A Phase 1/2a Pilot Study of Intravesical TSD-001 for Treatment of Low-Grade, Stage Ta, Non-Muscle Invasive Bladder Cancer

Study Number: TD-001

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Protocol Version 7.0

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Study Protocol

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Study Number:	**TD-001**
Version	**7.0**
Date	**04FEB2020**
Study Phase:	**Phase 1/2a**
Investigational Product:	**TSD-001**
Investigational New Drug (IND)/EudraCT Number:	**129419**
Indication:	**Non-Muscle Invasive Bladder Cancer (NMIBC)**
Sponsor:	**LIPAC Oncology LLC** **325 Sharon Park Drive, Suite 739** **Menlo Park, CA 94025-6805**

Compliance Statement: This study will be conducted in accordance with the clinical research guidelines established by the US Code of Federal Regulations (CFR) (Title 21, Parts 50 [including Subpart D], 54, 56, and 312), and the regulations and guidelines of the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP). Study documents will be maintained in accordance with applicable regulations.

PROTOCOL APPROVAL SIGNATURE PAGE

I, the undersigned, have reviewed this study protocol, and I agree to conduct this study in accordance with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP); the ethical principles set forth in the Declaration of Helsinki; the United States (US) Code of Federal Regulations (CFR) governing the protection of human subjects (21 CFR Part 50), financial disclosure by clinical investigators (21 CFR Part 54), Institutional Review Boards (21 CFR Part 56), and the obligations of clinical investigators (21 CFR Part 312); and other applicable local regulatory requirements.

The protocol may not be modified without written approval of the Sponsor. All changes to the protocol must be submitted to the applicable regulatory authorities and Institutional Review Board (IRB), and must be approved by the IRB prior to implementation except when necessary to eliminate immediate hazards to the subjects or when the change(s), as deemed by the Sponsor, involves only logistical or administrative changes. Documentation of IRB approval must be sent to the Sponsor immediately upon receipt.

I have read this protocol in its entirety and I agree to all aspects.

Investigator(s)

_____
Principal Investigator Signature

Investigator Printed Name:_____ Date: _____

Institution/Location:

Sponsor Approval

M. Oefelein 3/3/20

Michael G. Oefelein, MD, FACS
Chief Medical Officer
LIPAC Oncology LLC

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation or specialist term	Explanation
AE	adverse event
BCG	Bacillus Calmette-Guérin
CFR	Code of Federal Regulations
CIS	carcinoma in situ
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
HgbA1c	glycated hemoglobin
ICH	International Conference on Harmonisation
IPSS	International Prostate Symptom Score
IRB	Institutional Review Board
LIPAC	LIPAC Oncology LLC
MDD	maximum deliverable dose
MITT	modified intent-to-treat (population)
MTD	maximum tolerated dose
NCI	National Cancer Institute
NMIBC	non-muscle invasive bladder cancer
OAB-q	Overactive Bladder Questionnaire
PK	pharmacokinetic(s)
PP	per protocol (population)
SAE	serious adverse event
SAP	statistical analysis plan
SWFI	sterile water for injection
Ta	noninvasive papillary carcinoma
TCC	transitional cell carcinoma
Tis	carcinoma in situ
TURBT	transurethral resection of bladder tumor
US	United States
WHO	World Health Organization

1. SYNOPSIS

Sponsor: LIPAC Oncology LLC	**Name of Medical Product:** TSD-001	**Active Ingredient:** Paclitaxel United States Pharmacopeia (USP)
Study Title: A Phase 1/2a Pilot Study of Intravesical TSD-001 for Treatment of Low-Grade, Stage Ta, Non-Muscle Invasive Bladder Cancer		
Study Center(s): This is a multicenter study that will be conducted in the United States.		
Study Duration: **Part 1** – up to 20 weeks (up to 4-week screening period, 10-week treatment period, and 6-week follow-up period) **Part 2 Cohort 1** – up to 17 weeks (up to 4-week screening period, 5-week treatment period, and 8-week follow-up period). **Part 2 Cohort 2** – up to 20 weeks (up to 4-week screening period, 7-week treatment period, and 9-week follow-up period). **Part 3** – Standard-of-care cystoscopic surveillance every 3 months for up to 24 months from initial instillation.		**Study Phase:** 1/2a (phase 1 portion is first in human)

Study Objectives:

The primary objective of **part 1** is to establish the maximum tolerated dose (MTD), defined as the dose immediately preceding the dose at which dose-limiting toxicity (DLT) occurs or when a maximum deliverable dose (MDD) is determined.

