, the high discontinuation rate and shorter duration of exposure to capivasertib compared to placebo suggest that capivasertib was not well-tolerated. If capivasertib provided substantial clinical benefit when combined with abiraterone, one would expect patients in the capivasertib arm to remain on abiraterone therapy longer. However, the median abiraterone treatment duration was comparable between arms (capivasertib arm: 19.2 months vs. placebo arm: 19.0 months), suggesting that the addition of capivasertib did not meaningfully extend the duration of benefit from abiraterone therapy.

Table 18. FDA – Day 120 Update: Exposure to Capivasertib, Placebo, and Abiraterone

Treatment duration parameter	C+AAP N = 503	P+AAP N = 503
Actual treatment duration: capivasertib or placebo (months): Median (range)	16.8 (0.1, 55)	18.6 (0.1, 56)
Actual treatment duration: abiraterone (months): Median (range)	19.2 (0.1, 55)	19.0 (0.1, 56)

Note: Actual treatment duration = total treatment duration minus the total duration of dose interruptions and minus any forgotten to take dose days.
Abbreviations: C+AAP: capivasertib + abiraterone + prednisone/prednisolone; P+AAP: placebo + abiraterone + prednisone/prednisolone

Abiraterone increases ACTH due to feedback loops resulting in increased mineralocorticoid levels causing hypertension, hypokalemia, and fluid retention. Co-administration with a glucocorticoid suppresses ACTH. Prednisone 5 mg daily is recommended in the USPI for the non-micronized formulation of abiraterone acetate and is considered standard of care. While

administration of prednisone/prednisolone 5 mg was required on both arms per protocol, the electronic case report form (eCRF) did not include a dedicated field to document prednisone/prednisolone use. The Applicant states that this likely resulted in underreporting of glucocorticoid use. Only 60% of patients received prednisone/prednisolone per eCRF (63% in C+AAP arm, 58% in P+AAP arm).

As shown in Appendix 14 Table 39, an increased proportion of patients experienced hyperglycemia in the capivasertib treatment group among those with documented prednisone/prednisolone use vs. without (any-grade: 54 vs. 46%; Grade 3-4: 14% vs. 9%, with documented prednisone/prednisolone use vs. without, respectively), implying that some of the patients without documented corticosteroid use may not have actually received the drug.

Safety

As illustrated in the Applicant's Table 17, patients treated with C+AAP experienced a higher frequency of total, high-grade, serious, and fatal adverse reactions compared to those treated with P+AAP. The FDA provides further details of these adverse reactions in Table 19 and Table 20.

Table 19 FDA – Day 120 Safety Update: Most Common (Any Grade >=20%) Adverse Events

Treatment arm	C+AAP N=503		P+AAP N=503	
	Any Grade N (%)	Grade 3-4 N (%)	Any Grade N (%)	Grade 3-4 N (%)
Any Adverse Event	499 (99)	318 (63)	469 (93)	192 (38)
Infections*	286 (57)	91 (18)	222 (44)	32 (6)
Skin reactions*	267 (53)	87 (17)	84 (17)	2 (0.4)
Diarrhea*	265 (53)	33 (7)	45 (9)	2 (0.4)
Hyperglycemia*	257 (51)	74 (15)	80 (16)	6 (1.2)
Musculoskeletal pain*	138 (27)	8 (1.6)	152 (30)	7 (1.4)
Fatigue*	132 (26)	6 (1.2)	93 (18)	6 (1.2)
Decreased hemoglobin	293/500 (59)	29/500 (6)	220/500 (44)	12/500 (2.4)
Decreased potassium	236/500 (47)	77/500 (15)	175/500 (35)	42/500 (8)
Hypertension	124 (25)	37 (7)	133 (26)	44 (9)

Abbreviations: C+AAP: capivasertib + abiraterone + prednisone/prednisolone; P+AAP: placebo + abiraterone + prednisone/prednisolone
[a]Includes multiple terms

Table 20 FDA – Day 120 Safety Update: Deaths Due to Adverse Events

	C+AAP N=503 N (%)	P+AAP N=503 N (%)
Adverse Event (AE) leading to death	39 (7.8)	32 (6.4)
AE leading to death in first 3 months of therapy	14 (2.8)	6 (1.2)

AEs leading to death in >=2 patients[a]		
Sepsis[b]	6 (1.2)	5 (1)
Ischemic cardiovascular events[b]	5 (1)	3 (0.6)
Hemorrhage[b]	3 (0.6)	1 (0.2)
Pneumonia[b]	2 (0.4)	5 (1)

[a]Limited to AEs with clinically defined concepts (i.e., excludes "Death" and "Sudden death")
[b]Includes multiple terms
Abbreviations: C+AAP: capivasertib + abiraterone acetate + prednisone/prednisolone; P+AAP: placebo + abiraterone acetate + prednisone/prednisolone

The Applicant states that AEs leading to death were distributed over several Preferred Terms and most were not assessed as causally related to capivasertib. However, the most common causes of fatal adverse reactions (Table 20), including infections (sepsis and pneumonia), ischemic cardiovascular events, and hemorrhage, were also events that were noted to have an increased incidence in the capivasertib arm compared to the placebo arm in the Grade 3-4 AE analysis (infections: 18% vs 6%; ischemic cardiovascular events: 2.2% vs 1.8%; hemorrhage: 2.8% vs. 1.2%, in capivasertib vs. placebo arms, respectively). Additionally, the risk of infections and ischemic cardiovascular events may be increased with hyperglycemia, a known risk of capivasertib treatment. Therefore, it is plausible that capivasertib increased the risk for death in some of these cases.

The FDA agrees that many of the common events in the capivasertib treatment group are known on-target toxicities for capivasertib and are associated with inhibition of the AKT pathway. However, the FDA's perspective includes the following points:

1. The Applicant states that many of these events were successfully managed and reversible with supportive treatments or dose modification. The increase in fatal adverse reactions suggests that some events were not successfully managed. Additionally, among the deaths due to adverse events on the capivasertib arm, more than a third occurred within the first 3 months (Table 20). This was more than double the number of patients on the placebo arm who died due to adverse events within that timeframe. These are early deaths in a disease setting where median overall survival is at least several years and, despite a large proportion with high-volume disease, most patients had minimal symptoms prior to therapy with low rates of pain progression during the study.
2. The statement that "these events are likely to occur early in treatment" is juxtaposed by the Applicant's observation that among the 6 patients with DKA, the median time to onset was 265 days. While it appears that many of the rash and diarrhea events are likely to occur early in treatment, the risk of DKA late in the course of treatment highlights the risk of serious toxicities with cumulative and prolonged exposure to capivasertib.
3. Similarly, the Applicant's position that the addition of capivasertib to abiraterone + prednisone/prednisolone + ADT did not demonstrate new safety concerns compared to capivasertib monotherapy is not supported by the incidence and severity of hyperglycemia. The rates of Grade 3-4 hyperglycemia and initiation or change of anti-

hyperglycemic medications, such as insulin, were several fold higher in CAPItello-281 compared to CAPItello-291, the breast cancer trial that led to approval of the drug (Table 21). Given the similar eligibility restrictions with respect to baseline control of hyperglycemia, this increase in toxicity likely reflects the effect of combining prednisone/prednisolone with capivasertib in CAPItello-281 and the prolonged duration of treatment with capivasertib in CAPItello-281 compared to CAPItello-291 (approximately 17 versus 5 months). Additionally, ADT can lead to impaired glucose tolerance, insulin resistance, and weight gain, all of which may put patients with prostate cancer on ADT at further risk for severe hyperglycemia due to the addition of capivasertib. The higher incidence of severe hyperglycemia among the 63% of patients with documented prednisone/prednisolone use compared to the 37% without on the capivasertib arm (Table 39) suggests that if all patients had received corticosteroids, as per the US prescribing information for abiraterone, the risk of severe hyperglycemia would have been higher in capivasertib-treated patients than was observed in CAPItello-281.

4. The FDA's analyses of "rash" are represented by the term "skin reactions" and resulted in higher numbers of adverse events compared to the Applicant's analyses of rash. Inhibition of the AKT pathway results in a wide range of dermatologic adverse reactions which are thought to be linked to the role of the PI3K/AKT pathway in survival and regeneration of keratinocytes and other cells in the skin (Teng 2021). CAPItello-281 data demonstrated an increased incidence across almost 40 terms related to skin reactions. These included concepts that are not typically considered "rash" such as dry skin, skin fissures, and pruritus (FDA's Appendices, Table 40).

Table 21 FDA – Increased Hyperglycemia Risks in Combination with Abiraterone and Prednisone in mHSPC versus in Combination with Fulvestrant in Metastatic Breast Cancer

	CAPItello-281		CAPItello-291
Parameter	Capivasertib + Abiraterone + Prednisone N = 503 %	Placebo + Abiraterone + Prednisone N = 503 %	Capivasertib + Fulvestrant (mBC) %
Grade 3-4 hyperglycemia	15%	1%	3%
Required initiation or change in anti-hyperglycemic medications	44%	14%	12%
Initiated insulin	17%	3%	5%

Abbreviations: C+AAP: capivasertib + abiraterone + prednisone/prednisolone; mBC: metastatic breast cancer; P+AAP: placebo + abiraterone + prednisone/prednisolone

In summary, the addition of capivasertib to abiraterone and prednisone resulted in substantially increased toxicity compared to placebo. The safety profile raises significant concerns in the clinical context where the majority of patients enrolled had no or mild symptoms at baseline and the efficacy results are of uncertain clinical meaningfulness. Thus, the safety concerns must be carefully weighed against the efficacy benefit.

4 Clinical Outcome Assessment Analyses

The Applicant's Position:

Given the higher AE rates observed with the addition of capivasertib to abiraterone, differences favoring P+A were modest, and the majority (> 74%) of patients receiving capivasertib reported no or only minimal bother.

Patient-reported outcomes (PROs) were collected per protocol:

- PRO-CTCAE every 2 weeks for the first 12 weeks, and then every 4 weeks until 1 month post-last dose.
- Functional Assessment of Cancer Therapy – Prostate (FACT-P) every 4 weeks through to Week 52, and then every 8 weeks thereafter.
- BPI-SF and Brief Fatigue Inventory (BFI) daily for 7 consecutive days every 4 weeks.

Based on the PRO-CTCAE questionnaire, the most common symptomatic AEs of 'loose or watery stools', 'rash', 'dry skin', and 'itchy skin' were reported. Individual scales of FACT-P were reported, as well as the total score. FACT-P assesses overall health-related quality of life and disease-related symptoms, with subscales including physical well-being (PWB) (fatigue, nausea, pain, treatment side effects) and functional well-being (FWB) (sleep, work ability, enjoyment of life), as well as the single item (FACT-GP5) on treatment bother. Analyses included longitudinal summaries of actual scores and changes from baseline. Time to deterioration using established thresholds is not presented given the limited interpretability with applied statistical assumptions. Lastly, outcomes from the BPI-SF questionnaire assessing severity and interference of pain, and the BFI assessing fatigue severity and interference were reported. Details relating to the statistical analysis of these PROs are provided in Appendix 5.

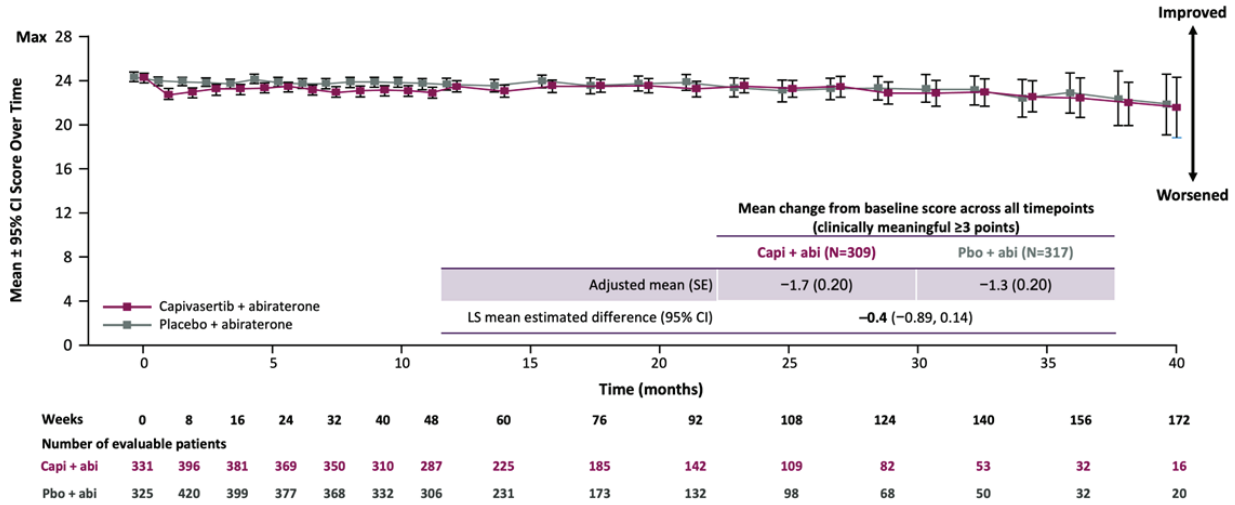
Completion was broadly balanced between arms and improved over time. Compliance was defined as evaluable divided by expected assessments multiplied by 100. For PRO-CTCAE, baseline compliance was approximately 55% to 56%, increasing to over 70% at post-baseline assessments. For FACT-P, baseline compliance exceeded 64%, and post-baseline assessments during the first year were consistently above 77%. Compliance was high for the BPI-SF and BFI at baseline (both over 93%), and remained high overall (C+A: 87.0% for BFI and 87.6% for BPI-SF; P+A: 89.1% for BFI and 89.5% for BPI-SF). To maximize interpretability and retain more patient data, actual scores in addition to analyses requiring change-from-baseline were summarized.

