MD Anderson IND Sponsor Cover Sheet

Protocol ID	2018-0785
Protocol Title	Pentoxifylline, Atorvastatin and Vitamin E (PAVE) as Treatment for Radiation-Induced Erectile Dysfunction
Protocol Phase	Phase II
Protocol Version	9
Version Date	03/10/2021
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Department	Radiation Oncology
IND Sponsor	MD Anderson Cancer Center
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1.0 TRIAL SUMMARY

Abbreviated Title	PAVE Therapy for Post-RT ED
Trial Phase	Phase II
Clinical Indication	Treatment of radiation-induced erectile dysfunction
Trial Type	Treatment
Type of control	Comparison to baseline in each patient
Route of administration	oral
Trial Blinding	NA
Treatment Groups	Three subgroups will be enrolled, patients who are not on any statins at the time of enrollment, those on atorvastatin, and those on other statins.
Number of trial subjects	50
Estimated duration of trial	4 years
Duration of Participation	1 year

2.0 Background & Rationale

Prostate Cancer is the most common cancer diagnosed among men in the US, accounting for roughly 33% of all non-skin cancer diagnoses each year. Standard first line

therapy for localized prostate cancer include surgery, external beam radiotherapy, and interstitial brachytherapy. The most common side effect of radiation therapy in any form is erectile dysfunction (ED). Depending on radiation technique and associated risk factors, the documented incidence of ED varies. However, reports indicate that anywhere from 10% to 84% of all patients who undergo radiation therapy (XRT) will develop some degree of ED after treatment. Rates vary widely due to heterogeneity of treatment techniques as well as patient populations and risk factors including age, race, comorbidities, etc. Difficulties in assessing ED arise with patient reported outcomes as well, as in one study only 43% of patients who verbally reported being fully potent were found to have normal IIEF scores[1]. However, objective analysis with the IIEF now makes assessment less inherently biased and easier to analyze. Regardless of exact incidence, post-XRT erectile dysfunction plays a significant role in patients' quality of life [2].

The molecular and cellular events leading to late toxicity after RT begin virtually immediately after the first exposure to ionizing radiation. Endothelial cell damage plays an important role in this process, and recent evidence suggests that the capillary endothelial cell may be the first cellular element to be damaged by RT [3]. Vascular damage is important in the phenotype of RT-induced rectal injury, where telangiectatic vessels are often responsible for the bleeding characteristic of this condition. The cholesterol lowering agents HMG coA reductase inhibitors (statins) have been demonstrated to reduce the risk of myocardial infarction, in part, through their vascular protective effects, which are not dependent on changes in serum cholesterol levels. In vitro, statins have been shown to protect human endothelial cells from ionizing radiation [4-6]. Multiple mechanisms appear to be involved, including attenuation of extracellular stress responses [7,8], down-regulation of chemokines and chemokine receptors [9], and by exerting anti-inflammatory and anti-thrombotic effects [4,10-12] on these cells. In vivo,

lovastatin has been shown to protect mice from the effects of whole lung irradiation for up to 24 weeks [13]. Mice receiving lovastatin demonstrated improved survival, a decreased inflammatory response in the lung and reduced fibrosis. Thus, statins may have the potential to protect against RT-induced late effects.

The exact mechanism of radiation induced erectile dysfunction is poorly understood currently. We know the veno-occlusive mechanism of achieving and maintaining a functional erection involves multiple processes which may be affected by radiation. One study in particular suggested a vasculogenic mechanism as the predominant factor contributing to radiation induced erectile dysfunction [14]. Another noted morphologic changes and resulting loss of tone in the internal pudendal artery after SBRT (stereotactic body radiation therapy) in canines [15]. Along with vascular damage playing a major role, chronic oxidative stress has recently been investigated in ED, as it is a known contributor to radiation induced normal-tissue injury in other situations. A recent study using single fraction radiotherapy in a rat model of RT induced ED investigated the role of chronic oxidative stress in development of post-radiation ED using an image guided radiation technique which mimics what is used in clinics currently [16]. Pathophysiologic evidence pointed to early events which may be inflammatory in nature with a resultant decrease in eNOS (endothelial nitric oxide synthase) and subsequent NO (nitric oxide) production. This may be the cause of noted damage to the Cavernosal Nerve and subsequent decreases in intracavernosal pressure, decrease in smooth muscle content, increase in collagen deposition and decreased perfusion in the corpora cavernosa.