The secondary objectives of **part 1** are to determine paclitaxel pharmacokinetic (PK) concentrations in the urine and the peripheral blood at all TSD-001 doses.

Exploratory objectives of **part 1** include evaluation of the change from baseline to Week 16 in International Prostate Symptom Score (IPSS) (men only) and Overactive Bladder Questionnaire (OAB-q).

The primary objective of **part 2** is to assess the marker lesion response rate using the MTD/MDD established in part 1.

The secondary objectives of **part 2** are to: 1) determine paclitaxel PK concentrations in the peripheral blood before and after the third intravesical exposure to TSD-001; and 2) characterize the severity and frequency of adverse events (AEs) following intravesical administration of TSD-001 at the MTD/MDD established in **part 1**, as defined according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

Exploratory objectives of **part 2** include change from baseline to the end of the treatment part in IPSS (men only) and OAB-q scores and paclitaxel levels in voided urine samples at 24, 48, and 72 hours after the third instillation of TSD-001.

The exploratory objective of **part 3** (surveillance) is to determine rates of disease-free (i.e., no histological tissue diagnosis evidence of recurrence) survival of subjects exposed to TSD-001 in **part 1** or **part 2**. Histological tissue diagnosis evidence is identification of any urothelial carcinoma (i.e., transitional cell carcinoma [TCC]), including all grades and stages.

Cystoscopic surveillance will be performed as standard of care approximately every 3 months from last endoscopic assessment in **part 1** or **part 2** until 24 months (from initial instillation).
Methodology: This is a single-arm, phase 1/2a study of formulated paclitaxel in subjects with low-grade, noninvasive papillary carcinoma (stage Ta) of the bladder. Subject eligibility will be determined during the screening period, and will enroll low-grade, stage Ta non-muscle invasive bladder cancer (NMIBC). Following screening, **part 1** of the study will enroll 6 subjects (3 per cohort) with low-grade (WHO, 2004) (i.e., grade 1 [G1] and or grade 2 [G2], [WHO, 1973]), uni- or multifocal, stage Ta TCC of the bladder who will receive escalating doses of paclitaxel formulated as TSD-001 every 2 weeks for 6 treatments. **Part 2** cohort 1 of the study will enroll at least 5 subjects with low-grade, stage Ta TCC of the bladder who will receive weekly TSD-001 for 6 administrations at the highest nontoxic dose established in **part 1** of the study. **Part 2** cohort 2 of the study will enroll up to 10 subjects with low-grade, stage Ta TCC of the bladder who will receive weekly TSD-001 for 8 administrations at the highest nontoxic dose established in **part 1** of the study. Subjects who receive at least two treatments in **part 1** or **part 2** may be followed further with standard-of-care cystoscopic surveillance in **part 3**. The objective of **part 3** is to determine rates of disease-free (no histological tissue diagnosis evidence of recurrence) survival of subjects exposed to TSD-001 in **part 1** or **part 2**. The study has a total of 17 planned clinic visits for **part 1** and 14 planned clinic visits for **part 2** cohort 1 subjects and 16 planned clinic visits for **part 2** cohort 2 subjects. **Part 3** has an additional 7 planned clinic visits. Potential subjects will undergo screening and once qualified will then receive intravesical instillations of TSD-001. In **part 1**, TSD-001 exposure will begin no sooner than 12 days (± 2 days) after the transurethral resection of bladder tumor (TURBT) procedure. In **part 2**, TSD-001 exposure will begin immediately (≤ 120 minutes) after completion of TURBT or as scheduled for subjects not undergoing TURBT (i.e., solitary tumor subjects). Paclitaxel PK concentrations in urine and peripheral blood will be obtained at 15 (± 15) minutes pre-instillation and 2 hours ± 10 minutes post-instillation for each TSD-001 intravesical exposure according to the schedule of events. For **part 2** cohort 1 subjects, the marker lesion response rate will be determined 12 weeks (± 7 days) after Day 1 (i.e., 7 weeks [± 7 days] after the last intravesical instillation), via cystoscopy, cytology, and biopsy under general/regional anesthesia. For **Part 2** cohort 2 subjects, the marker lesion response rate will be determined 15 weeks (± 7 days) after Day 1 (i.e., 8 weeks [± 7 days] after the last intravesical instillation). Complete marker lesion response requires no evidence of TCC on cystoscope-directed biopsy. Partial response is at least a 30% decrease in marker lesion size (Eisenhauer et al., 2009). The severity and frequency of AEs will be assessed in the weeks following TSD-001 administration and defined according to the CTCAE (Version 5.0). For **part 1** of the trial, an adaptive titration design with an intra-subject dose escalation scheme will be used to establish the MTD. For the first 3 subjects, the initial dose will be 10 mg in