PRO-CTCAE data for 'loose or watery stools' showed that a greater proportion of patients in the C+A arm reported occasional diarrhea (or worse) post-baseline compared with both baseline and with the P+A arm (Appendix 11). Similarly, patient-reported frequency of 'rash' and severity of 'dry skin' or 'itchy skin' assessed using PRO-CTCAE were low overall—with over 75% of all patients reporting no or mild 'dry skin' or 'itchy skin'—yet higher or worse in the C+A arm relative to the P+A arm.

Patients were high functioning at baseline. Mean baseline scores out of 24 were 24 for physical

well-being (FACT-P PWB) and 18 for functional well-being (FACT-P FWB), where higher scores indicate better function. Patients' self-reported physical well-being, as assessed by the FACT-P PWB scale, aligned with the study's clinical findings, with numerically greater deterioration observed in the C+A arm in early cycles, in line with the higher AE incidence (Figure 17).

Figure 17 CAPItello-281: Mean Score Over Time for FACT-P PWB (FAS)

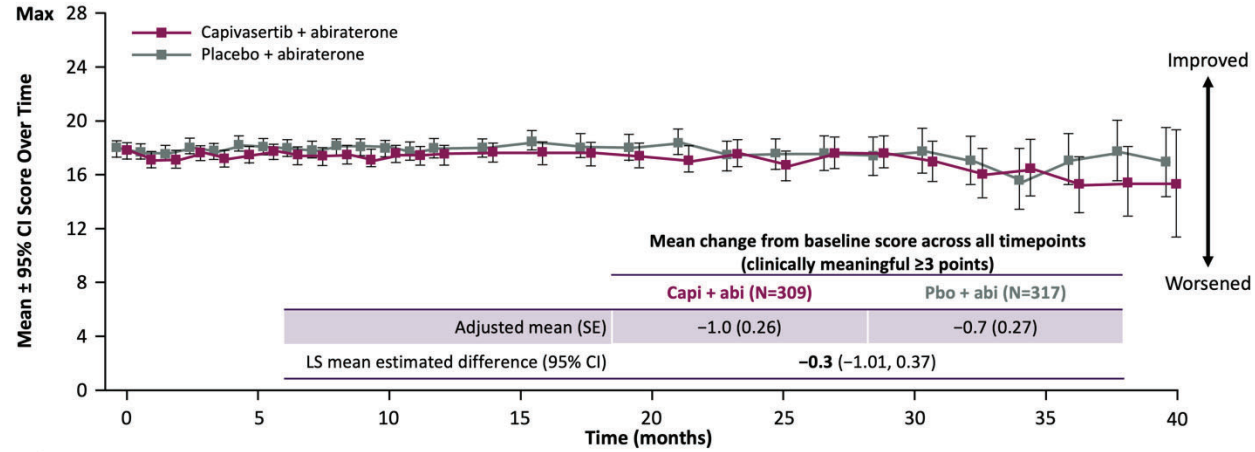


N, number of patients in analysis; SE, standard error.
Source: Table 14.2.10.16, CAPItello-281 Clinical Study Report.

Overall, outcomes of FACT-GP5 reported on a 5-point scale (bothered: not at all, a little bit, somewhat, quite a bit, and very much), indicated worse patient-reported side-effect bother in the C+A arm, reflecting the higher side-effect burden. Still, results for the C+A arm showed that at least 74% of patients reported no or little bother over the first year, and although 4% reported very much bother at Week 4, this proportion decreased over time (Appendix 11). Notably, this pattern did not translate into a meaningful deterioration in daily functioning (FACT-P FWB) or overall quality of life (FACT-P total) from the patient perspective.

PROs for FACT-P FWB, FACT-P total, BPI-SF, and BFI indicated that functioning, cancer pain, and fatigue were broadly comparable between treatment arms and largely stable over time, with only modest declines from baseline. Results for FACT-P FWB are shown in Figure 18, while FACT-P total, BPI-SF and BFI are summarized in Appendix 11.

Figure 18 CAPItello-281: Mean Score Over Time for FACT-P FWB (FAS)



Weeks	0	8	16	24	32	40	48	60	76	92	108	124	140	156	172
Number of evaluable patients															
Capi+abi	331	396	381	369	350	310	287	225	185	142	109	82	53	32	16
Pbo+abi	325	420	399	377	368	332	306	231	173	132	98	68	50	32	20

N, number of patients in analysis.
Source: Table 14.2.10.16, CAPItello-281 Clinical Study Report.

Overall, these findings indicate that the higher AE incidence in the C+A arm is reflected in the patient experience, yet PROs suggest a limited impact on perceived side-effect burden, functioning, and overall quality of life.

4.1.1 FDA – Clinical Outcome Assessment

The FDA's Position:

The FDA agrees with the Applicant's description of the PRO data collection methodology in CAPItello-281. The FDA also agrees with the described completion rates, which were broadly balanced between arms and generally amenable to data interpretation. However, the FDA disagrees with the Applicant's interpretation of the impact of side effects. The Applicant's characterization that differences favoring the control arm were "modest" does not adequately reflect the PRO evidence and minimizes the patient experience of treatment-related toxicity as observed when examining individual patient-reported symptoms and overall side effect bother.

Specifically, the PRO-CTCAE data clearly demonstrate that patients in the capivasertib arm consistently reported higher rates and severity of on-target effects throughout the treatment period. Most notably, at Week 8, only 38% of patients in the capivasertib arm reported never having diarrhea in the preceding 7 days, compared to 75% in the placebo arm. Similarly, patient-reported frequency of rash and severity of dry skin and itchy skin were consistently higher in the capivasertib arm.

The overall side effect bother data, as measured by FACT-GP5, further support concerns about the Applicant's interpretation. FDA notes 10% of patients in the capivasertib arm reported severe bother defined as “quite a bit” or “very much” bother, and a general pattern of increased bother consistent across all timepoints when compared to the control arm in the first

year. It is also likely that patients who discontinued treatment due to adverse events and poor tolerability did not respond to PROs at later timepoints.

The Applicant's own data regarding physical well-being further contradict the assertion of minimal impact on quality of life. The Applicant acknowledges that "patients' self-reported physical well-being, as assessed by the FACT-P PWB scale, aligned with the study's clinical findings, with numerically greater deterioration observed in the C+AAP arm in early cycles, in line with the higher AE incidence." This deterioration in physical well-being during early treatment cycles may represent an impact on patients' functional capacity.

The absence of deterioration in broader, more distal quality of life domains does not negate the clear and consistent evidence of increased symptomatic adverse events, increased overall side effect bother, and decreased physical well-being in early treatment cycles. These patient-reported impacts are more proximal to the treatment effect compared to general quality of life scores.

The PRO data from CAPItello-281 provide valuable complementary information to the clinician-reported adverse events and support the conclusion that patients in the capivasertib arm experienced a greater burden of treatment-related toxicity.

5 Other Significant Issues Pertinent to Clinical Conclusions on Efficacy and Safety

5.1 Applicability of the Results of the CAPItello-281 Study to the US population

The Applicant's Position:

CAPItello-281 is a large, multiregional study following ICH E17 principles and the results of the study generally apply to the US population. This conclusion is based on the similarities between the demographics of the patients randomized in the ITT population and that of real-world patients with PTEN-deficient mHSPC in the US (see Appendix 3), and the use of ADT + abiraterone in alignment with US medical practice. Therefore, the treatment effect data from the CAPItello-281 study are deemed generalizable to the US patient population.

5.1.1 FDA – Applicability of CAPItello-281 Results to the US Population

The FDA's Position:

The FDA agrees that the treatment effect size from the CAPItello-281 study should be generalizable to the US patient population. However, the following considerations are relevant when assessing the benefit-risk profile in US clinical practice:

The exclusion of patients with HbA1c ≥8% or requiring insulin at baseline may limit generalizability to real-world populations, particularly given the higher incidence of hyperglycemia among patients with documented prednisone/prednisolone use (Section 3.3.1). Additionally, the control arm therapy may not reflect the most active therapy for the enrolled population (Section 2.2.4). Clinical trial participants are generally healthier and more closely monitored than the broader patient population, which may affect the observed safety profile.

6 Points for the Advisory Committee to Consider

The Applicant's Position:

mHSPC is a biologically heterogenous disease, with tumor burden, disease-related symptoms, and life expectancy varying from patient to patient. An important treatment goal for mHSPC is to delay progression to a castration-resistant state, a biologic inflection point in the course of the patient's cancer journey, signaling increased risk for disease morbidity and lethality. Biomarker-driven approaches are now evolving to target specific drivers of the disease with the aim of improving the range of treatment options open to patients.

PTEN deficiency is widely recognized as a therapeutically relevant biomarker in a range of cancers. Loss of the PTEN tumor suppressor activates AKT signaling which, in turn, serves as a driver of tumor proliferation and can be addressed by inhibition of AKT. In mHSPC, this driver is in addition to that of AR signaling and exists in the tumors of 1 in 4 men with mHSPC. Despite compelling clinical and real-world data showing that patients with PTEN-deficient prostate cancer receiving standard of care therapies experience faster progression and die earlier than those with PTEN-proficient tumors, no targeted agents are approved specifically for the treatment of PTEN-deficient prostate cancer.

CAPItello-281 is the first pivotal Phase III study conducted specifically in patients with PTEN--deficient mHSPC, identified using a validated IHC-based diagnostic. In line with existing evidence, data from the control arm of the study indicate that patients with PTEN-deficient tumors suffer disease progression more rapidly than would be expected for an unselected mHSPC population, and this appears to be independent of traditional risk factors such as volume of disease. Furthermore, the high incidence of skeletal events in the control arm indicates that PTEN--deficient mHSPC is an aggressive phenotype.

The efficacy results of CAPItello-281 collectively show that the addition of capivasertib to abiraterone delayed both progression and the onset of other aggressive disease features in patients with PTEN-deficient mHSPC. The clinically meaningful improvement observed in median time to radiographic progression was supported by descriptive improvements in endpoints that relate directly to patient clinical experience and the way in which the disease course is managed in the clinic:

- Onset of skeletal events that can impair mobility and cause significant pain requiring surgery/radiotherapy/opioid treatment was delayed.
- Progression to the castration-resistant disease state was delayed.
- Patients were able to avoid the need for chemotherapy for longer.

The interim assessment of OS showed no detriment for patients treated with capivasertib. Further to this, the cumulative number of deaths reported by arm in the Day 120 safety update showed approximately twice as many deaths in the P+A arm than in the C+A arm since the time of the primary analysis.

The Applicant acknowledges that the addition of capivasertib to background therapy of

abiraterone + prednisone/prednisolone + ADT is associated with increased toxicity. Despite underlying comorbidities of the population studied, the tolerability profile of capivasertib is predictable, monitorable, and reversible, and did not result in a clinically meaningful reduction in overall quality of life during study treatment.

Whilst recognizing the limitations of cross-study comparisons and that none of the existing regimens were studied specifically in patients with PTEN-deficient tumors, AEs reported for patients receiving capivasertib in CAPItello-281 were of a similar incidence and nature to those observed with other intensification regimens recommended for mHSPC (Table 22).

Table 22 AEs in Phase III Studies Investigating Intensification Regimens in mHSPC

Study	CAPItello-281	AMPLITUDE	PEACE-1	ARASENS
mHSPC population	Newly diagnosed PTEN-deficient	HRR-altered	Newly diagnosed non-biomarker selected	Non-biomarker selected
Treatment	Capivasertib + abiraterone [a] + ADT	Niraparib + abiraterone [a] + ADT	Docetaxel + abiraterone [a] + ADT	Darolutamide + docetaxel + ADT
N	503	347	347	652
AE of Grade ≥ 3, %	67	75 [b]	63	70
SAE, %	43	39	Not reported	45
AE leading to death, %	7	4	2	4
AE leading to discontinuation, % [c]	18	15	Not reported	14

a Plus prednisone/prednisolone.
b Does not include AEs of Grade 5.
c Discontinuation of capivasertib in CAPItello-281, of niraparib or abiraterone or prednisone in AMPLITUDE, and of darolutamide in ARASENS.
Source: Table 14.3.2.1, CAPItello-281 Clinical Study Report; Attard et al 2025 [47], Fizazi et al 2022 [48], Smith et al 2022 [49].

The key risks associated with the addition of capivasertib to abiraterone + ADT are diarrhea, hyperglycemia, and rash. These are on-target effects of AKT inhibition. The burden to the patient has been characterized and is typified by early onset and for some patients persists while they receive treatment. Nevertheless, the burden of these risks can be mitigated by using established measures. These include dose modifications, antidiarrheal therapy for diarrhea, antihistamines or topical/systemic corticosteroids for rash, and, for hyperglycemia, pre-treatment optimization and pro-active monitoring of fasting blood glucose and HbA1c levels, antidiabetic treatments, and primary care or endocrinology follow-up.

In conclusion, the totality of evidence shows a positive benefit-risk profile for the addition of capivasertib to abiraterone as a treatment for the subpopulation of mHSPC patients with PTEN-deficient tumors, prolonging their hormone-sensitive disease state and thereby delaying progression to mCRPC.

The FDA's Position:
The FDA is uncertain whether the magnitude of rPFS improvement observed in CAPItello-281 represents a clinically meaningful treatment effect in the absence of an effect on OS, and whether the overall benefit-risk of the investigational treatment is favorable. The FDA requests the Committee to consider the following when assessing the benefit-risk of the addition of capivasertib to abiraterone.

