U.S. FOOD & DRUG ADMINISTRATION

ODAC Briefing Document

NDA 212578/S000
Padeliporfin di-potassium (TOOKAD)

FDA Briefing Document
Oncologic Drugs Advisory Committee Meeting

NDA 212578/S000
Padeliporfin di-potassium (TOOKAD)
Applicant: Steba Oncology, Inc.

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought this application 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.

Table of Contents

1. Executive Summary

TOOKAD is being brought to ODAC to discuss the following issues that pertain to results from the clinical trial PCM301 in patients with low-risk early stage prostate cancer:

- Are the study endpoints and their results adequate to characterize benefit?
- Is the demonstrated toxicity profile for TOOKAD acceptable?
- Do uncertainties around trial data allow for a reasonable overall assessment of risk/benefit?
- Is data from a separate trial necessary to adequately inform the benefit-risk profile?

The FDA will ask the committee to discuss the following issue: Do the results of PCM301 represent a favorable benefit/risk profile for TOOKAD in patients with low-risk early stage prostate cancer?

2. Introduction

In May 2019, Steba Oncology submitted a new drug application (NDA) for TOOKAD (padeliporfin di-potassium) for the following indication:

TOOKAD (padeliporfin di-potassium) is indicated for the treatment of patients with localized prostate cancer meeting the following criteria:

1. Stage T1-T2a
2. PSA <10 ng/mL
3. Gleason Grade group 1 based on TRUS biopsy or Unilateral Gleason Grade group 2 based on MP-MRI-targeted biopsy with < 50% of cores positive

[Limitation of Use: TOOKAD is not recommended for use in patients with a life expectancy of less than ten years, where the clinical guidelines recommend observation alone, because the therapeutic benefits may not outweigh the risks in that patient population.]

The primary trial submitted in support of this indication was PCM301, a randomized, open-label trial of TOOKAD vs active surveillance in men with localized low-risk prostate cancer. The study had two co-primary endpoints:

A: The rate of absence of definite cancer based on histology at 24 months,
B: The difference in rate of treatment failure associated with observed progression of disease from low to moderate or higher risk prostate cancer. Moderate/higher risk prostate cancer was defined as any of the following:

1. >3 cores radically positive for cancer;
2. Gleason primary or secondary pattern ≥4;
3. at least 1 cancer core length >5 mm;
4. PSA >10 ng/mL in 3 consecutive measures;

5. T3 prostate cancer;
6. metastasis; or
7. prostate cancer-related death.

PCM301 randomized 413 patients to TOOKAD (N=206) or active surveillance (N=207). The study met its primary endpoints, with superiority demonstrated on the TOOKAD arm for both. However, these endpoints have not been used to support a US regulatory approval in patients with localized prostate cancer due to uncertainty regarding their clinical meaningfulness and correlation with long-term outcomes. In addition, the toxicity profile of TOOKAD requires careful consideration due to the incidence of long-term toxicities noted in this trial.

This study was originally designed to follow patients for 24 months. The Applicant amended the study to continue following patients for an additional 5 years, for a total of 7 years of follow-up. The current application includes an interim report of the 5-year follow-up amendment. Since patients needed to be re-enrolled for this amendment, and there was limited data collection on the primary endpoints after 24 months, e.g. no scheduled biopsy collection, the agency considers the PCM301 data up to 24 months to be the primary support for this application

In review of efficacy, it is apparent that both co-primary endpoints rely on the accuracy and reliability of biopsy results. FDA notes the following issues related to the accuracy and reliability of the endpoints used to assess efficacy on PCM301:

- A quarter of the patients on the active surveillance arm either had missing biopsy data or a false negative biopsy.
    - The TOOKAD and active surveillance arm both had missing biopsies (13% and 15%, respectively) at month 24 due to reasons other than having undergone definitive therapy.
    - In addition, there is 13.5% rate of false negative biopsies in patients who had cancer at baseline but a negative subsequent month-24 biopsy on the surveillance arm. False negative biopsies may also have affected the TOOKAD arm but this is more difficult to assess, as any negative biopsies on that arm could be attributed to the TOOKAD procedure.
- If biopsies missed the presence of cancer in patients in the active surveillance arm, it is also possible that higher grade disease was missed at initial biopsy, and "progression" as defined, may not in fact be progression to a higher-grade group but rather missed pathology on initial biopsy.
- The TOOKAD procedure itself may also make obtaining a reliable follow-up biopsy from the treated lobe difficult due to scarring.

The absence of detectable cancer, as defined in coprimary endpoint A, is not the same as absence of actual cancer. This difference may in part be due to missing data and sampling errors including false negative biopsies. In addition, a change in grade of the cancer obtained from the biopsies has not been prospectively validated as affecting long-term outcomes.

These issues make the reliability of the efficacy results and the difference in magnitude of effect between the two arms uncertain.

Co-primary endpoint (B) was a composite endpoint with the overall goal of measuring progression to a higher risk stratum of prostate cancer. In this setting where disease-specific survival is high, co-primary endpoint (B) is of potential utility if it leads to 1.) a corresponding decrease in the rate of patients undergoing definitive therapy in the form of prostatectomy and prostate radiation and 2.) a decrease in resultant toxicity. Please note that the FDA will use the phrase "definitive therapy" in lieu of "radical therapy" in the remainder of the document, except for when specifically referencing the endpoints defined by the sponsor in the protocol. This is because these therapies (e.g. radical prostatectomy, radiation therapy) are commonly implemented and result in cure for many patients. FDA notes the following issues in assessing interpretation of this endpoint:

- The decision for a patient to undergo definitive therapy was subjective. Approximately half of the progressors did not undergo definitive therapy and a few patients underwent definitive therapy in the absence of progression.
- A supportive secondary endpoint was time to definitive therapy. The rate of definitive therapy was lower in patients randomized to TOOKAD, however this endpoint was not controlled for type 1 error. In addition, the decision to undergo definitive therapy was subjective, as noted above.
- Toxicity was generally higher on the TOOKAD arm, demonstrated by an early increase in toxicities (urinary and erectile dysfunction). This increase in early toxicity is supported both by adverse event reporting as well as patient-reported outcomes.
- Long-term toxicities have not been captured reliably, especially in patients who underwent definitive therapy and did not have subsequent toxicity recorded.
- There is also limited data from PCM301 on the safety and long-term effectiveness of definitive therapy after previous treatment with TOOKAD.

Decreasing rates of patients undergoing definitive therapy is of potential utility in patients with localized prostate cancer but the decision to undergo definitive therapy in PCM301 was subjective, and there was uncontrolled variability in who proceeded to these therapies. Decreasing toxicity is also of utility in this patient population but toxicity appeared increased in the TOOKAD arm, long term toxicity data was not captured reliably as data was missing for patients who underwent definitive therapy, and the lack of data on long-term safety confounds the benefit-risk assessment.

A randomized trial of TOOKAD vs. active surveillance in patients with intermediate risk prostate cancer (PCM306) has been designed with FDA input and has measures in place to overcome many of the issues with PCM301. This will be discussed in more detail below.

The Applicant has proposed an indication for the treatment of patients with low risk prostate cancer (the enrolled population) as well as patients with favorable intermediate risk prostate cancer (not studied in the trial). As patients with favorable intermediate risk prostate cancer were not enrolled on PCM301, the ODAC is asked to discuss only the issues surrounding the studied/enrolled population (i.e. patients with low risk localized prostate cancer).

