TOOKAD® VASCULAR-TARGETED PHOTODYNAMIC THERAPY

SPONSOR BRIEFING DOCUMENT

ONCOLOGIC DRUGS ADVISORY COMMITTEE

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LIST OF ABBREVIATIONS

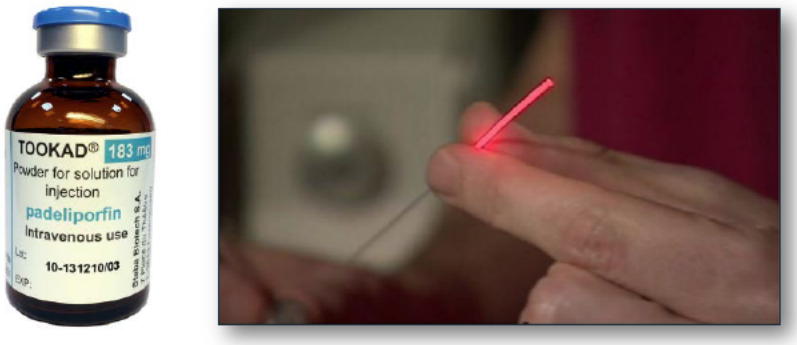
Abbreviation	Definition
AE	Adverse Event
CI	Confidence Interval
cT3	Clinical T3
EBRT	External beam radiation therapy
FDA	Food and Drug Administration
HIFU	High intensity focused ultrasound
HR	Hazard ratio
IIEF	International Index of Erectile Function
IPSS	International Prostate Symptoms Score
ITT	Intent-to-treat
IV	Intravenous
LDI	Light density index
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
mp-MRI	Multiparametric magnetic resonance imaging
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCE	New chemical entity
NDA	New Drug Application
ORP	Outcomes Review Panel
PP	Per-protocol
PSA	Prostate-specific antigen
RNS	Reactive nitrogen species
SAE	Serious adverse event
SOC	System organ class
TNM	Tumor, nodes, metastasis
TRUS	Transrectal ultrasound
US	United States
VTP	Vascular-Targeted Photodynamic Therapy

1 EXECUTIVE SUMMARY

1.1 Introduction

Steba Biotech SA (Steba) has developed TOOKAD® Vascular-Targeted Photodynamic Therapy (VTP), a novel, minimally invasive treatment option for patients with early stage prostate cancer that is more effective than active surveillance and less morbid than radical therapy. TOOKAD VTP is a partial gland ablation treatment targeting half of the prostate (ie, hemiablation) that eliminates the cancer and avoids the side effects of overtreatment with radical therapy while preserving surrounding normal tissue and, thereby, quality of life for many patients. TOOKAD VTP is a drug-device combination product composed of a photosensitizing drug and a light delivery system (Figure 1). The drug is administered intravenously and remains inactive until the cancerous area of the prostate is illuminated with low-energy, non-thermal, laser light channeled through optical fibers. After photoactivation, TOOKAD rapidly induces local vasoconstriction and occlusion of vessels, resulting in coagulative necrosis of the targeted lobe of the prostate gland.

Figure 1: TOOKAD Photosensitizing Drug and Light Delivery System



TOOKAD VTP has been studied in 429 patients with prostate cancer across five Phase 2 and 3 studies. The primary efficacy and safety data are derived from Study PCM 301 (Study 301), the pivotal Phase 3 study that compared TOOKAD VTP to active surveillance in men with early stage prostate cancer over a 2-year follow-up period. In addition, long-term follow-up is ongoing in Study PCM 301-FU5 (Study 301-FU5), with a total follow-up time of 7 years from randomization. Interim results are available through 5 years. Notably, Study 301 provides the first reported level 1 evidence of safety and efficacy of partial gland ablation for localized prostate cancer.

The design of the pivotal study closely aligns with recommendations made at the July 2018 Food and Drug Administration (FDA) Oncology Center of Excellence Public Workshop held to discuss trial design and endpoints for registration studies in patients with localized prostate cancer (Weinstock et al 2019). During the workshop, there was general agreement that a trial designed with a primary endpoint of local progression and a secondary endpoint of delay or avoidance of radical therapy—combined with a post-marketing requirement demonstrating no

delayed harm—could be acceptable in place of the traditional survival measures, which are not practical in this disease setting.

Steba is seeking accelerated approval of TOOKAD VTP based upon the following:

- The surrogate endpoint of local disease progression in Study 301 served as an objective measure of efficacy and was further supported by the secondary endpoint of time to radical therapy.
- Delay or avoidance of radical therapy can reasonably predict a reduction in the morbidities commonly associated with radical therapy, which is a clear clinical benefit.
- A confirmatory study (Study PCM 306 [Study 306]) is being conducted to measure delay of harm, fulfilling the requirements of accelerated approval.

In the pivotal study, TOOKAD VTP demonstrated clinically meaningful and statistically significant reductions in local disease progression and conversion to radical therapy compared to active surveillance. The safety profile of TOOKAD VTP was primarily composed of mild, transient events and did not preclude future treatment options. Follow-up data 5 years after randomization have not identified any new safety signals and indicate durability of the clinical benefit.

As will be described, hemiablation with TOOKAD VTP can provide an important, safe, and effective treatment that fills a therapeutic gap between the diametrically opposed options currently recommended to men diagnosed with early stage localized prostate cancer, namely conservative management with active surveillance or whole gland treatment with radical therapies.

1.2 Background and Unmet Need

Prostate cancer is the most commonly diagnosed internal cancer in men in the United States (US). It is estimated that over 190,000 new cases will be diagnosed in the US in 2020 (Siegel et al 2020). The high diagnosis rates are due in part to the use of prostate-specific antigen (PSA) testing, which has enabled detection at earlier stages of prostate cancer, resulting in a reduction in mortality rates. Biopsy methods have also evolved from simple transrectal ultrasound-guided, systematic biopsies to multiparametric magnetic resonance imaging (mp-MRI) guided targeted biopsies of MRI visible lesions (Litwin and Tan 2017).

Although it is estimated that more than 33,000 men will die from prostate cancer in 2020 in the US (Siegel et al 2020), survival is very high for patients with localized prostate cancer. The overall 5-year survival rate for patients with prostate cancer is approximately 98%. Localized prostate cancers, especially those detected at an early stage, grow slowly and progression to metastases within 10 years is uncommon. Thus, for patients with localized prostate cancer, radical therapy, such as radical prostatectomy or radiation therapy, may be an overtreatment that offers no survival benefit. Nevertheless, many patients select immediate radical therapy over active surveillance and are subjected to the high morbidity, such as genitourinary-related adverse effects, that are associated with this treatment option. In addition, a large proportion of patients

who initially elect to active surveillance eventually convert to radical therapy (Hamdy et al 2016). This has led to a need for treatment options with reduced morbidity.

This need for alternative treatment options was recognized by the FDA and the urologic community in the 2018 public workshop. Due to the high survival rates, it was agreed that overall survival, cancer-specific survival, and metastasis-free survival are not practical endpoints for clinical trials in patients with prostate cancer due to the high survival rates. Therefore, other criteria, such as preventing disease progression, reducing morbidity of therapy, and preserving genitourinary and bowel functions, should be considered when assessing treatment options (Weinstock et al 2019). Importantly, it was noted that it is not the delay or prevention of a curative therapy itself that is the benefit for patients–it is the delay in the morbidity associated with radical treatment.

1.2.1 Prostate Cancer Staging and Management

Approximately 80% of newly diagnosed cases of prostate cancer are clinically localized (Siegel et al 2020). The National Comprehensive Cancer Network (NCCN) has developed risk groups, which are regularly updated, to help determine the best treatment for each patient. The NCCN guidelines stratify prostate cancer patients into the following prognostic risk groups based on tumor stage, Grade Group (which correlates with Gleason score), PSA levels, and tumor burden: very low and low risk, favorable and unfavorable intermediate risk, and high and very high risk (Table 1).

Table 1: NCCN Prostate Cancer Staging Guidelines

Risk Groups	Criteria		
Very low risk	• T1c AND • Grade Group 1 • PSA < 10 ng/mL AND • Fewer than 3 prostate biopsy fragments/cores positive, ≤ 50% in each fragment/core AND • PSA density < 0.15 ng/mL/g.		
Low Risk	• T1–T2a AND • Grade Group 1 AND • PSA < 10 ng/mL		
Intermediate Risk	Has no high-or very-high risk features and has one or more intermediate risk factors (IRF): • T2b-T2c, • Grade Group 2 or 3 • PSA 10–20 ng/mL	Favorable intermediate risk	• 1 IRF and • Grade Group 1 or 2 and • < 50% positive biopsy fragment/cores*
		Unfavorable intermediate risk	• 2 or 3 IRF and/or • Grade Group 3 and/or • ≥ 50% biopsy fragment/cores positive*
High risk	• T3a OR • Grade Group 4 or Grade Group 5 OR • PSA > 20 ng/mL		
Very high	• T3b–T4 OR • Primary pattern 5 OR • > 4 cores with Group Grade 4 or Grade Group 5		

DRE = digital rectal exam; IRF = intermediate risk factors; MRI = magnetic resonance imaging; PSA = prostate-specific antigen

* An ultrasound- or MRI- or DRE-targeted lesion that is biopsied more than once and demonstrates cancer (regardless of percentage core involvement or number of cores involved) counts as a single positive core.

A paradigm shift has recently occurred with the inclusion of tumor imaging into the prognostic evaluation of localized prostate cancer (Figure 2). Until recently, prostate cancer was the only solid tumor that was not imaged as part of staging. Two landmark studies, PROMIS and PRECISION, have shown that the majority of patients diagnosed with Grade Group 1 based on a transrectal ultrasound (TRUS) biopsy are upgraded to Grade Group 2 based on a transperineal or mp-MRI guided biopsy (Ahmed et al 2017; Kasivisvanathan et al 2018). Specifically, in PROMIS, approximately 70% of men who had Grade Group 1 disease on TRUS were assigned to Grade Group 2 disease when the more accurate mp-MRI biopsy technique was used. Many men previously diagnosed with low risk localized prostate cancer have, in fact, had higher grade disease but were not labeled as such due to the limitations of TRUS biopsy.

Figure 2: Comparison of Prostate Cancers Staging by Biopsy Method

fav = favorable; MRI = magnetic resonance imaging; TRUS = transrectal ultrasound

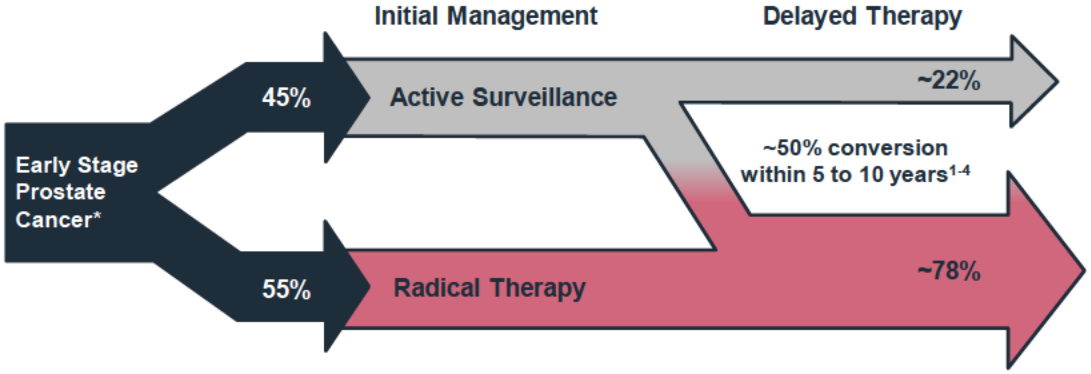
In this context, the NCCN and American Urological Association/American Society for Radiation Oncology/Society of Urologic Oncology guidelines have been amended recently to recommend active surveillance not only for very low and low risk patients, but also those diagnosed with favorable intermediate risk cancer.

For patients with very low, low, and favorable intermediate risk, the NCCN guidelines recommend either active surveillance or radical therapy (eg, radical prostatectomy, external beam radiation therapy [EBRT], brachytherapy) as an initial treatment for men with a sufficiently long life expectancy. Approximately 45% of patients with very low, low, and intermediate risk prostate cancer choose active surveillance as their initial treatment and 55% undergo immediate radical therapy (Godtman et al 2016; Womble et al 2015). These management strategies are vastly different and must be carefully selected by patients and physicians.

Active surveillance avoids treatment-related side effects and preserves genitourinary and bowel functions. However, it also has disadvantages. Active surveillance requires careful monitoring that typically includes a PSA test every 6 months, a digital rectal exam at least annually, a prostate MRI every 1 to 3 years, and a planned prostate biopsy every 2 to 5 years (Matulewicz et al 2017). One risk of active surveillance is disease progression. Local progression could trigger more intensive or multi-modal treatment, while metastasis leads to an incurable condition. In addition, many patients suffer from the anxiety of knowing that their cancer could progress. Eventually, approximately 50% of patients convert to radical therapy within 5 to 10 years with or

without objective disease progression (Figure 3) (Hamdy et al 2016; Tosoian et al 2015). Therefore, while active surveillance does preserve important functions, it is not the ultimate solution for most men.

Figure 3: Patient Conversion from Active Surveillance to Radical Therapy



*Very low, low, and favorable intermediate risk cancers
1. Klotz et al 2015; 2. Neal et al 2019; 3. Hamdy et al 2016; 4. Tosoian et al 2015

Radical therapies (ie, whole gland treatment techniques) offer control over disease progression, but can significantly impact quality of life. There are risks of damage to the urinary sphincter responsible for urinary continence, the neurovascular bundles responsible for erectile function, and the rectum, which can lead to troublesome effects on urinary, sexual, and bowel function. For many patients, these functions worsen immediately after radical therapy and do not return to baseline levels (Resnick et al 2013). As reported in the ProtecT study, a large randomized trial which prospectively collected patient reported incontinence and erectile dysfunction rates after radiotherapy and radical prostatectomy, the rates of urinary incontinence and erectile dysfunction ranged from 4–20% and 66–82%, respectively (Donovan et al 2016).

Despite these risks, more than half of the patients with low or very low risk disease choose a radical therapy over active surveillance as their initial treatment (Mahal et al 2019). Furthermore, even after surgery or radiation therapy, approximately 20% of patients experience biochemical recurrence and require salvage treatment (ie, either radical prostatectomy, additional radiotherapy, or androgen deprivation therapy) within 5 years (Merino et al 2013), which can lead to further complications and may be less effective than the initial therapy.

In summary, men with early stage prostate cancer have 2 diametrically opposed recommended treatment options: monitoring the cancer with active surveillance or treating immediately with radical prostatectomy or radiotherapy. Thus, there is an unmet need for treatment options that fill the gap between active surveillance and radical therapy. In an effort to fill this need, focal therapies such as high-intensity focused ultrasound (HIFU) and cryoablation are performed by some practitioners, yet these methods are not supported by level 1 evidence (ie, high quality randomized, controlled clinical trials), not approved for the treatment of prostate cancer, nor recommended in treatment guidelines for prostate cancer (Sanda et al 2017). Patients need a

well-studied option that can control the cancer and safely delay the need for initiation of radical therapy along with its attendant short and long-term morbidity.

1.3 Product Description and Proposed Indication

TOOKAD VTP provides an alternative, localized treatment option for men with early prostate cancer. Hemiablation of the prostate gland with TOOKAD VTP is mediated by intravenous administration of inactive TOOKAD, a new chemical entity (NCE) in the bacteriochlorophyll photosensitizers family. TOOKAD is maintained in the vasculature and has a relatively short half-life (approximately 70 min). It is activated within the lobe of the prostate targeted for treatment with low-energy, non-thermal, laser light illumination from optical fibers positioned percutaneously.

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

- Stage T1–T2a, and
- PSA ≤ 10 ng/mL, and
- 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.

The proposed indication encompasses patients for whom NCCN guidelines recommend active surveillance, namely very low or low risk prostate cancer diagnosed with any biopsy technique and favorable intermediate risk prostate cancer patients diagnosed with mp-MRI targeted biopsy.

A Limitation of Use is also being proposed that TOOKAD is not recommended for use in patients with a life expectancy of less than 10 years, where the clinical guidelines recommend observation alone, because the therapeutic benefits may not outweigh the risks in that patient population. Additional information supporting the proposed indication is provided in Section 3.1.1.

1.3.1 TOOKAD VTP Procedure

Hemiablation with TOOKAD VTP is an outpatient procedure that is similar to other common urologic procedures such as transperineal biopsy and brachytherapy. The procedure takes approximately 2 hours to complete and is performed by a urologic surgeon who has completed TOOKAD VTP training (see Section 3.2.4). The procedure can be repeated in the same or contralateral lobe if needed. The standardized procedure includes the following steps:

1. The patient is placed in the lithotomy position under anesthesia.
2. The tumor-bearing lobe of the prostate is identified and optical fibers are placed guided with the assistance of TOOGUIDE TRUS® software.
3. Light diffusing optical fibers are connected to a low-energy, non-thermal laser light generator and calibrated.

4. Calibrated optical fibers are inserted into the recommended positions in the prostate using a template. Placement of the fibers is verified using ultrasound and a light-detecting probe placed in the rectum of the patient.
5. At a dose of 4 mg/kg, TOOKAD is administered intravenously for 10 min. The drug circulates in the vascular system but remains inactive.
6. Near-infrared illumination (753 nm with a fixed power of 150 mW/cm) is delivered through the optical diffusers for 22 minutes and 15 seconds. This activates the drug locally and triggers a cascade of events leading to vascular occlusion and coagulative necrosis resulting in hemiablation of the targeted lobe of the prostate.
7. The optical fibers are removed and the patient is transferred to a dimly lit room for at least 6 hours as they recover from anesthesia.

Additional details are provided in Section 3.2.2.

1.3.2 Mechanism of Action

Localized treatment is achieved by activating TOOKAD with non-thermal laser light. The activated TOOKAD transfers electrons to blood-born oxygen molecules creating oxygen radicals and causing hypoxia that leads to cogeneration of nitric oxide (NO) radicals and endothelin-1 causing vascular occlusion. This is followed by self-propagating tumor cell necrosis, which results in tumor and whole lobe ablation within a few hours after illumination. The combination of a spatially precise illumination and the tissue biology controls the ablation, leading to discrete and highly confined volumes of treated tissue.

1.4 Clinical Development Program

The clinical development program for TOOKAD VTP supporting the New Drug Application (NDA) consists of 5 clinical studies, including a supportive single-arm study and a pivotal Phase 3 study. Overall, 652 patients were enrolled in these studies, and 429 patients were treated with TOOKAD VTP.

The primary efficacy and safety data are derived from the pivotal study, Study 301. This study accrued patients from 2011 to 2013 and was designed using standards of care at the time, which included systematic TRUS biopsy results for both enrollment and endpoint evaluation.

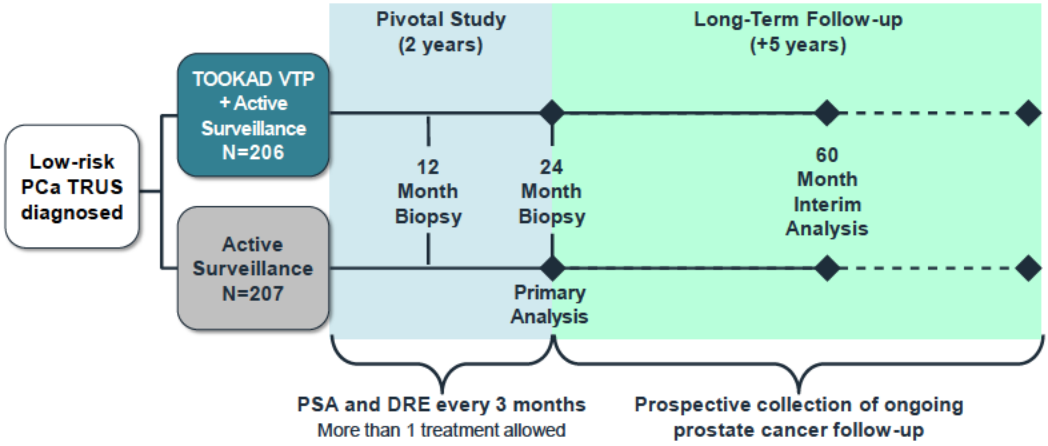
1.5 Efficacy Findings

1.5.1 Study Design

The pivotal study, Study 301, was a multicenter, Phase 3, randomized, open-label trial that compared treatment with TOOKAD VTP to active surveillance in men with low-risk, localized prostate cancer confirmed by TRUS-guided biopsy. A total of 413 patients were enrolled from 47 sites in Europe and randomized 1:1 to either treatment arm. Patients in the TOOKAD VTP arm received a 10-minute intravenous (IV) infusion of 4 mg/kg TOOKAD followed by non-thermal laser light (753 nm, 150 mW/cm) for 22 minutes and 15 seconds. For patients in the TOOKAD arm, more than 1 treatment was allowed within the 24-month period.

A TRUS-guided biopsy was performed at Month 12 and Month 24. Every 3 months, PSA was measured and a digital rectal exam was performed (Figure 4). After the 24-month follow-up period, patients were eligible to enter a long-term follow-up program (Study 301-FU5) in which outcomes are being recorded for an additional 5 years, for a total of 7 years of follow-up. At the time of the NDA submission, all patients had been followed for 5 years or more post-randomization; an interim analysis was performed with these follow-up data (see Section 5.4).

Figure 4: Design of Pivotal Study 301 and Study 301-FU5



DRE = digital rectal exam; PCa = prostate cancer; PSA = prostate-specific antigen; TRUS = transrectal ultrasound; VTP = vascular-targeted photodynamic therapy

Study 301 had 2 co-primary endpoints evaluated at 24 months: the rate of local disease progression and the rate of absence of cancer, as defined in Table 2. A central reading of biopsies was performed by an independent, blinded pathologist to ensure consistency of results. No treatment decisions were made based upon the central reading results; all treatment decisions were based on the local pathologist's report.

The Outcomes Review Panel (ORP), an independent and blinded panel (composed of a urologist, a pathologist with demonstrated expertise in prostate cancer, and a statistician) reviewed efficacy data to assess the 2 primary endpoints.

Table 2: Co-Primary Endpoints in Study 301

Co-Primary Endpoints	Definition
Disease progression	Progression of cancer from low to moderate or higher risk over the course of the study and at least 1 of the following events: • Any Gleason primary or secondary pattern of 4 or more, • more than 3 cores definitively positive for cancer when considering all histological results available, • At least 1 cancer core length greater than 5 mm, • PSA > 10 ng/mL in 3 consecutive measures, • Any T3 prostate cancer, • Metastasis, or • Prostate cancer-related death
Rate of absence of cancer	Absence of any histology result definitively positive for cancer at 24 months (ie, a negative biopsy)

PSA = prostate-specific antigen

Secondary efficacy endpoints included the proportion of patients who received radical therapy and the proportion of patients with a severe prostate cancer-related event such as cancer extension to T3, metastasis, or prostate cancer-related death. Secondary safety endpoints that included quality of life questionnaires on urinary and erectile function (International Prostate Symptoms Score [IPSS] and International Index of Erectile Function [IIEF]) were also used for descriptive purposes. Additional endpoints are discussed in Section 5.3.1.3.

1.5.2 Patient Population

A total of 413 patients were randomized in Study 301: 206 to TOOKAD VTP and 207 to active surveillance. Of these, 87% completed the study through the 24-month follow-up period. Patient demographics were balanced across treatment arms. The mean age was 63 years with the majority of patients aged 75 or younger. Study 301 was conducted in Europe, and the vast majority of patients were Caucasian.

The baseline disease characteristics were representative of the target population. The mean time since diagnosis was approximately 6 months and the estimated prostate volume was 43 cm^3. Clinical characteristics were similar across arms. Mean PSA at baseline was 6 ng/mL with an average of 14 cores observed in each treatment group. On average, there were approximately 2 positive cores with a mean cancer core length of 4 mm. All patients had a TRUS biopsy defined Gleason score of 3 + 3 or less, and 78% of patients had unilateral cancer.

1.5.3 Results

Results from the primary and secondary endpoints demonstrate that TOOKAD VTP is an effective treatment that destroys the targeted cancer.

Co-Primary Endpoints

Both co-primary endpoints were met, with a p-value less than 0.001 for each endpoint (Table 3). The hazard ratio (HR) for the freedom from local disease progression at 24 months was 0.34 (crude HR 95% confidence interval [CI]: 0.25–0.47). Thus, TOOKAD VTP therapy resulted in a 66% reduction in risk of progression compared to active surveillance.

Similarly, at 24 months, patients in the TOOKAD VTP arm were 3.6 times more likely to not have a definitively positive biopsy than patients in the active surveillance arm.

Table 3: Co-Primary Endpoint Results – Study 301 ITT Population

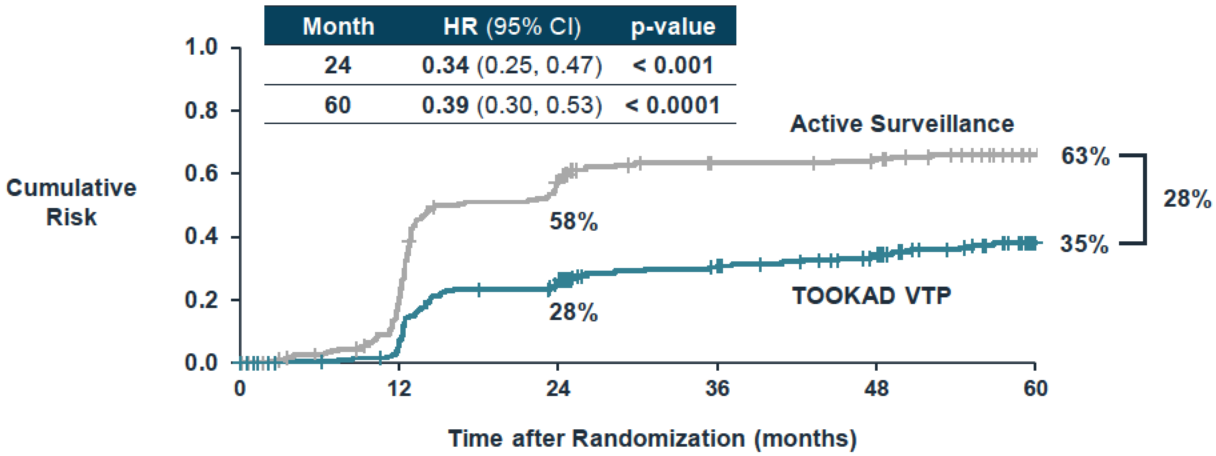
Co-Primary Endpoint	TOOKAD VTP N=206 n (%)	Active Surveillance N=207 n (%)	Estimate (95% CI)	p-value
Freedom from local disease progression	58 (28.2)	121 (58.5)	HR = 0.34 (0.25–0.47)	< 0.001
Absence of prostate cancer*	101 (49.0)	28 (13.5)	RR = 3.62 (2.50–5.26)	< 0.001

CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; RR = relative risk; VTP = vascular-targeted photodynamic therapy
*Anywhere in the prostate

For the primary analysis of local disease progression by treatment arm, significant separation was observed 12 months post-treatment and was maintained through 24 months (Figure 5). At 24 months, approximately twice as many patients in the active surveillance arm as in the TOOKAD VTP arm progressed (28% of patients in the TOOKAD VTP arm vs 58% in the active surveillance arm). The most common criterion for progression was presence of any Gleason pattern 4 or above.

Interim results from Study 301-FU5 showed significantly longer time to progression in the TOOKAD VTP arm compared to active surveillance over the 5-year period from randomization. In the TOOKAD VTP arm, the median time had not yet been reached, while in the active surveillance arm the median time to progression was 14.7 months. The observed difference between the TOOKAD VTP and active surveillance arms was clinically and statistically significant, as shown by the absolute risk reduction of 28% by Month 60.