1. **Clinical meaningfulness of efficacy results**: The rPFS result represents a small treatment effect in the context of previous approvals in mHSPC, with previous approvals based on rPFS demonstrating large magnitudes of effects. In CAPItello-281, the rPFS HR estimate was 0.81 (95% CI: 0.66, 0.98). There was no statistically significant OS benefit observed at this interim analysis and OS results are immature at 51% information fraction with no evidence of a potential detriment for patients treated with capivasertib (HR 0.90; 95% CI: 0.71, 1.15). Further, the FDA acknowledges that the Day 120 Safety Update data continue to show no OS detriment with 156 deaths in the capivasertib arm and 188 deaths in the placebo arm. However, in the absence of a large improvement in rPFS, a statistically significant improvement in OS may be needed to support clinically meaningfulness.
2. **Safety, tolerability, and clinical context**: The addition of capivasertib resulted in increased serious toxicities, including early fatal adverse reactions, increased healthcare utilization, and worse patient-reported outcomes. CAPItello-281 enrolled patients in an early metastatic disease setting with time to progression of approximately 2-3 years. The majority of enrolled patients had no or mild symptoms at baseline, and fewer than 10% reported progression of pain on trial. The toxicity tolerance for this population differs from patients with more advanced, symptomatic, and/or rapidly progressive disease.
3. **Combination therapy challenges**: The addition of capivasertib to an effective and well-tolerated backbone therapy (abiraterone) creates clinical challenges. The contribution of capivasertib cannot be distinguished from that of the backbone therapy for a given patient. While this challenge exists for any add-on therapy, it is of heightened concern for capivasertib which adds substantial toxicity and may be given for many months, increasing the risk that patients may be exposed to toxicities for extended periods without benefit.
4. **Control Arm Considerations**: The control arm therapy may not reflect the most active or preferred therapy for the enrolled population. Guidelines and expert consensus encourage triplet therapy for patients who are fit for chemotherapy and have synchronous high-volume mHSPC.

The FDA has the following key disagreements with the Applicant's position:

1. **PTEN deficiency as a prognostic factor and therapeutic target:** The FDA agrees that PTEN deficiency appears to be associated with poor prognosis. However, the FDA does not agree that data from CAPItello-281 clearly demonstrated that inhibition of the AKT pathway results in clinically meaningful efficacy in PTEN-deficient prostate cancer.

   The prognostic role of PTEN deficiency impacts both treatment arms. From a clinical and regulatory perspective, poor prognosis does not alter the FDA's benefit-risk framework. The magnitude of the treatment effect must still be weighed against toxicity, regardless of the population studied. The demonstration of poor prognosis in a biomarker-defined

subgroup does not, in and of itself, establish that a modest treatment effect represents clinically meaningful efficacy.

2. **Interpretation of secondary endpoints:** The descriptive analyses for the secondary endpoints in testing plan provide HR of 0.91 (95% CI: 0.75, 1.11) for time to subsequent therapy, 0.82 (95% CI: 0.66, 1.02) for symptomatic skeletal event-free survival and HR of 1.14 (95% CI: 0.75, 1.75) for time to pain progression. Due to the exploratory nature of these analyses and endpoint limitations, the FDA does not consider these results to be interpretable or that they can overcome the uncertainty regarding clinical meaningfulness of the rPFS results. See FDA's detailed assessment of these endpoints in Section 2.3.8.

3. **Safety profile and benefit-risk uncertainty:** The FDA notes that toxicity may be increased in the real-world US population compared to the clinical trial population with particular concern regarding the high incidence of severe hyperglycemia with increased resultant healthcare utilization. The continued observance of DKA events after many months of therapy suggests that not all serious events can be mitigated or prevented by monitoring, dose modifications, and/or supportive care, but rather may be an inherent risk with prolonged therapy. Overall, the FDA is concerned that the toxicity and tolerability of capivasertib is poor for an add-on therapy in an early metastatic disease context and when considering the magnitude of the treatment effect.

   The Applicant states that the adverse events with capivasertib in combination with abiraterone are of similar incidence and nature to those observed with other intensification regimens in mHSPC. However, the FDA disagrees that all intensified regimens in mHSPC are comparable to capivasertib. For example, most of the high-grade toxicity reported with triplet regimens containing chemotherapy was hematologic, which is qualitatively distinct from the safety profile of capivasertib, particularly in the impact on patient experience and in the context of the shorter duration of chemotherapy compared to capivasertib.

In conclusion, the FDA is concerned that the magnitude of improvement in rPFS demonstrated for the capivasertib arm in CAPItello-281 may not be sufficient to be considered clinically meaningful given a) the absence of an effect on OS, b) the added toxicity including increased early deaths, c) the early metastatic disease state, d) the lack of external data supporting clinically meaningful efficacy of capivasertib or other AKT inhibitors in patients with PTEN-deficient metastatic prostate cancer, and, due to addition of capivasertib to an effective and well-tolerated backbone therapy, e) the inability to distinguish whether an individual patient may be benefiting, leading to a prolonged duration of exposure.

7 Draft Topics for Discussion by the Advisory Committee

The FDA asks the committee to discuss the overall benefit:risk demonstrated by CAPItello-281.

The voting question is as follows:

Based on the CAPItello-281 results, does the benefit of adding capivasertib to abiraterone and prednisone outweigh the risk?

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9 Appendix

9.1 Applicant's Appendices

Appendix 1. Key Interactions Between the Applicant and the FDA

Relevant formal interactions held with the FDA for the development of capivasertib in the proposed indication are summarized below. For a summary of important changes to study design over time (including changes to endpoints), see Appendix 4.

January 16, 2020, Type B End-of-Phase 2 Meeting
Primary Endpoint: • rPFS was agreed as an acceptable regulatory endpoint. The FDA noted rPFS should be supported by OS. • The FDA recommended OS as a co-primary endpoint. The Applicant proposed OS as a key secondary endpoint, with interim OS data to enable adequate characterization and to show a trend in OS. The FDA agreed the proposal was reasonable but noted, a large magnitude benefit in rPFS and no detriment in OS should be observed. • FDA feedback was acknowledged on disease assessments from randomization to progression; scan frequency was set at 16 weeks. Secondary Endpoints: • OS –See second bulleted point above. The FDA noted other secondary endpoints appear acceptable. General Design: • Eligibility criteria, stratification factors, comparator, standard-of-care background therapy and use of the Ventana PTEN IHC assay were all deemed acceptable. • The FDA noted abiraterone is indicated in high-risk mHSPC, the Applicant should justify inclusion of low-risk patients and manage the sample size. The Applicant confirmed this would be taken into account.
January 24, 2025, Type B pre-sNDA Meeting
Unmet Medical Need: • The FDA agreed that patients with tumor PTEN-loss mHSPC may have a worse prognosis than patients without tumor PTEN loss. Benefit/Risk Profile: • The FDA agreed that the primary endpoint of investigator-assessed rPFS was statistically significant but that it does not consider the magnitude of improvement to reflect clinical benefit in the context of the additional toxicity from adding capivasertib to abiraterone. • The FDA noted the interim OS results are immature and discouraged an ad hoc analysis. • The FDA did not consider the totality of data supportive of a favorable benefit/risk profile for the combination and recommended not to submit an sNDA based on the current [primary] DCO.

Appendix 2. Clinical and Real-World Data on the Impact of PTEN Deficiency on Outcomes in Prostate Cancer

Before the start of CAPItello-281 (first patient screened: 13 July 2020), clinical data were available showing PTEN deficiency to be associated with increased risk of recurrence and poorer survival in the localized prostate cancer setting (Table 23).

Since the start of CAPItello-281, clinical and real-world data have emerged showing PTEN tumor deficiency to be an indicator of poor prognosis in the metastatic setting (Table 24 and Table 1).

Results from CAPItello-281 are the first clinical data specifically relating to patients with PTEN deficient mHSPC. Patients in the control arm of CAPItello-281 received abiraterone + prednisone/prednisolone + ADT, which was established as a standard of care based on its performance in the registrational Phase III LATITUDE study in high-risk biomarker-agnostic mHSPC [9]. Median rPFS in the control arm of CAPItello-281 (25.7 months) was shorter than that in the abiraterone arm of LATITUDE (33.0 months), even though the CAPItello-281 population appeared to have a baseline profile of traditional risk factors suggesting a better prognosis compared with the non-biomarker selected patients in LATITUDE (Table 25). For example, one-third of patients in CAPItello-281 were classified as having low-risk disease. This cross-study comparison of outcomes indicates that patients with PTEN deficiency derived less clinical benefit from a standard of care than would be expected for the mHSPC population in general.

Table 23 Data on PTEN Deficiency in Studies of Localized Prostate Cancer

Study	N	PTEN deficient n (%) [a]	Results
Cuzick et al 2013 [12]	675	119 (18)	PTEN deficiency was significantly associated with prostate cancer death (HR: 3.51; 95% CI: 2.60, 4.73; $p = 3.1 \times 10^{14}$)
Chaux et al 2012 [17]	902	NR [b]	PTEN deficiency was associated with a higher risk of clinical recurrence after prostatectomy • Protein loss (> 90% loss) HR: 1.50; 95% CI: 0.65, 3.47; p = 0.34 • Complete protein loss (100% loss) HR: 2.52; 95% CI: 1.07, 5.95; p = 0.03
Lotan et al 2016 [14]	1095	258 (24)	PTEN deficiency (any degree of loss >10%) was associated with shorter recurrence free survival (HR: 1.66; p < 0.0001) • Heterogenous protein loss (>10% to <100% loss) HR: 1.43; p = 0.03 • Homogenous protein loss (100% loss) HR: 2.04; p < 0.0001
Leinonen et al 2013 [13]	276	41 (15)	PTEN deficiency was associated with shorter PFS in prostatectomy-treated patients (p = 0.0133)
Ahearn et al 2015 [11]	1044	166 (16)	PTEN deficiency was associated with lethal progression (HR: 1.8, 95% CI: 1.2, 2.9)
Lotan et al 2017 [18]	4417	1087 (25)	PTEN deficiency was associated with reduced PSA recurrence free survival (HR: 1.3; 95% CI: 1.16, 1.47)

a Absence of PTEN protein expression was identified using IHC.
b Nested case-control study that included 451 men who recurred and 451 men who did not recur.
NR, not reported.

Table 24 Clinical and Real-world Data on PTEN Deficiency in Studies of mCRPC

Identifier	Treatment	N	PTEN-deficient/ altered n (%)	Endpoint	PTEN-deficient/ altered Median (95% CI) /months	Non-PTEN-deficient/ altered Median (95% CI) /months	HR (95% CI) [a]
IPATential150 [19]	1L abiraterone + ADT	258 [b]	103 (40%)	rPFS	14.2 (10.9, 18.7)	16.6 (13.7, 24.9)	1.36 (0.99, 1.88)
IPATential150 [19]	1L abiraterone + ADT	554 [c]	261 (47%)	rPFS	16.5 (13.9, 17.0)	19.1 (16.4, 21.9)	1.22 (0.98, 1.53)
IPATential150 [20]	1L abiraterone + ADT	258 [b]	103 (40%)	OS	NR	NR	1.28 (0.94, 1.72)
IPATential150 [20]	1L abiraterone + ADT	554 [c]	261 (47%)	OS	NR	NR	1.12 (0.91, 1.39)
Gupta et al 2024 [21]	ARPI	323 [b]	132 (41%)	Real-world OS	18.2 (13.4, 25.8)	24.3 (22.5, 26.4)	NR

a HR > 1 favors shorter outcomes in PTEN-deficient/altered population. In some cases, the HR and 95% CI have been manually calculated from the reciprocal values reported in the source data.
b *PTEN*-altered: genetic alterations in the *PTEN* gene identified using NGS.
c PTEN-deficient: absence of PTEN protein expression identified using IHC.
IPATential150 was a clinical study. Results reported by Gupta et al 2024 [21] are for a database study.
1L, first line; de novo, newly diagnosed; NC, not calculated; NGS, next-generation sequencing; NR, not reported

Table 25 CAPItello-281 and LATITUDE: Patient Baseline Characteristics

Study population	CAPItello-281 (PTEN-deficient)	CAPItello-281 (PTEN-deficient)	LATITUDE (Non-biomarker selected)	LATITUDE (Non-biomarker selected)
Enrolled participants	**6566**	**6566**	**1209**	**1209**
Randomized participants	**1012**	**1012**	**1199**	**1199**
Treatment arm	**C+A**	**To request**	**Abiraterone arm [a]**	**Placebo arm [b]**
Participants randomized in treatment arm, n (%) [c]	507	505	597	602
Gleason score ≥ 8, n (%) [c]	398 (78.5)	399 (79.0)	584 (97.8)	586 (97.3)
High volume disease, n (%) [c, d]	374 (73.8)	378 (74.9)	487 (81.6)	468 (77.7)
Visceral metastases present, n (%) [c]	98 (19.3)	95 (18.8)	114 (19.1)	114 (18.9)
Bone metastases present, n (%) [c]	462 (91.1)	467 (92.5)	580 (97.2)	585 (97.2)

a Patients received abiraterone acetate 1000 mg orally once daily and prednisone 5 mg orally once daily plus ADT.
b Patients received placebo plus ADT.
c Percentages are calculated based on the number of randomized patients for the treatment arm.
d High volume is defined as 4 or more bone metastases on bone scan, including one or more outside the vertebral bodies or pelvis, and/or visceral metastases.
Source: Table 14.1.1, Table 14.1.10, Table 14.1.11, Table 14.2.1.8, CAPItello-281 Clinical Study Report; Fizazi et al 2019 [10].