3. Drug, Disease, and Regulatory Background

Disease Setting

Patients with low risk localized prostate cancer are generally managed with active surveillance or definitive treatment (e.g. prostatectomy or radiation therapy). Active surveillance has become increasingly used in this setting with emerging data, as these patients delay or avoid the genitourinary toxicity associated with definitive treatment. Approximately 20-40% of patients on active surveillance eventually undergo prostatectomy or radiation due to disease progression within 5 years of initial diagnosis[1,2] Focal ablative options (e.g. high intensity focused ultrasound) are alternatives for patients unfit for definite treatment, and observation alone is appropriate for those with limited life expectancies.

Drug Background

TOOKAD/padeliporfin-di-potassium is a derivative of bacteriochlorophyll, a photosynthetic pigment of aquatic bacteria. Local laser light activates TOOKAD after it is administered intravenously. Patients undergo the TOOKAD administration and laser activation procedure under general anesthesia after rectal preparation. The practitioner positions guidance needles in the prostate gland covering the treatment zone with a $\geq$5mm margin for the rectal wall, prostate apex, and urethra, and then positions interstitial optical fibers in the prostate. TOOKAD at a dose of 4 mg/kg is administered as a single 10-minute intravenous infusion and activated in the prostate by the laser illumination. After the procedure, patients are kept in dimmed light for at least 6 hours to avoid systemic activation and phototoxicity.

Regulatory History

In March 2011, Steba met with FDA to discuss the design of a trial of TOOKAD vs active surveillance for patients with low risk localized prostate cancer. FDA stated that the proposed co-primary endpoints of rate of pathologic upgrade and absence of definitive cancer were not well-accepted endpoints to support a marketing application given their unknown clinical significance in patients with early stage localized prostate cancer and did not agree to the trial design and endpoints. Steba then conducted PCM301 exclusively in Europe with the same design originally proposed to FDA.

FDA workshop on localized prostate cancer

FDA held a workshop in September 2018 to discuss design issues related to trials of novel treatments for localized prostate cancer (FDA Oncology Center of Excellence Public Workshop: Development of Treatments for Localized Prostate Cancer).

Due to the long disease-specific survival in localized prostate cancer and long resultant trial readout times, endpoints previously used to assess efficacy on prostate cancer trials such as metastasis-free survival and overall survival may not be practical in this setting. Workshop

participants discussed other endpoints that might be more feasible, including an endpoint of decreased rates of pathologic upgrade. They opined that this endpoint might represent clinical benefit if also accompanied by a decreased rate of patients undergoing definitive therapy during the course of the trial due to decreased overall rates of cancer progression. However, and just as importantly, this would also have to be accompanied by an overall reduction in patient- and physician-reported toxicities and no decrement in long-term cancer control[3].

4. PCM301 Trial Design

The application under discussion is supported by the Phase 3 study PCM301.

PCM301 was an open-label randomized trial of TOOKAD vs active surveillance in men with localized low-risk prostate cancer. The applicant conducted PCM301 in 10 European countries with the first patient being randomized on March 8, 2011 and a database lock on August 20, 2015. The study randomized 413 patients in a 1:1 ratio between TOOKAD (N=206) and active surveillance (N=207).

Below are additional details on PCM301.

Study Design of PCM301

Main inclusion criteria:

- Men with previously untreated low-risk localized prostate cancer diagnosed by transrectal ultrasound (TRUS)-guided biopsy from 10 to 24 cores performed less than 12 months prior to enrolment (biopsy criteria updated in protocol versions 3.0 and 4.0)
- 2 to 3 cores positive for cancer; subjects with 1 positive core allowable if at least 3 mm of cancer core length
- maximum Gleason score of 3 + 3
- maximum cancer core length of 5 mm in any core
- Cancer clinical stage up to T2a
- PSA ≤ 10 ng/mL (≤5 ng/mL for subjects using a 5-α-reductase inhibitor [5-ARIs])
- Prostate volume ≥ 25 cc and < 70 cc

Main exclusion criteria:

- Any prior or current prostate cancer treatment, including surgery, radiation therapy (external or brachytherapy) or chemotherapy
- Any surgical intervention for benign prostatic hypertrophy (added in protocol Version 6.0)
- Life expectancy < 10 years
- Major illness
- History of sun hypersensitivity or photosensitive dermatitis

An independent web-based allocation system performed central randomization of patients to TOOKAD or Active Surveillance in a 1:1 ratio, stratified by center using balanced blocks of variable size.

Patients randomized to TOOKAD were treated as described previously in this document (Section 3). For bilateral disease discovered at entry or during follow-up, the practitioner could apply bilateral treatment, either simultaneously or consecutively. The practitioner could also retreat lobes found positive for cancer at 12 months' follow-up.

Patients randomized to the active surveillance arm had surveillance conducted in line with existing recommendations[4 5]. This included deferral of active treatment and periodic monitoring with PSA tested every 3 months, physical examinations and annual prostate biopsy.

Follow-up

Patients in both treatment groups were followed for 24 months after randomization with a TRUS-guided biopsy of 10 to 24 cores at Month 12 and Month 24 and PSA measurements and digital rectal examination (DRE) every 3 months. PCM301 was originally designed to follow patients for 24 months. The Applicant amended the study to continue following patients for an additional 5 years, for a total of 7 years of follow-up. The current application includes an interim report of the 5-year follow-up amendment. Since this amendment required re-enrollment, only 354 patients were eligible. Due to limited data collection on the primary endpoints after 24 months, e.g. no scheduled biopsy collection, PCM301 data up to 24 months remains the primary support for this application and subsequent data is not interpretable.

Central Review

Histologix, a central laboratory based in the UK, conducted central scanning and independent blinded assessment of the on-treatment biopsies for all patients entered into the study.

Study objectives

The co-primary objectives were:

A. To assess the impact of TOOKAD on the rate of absence of definite cancer using patients on active surveillance as a comparison, measured as absence of any histology result radically positive for cancer at 24 months

B. To determine the difference in rate of treatment failure associated with observed progression of disease from low risk prostate cancer to moderate or higher risk prostate cancer in men who undergo TOOKAD compared to men on active surveillance.

The primary efficacy endpoints were defined as follows:

- Co-primary endpoint (A): Rate of absence of radical cancer: Absence of any histology result radically positive for cancer at 24 months
- Co-primary endpoint (B): Rate of treatment failure associated with observed progression of cancer from low to moderate or higher risk over the 24 months of

follow-up. Moderate or higher risk is defined as the observation of 1 of the following events:

- More than 3 cores radically positive for cancer when considering all histological results available during follow-up in the study
- Any Gleason primary or secondary pattern of 4 or more
- At least 1 cancer core length > 5 mm
- PSA > 10 ng/mL in 3 consecutive measures
- Any T3 prostate cancer
- Metastasis
- Prostate cancer-related death

For both co-primary endpoints, the blinded adjudication of the biopsy results by the Outcomes Review Panel (ORP), accounting for the local and pathology evaluations, was the basis for analysis.

Secondary objectives were:

To determine the differences between men who undergo TOOKAD and men on active surveillance regarding:

- total cancer burden in the prostate (total number of positive cores)
- rate of additional prostate cancer radical therapy including surgery, radiotherapy [external beam, brachytherapy], high-intensity focused ultrasound, cryotherapy, hormonal therapy or chemotherapy
- rate of severe prostate cancer-related events: cancer extension to T3, metastasis and prostate cancer-related death
- rate of adverse events (AEs)
- rate of incontinence, erectile dysfunction and urinary symptoms

The 3 instruments used to collect patient-reported outcomes were the IPSS, IIEF, and the EQ-5D.