sterile water for injection (SWFI). Unless DLT is observed, subsequent intravesical doses will be increased every 14 days according to the following schedule: 25, 50, 75, 100, 150 mg. The starting dose for all subsequent study subjects will be determined based on the MTD/MDD observed in subjects exposed to TSD-001; MTD is established by the presence or absence of DLT (see Section 7.2 for details). If grade 2 toxicity is observed and resolves or improves to grade 1, the intravesical dose to be administered 14 days later in the subject with grade 2 toxicity will be reduced according to the rules established in Section 7.2.
The concentration of paclitaxel in TSD-001 is dynamic over the course of intravesical dwell time based on the rate of urine production and on the reconstitution instructions for each dose. The primary endpoint of **part 1** is to determine the MTD, defined as the dose immediately preceding the dose at which DLT occurs or when a MDD is determined in the dose escalation scheme described below without any DLT. Dose-limiting toxicity is defined as any toxic effect potentially related to drug that is considered unacceptable and limits further dose escalation. Specifically, DLT will be defined by any grade 3 or 4 (G3 or G4) or prolonged (greater than 14 days) grade 2 CTCAE toxicity related to study drug. If no G3 or G4 (or prolonged grade 2) CTCAE toxicity related to study drug is observed, MTD will be defined by the dose just before the dose at which > 33% of the study subjects experience G2 CTCAE toxicity related to study drug. If no DLT is observed in the first 6 subjects after titration, then 360 mg will be the dose recommended for **part 2** of the study, as this paclitaxel concentration is substantially higher than the half-maximal inhibitory concentration (IC_{50}) observed in bladder cancer cell lines exposed to TSD-001. Subjects in **part 2** cohort 1 will receive intravesical instillations of TSD-001 via sterile urethral catheterization of the urinary bladder at the MTD/MDD established in **part 1** at weekly intervals for 6 consecutive weeks. Subjects in **part 2** cohort 2 will receive intravesical instillations of TSD-001 at weekly intervals for 8 consecutive weeks. The first instillation of TSD-001 will be immediately (≤ 120 minutes) post-TURBT or as scheduled for subjects not undergoing TURBT (i.e., solitary tumor subjects). The instillation will be retained in the bladder for 2 hours (1 hour or more will be acceptable, depending on subject's tolerability of the procedure). When local AEs occur, treatment may be delayed (up to 14 days) and/or the dose reduced (per rules detailed in Section 7.2) at the investigator's discretion. Paclitaxel PK concentration measurements of peripheral blood during **part 2** will be obtained 2 hours (± 10 minutes) after the first intravesical instillation, and 15 minutes (± 15 minutes) before and 2 hours (± 10 minutes) after the third intravesical instillation. Paclitaxel levels will also be measured in voided urine samples at 24, 48, and 72 hours after the third instillation of TSD-001. Subject questionnaires (IPSS [men only] and OAB-q) will be administered at baseline enrollment, day of last treatment, and at the end of the treatment part. Safety analyses will be performed on data collected throughout the study.