Figure 5: Time to Progression – Kaplan-Meier Curve –Studies 301 and 301-FU5 ITT Population



Patients at risk						
TOOKAD VTP	206	184	143	119	104	67
Active Surveillance	207	157	81	58	54	31

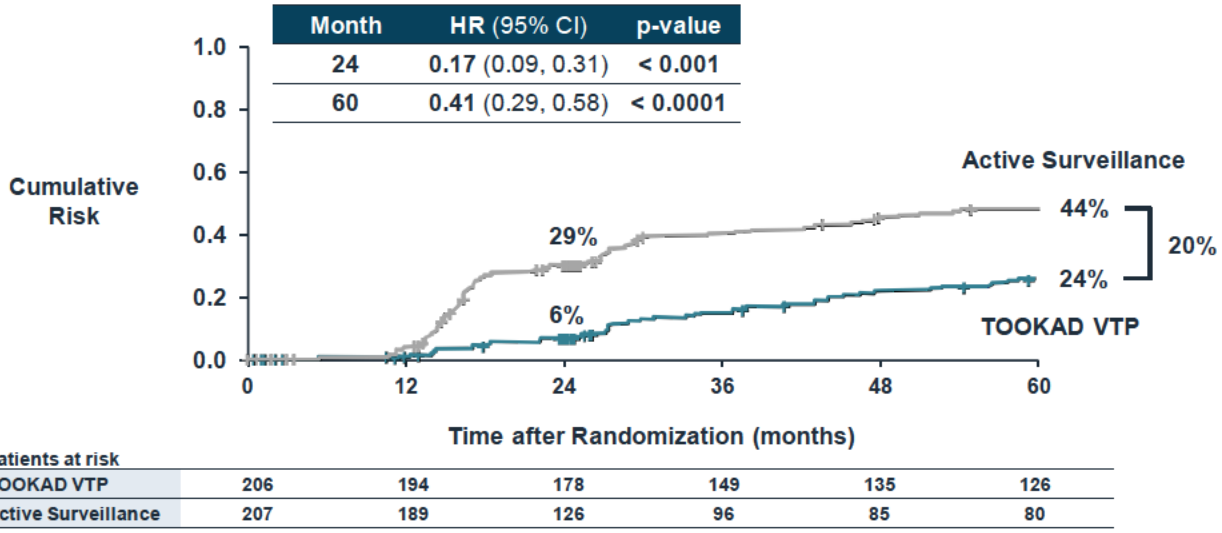
CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; VTP = vascular-targeted photodynamic therapy
Note 1: Unadjusted HR presented using Cox proportional hazards model with treatment as fixed effect.
Note 2: The interim analysis for Study 301-FU5 was conducted in October 2018, after the last randomized patient had reached 5 years of total follow-up time since randomization.

Time to Radical Therapy

In Study 301, at 24 months, TOOKAD VTP significantly reduced the rate of conversion to radical therapy compared with active surveillance with an absolute difference of 23% (6% vs 29%; $p < 0.001$). At each follow-up time point, statistically fewer patients underwent radical therapy in the TOOKAD VTP arm than in the active surveillance arm. Given the known side effects related to genitourinary functions associated with radical therapy, this reduction in the proportion of patients who required radical therapy strongly supports the clinically meaningful benefit of TOOKAD VTP.

Interim data from the long-term follow-up study show that this clinical benefit is maintained through 60 months. TOOKAD consistently reduced the number of patients converting to radical therapy by 20% (Figure 6).

Figure 6: Time to Initiation of Radical Therapy by Treatment Group – Kaplan-Meier Curves—Study 301-FU5 ITT Population



Patients at risk						
TOOKAD VTP	206	194	178	149	135	126
Active Surveillance	207	189	126	96	85	80

CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; VTP = vascular-targeted photodynamic therapy
Note 1: Unadjusted HR presented using Cox proportional hazards model with treatment as fixed effect.
Note 2: The interim analysis for Study 301-FU5 was conducted in October 2018, after the last randomized patient had reached 5 years of total follow-up time since randomization.

Given that Study 301 was not blinded, data were analyzed to determine if the decision to receive radical therapy was different between treatment arms. At 60 months, a similar proportion of patients in both treatment groups converted to radical therapy after detection of disease progression based on the local biopsy read (67% and 66%). Furthermore, among patients who received radical therapy, there was a similar proportion of patients who had a prior disease progression in both treatment groups (80% and 83%).

The primary endpoint results are also supported by the sensitivity analysis that censored patients who converted to radical therapy but did not have disease progression. The results were consistent with the intent-to-treat (ITT) population results for conversion to radical therapy (Month 60 HR: 0.41 [0.28, 0.60]; $p < 0.0001$).

Severe Prostate Cancer-Related Events

Fewer severe prostate cancer-related events, defined as progression to T3, metastasis, or death due to prostate cancer, were reported in the TOOKAD VTP arm than in the active surveillance arm. As expected in this patient population, there was no prostate cancer-related death in either arm through Month 60.

By 24 months, one patient in the TOOKAD VTP arm and 11 in the active surveillance arm reported T3 disease and one patient in each arm had metastasis. At Month 60, T3 disease was found in 5 patients in the TOOKAD VTP arm and 14 patients in the active surveillance arm and metastasis was diagnosed in 2 patients in each arm. This assessment did not differentiate between clinical T3 (cT3) disease versus T3 status being determined based on a radical

prostatectomy specimen or clinically observed metastasis (for example, diagnosed following a bone scan) versus a positive node found during radical prostatectomy.

A post hoc analysis was conducted to determine the rate of cT3 disease versus any T3 disease, as well the rate of clinically observed metastasis versus metastasis found during radical prostatectomy. ORP assessment were used when available; local read results were used after 24 months as there was no ORP assessment. Patients whose T3 disease or metastasis was associated with radical prostatectomy were excluded from the sum. Through Month 24, no TOOKAD VTP treated patients had either cT3 disease or clinical diagnosis of metastasis. Four patients in the active surveillance arm had cT3 disease and none had clinically diagnosed metastasis. At Month 60 cT3 disease had been found in 3 TOOKAD VTP treated patients and 7 active surveillance patients. Clinical metastasis was diagnosed in one subject in each treatment arm.

1.6 Safety Findings

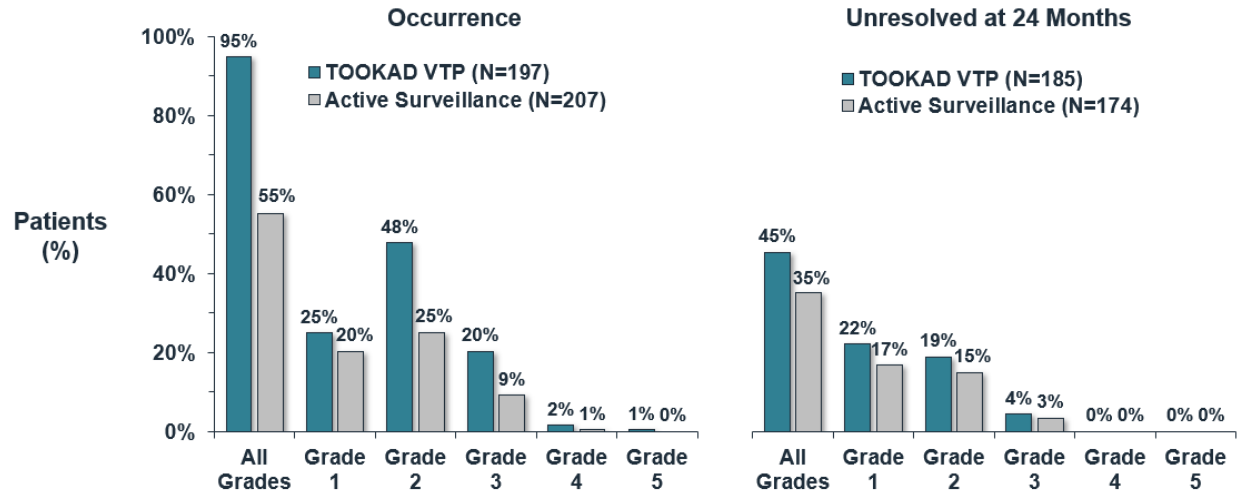
The Safety Population from Study 301 provides the primary safety data supporting the proposed indication. The Safety Population includes 197 patients randomized to TOOKAD VTP who were administered any amount of TOOKAD or initiated any study treatment-related procedure and 207 patients randomized to active surveillance. Nine patients randomized to TOOKAD VTP did not receive TOOKAD and are not included in the Safety Population. An additional patient had an anaphylactic reaction to VTP procedure anesthesia and did not receive any amount of TOOKAD. This patient is included in the safety populations, but not included among patients who received TOOKAD. As described below, most adverse events (AEs) were mild, transient events and did not preclude future treatment options.

1.6.1 Overview of Adverse Events

Overall, 95% of patients in the TOOKAD VTP arm reported at least 1 AE compared to 55% in the active surveillance arm. The most frequently reported AEs (comprising Grade 1, 2 and 3) in the TOOKAD VTP arm were erectile dysfunction (38%), hematuria (28%), and dysuria (27%). No events of significant extra-prostatic necrosis with possible recto-urethral fistula formation occurred.

The majority of AEs reported in both arms were Grade 1 or 2, and the majority of AEs had resolved without sequelae at 24 months (Figure 7). Approximately twice as many patients in the TOOKAD VTP arm as in the active surveillance arm experienced AEs of Grades 3 or 4.

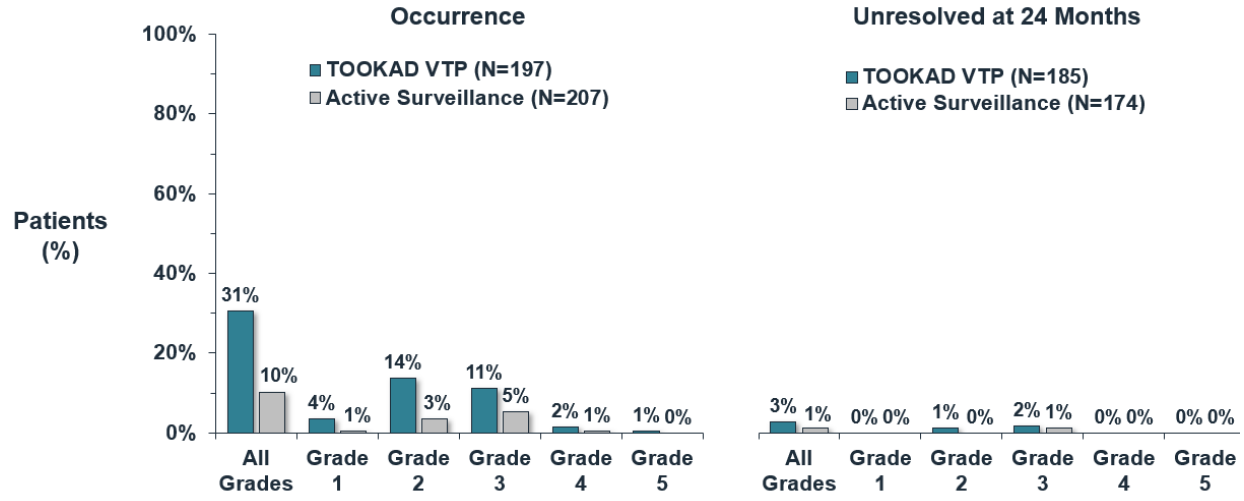
Figure 7: Adverse Events by Severity – Study 301 Safety Population



VTP = vascular-targeted photodynamic therapy

Serious AEs (SAEs) occurred in more patients who received TOOKAD VTP than those who received active surveillance. Most SAEs resolved within 1 month, and nearly all resolved within 24 months (Figure 8). One death (myocardial infarction) was reported in the TOOKAD VTP arm but was unrelated to treatment.

Figure 8: Serious Adverse Events by Severity and Resolution – Study 301 Safety Population



VTP = vascular-targeted photodynamic therapy

The most frequently reported SAE in the TOOKAD VTP arm was temporary urinary retention, which occurred in 16 patients (8%) (Table 4). Of note, in Europe, unlike in the US, urinary retention most often leads to hospitalization or prolongation of hospitalization, which triggers

classification as an SAE. There were three Grade 4 SAEs in the TOOKAD VTP arm: one bronchospasm related to an anesthetic drug, one anaphylactic reaction to anesthesia drugs, and one unstable angina. In the active surveillance there was one Grade 4 SAE which was a myocardial infarction. One Grade 5 SAE occurred in the TOOKAD VTP arm where a patient died of a myocardial infarction approximately 34 weeks after receiving TOOKAD VTP treatment; however, the event, which occurred while the patient was hiking, was deemed unrelated to drug, device, or procedure.

Table 4: Serious Adverse Events Reported in ≥ 2 Patients in TOOKAD VTP Arm – Study 301 Safety Population

Category	TOOKAD VTP N = 197 n (%)	Active Surveillance N = 207 n (%)
Urinary retention	16 (8.1)	1 (0.5)
Prostatitis	4 (2.0)	0
Urinary tract infection	4 (2.0)	2 (1.0)
Dysuria	3 (1.5)	0
Haematuria	3 (1.5)	0
Orchitis	3 (1.5)	0
Cerebrovascular accident	2 (1.0)	0
Inguinal hernia	2 (1.0)	0
Myocardial infarction	2 (1.0)	3 (1.4)
Urethral stenosis	2 (1.0)	0

VTP = vascular-targeted photodynamic therapy

In both treatment arms, there were very few discontinuations due to an AE. In the TOOKAD VTP arm, 1 patient discontinued due to an anaphylactic reaction and 1 patient discontinued due to a myocardial infarction that resulted in death. One patient in the active surveillance arm discontinued due to ureteral cancer.

1.6.2 Adverse Events of Interest

Genitourinary-related AEs were closely evaluated in the Phase 2 and 3 studies. Phototoxicity was also examined since TOOKAD is a photosensitizing drug.

Phototoxicity

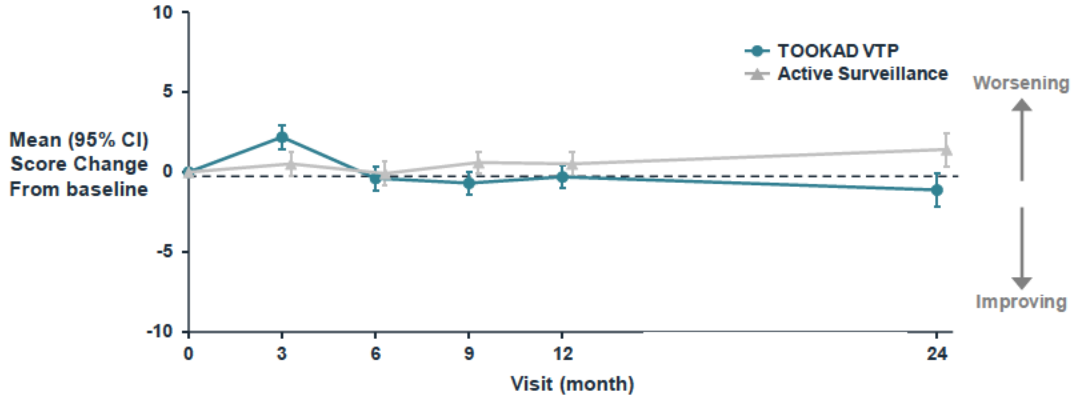
The potential for possible phototoxic AEs is short-lived due to TOOKAD's short half-life (70 min). In the TOOKAD clinical development program, 1 case of a mild optic AE (ischemic optic neuropathy) was reported 33 days after treatment. The ophthalmologist noted the event to be resolved, but with a small defect in the visual field. No other phototoxicity events occurred in the clinical program. With the precautions required at the time of the procedure and subsequent 2 days, the risk of generalized phototoxicity is minimal.

Transient Urinary Adverse Events

Transient urinary symptoms were commonly reported in patients treated with TOOKAD VTP. The AEs were mainly related to inserting the needles into the prostate and urinary catheterization; events may have also been associated with the development of necrosis (an objective of the procedure). In Study 301, hematuria was the most commonly reported urinary AE in the TOOKAD VTP arm (28%), followed by dysuria (27%), and urinary retention (16%). Most events were Grade 1–2 in severity and resolved by 24 months.

Although urinary-related AEs were frequently reported, patient-reported outcome data collected in Study 301 showed an absence of impact on prostate symptom scores and were consistent with the finding that events resolved at 24 months. There was an initial increase (worsening) in symptoms in the TOOKAD VTP arm that returned to baseline by 6 months and remained at baseline level through 24 months. At 24 months, there was no significant difference in symptom scores between groups, indicating no worsening of urinary symptoms (Figure 9).

Figure 9: International Prostate Symptom Scores (Questions 1 to 7) - Mean Change from Baseline Over Time – Study 301 Safety Population, Patients without Radical Therapy



Observations (n)						
TOOKAD VTP	168	154	159	156	153	145
Active Surveillance	128	119	117	118	105	101

CI = confidence interval; VTP = vascular-targeted photodynamic therapy
Note: Potential range of change in scores: from -35 (best) to +35 (worst).

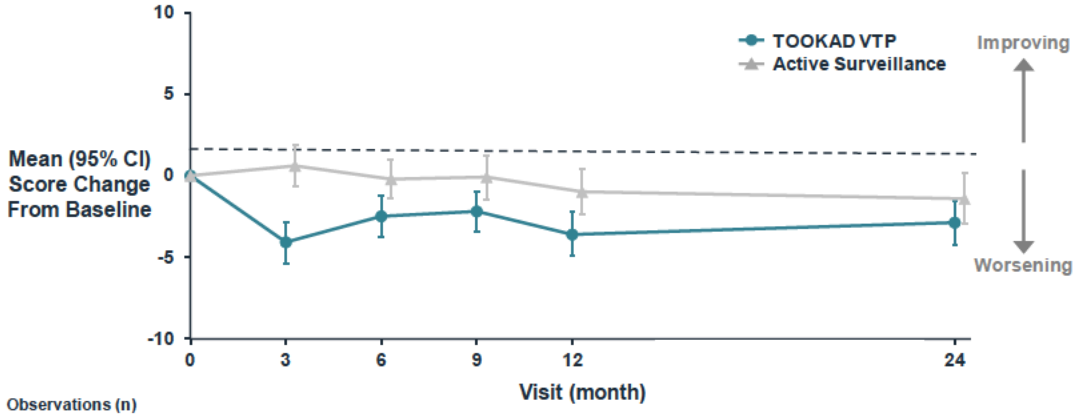
Erectile Dysfunction

One of the key benefits of TOOKAD VTP is its ability to preserve erectile function and continence. In Study 301, erectile dysfunction was reported by 38% of patients in the TOOKAD VTP arm and 12% of patients in the active surveillance arm. Most events were Grade 1–2. By 24 months, many of the events in the TOOKAD VTP group had resolved, including 50% of Grade 2 and 3, while the erectile dysfunction events in the active surveillance group generally remained the same. Additional details are provided in Section 6.9.

There was a decrease from baseline in long-term erectile function, which was consistent with the AEs reported. In Study 301, the IIEF questionnaire results showed a decrease in IIEF score in the

TOOKAD VTP arm at Month 3 that remained stable thereafter; scores remained stable in the active surveillance arm for the first 12 months (Figure 10). Notably, the change from Baseline at Month 24 showed a similar decrease in erectile function in both treatment arms.

Figure 10: International Index of Erectile Function - Erectile Function Domain - Mean Change from Baseline Over Time – Study 301 Safety Population, Patients without Radical Therapy



Observations (n)						
TOOKAD VTP	173	153	156	156	153	143
Active Surveillance	135	120	123	120	110	105

CI = confidence interval; VTP = vascular-targeted photodynamic therapy
Note: Potential range of change in scores: from -29 (worst) to +29 (best).

1.6.3 Salvage Radical Therapy

Salvage radical therapy is feasible if needed after TOOKAD VTP. A retrospective analysis was conducted for patients across the TOOKAD VTP development program who received salvage radical prostatectomy after TOOKAD VTP (n = 42) (Pierrard et al 2019). Generally, the outcomes were similar to treatment-naïve patients. The radical prostatectomy procedure was performed with no unusual challenges in 69% of patients, and 88% of patients had undetectable PSA levels at 6 to 12 months after the procedure. Only 12% of patients had postoperative complications. These results show that when necessary, prostatectomy can be performed safely and effectively in patients who received TOOKAD VTP.

1.7 Post-Approval Confirmation Study

A confirmatory post-approval study, Study 306, has been designed in consultation with the FDA and will begin enrollment in the first quarter of 2020. Eligible patients will include patients with favorable intermediate risk prostate cancer diagnosed by mp-MRI-guided biopsy. Study 306 will evaluate: 1) objective disease progression, 2) conversion to radical therapy, and 3) delayed harm (eg, urinary incontinence, sexual dysfunction) over the treatment course with either TOOKAD VTP or active surveillance. Patients will be followed up for 6 years irrespective of disease progression or conversion to radical therapy for assessment of the 3 aforementioned objectives.

The primary endpoint of the study will be time to objective progression of cancer over 30 months. Secondary endpoints will include time to conversion to radical local or systemic therapy, the consequent morbidity following objective disease progression, and a series of patient-reported outcome measurements, each evaluated at 30 and 72 months. Prostate biopsies will occur at Month 12, 24, 42, and 60, and when medically indicated thereafter. Long-term follow-up will continue for a total of 10 years after randomization to evaluate overall survival. Additional details are provided in Section 7.

1.8 Benefit-Risk Summary

Men diagnosed with localized prostate cancer have 2 recommended options: active surveillance or treating immediately with radical therapy. Radical treatments are effective but frequently impair genitourinary and bowel functions. Active surveillance can defer the need for radical therapy, but only temporarily for many men. These patients need alternatives that target the cancer area and preserve the surrounding tissues and, consequently, quality of life.

Hemiablation with TOOKAD VTP is a novel approach that fills the treatment gap by offering an alternative treatment that can further delay or avoid radical therapy while preserving surrounding tissue and organ function. In the pivotal study, hemiablation with TOOKAD VTP resulted in an increase in the probability of a negative prostate biopsy at 24 months after treatment compared to active surveillance and a statistically significant reduction in local disease progression. Multiple sensitivity analyses confirmed the robustness of the time to progression endpoint. Importantly, treatment with TOOKAD VTP also reduced the rate of conversion to radical therapy compared with active surveillance, which predicts a reduction in the morbidities of radical therapy and shows a clear clinical benefit for patients. The results are supported by 5-year follow-up data for both local disease progression and time to radical therapy and will be further evaluated in the confirmatory study, Study 306.

Overall, the AEs associated with TOOKAD VTP were mostly Grade 1–2 and self-limiting. The most commonly reported AEs, transient urinary symptoms, were mainly related to the procedure, and nearly all of these events resolved by 24 months. Erectile dysfunction was reported in approximately 38% of patients treated with TOOKAD VTP, 97% of which were Grade 1–2. At 24 months, many of the erectile dysfunction events resolved, including half of the Grade 2 and 3 events. The IIEF outcome data show similar trends in erectile function in both treatment arms at 24 months.

When compared to results from a large prospective randomized trial of radiotherapy and radical prostatectomy (ProtecT), hemiablation with TOOKAD VTP is a less morbid treatment option (Table 5). In a comparable population to Study 301, the events rates of urinary incontinence and erectile dysfunction ranged from 4–20% for urinary dysfunction and 66–82% for erectile dysfunction in patients who received radical therapy. In contrast, the rates of these events were 1.2% and 9.5% in patients treated with TOOKAD VTP.

Table 5: Comparison of Adverse Events from Radical Therapy and TOOKAD VTP

Category	ProtecT[1]		Study 301	
	Radiotherapy	Radical Prostatectomy	TOOKAD VTP	Active Surveillance
Mean age (years)	62	62	64	63
Urinary incontinence	4% (pad use)	20% (pad use)	1.2% (> Grade 1)	1.6% (> Grade 1)
Erectile dysfunction	66% (not firm enough for intercourse)	82% (not firm enough for intercourse)	9.5% (> Grade 1)	6.3% (> Grade 1)

VTP = vascular-targeted photodynamic therapy
Source: 1. Donovan et al 2016

The safety profile of TOOKAD VTP is supported by the interim analysis of 5-year data which shows no new safety signals. When needed, radical prostatectomy can be performed safely and effectively after TOOKAD VTP. The safety of TOOKAD VTP and the ability to perform radical therapy after TOOKAD VTP will be further evaluated in Study 306.

The totality of the data supports the positive benefit-risk profile for TOOKAD VTP, an important new option for patients with prostate cancer that is more effective than active surveillance and less morbid than radical therapy. For thousands of men diagnosed with localized prostate cancer each year, hemiablation with TOOKAD VTP can provide a safe and effective treatment that destroys the targeted cancer. In many patients, this minimally invasive and non-thermal therapy delays or avoids the need for radical therapy while preserving surrounding normal tissue and, thereby, quality of life.

2 BACKGROUND ON PROSTATE CANCER

Summary

- Prostate cancer is the most commonly diagnosed internal cancer in men (Siegel et al 2020). The ACS estimates that over 190,000 patients will be diagnosed in the US in 2020.
- The use of PSA testing has enabled early detection. Approximately 80% of newly diagnosed cases are localized (Seigel et al 2020).
- Current NCCN guidelines stratify patient risk to help guide treatment selection. Risk groups include very low, low, favorable intermediate, unfavorable intermediate, high and very high.
- Current NCCN guidelines recommend active surveillance and radical therapies for patients with very low, low, and favorable intermediate risk (NCCN 2019).
- Active surveillance preserves genitourinary function only temporarily since nearly 50% of these patients will convert to radical therapy within 5–10 years (Hamdy et al 2016).
- Radical therapies offer good control over disease progression but can significantly impair sexual, urinary, and bowel functions (Donovan et al 2016; Lebdai et al 2015; Parker et al 2009; Thomsen et al 2014; Wilt et al 2012).
- There is a need for a treatment option that fills the gap by controlling the cancer while avoiding the morbidities of radical therapy. Patients need alternatives that target the cancer area and preserve the surrounding tissues and, consequently, quality of life.

2.1 Overview of Prostate Cancer

2.1.1 Epidemiology

Prostate cancer is the most commonly diagnosed internal cancer in men and represents a major health issue among men in the US. An estimated 190,000 new cases of prostate cancer will be diagnosed in 2020, accounting for 20% of new cancer cases in men (Siegel et al 2020). Risk factors for prostate cancer include older age (> 50 years), being African American, and having a family history of prostate cancer. In addition, obesity, smoking, and poor diet have also been linked to prostate cancer.

Approximately 33,000 men will die from prostate cancer in 2020 in the US (Siegel et al 2020). Yet in most patients, prostate cancer is a slowly progressing disease with a high survival rate. The 5-year survival rate is nearly 98%, with little change observed at 10 years. Because of this, other factors, such as disease progression and quality of life, play an important role in making treatment decisions, as described in Section 2.2.

2.1.2 Diagnosis

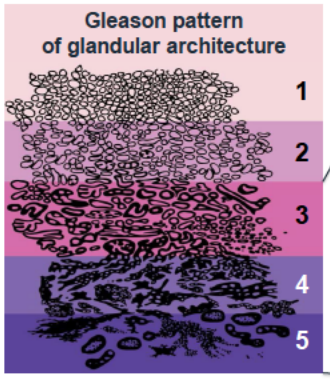
Prostate cancer is initially identified through a PSA test or digital rectal exam and then confirmed with an ultrasound- or MRI-guided biopsy. The increased use of PSA testing in recent decades has enabled detection of prostate cancer at earlier stage, which has led to a reduction in the mortality rate (Litwin and Tan 2017). Approximately 80% of the newly diagnosed cases of prostate cancer are localized, while the remaining 5% include locally advanced and metastatic forms (Seigel et al 2020). As noted in the NCCN guidelines, however, the increased sensitivity of diagnosis also presents concerns regarding overtreatment (NCCN 2019).

Biopsy methods have also evolved over the last decade, which has contributed to more accurate results. Multiparametric MRI-targeted biopsies, which allow for a biopsy to be taken from a visible lesion, are often performed in place of systematic TRUS-guided biopsies. Thus, sensitivity and specificity of the diagnosis have vastly improved, which is reflected in the current staging criteria.

2.1.3 Prostate Cancer Staging

Prostate cancer staging is based on several criteria including tumor, nodes, metastasis (TNM) stage, PSA level, Gleason Score, and number of positive cores. A Gleason Grade is assigned based on the extent to which prostate cells retain their ability to form glands. Grade 1 cells are well differentiated and resemble normal prostate tissue while cells closest to Grade 5 are highly mutated, undifferentiated, and considered "high-grade" (Figure 11). A primary Gleason Grade is assigned to the most predominant pattern in the biopsy and a secondary Gleason Grade to the second most predominant pattern, such as 3 + 4. The grades are then added together to determine the Gleason score.

Figure 11: Gleason Scoring



Gleason Score* (primary + secondary pattern)	ISUP Grade Group
6 (3 + 3)	**Grade Group 1**
7 (3 + 4)	**Grade Group 2**
7 (4 + 3)	**Grade Group 3**
8 (4 + 4)	**Grade Group 4**
9 (4 + 5) **10** (5 + 5)	**Grade Group 5**

*Gleason score = primary (largest) grade + secondary grade
ISUP = International Society of Urologic Pathologists
Source: Epstein et al 2016

The NCCN is continually updating their guidelines to ensure that the latest information is reflected in their recommendations. As of 2019, the risk stratification scheme has been divided further to help select the best treatment. Current NCCN groups include very low and low risk, favorable and unfavorable intermediate risk, and high and very high risk, as described in Table 1.

The current risk groups do not account for the nature of the biopsy used to establish the diagnosis, even though differences in sensitivity have been reported for various biopsy methods (Ahmed et al 2017).

2.2 Current Treatment/Management Options

There are no drugs or biologic products currently approved for localized prostate cancer. The current NCCN guidelines recommend that active surveillance and radical therapies (radical prostatectomy, EBRT, or brachytherapy) be proposed to patients with very low, low, and favorable intermediate risk patients who have a life expectancy of at least 10 years (NCCN 2019). The American Urological Association/American Society for Radiation Oncology/Society of Urologic Oncology guidelines also consider active surveillance an appropriate option for patients with favorable intermediate risk localized prostate cancer (Sanda et al 2018).