Appendix 3. Demographic and Disease Characteristics of Patients in the US

Table 26 Comparison of Patient Characteristics Between Global and US Patients in CAPItello-281 and Real-world US Patients with mHSPC

	Source	CAPItello-281	CAPItello-281	Flatiron Health	Tempus Lens Prostate	TriNetX	SEER	US census
	Population	Global population	US patients	US Patients with PTEN-deficient mHSPC	US Patients with PTEN-deficient mHSPC on ADT + abiraterone	US Patients with PTEN-deficient mHSPC on ADT + abiraterone	Metastatic prostate cancer	18 + males
	Total number of patients, N	1012	19	378	351	560	21,230	130,932,627
Characteristic	**Parameter**							
Age (years)	Median (min, max)	68.0 (43, 88)	69.0 (43, 83)	68 (44, 85)	64 (40, 87)	72 (42, 85)	69 (36, 90)	NA
Race, n (%)	Black	12 (1.2)	4 (21.1)	23 (7.2)	24 (6.8)	120 (21.4)	3,615 (17.0)	16,616,702 (12.7)
Race, n (%)	American Indian or Alaska Native	44 (4.3)	0	NA [a]	0 (0.0)	10 (1.8)	141 (0.7)	1,721,084 (1.3)
Race, n (%)	Asian	375 (37.1)	0	2 (0.6)	8 (2.3)	20 (3.6)	1,237 (5.8)	8,652,352 (6.6)
Race, n (%)	White	525 (51.9)	13 (68.4)	258 (80.9)	216 (61.5)	370 (66.1)	15,852 (74.7)	100,562,278 (76.8)
Race, n (%)	Other	4 (0.4)	0	36 (11.3)	NA	10 (1.8)	NA	NA
Race, n (%)	Not Reported	41 (4.1)	2 (10.5)	NA	103 (29.3)	-	NA	Not applicable
Race, n (%)	Missing	11 (1.1)	0	59 (15.6)	NA	50 (8.9)	243 (1.1)	Not applicable
Ethnic group, n (%)	Hispanic or Latino	127 (12.5)	1 (5.3)	21 (7.4)	8 (2.3)	30 (5.4)	2,789 (13.1)	24,413,407 (18.6)
Ethnic group, n (%)	Not Hispanic or Latino	870 (86.0)	16 (84.2)	261 (92.6)	147 (41.9)	460 (82.1)	18,441 (86.9)	106,519,220 (81.4)
Ethnic group, n (%)	Missing	15 (1.5)	2 (10.5)	96 (25.4)	196 (55.8)	70 (12.5)	0	Not applicable
WHO/ECOG PS, n (%) [b]	(0) Normal activity	649 (64.1)	11 (57.9)	103 (51.2)	36 (10.3)	NA	NA	Not applicable
WHO/ECOG PS, n (%) [b]	(1) Restricted activity	363 (35.9)	8 (42.1)	82 (40.8)	21(6.0)	NA	NA	Not applicable
Total Gleason Score at diagnosis, n (%)	< 8	189 (18.7)	1 (5.3)	71 (18.8)	NA [c]	NA [c]	3,264 (15.4)	Not applicable
Total Gleason Score at diagnosis, n (%)	≥ 8	797 (78.8)	16 (84.2)	238 (63.0)	NA [c]	NA [c]	12,537 (59.1)	Not applicable

	Source	CAPItello-281	CAPItello-281	Flatiron Health	Tempus Lens Prostate	TriNetX	SEER	US census
	Population	Global population	US patients	US Patients with PTEN-deficient mHSPC	US Patients with PTEN-deficient mHSPC on ADT + abiraterone	US Patients with PTEN-deficient mHSPC on ADT + abiraterone	Metastatic prostate cancer	18 + males
Total Gleason Score at diagnosis, n (%)	Missing [d]	26 (2.6)	2 (10.5)	69 (18.3)	NA [c]	NA [c]	5,429 (25.6)	Not applicable

a Captured in 'Other' category'
b In Tempus Lens Prostate, 4 (1.1) patients had a performance score ≥ 2 and 290 (82.6) patients with unknown performance score.
c Not reliably captured in these data sources.
d Missing Gleason score includes patients with unreported primary and/or secondary Gleason grades.
NA, not available; SEER, Surveillance, Epidemiology, and End Results.
Source: Table 14.1.5 and Table 14.1.10, CAPItello-281 Clinical Study Report; IEMT587.1, IEMT587.2; Flatiron, Tempus Lens Prostate, SEER, TriNetX and US Census [50].

Appendix 4. Changes in the Conduct of the CAPItello-281 Study and Planned Analyses

Table 27 CAPItello-281: Protocol Amendments Related to Changes in Study Conduct

Key details of amendment	Main reason(s) for amendment
Amendments made *after* the start of patient recruitment	
Amendment 1, 18 May 2022	
Addition of text to define a China cohort of study patients.	To allow recruitment of patients in China to continue beyond the close of the global cohort and to define whether a patient will be included in both the global and China cohorts or only the China cohort.
Timeframe from diagnosis of metastatic prostate cancer to randomization extended from 3 months to 180 days.	To introduce increased flexibility to the recruitment process.
Additional electrocardiogram assessment on Cycle 1, Day 1 at 2 hours post-dose.	To align with program-level electrocardiogram assessment frequency.
Brief section added on impact of COVID-19 pandemic on the benefit-risk assessment for this study.	To acknowledge potential risk from COVID-19 pandemic and the implementation of risk mitigation to study.
New section and appendix providing guidance on study conduct during the of Coronavirus Disease 2019 (COVID 19) pandemic.	To prioritize study patient safety and ensure continuity of the study.
Update to exclusion criterion regarding prior treatments for prostate cancer.	Clarification as a consequence of widening the time window from diagnosis to randomization.
Restrictions due to potential CYP2D6 and CYP2C9 drug-drug interactions with capivasertib removed, and update to exclusion criterion.	Update in line with latest drug-drug interaction data for the capivasertib program and clarifications for study sites.
Update to instructions for management of capivasertib-related toxicities.	Update in line with latest safety management guidelines for the capivasertib program. To restructure the format and to make it more investigator friendly. Enhance instructions/ options for management of key capivasertib toxicities as program expands and emphasize the importance of early management of AEs.
Amendment 2, 01 Sept 2023	
Update to study design characteristics. Update of the planned study statistical analyses to add an interim futility analysis (to be analyzed by the Independent Data Monitoring Committee) and adjust the number of events to trigger the interim rPFS, final rPFS, and timing of the final OS follow-up to allow for increased maturity for both rPFS and OS.	Updated the study design in line with AstraZeneca policy for futility analyses in Phase 3 oncology studies and updated assumptions based on recent external data within the mHSPC setting.
Updated the MTP to a simple hierarchy structure with a focus on OS.	Update based on external data for other therapeutic options within the mHSPC indication that achieved positive OS results.
Update to capivasertib drug classification as a mild inhibitor of CYP3A. Update to text for exclusion criterion: removal of the 1-week requirement to stop CYP3A4 sensitive substrates with a narrow therapeutic window prior to study treatment.	Updated to provide the most current data available within the capivasertib program regarding drug-drug interactions and the risk of combination with capivasertib in order for investigators to make informed decisions regarding concomitant therapy.

Key details of amendment	Main reason(s) for amendment
Update to recommendations for concomitant treatment with medications sensitive to inhibition of CYP3A4 to 'may require dose adjustment.' Clarification that itraconazole increased capivasertib area under the curve after a single dose of 80 mg capivasertib.	
Update to exclusion criterion: Clarification and streamlined presentation of excluded cardiac medical history. Removal of requirement for left ventricular ejection fraction assessment for eligibility assessment. Decreased time from select cardiac events (e.g. myocardial infarction) to randomization from 6 months to 3 months.	Updated to align with new project specific safety requirements post risk assessment in light of available capivasertib Phase 3 data and to reduce patient burden.
Update to exclusion criterion: decreased exclusionary time for patients with a history of another primary malignancy to ≥ 2 years and clarified the exclusion of non-melanoma skin cancer and curatively treated in situ disease.	Updated to align with project specific safety requirements.

Appendix 5. Statistical Methods in CAPItello-281

Statistical Methods for Efficacy Endpoints

Methods for Multiplicity Control

The key secondary endpoints of OS, TFST, SSE-FS, and TTPP were to be tested following an MTP with an alpha -exhaustive recycling strategy [51]. At the primary rPFS analysis, rPFS would be tested first and depending on whether statistical significance was achieved, further testing would follow for each key secondary endpoint in the hierarchy (OS, TFST, SSE-FS, and TTPP) in turn. That is, OS would be tested only if rPFS met statistical significance, and TFST would be tested only if rPFS and OS met statistical significance, and so forth.
Implementation of this pre-defined ordered testing procedure, including recycling, would strongly control type I error at 5% (2-sided), among all key hypotheses.
Pre-specified alpha spending functions were applied to the endpoints of OS, SSE-FS and TTPP, as appropriate, in order to preserve the overall type-1-error (familywise error rate) at 5% in the strong sense:

- For rPFS, which would be analyzed only once at the primary rPFS analysis, no spending function was required.
- For OS, alpha allocation at the primary rPFS analysis was to be using the Lan-DeMets spending function [52] that approximates the O'Brien-Fleming approach, where the significance level applied at an interim analysis depends upon the proportion of information (ie, information fraction: the actual number of events at interim analysis/the planned number of events at final analysis) available. The significance levels would be calculated at the time of the analyses based on the actual number of events observed.
- For TFST, which would be analyzed only once at the primary rPFS analysis, no spending function was required.
- For SSE-FS and TTPP, alpha allocation at the primary rPFS analysis was to be controlled using the Lan-DeMets spending function.

The significance level, planned/observed number of events, approximate critical value, and power for rPFS testing are summarized in Table 19.
The observed information fraction and corresponding significance levels for the primary and key secondary endpoints at the primary rPFS analysis are shown in Table 20.

Table 28 CAPItello-281: Statistical Considerations for Primary rPFS Endpoint

Analysis	Significance Level	Number of Events Planned / Observed	Approximate Critical Value HR for statistical significance	Power (Assuming HR = 0.70)
rPFS Final Analysis (overall population assuming 39% maturity)	0.05	386 / 398	0.82	94%

Table 29 CAPItello-281: Calculated Significance Levels based on the observed number of events for Primary and Key Secondary Endpoints

Timepoint	Primary rPFS analysis	Primary rPFS analysis	Final OS analysis	Final OS analysis
Variable	Number of events observed (information fraction %) at timepoint	Significance level at timepoint	Number of events expected (information fraction %) at timepoint	Expected significance level at timepoint [a]
rPFS	398 (100%)	0.05	NA	NA
OS	267 (51%)	0.00345 [a]	522 (100%)	0.04887 [ab]
TFST	398 (100%)	0.05	NA	NA
SSE-FS	326 (60%)	0.00757 [a]	544 (100%)	0.04761 [a]
TTPP	87 (17%)	<0.00001 [a]	507 (100%)	0.04999 [a]

a Significance levels as per the pre-specified O'Brien-Fleming spending function that were re-calculated based on the observed number of events (information fraction) at the primary rPFS analysis timepoint.
b The expected OS critical value HR for statistical significance at the final DCO4 is approximately 0.84.
NA refers to when an endpoint is not analyzed at that timepoint.

Statistical Methods for Clinical Outcome Assessments

BPI-SF, BFI, and FACT-P were secondary endpoints in the study, while PRO-CTCAE was an exploratory endpoint. None of these were part of the MTP. Analysis details specific to these endpoints are as follows.

PRO-CTCAE
PRO-CTCAE responses were summarized descriptively as number of patients and corresponding percentages for each category in the questionnaire at each visit by treatment group.
FACT-P
More than 80% of questions in a questionnaire had to be completed for the questionnaire to have the FACT-P total score evaluable. For each domain (eg, PWB, FWB) if more than 50% of the items were answered (eg, a minimum of 4 of 7 items), the subscale score was calculated by multiplying the sum of subscale by the number of items in the subscale, then dividing by the number of items actually answered: Subscale score= (sum of item scores x N of items in subscale)/ N of items answered. Changes from baseline were analyzed using a mixed model for repeated measures analysis of of all the post-baseline scores for each visit.
BPI-SF
Pain severity domain This domain consists of 4 items. A composite pain severity domain score was derived from all the 4 items, calculated as a mean score where all items had to be non-missing. The average pain severity domain score at each visit was calculated as the average of 7 days starting from the date of the first BPI-SF pain severity domain entry. There had to be at least 4 out of the 7 days with a non-missing pain severity domain score to calculate the average pain severity domain score. *Pain interference domain*

This domain consists of 7 items. The pain interference domain score was derived from all 7 items, calculated as a mean score where at least 50% of the items, or 4 out of 7, had to have a response for a mean score to be calculated. The average pain interference domain score at each visit was calculated as the average of 7 days starting from the date of the first BPI-SF pain interference domain entry. There had to be at least 4 out of the 7 days with a non-missing pain interference domain score to calculate the average pain interference domain score.
Changes from baseline were analyzed using a mixed model for repeated measures analysis of all the post-baseline scores for each visit.

BFI

The questionnaire includes 9 items. As the mean domain scores of fatigue severity and fatigue interference were derived from 3 and 6 items respectively, these were calculated as a mean score where at least 50% of the items, or 2 out of 3, or 3 out of 6 respectively, must have had a response for a mean score to be calculated. The average score at each visit was calculated as the average of 7 days starting from the date of the first completed BFI entry. There had to be at least 4 out of the 7 days with a non-missing score to calculate the average score.
Changes from baseline were analyzed using a mixed model for repeated measures analysis of all the post-baseline scores for each visit.