Diagnosis and Inclusion Criteria:

These criteria apply to study entry into part 1 or part 2. Subjects have to meet all of the following inclusion criteria:

1. 18 to 85 years of age at time of study enrollment.
2. Able to meet the requirements of the study; give voluntary, written informed consent; and adhere to dosing and visit schedules.
3. Has a diagnosis of low grade (WHO, 2004) (i.e., G1 or G2 [WHO, 1973]), uni- or multifocal papillary-appearing bladder tumor, stage Ta. In part 2, a subject meets this inclusion without this histological tissue diagnosis if on cystoscopic assessment they have a solitary papillary tumor (≥ 0.5 cm and ≤ 2.0 cm in diameter).
4. For **part 1**, subject will have ≥ 1 and ≤ 5 tumors (prior to TURBT), none of which exceeds 3.0 cm in diameter; for **part 2**, patient will have ≥ 2 and ≤ 5 tumors (prior to TURBT), none of which exceeds 3.0 cm in diameter (resection loop ~1 cm), OR, for **part 2**, subject meets this inclusion criterion if on cystoscopic assessment they have a solitary papillary tumor (≥ 0.5 cm and ≤ 2.0 cm in diameter).
5. Subject is surgical candidate for TURBT as part of normal NMIBC treatment plan. For **part 1**, successful completion of TURBT procedure. For **part 2**, successful completion of cystoscopic assessment/TURBT procedure with one marker lesion left intact; the marker lesion should be ≥ 0.5 cm and ≤ 2.0 cm in diameter.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
7. Peripheral neuropathy grade 1 or less (NCI CTCAE Version 5.0).
8. Adequate hematological, hepatic, and renal parameters; i.e., hemoglobin > 10 g/dL, creatinine < 3.5 mg/dL, bilirubin < 1.5 mg/dL, aspartate aminotransferase < 50 U/L, alanine aminotransferase < 50 U/L, and alkaline phosphatase < 130 U/L.
9. All sexually active subjects of reproductive potential are required to use or start using a reliable method of birth control at least 2 weeks prior to study enrollment, throughout the treatment part, and for at least 3 months following completion of study drug treatment. A reliable method of birth control is defined in Section 7.6.
10. Females of childbearing potential must have a negative pregnancy test within 30 days prior to enrollment. Females who are postmenopausal for at least 1 year (defined as more than 12 months since last menses) or are surgically sterilized do not require this test.
11. Adequate venous access to allow collection of blood samples by venipuncture.

12. For male subjects, the digital rectal examination must not be suspicious for carcinoma of the prostate.
13. Able to retain bladder instillations for up to 120 minutes (± 15 minutes).

These criteria apply to study entry into **part 1** or **part 2**. Potential study subjects will be excluded if one (or more) of the following exclusion criteria is present:

1. Has an active concurrent malignancy/life-threatening disease. If there is a history of prior malignancies/life-threatening diseases, the subject is to be disease free for at least 5 years. Subjects with other prior malignancies less than 5 years before study entry may still be enrolled if they have received treatment resulting in complete resolution of the cancer and currently have no clinical, radiologic, or laboratory evidence of active or recurrent disease. Subjects will not be excluded for recurrent NMIBC, basal or squamous cell skin cancers, or noninvasive cancer of the cervix.
2. Has positive urine cytology for urothelial malignancy (i.e., high-grade) at screening.
3. Has Cis or T1 transitional cell carcinoma (TCC).
4. Has Bacillus Calmette-Guérin (BCG)-refractory TCC.
5. Has an active uncontrolled infection, including a urinary tract infection, underlying medical condition (e.g., systolic blood pressure ≥ 160 mm Hg and/or diastolic blood pressure ≥ 92 mm Hg), or other serious illness that would impair the ability of the subject to receive protocol treatment.
6. Previous intravesical therapy (e.g., BCG, mitomycin C, chemotherapeutic agent) within 6 months of study entry.
7. Participated in a previous clinical trial or used any investigational drugs, biologics, or devices within 90 days prior to study treatment or plans to use any of these during the course of the study.
8. Has had any previous exposure to paclitaxel or docetaxel in the last 5 years.
9. Has or has ever had: upper tract TCC; urethral tumor (prostatic urethra included); any invasive bladder tumor (T2 or greater); any evidence of lymph node or distant metastasis; any bladder tumor with histology other than TCC.
10. Has a tumor in a bladder diverticulum.
11. Concurrent treatment with any chemotherapeutic agent.
12. History of vesicoureteral reflux.
13. An indwelling ureteral stent.
14. Has received any pelvic radiotherapy (including external beam and/or brachytherapy).
15. Has a bleeding disorder or a screening platelet count < 100×10^9/L.
16. Has any unstable medical condition that would make it unsafe to undergo

TURBT or receive instillation (e.g., presence of uncontrolled gross hematuria). Subject experienced any procedure-related adverse effect during TURBT that, in the opinion of the investigator, would put the subject at unacceptable risk to receive intravesical treatment or participate in the study (e.g., bladder perforation).