The recommended treatment options offer 2 dramatically different methods of managing the disease. Radical therapy refers to either radical prostatectomy or definitive radiation therapy to the prostate, seminal vesicles, and surrounding tissue. In contrast, active surveillance requires careful monitoring which typically includes a PSA test every 6 months, a digital rectal exam at least annually, a prostate MRI every 1 to 3 years, and a planned prostate biopsy every 2 to 5 years.

Approximately 45% of patients with very low, low, and favorable risk prostate cancer are currently being managed with active surveillance and 55% with immediate radical therapy (Godtman et al 2016; Womble et al 2015). Studies have shown that for any of the recommended options, the case-specific survival at 10 years is greater than 95% (Hamdy et al 2016; Wilt et al 2017). Studies have also shown that death rates at 10 years of untreated low risk prostate cancer are very low (Bill-Axelson et al 2014). Hence, in this patient population, survival rate is not discriminatory for treatment selection, and other criteria such as preventing disease progression and preserving genitourinary functions must be considered to differentiate the relative benefits of the different treatment options. This view is supported by the current NCCN guidelines, which indicate that the recommendation for active surveillance versus radical treatment "*must be based on careful individualized weighing of a number of factors: life expectancy, general health condition, disease characteristics, potential side effects of treatment, and patient preference.*"

2.2.1 Limitations of Current Treatment Options

Although radical therapies offer good control of disease progression, they significantly impair genitourinary functions and can negatively affect quality of life. Patients treated with radical therapy frequently suffer from complications related to erectile function, urinary function and continence as well as bowel function (Donovan et al 2016; Lebdai et al 2015; Parker et al 2009; Thomsen et al 2014; Wilt et al 2012). These events were specifically studied in the ProtecT study, a large randomized trial that prospectively collected patient reported outcomes data; urinary incontinence was reported in up to 20% of patients and erectile dysfunction in over 80% of patients following radical prostatectomy (Table 6) (Donavan et al 2016). In addition, patients who undergo radical prostatectomy become ineligible for brachytherapy in the case of recurrence, as there is no prostate tissue in which to embed the radioactive seeds; and salvage

radical prostatectomy after radiotherapy or brachytherapy is much more difficult than in treatment-naïve patients. This is an important consideration given that approximately 20% of patients require salvage treatment at 5 years (Merino et al 2013).

Table 6: Comparison of Adverse Events from Radical Therapy

Category	ProtecT[1]	
	Radiotherapy	Radical Prostatectomy
Mean age (years)	62	62
Urinary incontinence	4% (pad use)	20% (pad use)
Erectile dysfunction	66% (not firm enough for intercourse)	82% (not firm enough for intercourse)

1. Donovan et al 2016

At the other end of the care spectrum, active surveillance offers an alternative to radical therapies that enables good preservation of genitourinary functions, but has its own limitations. A major risk of active surveillance that must be carefully considered by patients and physicians is that the cancer may progress. In addition to causing anxiety for patients, local progression could require much more intensive or multi-modal treatment, while metastasis could lead to an incurable condition. Eventually, approximately 50% of patients convert to radical therapy within 5 to 10 years (Hamdy et al 2016). Therefore, while active surveillance does preserve important functions, it is not the ultimate solution for most men.

Focal therapies such as HIFU and cryotherapy have emerged as alternative treatment options for patients with prostate cancer, but their use remains limited. These focal treatments are not indicated by the FDA as focal treatments for prostate cancer, are not recommended in prostate cancer treatment guidelines, and are not supported by level 1 evidence of efficacy (Sanda et al 2017). However, the increased use of these options supports the need for alternative treatment options.

2.3 Patient Unmet Medical Need

Patients diagnosed with localized prostate cancer only have 2 recommended options: monitoring with active surveillance or treating immediately with radical therapy. Thus, there is an unmet need for new approaches that can fill the treatment gap by more effectively delaying disease progression while avoiding the morbidities of radical therapy. This need aligns with the discussion at the 2018 Public Workshop held by the FDA in which meeting participants described avoidance of morbidity as the true clinical benefit associated with delaying local therapy with curative intent (Weinstock et al 2019).

3 PRODUCT DESCRIPTION

Summary

- The proposed indication of TOOKAD VTP is for the treatment of patients meeting specific criteria for low to favorable intermediate risk localized prostate cancer.
- TOOKAD VTP is a minimally invasive form of photodynamic therapy that consists of IV administration of inactive padeliporfin and local activation of the circulating padeliporfin in the target tissue by non-thermal laser light illumination.
    - The procedure includes a 10-minute infusion of TOOKAD followed by laser illumination of the cancer-containing tissue for 22 minutes and 15 seconds.
- Hemiablation by TOOKAD VTP delays or avoids the need for radical therapy in many patients while preserving surrounding normal tissue.

3.1 Proposed Indication and Administration

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

- Stage T1–T2a and
- PSA ≤ 10 ng/mL and
- 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.

The following Limitation of Use is proposed: TOOKAD is not recommended for use in patients with a life expectancy of less than 10 years, where the clinical guidelines recommend observation alone, because the therapeutic benefits may not outweigh the risks in that patient population.

The recommended dose of TOOKAD is one single dose of 4 mg/kg of body weight, injected intravenously by a healthcare provider. The injection lasts 10 minutes. TOOKAD is administered as part of a VTP procedure performed under anesthesia, described in Section 3.2.

3.1.1 Rationale for Proposed Indication

The proposed indication was selected to be consistent with the study population of the pivotal Study 301 but diagnosed with contemporary means (namely mp-MRI-targeted biopsy) while remaining in line with the current NCCN guidelines (Figure 2). Patients included in Study 301 had a life expectancy of at least 10 years and were described as "low risk" based on systematic TRUS biopsy findings, which was the standard practice at the time of the trial accrual (2011–2013). Since that time, extensive research has been conducted to develop more sensitive and specific diagnostics, namely using a combination of systematic TRUS biopsy with mp-MRI-targeted biopsy. In addition, the current NCCN guidelines (August 2019) stratify intermediate risk prostate cancer patients based on laboratory and radiological finding, with patients who have a more favorable prognosis, essentially overlapping with the study population from Study 301.

3.2 Product Overview

TOOKAD VTP is a minimally invasive therapy developed by Steba in collaboration with the Weizmann Institute of Science in Israel to provide an alternative therapy option for patients with low or favorable intermediate risk prostate cancer. TOOKAD VTP therapy consists of IV administration of inactive padeliporfin and illumination by non-thermal laser light using optical fibers positioned percutaneously in the prostate. Hemiablation of the prostate is then achieved through the local activation of TOOKAD.

Padeliporfin is an NCE of the family of bacteriochlorophyll photosensitizers. It is retained in the vascular system of the patient and remains inactive until focal illumination of the prostate cancerous area with low-energy, non-thermal laser light. TOOKAD photoactivation rapidly induces a local vasoconstriction and occlusion of vessels, followed by a cascade of biological events that result in coagulative necrosis of the treated lobe. The mechanism of action is further described in Section 3.3.

The light delivery system used to activate the drug includes 6 devices:

- Low-energy, non-thermal laser emitting light at 753 nm plus dosimeter
- Treatment guidance software (TOOGUIDE TRUS)
    - optimizes the parameters of treatment, including the number of optical fibers, accurate positioning of the fibers within the prostate, and length of the light diffuser of each diffusing optical fiber
- Light diffuser (TOO-Diffusers)
    - transmits the light from the laser to the patient's prostate along a diffuser tip
- Light-collecting fiber (TOO-Probe)
    - collects the irradiance rate (fluence) in the rectum and transmits it to the dosimeter for measurement
- Sharp catheters (TOO-Cath S)
    - allows introduction of TOO-Diffusers into the prostate
- Blunt catheter (TOO-Cath)
    - allows insertion of the TOO-Probe into the rectum

Of particular importance is the fact that TOOKAD remains within the blood circulation and is rapidly cleared (half-life of 1.19 h ± 0.08 [approximately 70 min]). This allows for the treatment effects to be limited only to the vasculature of the tumor and reduces the risk of photosensitivity following treatment. In addition, the long wavelength of the activation light allows for treatment of solid tumors of a diameter of several centimeters. Furthermore, the non-thermal approach aids in the precise targeting of the tumor and limits damage to surrounding tissues and fibrosis—both of which are important for feasibility of radical therapy in the case of treatment failure.

3.2.1 Dose Selection

A robust nonclinical development program was undertaken to support the use of padeliporfin in patients with localized prostate cancer. The program includes proof-of-concept efficacy studies; mechanism of action studies; cardiovascular, respiratory, and central nervous system safety evaluations; pharmacokinetic assessments; pivotal and dose range finding toxicology studies; genotoxicity; sensitization; and phototoxicity assessments. This nonclinical program included the following models: nude, OF1 and CD1 mice, Sprague-Dawley rats, New Zealand albino rabbits, Hartley Guinea pig, fetal calves, and Cynomolgus monkeys.

3.2.1.1 Light Exposure Time

The non-clinical development program determined the parameters for necrosis of prostate tissue in humans to be a total energy delivery of 60 J with a light fluency of 100 mW/cm^2. However, it would not be efficacious or controllable to deliver this energy in a single short burst. In terms of efficacy, the energy must be delivered over a minimum time of 10 minutes to allow for occlusion of temporarily non-functional vessels. To maintain safety, the temperature must not increase more than 5 ºC, which limits the optical power to be a maximum of 150 mW per cm of illuminated laser fiber. To ablate 5 mm from the fiber surface, one must deliver 60 J of energy 5 mm from the probe surface, which requires each centimeter of the illuminated tip to deposit 200 J of energy. The mathematical solution to deliver 200 J/cm at a power of 150 mW/cm is an exposure time of 1333 seconds, or 22 minutes and 15 seconds. This was a fixed parameter in the phase 2 studies.

3.2.1.2 Optimal Dose

Phase 2 studies investigated doses of 2 mg/kg, 4 mg/kg, and 6 mg/kg (see Section 5.1). The dose of 2 mg/kg resulted in insufficient ablation, whereas the 6 mg/kg dose resulted in complete ablation. The 4 mg/kg dose was found to result in reproducible confluent and consistent necrosis, provided it was associated with a light density index ≥ 1. Note, the Light Density Index (LDI) corresponds to the ratio of cumulated lengths (in centimeters) of illumination tip of the fiber used to the volume of prostate intended to be treated (in cubic centimeters) (LDI= X cm of illumination tip of the fibers/Y cm^3 of targeted prostate volume).

The light exposure-dose combination determined and verified in the phase 2 studies was 4 mg/kg TOOKAD in combination with a 22 minute 15 second exposure and a LDI ≥ 1. This was the dose used in Study 301.

3.2.2 TOOKAD Vascular-Targeted Photodynamic Therapy Procedure

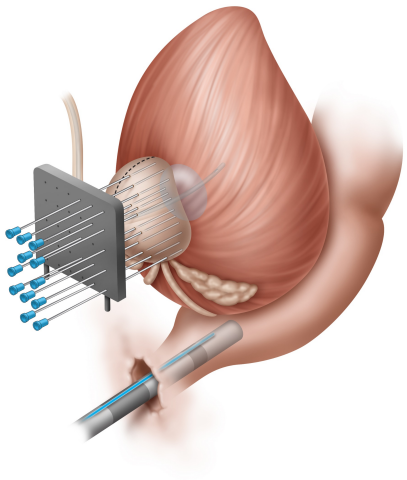
The TOOKAD VTP treatment is a standardized procedure that will be performed by a trained urologic surgeon (training program describe in Section 3.2.3). The standardized VTP procedure, which lasts approximately 2 hours, includes the following steps:

1. The patient is placed in the lithotomy position under anesthesia.
2. Peri-procedure treatment guidance is performed using ultrasound and the TOOGUIDE TRUS software to define the target volume and safety margin with regard to the urethra,

posterior and lateral capsule, and rectal wall (see Section 3.2.3); the optical fiber placement is guided with the assistance of TOOGUIDE TRUS software.

3. Non-thermal laser light diffusing optical fibers (TOO-Diffusers) are connected to a low-energy, non-thermal laser light generator and calibrated.
4. Calibrated TOO-Diffusers are inserted into transparent catheters (TOO-Cath S) placed transperineally into the prostate through a template based on treatment guidance (TOOGUIDE TRUS software) (Figure 12). Fiber placement is verified on ultrasound and absence of light in the rectum (measured by the TOO-Probe) to prevent the risk of urethro-rectal fistula when fibers are connected to the non-thermal laser.

Figure 12: Optical Fiber Placement for TOOKAD VTP



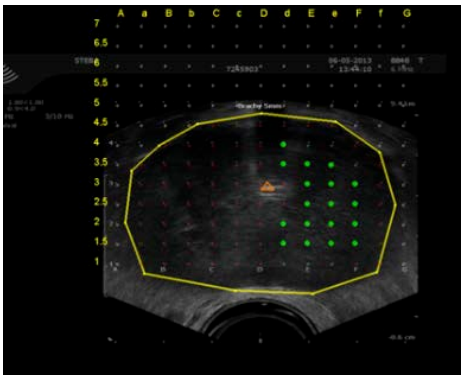
5. At a dose of 4 mg/kg, TOOKAD is administered intravenously for 10 min. The drug circulates in the vascular system but remains inactive.
6. Near-infrared illumination (753 nm with a fixed power of 150 mW/cm) is delivered through the optical diffusers for 22 minutes and 15 seconds. This activates the drug locally and triggers a cascade of events leading to vascular occlusion and coagulative necrosis resulting in hemiablation of the targeted lobe of the prostate.
7. Once illumination is complete, the optical fibers are removed, and the patient is transferred to a dimly lit room for at least 6 hours as they recover from anesthesia.

Patients remain under the care of healthcare professionals in a dimly lit recovery room as they awaken from anesthesia until they are ready for discharge. Patients are instructed to avoid bright light for 48 hours.

3.2.3 Treatment Planning

The treatment guidance software, TOOGUIDE TRUS, is a stand-alone device that enables physicians to prepare a treatment plan in advance of the TOOKAD VTP procedure. After mapping the prostate on sequential transverse TRUS images, TOOGUIDE TRUS will determine an effective configuration of the laser fibers to achieve sufficient and confluent light coverage of the targeted tissue. The guidance provides locations for the transverse light fibers (Figure 13), as well as the illumination length of each fiber to ensure light coverage from apex to base; light fibers come with illumination lengths from 1 cm to 5 cm in half cm increments. Importantly, TOOGUIDE TRUS ensures a LDI ≥ 1. Note, the urologist can modify the positions of the fibers proposed by TOOGUIDE TRUS for safety reasons and the software will automatically calculate the LDI of the modified plan.

Figure 13: TOOKAD VTP Treatment Planning Software



3.2.4 TOOKAD VTP Training Program

The physician training program used in the US will mirror that which was used in Study 301. Specifically, this is a two-phase process with the first phase being didactic training and case observation. The mechanism of action, indication, benefits, risks, fundamentals of the procedure as well as patient selection and patient counselling will be covered in detail. Graduation to Phase 2 requires passing of a knowledge test. Phase 2 involves cases performed by the trainee physician at their clinic under the proctorship of a practicing urologist certified in the TOOKAD procedure. A minimum of 5 procedures with a proctor are required during this phase and it is not complete until the proctor is comfortable with the skills of the trainee physician. Note, as an additional safety precaution, TOOKAD will not be shipped to a site without the site providing a physician certification number unless a physician at that site is undergoing training.

Training is also provided to the clinical team managing the technical procedures related to the laser during the VTP procedures. All trained clinicians receive a certificate issued by Steba attesting to their ability to perform the procedure independently.

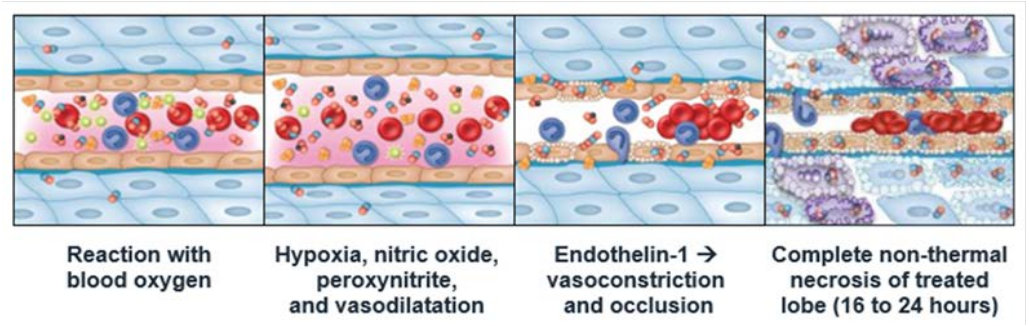
3.3 Mechanism of Action

The treatment effect is achieved through photoactivation of TOOKAD by 753 nm wavelength laser light. Once activated, TOOKAD triggers a cascade of pathophysiological events resulting in localized tumor necrosis within a few days. As illustrated in Figure 14, activation generates

oxygen radicals causing local hypoxia, which induces the release of NO radicals resulting in transient vasodilatation of arteries. Vasodilation then triggers the release of the vasoconstrictor, endothelin-1. Rapid consumption of the NO radicals by oxygen radicals leads to the formation of reactive nitrogen species (RNS; eg, Peroxynitrite), which, in the absence of NO and the antagonistic action of endothelin, induces arterial constriction. In model systems, the vascular response observed after a short drug-light interval correlated with a histopathological tumor response (Eymerit-Morin et al 2013).

In addition, impaired deformability and reduced adhesion to endothelial cells, under low shear force in reduced blood flow, is considered to enhance erythrocyte aggregability. This leads to the formation of blood clots at the interface of the arterial supply with the tumor microcirculation, resulting in permanent occlusion of the entire tumor vasculature, including the rim, which is further enhanced by RNS-induced endothelial cell necrosis and apoptosis.

Figure 14: TOOKAD VTP Mechanism of Action



4 REGULATORY AND DEVELOPMENT HISTORY

Summary

- The pivotal Phase 3 study (Study 301) was initiated in 2011 following advice from the European Medicines Agency. Marketing authorization for TOOKAD VTP was granted by the European Commission in 2017.
- Steba and the FDA have had ongoing communication regarding the selection of a clinically meaningful endpoint, the appropriate study population, and an approval pathway.
- Following the 11 July 2018 Public Workshop discussing treatment in patients with localized prostate cancer, the FDA and Steba reached agreement on pursuing accelerated approval based on the surrogate endpoint of decrease in progression of local disease. A post-approval confirmatory study will be conducted.
- The clinical program supporting approval of TOOKAD in patients with localized prostate cancer include 3 Phase 2 studies, a pivotal Phase 3 study, and 1 supportive single-arm study.

4.1 Regulatory Milestones

Steba initiated discussion with the FDA in 2011 regarding design of a Phase 3 study in the US. A special protocol assessment request was submitted, but agreement was not reached on a clinically meaningful endpoint.

Steba pursued development in the European Union (EU) with guidance from the European Medicines Agency supporting Steba's proposed study design as suitable to demonstrate the safety and efficacy of TOOKAD VTP. Phase 3 Study 301 began in 2011 and was completed in 2015. On 10 November 2017, marketing authorization was granted by the European Commission following the favorable opinion of the Committee for Medicinal Products for Human Use on TOOKAD as monotherapy for patients with previously untreated, unilateral, low-risk, adenocarcinoma of the prostate excluding very low risk patients.

After marketing authorization was granted, Steba reviewed results from Phase 3 Study 301 in a Type C meeting with the FDA in November 2017 and discussed a path toward approval in the US. The FDA stated that Steba's proposed trial endpoints of progression from low-risk to moderate or high risk prostate cancer had not been validated as clinically meaningful. The accelerated approval pathway was discussed with the understanding that a confirmatory trial would be necessary. Accelerated approval was further discussed during a Type B meeting held in March 2018 regarding the use of the prevention of progression to Gleason score ≥ 7 as a surrogate endpoint for initial approval.

On 11 July 2018, the FDA's Oncology Center of Excellence held a Public Workshop for the development of treatments for patients with localized prostate cancer. Meeting participants

generally agreed that criteria such as preventing disease progression, reducing morbidity of therapy, and preserving genitourinary and bowel functions are just as important in assessing treatment options and should be considered for new treatments for prostate cancer (Weinstock et al 2019). In addition, it was agreed that there was clinical benefit in the avoidance of morbidity associated with radical treatments.

Steba continued the discussion of clinically meaningful endpoints with the FDA in a pre-NDA meeting in October 2018. During the Pre-Submission meeting, the FDA indicated that the data from Study 301 seemed most appropriate for a potential accelerated approval based on a surrogate endpoint of decrease in pathological upgrade/local progression free survival although final determination would be a review issue.

Steba is now pursuing an accelerated approval pathway based on the data available from Study 301 as the pivotal clinical study and with an agreed upon confirmatory study (see Section 7). The NDA for the combination product was submitted on 3 May 2019.

4.2 Clinical Development Program

TOOKAD VTP is being investigated for several indications, including prostate cancer, age-related macular degeneration, cholangiocarcinoma, non-small cell lung cancer, renal cancer, upper tract urothelial cancer, and esophagogastric carcinoma. In total, approximately 600 patients have received TOOKAD.

The clinical development program for TOOKAD VTP supporting the NDA includes one Phase 1 study, three Phase 2 studies, one pivotal Phase 3 study, and a supportive single-arm study. The studies included 652 patients with prostate cancer, 429 of whom were treated with TOOKAD VTP. Key Phase 2 and 3 studies are presented in Table 7.

The dosing regimen of 4 mg/kg of TOOKAD, 200 J/cm of fiber and an LDI $\geq$ 1 was selected based on the results of two Phase 2 dose-escalation trials of TOOKAD, Studies PCM 201 (Study 201) and 202 (Study 202). An additional Phase 2 study, Study PCM 203 (Study 203), confirmed the optimal treatment parameters for hemiablation (Azzouzi et al 2013).

The primary safety and efficacy data supporting accelerated approval are derived from Study 301. Study 301 is a multicenter, international, randomized, open-label, Phase 3 study in Europe, designed to compare the effect of TOOKAD VTP versus active surveillance in treatment-naïve men with low-risk localized prostate cancer (Azzouzi et al 2017). The 2-year follow-up period of the study was completed in 2015. The co-primary endpoints of Study 301 (progression of localized disease and rate of absence of cancer) represent objective measures of efficacy. The secondary endpoint of initiation of radical therapy supports the clinically meaningful benefit of TOOKAD VTP and is in line with the secondary endpoint suggested by Weinstein et al (2019).

Patients from Study 301 are currently being followed (in a follow-up protocol) for long-term safety and outcomes over an additional 5 years (Study 301-FU5). An interim analysis was conducted after the last patient enrolled reached the 5-year time point after randomization. Another multicenter international, single-arm, open-label study in Latin America, Study PCM

304 (Study 304), was completed in December 2014. In addition, a Phase 2 clinical study in moderate risk, unilateral, Gleason 3 + 4 prostate cancer is currently ongoing in the US (Study 204).

A post-marketing confirmatory study (Study 306) has been designed to evaluate the efficacy of TOOKAD VTP versus active surveillance for men with favorable intermediate risk localized prostate cancer diagnosed with mp-MRI-guided biopsy. The objective of Study 306 is to provide evidence that morbidity is reduced in the TOOKAD arm compared to active surveillance at multiple follow-up time points and that longer-term prostate cancer outcomes (recurrence rates following definitive therapy) are not degraded. Enrollment will begin in the first quarter of 2020.

Table 7: Phase 2 and Phase 3 Studies in the TOOKAD VTP Prostate Cancer Clinical Development Program

Study	Description	Number of Patients Included	Location
Study 201	Phase 2a dose-escalation, multicenter	42	France, UK, Canada, Netherlands
Study 202	Phase 2a Dose-escalation, multicenter	30	US
Study 203	Phase 2b Multicenter	86	France, UK, Netherlands
Study 304	Multicenter, open-label, single-arm	81*	Mexico, Panama, Peru
Study 301	Phase 3 Multicenter, open-label study randomized vs Active surveillance	206 on TOOKAD VTP 207 on active surveillance	France, Germany, UK, Spain, Italy, Netherlands, Belgium, Switzerland, Sweden, Finland
Study 301-FU5	Phase 3 long-term follow-up study of Study 301	182 on TOOKAD VTP 172 on active surveillance	France, Germany, UK, Spain, Italy, Netherlands, Belgium, Switzerland, Sweden, Finland
Study 204	Ongoing Phase 2b	50	US
Study 306	Proposed Phase 3 confirmatory post-approval study	400 Planned	US and Europe

UK = United Kingdom; US = United States; VTP = vascular- targeted photodynamic therapy

5 CLINICAL EFFICACY

Summary

- The pivotal study (Study 301) compared treatment with TOOKAD VTP to active surveillance in men with low-risk, localized prostate cancer confirmed by TRUS-guided biopsy. Both co-primary efficacy endpoints were met with a significant statistical difference between the TOOKAD VTP and active surveillance arms ($p < 0.001$).
    - TOOKAD VTP reduced the risk of progression over 24 months by 66% compared to active surveillance (HR = 0.34).
    - TOOKAD VTP also increased the probability (relative risk) of a negative prostate biopsy in the whole gland at 24 months after treatment by 3.62 times (from 14% to 49%) compared to active surveillance.
- In Study 301, TOOKAD VTP reduced the need for radical therapies compared with active surveillance at 24 months (6% vs 29%; absolute risk reduction of 23%).
    - Avoidance of radical therapy is important for preserving genitourinary functions and reasonably predicts a reduction in harm for early stage/favorable risk prostate cancer patients.
- Durability of the results is supported by the 3-year interim analysis of the 5-year follow-up study.
    - Time to progression was significantly lower in the TOOKAD VTP arm compared to active surveillance 5 years after randomization (HR: 0.39).
    - TOOKAD VTP maintained the reduction in patients converting to radical therapy (24% vs 44%; absolute reduction of 20%) resulting in avoidance of 1 out of 2 radical therapies in the active surveillance arm, a clinically meaningful benefit that lowers the risk of morbidities associated with radical therapies.

5.1 Phase 2 Studies

Two Phase 2 dose-escalation studies of TOOKAD, Studies 201 and 202, were conducted to identify the optimal TOOKAD dose and light energy parameters to treat low-risk localized prostate cancer patients diagnosed by TRUS biopsy.

Three doses of TOOKAD (2, 4, and 6 mg/kg) and two 753 nm light doses (200 and 300 J/cm of fiber) were tested. LDI, which considers the total illumination length of fibers and size of the prostate, was evaluated in addition to the dose and light energy (Moore et al 2015).

In Study 201, a correlation was observed between the total energy delivered and volume of necrosis. Three patients were evaluated at 2 mg/kg. Their clinical response showed relatively poor volume of necrosis by MRI, the inadequacy of which was subsequently confirmed by biopsies at 6 months which were still positive for prostate cancer in 2 of the 3 patients.

Therefore, subsequent patients received higher doses of TOOKAD. The next 8 patients treated with 4 mg/kg had better clinical responses based on the volume of necrosis, and since overall safety in these patients was good, a small cohort of patients was then evaluated with the 6 mg/kg dose. However, based on extra-prostatic adverse effects with the 6 mg/kg dose, investigators and the sponsor concluded risks were too great to proceed further with this treatment dose. Based on these initial dose-range findings, all subsequent patients were treated at 4 mg/kg. Investigators concluded that treatment conditions of 4 mg/kg and light energy level of 200 J/cm with an LDI ≥ 1 provided optimal efficacy and safety. A minimum threshold of 1 for the LDI was shown to be a strong predictor of the percentage of necrosis at Day 7. A post hoc analysis showed that in the patients treated with the optimal dose of 4 mg/kg and LDI ≥ 1, the mean percentage of necrosis was 94.8% compared to 56.4% in patients with LDI < 1, and 83.3% of patients with LDI ≥ 1 subsequently had a negative biopsy at Month 6. Therefore, in Study 201 the optimal treatment dose was found to be 4 mg/kg TOOKAD, 200 J/cm of fiber, and LDI ≥ 1.

In Study 202, the results confirmed the conclusion from Study 201 that 4 mg/kg TOOKAD, 200 J/cm of fiber and LDI ≥ 1 provided the optimal balance between efficacy and safety. Overall, 19 patients out of 30 (63.3%) had negative biopsies in the treated lobe at Month 6. In patients treated with optimal dose and light optimal conditions and an LDI ≥ 1, the percentage of negative biopsies was 73.3%.

An additional Phase 2 study (Study 203), conducted in parallel with Study 202, confirmed the optimal treatment parameters for hemiablation with 4 mg/kg of TOOKAD, 200 J/cm of fiber and an LDI ≥ 1. In the subgroup of 8 patients who were retreated after 6 months, efficacy endpoints were similar as in the initial treatment.