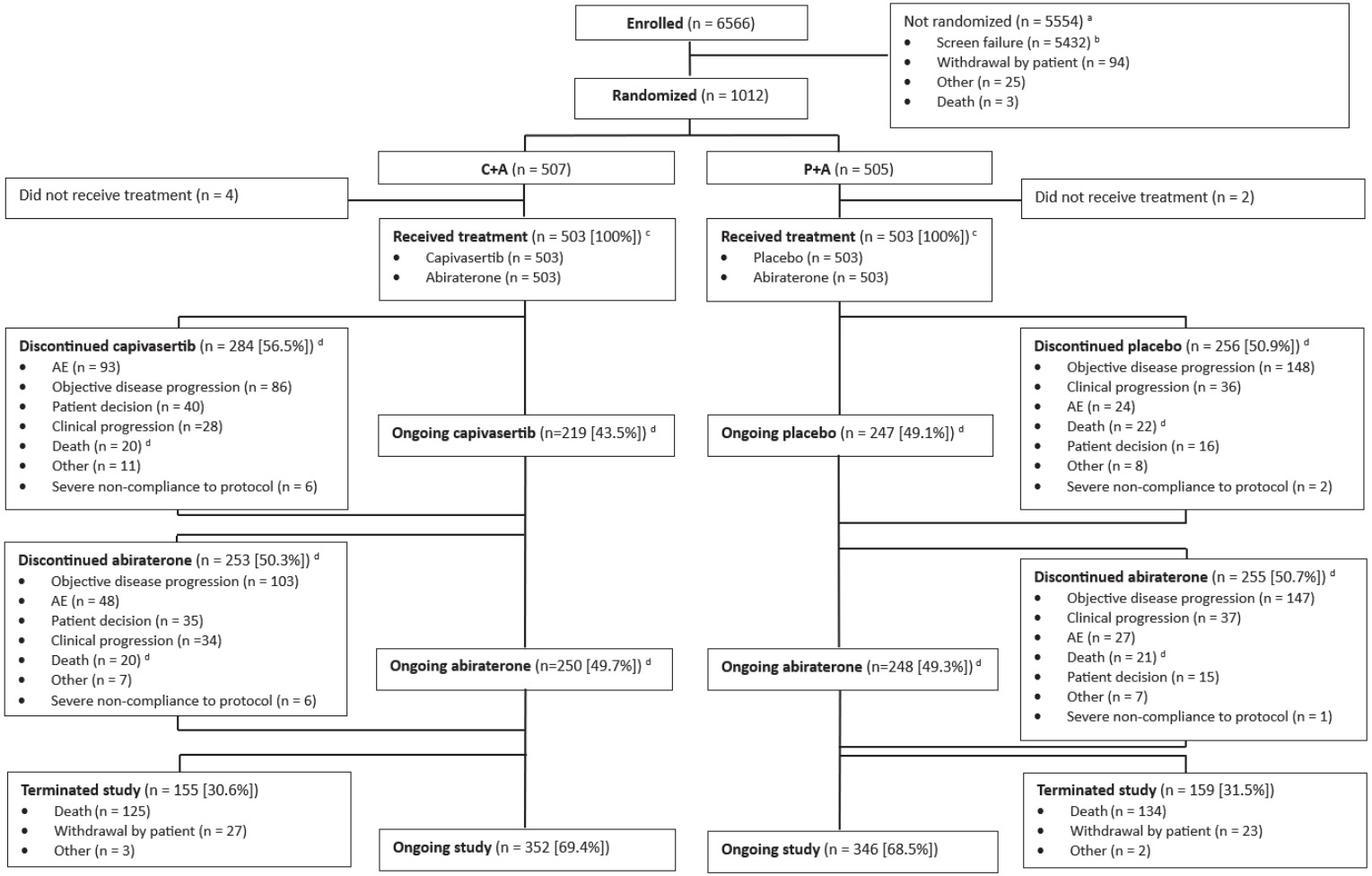
Compliance

Compliance measures were based on:

- Received questionnaire = a questionnaire that has been received and has a completion date and at least one individual item completed.
- Expected questionnaire = a questionnaire that is expected to be completed at a scheduled assessment time e.g. a questionnaire from a patient who has not withdrawn from the study at the scheduled assessment time but excluding patients in countries with no available translation. For patients that have progressed, the latest of progression and safety follow-up was used to assess whether the patient was still under PRO follow-up at the specified assessment time. Date of study discontinuation was mapped to the nearest visit date to define the number of expected forms.
- Evaluable questionnaire = a questionnaire with a completion date and at least one subscale that is non-missing.
- Overall PRO compliance rate was defined as: Total number of evaluable questionnaires across all time points, divided by total number of questionnaires expected to be received across all time points multiplied by 100.
- Overall patient compliance rate was defined for each randomized treatment group as: Total number of patients with an evaluable baseline and at least one evaluable follow-up questionnaire (as defined above), divided by the total number of patients expected to have completed at least a baseline questionnaire multiplied by 100.

Appendix 6. Patient Disposition in CAPItello-281

Figure 19 CAPItello-281: Patient Disposition Through the Study (All Patients)



a Patients may have had more than one reason for not being randomized.
b Includes 4484 patients who were PTEN proficient within the tumor tissue, and 198 patients with no PTEN test results (Table 14.1.1.cd).
c One patient randomized to C+A only received P+A, and one patient randomized to the P+A arm received one dose of capivasertib in error (see Section 10.3, CAPItello-281 Clinical Study Report).
d In the Clinical Study Report, patients who had discontinued study treatment due to death were erroneously counted as ongoing study treatment.
Source: Table 14.1.1, CAPItello-281 Clinical Study Report and IEMT917.1.

Appendix 7. Baseline Characteristics in CAPItello-281

Table 30 CAPItello-281: Baseline Characteristics (FAS)

	Treatment arm	C+A	P+A
	Total number of patients, N	507	505
Characteristic	Parameter		
Age, years	Median (range)	67.0 (42-87)	68.0 (43-88)
Race, n (%)	Black or African American	6 (1.2)	6 (1.2)
Race, n (%)	American Indian or Alaska Native	22 (4.3)	22 (4.4)
Race, n (%)	Asian	186 (36.7)	189 (37.4)
Race, n (%)	White	266 (52.5)	259 (51.3)
Race, n (%)	Other	1 (0.2)	3 (0.6)
WHO/ECOG PS, n (%)	(0) Normal activity	329 (64.9)	320 (63.4)
WHO/ECOG PS, n (%)	(1) Restricted activity	178 (35.1)	185 (36.6)
Metastases, n (%)	Bone	462 (91.1)	467 (92.5)
Metastases, n (%)	Liver	30 (5.9)	25 (5.0)
Metastases, n (%)	Lung	69 (13.6)	72 (14.3)
Metastases, n (%)	Non-regional lymph node	217 (42.8)	214 (42.4)
Metastases, n (%)	Other [a]	21 (4.1)	19 (3.8)
Time from diagnosis to randomization, months	Median (range)	2.46 (0.3-12.8)	2.45 (0.6-27.4)
Total Gleason score at diagnosis, n (%)	< 8	94 (18.5)	95 (18.8)
Total Gleason score at diagnosis, n (%)	≥ 8	398 (78.5)	399 (79.0)
Volume of disease/visceral metastases, n (%) [b]	High volume disease with visceral metastases	98 (19.3)	95 (18.8)
Volume of disease/visceral metastases, n (%) [b]	High volume disease without visceral metastases	276 (54.4)	283 (56.0)
Volume of disease/visceral metastases, n (%) [b]	Low volume disease	131 (25.8)	126 (25.0)

a Other category includes any metastatic site that is not bone, liver, lung, or non-regional lymph node.
b Stratification factors as defined by eCRF data.
Categories not included in the table are as follows. Race: 'Not reported' (C+A: n= 21 [4.1%], P+A: n=20 [4.0%]) and 'Missing' (C+A: 5 [1.0%], P+A: 6 [1.2%]). Total Gleason score at diagnosis: 'Missing' (C+A: 15 [3.0%], P+A: 11 [2.2%]). Volume of disease/visceral metastases: 'Unknown' (C+A: 2 [0.4%], P+A: 1 [0.2%]). Missing Gleason score includes patients with unreported primary and/or secondary Gleason grades.
Source: Table 14.1.5, Table 14.1.10, Table 14.1.11, Table 14.2.1.8, CAPItello-281 Clinical Study Report.

Appendix 8. Further Efficacy Data in CAPItello-281

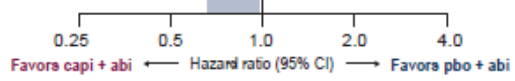
Table 31 CAPItello-281: Further Efficacy Endpoints (FAS)

Type of endpoint	Endpoint	Events (%) C+A (N = 507)	Events (%) P+A (N = 505)	Median C+A (months)	Median P+A (months)	HR / OR [a]	95% CI	Nominal 2-sided p-value
Key Secondary	TFST	192 (37.9)	206 (40.8)	37.0	28.5	0.91	0.75, 1.11	0.364
Key Secondary	TTPP	46 (9.1)	41 (8.1)	NC	NC	1.14	0.75, 1.75	0.536
Secondary	PFS2	135 (26.6)	146 (28.9)	41.4	NC	0.90	0.71, 1.13	0.360
Exploratory	ORR	147 (66.5) [a]	128 (61.8) [a]	NA	NA	1.30 [a]	0.87, 1.96	0.205
Exploratory	DoR	61 (41.5) [b]	43 (33.6) [b]	21.4	NC	NA	NA	NA

a ORR endpoint shows the number of responders out of the number of patients with measurable disease at baseline by the investigator. Odds ratio (OR) is also presented. OR > 1 favors C+A. HR is presented for all other endpoints.
b The analysis set for DoR comprises patients who had measurable disease at baseline and had a complete/partial response: 147 patients in the C+A arm, 128 patients in the P+A arm.
DoR, duration of response; NA, not available; NC, not calculable; ORR, objective response rate, PFS2, progression-free survival after next-line treatment. Source: Table 14.2.3.1, Table 14.2.5.1, Table 14.2.8.1, Table 14.2.9.1, Table 14.2.9.3, CAPItello-281 Clinical Study Report.

Figure 20 CAPItello-281: rPFS by Investigator in Pre-specified Subgroups (FAS)

	Number of events/number of patients (%) Capi + abi	Pbo + abi	HR (95% CI)
All patients	**183/507 (36.1)**	**215/505 (42.6)**	**0.81 (0.66, 0.98)**
Metastatic volume of disease/visceral mets: high with mets	49/98 (50.0)	52/95 (54.7)	0.77 (0.52, 1.14)
Metastatic volume of disease/visceral mets: high without mets	110/276 (39.9)	129/283 (45.6)	0.91 (0.70, 1.17)
Metastatic vol of disease/visceral mets: low	24/131 (18.3)	34/126 (27.0)	0.67 (0.39, 1.12)
Metastatic vol of disease/visceral mets: unknown	0/2 (0)	0/1 (0)	NC (NC, NC)
Geographic location: Western Europe, Australia, plus North America	56/149 (37.6)	62/145 (42.8)	0.89 (0.62, 1.28)
Geographic location: Latin America plus Eastern Europe	46/123 (37.4)	57/125 (45.6)	0.79 (0.54, 1.17)
Geographic location: Asia	81/235 (34.5)	96/235 (40.9)	0.83 (0.61, 1.11)
Disease risk: high-risk disease	132/311 (42.4)	160/333 (48.0)	0.88 (0.70, 1.11)
Disease risk: low-risk disease	49/184 (26.6)	50/164 (30.5)	0.88 (0.59, 1.31)
Disease risk: unknown	2/12 (16.7)	5/8 (62.5)	NC (NC, NC)
Metastatic volume: high-volume disease	159/374 (42.5)	181/378 (47.9)	0.88 (0.71, 1.09)
Metastatic volume: low-volume disease	24/131 (18.3)	34/126 (27.0)	0.67 (0.39, 1.12)
Metastatic volume: unknown	0/2 (0)	0/1 (0)	NC (NC, NC)
Prior use of abiraterone: yes	20/56 (35.7)	21/58 (36.2)	0.91 (0.49, 1.68)
Prior use of abiraterone: no	163/451 (36.1)	194/447 (43.4)	0.83 (0.67, 1.02)
Prior ADT: yes	180/499 (36.1)	212/498 (42.6)	0.83 (0.68, 1.01)
Prior ADT: no	3/8 (37.5)	3/7 (42.9)	NC (NC, NC)
Soft tissue disease only: yes	9/44 (20.5)	12/37 (32.4)	0.60 (0.25, 1.43)
Soft tissue disease only: no	174/463 (37.6)	203/468 (43.4)	0.87 (0.71, 1.06)
Soft tissue disease present: yes	149/380 (39.2)	167/363 (46.0)	0.85 (0.68, 1.06)
Soft tissue disease present: no	34/127 (26.8)	48/142 (33.8)	0.76 (0.48, 1.17)
Lung or liver metastases: yes	44/90 (48.9)	48/88 (54.5)	0.76 (0.51, 1.15)
Lung or liver metastases: no	139/417 (33.3)	167/417 (40.0)	0.84 (0.67, 1.06)
Baseline PSA: below/equal to median at baseline (6.415 ng/mL)	86/260 (33.1)	92/242 (38.0)	0.93 (0.69, 1.24)
Baseline PSA: above median at baseline (6.415 ng/mL)	97/245 (39.6)	119/256 (46.5)	0.79 (0.60, 1.03)
Baseline PSA: unknown	0/2 (0)	4/7 (57.1)	NC (NC, NC)
Gleason score: <8	38/94 (40.4)	34/95 (35.8)	1.06 (0.66, 1.69)
Gleason score: ≥8	141/398 (35.4)	175/399 (43.9)	0.82 (0.65, 1.02)
Gleason score: unknown	4/15 (26.7)	6/11 (54.5)	NC (NC, NC)
Number of bone lesions at baseline: none	9/42 (21.4)	11/34 (32.4)	0.64 (0.26, 1.54)
Number of bone lesions at baseline: 1–3	20/105 (19.0)	23/94 (24.5)	0.79 (0.43, 1.45)
Number of bone lesions at baseline: 4–9	44/118 (37.3)	39/114 (34.2)	1.16 (0.75, 1.79)
Number of bone lesions at baseline: 10–30	49/124 (39.5)	75/143 (52.4)	0.71 (0.50, 1.02)
Number of bone lesions at baseline: >30	60/115 (52.2)	66/117 (56.4)	0.89 (0.63, 1.27)
Number of bone lesions at baseline: unknown	1/3 (33.3)	1/3 (33.3)	NC (NC, NC)
ECOG performance at baseline: 0	109/329 (33.1)	127/320 (39.7)	0.82 (0.63, 1.06)
ECOG performance at baseline: 1	74/178 (41.6)	88/185 (47.6)	0.87 (0.64, 1.19)
Age at randomization: <65 years	65/174 (37.4)	89/190 (46.8)	0.75 (0.55, 1.04)
Age at randomization: ≥65 years	118/333 (35.4)	126/315 (40.0)	0.90 (0.70, 1.15)
Race: white	94/266 (35.3)	122/259 (47.1)	0.72 (0.55, 0.95)
Race: black African American	3/6 (50.0)	3/6 (50.0)	NC (NC, NC)
Race: Asian	62/186 (33.3)	71/189 (37.6)	0.87 (0.62, 1.23)
Race: other	14/23 (60.9)	9/25 (36.0)	2.49 (1.08, 6.02)
Race: unknown	10/26 (38.5)	10/26 (38.5)	0.82 (0.33, 2.02)



* Baseline PSA may have been impacted by earlier initiation of ADT.
mets, metastases; NC, not calculable; PSA, prostate-specific antigen.
Source: Table 14.2.1.8, CAPItello-281 Clinical Study Report.