17. Has an active diagnosis of interstitial cystitis.
18. For subjects with recurrent tumor, the subject did not have at least a 6-month cystoscopically confirmed tumor-free interval between the last tumor recurrence and screening cystoscopic examination.
19. Females of childbearing potential who are nursing, pregnant, intending to become pregnant, or intending to nurse during the time of the study, or who have a positive pregnancy test at baseline.
20. Currently seeking to father a child or is seeking fertility within one year of trial participation.
21. Presence of poorly controlled diabetes mellitus (glycated hemoglobin [HgbA1c] > 9.0%).
22. Clinically significant co-morbid conditions that would interfere with the subject's participation or compromise the subject's safety.
23. Any significant history of allergy and/or sensitivity to the drug products or their excipients, including any history of sensitivity to paclitaxel.
24. Undergone surgery or had a medical condition that in the judgment of the principal investigator places the subject at unacceptable risk to participate in the study.
25. Any contraindication to blood sampling.
26. Intent to have an elective surgical procedure (other than TURBT) during the course of the trial.
27. Donated blood or blood products or had a significant loss of blood within 90 days before dosing.
28. Donated bone marrow within 6 months before dosing.
29. Positive urine drug screen or history of drug or alcohol abuse in the past 6 months.
30. Any condition that the investigator believes would interfere with the intent of this study or would make participation not in the best interests of the subject.

Number of Subjects (planned): An enrollment of up to 21 subjects is planned, with 6 subjects in **part 1** and up to 15 additional subjects in **part 2** (at least 5 in cohort 1 and up to 10 in cohort 2). Any subject that receives at least two treatments in **part 1** or **part 2** is eligible for surveillance in **part 3**.

Test Product, Dose, and Mode of Administration:

The test product is TSD-001 (Paclitaxel USP) administered via intravesical instillation. In **part 1**, the study drug starting dose for the first three subjects (cohort 1) will be 10 mg, and increased according to the schedule (25, 50, 75, 100, 150 mg) every 2 weeks, or until DLT is reached, for a total of 6 intravesical instillations via urethral catheterization. The study drug starting dose for the next three subjects in **part 1** (cohort 2) will be 90 mg, and increased according to the schedule (180, 270, 360, 450, 540 mg). The study drug dose will be up- or down-titrated per protocol (see Section 7.2). For subjects in **part 2** cohort 1, the MTD or MDD will be administered every 7 days for 6 consecutive intravesical administrations via urethral catheterization. For subjects in **part 2** cohort 2, the MTD or MDD will be administered every 7 days for 8 consecutive administrations.

Criteria for Evaluation:

The primary endpoint for **part 1** is the MTD, defined as the dose immediately preceding the dose at which dose-limiting toxicity (DLT) occurs or when a maximum deliverable dose (MDD) is determined. The severity and frequency of AEs will be assessed in the weeks following TSD-001 administration, and defined according to CTCAE.

The secondary endpoints for **part 1** are to determine paclitaxel concentrations in the urine and the peripheral blood at all TSD-001 doses.

Exploratory endpoint for **part 1** include evaluation of the change from baseline to Week 16 in IPSS (men only) and OAB-q scores.

The primary endpoint of **part 2** is the marker lesion response rate using the MTD/MDD established in **part 1**.

The secondary endpoints of **part 2** are to: 1) determine paclitaxel PK concentrations in the peripheral blood; and 2) characterize the severity and frequency of AEs following intravesical administration of TSD-001 at the MTD/MDD established in **part 1**, as defined according to CTCAE.

Exploratory endpoints of **part 2** include change from baseline to the end of the treatment part in IPSS (men only) and OAB-q scores and paclitaxel levels in voided urine samples at 24, 48, and 72 hours after the third instillation of TSD-001.