The therapy conditions ultimately chosen as optimum (ie, 4 mg/kg with 200 J/cm illumination and LDI ≥ 1) resulted in apparently successful ablation of prostate cancer in approximately 50–86% of patients. Greater TOOKAD exposure did not achieve superior results; therefore, the final dosing recommendations are considered the safest effective treatment conditions.

5.2 Supportive Study 304

5.2.1 Study Design

Study 304 was a multicenter, supportive Phase 3, open-label trial performed to confirm that a significant proportion of patients would be prostate cancer-free on the Month 12 biopsy. This study demonstrated a high rate of negative biopsy and the absence of difference in efficacy between the Gleason Score 3 + 4 and Gleason Score 3 + 3 patients supports the positive treatment effect of TOOKAD VTP at 12 months.

A total of 81 patients with low and intermediate risk were enrolled in the study. Prostate cancer was unilateral in 63 patients and bilateral in 18 patients. The Gleason grade was 3 + 3 in 69 patients (85.2%) and 3 + 4 in 12 patients (14.8%). The mean PSA level at entry was 8.69 ng/mL (range, 1–40.7 ng/mL). Of the 78 patients who received TOOKAD VTP, 76 received the first VTP procedure according to protocol (4 mg/kg and light energy 200 J/cm). Seventeen (17)

patients who had bilateral disease at Baseline underwent a second VTP procedure in order to treat contralateral disease.

5.2.2 Results

Among the 71 patients who had Month 12 biopsies results available, 60 (84.5%) patients had a negative biopsy. Among the 11 patients with a positive biopsy, 9 patients had a positive biopsy in the treated lobe and 2 had positive biopsies in the contralateral, untreated lobe. The percentage of negative biopsies was consequently 74.1% (60/81) in the ITT Population (95% CI: [63.1%; 83.2%]) (Table 8). Evidence of a difference in efficacy was not noted between patients with Gleason 3 + 4 and those with Gleason 3 + 3 prostate cancer.

Table 8: Prostate Biopsies at 6 and 12 Months in Study 304 ITT Population

	VTP Therapy, 6 Months	VTP Therapy, 12 Months
Prostate Biopsy	(n = 81)	(n = 81)
Negative biopsy, n (%)	59 (72.8)	60 (74.1)
Exact 95% CI[a]	[61.8%; 82.1%]	[63.1%; 83.2%]
Positive biopsy, n (%)	15 (18.5)	11 (13.6)
Missing biopsy, n (%)	7 (8.6)	10 (12.3)
Gleason Score in Cases of Positive Biopsy	(n = 15)	(n = 11)
3 + 3, n (%)	9 (60)	9 (81.8)
3 + 4, n (%)	4 (26.7)	1 (9.1)
5 + 4, n (%)	2 (13.3)	1 (9.1)

a. For the percentage of patients with negative biopsy assessment.
CI = confidence interval; ITT = intent-to-treat; VTP = vascular-targeted photodynamic therapy

MRI evaluation showed 87.3% necrosis overall on Day 7 after the procedure, including 85.7% with extra-prostatic necrosis. Extra-prostatic necrosis was asymptomatic with no apparent sequalae and considered to be of no clinical significance. In addition, PSA levels dropped considerably from baseline at 3 months and remained decreased through 12 months (Table 9).

Table 9: PSA Levels Over Time in Study 304 ITT Population

Time Point	PSA (ng/mL)	Change from Baseline
Baseline	8.7 ± 5.7	-
3 months	4.1 ± 4.1	-4.9
6 months	4.1 ± 5.4	-4.9
12 months	5.7 ± 9.2	-3.3

ITT = intent-to-treat; PSA = prostate-specific antigen

5.3 Pivotal Phase 3 Study—Study 301

5.3.1 Study Design

Study 301 was a Phase 3, open-label, multicenter, randomized, clinical trial of the efficacy and safety of TOOKAD VTP for treatment of low-risk, localized prostate cancer. Patients were enrolled from 47 centers in 10 European countries. Although the study was open-label (patients and investigational site staff were not blinded to study treatment), evaluation of the primary efficacy outcomes was conducted in a blinded fashion. The co-primary objectives of this study were to assess the impact of TOOKAD VTP on the rate of absence of cancer and to determine the difference in rate of treatment failure associated with observed progression of disease in men who undergo TOOKAD VTP compared to men on active surveillance. Patients were randomized 1:1 to receive TOOKAD VTP or active surveillance (Figure 4). Patients in both treatment groups were followed for 24 months after randomization and underwent the same efficacy and safety assessments. A TRUS-guided biopsy of 10 to 24 cores was performed at Month 12 and Month 24. Every 3 months, PSA was measured and a digital rectal examination was performed. After completion of the 24 month follow-up period, patients were then eligible to enter a long-term follow-up program in which outcomes are being recorded for an additional 5 years, for a total of 7 years of follow-up. The 5-year follow-up study, Study 301-FU5, is described in Section 5.4.

5.3.1.1 Treatment

5.3.1.1.1 TOOKAD VTP

Patients randomized to receive TOOKAD VTP underwent pre-treatment mp-MRI as described in Section 3.2.1. Patients received a 10-minute IV infusion of 4 mg/kg TOOKAD. The drug was activated in the predetermined treatment zone by local illumination with laser light at 753 nm with a fixed power of 150 mW/cm over 22 minutes and 15 seconds.

The patient was then kept under medical surveillance in dim light for at least 6 hours. The patient was discharged from the hospital either on the evening after the procedure or on the day after the procedure if the Investigator decided to keep him hospitalized overnight. Post-treatment mp-MRI was performed 7 days after the TOOKAD VTP procedure.

If a patient had bilateral cancer, the lobe with the largest tumor burden was treated first; a second TOOKAD VTP hemiablation of the contralateral could be performed within 12 months. Additional treatment of lobes found positive for cancer at 12 months of follow-up was allowed. No additional TOOKAD VTP treatment occurred after 24 months.

5.3.1.1.2 Active Surveillance

Active surveillance was conducted in line with existing recommendations at the time (Mottet et al 2015; Thompson et al 2007) and included PSA testing at 3-month intervals, physical examinations, and annual prostate biopsy (Azzouzi et al 2015). No initial therapeutic intervention was included as part of active surveillance.

5.3.1.2 Enrollment Criteria

A full list of inclusion and exclusion criteria can be found in Appendix 11.1.

To participate in Study 301, patients had to meet the following key inclusion criteria:

- Low-risk prostate cancer diagnosed with 1 existing TRUS-guided biopsy using from 10 to 24 cores performed less than 12 months prior to enrollment and showing the following:
  - Gleason 3 + 3 prostate adenocarcinoma, as a maximum
  - 2 to 3 cores positive for cancer (patients with only 1 positive core could be included provided they had at least 3 mm of cancer core length)
  - A maximum cancer core length of 5 mm in any core
- Cancer clinical stage up to T2a (pathological or radiological up to T2c disease permitted)
- PSA of 10 ng/mL or less (5 ng/mL or less for patients using a 5-α-reductase inhibitor)

Patients with any prior or current treatment for prostate cancer, including surgery, radiation therapy (external or brachytherapy), or chemotherapy; any surgical intervention for benign prostatic hypertrophy; or a life expectancy < 10 years were excluded from the study.

5.3.1.3 Efficacy Endpoints

Study 301 included 2 co-primary endpoints:

- Rate of local disease progression: defined as progression of cancer from low to moderate or higher risk over the 24 months of follow-up where progression is defined as one of the following events.
  - More than three cores definitively positive for cancer when considering all histological results available during follow-up in the study
  - Any Gleason primary or secondary pattern of four or more
  - At least one cancer core length >5 mm
  - PSA > 10 ng/mL in three consecutive measures
  - Any T3 prostate cancer
  - Metastasis
  - Prostate cancer-related death
- Rate of absence of cancer: defined as absence of any histology result definitively positive for cancer at 24 months. To meet this endpoint patients needed a negative biopsy result. Within the ITT analysis, a missing biopsy and a positive biopsy from a previously untreated lobe were counted as positive.

The secondary efficacy endpoints were defined as follows:

- Total number of cores positive for cancer: the total number of positive cores observed during follow-up is calculated, for each biopsy, by adding the number of positive cores observed in each of the right and left lobes.

- Notification of initiation of any radical therapy (any radical treatment for prostate cancer other than the treatment to which the patient was randomized, including surgery, radiotherapy [external beam, brachytherapy], whole gland HIFU or cryotherapy, hormonal therapy for cancer, or chemotherapy for cancer)
- Proportion of patients with a severe prostate cancer-related event: cancer extension to T3, metastasis, or prostate cancer-related death

Validated questionnaires, the IPSS and IIEF, were included as safety assessment to assess genitourinary-associated effects, specifically incontinence, erectile dysfunction, and urinary symptoms (see Appendices 11.2 and 11.3). Data from the questionnaires were also used to support the potential clinical benefit of treatment with TOOKAD VTP compared to active surveillance

5.3.1.4 Adjudication Committee

The Month 12 and Month 24 biopsies were read centrally by an independent pathologist who was blinded to treatment assignment and to the local pathologist reading, and all the cases for which this reading was discrepant with the local pathologist reading were adjudicated by the pathologist of an ORP. The ORP, an independent and blinded panel (composed of a urologist, a pathologist with demonstrated expertise in prostate cancer, and a statistician) reviewed efficacy data to assess the co-primary endpoints. The ORP reviewed TRUS-guided biopsy reports for all patients and any other pathological report available at any time during the follow-up period to determine the characteristics of cores positive for cancer (ie, Gleason Score, cancer length, number of cores positive) observed per lobe.

5.3.1.5 Statistical Methods

5.3.1.5.1 Sample Size

The sample size calculation was based on co-primary endpoint of progression to moderate- or higher risk cancer. The expected rate of progression of cancer from low to moderate or higher risk in the active surveillance group was expected to be of at least 15% over 2 years (or 7.5 per 100 person-years). This rate was derived from several sources:

- The percentage of patients crossing over to radical therapy in studies of active surveillance varies from 25% to 38% over 2 to 5 years.
- A model developed by the Sponsor using the probability of observed progression at each TRUS core.

The expected rate of failure in the TOOKAD VTP group was estimated to be 5% over 2 years or 2.5 per 100 person-years on the basis of Phase 2 trial results accumulated to date.

The following assumptions were made to calculate the sample size:

- The proportion of patients with treatment failure at 2 years would be 15% in the active surveillance group and 5% in the TOOKAD VTP group (an HR of 0.32 in favor of TOOKAD VTP).

- For the purposes of sample size calculation, the 2-sided significance level was set to 0.025 to account for the fact that 2 co-primary endpoints were to be tested; however, each co-primary endpoint was analyzed at the 0.05 significance level using the Hochberg procedure to control for multiplicity.
- The power required for each co-primary endpoint was 80%.

Using these assumptions, the sample size required for the co-primary disease progression endpoint was 400 patients (200 patients per group) with at least 40 events (patients with progression of cancer) needed for the final analysis to take place.

5.3.1.5.2 Analysis Populations

The analysis populations included the following:

- Intent-To-Treat (ITT) Population: all randomized patients; patients were analyzed as randomized.
- Modified ITT (mITT) Population: all patients in the ITT Population randomized to the TOOKAD VTP group who received any amount of TOOKAD or initiated any study treatment-related procedure (including initiation of pre-procedure anesthesia) and all patients in the ITT Population randomized to the active surveillance group. The patients were analyzed as randomized.
- Per-protocol (PP) Population: all patients in the ITT Population, randomized to either group, who had no major protocol violations.
- Safety Population: The Safety Population includes all patients randomized to the TOOKAD VTP treatment group who received any amount of TOOKAD or initiated any study treatment-related procedure (including initiation of pre-procedure anesthesia) and all patients randomized to the active surveillance group. The patients were analyzed as treated.

The ITT Population was used for all demographic and efficacy endpoints; the mITT and the PP Populations were used for primary efficacy endpoints, and the Safety Population was used for safety endpoints.

5.3.1.5.3 Endpoint Assessments

Co-primary Endpoint: Local Disease Progression

Local disease progression was analyzed using survival analysis methods. Progression was defined as the first occurrence of an examination meeting the criteria for progression to moderate- or higher risk cancer. Distribution of events occurring over time during follow-up was estimated using the Kaplan-Meier method. The estimated progression rates and associated 95% CI were calculated at Months 6, 12, 18, and 24.

Time to progression was compared between the 2 treatment groups using the log-rank test and the crude HR at 24 months comparing TOOKAD VTP versus active surveillance and the associated 95% CI were calculated, using a Cox proportional hazards regression model.

Co-primary Endpoint: Absence of Cancer

Absence of cancer was analyzed as a dichotomous outcome, ie, success (absence of any histology result definitely positive for cancer) or failure (presence of at least 1 result definitely positive for cancer). Patients who dropped out before Month 3 or before the administration of TOOKAD VTP were counted as failures. Patients who dropped out between Month 3 and Month 24 were asked to undergo a biopsy at Month 24 in order to avoid missing values. If a patient did not undergo the Month 24 biopsy, he was counted as a failure. Proportions of patients with observed success were compared between the 2 treatment arms using a Pearson's chi-square test. In addition, the crude odds ratio and the risk ratio at 24 months comparing TOOKAD VTP versus active surveillance and the associated 95% CI were presented.

Adjustment for Multiplicity

The analysis of both co-primary efficacy endpoints took place when at least 40 events (patients with disease progression) were observed and all patients had undergone the Month 24 TRUS-guided biopsy. The Hochberg procedure was used to adjust for multiplicity of the 2 co-primary endpoints.

Initiation of Any Radical Therapy

Additional radical prostate cancer therapy was defined as any whole gland treatment for prostate cancer other than the treatment to which the patient was randomized. The time to initiation of radical therapy was estimated using the Kaplan-Meier method. The median and quartiles of time to initiation of radical therapy were presented together with the corresponding 95% CI. The log-rank test was used to compare the time to initiation of radical therapy between the 2 treatment groups. Patients who did not initiate any radical therapy were censored at the time of study completion.

Tumor Burden

The total number of positive cores observed during follow-up was calculated for each biopsy by adding the number of positive cores observed in each of the right and left lobes. The mean total number of cores positive for cancer was compared between the 2 treatment groups using a Student t-test. The mean of the maximum cancer core length was compared between the 2 treatment groups at Month 12 and Month 24 using a Student t-test. In addition, the number and percentage of patients with a maximum cancer core length $\geq$ 5 mm or < 5 mm at Months 12 and 24 were also presented by treatment group.

5.3.1.5.4 Subgroups

A subgroup efficacy analysis was performed by disease status at Baseline (unilateral or bilateral). A post hoc analysis was also performed in which patients with unilateral disease were further divided into subgroups of very low and low risk patients.

5.3.1.5.5 Sensitivity

Sensitivity analyses included parametric estimations of time to progression for the ITT Population. Adjusted analyses for both co-primary endpoints were also conducted.

For local disease progression, since patients who withdrew from the study or opted for radical treatment before prostate cancer progression were censored at the time they left the study (ie, they were not considered failures for the purposes of the primary analysis), a sensitivity analysis using a Cox proportional hazards model was conducted in which all those patients were assumed to be failures (defined as worst-case scenario per the Statistical Analysis Plan) to assess the potential impact of withdrawals and patient choice on the study outcome.

For absence of cancer, multivariate modeling using a logistic regression was applied. The regression model incorporated Baseline assessment of age, number of cores positive with cancer, prostate volume, and disease status (ie, unilateral or bilateral) in addition to treatment to provide an adjusted comparison of the 2 treatment groups with respect to the probability of success/failure for co-primary of absence of cancer and the HR of disease progression. In the Cox model analysis, the proportional hazard assumption was checked graphically by plotting the log(-log[survival]) and was to be relaxed if necessary.

Post hoc sensitivity analyses included time to progression in patients with retreatment and assessment on a per initially treated lobe basis, as well as in patients meeting various definitions of disease progression as requested by the FDA.

5.3.1.5.6 Missing Data

As described in Section 5.3.1.5.3, a sensitivity analysis was conducted to test the robustness of primary efficacy results with respect to patients who withdrew from the study or opted for radical treatment before prostate cancer progression. No other imputation process was undertaken for missing data.

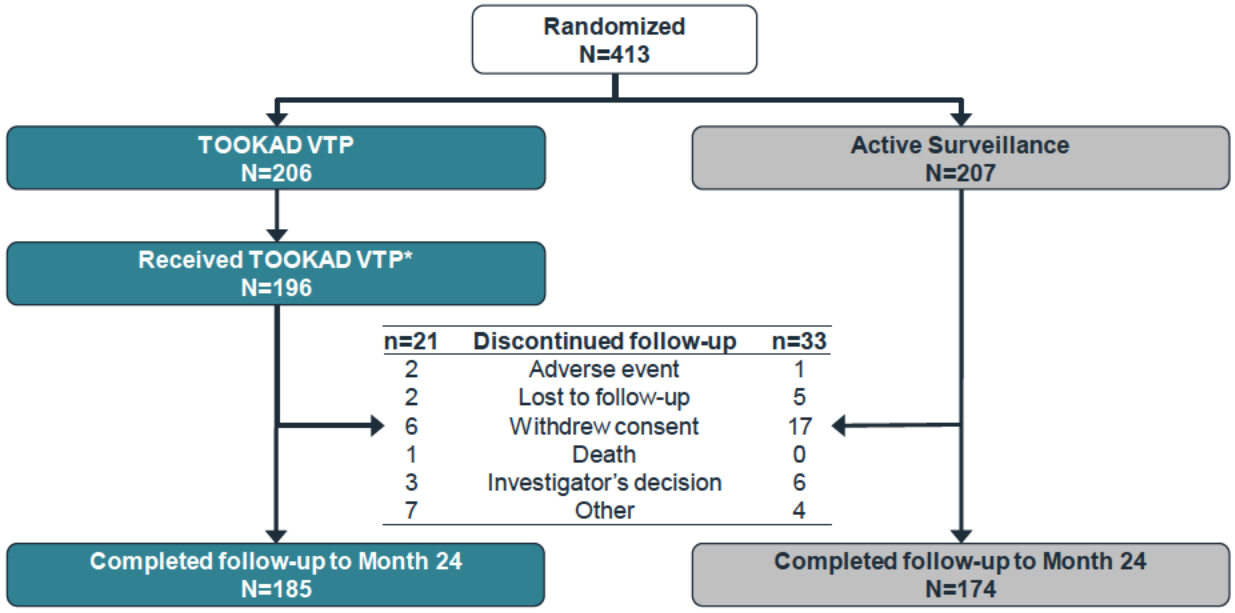
5.3.2 Study Population

5.3.2.1 Patient Disposition

For the primary endpoint analysis at 24 months, fewer patients in the TOOKAD VTP group than in the active surveillance group withdrew consent before study completion (3% in the TOOKAD VTP arm vs 8% in the active surveillance arm) (Figure 15). Percentage of study completion (90% in the TOOKAD VTP arm and 84% in the active surveillance arm) and reasons for termination were similar between the treatment arms. Few patients in either arm discontinued because of an AE (1.0% in the TOOKAD VTP arm and 0.5% for the active surveillance arm).

A summary of VTP treatments received by patients in the TOOKAD VTP treatment arm is provided in Section 5.3.2.1.1.

Figure 15: Patient Disposition in Study 301

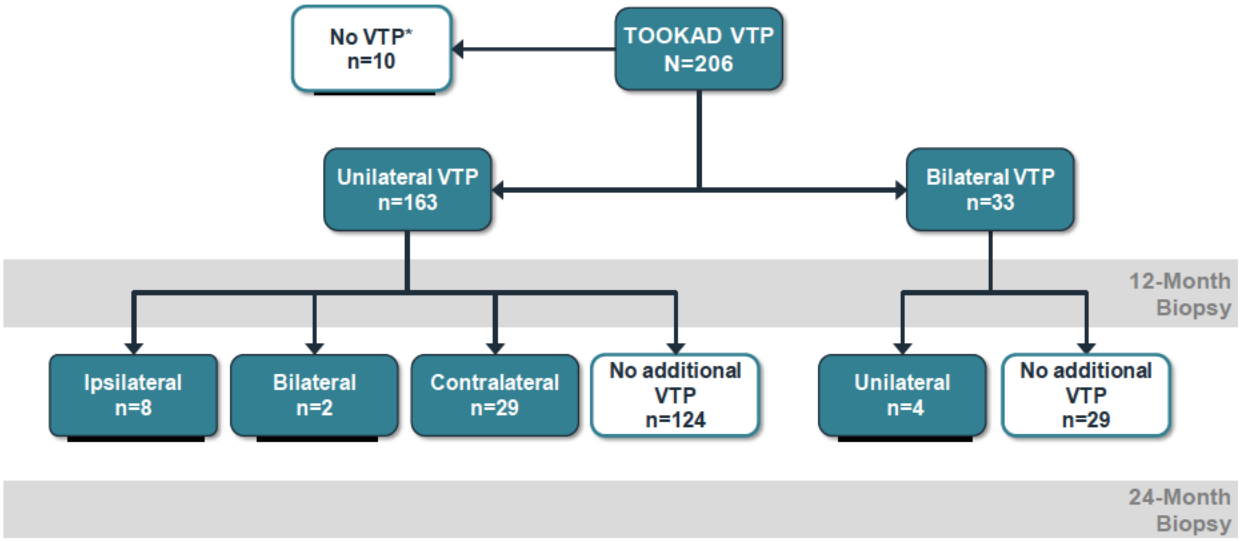


VTP = vascular-targeted photodynamic therapy
* one patient had an anaphylactic reaction to procedure anesthesia and did not receive any amount of TOOKAD. This patient is included in the mITT and safety populations but is not included among patients who received TOOKAD.

5.3.2.1.1 TOOKAD VTP Treatment Flow

Per protocol, retreatment was permitted in Study 301. Of the 206 patients randomized to the TOOKAD VTP arm, 10 patients did not receive TOOKAD VTP (Figure 16). A total of 163 patients received planned unilateral treatment and 33 received planned bilateral treatment. Following the 12 months biopsy, 29 of the 163 patients who received planned unilateral treatment received sequential contralateral treatment and 4 of the 33 patients who received planned bilateral treatment received an additional TOOKAD VTP. Overall, 14 patients received retreatment of a previously treated lobe.

Figure 16: TOOKAD VTP Treatment Patterns in Study 301



mITT = modified intent-to-treat; VTP = vascular-targeted photodynamic therapy
* One patient had an anaphylactic reaction to procedure anesthesia and did not receive any amount of TOOKAD. This patient is included in the mITT and safety populations but is not included among patients who received TOOKAD.

5.3.2.2 Patient Demographics and Baseline Characteristics

The demographic characteristics were well-balanced between the 2 treatment groups (Table 10). The age of patients enrolled was similar to the target population for TOOKAD VTP, men diagnosed with low-risk localized prostate cancer. As expected for a European study, almost all of the patients were Caucasian.

Table 10: Patient Demographics in Study 301

Characteristic	TOOKAD VTP N = 206	Active Surveillance N = 207
Age (years)[a]		
Mean (SD)	64.2 (6.7)	62.9 (6.7)
Q1	59.0	59.0
Q3	68.0	67.0
Race		
Caucasian, n (%)	202 (98.1)	206 (99.5)
Black, n (%)	3 (1.5)	0
Asian, n (%)	0	1 (0.5)
Other, n (%)	1 (0.5)	0
Body mass index (kg/m^2)		
Mean (SD)	26.5 (3.4)	27.3 (3.9)
Range: minimum, maximum	18.8, 38.6	18.8, 44.8

Q = quartile; SD = standard deviation; VTP = vascular-targeted photodynamic therapy
a. $p = 0.051$ from Student *t*-test

The baseline disease characteristics were also well-balanced between the 2 groups and fit the profile of low-risk prostate cancer patients (Table 11).

Table 11: Patient Baseline Disease Characteristics – Study 301 ITT Population

Characteristic	TOOKAD VTP N = 206	Active Surveillance N = 207
Time since diagnosis (months)		
Mean (SD)	6.34 (8.536)	6.02 (7.887)
Range: minimum, maximum	0.2, 54.2	0.2, 47.4
TNM staging		
T1a, n (%)	1 (0.5)	0
T1c, n (%)	177 (85.9)	180 (87.0)
T2a, n (%)	28 (13.6)	27 (13.0)
PSA (ng/mL)		
Mean (SD)	6.19 (2.114)	5.91 (2.049)
Range: minimum, maximum	0.1, 10.0	0.5, 10.0
Estimated prostate volume (cc)[a]		
Mean (SD)	42.5 (12.49)	42.5 (11.76)
Range: minimum, maximum	25, 70	25, 70
Unilateral disease, n (%)	157 (76.2)	163 (78.7)
Bilateral disease, n (%)	49 (23.8)	44 (21.3)
Total number of cores		
Mean (SD)	13.6 (3.31)	13.6 (3.55)
Range: minimum, maximum	10, 25	10, 26
Total number of positive cores[b]		
Mean (SD)	2.1 (0.68)	2.0 (0.72)
Range: minimum, maximum	1, 3	1, 3
1 positive core, n (%)	39 (18.9)	52 (25.1)
2 positive cores, n (%)	110 (53.4)	100 (48.3)
3 positive cores, n (%)	57 (27.7)	55 (26.6)
Total cancer core length (mm)		
Mean (SD)	4.3 (2.31)	3.8 (2.40)
Range: minimum, maximum	0[c], 14	0[c], 11

PSA = prostate-specific antigen; SD = standard deviation; TNM = tumor, nodes, metastasis; VTP = vascular-targeted photodynamic therapy
a. p = 0.995 from Student t-test
b. p = 0.291 from Student *t*-test
c. Some of the patients included on the basis of 2 biopsies at the beginning of the study had 1 of those 2 biopsies negative.

5.3.3 Co-Primary Efficacy Endpoints

5.3.3.1 Local Disease Progression (Treatment Failure)

The study met the co-primary endpoint of local disease progression with significantly longer time to progression (Table 12). The HR for the rate of progression over 24 months was 0.34 (crude 95% HR CI: 0.25–0.47), indicating that the rate of progression in the TOOKAD VTP arm

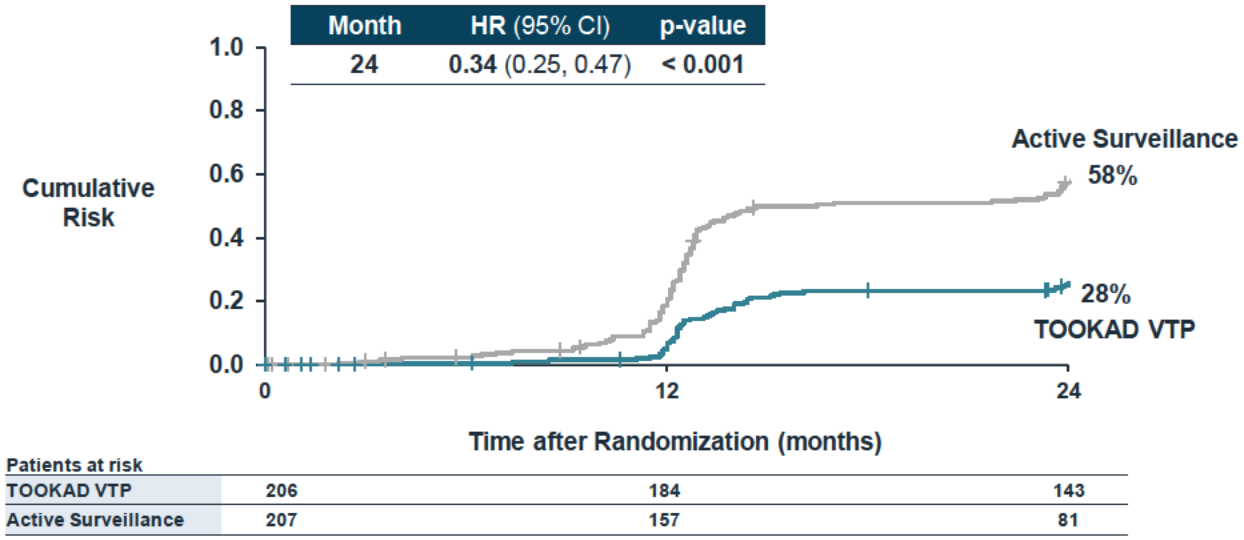
was approximately one-third that of patients in the active surveillance arm. The time to progression Kaplan-Meier analysis is shown in Figure 17.