Table 32 CAPItello-281: Time to Castration Resistance Events by Category (FAS)

Treatment arm	C+A	P+A
Total number of patients in treatment arm, N	**507**	**505**
Total events, n (%) [a]	185 (36.5)	231 (45.7)
Radiographic disease progression (including death), n (%)	85 (16.8)	102 (20.2)
PSA progression, n (%)	49 (9.7)	65 (12.9)
Symptomatic skeletal event, n (%)	20 (3.9)	32 (6.3)
Multiple castration-resistant events, n (%)	31 (6.1)	32 (6.3)

a Includes patients who experienced a castration-resistant event before receiving subsequent anti-cancer therapy. Multiple castration-resistant events show patients with multiple events at the same date. Patients not known to have experienced a castration-resistant event at time of analysis are censored at the last known time not having had a castration-resistant event. Patients who received subsequent anti-cancer therapy are censored at the last known time not having had a castration-resistant event prior to start of subsequent anti-cancer therapy.

Source: Table 14.2.7.1, CAPItello-281 Clinical Study Report.

Appendix 9. Evaluation of the Sensitivity Analysis of rPFS by BICR

The sensitivity analysis of rPFS by BICR was subject to some limitations, as discussed below.

The imaging charter followed by BICR did not include detailed instructions on classifying bone scans as 'superscans'[7], ie, scans on which it is not considered possible to count the number of bone lesions present. Central reviewers conducting BICR appeared to take a more conservative approach to identifying superscans than investigators at site. The number of baseline and first post-baseline bone scans classified as superscans was higher by BICR than by investigator assessment.

This translated to a higher proportion of patients with non-evaluable post baseline bone responses in the BICR analysis. In turn, this meant substantially more patients who were censored at Day 1 in the rPFS by BICR analysis (10.6% of patients; C+A vs P+A: 10.5% vs 10.7%). Only 10 patients (1.0%) were classified as having superscans at baseline by investigator assessment. Overall, the higher number of superscans by BICR resulted in a lower number of bone progressions, lower overall maturity, increased uncertainty, and shorter follow-up in censored patients for the rPFS by BICR analysis compared to the investigator-assessed primary analysis.

Another limitation of the BICR analysis was that imaging assessments were planned until investigator-assessed radiographic progression. As the BICR analysis was retrospective rather than real-time, it was likely impacted by informative censoring. Overall, 66 patients (6.5%) were censored in the BICR analysis at the same time as or later than the time of investigator-assessed progression.

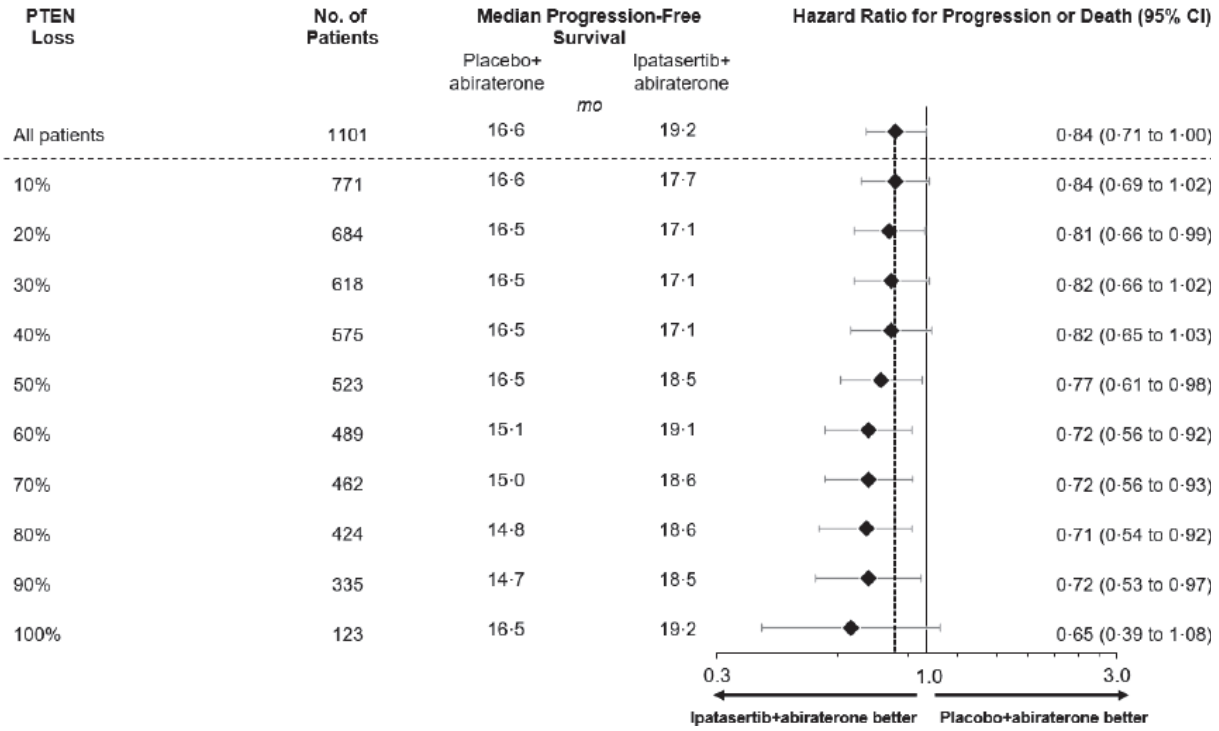
Owing to the overall limitations of the BICR sensitivity analysis, the investigator-assessed primary rPFS analysis is more reflective of the treatment effect of capivasertib added to abiraterone in CAPItello-281.

[7] A superscan pattern on bone scintigraphy is characterized by a diffuse and intense uptake of radiotracer throughout the entire skeleton and diminished renal and background soft tissue uptake, potentially limiting the opportunity to identify new bone lesions during follow-up [53].

Appendix 10. Clinical Data on a Gradient Effect Associated with PTEN Deficiency

IPATential150 was a Phase III study of the AKT inhibitor ipatasertib in combination with abiraterone + ADT in mCRPC. Co-primary efficacy endpoints were investigator-assessed rPFS in the ITT population and in patients with PTEN-deficient tumors, defined as ≥ 50% of specimen's tumor area having no detecTable PTEN staining by IHC. While no statistically significant treatment effect was observed in the ITT population, the addition of ipatasertib to abiraterone statistically significantly improved rPFS in patients with PTEN-deficient tumors (at a 50% diagnostic cut-off) (median: 18.5 vs 16.5 months; HR: 0.77, 95% CI: 0.61, 0.98; p = 0.034) [38]. A post-hoc analysis of the study revealed increasing treatment effect with increasing extent of PTEN deficiency, ranging from ≥ 10% to 100% of tumor cells with no detecTable PTEN staining. The performance of the control arm showed a general trend for worsening prognosis with increasing extent of PTEN deficiency (Figure 21).

Figure 21 **IPATential150 Study of Ipatasertib + Abiraterone in mCRPC: rPFS by Percentage of Tumor Cell PTEN Staining Loss**

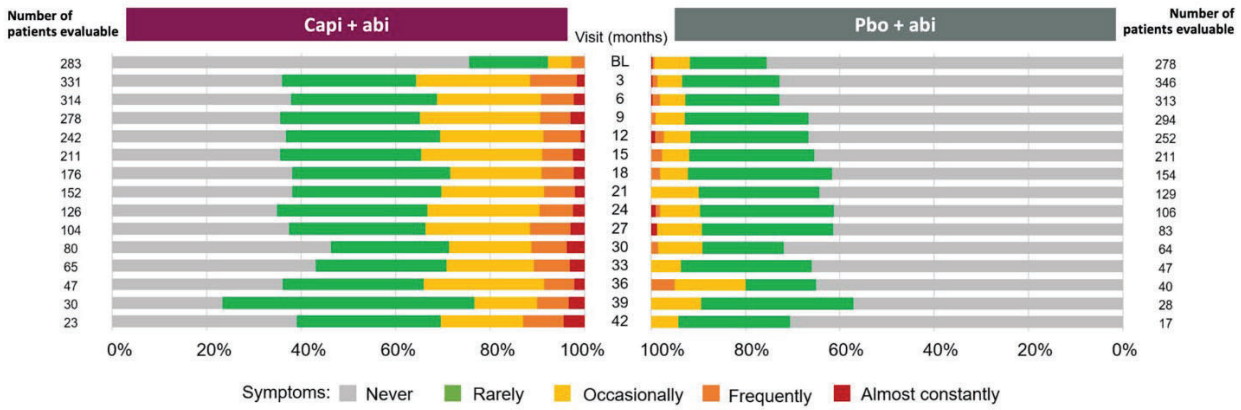


PTEN loss status by IHC by % cut-off. PTEN deficiency/loss determined by VENTANA PTEN SP218 IHC assay, by % of specimen's tumor area having no detecTable PTEN staining. Analysis of rPFS in all patients and in the subgroup defined with a cut-off of >50% were pre-specified, while analysis of rPFS in all other subgroups was exploratory. HR < 1 favors ipatasertib + abiraterone over placebo + abiraterone.
mo, months.
Source: Sweeney et al 2021 [38].

Appendix 11. Further Clinical Outcomes Assessment Analyses

PRO-CTCAE

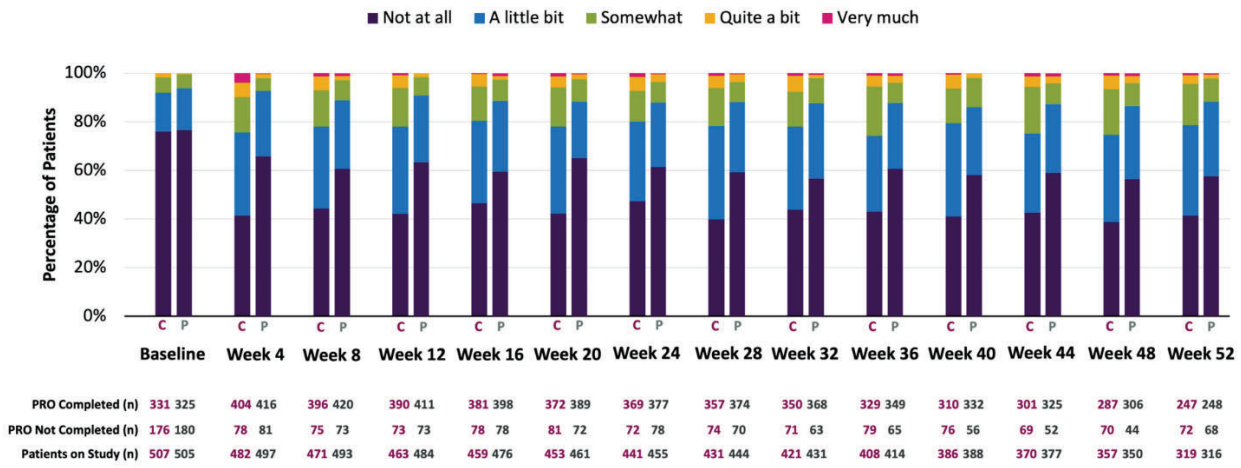
Figure 22 CAPItello-281: 'Loose or Watery Stools' Over Time (PRO-CTCAE) (FAS)



BL, baseline.
Source: Table 14.2.10.33, CAPItello-281 Clinical Study Report.

FACT-P

Figure 23 CAPItello-281: How Bothered Patients were by Treatment Side Effects Over Time (FACT-GP5) (FAS)



Source: IEMT899.1.16.

FACT-P total score ranges from 0 to 156, where a higher score represents better quality of life.

Mean FACT-P total scores at baseline were 112.4 in the C+A arm, and 113.8 in the P+A arm. Mean post-baseline scores for the first year of treatment ranged from 109.6 (Week 4) to 112.2 (Week 20) in the C+A arm, and from 112.1 (Week 48) to 114.7 (Week 20) in the P+A arm.

BPI-SF and BFI

Scores on both the BPI-SF and BFI range from 0 to 10, where a higher score represents a worse outcome.

Mean pain severity score at baseline was low in both arms (C+A: 1.2, P+A: 1.3). Changes in pain severity were minor in both arms, with mean changes ranging from −0.4 to 0.5 in the C+A arm and −1.2 to 0.1 in the P+A arm. Mean pain interference score at baseline was low in both arms (C+A: 1.1, P+A: 1.4). Changes from baseline were minor in both arms, with mean changes ranging from −0.2 to 0.5 in the C+A arm and −1.1 to −0.2 in the P+A arm.