For treatment of post-RT erectile dysfunction, 5-PDE inhibitors are typically the first line therapy (i.e. Sildenafil). However, although these drugs are effective, the cost is prohibitive for

most patients, and these agents are rarely covered by patients' health insurance. This explains the need for less-expensive, yet effective treatment options.

Statins have been studied for a role in the treatment of established ED, although, until recently, not in the setting of radiation induced ED. A recent meta-analysis of all trials investigating the efficacy of Statin use on non-radiation induced ED showed a clinically and statistically significant increase of 3.4 points on the IIEF [17]. Of note, this was roughly 1/3 to ½ of the effect seen with PDE inhibitors. The most commonly used statins were atorvastatin followed by simvastatin. Statins improve endothelial function both by lowering LDL (low density lipoprotein) levels and by increasing the availability of NO. Thus, statins appear to counteract one of the primary molecular processes implicated in the development of radiation induced ED. A recent secondary analysis of a trial studying the ability of lovastatin to prevent radiation induced rectal injury demonstrated that this agent was effective in preserving erectile function across most domains of the IIEF with a minimum of 2 years follow-up [18,19]. More potent statins, such as atorvastatin, might prove even more effective in this setting.

As noted above, along with decrease in NO production resulting from the inflammatory response to RT, fibrosis also appears to be a component of radiation induced ED. As such, the combination of Vitamin E and Pentoxifylline may provide a benefit as this combination has a proven role in the treatment of established soft tissue fibrosis from radiation. These drugs have been used for radiation induced proctitis as well as cystitis. Additionally, a recent study has shown that prophylactic Vit E and Pentoxifylline reduces the rate of post-mastectomy fibrosis and implant loss [20] in women with breast cancer. Thus, the addition of Vitamin E plus Pentoxifylline to atorvastatin, as proposed in this study, will target both the proinflammatory and profibrotic pathways known to play a role in late radiation injury.

Another rationale for the combination of these agents is their well-established favorable side effect profile. All of these agents have been used for many years in the clinic and are generally well-tolerated. In addition, are all off-patent and are less costly than the 5-PDE inhibitors.

3.0 Objectives

A. **Primary Objective**: To estimate the proportion of patients who achieve a clinically significant improvement in erectile dysfunctin (ED) when treated with a combination of Atorvastatin or patient's currently prescribed statin, Vitamin E, and Pentoxifylline (PAVE). Clinically significant improvement is defined as an improvement by one category, e.g., from mild-moderate to mild, on the IIEF-5 [International Index of Erectile Function] score, in men with established ED who have completed radiation therapy for prostate adenocarcinoma.

B. **Secondary Objectives**

i. To report the safety profile of PAVE.

ii. To report the rate of choosing other ED treatments after PAVE.

4.0 Patient Selection

Subject Inclusion Criteria:

1. Histologically or cytologically confirmed diagnosis of adenocarcinoma of the prostate

2. Previous radiation therapy (any form) with curative intent for prostate cancer

3. Erectile dysfunction, as determined by an IIEF-5 score of <22

4. Normal testosterone (including men on testosterone replacement), defined as testosterone >150 ng/dl at the time of screening

5. Age ≥18 years

6. Karnofsky Performance Status (KPS) ≥70, or ECOG 0-2

7. Patients may be taking an HMG-coA-reductase inhibitor

8. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3X upper limits of normal (ULN)