Necrosis from TOOKAD may prevent true blinding of the central pathologists.

5. PCM301 Study Results

Patient Demographics and Baseline Disease Characteristics

Demographic and disease characteristics were well balanced between arms. The vast majority of patients were Caucasian, as this study was performed in Europe.

Table 1 Demographic Characteristics

	TOOKAD N = 206	**Active Surveillance N = 207**	**Total N = 413**
Age (years)			
Mean (SD)	64.2 (6.70)	62.9 (6.68)	63.5 (6.71)
Range: minimum, maximum	45, 85	44, 79	44, 85
Race			
Caucasian, n (%)	202 (98.1)	206 (99.5)	408 (98.8)
Black, n (%)	3 (1.5)	0	3 (0.7)
Asian, n (%)	0	1 (0.5)	1 (0.2)
Other, n (%)	1 (0.5)	0	1 (0.2)
Body mass index (kg/m^2)			
Mean (SD)	26.47 (3.337)	27.34 (3.947)	26.91 (3.677)
Range: minimum, maximum	18.8, 38.6	18.8, 44.8	18.8, 44.8

SD = standard deviation

Table 2 Baseline Disease Characteristics

	TOOKAD N = 206	**Active Surveillance N = 207**	**Total N = 413**
Risk Group			
Low	80 (38.8)	78 (37.7)	158 (38.3)
Very Low	126 (61.2)	129 (62.3%)	255 (61.7)
Time since diagnosis (months)			
Mean (SD)	6.3 (8.54)	6.0 (7.89)	6.2 (8.21)
Range: minimum, maximum	0.2, 54.2	0.2, 47.4	0.2, 54.2
TNM staging			
T1a, n (%)	1 (0.5)	0	1 (0.2)
T1c, n (%)	177 (85.9)	180 (87.0)	357 (86.4)
T2a, n (%)	28 (13.6)	27 (13.0)	55 (13.3)
PSA (ng/mL)			
Mean (SD)	6.19 (2.114)	5.91 (2.049)	6.05 (2.084)
Range: minimum, maximum	0.1, 10.0	0.5, 10.0	0.1, 10.0
Estimated prostate volume (cc)[a]			
Mean (SD)	42.5 (12.49)	42.5 (11.76)	42.5 (12.11)
Range: minimum, maximum	25, 70	25, 70	25, 70
Unilateral disease, n (%)	157 (76.2)	163 (78.7)	320 (77.5)
Bilateral disease, n (%)	49 (23.8)	44 (21.3)	93 (22.5)
Total number of cores			
Mean (SD)	13.6 (3.31)	13.6 (3.55)	13.6 (3.43)
Range: minimum, maximum	10, 25	10, 26	10, 26
Total number of positive cores[b]			

Mean (SD)	2.1 (0.68)	2.0 (0.72)	2.1 (0.70)
Range: minimum, maximum	1, 3	1, 3	1, 3
1 positive core, n (%)	39 (18.9)	52 (25.1)	91 (22.0)
2 positive cores, n (%)	110 (53.4)	100 (48.3)	210 (50.8)
3 positive cores, n (%)	57 (27.7)	55 (26.6)	112 (27.1)
Total cancer core length (mm)			
Mean (SD)	4.3 (2.31)	3.8 (2.40)	4.1 (2.37)
Range: minimum, maximum	0[c], 14	0[c], 11	0,14

SD = standard deviation; TNM = tumour, nodes, metastasis;

[c] Some of the subjects included on the basis of 2 biopsies at the beginning of the study had 1 of those 2 biopsies negative.

Efficacy Results

Primary Analysis

PCM301 met both of its co-primary endpoints. (A) the rate of absence of definite cancer based on histology at 2 years, and (B) the rate of treatment failure associated with observed progression of cancer from low to moderate or higher risk over the 2 years of follow-up.

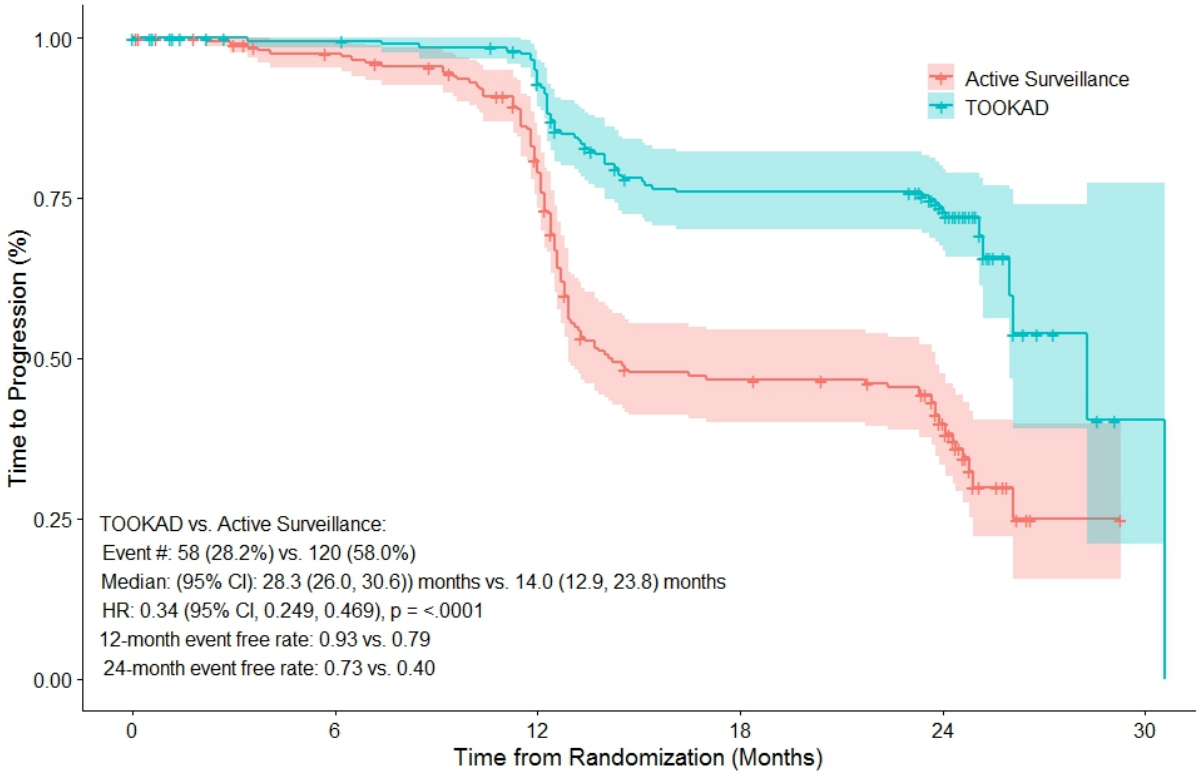
Analysis of co-primary endpoint (A) is presented below:

Table 3 Analysis of Co-Primary Endpoint (A): Rate of Absence of Cancer at 2 Years

Biopsy Result at 2 years	**TOOKAD N = 206**	**Active Surveillance N = 207**
Negative	101 (49.0%)	28 (13.5%)
Positive	67 (32.5%)	93 (44.9%)
Missing	38 (18.4%)	86 (41.5%)
Due to definitive therapy	12 (5.8%)	55 (26.6%)
Due to other reasons	26 (12.6%)	31 (15.0%)

* including subject withdrawal, medical reason, subject refusal

Figure 1 Kaplan-Meier Curves of Co-Primary Endpoint (B) Time-to-Progression



Analysis of each components of co-primary endpoint (B) is summarized in Table 4.