Table 12: Progression by Treatment Group – Kaplan-Meier Analysis – Study 301 ITT Population

Estimated proportion (95% CI) of patients progressed by	TOOKAD VTP N = 206 n (%)	Active Surveillance N = 207 n (%)
6 months	0.5 (0.1, 3.5)	2.5 (1.0, 5.9)
12 months	7.2 (4.3, 11.8)	21.1 (16.0, 27.6)
18 months	24.1 (18.6, 30.8)	53.3 (46.4, 60.6)
24 months	27.1 (21.3, 34.1)	60.1 (53.1, 67.3)
p-value[a]	< 0.001	

CI = confidence interval; ITT = intent-to-treat; VTP = vascular-targeted photodynamic therapy.
a. From the log-rank test of equality of survival curves across treatment groups

Figure 17: Time to Progression – Kaplan-Meier Curves – Study 301 ITT Population



CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; VTP = vascular-targeted photodynamic therapy
Note: unadjusted HR presented using Cox proportional hazards model with treatment as fixed effect

The most common criteria met for progression was Gleason score ≥ 4 (Table 13). Compared to active surveillance, fewer patient treated with TOOKAD VTP progressed for each criteria. Thus, TOOKAD VTP was effective against each of the individual parameters of the composite progression endpoint.

Table 13: Criteria for Progression by Treatment Group – Study 301 ITT Population

Number of Patients with	TOOKAD VTP N = 206 n (%)	Active Surveillance N = 207 n (%)	*p*-value[a]
Progression (all criteria)	58 (28.2)	120 (58.0)	< 0.001
Criteria for progression[b]			
Gleason ≥ 4	49 (23.8)	91 (44.0)	< 0.001
More than 3 cores positive	23 (11.2)	58 (28.0)	< 0.001
Cancer core length > 5 mm	25 (12.1)	51 (24.6)	0.001
PSA > 10 ng/mL in 3 consecutive measures	3 (1.5)	14 (6.8)	0.007
Any T3 prostate cancer	0	4 (1.9)	NA
Metastasis	0	0	NA
Prostate cancer-related death	0	0	NA

NA = not applicable; PSA = prostate-specific antigen; VTP = vascular-targeted photodynamic therapy.
a. From Pearson's chi-square test
b. A patient might have met > 1 criterion for progression.

5.3.3.1.1 Sensitivity Analyses

Several predefined sensitivity analyses were performed for local disease progression in the ITT Population. Although different worst-case scenarios could be envisioned, the SAP defined "Worst Case Scenario" considered all patients who withdrew from the study or opted for radical treatment before prostate cancer progression to be treatment failures. Within the primary analysis, if a patient progressed but then had an additional VTP procedure they were considered as failures at the time of first progression. Within the "Including Retreatment" sensitivity analysis the Month 12 biopsy result was ignored and only the Month 24 result was taken into account which allowed a patient to be reverted back to non-progressor status following a repeat VTP. The "Treated Lobe" sensitivity analysis looked at progression only in the initially treated lobes which are the 163 unilaterally treated lobes and 33 bilaterally treated lobes prior to the 12-month biopsy. In all these analysis, the results remained statistically significant (Figure 18). Sensitivity analysis results in the mITT and PP populations were similar to those observed in the ITT Population.

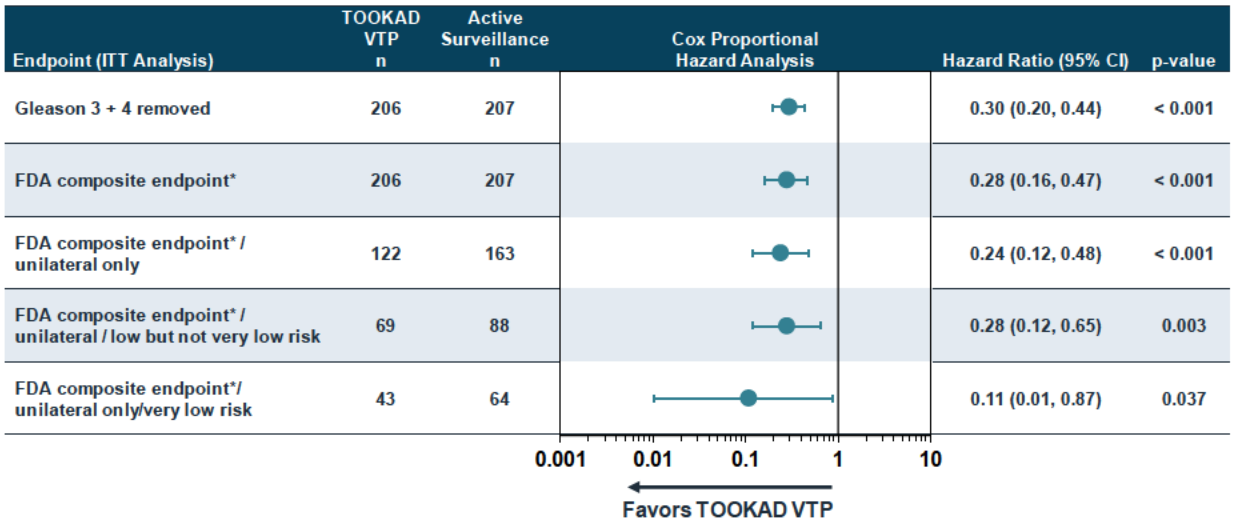
Figure 18: Local Disease Progression – Unadjusted Cox Proportional Hazard Sensitivity Analyses – Study 301

Population	TOOKAD VTP n	Active Surveillance n	Cox Proportional Hazard Analysis	Hazard Ratio (95% CI)	p-value*
ITT	206	207		0.34 (0.25, 0.47)	< 0.001
mITT	197	207		0.34 (0.25, 0.47)	< 0.001
PP	167	181		0.33 (0.24, 0.46)	< 0.001
Worst Case Scenario – ITT	206	207		0.38 (0.29, 0.51)	< 0.001
Worst Case Scenario – mITT	197	207		0.33 (0.25, 0.45)	< 0.001
Worst Case Scenario – PP	167	181		0.32 (0.23, 0.45)	< 0.001
Including Retreatment – ITT	206	207		0.24 (0.17, 0.34)	< 0.001
Including Retreatment – mITT	197	207		0.24 (0.17, 0.34)	< 0.001
Including Retreatment – PP	167	181		0.22 (0.15, 0.32)	< 0.001
Treated Lobe – ITT	206	207		0.18 (0.12, 0.28)	< 0.001
Treated Lobe – mITT	197	207		0.18 (0.12, 0.28)	< 0.001
Treated Lobe – PP	167	181		0.17 (0.11, 0.26)	< 0.001

CI = confidence interval; ITT = intent-to-treat; mITT = modified intent-to-treat; PP = per-protocol
*p-value comes from a Cox proportional hazard model with treatment as fixed effect
Note 1: Per the Statistical Analysis Plan, worst case was defined as counting patients who withdrew from study or opted for radical prostate treatment before prostate cancer progression to be failures.
Note 2: Including retreatments defined as including patients who have progressed at Month 12 and have had a subsequent retreatment by VTP, the Month 12 result is ignored and only the Month 24 result is taken into account. For all the other patients (including active surveillance), the date taken is the first occurrence of progression.

In addition, sensitivity analyses were conducted using various definitions of disease progression as requested by the FDA (Figure 19). With the exception of the composite endpoint in the very low risk patients with unilateral treatment, the results remained statistically significant.

Figure 19: Local Disease Progression – Additional Sensitivity Analyses – Study 301



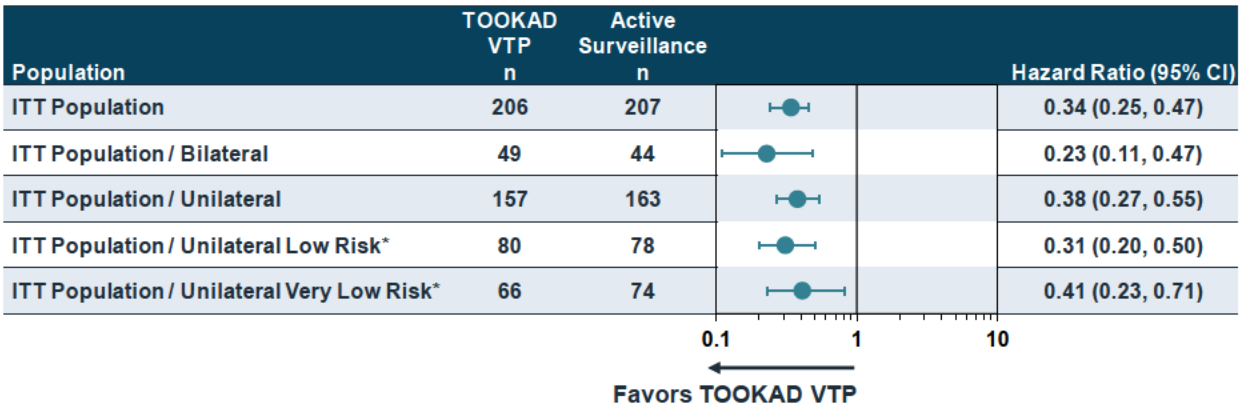
CI = confidence interval; FDA = Food and Drug Administration; PSA = prostate-specific antigen; ITT = intent-to-treat
*Failure is observation of 1 of the following events: a) at least 2 of the followings: i. T2b–T2c, ii. Gleason 3+4 or Gleason 4+3, iii. PSA 10–20 ng/mL; b) Gleason ≥ 4+3 (including both 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; f) metastasis; g) prostate cancer-related death

5.3.3.1.2 Subgroup Analyses

A subgroup efficacy analysis was performed by disease status at Baseline (unilateral, or bilateral). Analysis of rate of progression rate and time to progression in the other analysis populations and in the disease status subgroups (unilateral or bilateral disease at Baseline) showed similar results to those in in the ITT Population (Figure 20).

When the unilateral subgroup is further divided into very low and low risk patients, the hazard ratio is lower for the low risk than in the very low risk subgroup, which indicates a greater benefit in terms of reduction of need for radical treatment. However, the 95% CIs overlap for the different subgroups.

Figure 20: Progression Hazard Ratios and 95% Confidence Intervals – Cox Proportional Hazards Model – Study 301



CI = confidence interval; ITT = intent-to-treat; VTP = vascular-targeted photodynamic therapy
* Excludes patients older than 75 or with significant morbidities
Note: very low = up to 2 positive cancer cores and PSA density ≤ 0.15ng/mL/cm^3

5.3.3.2 Absence of Cancer

TOOKAD VTP produced a statistically significant improvement in the patient's probability of a negative biopsy result at 24 months after treatment (Table 14); patients in the TOOKAD VTP arm were 3.62 times as likely to have a negative biopsy as patients in the active surveillance arm. Results at 12 months after treatment showed an improvement of 2.40 times.

Table 14: Absence of Any Histology Result Definitively Positive for Cancer – Study 301 ITT Population

Visit	Patients with Negative Biopsy		TOOKAD VTP vs Active Surveillance		
	TOOKAD VTP N = 206 n (%)	Active Surveillance N = 207 n (%)	Risk Ratio (95% CI)	Odds Ratio (95% CI)	*p*-value[a]
Month 12	98 (47.6)	41 (19.8)	2.40 (1.76, 3.27)	3.67 (2.37, 5.69)	< 0.001
Month 24	101 (49.0)	28 (13.5)	3.62 (2.50, 5.26)	6.15 (3.79, 9.97)	< 0.001

CI = confidence interval; ITT = intent-to-treat; VTP = vascular-targeted photodynamic therapy
a. From Pearson's chi-square test for observed success

At Month 24, the number of patients for whom a prostate biopsy was expected (ie, patients who had not converted to radical therapy) but for whom no biopsy was performed was low and equivalent in the treatment arms (Table 15). The apparently high overall number of patients with no biopsies at Month 24 was driven by treatment failure and consequent radical therapy, particularly in the active surveillance arm. Note that if a patient received radical therapy, it was not possible to perform a biopsy.

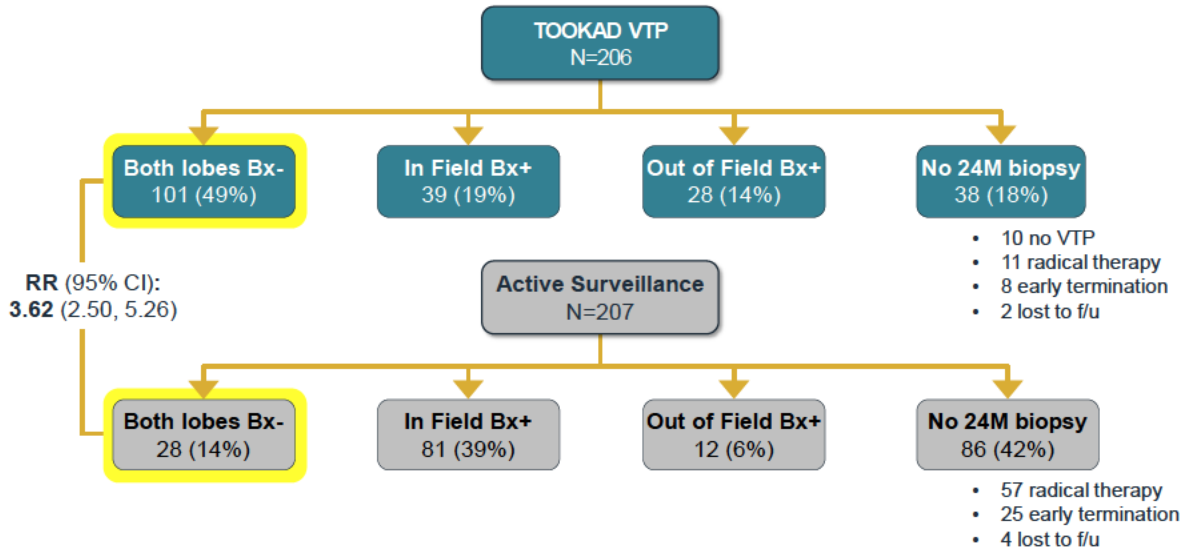
Table 15: Biopsy Results at Month 24 – Study 301 ITT Population

Number of Patients with	TOOKAD VTP N = 206	Active Surveillance N = 207
Negative biopsy, n (%)	101 (49.0)	28 (13.5)
Relative Risk (95% CI)	3.62 (2.50–5.26)	
No biopsy result, n (%)	38 (18.4)	86 (41.5)
Patients who had radical therapy, n (%)	12 (5.8)	55 (26.6)
Other reasons[a], n (%)	26 (12.6)	31 (15.0)
Positive biopsy, n (%)	67 (32.5)	93 (44.9)

CI = confidence interval; ITT = intent-to-treat; VTP = vascular-targeted photodynamic therapy
a. For example: Study withdrawal, medical reason, patient refusal

In Figure 21, the 24-month biopsy results for the ITT Population are presented by treatment field. The in-field biopsy rate was 19% for the TOOKAD VTP arm compared with 39% in the active surveillance arm.

Figure 21: In-field and Out-of-field 24-Month Biopsy Results Study – 301 ITT Population



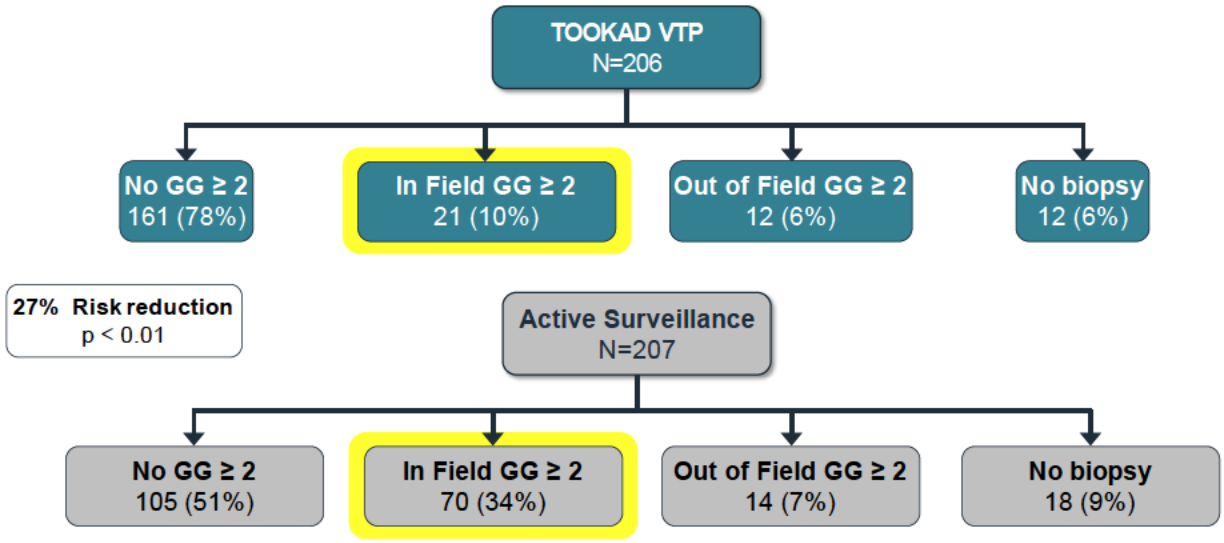
Bx+ = positive biopsy; Bx - = negative biopsy; f/u = follow up; VTP = vascular-targeted photodynamic therapy
In field = within a lobe that was diagnosed as positive at baseline; Out of field = within a lobe without cancer diagnosis at baseline

5.3.3.3 Absence of Grade Group ≥ 2 Cancer

Because the ITT analysis loses the resolution of the biopsy that resulted in conversion to radical therapy, an analysis was performed which included only the most recent biopsy results through to Month 24 (instead of only including those with Month 24 biopsy results) and only progression to Grade Group 2 or higher. This analysis provided information regarding the biopsy results at 12 months that likely triggered conversion to radical therapy and provided an assessment of local control of disease. The missing biopsy rate was less than 10% and similar in both treatment arms,

as was the out of field Grade Group ≥ 2 rate. There was a > 3 fold difference between the rate of Grade Group ≥ 2 being observed in field (within lobes initially diagnosed with cancer) which corresponds to a 24% reduction. Considering the prostate as a whole, within the ITT analysis, a highly significant 27% reduction in the Grade Group ≥ 2 was observed at 24 months ($p < 0.01$) (Figure 22). This reduction is driven almost exclusively by the reduction in Grade Group ≥ 2 disease in field for those patients treated with TOOKAD VTP.

Figure 22: Progression Grade Group ≥ 2 Using Most Recent Biopsy – Study 301



GG = Group Grade; VTP = vascular-targeted photodynamic therapy
In field = within a lobe that was diagnosed as positive at baseline; Out of field = within a lobe without cancer diagnosis at baseline

5.3.4 Secondary Endpoints

5.3.4.1 Initiation of Radical Therapy

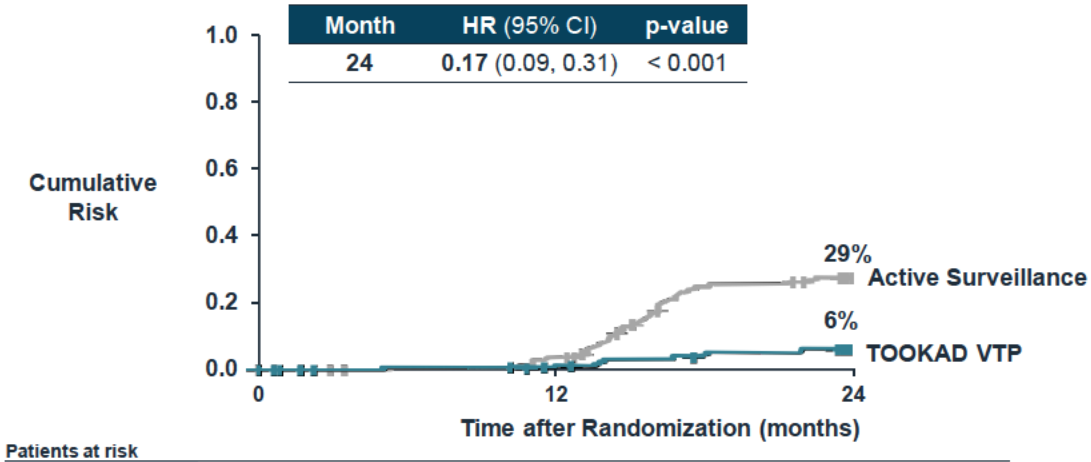
Avoidance of radical therapy is a key goal of conservative treatments such as targeted therapy and active surveillance, as it is typically associated with preserving genitourinary functions. Table 16 and Figure 23 show that statistically fewer patients required radical therapy after TOOKAD VTP, and when radical therapy occurred, it tended to occur later for patients who had received TOOKAD VTP ($p < 0.001$).

Table 16: Time to Initiation of Radical Therapy by Treatment Group – Kaplan- Meier Analysis – Study 301 ITT Population

Characteristic	TOOKAD VTP N = 206	Active Surveillance N = 207
Number of patients who initiated a radical treatment, n (%)[a]	12 (5.8)	60 (29.0)
Patients who initiated radical therapy at, % (95% CI)[a,b]		
6 months	0.5 (0.1, 3.5)	0.0 (0.0, 0.0)
12 months	1.0 (0.3, 4.0)	4.1 (2.1, 8.0)
18 months	4.7 (2.5, 8.8)	26.5 (20.8, 33.4)
24 months	6.2 (3.6, 10.7)	30.8 (24.8, 38.0)

CI = confidence interval; VTP = vascular-targeted photodynamic therapy.
a. The percentage of patients who had radical therapy at each time point is an estimate from Kaplan-Meier analysis and thus differs from the percentage of patients who initiated radical therapy over the course of the study.
b. Calculated from the standard Kaplan-Meier curve analysis

Figure 23: Time to Initiation of Radical Therapy by Treatment Group – Kaplan-Meier Curves – Study 301 ITT Population



ITT= intent-to-treat; VTP = vascular-targeted photodynamic therapy

5.3.4.2 Severe Prostate Cancer-Related Events

By 24 months, one patient in the TOOKAD VTP arm and 11 in the active surveillance arm reported T3 disease, and one patient in each arm had metastasis based on local assessment. This assessment did not differentiate between cT3 disease versus T3 status being determined based on a radical prostatectomy specimen or clinically observed metastasis (for example, diagnosed following a bone scan) versus a positive node found during radical prostatectomy.

A post hoc analysis was done determine the rate of cT3 disease versus any T3, as well the rate of clinically observed metastasis versus metastasis found during radical prostatectomy. ORP assessments were used. Patients whose T3 disease or metastasis was associated with radical

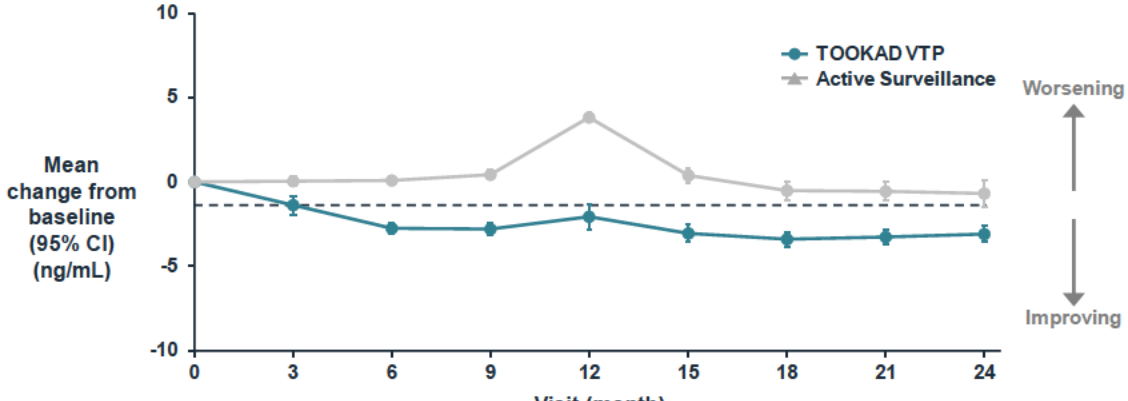
prostatectomy were excluded from the sum. No TOOKAD VTP treated patients had either cT3 disease or clinical diagnosis of metastasis. Four patients in the active surveillance arm had cT3 disease and none had clinically diagnosed metastasis.

5.3.5 Other Efficacy Endpoints

5.3.5.1 PSA Levels

The post-Baseline mean PSA values in the TOOKAD VTP arm were substantially lower than both the mean values at the corresponding time points in the active surveillance arm and the TOOKAD VTP arm baseline value (Figure 24). Mean PSA values in the active surveillance arm remained at about the same level throughout the study, except for an increase at Month 12. The increase at Month 12 is likely caused by outlier values in 4 patients from samples obtained after TRUS-guided biopsy. A stable reduction of about 3 ng/mL occurred over the study period in the TOOKAD VTP arm.

Figure 24: Prostate-Specific Antigen Mean Change from Baseline by Treatment Group – Study 301 ITT Population



Observations (n)									
TOOKAD VTP	206	176	189	184	185	164	171	175	178
Active Surveillance	207	192	193	186	182	163	161	148	160

CI = confidence interval; ITT = intent-to-treat; VTP = vascular-targeted photodynamic therapy

5.3.5.2 Tumor Burden

The differences between the 2 treatment arms in all measures of tumor burden (total number of positive cores, total cancer core length, and maximum cancer core length) were statistically significant at Month 12, and the differences were maintained through 24 months after treatment (Table 17).

The percentage of patients undergoing a biopsy at Month 12 were similar in the 2 arms (93% in the TOOKAD VTP arm, 90% in the active surveillance arm). In contrast, the difference in percentages at Month 24 (82% in the TOOKAD VTP arm, 59% in the active surveillance arm) is a result of the large number of patients whose disease progression was observed at the Month 12 biopsy and underwent radical prostatectomy or other radical treatment, making them unavailable for biopsy at Month 24.

Table 17: Tumor Burden by Treatment Group at Months 12 and 24 (Local Pathologist Assessment) – Study 301 ITT Population

Characteristic	Month 12		Month 24	
	TOOKAD VTP N = 206	Active Surveillance N = 207	TOOKAD VTP N = 206	Active Surveillance N = 207
Total number of cores				
Number of observations	192	186	168	121
Mean (SD)	12.8 (2.41)	13.4 (3.32)	12.6 (2.14)	13.0 (3.26)
p-value	0.056		0.249	
Range: minimum, maximum	8, 27	9, 32	8, 23	4, 27
Total number of positive cores				
Number of observations	192	186	169	120
Mean (SD)	0.9 (1.32)	2.3 (1.98)	0.6 (1.06)	1.7 (1.59)
p-value	< 0.001		< 0.001	
Range: minimum, maximum	0, 6	0, 10	0, 5	0, 7
Change from Baseline				
Mean (SD)	-1.2 (1.42)	0.2 (1.95)	-1.5 (1.23)	-0.3 (1.71)
p-value	< 0.001		< 0.001	
Range: minimum, maximum	-3, 4	-3, 7	-3, 4	-3, 6
Total cancer core length (mm)				
Number of observations	188	184	168	121
Mean (SD)	2.6 (5.26)	6.8 (9.26)	1.5 (4.05)	5.0 (7.88)
p-value	< 0.001		< 0.001	
Range: minimum, maximum	0, 33	0, 76	0, 32	0, 46
Change from Baseline				
Mean (SD)	-1.7 (5.71)	3.0 (9.30)	-2.8 (4.81)	1.3 (7.88)
Range: minimum, maximum	-12, 28	-8, 76	-12, 29	-8, 42
Maximum cancer core length (mm)				
Number of observations	188	184	168	121
Mean (SD)	1.6 (2.74)	3.4 (3.49)	1.0 (2.27)	3.0 (4.06)
p-value	< 0.001		< 0.001	
Range: minimum, maximum	0, 18	0, 16	0, 14	0, 21
Length categories				
< 5 mm, n (%)	165 (87.8)	133 (72.3)	156 (92.9)	97 (80.2)
≥ 5 mm, n (%)	23 (12.2)	51 (27.7)	12 (7.1)	24 (19.8)
Change from Baseline				
Mean (SD)	-1.3 (3.16)	0.8 (3.64)	-1.9 (2.68)	0.4 (4.14)
Range: minimum, maximum	-6, 17	-5, 15	-6, 11	-5, 18

ITT = intent-to-treat; SD = standard deviation; VTP = vascular-targeted photodynamic therapy.
All p-values from Student *t*-test

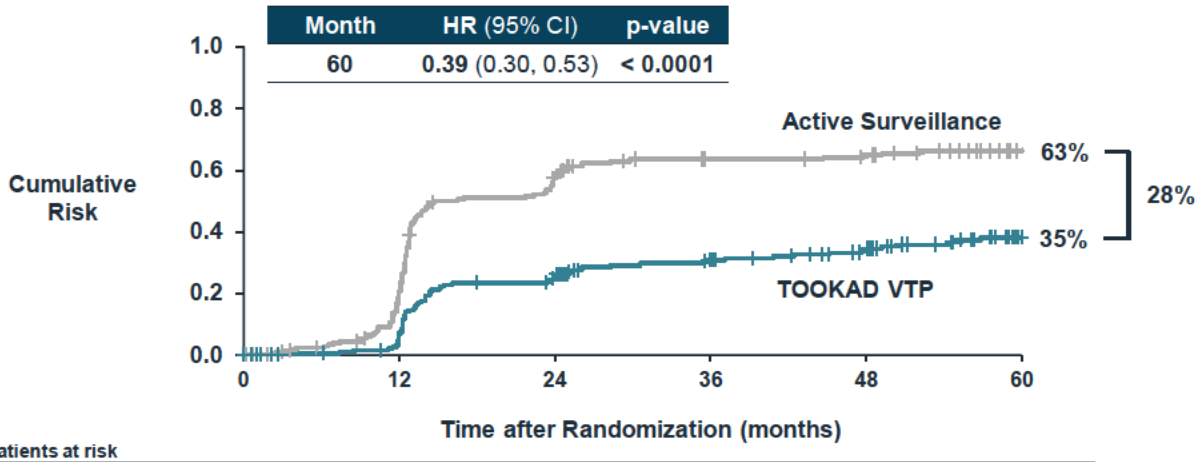
5.4 Long-term Efficacy—Study 301-FU5

Study 301-FU5 is ongoing to assess disease progression, conversion to radical therapy, and long-term safety. Following mandated prostate biopsies at 12 and 24 months, patients enrolled in the follow-up trial are being monitored at months 36, 48, 60, 72, and 84. The primary objective of the ongoing study is to assess the impact of initial treatment allocation to TOOKAD VTP on the progression from low to moderate or higher risk prostate cancer, use of other cancer therapy, or prostate cancer-related death, whichever comes first. Clinical decisions were left to physicians and patients, and management was according to local standard of care. Time to progression was also analyzed using the definition of progression from Study 301 to allow for continued long-term evaluation of the Study 301 co-primary endpoint. Interim results are presented below.