The exploratory endpoint of **part 3** (surveillance) will be disease-free survival of subjects exposed to TSD-001 in **part 1 or part 2**. The endpoint will be a time to event (recurrence) after the TURBT (Day -12 in Part 1) or after complete response or Week 12 TURBT in Part 2. Cystoscopic surveillance as per standard of care will be performed approximately every 3 months from last endoscopic assessment in **part 1** or **part 2** until 24 months (from initial instillation). Disease-free survival will be defined as no histological tissue diagnosis evidence of recurrence.

Statistical Methods:

All efficacy analyses will be conducted based on the modified intent-to-treat (MITT) population as well as the per protocol (PP) population. All safety analyses will be conducted on the safety population. Additional exploratory analyses of the data may be conducted as appropriate. Unless otherwise stated, all tests of significance will be performed at alpha = 0.05, two-sided. All study data, including data not appearing in tables, will be presented in by-subject data listings. Descriptive statistics (number of subjects, mean, standard deviation, standard error of the mean, coefficient of variation, minimum, median, and maximum values) will be presented for continuous variables by treatment group and time point (if applicable). Categorical variables will be summarized using number and percentage of subjects per category for each treatment group and time point (if applicable).

2. SCHEDULE OF EVENTS

Table 1: Part 1 Schedule of Assessments

Visit	Screening	Day -12	Day 1	Day 8 Week 1	Day 15 Week 2	Day 22 Week 3	Day 29 Week 4	Day 36 Week 5	Day 43 Week 6	Day 50 Week 7	Day 57 Week 8	Day 64 Week 9	Day 71 Week 10	Day 78 Week 11	Day 99 Week 14	Day 106 Week 15	Day 113 Week 16
Visit Window	**≤ 28 days before Day 1**	**±2 days**	**N/A**	**±1 day**	**±1 day**	**±1 day**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±7 days**	**±7 days**	**±7 days**
Informed consent	X																
Subject demographics	X																
Eligibility criteria	X	X	X														
Medical/surgical history	X																
Hemoglobin A1c	X																
Weight and height	X																X
Drug screen	X																X
Urinalysis with pH[1]	X		X		X		X		X		X		X				X
Pregnancy test (urine)[2]	X		X														X
12-lead ECG[1]	X																X
Vital signs (BP, HR, RR, BT) [1]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[1]	X																X
Chemistry panel (fasted ≥ 2 hours)[1]	X						X										X
Hematology panel[1]	X		X	X	X	X	X	X	X	X	X	X	X	X			X
Prior/concurrent medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Endoscopic assessment[3]	X[7]	X[8]												X[9]			
Enrollment			X														
Administer study drug[4]			X		X		X		X		X		X				
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Paclitaxel level plasma[5]			X		X		X		X		X		X				
Paclitaxel level urine[6]			X		X		X		X		X		X				
IPSS, OAB-q	X												X				X
Treatment exit[10]																	X

BP = blood pressure; BT = body temperature; ECG = electrocardiogram; HR = heart rate; IPSS = International Prostate Symptom Score (men only); N/A = not applicable; OAB-q = Overactive Bladder Questionnaire; RR = respiratory rate; TURBT = transurethral resection of bladder tumor

1. May also be performed at principal investigator's discretion at any visit (including unscheduled visits).
2. For women of childbearing potential.
3. Endoscopic assessment includes TURBT (Day -12), voided cytology (screening/Day 78), and/or cystoscopy (screening/Day 78).
4. Study drug is administered intravesically using sterile urethral catheter. Intravesical dwell time = 2 hours (1 hour or more will be acceptable, depending on subject's tolerability of the procedure). For study dose escalation, study drug reconstitution, and administration instructions, see Section 7 and Section 8.
5. Peripheral venous blood will be obtained 15 ± 15 minutes before, and 2 hours ± 10 minutes after, intravesical instillation of TSD-001.
6. Urine (duplicate aliquots via catheterized or voided) will be obtained 15 ± 15 minutes before, and 2 hours ± 10 minutes after, intravesical instillation of TSD-001. Urine pH will be measured by urine pH test strips at each timepoint. Select sites will make observations on urine appearance (turbidity and precipitation).
7. Voided cytology and cystoscopy will be performed at screening visit. Positive cytology finding will result in screen failure.
8. TURBT to be performed on Day -12.
9. Voided cytology and cystoscopy performed in office as bladder tumor standard-of-care at screening and Day 78 ± 2 days. A cystoscope and voided urine cytology should be performed at any early treatment part withdrawal visit prior to Day 78.
10. End treatment part, begin surveillance portion of study (**part 3**).