Table 4 Criteria for Progression

	TOOKAD N = 206	**Active Surveillance N = 207**
Progression (all criteria)	58 (28.2%)	120 (58.0%)
Component of		
More than 3 cores positive	23 (11.2%)	58 (28.0%)
Gleason ≥ 4 (including both 3+4 and 4+3)	49 (23.8%)	91 (44.0%)
Cancer core length > 5 mm	25 (12.1%)	51 (24.6%)
Any T3 prostate cancer	0	4 (1.9%)
Metastasis	0	0
PSA > 10 ng/mL in 3 consecutive measures	3 (1.5%)	14 (6.8%)

Sensitivity Analyses

FDA performed additional sensitivity analyses on co-primary endpoint (B).

Table 5: Additional Sensitivity Analyses, Co-Primary Endpoint (B) Time-to-Progression

	TOOKAD N = 206	Active Surveillance N = 207
Sensitivity Analysis 1: Varying the definition of treatment failure to only include follow-up biopsy results demonstrating Gleason 4+3 disease.		
Event #	58 (28.2%)	96 (46.4%)
Hazard Ratio (95% CI)	0.43 (0.31, 0.60)	
Sensitivity Analysis 2: Varying the definition of treatment failure to be in line with guideline-defined unfavorable intermediate risk prostate cancer, i.e. observation of 1 of the following events. a. At least two of the followings: i. T2b-T2c, ii. Gleason 3+4 or Gleason 4+3 iii. PSA 10-20 ng/ml b. Gleason ≥4+3 (including both prostate biopsy pathology Gleason score, as well as prostatectomy pathology Gleason score if available) c. >50% biopsy core positive d. Any T3 or higher prostate cancer e. PSA>20 ng/ml in addition to metastasis or prostate-cancer related death.		
Event # (%)	18 (8.7%)	53 (25.6%)
Hazard Ratio (95% CI)	0.29 (0.17, 0.50)	

In all cases, the TOOKAD arm demonstrated favorable results compared to the active surveillance arm.

To attempt to address the concern that biopsies might have been more difficult to obtain after TOOKAD treatment, FDA reviewed the number of biopsy cores obtained at each follow-up point for patients on each arm and did not find any significant difference.

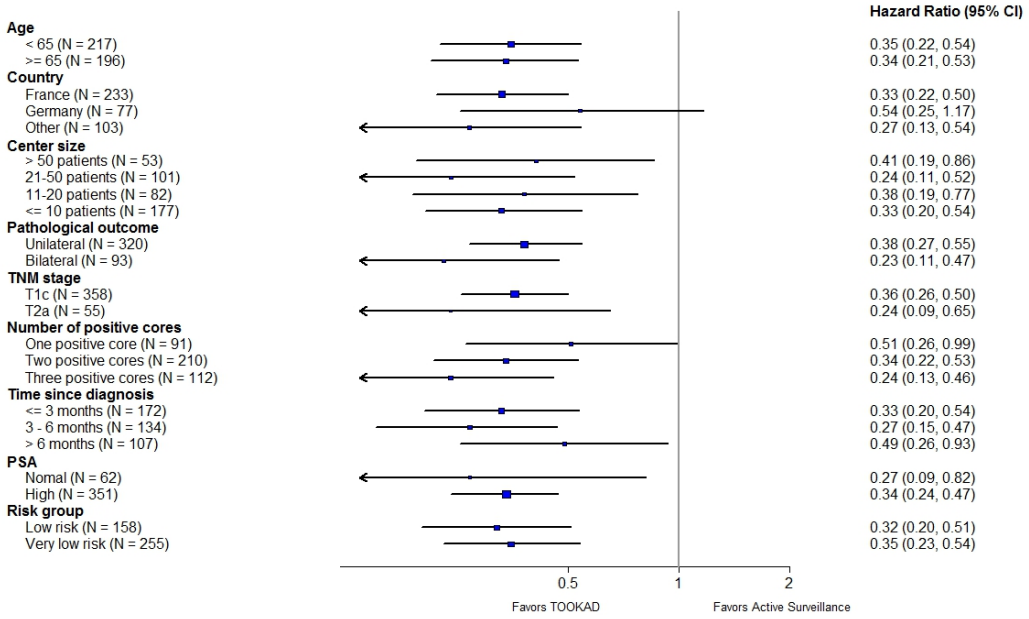
TOOKAD is meant to be used for a single treatment of unilateral disease. A sensitivity analysis excluding any patients with more than one treatment remained consistently favorable for TOOKAD.

The study met its primary endpoints and sensitivity analyses conducted by FDA were consistent with the primary result. However, it should be noted that the unreliability of the endpoint assessments and the interpretation of the results reviewed in the introduction are an issue and may also affect the sensitivity analyses.

Subgroup Analyses

Subgroup analyses were performed in patients with very-low-risk prostate cancer versus low-risk prostate cancer. The study-defined risk reductions were consistent for the TOOKAD arm for both groups, as outlined below:

Figure 2 Subgroup Analysis of Co-Primary Endpoint (B) Time-to-Progression



Secondary Endpoint

Regarding the secondary endpoint of time to definitive therapy, the Study PCM301 also demonstrated results in favor of TOOKAD as outlined below. At 2 years, 6.2% of patients in the TOOKAD arm and 30.8% of patients in the active surveillance arm went on to receive definitive therapy (Hazard ratio = 0.17, 95% CI [0.090, 0.313]).

This analysis is not controlled for multiplicity. In addition, the decision to undergo definitive treatment was subjective and may have been impacted by the open-label nature of the trial.

Other Studies

The Applicant has submitted other studies of TOOKAD in prostate cancer. Due to small sample size and inconsistencies in follow-up, these were not reviewed as part of the primary population.

The Applicant has discussed an additional proposed study of TOOKAD in prostate cancer patients, study PCM306. PCM306 is proposing to evaluate TOOKAD vs. active surveillance for men with intermediate risk localized prostate cancer. The protocol has been finalized but the study has not begun enrollment.

Safety and PROs Results

The safety analysis of TOOKAD is based on the main (2-year) analysis from Study PCM301. Additional data from other studies, including pooled safety analyses of submitted data

collected from other studies side from PCM301 were not considered in this safety review due to lack of randomization and shorter overall follow-up times. Preferred terms that were considered clinically synonymous were grouped to accurately reflect the incidence of these adverse events.

No adverse event data was collected for 19% of patients after the definitive therapy on the active surveillance arm compared with 2% of patients on the TOOKAD arm overall. This missing data confounds interpretation of long-term toxicity comparisons between arms.

Overall Exposure

Of the 206 patients randomized to TOOKAD, 196 patients received at least one treatment of TOOKAD. An additional 1 patient had an anaphylactic reaction prior to TOOKAD administration but is included in the total safety population of 197 patients. No patients in the active surveillance arm received TOOKAD.

Summary of Adverse Events

Table 6 provides a summary of safety in all treated patients in PCM301. Table 7 lists all grade adverse events occurring in ≥10% of patients in either arm. The most frequent adverse events in the TOOKAD arm involved the genitourinary tract.