9. Creatinine Kinase < 5 times ULN.

10. Normal renal function as defined below:

Normal renal function is defined as creatinine clearance ≥30 ml/min via the Cockroft Gault Formula:

$$\textit{Female}\ \text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$$

$$\textit{Male}\ \text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$$

Subject Exclusion Criteria:

1. No androgen deprivation therapy within the past 12 months

2. No contraindication to an HMG-coA-reductase inhibitor, Vitamin E or Pentoxifylline

3. Not currently taking cyclosporine, the HIV protease inhibitors, hepatitis C protease inhibitors, Gemfibrozil, other fibrates, Clarithromycin, itraconazole or strong inhibitors of CYP3A4

4. No recent cerebral or retinal hemorrhage that in the opinion of the treating physician would make PAVE unsafe (within 6 months)

5. No current chemotherapy during study participation

6. No active liver or muscle disease that in the opinion of the treating physician would make PAVE unsafe.

7. No prior radical prostatectomy, cystoprostatectomy, abdominoperineal resection or retroperitoneal lymph node dissection

8. Not currently taking a 5PDE inhibitor nor have used one within 30 days of enrolling in the study

9. No recent deep venous thrombosis, myocardial infarction or pulmonary embolism (within 6 months) requiring continued anticoagulation other than ASA.

10. No cardiac arrhythmias or artificial heart valves requiring anticoagulation other than ASA.

11. No concurrent drugs with anti-platelet properties (e.g., P2Y12 inhibitors, non-steroidal anti-inflammatory agents, selective serotonin reuptake inhibitors) other than low dose ASA (81mg/d).

12. Not currently taking high dose statin therapy, defined as Rosuvastatin >10mg/d or Atorvastatin >40mg/d.

13. Not currently taking theophylline

14. No history of active peptic ulcer disease in the past 6 months.

15. no history of intolerance to pentoxifylline or methylxanthines such as caffeine, theophylline and theobromine that in the opinion of the treating physician would make PAVE unsafe.

16. No concurrent use of CYP1A2 inhibitors (e.g., ciprofloxacin), ketorolac, or vitamin K antagonists (e.g. warfarin).

5.0 Pre-treatment evaluation

(must be completed within 8 weeks prior to the completion of second step enrollment in CORe; In the event that a patient cannot be seen in person to consent and is consented remotely, physical exam and vitals are not required prior to enrollment. KPS/ECOG maybe conducted from the telephone calls. Baseline labs could be drawn at outside facility and IIEF-5 questionnaire can be completed at home and both can be submitted via secure email or fax.)

A. History and Physical, including KPS or ECOG. Include the following information at a minimum:

1. Age

2. Race and ethnicity

3. T-stage, N-stage, M-stage, Gleason score, initial PSA, PSA prior to radiation

4. Radiation therapy details:

a. treatment dates

b. modality: protons, photons, brachytherapy (include isotope used and dose), or any combination of these modalities

c. for external beam (photon, proton, or combination):

1. include whether or not pelvic lymph nodes were treated, and if so, report total and daily dose/fraction

2. report total dose and dose per fraction for treatment to prostate +/- seminal vesicles

5. Most recent androgen deprivation therapy: report dates of treatment and drugs used

6. smoking history

7. alcohol history

8. current medications including non-prescription substances will be recorded in the medical chart.

9. Most recent treatment tried for ED

10. complete past medical history including history or presence of diabetes mellitus, hypertension, hyperlipidemias, endocrinopathies, cardiovascular diseases (e.g., coronary artery disease, CVA, TIA), hematologic diseases and psychiatric conditions will be recorded in the medical chart.