5.4.1 Time to Progression

Results from the interim follow-up data show that the time to progression, as defined in Study 301, was significantly longer in the TOOKAD VTP arm compared to active surveillance over the 5 year follow-up period (results based on ORP) (Figure 25). Overall, 220 patients reported an event: 72 (35.0%) in the TOOKAD VTP arm and 130 (62.8%) in the active surveillance arm. In the TOOKAD VTP arm, the median time had not yet been reached while in the active surveillance arm, the median time to progression was 14.7 months. The difference between the TOOKAD VTP and active surveillance arms is clinically and statistically significant, as shown by the absolute risk reduction of 28% by Month 60.

Figure 25: Time to Progression Kaplan-Meier Curves (Central Assessment) – Study 301-FU5 ITT Population

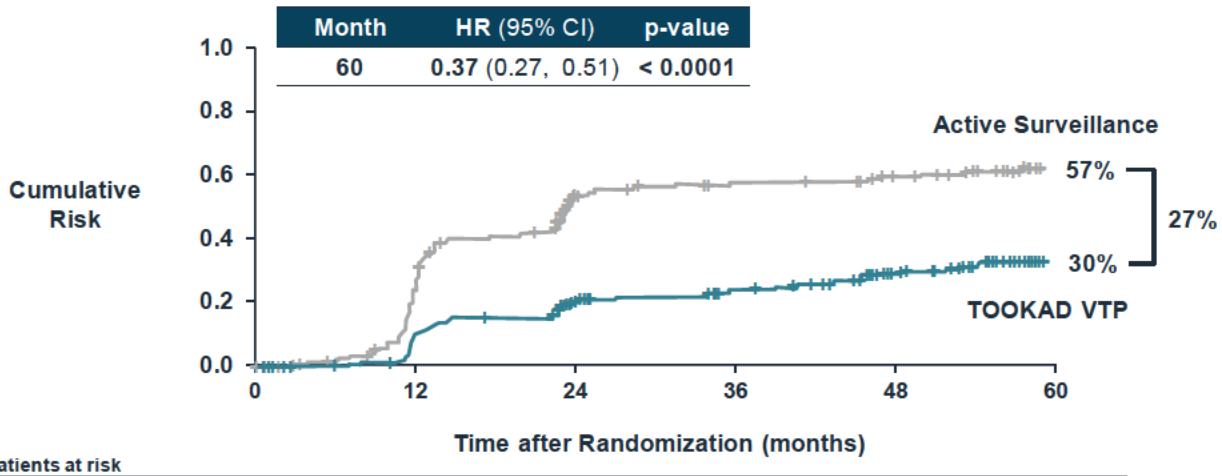


Patients at risk						
TOOKAD VTP	206	184	143	119	104	67
Active Surveillance	207	157	81	58	54	31

CI = confidence interval; HR = hazard ratio; ITT= intent-to-treat; VTP = vascular-targeted photodynamic therapy
Note: The interim analysis for Study 301-FU5 was conducted in October 2018, after the last randomized patient had reached 5 years of total follow-up time since randomization.

These results are supported by the readings based on local pathologists. Although rates of progression are lower than what was observed with the central read, the absolute difference between the 2 arms is similar and clinically meaningful (Figure 26). The results are also highly statistically significant ($p < 0.0001$), with an HR (95% CI) of 0.37 (0.27–0.51).

Figure 26: Time to Progression Kaplan-Meier Curves (Local Pathologist Assessment) – Study 301-FU5 ITT Population



Patients at risk						
TOOKAD VTP	206	188	158	131	113	73
Active Surveillance	207	163	98	66	60	39

CI = confidence interval; HR = hazard ratio; ITT= intent-to-treat; VTP = vascular-targeted photodynamic therapy

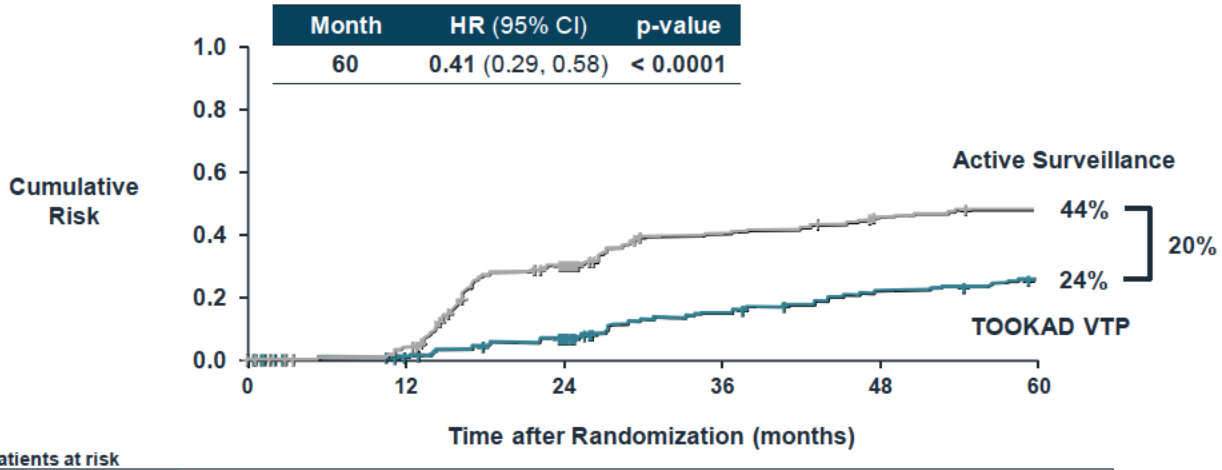
Note: The interim analysis for Study 301-FU5 was conducted in October 2018, after the last randomized patient had reached 5 years of total follow-up time since randomization.

5.4.2 Conversion to Radical Therapy

Conversion to radical treatment was further assessed in the 5-year interim analysis of Study 301-FU5. The reduction observed at Month 24 appears durable with similar absolute risk reduction observed at Month 60 in the Kaplan-Meier analysis (25.3% and 23.8% reduction respectively; Figure 27). These results show that the magnitude of absolute risk difference between arms was maintained from Year 2 through Year 5.

The clinical and statistical significance of the benefit of TOOKAD VTP versus active surveillance is further shown by the substantial HR: 0.41 (95% CI: 0.29–0.58; $p < 0.0001$). Overall, TOOKAD VTP reduced by half the number of patients converting to radical therapy, which lowers the risk of morbidities associated with radical therapies.

Figure 27: Time to Initiation of Radical Therapy by Treatment Group – Kaplan-Meier Analysis—Study 301-FU5 ITT Population



Patients at risk						
TOOKAD VTP	206	194	178	149	135	126
Active Surveillance	207	189	126	96	85	80

CI = confidence interval; HR = hazard ratio; ITT= intent-to-treat; VTP = vascular-targeted photodynamic therapy
Note: The interim analysis for Study 301-5FU was conducted in October 2018, after the last randomized patient had reached 5 years of total follow-up time since randomization.

Although fewer patients in the TOOKAD VTP arm reported disease progression than in the active surveillance arm, at 60 months, a similar proportion of patients received radical therapy after disease progression in both treatment groups (67.2% and 66.1%) (Table 18). In addition, of those patients receiving radical therapy a similar proportion had disease progression in both arms (80.4% and 83.0%).

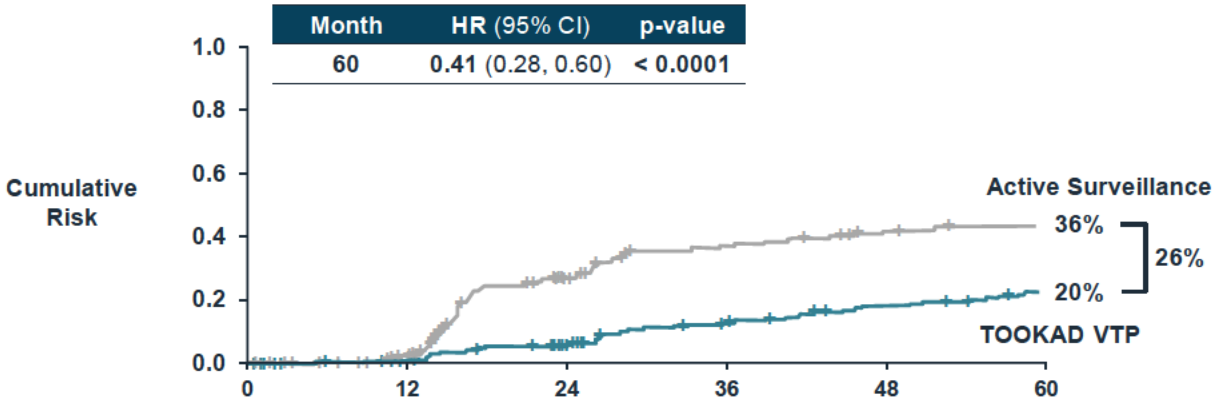
Table 18: Comparison of Patients who Received Radical Therapy – Study 301-FU5 ITT Population

Category	TOOKAD VTP N = 206	Active Surveillance N = 207
Reported disease progression, n	61	118
Received radical therapy or hormone therapy following disease progression, n (%)	41 (67.2)	78 (66.1)
Received radical therapy or hormone therapy, n	51	94
Reported disease progression prior to receiving radical therapy or hormone therapy, n (%)	41 (80.4)	78 (83.0)

VTP = vascular-targeted photodynamic therapy.

As requested by the FDA, a sensitivity analysis of conversion to radical therapy including only patients with disease progression showed similar results to the overall trial results for conversion to radical therapy (HR: 0.41 [95% CI: 0.28–0.60; p < 0.0001]) (Figure 28).

Figure 28: Time to Radical Therapy Sensitivity Analysis – Study 301-FU5



Patients at risk						
TOOKAD VTP	206	194	178	149	135	126
Active Surveillance	206	189	126	96	85	80

CI = confidence interval; HR = hazard ratio; ITT= intent-to-treat; VTP = vascular-targeted photodynamic therapy
Note 1: The interim analysis for Study 301-FU5 was conducted in October 2018, after the last randomized patient had reached 5 years of total follow-up time since randomization.
Note 2: sensitivity analysis included only patients with disease progression who had radical therapy.

5.4.3 Severe Prostate Cancer-Related Events

At Month 60, T3 disease was found in 5 patients in the TOOKAD VTP arm and 14 patients in the active surveillance arm, and metastasis was diagnosed in 2 patients in each treatment arm. As with the Month 24 assessment, this did not differentiate between cT3 disease versus T3 status being determined based on a radical prostatectomy specimen or clinically observed metastasis versus a positive node found during radical prostatectomy.

A post hoc analysis was done to determine the rate of cT3 disease versus any T3 disease, as well the rate of clinically observed metastasis versus metastasis found during radical prostatectomy. ORP assessment were used when available; local read results were used after 24 months as there was no ORP assessment. Patients whose T3 disease or metastasis was associated with radical prostatectomy were excluded from the sum. By Month 60, cT3 disease was found in 2 TOOKAD VTP treated patients and 7 active surveillance patients. Clinical metastasis was diagnosed in one patient in each treatment arm.

5.5 Efficacy Conclusions

Data from the Phase 2 and 3 studies constitute a substantial body of evidence showing the efficacy of the treatment with TOOKAD VTP. As demonstrated in Study 301, the pivotal trial, treatment with TOOKAD VTP results in a statistically significant reduction in local disease progression and increased the probability of a negative prostate biopsy at 24 months after treatment compared to active surveillance. Importantly, treatment with TOOKAD VTP reduced the rate of conversion to radical therapy compared with active surveillance.

Interim results from Study 301-FU5 show that the benefits of TOOKAD VTP at the 2 year primary endpoint of Study 301 are maintained over several subsequent years of observation through to 5 years after start of treatment. In particular, the recognition that far fewer patients converted to radical therapy with TOOKAD, thereby reducing radical treatment-related morbidity, is evidence of a clinically meaningful benefit.

Overall, for men with early prostate cancer, TOOKAD VTP can provide a treatment option to delay disease progression and reduce the need for radical therapy.

6 CLINICAL SAFETY

Summary

- The safety profile of TOOKAD VTP has been characterized from five Phase 2 and 3 studies. The primary safety data supporting the expanded indication are derived from the Safety Population in Study 301 (N = 404).
- The majority of AEs observed in the TOOKAD VTP arm were mild to moderate, self-limiting, and resolved without sequelae at 24 months.
- Transient urinary symptoms were the most commonly reported AEs and were mainly related to the procedure.
- Most SAEs were Grade 2–3 and resolved within 24 months. The most common SAE in the TOOKAD VTP arm was retention of urine, which all resolved within 1.5 months.
- Treatment with TOOKAD VTP preserves erectile function and continence in most patients.
    - Erectile dysfunction was reported in 38% of patients treated with TOOKAD VTP. Most events were Grade 1 and 2. Half of the Grade 2 and 3 events resolved at 24 months.
    - Urinary incontinence, reported in 8% of patients treated with TOOKAD VTP, occurred soon after the procedure, generally resolved within 6 months and was most often Grade 1.
    - Patient-reported outcome data confirmed that TOOKAD VTP has no negative impact on the urinary function compared to active surveillance. A moderate decrease of erectile function was observed after VTP treatment, which remained stable.
- Multiple treatments were possible with minimal increased risk to the patients.
    - Within the TOOKAD VTP arm of the Pooled Phase 2 and 3 Safety Population, 35 patients were retreated and 117 patients received sequential treatment with no clinically meaningful safety differences observed compared with single hemiablation.
- The interim analysis of the 5-year data from Study 301-FU5 has not identified any new safety signals.
- Overall, the indicated population as well as safety precautions already in place ensure that TOOKAD's safety profile is manageable and typically reversible.

6.1 Safety Population and Treatment Exposure

As of September 2019, across all indications studied, 578 patients received at least one injection of TOOKAD in 15 clinical trials (12 studies sponsored by Steba and 3 Investigator sponsored studies); 5 of the studies enrolled patients in localized prostate cancer (N = 429). The Safety Population from Study 301 provides the primary safety data supporting the indication and is the focus of this briefing document. The Safety Population includes all patients randomized to the TOOKAD VTP treatment arm who received any amount of TOOKAD or initiated any study treatment-related procedure (N = 197) and all patients randomized to the active surveillance arm (N = 207).

For select safety topics, safety data are presented for the Pooled Phase 2 and 3 Safety Population, which includes safety data from Studies 201, 202, 203, 301, and 304. These studies enrolled patients with localized low-risk Gleason Score ≤ 6 prostate cancer diagnosed based on TRUS biopsy. A total of 398 patients form the ITT Population for the pooled Phase 2/3 safety analysis. All patients who received TOOKAD (n = 391) received the recommended dose of 4 mg/kg and 200 J/cm.

6.2 Overview of Adverse Events

Most (95%) patients treated with TOOKAD VTP in Study 301 reported AEs compared to 55% in the active surveillance arm (Table 19). Similarly, SAEs occurred in more patients in the TOOKAD VTP arm than those receiving active surveillance. However, there were very few discontinuations due to an AE, and the proportions were comparable between treatment arms.

There was 1 death in the study, which occurred in the TOOKAD VTP arm. The patient died of a myocardial infarction approximately 34 weeks after receiving TOOKAD VTP treatment; however, the event, which occurred while the patient was hiking, was deemed unrelated to drug, device, or procedure. The narrative is provided in Appendix 11.4.

Table 19: Overview of Adverse Events – Study 301 Safety Population

Category	TOOKAD VTP N = 197 n (%)	Active Surveillance N = 207 n (%)
All AEs	187 (94.9)	114 (55.1)
All SAEs	60 (30.5)	21 (10.1)
AE leading to study discontinuation	2 (1.0)	1 (0.5)
AE leading to death	1 (0.5)	0

AE = adverse event; SAE = serious adverse event; VTP = vascular-targeted photodynamic therapy

6.3 Common Adverse Events

The most commonly reported AEs in the TOOKAD VTP arm of Study 301 were in the Medical Dictionary for Regulatory Activities (MedDRA) system organ classes (SOCs) of "renal and urinary disorders" (68% of patients) and "reproductive system and breast disorders" (61% of patients). The most frequently reported preferred terms were erectile dysfunction (38%), hematuria (28%), and dysuria (27%). These were most often considered related to the procedure (eg, insertion of needles into the prostate, catheter). These AEs have been self-limiting, were generally mild in nature and did not lead to long-lasting sequelae in the majority of cases. Urinary-related events are described in more detail in Section 6.8.

Notably, no events of significant extra-prostatic necrosis with possible recto-urethral fistula formation occurred.

6.4 Adverse Events by Severity

The majority of AEs reported in both arms were Grade 1–2, and the majority of AEs had resolved without sequelae at 24 months (Figure 7). Approximately twice as many patients in the TOOKAD VTP arm as in the active surveillance arm experienced AEs of Grades 3 or 4.

The most frequently reported severe (Grade 3) AEs were prostatitis (3 [2%] vs one [< 1%] patient), acute urinary retention (3 [2%] vs one [< 1%]) and erectile dysfunction (2 [1%] vs 3 [1%]). There were three life-threatening (Grade 4) events in the TOOKAD VTP arm: one each of bronchospasm (related to an anesthetic drug), anaphylactic reaction to an anesthesia drug and unstable angina. There was one life-threatening (Grade 4) event in the active surveillance arm which was a myocardial infarct. One Grade 5 event (myocardial infarct leading to death) was observed in the TOOKAD VTP. No Grade 5 events occurred in the active surveillance arm.

To evaluate the AE profiles of TOOKAD VTP and active surveillance alone, an analysis of AEs was performed that excluded any AEs that were reported to have occurred at or after the time of radical therapy. The 24-month assessment included a review of all AEs in terms of resolution and severity for patients with available follow-up data (185 patients treated with TOOKAD VTP and 174 patients treated with active surveillance). The vast majority of AEs in both treatment arms were Grade 1–2 and resolved by 24 months (Table 20). As expected, fewer Grade ≥ 3 AEs were observed in patients when evaluating each treatment before radical therapy. Results for the entire Safety Population are presented in Appendix 11.5.

Table 20: Summary of Adverse Events and Unresolved Adverse Events by Severity Reported Before Radical Therapy – Study 301 Safety Population

Adverse Events		All Grades	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Occurrence	TOOKAD VTP (N = 197)	187 (94.9)	53 (26.9)	93 (47.2)	37 (18.8)	3 (1.5)	1 (0.5)
	Active Surveillance (N = 207)	95 (45.9)	41 (9.8)	42 (20.3)	11 (5.3)	1 (0.5)	0
Unresolved at 24 Months	TOOKAD VTP (N = 185)	80 (43.2)	40 (21.6)	34 (18.4)	6 (3.2)	0	0
	Active Surveillance (N = 174)	42 (24.1)	23 (13.2)	17 (9.8)	2 (1.1)	0	0

VTP = vascular-targeted photodynamic therapy

Table 21 summarizes all AEs occurring in > 5% patients in either arm of the Safety Population in Study 301, excluding any AEs that occurred at or after the time of radical therapy. Most AEs were reported as resolved at 24 months and the AEs unresolved tended to be Grade 1 or Grade 2. The unresolved Grade 3 events at Month 24 included urinary incontinence, which occurred in the patient with a previous trans-urethral resection of the prostate, and ejaculation failure. Importantly, only one erectile dysfunction event Grade ≥ 3 was observed in the TOOKAD VTP arm, which resolved by 24 months.

Table 21: Adverse Events Occurring > 5% in Either Arm by Resolution and Severity Reported Before Radical Therapy – Study 301 Safety Population

		Occurrence					Unresolved at 24 months			
		Grade (no Grade 4 or 5 reported)					Grade (no Grade 4 or 5 reported)			
		Any Grade	Grade 1	Grade 2	Grade 3		Any Grade	Grade 1	Grade 2	Grade 3
Nausea	TOOKAD VTP (N = 197)	11 (5.6)	8 (4.1)	3 (1.5)	0	TOOKAD VTP (N = 185)	0	0	0	0
	Active Surveillance (N = 207)	1 (0.5)	1 (0.5)	0	0	Active Surveillance (N = 174)	0	0	0	0
Naso-pharyngitis	TOOKAD VTP (N = 197)	10 (5.1)	9 (4.6)	1 (0.5)	0	TOOKAD VTP (N = 185)	0	0	0	0
	Active Surveillance (N = 207)	9 (4.3)	9 (4.3)	0	0	Active Surveillance (N = 174)	0	0	0	0
UTI	TOOKAD VTP (N = 197)	20 (10.2)	7 (3.6)	11 (5.6)	2 (1.0)	TOOKAD VTP (N = 185)	0	0	0	0
	Active Surveillance (N = 207)	5 (2.4)	2 (1.0)	2 (1.0)	1 (0.5)	Active Surveillance (N = 174)	0	0	0	0
Perineal injury	TOOKAD VTP (N = 197)	15 (7.6)	12 (6.1)	3 (1.5)	0	TOOKAD VTP (N = 185)	0	0	0	0
	Active Surveillance (N = 207)	0	0	0	0	Active Surveillance (N = 174)	0	0	0	0
Back pain	TOOKAD VTP (N = 197)	11 (5.6)	6 (3.0)	5 (2.5)	0	TOOKAD VTP (N = 185)	1 (0.5)	0	1 (0.5)	0
	Active Surveillance* (N = 207)	7 (3.4)	4 (1.9)	2 (1.0)	0	Active Surveillance (N = 174)	0	0	0	0
Dysuria	TOOKAD VTP (N = 197)	53 (26.9)	32 (16.2)	18 (9.1)	3 (1.5)	TOOKAD VTP (N = 185)	4 (2.2)	3 (1.6)	1 (0.5)	0
	Active Surveillance (N = 207)	4 (1.9)	1 (0.5)	3 (1.4)	0	Active Surveillance (N = 174)	2 (1.1)	1 (0.6)	1 (0.6)	0

		Occurrence					Unresolved at 24 months			
		Grade (no Grade 4 or 5 reported)					Grade (no Grade 4 or 5 reported)			
		Any Grade	Grade 1	Grade 2	Grade 3		Any Grade	Grade 1	Grade 2	Grade 3
Haematuria	TOOKAD VTP (N = 197)	56 (28.4)	46 (23.4)	9 (4.6)	1 (0.5)	TOOKAD VTP (N = 185)	0	0	0	0
	Active Surveillance (N = 207)	6 (2.9)	4 (1.9)	2 (1.0)	0	Active Surveillance (N = 174)	0	0	0	0
Micturition urgency	TOOKAD VTP (N = 197)	21 (10.7)	13 (6.6)	8 (4.1)	0	TOOKAD VTP (N = 185)	2 (1.1)	0	2 1.1)	0
	Active Surveillance (N = 207)	2 (1.0)	1 (0.5)	1 (0.5)	0	Active Surveillance (N = 174)	0	0	0	0
Pollakiuria	TOOKAD VTP (N = 197)	20 (10.2)	14 (7.1)	6 (3.0)	0	TOOKAD VTP (N = 185)	2 (1.1)	0	2 (1.1)	0
	Active Surveillance (N = 207)	4 (1.9)	2 (1.0)	2 (1.0)	0	Active Surveillance (N = 174)	3 (1.7)	2 (1.1)	1 (0.6)	0
Urinary incontinence	TOOKAD VTP (N = 197)	16 (8.1)	12 (6.1)	3 (1.5)	1 (0.5)	TOOKAD VTP (N = 185)	5 (2.7)	4 (2.2)	0	1 (0.5)
	Active Surveillance (N = 207)	1 (0.5)	0	1 (0.5)	0	Active Surveillance (N = 174)	0	0	0	0
Urinary retention	TOOKAD VTP (N = 197)	32 (16.2)	5 (2.5)	24 (12.2)	3 (1.5)	TOOKAD VTP (N = 185)	1 (0.5)	1 (0.5)	0	0
	Active Surveillance (N = 207)	1 (0.5)	0	1 (0.5)	0	Active Surveillance (N = 174)	1 (0.6)	0	1 (0.6)	0
Ejaculation failure	TOOKAD VTP (N = 197)	16 (8.1)	41 (20.8)	31 (15.7)	1 (0.5)	TOOKAD VTP (N = 185)	10 (5.4)	5 (2.7)	4 (2.2)	1 (0.5)
	Active Surveillance (N = 207)	10 (4.8)	6 (2.9)	4 (1.9)	0	Active Surveillance (N = 174)	1 (0.6)	0	1 (0.6)	0

		Occurrence					Unresolved at 24 months			
		Grade (no Grade 4 or 5 reported)					Grade (no Grade 4 or 5 reported)			
		Any Grade	Grade 1	Grade 2	Grade 3		Any Grade	Grade 1	Grade 2	Grade 3
Erectile dysfunction	TOOKAD VTP (N = 197)	73 (37.1)	41 (20.8)	31 (15.7)	1 (0.5)	TOOKAD VTP (N = 185)	40 (21.6)	25 (13.5)	15 (8.1)	0
	Active Surveillance (N = 207)	10 (4.8)	6 (2.9)	4 (1.9)	0	Active Surveillance (N = 174)	7 (4.0)	3 (1.7)	4 (2.3)	0
Haemato-spermia	TOOKAD VTP (N = 197)	12 (6.1)	11 (5.6)	1 (0.5)	0	TOOKAD VTP (N = 185)	0	0	0	0
	Active Surveillance (N = 207)	5 (2.4)	5 (2.4)	0	0	Active Surveillance (N = 174)	0	0	0	0
Perineal pain	TOOKAD VTP (N = 197)	30 (15.2)	20 (10.2)	9 (4.6)	1 (0.5)	TOOKAD VTP (N = 185)	0	0	0	0
	Active Surveillance (N = 207)	0	0	0	0	Active Surveillance (N = 174)	0	0	0	0
Prostatitis	TOOKAD VTP (N = 197)	10 (5.1)	3 (1.5)	4 (2.0)	3 (1.5)	TOOKAD VTP (N = 185)	1 (0.5)	0	1 (0.5)	0
	Active Surveillance (N = 207)	10 (4.8)	4 (1.9)	5 (2.4)	1 (0.5)	Active Surveillance (N = 174)	1 (0.6)	0	0	1 (0.6)

UTI = urinary tract infection; VTP = vascular-targeted photodynamic therapy
*one missing grade

6.5 Adverse Events Leading to Discontinuation

In Study 301, AEs leading to study discontinuation occurred in 2 patients in the TOOKAD VTP arm and 1 patient in the active surveillance arm (Table 22). Neither event in the TOOKAD VTP arm was considered related to treatment. The anaphylactic reaction was to anesthesia administered at the start of the procedure; the patient had not received TOOKAD or VTP. The myocardial infarction, which resulted in death, occurred approximately 34 weeks after TOOKAD VTP while the patient was hiking.

Table 22: Adverse Events Leading to Discontinuation – Study 301 Safety Population

Preferred Term, n (%)	TOOKAD VTP N = 197 n (%)	Active Surveillance N = 207 n (%)
Myocardial infarction	1 (0.5)	0
Anaphylactic reaction	1 (0.5)	0
Ureteric cancer regional	0	1 (0.5)

VTP = vascular-targeted photodynamic therapy

6.6 Serious Adverse Events

A total of 84 SAEs occurred in 60 patients in the TOOKAD VTP arm and 25 SAEs occurred in 21 patients the active surveillance arm. Most SAEs were Grade 2–3 and resolved within 1 month. Nearly all SAEs resolved within 24 months (Figure 8).