Table 6. PCM301 Safety Summary

	PCM301	
	TOOKAD N = 197 N (%)	**Active Surveillance N = 207 N (%)**
Deaths		
≤ 30 Days of Study Drug	0	0
All	1 (0.5)	0
Discontinuation due to Grade 1-4 AEs	2 (1)	1 (0.5)
Serious Adverse Events	60 (30)	21 (10)
Grade 3-4 Adverse Events	43 (22)	20 (10)
All Grade Adverse Events	187 (95)	114 (55)

Table 7. All Grade Adverse Events Occurring in ≥10% of patients in PCM301

	TOOKAD N=197 N (%)	**Active Surveillance N=207 N (%)**
Erectile dysfunction	74 (38)	24 (12)
Hematuria	56 (28)	6 (3)
Dysuria	54 (27)	5 (2)
Urinary retention	32 (16)	2 (1)
Urinary incontinence	30 (15)	15 (7)
Perineal pain	30 (15)	1 (0.5)
Urinary tract infection	21 (11)	9 (4)
Micturition urgency	21 (11)	2 (1)
Pollakiuria	20 (10)	6 (3)

Deaths:

- No deaths occurred within 30 days of the single dose of study drug.
- One patient died due to a myocardial infarction 323 days after receiving TOOKAD and was not considered related to therapy.

Grade 3 and 4 Adverse Events:

- Occurred in 22% of patients on TOOKAD vs. 10% of patients on active surveillance.
- The most common Grade 3-4 adverse events in the TOOKAD arm were dysuria (1.5%), erectile dysfunction (1%), urinary incontinence (1%), ejaculation failure (1%), and urinary tract infection (1%).

Serious Adverse Events:

- Serious adverse events occurring in > 1% of TOOKAD patients and at a higher incidence than active surveillance were urinary retention (8%), prostatitis (2%), urinary tract infection (2%), hematuria (1.5%), dysuria (1.5%), and orchitis (1.5%).

Discontinuations due to Grade 1-4 Adverse Events:

- Temporary discontinuations were not applicable given the TOOKAD administration and dosing schedule.
- Two patients in the TOOKAD arm and 1 patient in the active surveillance arm were permanently discontinued from the study discontinuations unrelated to study drug within 30 days of dosing.

Toxicity Considerations Specific to TOOKAD Treatment

All of the most common adverse events in the TOOKAD arm (those reported in ≥10% of patients) involved the genitourinary tract and are listed in Table 7. Additional commonly reported genitourinary toxicities are noted in Table 8 .

Table 8. Genitourinary Toxicities in PCM301

	TOOKAD N=197 N (%)		**Active Surveillance N=207 N (%)**	
	All Grade	**Grade 3-4**	**All Grade**	**Grade 3-4**
Erectile dysfunction	74 (38)	2 (1)	24 (12)	3 (1)
Hematuria	56 (28)	1 (0.5)	6 (3)	0 (0)
Dysuria	54 (27)	3 (1.5)	5 (2)	0 (0)
Urinary retention	32 (16)	2 (1)	2 (1)	1 (0.5)
Urinary incontinence	30 (15)	2 (1)	15 (7)	1 (0.5)
Perineal pain	30 (15)	1 (0.5)	1 (0.5)	0 (0)
Urinary tract infection	21 (11)	2 (1)	9 (4)	0 (0)
Micturition urgency	21 (11)	0 (0)	2 (1)	0 (0)
Pollakiuria	20 (10)	0 (0)	6 (3)	0 (0)
Ejaculation failure	16 (8)	2 (1)	1 (0.5)	0 (0)
Perineal injury	15 (8)	0 (0)	0 (0)	0 (0)
Hematospermia	12 (6)	0 (0)	5 (2)	0 (0)
Prostatitis	10 (5)	0 (0)	10 (5)	1 (0.5)
Orchitis	7 (4)	1 (0.5)	0 (0)	0 (0)
Urinary tract disorder	1 (0.5)	0 (0)	2 (1)	0 (0)

Unresolved Toxicities:

- TOOKAD arm, 46% (91/197) of patients had a higher incidence of unresolved toxicity at the end of the 2 year follow up period compared to 33% (68/207) of patients in the active surveillance arm.
- In the TOOKAD arm 34% (67/197) of patients had an unresolved genitourinary toxicity at the end of 2 years. The most common unresolved adverse events were erectile dysfunction, urinary incontinence, and ejaculation failure.
- In the active surveillance arm, 16% (33/207) of patients had ongoing GU toxicity at the end of 2 years and the most common unresolved toxicity was erectile dysfunction.

Sexual Dysfunction:

- Patients in the TOOKAD arm reported erectile dysfunction (ED) more frequently than patients in the active surveillance arm.
- In the TOOKAD arm, 38% reported an AE of ED compared to 12% in the active surveillance arm.
- In the TOOKAD arm, 23% of patients had unresolved ED vs. 10% in the active surveillance arm at the end of the 2 year follow up.
- Among the 74 patients reporting ED as an adverse event, 59% (44/74) of patients had a Grade 1 event, 43% (32/74) had a Grade 2 event, and 3% (2/74) had a Grade 3 event. Some patients had more than one reported AE of ED during the study period.
- Table 9 summarizes the grade definitions of erectile dysfunction as defined by CTCAE Version 4 criteria.

Table 9. Erectile Dysfunction Grades According to CTCAE Version 4

Grade 1	Grade 2	Grade 3
Decrease in erectile function (frequency or rigidity of erections) but intervention not indicated (e.g., medication or use of mechanical device, penile pump)	Decrease in erectile function (frequency/rigidity of erections), erectile intervention indicated (e.g., medication or mechanical devices such as penile pump)	Decrease in erectile function (frequency/rigidity of erections) but erectile intervention not helpful (e.g., medication or mechanical devices such as penile pump); placement of a permanent penile prosthesis indicated (not previously present)

Urinary Dysfunction:

- Urinary dysfunction, as evidenced by episodes of urinary incontinence, were noted to occur in 15% of patients receiving TOOKAD and in 7% of patients on active surveillance.
- Rates of unresolved toxicity at 2 years were similar in both arms (6% vs. 5%, respectively).

Patient Report Outcomes and Quality of Life Assessments

The Applicant collected patient reported outcomes (PRO) in PCM301 using three instruments: The International Prostate Symptom Score (IPSS) and International Index of Erectile Function – 15 Questions (IIEF-15) questionnaires, which were administered at baseline and every 3 months through Month 12 and at Month 24 (and at 7 days post-treatment for subjects administered TOOKAD. The EuroQol-5D (EQ-5D) questionnaire was administered at baseline, Month 12 and Month 24.

The IPSS is an 8-item questionnaire evaluating urinary symptoms. The questions relate to the following areas:

- Incomplete emptying
- Frequency
- Intermittence
- Urgency
- Weak stream
- Straining
- Nocturia
- Quality of Life

Trial participants responded to each of the first 7 questions using a scale from 0 (not at all) to 5 (almost always) and to the QoL question (Question 8) by choosing 1 of 7 terms ranging from "delighted" to "terrible." The score range is thus 0 to 35, and a lower score corresponds to an improvement in urinary symptoms.