11. history of prior abdominal &/or pelvic surgery

12. current relationship status (i.e., married, widowed, divorced, presence of significant other)

B. Baseline assessment of erectile function using IIEF-5.

C. Laboratory studies: serum testosterone, CK, liver panel, BUN, Creatinine, GFR estimation, CBC, INR, PT, PTT

D. Baseline CTCAE V4.03 items grade 2 or higher: blurry vision, abdominal distension, abdominal pain, bloating, diarrhea, dyspepsia, flatulence, gastrointestinal pain, nausea, vomiting, malaise, pharyngitis, urinary tract infection, bruising, arthralgias, bone pain, generalized muscle weakness, myalgia, headache, rash (maculopapular), flushing

6.0 Registration Procedures

This protocol utilizes a two-step enrollment in the MD Anderson Cancer Center CORe database. Patients should be entered into the first-step CORe enrollment when consents are completed. Upon completion of all required materials for enrollment, second step enrollment will be completed to fully enroll the patient in CORe. No protocol-related therapies may be administered until the patient is fully enrolled in CORe.

7.0 Drug therapy

A. The HMG-coA reductase inhibitor used in this study will be Atorvastatin for patients not already on a different statin

B. Dosage: 10-80 mg PO once daily

1. Those patients not currently on a statin will receive 10 mg/d Atorvastatin

2. For those currently on a statin, the statin and dose will be maintained at the current dose, unless a change is indicated for management of hyperlipidemia.

a. If patients in this category are not taking at least a moderate intensity LDL lowering regimen, as defined in Appendix F, the prescribing physician

will be contacted for permission to modify the drug regimen, and if permission is granted, the regimen will be modified accordingly.

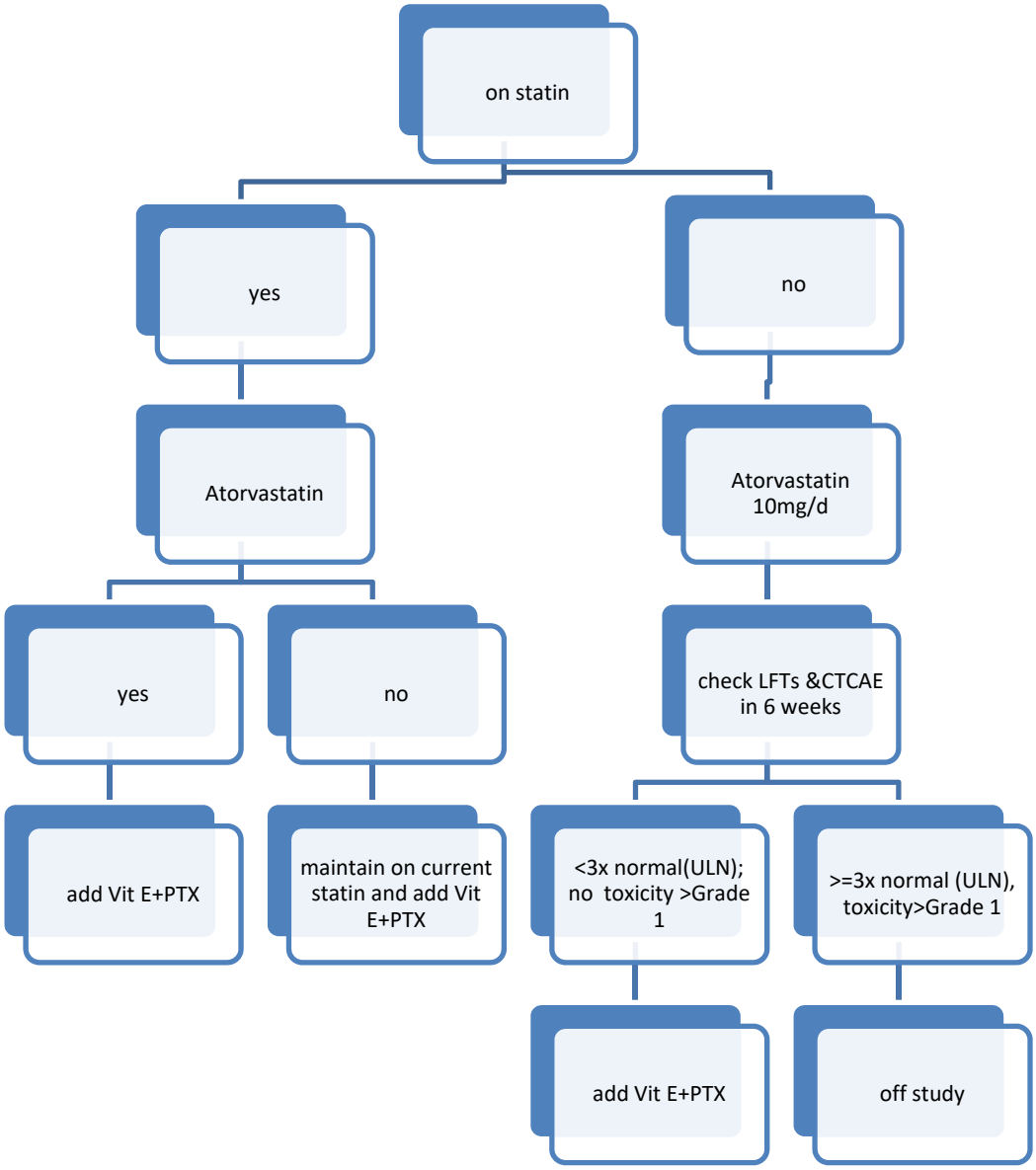
C. Vitamin E: 1000 international units PO once daily