The most commonly reported SAE in patients treated with TOOKAD VTP was temporary urinary retention (16 patients [8%] and 1 patient in the active surveillance arm). Approximately half of these cases resolved within 7 days and all cases resolved within 2 months. Of note, in Europe, urinary retention led to hospitalization, which would not generally occur in the US.

Other SAEs occurring in more than 1 patient are presented in Table 23.

Table 23: Serious Adverse Events Reported in ≥ 2 Patients in TOOKAD VTP Arm – Study 301 Safety Population

Preferred Term	TOOKAD VTP N = 197 n (%)	Active Surveillance N = 207 n (%)
Urinary retention	16 (8.1)	1 (0.5)
Prostatitis	4 (2.0)	0
Urinary tract infection	4 (2.0)	2 (1)
Dysuria	3 (1.5)	0
Haematuria	3 (1.5)	0
Orchitis	3 (1.5)	0
Cerebrovascular accident	2 (1.0)	0
Inguinal hernia	2 (1.0)	0
Myocardial infarction	2 (1.0)	3 (1.4)
Urethral stenosis	2 (1.0)	0

VTP = vascular-targeted photodynamic therapy

Table 24 summarizes the SAEs reported in the Safety Population of Study 301 (24-month analysis) excluding any AEs that occurred at or after the time of radical therapy. Like the overall AEs observed with each treatment before radical therapy, most SAEs resolved by 24 months. In the TOOKAD VTP arm, the SAEs unresolved at 24 months included two Grade 2 events (renal cancer and angina pectoris) and three Grade 3 events (urinary incontinence, depression, and testicular neoplasm). In the active surveillance arm, the unresolved SAEs in included one Grade 2 event of ischemic cardiomyopathy. Results for the entire Safety Population are presented in Appendix 11.5.

Table 24: Serious Adverse Events and Unresolved Serious Adverse Events Reported Before Radical Therapy – Safety Population Study 301

Serious Adverse Events		All Grades n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Occurrence	TOOKAD VTP (N = 197)	58 (29.4)	6 (3.0)	27 (13.7)	21 (10.7)	3 (1.5)	1 (0.5)
	Active Surveillance* (N = 207)	16 (7.7)	1 (0.5)	4 (1.9)	9 (4.3)	1 (0.5)	0
Unresolved at 24 Months	TOOKAD VTP (N = 185)	5 (2.7)	0	2 (1.1)	3 (1.6)	0	0
	Active Surveillance (N = 174)	1 (0.6)	0	1 (0.6)	0	0	0

VTP = vascular-targeted photodynamic therapy
*one missing grade

6.7 Photosensitivity Adverse Events

Although TOOKAD is considered a photosensitizing drug, the potential for possible phototoxic AE is relatively short-lived due to TOOKAD's short half-life (approximately 70 minutes). Precautions such as preventing exposure to bright light during the procedure and the need to wear clothes covering the skin and dark glasses for a day following injection help to reduce the risk of any phototoxic reaction.

During the course of the prostate cancer studies, there was only 1 case of a mild optic AE (ischemic optic neuropathy, reported in Study 203). No evidence of skin or eye phototoxicity was observed. The event occurred 33 days after treatment. An ophthalmologist was consulted and noted the event to be resolved, but with a small defect in the visual field. There were no other phototoxic events reported in any other study.

6.8 Urinary-Related Events

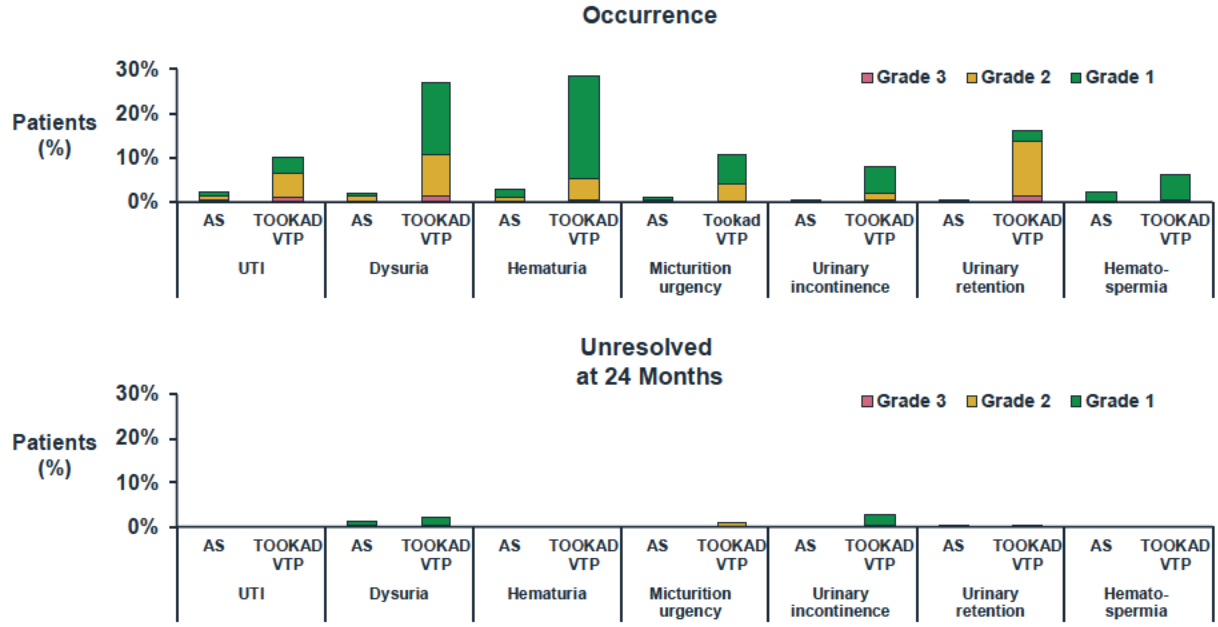
6.8.1 Transient Urinary Adverse Events

Transient urinary symptoms were commonly reported, mainly related to the procedure of inserting the needles into the prostate and urinary catheterization. Events may have also been associated with the development of necrosis (an objective of the procedure).

In Study 301, the most frequently reported urinary AEs excluding any AEs that occurred at or after the time of radical therapy were hematuria (28.4% of patients), dysuria (26.9%), and urinary retention (16.2%) in the TOOKAD VTP arm. Urinary AEs in the active surveillance arm excluding any AEs that occurred at or after the time of radical therapy were all under 5%. Most events were Grade 1–2 in severity and, importantly, most events in the TOOKAD VTP arm

resolved by 24 months and the rates of unresolved AEs at Month 24 were similar between treatment groups (Figure 29).

Figure 29: Urinary Adverse Events Occurring in > 5% of Patients Reported Before Radical Therapy– Study 301



AS = active surveillance; UTI = urinary tract infection; VTP = vascular-targeted photodynamic therapy

There was one SAE of urinary incontinence reported in the TOOKAD VTP arm, which was in a patient with a previous trans-urethral resection of the prostate. By contraindicating patients who had a previous trans-urethral resection of the prostate, this should not be a safety issue in the future.

Edema and swelling as a result of the insertion of needles into the prostate can lead to urinary retention and potentially bleeding that may appear as hematuria. This can also be a result of urethral catheterization which may itself give rise to irritation that manifest as urinary urgency, etc. These events are usually self-limiting.

6.8.2 International Prostate Symptom Scores

The results of the IPSS questionnaires in patients without radical therapy are presented in Figure 9. The potential range of IPSS scores is 0–35, an increase in score corresponds to a deterioration of the urinary function, whereas a decrease represents an improvement.

Other than a transient increase at Month 3, the post-treatment scores in the TOOKAD VTP arm remained equal to or less than Baseline from Month 6 onwards. The mean score at Month 24 in the TOOKAD arm is lower than baseline score, indicating no negative impact on the urinary function compared to active surveillance.

The IPSS results for the Safety Population are presented in Appendix 11.6.

6.9 Erectile Dysfunction

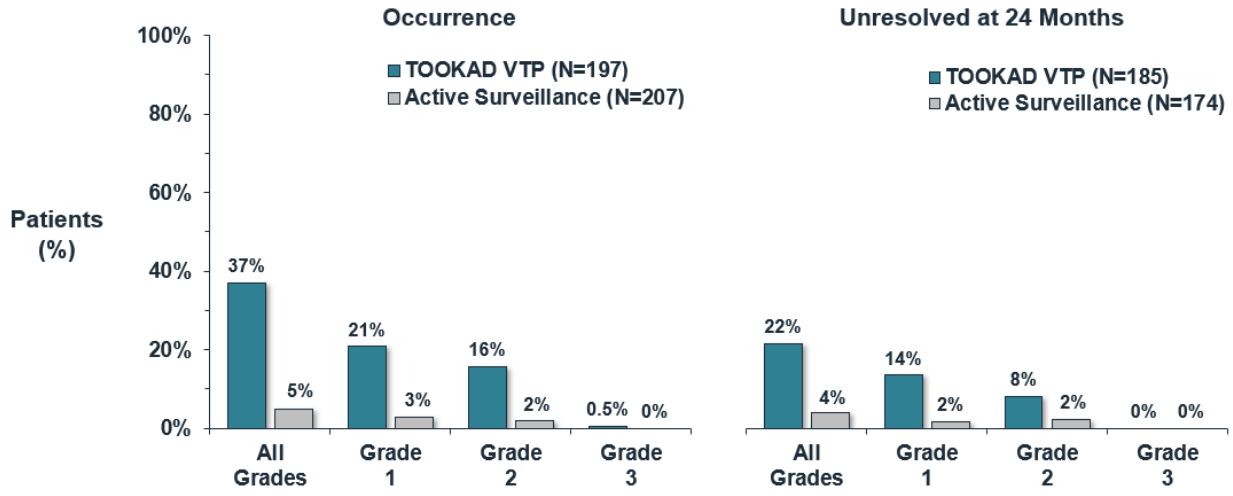
Erectile dysfunction was evaluated both as an AE and through patients responses to the IIEF questionnaire. Together the results demonstrate that most events were low grade and did not influence the quality of life of the patients.

6.9.1 Erectile Dysfunction Adverse Events

In Study 301, AEs of erectile dysfunction were reported by 37.6% of patients in the TOOKAD VTP arm and 11.6% of patients in the active surveillance arm. These events were not unexpected since any activity that affects the prostate has the potential to affect erectile function. Excluding any erectile dysfunction AEs that occurred at or after the time of radical therapy, erectile dysfunction was reported by 37.1% of the patients in the TOOKAD VTP arm and 4.8% of the patients in the active surveillance arm.

Most events in Study 301 were Grade 1 or 2, and many of the events in the TOOKAD VTP arm had resolved by 24 months, in particular the Grade 2 events; the numbers of events of erectile dysfunction in the active surveillance arm largely remained the same at 24 months (Figure 30). It is important to note that men with Grade 1 and Grade 2 erectile dysfunction are still able to have intercourse with or without pharmaceutical assistance. Within published reports of the outcomes of radical prostatectomies, the standard reporting of potency is with or without the assistance of PDE-5 inhibitors (Eastham et al 2008), and most of these cases would not be reported as erectile dysfunction. Grade 3 erectile dysfunction is unresponsive to medication. Two patients (1.0%) in the TOOKAD VTP arm reported a Grade 3 AE of erectile dysfunction; one before radical therapy and one after. No SAEs of erectile dysfunction have been reported.

Figure 30: Resolution of Erectile Dysfunction Events Reported Before Radical Therapy by Severity at Month 24 – Study 301 Safety Population



VTP = vascular-targeted photodynamic therapy

6.9.2 International Index of Erectile Function

In Study 301, the IIEF questionnaire was used to provide a detailed perspective on sexual function according to 5 domains, including erectile dysfunction. Results from the IIEF questionnaire, which assesses male sexual function including erection, orgasm, sexual desire, ejaculation, intercourse, and overall satisfaction, in patients without radical therapy, are shown in Figure 10. Expectedly, following treatment, there was a drop in IIEF score in the TOOKAD VTP arm at the first post-treatment assessment at Month 3, which remained stable thereafter. The change from Baseline at Month 24 shows a similar decrease in erectile function in both treatment arms.

The IIEF results from the Safety Population are presented in Appendix 11.6.

6.10 Adverse Events Single vs Sequential Hemiablation (Pooled Phase 2 and 3)

In the clinical studies, patients were either treated in one single lobe of the prostate (single treatment) or in both lobes (sequential treatment) with the VTP procedure. The sequential treatment arm includes 2 types of treatment for patients:

- Patients with bilateral disease indicated at baseline where treatment of both lobes was undertaken sequentially in 2 VTP procedures.
- Patients where retreatment was indicated in the contralateral lobe following the first per protocol biopsy, effectively resulting in both lobes of the prostate being treated.

A summary of the AEs for patients having single or sequential treatment is presented in Table 25 for all patients treated at the recommended dose level.

Table 25: Summary of AEs for Single and Sequential Treatment for All Studies (Pooled Phase 2 and 3) in Prostate Cancer at the Recommended Dose

Category, n (%)	Single Treatment N = 274 n (%)	Sequential Treatment N = 117 n (%)
Patients with At Least One AE	223 (81.4)	104 (88.9)
Patients with At Least One SAE	47 (17.2)	31 (26.5)
Patients with At Least One AE leading to Discontinuation	3 (1.1)	1 (0.9)
Patients with At Least One AE Leading to Death	1 (0.4)	0 (0.0)

AE = adverse event; SAE = serious adverse event

Overall, there was no obvious difference in frequency of events based on whether the procedure was single or sequential. More patients with sequential treatment reported worst toxicity of Grade 2 (for related events, 41.0% for bilateral compared to 34.3% for unilateral) or Grade 3 (for related events, 10.3% for bilateral compared to 5.8%) in nature. The increases in events for bilateral treatment were mainly in the “renal and urinary disorders” and “reproductive system and breast disorders” SOCs. In addition, a few more hospitalizations due to urinary retention,

dysuria, and hematuria led to an increase in the number of SAEs (26.5% for bilateral treatment group compared to 17.2% for the unilateral treatment group).

6.11 Retreatment (Ipsilateral Hemiablation) (Pooled Phase 2 and 3)

In the clinical studies, a subset of the patients received a retreatment VTP procedure in the same lobe of the prostate that had previously been treated. These retreatment procedures generally occurred after examination of the first on-study biopsy (at 6 months for the Phase 2 trials and Study 304, and at 12 months for Study 301). A comparison of the safety profile of patients receiving a second treatment in the same lobe with those who received only a single treatment in the lobe is presented in Table 26. The number of patients who received a retreatment is relatively low and no single event had a more profound effect on the overall percentage. As would be expected for patients undergoing a retreatment, there were higher percentages of AEs. However, these higher percentages did not represent a clinically meaningful higher risk of AEs for patients receiving retreatment compared with those who received only one hemiablation. This demonstrated that repeat procedures are possible with minimal increased risk to the patients.

Table 26: Summary of AEs for Retreated Patients and Patients with Lobes Treated Only Once for All Studies (Pooled Phase 2 and 3) in Prostate Cancer at the Recommended Dose

Category, n (%)	Patients with Lobes Treated Only Once* N = 356 n (%)	Patients with Retreated Lobes N = 35 n (%)
Patients with At Least One AE	294 (82.6)	33 (94.3)
Patients with At Least One SAE	69 (19.4)	9 (25.7)
Patients with At Least One AE leading to Discontinuation	4 (1.1)	0 (0.0)
Patients with At Least One AE Leading to Death	1 (0.3)	0 (0.0)

AE = adverse event; SAE = serious adverse event

* May be unilateral or bilateral

6.12 Salvage Radical Therapy

Salvage radical prostatectomy was feasible and safe following previous TOOKAD VTP. Based on the interim analysis of the Study 301-FU5, 47 patients in the TOOKAD VTP arm had converted to radical therapy at 5 years. Patients have received either radical prostatectomy, EBRT or brachytherapy and although the study was not designed to evaluate the safety of subsequent salvage therapy, overall there was a lack of unexpected complications. These results are similar to those described in a retrospective review of patients treated with TOOKAD VTP between 2008–2017 who later underwent radical prostatectomy salvage therapy (Pierrard et al 2019). Of 313 patients undergoing TOOKAD VTP at 18 EU centers, 45 patients (9%) underwent radical prostatectomy for recurrent cancer after TOOKAD VTP. Procedures were generally successful with typical difficulty, hospital stays and outcomes, including feasibility of nerve sparing. There was no correlation between bilateral TOOKAD VTP and surgical difficulties. The

radical prostatectomy procedure was performed with no unusual challenges in 69% of patients and efficacy results were satisfactory with 88% of patients having undetectable PSA levels 6–12 months after the procedure. Postoperative complications were reported in 12% of patients. Incontinence risks were as standard for prostatectomy, with 24% showing low incontinence and 64% completely continent at one year. Potency was recovered in 75% of patients overall.

6.13 Long-Term Safety—Study 301-FU5

At the time of the 3-year follow-up analysis (ie, 5 years post-randomization), a total of 354 patients were entered in the follow-up study (182 in the TOOKAD VTP arm and 172 in the active surveillance arm). All patients eligible for long-term follow-up have reached 5 years of follow-up since randomization, while some have reached 7 years of follow-up since randomization (Table 27).

Table 27: Disposition in Study 301-FU5

Time Point, n (%)	TOOKAD VTP N = 206	Active Surveillance N = 207
Number of patients with data entered at each follow-up time point		
Month 36	170 (82.5)	148 (71.5)
Month 48	162 (78.6)	139 (67.1)
Month 60	141 (68.4)	129 (62.3)
Month 72	92 (44.7)	79 (38.2)

VTP = vascular-targeted photodynamic therapy

The long-term safety analysis was intended to capture late-occurring AEs, in particular outcomes of erectile dysfunction, urinary incontinence, and urinary retention. All the AEs and SAEs reported in the follow-up phase were nonspecific and expected in the aging population. The distribution of the AEs and SAEs in the other SOCs appears to be relatively similar between the 2 arms (Table 28).

Table 28: Common Adverse Events in Study 301-FU5 Compared with Study 301

Preferred Term	2 Year Analysis		5 Year Analysis	
	TOOKAD VTP N = 197 n (%)	Active Surveillance N = 207 n (%)	TOOKAD VTP N = 197 n (%)	Active Surveillance N = 207 n (%)
Any AE	187 (94.9)	114 (55.1)	190 (96.4)	138 (66.7)
Erectile dysfunction	74 (37.6)	24 (11.6)	89 (45.2)	57 (27.5)
Dysuria	54 (27.4)	5 (2.4)	64 (32.5)	12 (5.8)
Urinary tract infection	21 (10.7)	9 (4.3)	27 (13.7)	10 (4.8)
Urinary incontinence	19 (9.6)	10 (4.8)	28 (14.2)	23 (11.1)
Pollakiuria	20 (10.2)	6 (2.9)	27(13.7)	13 (6.3)
Prostatitis	10 (5.1)	10 (4.8)	15 (7.6)	14 (6.8)
Benign prostatic hyperplasia	2 (1.0)	2 (1.0)	6 (3.0)	2 (1.0)
Nocturia	1 (0.5)	0	5 (2.5)	1 (0.5)

AE = adverse event; VTP = vascular-targeted photodynamic therapy

In addition, when comparing the 2-year versus 5-year analysis, there was very little increase in severity of events and the number of patients with Grade 4 (life-threatening) (Table 29). The increase in Grade 5 (fatal) events were comparable in the 2 arms.

Table 29: Adverse Events by Severity in Study 301-FU5 Compared with Study 301

CTCAE Grade	2 Year Analysis		5 Year Analysis	
	TOOKAD VTP N = 197 n (%)	Active Surveillance N = 207 n (%)	TOOKAD VTP N = 197 n (%)	Active Surveillance N = 207 n (%)
Grade 1 (mild)	49 (24.9)	42 (20.3)	30 (15.2)	28 (13.5)
Grade 2 (moderate)	94 (47.7)	52 (25.1)	102 (51.8)	69 (33.3)
Grade 3 (severe)	40 (20.3)	19 (9.2)	45 (22.8)	31 (15.0)
Grade 4 (life-threatening)	3 (1.5)	1 (0.5)	3 (1.5)	2 (1.0)
Grade 5 (death)	1 (0.5)	0	10 (5.1)	8 (3.9)

CTCAE = Common Terminology Criteria for Adverse Events; VTP = vascular-targeted photodynamic therapy

Seventeen (17) patients died during the follow-up period comprising the end of the original trial and the three-year analysis (ie, until 5 years after randomization). Of the 17 reported deaths, 9 were in the TOOKAD VTP arm and 8 were in the active surveillance arm. No deaths were due to prostatic adenocarcinoma (Table 30).

Table 30: Deaths in Study 301-FU5

Treatment Group	Cause of Death
TOOKAD VTP	Cardiac arrest
TOOKAD VTP	Subdural hemorrhage
TOOKAD VTP	Carcinoma (neuroendocrine)
TOOKAD VTP	Metastatic pulmonary neoplasm
TOOKAD VTP	Pancreatic adenocarcinoma
TOOKAD VTP	Lung adenocarcinoma
TOOKAD VTP	Respiratory depression
TOOKAD VTP	Lung cancer
TOOKAD VTP	Heart attack
Active surveillance	Colon adenocarcinoma
Active surveillance	Heart disease
Active surveillance	Pancreatic cancer
Active surveillance	Otolaryngology cancer
Active surveillance	Esophageal cancer
Active surveillance	Febrile aplasia
Active surveillance	Heart failure
Active surveillance	Sudden death (cause unknown)

VTP = vascular-targeted photodynamic therapy

The SOC with the largest relative increase in number of patients with AEs was Neoplasms benign, malignant and unspecified. The number of SAEs in this SOC was higher in the TOOKAD VTP arm than in the active surveillance arm (18 cases vs 13), but the nature of those cases and their distribution along various organs does not indicate a possible safety concern. Events occurring in this SOC will be carefully monitored throughout the remainder of the trial.

The follow up of the patients randomized in Study 301, up to 5 years after their inclusion in the study confirm the safety profile initially described in the first 24 months in Study 301, and no new safety concern has arisen.

6.14 Safety Conclusions

As expected, incidence and severity of AEs were higher in the TOOKAD VTP arm than in the active surveillance arm. Almost all patients in the TOOKAD VTP arm (94.9%) experienced AEs, while just over half (55.1%) of patients in the active surveillance arm did. Similarly, compared to active surveillance, more patients in the TOOKAD VTP arm experienced SAEs.

Most of the AEs reported were in the renal and urinary disorders SOC and in the reproductive system and breast disorders SOC; these AEs accounted for the largest differences between the treatment arms. The most common SAE in the TOOKAD VTP arm was temporary urinary retention, which resolved in less than 1.5 months for all patients. Erectile dysfunction was

reported by 38% of patients in the TOOKAD VTP arm. However, most events were Grade 1 and 2 and generally recovered within 3 to 6 months; no SAE of erectile dysfunction was reported.

The safety data are supported by the patient-reported outcomes that showed no statistically significant difference between the TOOKAD VTP arm and the active surveillance arm other than a short-term impact on urinary function at Day 7 in the TOOKAD VTP arm.

The acceptable safety profile of TOOKAD VTP is supported by long-term data from Study 301-FU5. As of the interim 3 year analysis, no late onset safety signal has been detected. The safety profile held true also for those patients who had a second treatment for contralateral disease or retreatment for a lobe found to have residual disease at follow-up biopsy.

Overall, the indicated population as well as safety precautions already in place ensure that the safety profile of TOOKAD VTP is manageable and generally reversible.

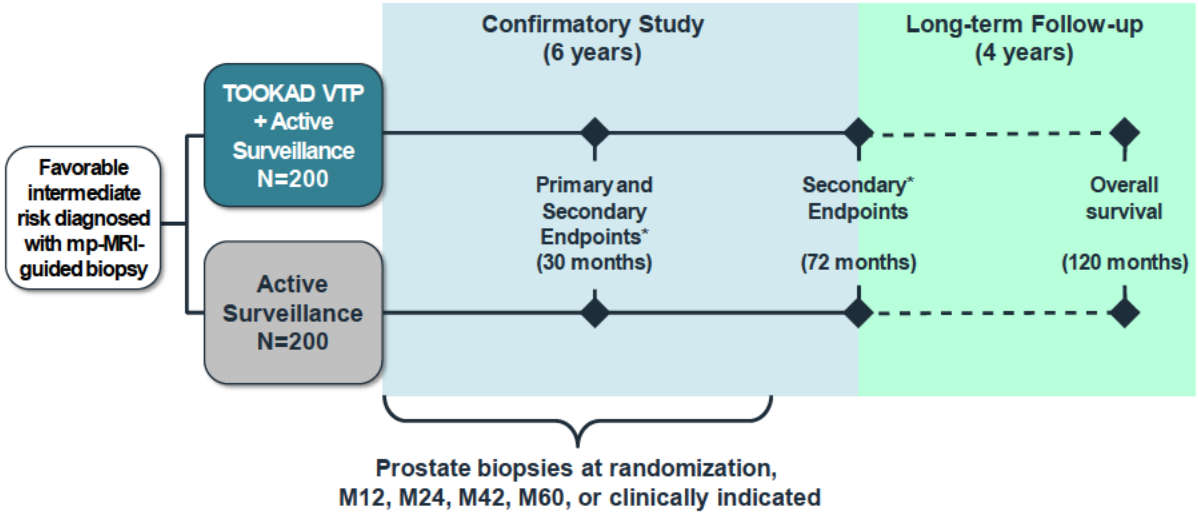
7 CONFIRMATORY STUDY—STUDY 306

7.1.1 Study Design

Confirmatory Study 306, an evaluation of the efficacy of TOOKAD VTP versus active surveillance for men with intermediate risk localized prostate cancer, has been designed in consultation with the FDA. The objective of Study 306 is to evaluate objective disease progression, conversion to radical therapy, and delayed harm (eg, urinary incontinence, sexual dysfunction) to provide evidence that morbidity (eg, sexual and urinary symptoms and other toxicities of both the local and definitive procedures) is reduced in the TOOKAD VTP arm compared to active surveillance at multiple follow-up time points and that longer-term prostate cancer outcomes (recurrence rates following definitive therapy) are not degraded.

Study 306 will be a randomized, adaptive design trial in the US and Europe enrolling 400 patients to evaluate the efficacy of TOOKAD VTP versus active surveillance for men with intermediate risk localized prostate cancer diagnosed with mp-MRI-targeted biopsy at 30 months (Figure 31). The adaptive design will utilize results accumulating in the trial to modify the trial's course in accordance with pre-specified rules. Secondary endpoints will be evaluated at 30 months and 72 months; follow-up for overall survival will be evaluated up to 10 years, irrespective of progression or conversion to radical therapy.

Figure 31: Design of Confirmatory Study 306



mp-MRI = multiparametric magnetic resonance imaging; VTP = vascular-targeted photodynamic therapy
*Primary endpoint: time to objective disease progression (30 months); Key secondary endpoints: conversion to radical therapy; patient-reported outcomes to assess harm

To detect an HR of 0.6 with a power of 0.9, using a two-sided significance level of 0.05, 166 cancer progression events need to be observed. The planned sample size is 400 patients and the number of events required for the primary analysis is 166.

Enrollment is scheduled to begin in the first quarter of 2020.

7.1.1.1 Endpoint

The primary endpoint will be time to objective progression of cancer over 30 months. A key secondary endpoint will include time to (or improvement in) conversion to radical local or systemic therapy. Patient-report outcome questionnaires will be administered to evaluate anxiety, urinary symptoms, sexual dysfunction, bowel symptoms, general bother, and fear of recurrence.

An interim analysis will be carried out at half information time (88 events), which is expected to occur at 29 months, when 300 patients are randomized. This analysis will be used only for the decision on trial size (adaptive design), not for efficacy conclusion.

7.1.2 Study Feasibility

Steba is working with the Society of Urologic Oncology Clinical Trials Consortium, a clinical research investigator network of over 400 members from more than 200 clinical sites in the US and Canada, to ensure efficient enrollment of 150–160 patients in the US. Patients will be recruited from large metropolitan areas to ensure the study population is reflective of the general US population. The remaining patients will be enrolled in Europe with the assistance of the European Organisation for Research and Treatment of Cancer.

8 POST-MARKETING EXPERIENCE

8.1.1 Post-Approval Experience

Marketing of TOOKAD VTP was initiated in Germany, Italy, the United Kingdom, Israel, and Mexico in 2018; negotiations for reimbursement are ongoing. As of 31 December 2019, 116 patients had been treated. No drug related safety reports have been received by Steba, and no new safety concerns have been identified.

8.1.2 Non-Study Post-Authorization Exposure and "Special Permission" Cases

A total of 40 patients have been treated under a special authorization procedure in Israel. All these patients were treated with 4 mg/kg TOOKAD and 200 J/cm laser. There have been 4 SAEs: 3 SAEs of orchitis (two Grade 3 and one Grade 2), all of which resolved, and one case of brain infarct which is currently under investigation. Four non-serious AEs have also been reported: 3 cases of acute urinary retention, all Grade 2 which resolved, and 1 case of metastasis in a patient who had 3 cores of Gleason 3 + 4 prostate cancer diagnosed more than one year before the VTP procedure.