Mean fatigue intensity at baseline was 1.7 in the C+A arm and 2.1 in the P+A arm. Mean fatigue interference at baseline was 1.2 in the C+A arm and 1.5 in the P+A arm. Mean changes from baseline in both domains were small in both arms (approximately −0.1 to 0.4 in C+A and −0.3 to 0.3 in P+A).

Appendix 12. Adverse Events Leading to Death in CAPItello-281

Table 33 CAPItello-281: AEs Leading to Death by SOC (SAS)

Treatment arm	C+A	P+A
Total number of patients in treatment arm, N	**503**	**503**
AE leading to death, n (%) [a]	36 (7.1)	26 (5.2)
Infections and infestations	11 (2.2)	10 (2.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.4)	6 (1.2)
Metabolism and nutrition disorders	2 (0.4)	0
Psychiatric disorders	0	1 (0.2)
Nervous system disorders	3 (0.6)	1 (0.2)
Cardiac disorders	3 (0.6)	3 (0.6)
Vascular disorders	3 (0.6)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	3 (0.6)	0
Gastrointestinal disorders	1 (0.2)	0
Hepatobiliary disorders	1 (0.2)	0
Renal and urinary disorders	1 (0.2)	1 (0.2)
General disorders and administration site conditions	5 (1.0)	3 (0.6)
Injury, poisoning and procedural complications	2 (0.4)	0

a Number (%) of patients with AE with outcome of death, sorted by international order for SOC and descending frequency for PT (C+A group).

Patients with multiple events in the same PT are counted only once in that PT.

Note: AEs with an onset date on/after date of the first dose and AEs with onset date prior to the first dose but worsen after the first dose are reported, up to 30 days (+7 days) following the date of last dose.

MedDRA version 27.0.

MedDRA, Medical Dictionary for Regulatory Activities.

Source: Table 14.3.5.3, CAPItello-281 Clinical Study Report.

Table 34 CAPItello-281: Listing of AEs Leading to Death by PT

Patient identifier	Investigator-reported term	PT	Time from first dose to AE (days)	Treatment period	Last dose prior to death, [capivasertib or placebo]/ abiraterone (mg)	Time from last dose to death (days)	Time from first dose to death (days)	Reasonable possibility AE caused by [capivasertib or placebo]/ abiraterone [a]
C+A								
(b) (6)	Urinary tract infection	Urinary tract infection	97	On treatment	800/1000	6	97	N/N
	Undetermined natural death	Death	296	On treatment	640/1000	9	296	N/N
	Peripheral arterial disease	Peripheral arterial occlusive disease	66	On treatment	800/1000	30	221	N/N
	Sudden death due homorragic shock	Shock hemorrhagic	221	On treatment	640/1000	24	221	N/N
	Sepsis	Sepsis	21	On treatment	800/1000	12	26	N/N
	Unknown cause of death	Death	10	On treatment	800/1000	3	10	N/N
	Massive nasal hemorrhage	Epistaxis	513	On treatment	800/100	36	513	N/N
	Aggravation of coronary atherosclerotic heart disease	Arteriosclerosis coronary artery		On treatment	400/1000	18	130	Y/Y
	Dyspnea	Dyspnea	20	On treatment	800/1000	9	22	N/N
	Chronic subdural hematoma	Subdural hematoma	179	On treatment	400/1000	14	199	N/N
	Aspiration pneumonia	Pneumonia aspiration	315	On treatment	800/1000	20	328	N/N
	Multiple organ failure	Multiple organ dysfunction syndrome	1295	On treatment	320/500	19	1295	N/N
	Transaminitis	Hypertransaminasemia	225	On treatment	800/1000	30	248	N/Y
	Myocardial infarction	Myocardial infarction	11	On treatment	800/1000	4	11	Y/Y
	Death of unknown cause	Death	1151	On treatment	800/1000	24	1151	N/N
	Infective myositis	Infective myositis	10	On treatment	400/1000	2	11	N/N
	Edema cerebral	Brain edema	239	On treatment	800/1000	23	240	N/N

Patient identifier	Investigator-reported term	PT	Time from first dose to AE (days)	Treatment period	Last dose prior to death, [capivasertib or placebo]/ abiraterone (mg)	Time from last dose to death (days)	Time from first dose to death (days)	Reasonable possibility AE caused by [capivasertib or placebo]/ abiraterone [a]
(b) (6)	Acute myocardial infarction	Acute myocardial infarction	83	On treatment	800/1000	9	83	N/N
	COVID-19 pneumonia	COVID-19 pneumonia	190	On treatment	800/1000	29	200	N/N
	Septic shock due to pyelonephritis	Septic shock	53	On treatment	800/1000	6	54	N/N
	Septic shock	Septic shock	153	On treatment	800/1000	6	153	N/N
	Pulmonary thromboembolism	Pulmonary embolism	332	On treatment	640/1000	17	332	N/N
	Lung adenocarcinoma	Lung adenocarcinoma	175	On treatment	400/1000	57	231	N/N
	Unknown cause(sudden death)	Sudden death	251	On treatment	400/1000	4	251	N/N
	Intoxication due to out-hospital bacterial pneumonia	Pneumonia bacterial	649	On treatment	800/1000	5	650	N/N
	Sudden death due to shock, ruptured thoracic aortic aneurysm	Aortic aneurysm rupture	585	On treatment	400/1000	4	585	N/N
	Cranial haemorrhage (atraumatic)	Cerebral hemorrhage	28	On treatment	800/1000	7	28	N/N
	Acute pancreatitis	Pancreatitis acute	491	On treatment	800/1000	32	508	N/N
	Sepsis	Sepsis	10	On treatment	800/1000	16	23	Y/Y
	Acute renal failure due to postrenal obstruction	Postrenal failure	169	On treatment	400/1000	10	172	N/N
	Traffic accident	Road traffic accident	357	On treatment	640/1000	14	357	N/N
	Primary colon CA	Colon cancer	162	On treatment	400/1000	4	180	N/N
	Urosepsis	Urosepsis	7	On treatment	800/1000	14	14	Y/N
	Diabetic ketoacidosis	Diabetic ketoacidosis	302	On treatment	640/1000	5	306	Y/Y

Patient identifier	Investigator-reported term	PT	Time from first dose to AE (days)	Treatment period	Last dose prior to death, [capivasertib or placebo]/ abiraterone (mg)	Time from last dose to death (days)	Time from first dose to death (days)	Reasonable possibility AE caused by [capivasertib or placebo]/ abiraterone [a]
(b) (6)	Cerebral vascular accident	Cerebrovascular accident	578	On treatment	800/1000	42	582	N/N
	Hyperglycemia	Hyperglycemia	10	On treatment	400/1000	2	11	Y/Y
	Septic shock	Septic shock	10	On treatment	400/1000	2	11	N/N
P+A								
(b) (6)	Acute non-traumatic heart failure	Cardiac failure acute	483	On treatment	800/1000	7	483	N/N
	Urosepsis	Urosepsis	15	On treatment	400/250	2	16	N/N
	COVID-19 pneumonia	COVID-19 pneumonia	193	On treatment	800/1000	6	197	N/N
	Sepsis	Sepsis	21	On treatment	800/1000	8	22	N/N
	Suicide attempt	Suicide attempt	349	On treatment	640/1000	13	349	N/N
	Sepstic shock	Septic shock	261	On treatment	800/1000	55	279	N/N
	Unknown cause of death	Death	647	On treatment	800/1000	1	647	N/N
	Myocardial infarction	Myocardial infarction	26	On treatment	800/1000	12	26	N/N
	Intracranial hemorrhage	Hemorrhage intracranial	297	On treatment	800/1000	8	309	N/N
	Acute myelogenous leukemia	Acute myeloid leukemia	532	On treatment	800/1000	23	548	N/N
	Pneumonia	Pneumonia	243	On treatment	800/1000	9	247	N/N
	Myeloma	Plasma cell myeloma	646	On treatment	800/1000	40	692	N/N
	Probable sepsis	Sepsis	315	On treatment	800/1000	6	315	N/N
	Small cell lung cancer	Small cell lung cancer	214	On treatment	800/1000	59	227	N/N
	Unknown cause of death	Death	148	On treatment	800/1000	1	148	Y/Y
	Nefrotic sindrom: nodular glomerulonephritis	Nephrotic syndrome	313	On treatment	800/1000	4	382	N/N
	Septic shock	Septic shock	73	On treatment	400/1000	34	97	N/N

Patient identifier	Investigator-reported term	PT	Time from first dose to AE (days)	Treatment period	Last dose prior to death, [capivasertib or placebo]/ abiraterone (mg)	Time from last dose to death (days)	Time from first dose to death (days)	Reasonable possibility AE caused by [capivasertib or placebo]/ abiraterone [a]
(b) (6)	Gastrointestinal stromal tumor - another separate neoplasm	Gastrointestinal stromal tumor	425	On treatment	800/1000	75	628	N/N
	Sudden cardiac arrest	Cardiac arrest	511	On treatment	800/1000	7	511	N/N
	Susp thrombembolus caused death. No procedures done	Embolism	73	On treatment	800/1000	3	73	N/N
	Worsening of general health	General physical health deterioration	224	On treatment	800/500	5	228	N/N
	Severe pneumonia	Pneumonia	385	On treatment	800/1000	21	387	N/N
	Pneumonia	Pneumonia	214	On treatment	800/1000	7	217	N/N
	Infectious pneumonia	Pneumonia	578	On treatment	400/1000	12	587	N/N
	Lung cancer	Lung neoplasm malignant	42	On treatment	800/1000	167	255	N/N
	Pancreatic cancer	Pancreatic carcinoma	253	On treatment	800/1000	429	674	N/N

a As assessed by the investigator.
Source: Table 14.3.5.4, CAPItello-281 Clinical Study Report.

9.2 FDA's Appendices

Appendix 13. FDA – Additional Efficacy Analyses

Table 35: FDA – CAPItello-281: Treatment Discontinuation Prior to Progression or Death

	C+AAP N=507	P+AAP N=505
Patients who discontinued both study treatments in the absence of (or prior to) PD/death, n (%)	128 (25.2)	92 (18.2)
Discontinued capivasertib due to AE or clinical progression in the absence of (or prior to) PD/death, n (%)	121 (23.9)	60 (11.9)
Discontinued capivasertib/placebo due to AE in the absence of (or prior to) PD/death, n (%)	93 (18.3)	24 (4.8)
Discontinued abiraterone due to AE in the absence of (or prior to) PD/death, n (%)	48 (9.5)	27 (5.3)

Source: Applicant's response to IR dated 11/18/2025 and IR dated 03/06/2026

Abbreviations: C+AAP: capivasertib + abiraterone acetate + prednisone; CI: confidence interval; P+AAP: placebo + abiraterone acetate + prednisone; PD: progression of disease

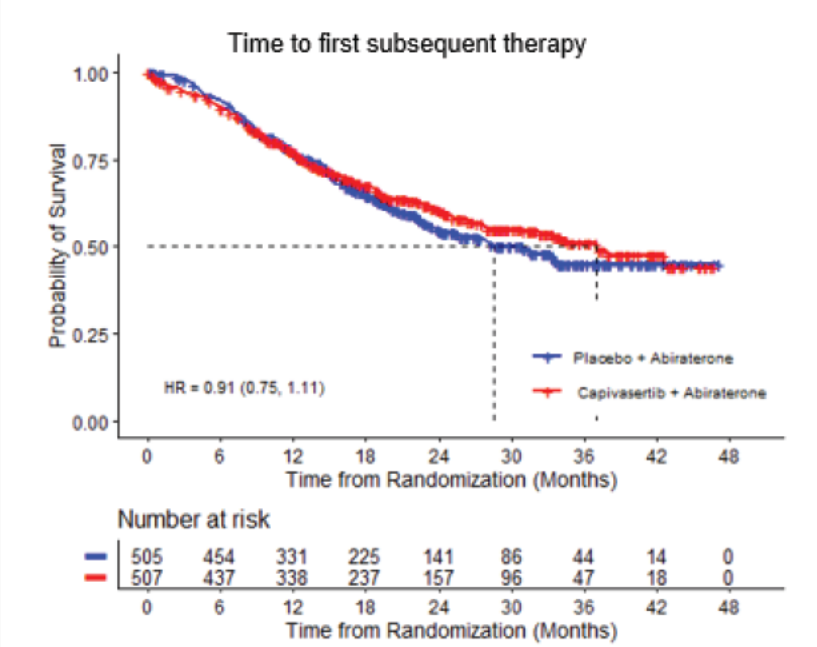
Table 36. FDA – CAPItello-281: Exploratory Efficacy Analysis of Subgroups Defined by Different PTEN Loss Cutoffs