D. Pentoxifylline: 400mg PO three times per day

E. Patients or their third party payers will be expected to cover the cost of the drugs.

F. Medication intake will be annotated in a pill diary as noted in the corresponding Appendix

G. Prescribing algorithm:



Vit E+PTX= Vitamin E 1000IU/d plus Pentoxifylline 400mg tid; LFTs=liver function tests (AST, ALT, total bilirubin)

8.0 Patient Assessments (see table 1)

A. **Atorvastatin:** most common side effects (generally mild) nasopharyngitis, arthralgia, pain in extremity, diarrhea and urinary tract infection

1. Liver function tests: check at 6 weeks (+/- 2 weeks), 3 months (+/- 2 weeks), while taking any statin.
2. Creatine kinase : check at 6 weeks (+/- 2 weeks), 3 months (+/- 2 weeks) and each subsequent visit while on any statin

B. **Vitamin E:** possible side effects: nausea, diarrhea, stomach cramps, fatigue, weakness, headache, blurred vision, rash, and bruising and bleeding

Pentoxifylline: most common side effects: dyspepsia, diarrhea, headache, nausea, vomiting, abdominal discomfort, bloating, flushing.

Table 1: Patient assessment schedule

Test	Baseline *** (within 8 wks of enrollment)	6 wk* ± 2 wks	3 mo* ± 2 wks	6 mo* ± 2 wks	9 mo* ± 2 wks	12 mo* ± 2 wks	18 mo ± 4 wks*
H&P	X			X		X	X
BP, Pulse, Respiratory Rate	X	X	X	X	X	X	
KPS or ECOG	X			X		X	
IIEF-5****	X		X	X	X	X	
CTCAE V4.03**	X	X	X	X	X	X	
Hepatic panel	X	X	X	X	X	X	
CK[!]	X	X	X	X	X	X	
BUN, Creatinine, calculated GFR, CBC, PT, PTT, INR, Testosterone	X	X	X	X	X	X	

[!]In addition to scheduled testing, obtain at any time patient notes muscular symptoms

*follow up times start from the day patient begins taking all 3 drugs concurrently. Can be done over the phone or in person, in the event that follow up can only be done over the phone, physical exam, KPS or ECOG, and vitals do not have to be obtained. Labs could be drawn at outside facility and IIEF-5 questionnarire can be completed at home and both can be submitted via secure email or fax.

**selected items with CTCAE grade 2 or higher: blurry vision, abdominal distension, abdominal pain, bloating, diarrhea, dyspepsia, flatulence, gastrointestinal pain, nausea, vomiting, malaise, pharyngitis, urinary tract infection, bruising, bleeding, arthralgias, bone pain, generalized muscle weakness, myalgia, headache, rash (maculopapular), flushing, chest pain, palpitations, dyspnea, cough, wheezing, lower extremity edema. This assessment can be done either over the phone or in person.