A single patient aged 52 years was granted "special permission" status to receive TOOKAD in Panama. This patient experienced severe extra-prostatic necrosis with urinary fistula following treatment resulting in hospitalization while in the US. The patient was subsequently released from the hospital. The event was considered to be probably related to the study treatment; examination of the ultrasound scans taken at the time of the procedure suggests that the lengths of the fibers were significantly longer than the ones recommended by the treatment guidance performed at the beginning of the procedure, which would have been responsible for extra-prostatic exposure and subsequent necrosis.

As of 31 December 2019, no other exposure has occurred outside the clinical trials.

9 BENEFIT-RISK

Prostate cancer is a serious condition with an unmet need in how it is currently being managed. Men with very low, low, or favorable intermediate risk can either monitor the cancer with active surveillance or treat immediately with radical therapy. Only a minority of these men choose active surveillance as their treatment. This treatment option preserves sexual, urinary, and bowel functions unless the patient converts to radical therapy, which is the case for most patients. Radical therapy is effective but it treats the whole prostate and results in erectile dysfunction, incontinence, and rectal symptoms in many men.

These vastly different treatment strategies leave a treatment gap for patients who desire a middle-ground therapy. Although some physicians have turned to focal therapies such as HIFU or cryoablation as an alternative treatment, these procedures are not specifically indicated for prostate cancer, are not recommended as a primary therapy in treatment guidelines, and lack robust evidence of efficacy (Sanda et al 2017). In addition, no focal therapies are recommended in guidelines due to the lack of evidence of efficacy.

Hemiablation with TOOKAD VTP is a novel approach that fills the treatment gap by offering an alternative treatment that can further delay or avoid radical therapy while preserving surrounding tissue and organ function. TOOKAD VTP has been evaluated in a clinical trial designed with clinically meaningful endpoints that closely aligns with those discussed at the 2018 FDA Oncology Center of Excellence Public Workshop. The co-primary endpoints provide objective measures of efficacy and are supported by the clinically meaningful secondary endpoint of time to radical therapy, which is appropriate for accelerated approval.

Data from Study 301 showed a clear and statistically significant benefit from TOOKAD VTP therapy compared to active surveillance. A significant increase in the number and percent of patients with negative biopsy following TOOKAD VTP was observed. There was also a significant reduction in disease progression by TOOKAD VTP. This is a robust observation confirmed with sensitivity analyses. As progression is the major reason men convert to radical therapy, it is not surprising that Study 301 also showed a significant reduction in the rate of conversion to radical therapy for TOOKAD VTP in comparison to active surveillance. Reducing the number of patients who initiate radical therapy is an important endpoint as it measures the number of patients who can be protected against the morbidities associated with radical therapy, which has been recently recognized as a potentially approvable endpoint for drugs indicated for the treatment of localized prostate cancer.

The risks associated with TOOKAD VTP are that it may not completely ablate all cancer cells or halt progression in all patients. It has been shown to delay, but not always avoid radical therapy, which could result in missing the window for curative treatment or necessitate more aggressive therapy or even make radical therapy less efficacious. Although Pierrard et al (2019) showed a feasibility of prostatectomy after TOOKAD VTP if needed, this is a small experience and the patient has not been robustly studied. The reproducibility of these finding will be further studied in the confirmatory Study 306.

As with any procedure, there are attendant risks of the TOOKAD VTP procedure in the form of AEs and post procedure recovery. It can be discouraging to consider that 95% of men in the VTP arm experienced an AE but this compares to 55% of men in the active surveillance arm experiencing an AE. The most important AEs are related to bowel, urinary, and sexual function. With regards to bowel function, there was no meaningful bowel toxicity associated with TOOKAD VTP, notably no urethral rectal fistulae which have been associated with other prostate ablation procedures.

In Study 301 the most common AEs following TOOKAD fell into the CTCAE 'renal or urinary' classification; these events were experienced by 68% of men in the TOOKAD VTP arm. In addition, 11% had a urinary tract infection. The vast majority of AEs were Grade 1 and 2, indicating that they were responsive to medication. Almost without exception, these AEs were resolved by 24 months. This is supported by the IPSS data where no significant difference in IPSS score was observed between baseline and 24 months.

Erectile dysfunction was reported in 38% of men following TOOKAD VTP, however, over 98% of events were Grade 1 or 2. Men with Grade 1 and Grade 2 erectile dysfunction are still able to have intercourse with or without pharmaceutical assistance. Notably, within published surgical series, the standard reporting of potency is with or without the assistance of PDE-5 inhibitors and these events would not be reported as erectile dysfunction. There were few cases of Grade 3 erectile dysfunction (unresponsive to medication) in either arm in Study 301, which is consistent with the IIEF data that showed no meaningful difference between TOOKAD VTP and active surveillance in terms of sexual function. Unlike radical therapy, TOOKAD VTP is not removing sex from the lives of men any more than active surveillance.

The clinical significance of the TOOKAD VTP safety profile is evident when it is compared to radical therapy. In the ProtecT study, a large randomized trial which prospectively collected patient reported incontinence and erectile dysfunction rates after radiotherapy and radical prostatectomy, and in a radical prostatectomy study from Memorial Sloan Kettering, the rates urinary incontinence and erectile dysfunction ranged from 4–20% and 41–82%, respectively. The rates of urinary incontinence and erectile dysfunction with TOOKAD VTP are substantially lower compared to the rates reported after radiotherapy and radical prostatectomy (Table 5). These data further support the acceptable safety profile of TOOKAD VTP.

The safety profile of TOOKAD VTP is also supported by the interim analysis of 5-year data which shows no new safety signals. All AEs and SAEs reported in the follow-up phase were nonspecific and expected in the aging population. The distribution of the AEs and SAEs in the other SOCs were relatively similar between the treatment arms. Safety will be further evaluated in the confirmatory study.

Overall, the data from the TOOKAD VTP clinical development program support the positive benefit-risk profile for TOOKAD VTP, an important new option for patients with prostate cancer that is more effective than active surveillance and less morbid than radical therapy. For thousands of men diagnosed with localized prostate cancer each year, hemiablation with TOOKAD VTP can provide a safe and effective treatment that destroys the targeted cancer. This

minimally invasive and non-thermal therapy delays or avoids the need for radical therapy in many patients while preserving surrounding normal tissue and, thereby, quality of life.

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11 APPENDICES

11.1 Study 301 Enrollment Criteria

11.1.1 Inclusion Criteria

Each patient had to meet the following criteria to be enrolled in the study:

1. Low-risk prostate cancer diagnosed with 1 existing TRUS-guided biopsy using from 10 to 24 cores performed less than 12 months prior to enrollment and showing the following:
    - Gleason 3 + 3 prostate adenocarcinoma, as a maximum
    - 2 to 3 cores positive for cancer (Patients with only 1 positive core could be included provided they had at least 3 mm of cancer core length.)
    - A maximum cancer core length of 5 mm in any core
2. Cancer clinical stage up to T2a (pathological or radiological up to T2c disease permitted)
3. PSA of 10 ng/mL or less (5 ng/mL or less for patients using a 5-α-reductase inhibitor [5-ARI])
4. Prostate volume ≥ 25 cc and < 70 cc
5. Male patients aged 18 years or older

11.1.2 Exclusion Criteria

Patients who met any of the following criteria were excluded from the study:

1. Unwillingness to accept randomization to either of the 2 arms of the study
2. Any prior or current treatment for prostate cancer, including surgery, radiation therapy (external or brachytherapy), or chemotherapy
3. Any surgical intervention for benign prostatic hypertrophy
4. Life expectancy < 10 years
5. Any condition or history of illness or surgery that may pose an additional risk to men undergoing the TOOKAD® Soluble VTP procedure
6. Participation in another clinical study or recipient of an investigational product within 1 month of study entry
7. Patient unable to understand the patient's information document, to give consent or complete the study tasks
8. Patient in custody and or in residence in a nursing home or rehabilitation facility
9. Contra-indication to MRI (eg, pacemaker, history of allergic reaction to gadolinium), or factors excluding accurate reading of pelvic MRI (eg, hip prosthesis)
10. Any condition or history of illness or surgery that may pose an additional risk to men undergoing the TOOKAD® Soluble VTP procedure such as:

- Medical conditions which preclude the use of general anesthesia
- A history of active rectal inflammatory bowel disease or other factors which may increase the risk of fistula formation
- Hormonal manipulation (excluding 5-ARIs) or androgen supplements within the previous 6 months
- History of urethral stricture disease
- History of acute urinary retention within 6 months of study entry
- Men whose medical conditions need the following medication which have potential photosensitizing effects (such as tetracyclines, sulphonamides, phenothiazines, sulfonylurea hypoglycemic agents, thiazide diuretics, griseofulvin and amiodarone) if these treatments cannot be stopped or replaced by other treatments without photosensitizing properties
- Men who have an absolute need for anticoagulant drugs or antiplatelet drugs (eg, warfarin, aspirin) which cannot be withdrawn during the 10 days prior to the TOOKAD Soluble VTP procedure
- Renal and hepatic disorders with values of > 1.5 times the upper limit of normal and blood disorders (clinician judgment)
- A history of sun hypersensitivity or photosensitive dermatitis

11.2 International Prostate Symptom Score (IPSS) Questionnaire

1. **Incomplete emptying:** Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?

Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your Score
0	1	2	3	4	5	

2. **Frequency:** Over the past month, how often have you had to urinate again less than 2 hours after you finished urinating?

Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your Score
0	1	2	3	4	5	

3. **Intermittency:** Over the past month, how often have you found that you stopped and started again several times when you urinated?

Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your Score
0	1	2	3	4	5	

4. **Urgency:** Over the past month, how often have you found it difficult to postpone urination?

Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your Score
0	1	2	3	4	5	

5. **Weak-stream**: Over the past month, how often have you had a weak stream?

Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your Score
0	1	2	3	4	5	

6. **Straining:** Over the past month, how often have you had to push or strain to begin urination?

Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your Score
0	1	2	3	4	5	

7. **Nocturia:** Over the past month or so, how many times did you get up to urinate from the time you went to bed until the time you got up in the morning?

None	1 time	2 times	3 times	4 times	5 times or more	Your Score
0	1	2	3	4	5	

8. **Quality of Life Due to Urinary Symptoms:** If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that? (Bold, Highlight or Underline)

Delighted - Pleased - Mostly satisfied - Mixed - Mostly dissatisfied - Unhappy – Terrible

11.3 International Index of Erectile Function (IIEF-15) Questionnaire

These questions ask about the effect your erection problems have had on your sex life over the past 4 weeks. Please answer these questions as honestly and as clearly as possible. Please answer every question by marking one box with a tick [√]. If you are unsure about how to answer, please give the best answer you can.

In answering these questions, the following definitions apply:

*Sexual intercourse
Is defined as sexual penetration (entry) of the partner.
**Sexual activity
Includes intercourse, caressing, foreplay and masturbation.
***Ejaculate
Is defined as the ejection of semen from the penis (or the sensation of this).
****Sexual stimulation

Includes situations such as love play with a partner, looking at erotic pictures, etc.

1. Over the past 4 weeks how often were you able to get an erection during sexual activity**?

Please tick one box only.

No sexual activity ..... ☐
Almost always or always ..... ☐
Most times (much more than half the time)..... ☐
Sometimes (about half the time) ..... ☐
A few times (much less than half the time) ..... ☐
Almost never or never..... ☐

2. Over the past 4 weeks when you had erections with sexual stimulation****, how often were your erections hard enough for penetration?

Please tick one box only.

No sexual stimulation ..... ☐
Almost always or always ..... ☐
Most times (much more than half the time)..... ☐
Sometimes (about half the time) ..... ☐
A few times (much less than half the time) ..... ☐
Almost never or never..... ☐

The next 3 questions will ask about the erections you may have had during sexual intercourse*.

3. Over the past 4 weeks when you attempted sexual intercourse* how often were you able to penetrate (enter) your partner?

Please tick one box only.

Did not attempt intercourse ☐
Almost always or always ☐
Most times (much more than half the time) ☐
Sometimes (about half the time) ☐
A few times (much less than half the time) ☐
Almost never or never ☐

4. Over the past 4 weeks during sexual intercourse* how often were you able to maintain your erection after you had penetrated (entered) your partner?

Please tick one box only.

Did not attempt intercourse ☐
Almost always or always ☐
Most times (much more than half the time) ☐
Sometimes (about half the time) ☐
A few times (much less than half the time) ☐
Almost never or never ☐

5. Over the past 4 weeks during sexual intercourse* how difficult was it to maintain your erection to completion of intercourse?

Please tick one box only.

Did not attempt intercourse ☐
Extremely difficult ☐
Very difficult ☐
Difficult ☐
Slightly difficult ☐
Not difficult ☐

6. Over the past 4 weeks how many times have you attempted sexual intercourse*?

Please tick one box only.

No attempts ☐

1-2 attempts ☐
3-4 attempts ☐
5-6 attempts ☐
7-10 attempts ☐
11 + attempts ☐

7. Over the past 4 weeks when you attempted sexual intercourse* how often was it satisfactory for you?

Please tick one box only.

Did not attempt intercourse ☐

Almost always or always ☐
Most times (much more than half the time) ☐
Sometimes (about half the time) ☐
A few times (much less than half the time) ☐
Almost never or never ☐

8. Over the past 4 weeks how much have you enjoyed sexual intercourse*?

Please tick one box only.

No intercourse ☐

Very highly enjoyable ☐
Highly enjoyable ☐
Fairly enjoyable ☐
Not very enjoyable ☐
Not enjoyable ☐

9. Over the past 4 weeks when you had sexual stimulation**** or intercourse* how often did you ejaculate***?

Please tick one box only.

No sexual stimulation or intercourse ☐
Almost always or always ☐
Most times (much more than half the time) ☐
Sometimes (about half the time) ☐
A few times (much less than half the time) ☐
Almost never or never ☐

10. Over the past 4 weeks when you had sexual stimulation**** or intercourse* how often did you have the feeling of orgasm with or without ejaculation***?

Please tick one box only.

No sexual stimulation or intercourse ☐
Almost always or always ☐
Most times (much more than half the time) ☐
Sometimes (about half the time) ☐
A few times (much less than half the time) ☐
Almost never or never ☐

The next 2 questions ask about sexual desire. Let's define sexual desire as a feeling that may include wanting to have a sexual experience (e.g. masturbation or intercourse*), thinking about sex, or feeling frustrated due to lack of sex.

11. Over the past 4 weeks how often have you felt sexual desire?

Please tick one box only.

Almost always or always ☐
Most times (much more than half the time) ☐
Sometimes (about half the time) ☐
A few times (much less than half the time) ☐
Almost never or never ☐

12. Over the past 4 weeks how would you rate your level of sexual desire?

Please tick one box only.

Very high ☐
High ☐
Moderate ☐
Low ☐
Very low or none at all ☐

13. Over the past 4 weeks how satisfied have you been with your overall sex life?

Please tick one box only.

Very satisfied ☐
Moderately satisfied ☐
About equally satisfied and dissatisfied ☐
Moderately dissatisfied ☐
Very dissatisfied ☐

14. Over the past 4 weeks how satisfied have you been with your sexual relationship with your partner?

Please tick one box only.

Very satisfied ☐
Moderately satisfied ☐
About equally satisfied and dissatisfied ☐
Moderately dissatisfied ☐
Very dissatisfied ☐

15. Over the past 4 weeks how would you rate your confidence that you could get and keep an erection?

Please tick one box only.

Very high ..... ☐
High..... ☐
Moderate ..... ☐
Low ..... ☐
Very low..... ☐

11.4 Patient Death Narrative

Study 301: A 59 year-old man in the TOOKAD VTP arm, with medical history of cerebrovascular accident and hypercholesterolemia, died of a myocardial infarction. Thirty-four weeks and 2 days after treatment with TOOKAD VTP, the patient experienced a fatal myocardial infarction and cardiac arrest after intensive physical exertion on a mountain. An attempt to resuscitate him with a defibrillator was made, but the patient died on the same day.

Considering the patient's cardiovascular risk factors, the circumstances of the event, and the interval of time after TOOKAD VTP, the event was assessed as unrelated to drug, device, or procedure by both the Investigator and the Sponsor.

11.5 Additional Adverse Event Analyses – Study 301 Safety Population

Table 31: Summary of Adverse Events and Unresolved Adverse Events by Severity – Study 301 Safety Population

Adverse Events		All Grades	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Occurrence	TOOKAD VTP (N = 197)	187 (94.9)	49 (24.9)	94 (47.7)	40 (20.3)	3 (1.5)	1 (0.5)
	Active Surveillance (N = 207)	114 (55.1)	42 (20.3)	52 (25.1)	19 (9.2)	1 (0.5)	0
Unresolved at 24 Months	TOOKAD VTP (N = 185)	85 (45.4)	41 (22.2)	35 (18.9)	8 (4.3)	0	0
	Active Surveillance (N = 174)	61 (35.1)	29 (16.7)	26 (14.9)	6 (3.4)	0	0

VTP = vascular-targeted photodynamic therapy

Table 32: Adverse Events Occurring > 5% in Either Arm by Resolution and Severity – Study 301 Safety Population

		Occurrence					Unresolved at 24 months			
		Grade (no Grade 4 or 5 reported)					Grade (no Grade 4 or 5 reported)			
		Any Grade	Grade 1	Grade 2	Grade 3		Any Grade	Grade 1	Grade 2	Grade 3
Nausea	TOOKAD VTP (N = 197)	11 (5.6)	8 (4.1)	3 (1.5)	0	TOOKAD VTP (N = 185)	0	0	0	0
	Active Surveillance (N = 207)	1 (0.5)	1 (0.5)	0	0	Active Surveillance (N = 174)	0	0	0	0
Naso-pharyngitis	TOOKAD VTP (N = 197)	10 (5.1)	9 (4.6)	1 (0.5)	0	TOOKAD VTP (N = 185)	0	0	0	0
	Active Surveillance (N = 207)	9 (4.3)	9 (4.3)	0	0	Active Surveillance (N = 174)	0	0	0	0
UTI	TOOKAD VTP (N = 197)	21 (10.7)	8 (4.1)	11 (5.6)	2 (1.0)	TOOKAD VTP (N = 185)	0	0	0	0
	Active Surveillance (N = 207)	9 (4.3)	3 (1.4)	4 (1.9)	2 (1.0)	Active Surveillance (N = 174)	0	0	0	0
Perineal injury	TOOKAD VTP (N = 197)	15 (7.6)	12 (6.1)	3 (1.5)	0	TOOKAD VTP (N = 185)	0	0	0	0
	Active Surveillance (N = 207)	0	0	0	0	Active Surveillance (N = 174)	0	0	0	0
Back pain	TOOKAD VTP (N = 197)	11 (5.6)	0	6 (3.0)	5 (2.5)	TOOKAD VTP (N = 185)	1 (0.5)	1 (0.5)	0	0
	Active Surveillance* (N = 207)	7 (3.4)	1 (0.5)	4 (1.9)	2 (1.0)	Active Surveillance (N = 174)	0	0	0	0
Dysuria	TOOKAD VTP (N = 197)	54 (27.4)	33 (16.8)	18 (9.1)	3 (1.5)	TOOKAD VTP (N = 185)	4 (2.2)	3 (1.6)	1 (0.5)	0
	Active Surveillance (N = 207)	5 (2.4)	2 (1.0)	3 (1.4)	0	Active Surveillance (N = 174)	2 (1.1)	1 (0.6)	1 (0.6)	0

		Occurrence					Unresolved at 24 months			
		Grade (no Grade 4 or 5 reported)					Grade (no Grade 4 or 5 reported)			
		Any Grade	Grade 1	Grade 2	Grade 3		Any Grade	Grade 1	Grade 2	Grade 3
Haematuria	TOOKAD VTP (N = 197)	56 (28.4)	46 (23.4)	9 (4.6)	1 (0.5)	TOOKAD VTP (N = 185)	0	0	0	0
	Active Surveillance (N = 207)	6 (2.9)	4 (1.9)	2 (1.0)	0	Active Surveillance (N = 174)	0	0	0	0
Micturition urgency	TOOKAD VTP (N = 197)	21 (10.7)	13 (6.6)	8 (4.1)	0	TOOKAD VTP (N = 185)	2 (1.1)	0	2 (1.1)	0
	Active Surveillance (N = 207)	2 (1.0)	1 (0.5)	1 (0.5)	0	Active Surveillance (N = 174)	0	0	0	0
Pollakiuria	TOOKAD VTP (N = 197)	20 (10.2)	14 (7.1)	6 (3.0)	0	TOOKAD VTP (N = 185)	2 (1.1)	0	2 (1.1)	0
	Active Surveillance (N = 207)	6 (2.9)	3 (1.4)	3 (1.4)	0	Active Surveillance (N = 174)	3 (1.7)	2 (1.1)	1 (0.6)	0
Urinary incont-inence	TOOKAD VTP (N = 197)	19 (9.6)	12 (6.1)	5 (2.5)	2 (1.0)	TOOKAD VTP (N = 185)	8 (4.3)	5 (2.7)	1 (0.5)	2 (1.1)
	Active Surveillance (N = 207)	10 (4.8)	5 (2.4)	4 (1.9)	1 (0.5)	Active Surveillance (N = 174)	6 (3.4)	4 (2.3)	1 (0.6)	1 (0.6)
Urinary retention	TOOKAD VTP (N = 197)	32 (16.2)	5 (2.5)	24 (12.2)	3 (1.5)	TOOKAD VTP (N = 185)	1 (0.5)	1 (0.5)	0	0
	Active Surveillance (N = 207)	2 (1.0)	0	1 (0.5)	1 (0.5)	Active Surveillance (N = 174)	1 (0.6)	0	1 (0.6)	0
Ejaculation failure	TOOKAD VTP (N = 197)	16 (8.1)	10 (5.1)	4 (2.0)	2 (1.0)	TOOKAD VTP (N = 185)	10 (5.4)	5 (2.7)	4 (2.2)	1 (0.5)
	Active Surveillance (N = 207)	1 (0.5)	0	1 (0.5)	0	Active Surveillance (N = 174)	1 (0.6)	0	1 (0.6)	0

		Occurrence					Unresolved at 24 months			
		Grade (no Grade 4 or 5 reported)					Grade (no Grade 4 or 5 reported)			
		Any Grade	Grade 1	Grade 2	Grade 3		Any Grade	Grade 1	Grade 2	Grade 3
Erectile dysfunction	TOOKAD VTP (N = 197)	74 (37.6)	40 (20.3)	32 (16.2)	2 (1.0)	TOOKAD VTP (N = 185)	43 (23.2)	26 (14.1)	16 (8.6)	1 (0.5)
	Active Surveillance (N = 207)	24 (11.6)	12 (5.8)	9 (4.3)	3 (1.4)	Active Surveillance (N = 174)	20 (11.5)	9 (5.2)	8 (4.6)	3 (1.7)
Haemato-spermia	TOOKAD VTP (N = 197)	12 (6.1)	11 (5.6)	1 (0.5)	0	TOOKAD VTP (N = 185)	0	0	0	0
	Active Surveillance (N = 207)	5 (2.4)	5 (2.4)	0	0	Active Surveillance (N = 174)	0	0	0	0
Perineal pain	TOOKAD VTP (N = 197)	30 (15.2)	20 (10.2)	9 (4.6)	1 (0.5)	TOOKAD VTP (N = 185)	0	0	0	0
	Active Surveillance (N = 207)	1 (0.5)	1 (0.5)	0	0	Active Surveillance (N = 174)	1 (0.6)	1 (0.6)	0	0
Prostatitis	TOOKAD VTP (N = 197)	10 (5.1)	3 (1.5)	4 (2.0)	3 (1.5)	TOOKAD VTP (N = 185)	1 (0.5)	0	1 (0.5)	0
	Active Surveillance (N = 207)	10 (4.8)	4 (1.9)	5 (2.4)	1 (0.5)	Active Surveillance (N = 174)	1 (0.6)	0	0	1 (0.6)

AE = adverse event; UTI = urinary tract infection; VTP = vascular-targeted photodynamic therapy
*one missing grade

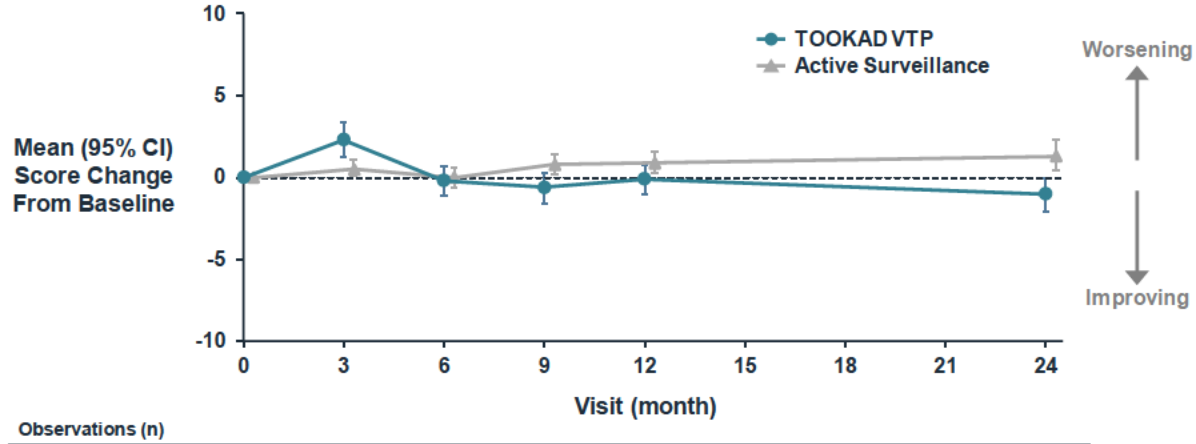
Table 33: Serious Adverse Events and Unresolved Serious Adverse Events – Safety Population Study 301

Serious Adverse Events		All Grades n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Occurrence	TOOKAD VTP (N = 197)	60 (30.5)	7 (3.6)	27 (13.7)	22 (11.2)	3 (1.5)	1 (0.5)
	Active Surveillance* (N = 207)	21 (10.1)	1 (0.5)	7 (3.4)	11 (5.3)	1 (0.5)	0
Unresolved at 24 Months	TOOKAD VTP (N = 185)	5 (2.7)	0	2 (1.1)	3 (1.6)	1 (0.5)	0
	Active Surveillance (N = 174)	2 (1.1)	0	0	2 (1.1)	0	0

VTP = vascular-targeted photodynamic therapy
*one missing grade

11.6 Patient Reported Outcome Results – Study 301 Safety Population

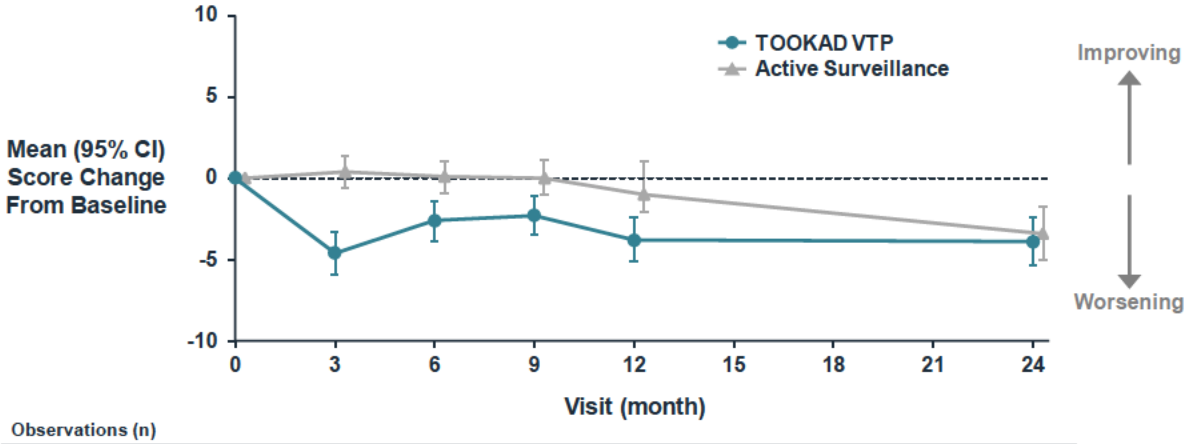
Figure 32: International Prostate Symptom Scores (Questions 1 to 7) - Mean Change from Baseline Over Time – Study 301 Safety Population



Observations (n)						
TOOKAD VTP	179	164	169	164	162	151
Active Surveillance	185	172	170	169	155	138

CI = confidence interval; VTP = vascular-targeted photodynamic therapy

Figure 33: International Index of Erectile Function - Erectile Function Domain - Mean Change from Baseline Over Time – Study 301 Safety Population



Observations (n)						
TOOKAD VTP	184	163	166	164	162	150
Active Surveillance	188	167	171	165	154	140

CI = confidence interval; VTP = vascular-targeted photodynamic therapy
Note: Potential range of change in scores: from -35 (best) to +35 (worst).