Table 2: Part 2 Cohort 1 Schedule of Assessments

Visit	Screening	Day 1	Day 8 Week 1	Day 15 Week 2	Days 16,17,18	Day 22 Week 3	Day 29 Week 4	Day 36 Week 5	Day 43 Week 6	Day 64 Week 9	Day 85 Week 12	Day 92 Week 13
Visit Window	**≤ 28 days before Day 1**	**N/A**	**±1 day**	**±2 days**		**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±7 days**	**±7 days**	**±7 days**
Obtain informed consent	X											
Subject demographics	X											
Eligibility criteria	X	X										
Medical/surgical history	X											
Hemoglobin A1c	X											
Weight and height	X											X
Drug screen	X											X
Urinalysis with pH[1]	X	X	X	X		X	X	X				X
Pregnancy test (urine)[2]	X	X										X
12-lead ECG[1]	X											X
Vital signs (BP, HR, RR, BT)[1]	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[1]	X											X
Chemistry panel (fasted ≥ 2 hours)[1]	X											X
Hematology panel[1]	X	X	X	X		X	X	X	X			X
Prior/concurrent medications	X	X	X	X	X	X	X	X	X	X	X	X
Endoscopic assessment[3]	X[7]	X[8]									X[9,10]	
Enrollment		X										
Administer study drug[4]		X	X	X		X	X	X				
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Paclitaxel level plasma[5]		X		X								
Paclitaxel level urine[6]				X	X							
IPSS, OAB-q	X							X				X
Treatment exit[11]												X

BP = blood pressure; BT = body temperature; ECG = electrocardiogram; HR = heart rate; IPSS = International Prostate Symptom Score (men only); N/A = not applicable; OAB-q = Overactive Bladder questionnaire; RR = respiratory rate; TURBT = transurethral resection of bladder tumor

1. May also be performed at principal investigator's discretion at any visit (including unscheduled visit).
2. For women of childbearing potential.

3. Endoscopic assessment includes TURBT (Day 1 for multiple tumor subjects), voided cytology (screening/Day 85), cystoscopy (screening/Day 85), and/or biopsy or TURBT (Day 85).
4. Study drug is administered intravesically using sterile urethral catheter. Intravesical dwell time = 2 hours (1 hour or more will be acceptable, depending on subject's tolerability of the procedure). For study dose escalation, study drug reconstitution and administration instructions see Section 7.
5. Peripheral venous blood samples will be obtained 2 hours ± 10 minutes after the first intravesical instillation of TSD-001. Peripheral venous blood will also be obtained 15 ± 15 minutes before, and 2 hours ± 10 minutes after the third intravesical instillation of TSD-001.
6. Urine (duplicate aliquots via catheterized or voided) will be obtained 15 ± 15 minutes before, and 2 hours ± 10 minutes after, the third intravesical instillation of TSD-001 only. Urine pH will be measured by urine pH test strips at each timepoint. Select sites will make observations on urine appearance (turbidity and precipitation). Additional urine samples should be obtained on days 16, 17, and 18 (24, 48, and 72 hours, respectively, following the third dose of TSD-001).
7. Voided cytology and cystoscopy will be performed at screening visit. Positive cytology finding will result in screen failure.
8. TURBT to be performed on Day 1 for subjects not meeting solitary tumor eligibility; all tumors except the marker lesion tumor will be removed on Day 1.
9. TURBT performed if evidence of lesion is present.
10. On Day 85, if there is no cystoscopic evidence of bladder tumor, biopsy marker lesion site and obtain urine cytology. Performed at Day 85 or any early treatment part withdrawal before week 12.
11. End treatment part, begin surveillance portion of study (**part 3**).