***please refer to section 5.0 for pre-treatment evaluation

****please refer to the appendix for the IIEF-5 questionnaire

D. **Modification of statin dosing**

1. discontinue if transamimases become ≥ 3 times ULN
2. discontinue if creatine kinase becomes ≥ 5 times ULN
3. If not on a statin prior to enrollment in the trial, discontinue if signs or suspicion of cardiovascular issues appear per the discretion of the treating physician.

For other side effects listed in section 8 above:

a. if dose is ≥20mg and if toxicity isGrade 2, decrease dosage by 50%. If toxicity resolves or decrease to Grade 1, maintain atorvastatin at this lower dose. If toxicities are ≥Grade 3, stop atorvastatin and the patient should be removed from the study.
b. If dose=10mg, hold atorvastatin. If toxicity resolves or decrease to Grade 1, restart at 10 mg every other day. If toxicities are ≥Grade 3, stop atorvastatin and the patient should be removed from the study.

E. **Modification of Vitamin E dosing:**

1. If toxicity is Grade 2, decrease dosage by 50%. If toxicity resolves or decrease to Grade 1, maintain Vitamin E at this lower dose. If toxicities are ≥Grade 3, stop Vitamin E and the patient should be removed from the study.

2. Discontinue if signs or suspicion of cardiovascular issues appear.

F. **Modification of Pentoxifylline dosing:**

1. If toxicity is Grade 2, decrease dosage to 400 mg bid. If toxicity resolves or decrease to Grade 1, maintain at this lower dose. If toxicities are ≥Grade 3, stop Pentoxifylline and the patient should be removed from the study.

2. Discontinue if signs or suspicion of cardiovascular issues appear.

G. **Modification of drug dosing where side effect can't be attributed to one specific drug:**

1. Since the 3 study drugs have overlapping toxicities, circumstances may arise in which it is not clear which drug is responsible for the toxicity.

2. If the toxicities are ≥Grade 3, stop all 3 drugs and the patient should be removed from the study.

3. If toxicity is Grade 2, first reduce the dose of atorvastatin as per guidelines above. If after 1 week the toxicity has not decreased to Grade 1 or resolved, reduce the dose of Pentoxifylline as per guidelines above. If after an additional week the toxicity has not decreased to Grade 1 or resolved, reduce the dose of Vitamin E as per guidelines above. If after another week the toxicity has not resolved or decreased to Grade 1, all 3 drugs should be stopped and the patient should be removed from the study.

4. Cardiovascular issues: for toxicity of Grade 3 or higher, all 3 drugs will be discontinued, and the patient directed to the nearest emergency department for urgent evaluation. For toxicity of Grade 2, guidelines delineated in sections 8.G.1-3 above will be followed for drug dosing modifications, while concurrently obtaining a cardiovascular evaluation from the patient's cardiologist (if he has one), or his personal primary care physician. At the patient's preference, cardiology evaluation may be obtained at MD Anderson. Continuation on study medications will be contingent on cardiology approval.

9.0 Data Collection

A. Collection of study data listed in the table in section 7 will be the responsibility of the research nurse at each study site.

B. Clinical study data for this trial will be collected and managed using the RedCap database within patient registry in the instituation CORe database. RedCap is a secure portal that requires users to login with validated credentials. Electronic data will be stored on a password-protected computer. Paper data will be stored in a locked cabinet. Data will be maintained in the Radiation Oncology Clinical Research Office.

10.0 Adverse Events

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after the first protocol intervention, even if the event is not considered to be related to study treatment. Medical conditions/diseases present before starting study therapy are only considered adverse events if they worsen after starting study treatment. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events ≥ grade 2 and assigning the attribution for all adverse events ≥ grade 2 for subjects enrolled.