The IIEF-15 is a 15-item questionnaire evaluating male sexual function that covers 5 domains:

- Erectile function (6 items)
- Orgasmic function (2 items)
- Sexual desire (2 items)
- Intercourse satisfaction (3 items)
- Overall satisfaction (2 items)

Trial participants choose from among 6 response options for each question. A decrease in IIEF score corresponds to a worsening in erectile function. The erectile function domain response categories are as follows:

- Score 1-10: Severe erectile dysfunction
- 11-16: Moderate dysfunction
- 17-21: Mild to moderate dysfunction
- 22-25: Mild dysfunction
- 26-30: No dysfunction

The EQ-5D is a 6-item questionnaire measuring QoL. Five questions relate to the following areas:

- Mobility
- Self-care
- Usual activities
- Pain/discomfort
- Anxiety/depression

The subject choose from among 3 response options for each question. A final question asked the subject to mark on a visual analogue scale (VAS) from 0 to 100 to indicate how good or bad his health was on the day.

Because the EQ-5D is a generic tool used for health technology assessment and was assessed at only two post-baseline timepoints (month 12 and month 24), the FDA analysis focused on the IPSS and IIEF results.

Completion rate of IIEF and IPSS:

IIEF was completed by 84.8% of patients randomized to TOOKAD and 85% of patients randomized to active surveillance at month 6. The completion rate for IIEF was 85.6% and 78% in TOOKAD and active surveillance, respectively, at month 12. At month 24, it was 80.4% and 72.4% in TOOKAD and active surveillance, respectively. The majority of patients in the active surveillance arm who did not complete IIEF at month 24 were those who received definitive therapy. Of the 64 patients randomized to active surveillance who received definitive therapy, 23 patients (35%) did not complete the IIEF at the next scheduled assessment post-definitive therapy. Of the 12 patients randomized to TOOKAD who received definitive therapy, 5 patients (42%) did not complete the IIEF at the next scheduled assessment post-definitive therapy. Therefore, it is likely that the reported PRO results from the active surveillance do not include the expected toxicities associated with definitive therapy from many applicable patients.

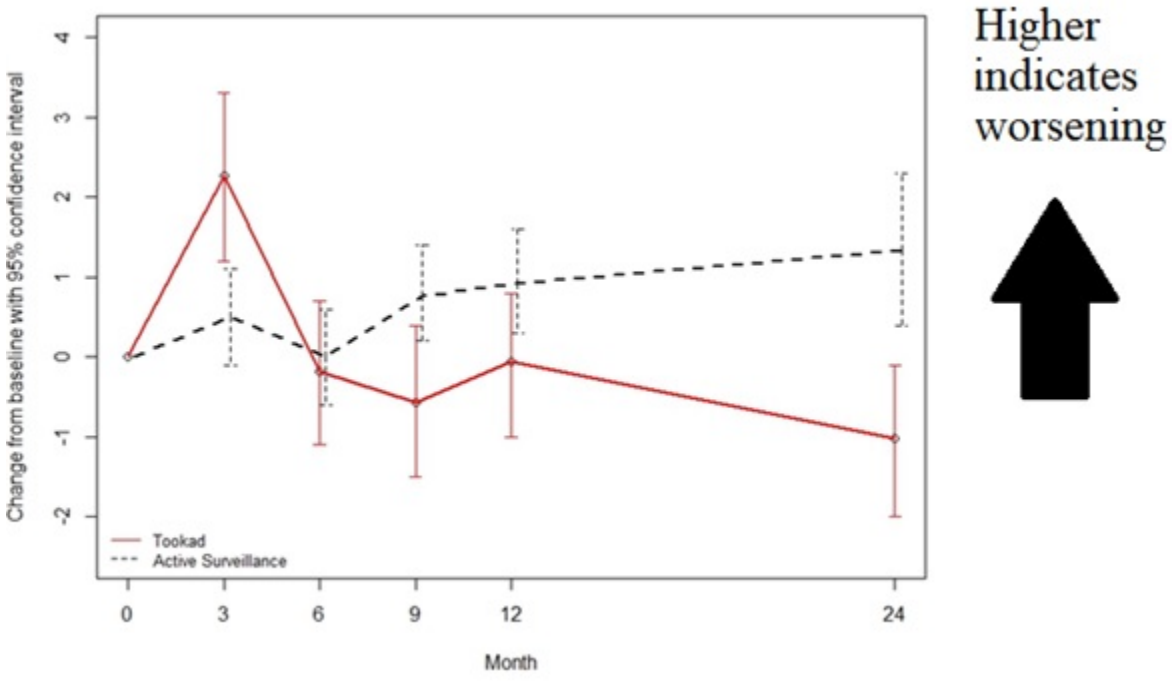
IPSS completion rates were similar to IIEF completion rates. The completion rate for IPSS was 92.4% and 91.7% at month 6 and 90.8% and 84.4% at month 12 in the TOOKAD and active surveillance arms, respectively. At month 24, the completion rate was 84.5% and 75.9% for TOOKAD and active surveillance, respectively.

IPSS results

At month 3, patients in the TOOKAD arm experienced more urinary symptoms as compared to patients in the active surveillance arm: 50% in the TOOKAD arm and 37.9% in the active surveillance arm experienced moderate or severe urinary symptoms. At month 6, the proportion of patients who had moderate or severe urinary symptoms was 40.1% and 32.3% in the TOOKAD and active surveillance arms, respectively.

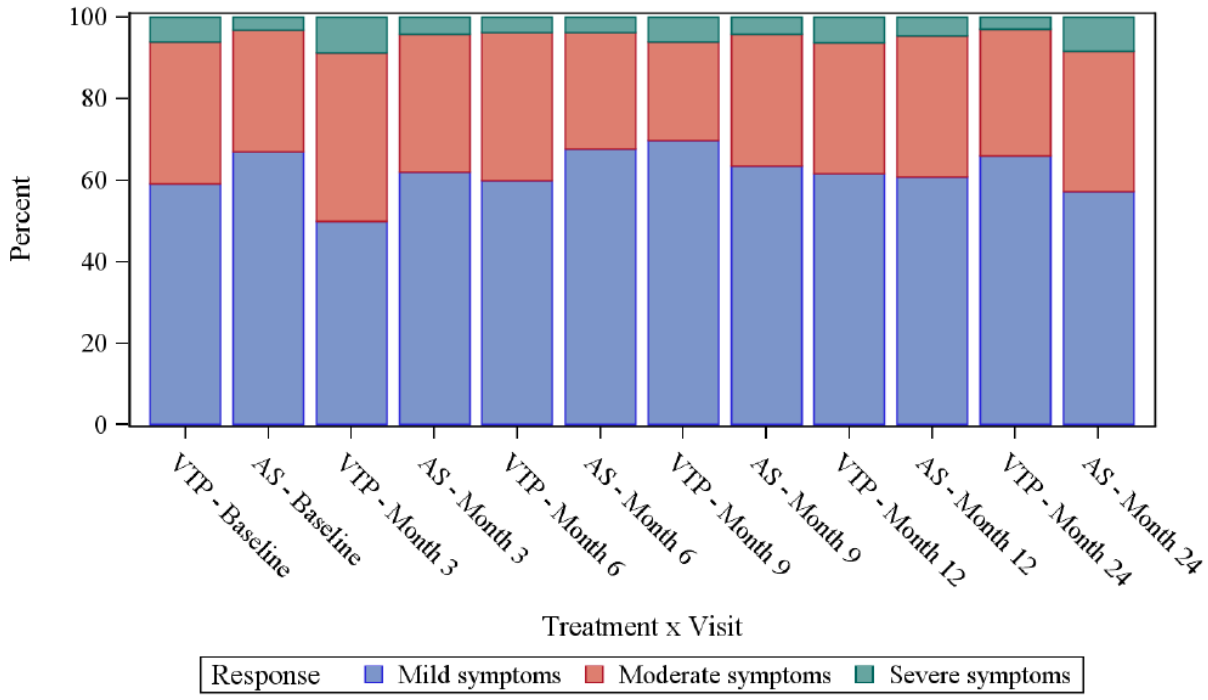
Patients in the active surveillance arm reported gradual worsening of urinary symptoms over time. At month 24, the proportion of patients in each arm with mild or severe urinary symptoms was 33.9% in the TOOKAD arm and 42.8% in the active surveillance arm. As described above, completion rates for the IPSS at month 24 were below 80% in the active surveillance arm, which limits interpretation at this time point.