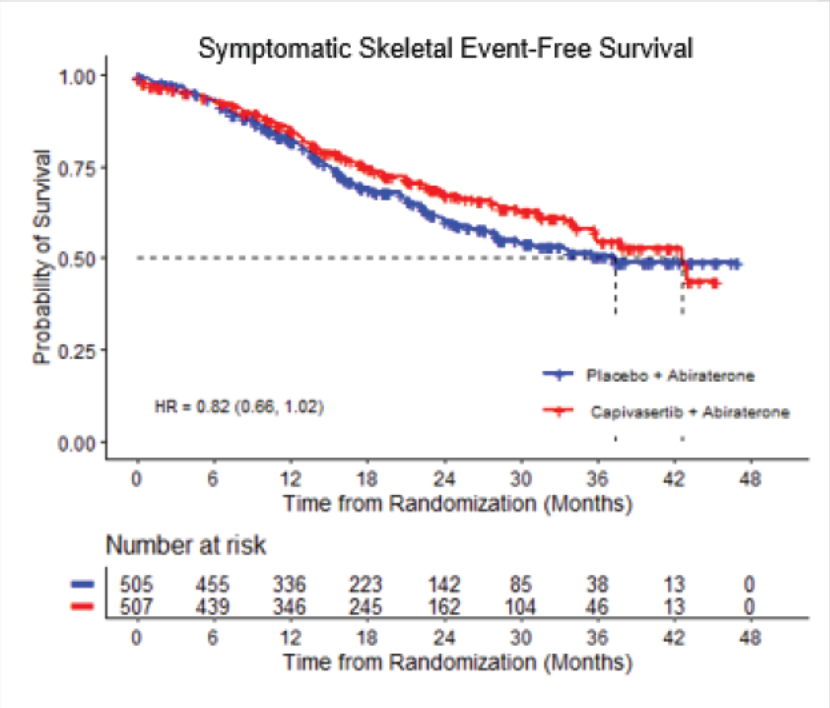
Endpoint	rPFS by INV		OS	
PTEN loss >=90 (ITT)	N=1012		N=1012	
Median (C+AAP vs. P+AAP), months	33 vs 26		NE vs NE	
HR (95% confidence interval)	0.81 (0.66, 0.98)		0.9 (0.71, 1.15)	
PTEN loss >=95 (n, proportion of ITT)	Yes (n=814, 80%)	No (n=198, 20%)	Yes (n=814, 80%)	No (n=198, 20%)
Median (C+A vs. P+A), months	33 vs 23	38 vs NE	NE	43 vs NE
HR (95% confidence interval)	0.77 (0.62, 0.95)	1.25 (0.77, 2.04)	0.8 (0.62, 1.05)	1.72 (0.92, 3.22)
PTEN loss >=99 (n, proportion of ITT)	Yes (n=401,40%)	No (n=611, 60%)	Yes (n=401,40%)	No (n=611, 60%)
Median (C+A vs. P+A), months	34 vs 22	33 vs 29	NE	NE
HR (95% confidence interval)	0.71 (0.51, 0.96)	0.94 (0.72, 1.21)	0.77 (0.53, 1.11)	1.02 (0.74, 1.39)
PTEN loss =100 (n, proportion of ITT)	Yes (n=331, 33%)	No (n=681, 67%)	Yes (n=331, 33%)	No (n=681, 67%)
Median (C+A vs. P+A), months	34 vs 22	33 vs 29	NE	NE
HR (95% confidence interval)	0.70 (0.49, 0.98)	0.92 (0.72, 1.17)	0.76 (0.51, 1.13)	1 (0.74, 1.36)

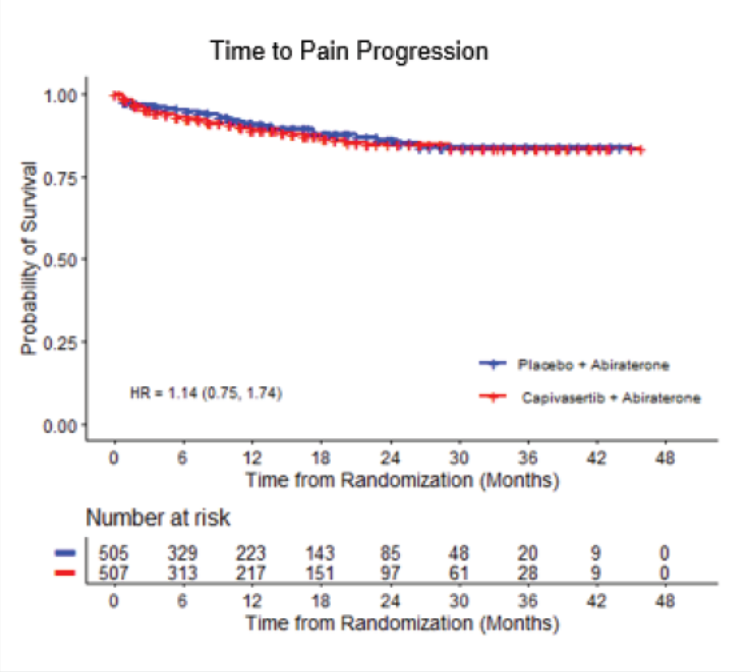
Source: Applicant's response to Information Request dated 11/18/2025

Note: PTEN loss refers to percentage of malignant cells with no cytoplasmic immunohistochemical staining.
Abbreviation: C+A: capivasertib + abiraterone acetate + prednisone; HR: hazard ratio, ITT: intent-to-treat; NE: not evaluable; OS; overall survival; P+A: placebo + abiraterone acetate + prednisone; rPFS: radiographic progression-free survival

Figure 24. FDA – CAPItello-281: Kaplan-Meier Curves of the Secondary Endpoints in Testing Plan







Abbreviation: HR: hazard ratio

Table 37. FDA – CAPItello-281: Summary of other exploratory endpoints

Endpoint	Events (%) C+AAP (N = 507)	Events (%) P+AAP (N = 505)	Median C+AAP (months)	Median P+AAP (months)	HR	95% CI
Time to PSA progression	60 (11.8)	82 (16.2)	NC	NC	0.73	0.52, 1.01
Time to castration resistance (TTCR)	185 (36.5)	231 (45.7)	29.5	22.0	0.77	0.63, 0.94
Time to second progression or death (PFS2)	135 (26.6)	146 (28.9)	41.4	NC	0.90	0.71, 1.13
Time to first subsequent chemotherapy (TFSC)	159 (31.4)	192 (38.0)	46.8	32.9	0.79	0.64, 0.97

Abbreviations: C+A: capivasertib + abiraterone + prednisone; CI: confidence interval; HR: hazard ratio; P+A: placebo + abiraterone + prednisone; rPFS: radiographic progression-free survival

Table 38. FDA – Topline Efficacy Results of CAPItello-280

	Population	Event rate (%) Capivasertib +Docetaxel	Median Placebo +Docetaxel	HR (95% CI)

OS	ITT (n=1034)	201 (39.0) vs 178 (34.4)	16·7 vs 19.4	1.22 (1.00, 1.49)
	PTEN-proficient (n=436)	88 (39.1) vs 68 (32.2)	16.8 vs 21.1	1.19 (0.87, 1.64)
	PTEN-deficient (n=257)	53 (43.8) vs 49 (36.0)	16.7 vs 19.7	1.42 (0.95, 2.11)
rPFS by INV	ITT (n=1034)	291 (56.4) vs 327 (63.1)	8.3 vs 8.3	0.98 (0.84, 1.15)
	PTEN-proficient (n=436)	125 (55.6) vs 136 (64.5)	8.4 vs 8.3	0.98 (0.77, 1.26)
	PTEN-deficient (n=257)	87 (71.9) vs 84 (61.8)	8.3 vs 8.3	1.07 (0.78, 1.47)

PTEN status: a valid PTEN-proficient or PTEN-deficient biomarker result as determined by retrospective central IHC testing of tumor tissue.
PTEN-proficient status is scored as >10% viable malignant cells with any specific cytoplasmic stain intensity (PTEN-intact).
PTEN-deficient status is scored as >=90% of viable malignant cells with no specific cytoplasmic staining (PTEN-loss).
Source: Clinical Study Report, CAPItello-280

Appendix 14. FDA – Additional Safety Analyses

Table 39. FDA – Prednisone/Prednisolone Reported Use[a] and Hyperglycemia

	C+AAP		P+AAP	
	Predniso(lo)ne users n=316 n (%)	Not documented n=184 n (%)	Predniso(lo)ne users n=294 n (%)	Not documented n=204 n (%)
Hyperglycemia[b] (Grouped Term) Any-Grade	171 (54)	86 (46)	49 (17)	31 (15)
Grade 1-2	126 (40)	69 (37)	46 (16)	28 (14)
Grade 3-4	44 (14)	17 (9)	3 (1)	3 (1.4)

Source: FDA analysis
[a] Documented in eCRF. The analysis excludes patients who received other glucocorticoids (7 patients in each arm who received other glucocorticoids such as dexamethasone).
[b] Patients are categorized (counted once) according to highest grade observed
Abbreviations: C+AAP: capivasertib + abiraterone acetate + prednisone; P+AAP: placebo + abiraterone acetate + prednisone;

Table 40. FDA – Terms Included in "Skin Reactions" and Number of Patients with Each Preferred Term

	C+AAP N=503		**P+AAP N=503**	
	All Grade n (%)	**Grade 3-4 n (%)**	**All Grade n (%)**	**Grade 3-4 n (%)**
Skin reactions (Grouped Term)	**267 (53)**	**87 (17)**	**84 (17)**	**2 (0.4)**

	C+AAP N=503		P+AAP N=503	
	All Grade n (%)	Grade 3-4 n (%)	All Grade n (%)	Grade 3-4 n (%)
Rash maculo-papular	115 (23)	47 (9)	23 (4.6)	1 (0.2)
Rash	57 (11)	13 (2.6)	13 (2.6)	0
Pruritus	53 (11)	1 (0.2)	13 (2.6)	0
Dry skin	43 (9)	1 (0.2)	23 (4.6)	0
Erythema multiforme	13 (2.6)	8 (1.6)	1 (0.2)	0
Eczema	12 (2.4)	0	6 (1.2)	1 (0.2)
Rash macular	12 (2.4)	4 (0.8)	0	0
Urticaria	8 (1.6)	1 (0.2)	4 (0.8)	0
Erythema	8 (1.6)	0	2 (0.4)	0
Rash erythematous	8 (1.6)	1 (0.2)	0	0
Dermatitis	7 (1.4)	2 (0.4)	1 (0.2)	0
Dermatitis allergic	6 (1.2)	2 (0.4)	0	0
Rash pruritic	5 (1)	0	0	0
Drug eruption	4 (0.8)	4 (0.8)	1 (0.2)	0
Dermatitis exfoliative generalised	4 (0.8)	2 (0.4)	0	0
Rash papular	4 (0.8)	0	0	0
Dermatitis acneiform	3 (0.6)	0	1 (0.2)	1 (0.2)
Dermatitis atopic	3 (0.6)	1 (0.2)	0	0
Eczema asteatotic	3 (0.6)	1 (0.2)	0	0
Rash pustular	2 (0.4)	0	3 (0.6)	0
Skin fissures	2 (0.4)	0	1 (0.2)	0
Purpura	2 (0.4)	2 (0.4)	0	0

	C+AAP N=503		P+AAP N=503	
	All Grade n (%)	Grade 3-4 n (%)	All Grade n (%)	Grade 3-4 n (%)
Stevens-Johnson syndrome	2 (0.4)	2 (0.4)	0	0
Eczema nummular	2 (0.4)	0	0	0
Eye pruritus	2 (0.4)	0	0	0
Skin ulcer	2 (0.4)	0	0	0
Skin exfoliation	1 (0.2)	0	1 (0.2)	0
Dermatitis exfoliative	1 (0.2)	1 (0.2)	0	0
Brachioradial pruritus	1 (0.2)	0	0	0
Erythema ab igne	1 (0.2)	0	0	0
Exfoliative rash	1 (0.2)	0	0	0
Eyelids pruritus	1 (0.2)	0	0	0
Genital erythema	1 (0.2)	0	0	0
Mucocutaneous rash	1 (0.2)	0	0	0
Pruritus allergic	1 (0.2)	0	0	0
Pruritus genital	1 (0.2)	0	0	0
Stoma site rash	1 (0.2)	0	0	0
Urticaria papular	1 (0.2)	0	0	0
Skin discolouration	0	0	3 (0.6)	0
Erythema nodosum	0	0	1 (0.2)	0
Palmar-plantar erythrodysaesthesia syndrome	0	0	1 (0.2)	0
Penile dermatitis	0	0	1 (0.2)	0

Note: Rows do not total "Skin reactions" Grouped Term because patients may have had more than 1 Preferred Term.

Abbreviation: C+A: capivasertib + abiraterone acetate + prednisone; P+A: placebo + abiraterone acetate + prednisone;

Table 41. FDA – Laboratory Abnormalities (≥ 10% Any Grade and ≥ 1% Grade 3-4) in Either Arm in CAPItello-281

Laboratory Abnormality	C+AAP		P+AAP	
	All Grades n/N* (%)	Grade 3 or 4 n/N* (%)	All Grades n/N* (%)	Grade 3 or 4 n/N* (%)
Increased fasting glucose	341/499 (68)	58/499 (12)	241/496 (49)	11/496 (2.2)
Decreased hemoglobin	293/500 (59)	29/500 (6)	220/500 (44)	12/500 (2.4)
Decreased lymphocytes	262/500 (52)	60/500 (12)	164/499 (33)	35/499 (7)
Increased random glucose	237/472 (50)	84/472 (18)	208/485 (43)	14/485 (2.9)
Decreased potassium	236/500 (47)	77/500 (15)	175/500 (35)	42/500 (8)
Increased creatinine	221/500 (44)	21/500 (4.2)	111/501 (22)	9/501 (1.8)
Increased triglycerides	167/460 (36)	13/460 (2.8)	144/464 (31)	11/464 (2.4)
Increased ALT	177/499 (35)	38/499 (8)	174/500 (35)	26/500 (5)
Increased AST	170/499 (34)	30/499 (6)	176/501 (35)	16/501 (3.2)
Decreased sodium	127/500 (25)	15/500 (3)	105/499 (21)	12/499 (2.4)
Decreased leukocytes	100/500 (20)	8/500 (1.6)	101/500 (20)	4/500 (0.8)

*N varies depending the number of patients with baseline evaluable laboratory result for each parameter.

Abbreviation: C+A: capivasertib + abiraterone acetate + prednisone;HR: hazard ratio, ITT: intent-to-treat; NE: not evaluable; OS; overall survival; P+A: placebo + abiraterone acetate + prednisone; rPFS: radiographic progression-free survival