Recommended Adverse Event Recording Guidelines

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

Serious Adverse Event (SAE) Reporting

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

11.0 Biostatistics

A. **Goal:**

The purpose of this trial and design is to provide inexpensive treatment for ED following XRT. While we hypothesize a smaller success rate than prescription ED treatments, this combination may be a less expensive alternative for those patients who do benefit. Three planned subgroups

will be enrolled, patients who are not on any statins at the time of enrollment, those on atorvastatin, and those on other statins. Patients will remain on study from enrollment until 1 year, disease relapse requires therapy, the physician withdraws the patient for safety reasons, or the patient withdraws for any reason.

Revision 2021. Since this trial was closed to accrual during the pandemic and new telemedicine practices and pandemic limitations are stifling accrual, this trial is being revised to enroll 50 patients with planned subgroups based on prior statin experience rather than the original 270 with 90 patients per statin cohort. This will still allow us to honor the patients already enrolled, learn something new, and also complete the trial in a reasonable amount of time under the new conditions. At the time of revision, there are 11 patients enrolled, and the first interim analyses as described in this revision allow the trial to continue.

B. <u>Endpoints</u>

i. IIEF-5 (International Index of Erectile Function)

This validated instrument will be completed as per study calendar. The instrument categorizes ED severity into 5 categories as none (22-25), mild (17-21), mild to moderate (12-16), moderate (8-11), or severe (5-7). A patient will demonstrate improvement at any time point if his score goes up enough to move at least 1 category less severe compared to baseline. A patient with improvement will be considered to have a response. Pateints who drop out of the trial without any measurements will count as a non-responder.

ii. Adverse Events

Patients' adverse events will be recorded by CTCAE v 4.03 at baseline and throughout this trial and at 30 days after stopping the active treatment portion of this trial (1 year on PAVE).

iii. Use of other ED treatment after PAVE.

ED treatment medications prescribed during or upon leaving this trial will be collected at 18 months

C. **Sample Size**

A total of 50 patients will be enrolled. With 50 patients, if the response rate is 33%, then assuming an uninformative prior of beta(0.33, 0.67), the 95% credible interval would be (20.1%, 45.3%) if 16/50 respond and (21.8%, 47.4%) if 17/50 patients respond. The selection of 50 patients provides a 95% credible interval that has a width less than 26% at approximately 33%.

D. **Interim Analyses for Safety and Futility**

Interim analyses will begin after 10 patients have been enrolled. Monitoring will then be performed every 10 patients to ensure that patients are exhibiting reasonable toxicity and efficacy rates to continue with the trial. Patients who receive treatment less than 8 weeks will still be counted in toxicity and futility monitoring as long as they received at least 1 dose of the study drug. For patients already on statins, this means the patient must have started the combination. For patients who are starting on atorvastatin, patients will count as long as they received at least one dose of atorvastatin. If the trial can continue after 40 patients, then interim analyses will be complete. Adverse events will continue to be recorded and reported for all patients. If the toxicity or efficacy rates are noted to be different among the patient subgroups, the same stopping rules may be applied to any subgroup of concern to discontinue enrollment of that subgroup.

A Bayesian sequential monitoring design (Thall et al. 1995 and 1998) will be used to monitor the trial for toxicity and futility. Calculations were performed in MultcLean 2.1.

Toxicities will be monitored assuming a prior probability of toxicity following Beta(1,1) against a constant rate of 30% as the maximum acceptable toxicity rate. Trial limiting toxicities (TOX) are any grade 3 or higher toxicities at least possibly related to the study drug that occur in the first 8 weeks of therapy. The trial will be terminated if Prob(TOX > 0.30 | data) > 0.95. Following this rule, the trial will be terminated according to the table below once the first 10 patients have enrolled.

Similarly, efficacy will be monitored assuming a prior probability of response following Beta(0.33,0.67) against a constant rate of 33% as the minimum acceptable response rate. A patient will have a response if there is documented improvement at any time point on the trial. The trial will be terminated if Prob(Response < 0.33 | data) > 0.975. Following this rule, the trial will be terminated according to the following table once the first 10 patients have enrolled.