Figure 3: IPSS Summary Score – Mean Change from Baseline



Source: FDA Analysis

Figure 4: IPSS Symptom Score Category by Arm



(VTP-TOOKAD arm, AS-active surveillance arm)
Source: Applicant response to FDA Information Request

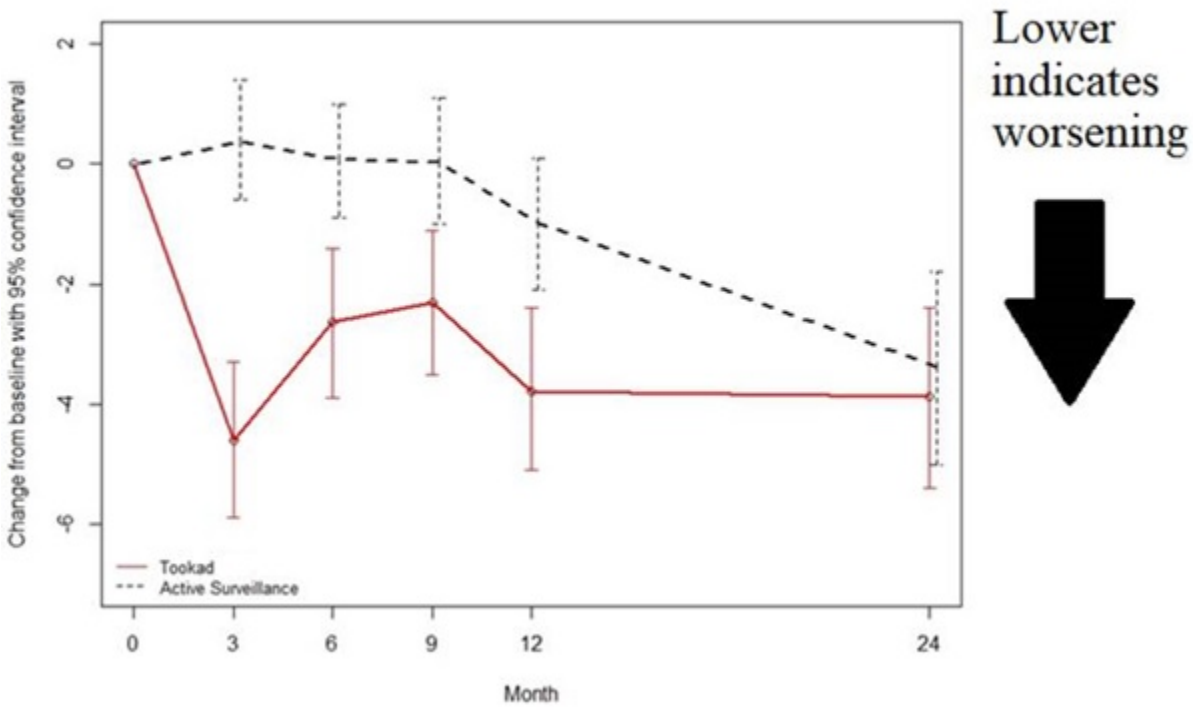
IIEF Results

At months 3 through 12, patients in the TOOKAD arm experienced a higher degree of erectile dysfunction compared to patients in the active surveillance arm. This decrement in erectile function does not appear to improve over time. At month 24, the degree of erectile dysfunction was similar between arms, presumably as more patients in the active surveillance arm received definitive therapy.

As noted above, there was a lower completion rate at month 24, particularly in active surveillance patients who received definitive therapy, which limits the interpretability at that time point. In general, the IIEF results corroborate the clinician observed higher incidence and severity of erectile dysfunction in the TOOKAD arm.

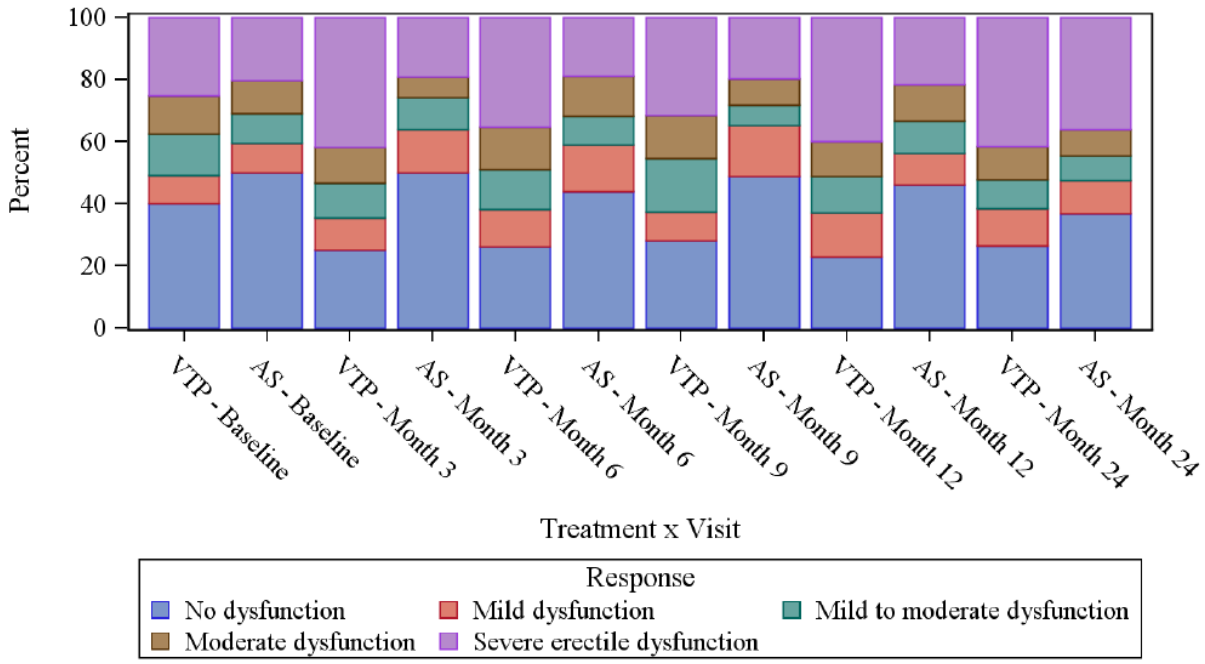
The other domains in the IIEF (orgasmic function, sexual desire, intercourse satisfaction, overall satisfaction) showed similar results as the erectile dysfunction domain for the TOOKAD arm.