If there are this many patients treated who are evaluable (i.e., have TOX or completed the first 8 weeks without TOX for TOX, or have at least one IIEF result post-baseline for response)	10	20	30	40
Stop the trial if there are this many (or more) patients who have TOX	6	10	14	17
Stop the trial if there are this many (or fewer) patients who have responded.	0	2	5	7

The first 10 patients will be accrued before the first analysis. If 6 or more of the 10 patients have TOX events, stop the trial and the treatment will be declared as too toxic for this population. If there are 5 or fewer patients with TOX events and at least 1 patient with response, enroll the

next 10 patients and compare the number of patients with TOX and response against the table's rules.

The futility rule will be checked at the same time as the safety check even though the assessment time is later. As long it is safe and there are enough responses to continue, the trial will continue without delay. If there are not enough responses to continue but enough patients are pending response that it will be possible to continue once they are assessed, enrollment will hold until enough responses occur or enough patients go off study without response to prevent the possibility of passing the rule. Since response can occur at any of the planned times, a patient who was previously a non-responder can become a responder at a later follow-up and will count as a responder in the current analysis even if counted as non-responder in a previous analysis. A patient will not change from a responder to non-responder later.

The operating characteristics for these rules are summarized in the following table, based on simulations performed in Multc Lean Desktop version 2.1.

Operating characteristics

		Stop if Prob{TOX > 0.30 | data} > 0.95 Or Prob{Response < 0.33 | data} > 0.975	
True Toxicity Rate	True Response Rate	Pr(stop early)	Median (25^{th} %ile, 75^{th} %ile)
0.10	0.15	0.81	30 (20, 40)
0.20	0.15	0.82	30 (20, 40)
0.30	0.15	0.84	30 (20, 30)

0.40	0.15	0.91	20 (10, 30)
0.50	0.15	0.98	20 (10, 20)
0.10	0.25	0.28	50 (40, 50)
0.20	0.25	0.28	50 (40, 50)
0.30	0.25	0.36	50 (30, 50)
0.40	0.25	0.64	30 (20, 50)
0.50	0.25	0.92	20 (10, 30)
0.10	0.33	0.06	50 (50, 50)
0.20	0.33	0.07	50 (50, 50)
0.30	**0.33**	**0.17**	**50 (50, 50)**
0.40	0.33	0.54	40 (20, 50)
0.50	0.33	0.90	20 (10, 30)
0.10	0.45	0.004	50 (50, 50)
0.20	0.45	0.01	50 (50, 50)
0.30	0.45	0.12	50 (50, 50)
0.40	0.45	0.51	40 (20, 50)
0.50	0.45	0.89	20 (10, 30)
0.10	0.55	0.001	50 (50, 50)
0.20	0.55	0.01	50 (50, 50)
0.30	0.55	0.12	50 (50, 50)
0.40	0.55	0.51	40 (20, 50)
0.50	0.55	0.89	20 (10, 30)

E. **Analysis Plan**

Patients' baseline ED levels will be reported along with the proportion for patients who improve by at least 1 level according to the IIEF-5 for each time point measured. The proportion will be reported along with a 95% credible interval implementing a non-informative prior of beta(0.33, 0.67). Additionally, the proportion of patients who ever improve by at least 1 level will be reported overall. For secondary measures, the safety profile of the PAVE combination will be reported overall and for each planned subgroup based on prior statin treatment, with adverse events summarized by grade and time to onset to first grade 3 adverse event. Finally, the number of patients who drop out of the study to start an ED prescription medication will be reported. Exploratory analyses will be utilized to determine whether baseline patient features can predict response to PAVE or adverse events.

The Investigator is responsible for completing an efficacy/safety summary report, and submitting it to the IND Office Medical Affairs and Safety Group, for review and approval. This should be submitted every 10 evaluable patients, complete 8 weeks of study treatment until enrollment is complete

A copy of the summary should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

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