Figure 5: IIEF Erectile Function Domain – Mean Change from Baseline



Source: FDA Analysis

Figure 6: IIEF Erectile Dysfunction Category by Arm



(VTP-TOOKAD arm, AS-active surveillance arm)
Source: Applicant response to FDA Information Request

Notably there was a difference in baseline erectile dysfunction. At baseline 40.1% of patients in the TOOKAD arm and 50% of patients in the active surveillance arm had no erectile dysfunction.

Limitations of Patient Reported Outcomes Data from PCM301:

- Missing patient reported data at month 24, particularly in active surveillance patients who received definitive therapy hinders the ability to make meaningful comparisons at that time point.
- More frequent collection of patient-reported outcomes between baseline and month 6 would provide a clearer post-TOOKAD side effect trajectory, particularly for urinary dysfunction.
- Although urinary obstructive symptoms, continence and sexual function are important symptoms of interest, the Applicant did not collect patient-reported pelvic pain, dysuria, bowel symptoms, or hematuria which are also important symptoms to assess in this patient population.
- PRO data from PCM301 is descriptive, as the trial was not designed to compare differences in patient-reported symptoms and side effects, nor were these patient-reported endpoints prospectively identified and statistically tested.

Based on the above limitations in the PRO data presented in PCM301, there is significant residual uncertainty regarding the difference in level of patient-reported symptomatic morbidity between TOOKAD compared with active surveillance.

6. Summary of Issues

Issue 1- Are the study endpoints and their results adequate to characterize benefit?

Co-primary endpoint (A) was the absence of definite cancer at 24 months, of which the clinical meaningfulness in early stage prostate cancer is unknown. The ability to use and interpret this endpoint is compromised by the limited sensitivity of the biopsies, the potential for false negatives and inaccurate pathologic grading, and missing data in the study.

Co-primary endpoint (B), is related to disease progression from a lower to a higher risk of disease. This endpoint has not been previously used as an endpoint for regulatory approval, partially based on lack of validated data supporting improvement in long-term outcomes due to treatment-related change in grade of cancer.

There is a theoretical concern obtaining a reliable biopsy due to scarring which would make obtaining after treatment with TOOKAD may amplify sampling error. In addition, there is a theoretical concern that scarring may affect the outcomes of a subsequent definitive therapy.

Time to definitive therapy was a secondary endpoint for PCM301. Results demonstrated an increased time to definitive therapy in the TOOKAD arm compared to the active surveillance arm, however this endpoint was not controlled for Type 1 error. In addition, many of the issues described above also affect the reliability of this endpoint's result. Approximately 50% of patients on both arms who progressed did not undergo subsequent definitive therapy. There were also patients who underwent definitive therapy despite having met no demonstrated criteria for disease progression highlighting the subjective nature of this endpoint.

Issue 2- Is the demonstrated toxicity profile for TOOKAD acceptable?

For a favorable toxicity profile for TOOKAD, the effectiveness and potential lack of improvement long-term outcome should be balanced an improved overall toxicity compared to the active surveillance arm. Patients on the control arm received definitive treatment at disease progression. All patients on the TOOKAD arm, however, were exposed to potential toxicities of the treatment.

Genitourinary toxicity was overall higher on the TOOKAD arm. Erectile dysfunction that did not resolve at the end of PCM301 was noted in 23% of patients on TOOKAD vs. in 10% of patients on active surveillance.

Toxicity assessment is affected by missing data both by adverse event reporting and by PROs, especially for patients who underwent definitive therapy. In the active surveillance arm no adverse event data was collected for 40 out of the 64 patients who underwent definitive therapy (19% of patients in active surveillance arm overall) compared with 5 out of 12

patients who underwent definitive therapy in the TOOKAD arm (2% of patients in TOOKAD arm overall).

There is limited data on definitive therapy in patients who progress after TOOKAD as there were only 12 such patients on PCM301, and there is limited surgical outcome literature available[6]. TOOKAD patients who underwent definitive therapy during PCM301 and subsequently recorded PROs (n = 7) appeared to report particularly poor erectile function.

It is not known if previous treatment with TOOKAD would adversely affect subsequent definitive therapy, for example from the ensuing local necrosis. Long-term data is lacking on the overall disease-specific safety of TOOKAD, including the theoretical possibility of a reduced long-term cure rate.

Issue 3- Do uncertainties around trial data allow for a reasonable overall assessment of risk/benefit?

Both primary endpoints of PCM301 rely on accuracy and reliability of biopsies. Given that many patients had missing data (13%) or false negative biopsies (13.5% on the active surveillance arm), potential for errors in pathologic grading due to sampling error, the reliability of results and the difference in magnitude of effect in the two arms is of concern. Sensitivity analyses cannot overcome most of the limitations of the co-primary endpoints and results the sensitivity analyses are based upon.

In terms of safety, toxicity data is missing in many patients after definitive therapy and appears to disproportionately affect the active surveillance arm and confounds the interpretation of trial results.

Issue 4- Is data from a separate trial necessary to adequately inform the benefit-risk profile?

With input from FDA, Steba designed trial PCM306, “An Evaluation of the Efficacy of Partial Gland Ablation (PGA) with TOOKAD Vascular Targeted Photodynamic Therapy (VTP) versus Active Surveillance for Men with Intermediate Risk Localized Prostate Cancer.” The primary endpoint will be the difference between arms in the rate of objective progression of cancer over 30 months, with a key secondary endpoint being the difference in the rate of conversion to definitive local or systemic therapy following objective progression of cancer over 30 and 72 months. Other key metrics evaluated will be the rate, severity, onset and duration of AEs and SAEs, and the patient-reported measures of incontinence, erectile dysfunction, bowel disease, urinary symptoms and prostate cancer specific anxiety collected with validated questionnaires (including after potential conversion to definitive local or systemic treatment). Additionally, the physician-evaluated feasibility, safety (complications within 90 days) and outcomes (biochemical response at 6 weeks and 24 months and clinical or biochemical recurrence) of definitive local or systemic treatment will be collected. There is a requirement for identification of the primary cause for conversion to definitive treatment by the physician, including cases not meeting pre-defined criteria for cancer progression.

Additional rigorously collected data may aid in better characterizing the benefit-risk profile of TOOKAD.

7. Issue for ODAC

ISSUE FOR THE COMMITEE: Do the results of PCM301 represent a favorable benefit/risk profile for TOOKAD in patients with low-risk early stage prostate cancer?

[1]Inoue LYT, Lin DW, Newcomb LF, et al. Comparative analysis of biopsy upgrading in four prostate cancer active surveillance cohorts. Ann Intern Med 2018; 168: 1

[2] Tosoian JJ, Carter HB, Lepore A, Loeb S, Active surveillance for prostate cancer: current evidence and contemporary state of practice. Nature Reviews Urology volume 13, pages 205–215(2016)

[3]Weinstock C, Suzman D, Kluetz P, et al. Development of Treatments for Localized Prostate Cancer in Patients Eligible for Active Surveillance: U.S. Food and Drug Administration Oncology Center of Excellence Public Workshop. J Urol. 2020 Jan;203(1):115-119

[4] Mottet N, van den Bergh RCN, Briers E, et al. EAU Guidelines: Prostate Cancer 2015

[5] American Urological Association Clinically Localized Prostate Cancer: 2007 Update)

[6] Pierrard V, Lebdai S, Kleinclauss F, et al. Radical Prostatectomy after Vascular Targeted Photodynamic Therapy with Padeliporfin: Feasibility, and Early and Intermediate Results. J Urol. 2019;201(2):315-21.