Table 3: Part 2 Cohort 2 Schedule of Assessments

Visit	Screening	Day 1	Day 8 Week 1	Day 15 Week 2	Days 16, 17, 18	Day 22 Week 3	Day 29 Week 4	Day 36 Week 5	Day 43 Week 6	Day 50 Week 7	Day 64 Week 9	Day 85 Week 12	Day 106 Week 15	Day 113 Week 16
Visit Window	**≤ 28 days before Day 1**	**N/A**	**±1 day**	**±2 days**		**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**
Obtain informed consent	X													
Subject demographics	X													
Eligibility criteria	X	X												
Medical/surgical history	X													
Hemoglobin A1c	X													
Weight and height	X													X
Drug screen	X													X
Urinalysis with pH[1]	X	X	X	X		X	X	X	X	X				X
Pregnancy test (urine)[2]	X	X												X
12-lead ECG[1]	X													X
Vital signs (BP, HR, RR, BT)[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[1]	X													X
Chemistry panel (fasted ≥ 2 hours)[1]	X													X
Hematology panel[1]	X	X	X	X		X	X	X	X	X	X			X
Prior/concurrent medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Endoscopic assessment[3]	X[7]	X[8]											X[9,10]	
Enrollment		X												
Administer study drug[4]		X	X	X		X	X	X	X	X				
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Paclitaxel level plasma[5]		X		X										
Paclitaxel level urine[6]				X	X									
IPSS, OAB-q	X									X				X
Treatment exit[11]														X

BP = blood pressure; BT = body temperature; ECG = electrocardiogram; HR = heart rate; IPSS = International Prostate Symptom Score (men only); N/A = not applicable; OAB-q = Overactive Bladder questionnaire; RR = respiratory rate; TURBT = transurethral resection of bladder tumor

1. May also be performed at principal investigator's discretion at any visit (including unscheduled visit).
2. For women of childbearing potential.

3. Endoscopic assessment includes TURBT (Day 1 for multiple tumor subjects), voided cytology (screening/Day 106), cystoscopy (screening/Day 106), and/or biopsy or TURBT (Day 106).
4. Study drug is administered intravesically using sterile urethral catheter. Intravesical dwell time = 2 hours (1 hour or more will be acceptable, depending on subject's tolerability of the procedure). For study dose escalation, study drug reconstitution and administration instructions see Section 7.
5. Peripheral venous blood samples will be obtained 2 hours ± 10 minutes after the first intravesical instillation of TSD-001. Peripheral venous blood will also be obtained 15 ± 15 minutes before, and 2 hours ± 10 minutes after the third intravesical instillation of TSD-001.
6. Urine (duplicate aliquots via catheterized or voided) will be obtained 15 ± 15 minutes before, and 2 hours ± 10 minutes after, the third intravesical instillation of TSD-001 only. Urine pH will be measured by urine pH test strips at each timepoint. Select sites will make observations on urine appearance (turbidity and precipitation). Additional urine samples should be obtained on days 16, 17, and 18 (24, 48, and 72 hours, respectively, following the third dose of TSD-001).
7. Voided cytology and cystoscopy will be performed at screening visit. Positive cytology at screening will result in screen failure.
8. TURBT to be performed on Day 1 for subjects not meeting solitary tumor eligibility; all tumors except the marker lesion tumor will be removed on Day 1.
9. TURBT performed if evidence of lesion is present.
10. On Day 106, if there is no cystoscopic evidence of bladder tumor, biopsy marker lesion site and obtain urine cytology. Performed at Day 106 or any early treatment part withdrawal before Week 15.
11. End treatment part 2, begin surveillance portion of study (**part 3**).

Table 4: Surveillance Schedule of Assessments (Part 3)

Visit[1]	Treatment part exit	Month 6 (Day 181)	Month 9 (Day 271)	Month 12 (Day 366)	Month 15 (Day 456)	Month 18 (Day 546	Month 21 (Day 636)	Exit Month 24 (Day 731)
Visit Window		**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**
Obtain informed consent[2]	X							
Cystoscopy		X	X	X	X	X	X	X
Prior/concurrent medications[3]	X	X	X	X	X	X	X	X
Adverse events[4]/Serious adverse events	X	X	X	X	X	X	X	X
Study surveillance exit								X

AE = adverse event; eCRF = electronic case report form

1. Visit timing is from initial instillation in previous (treatment) part (e.g. Month 6 is approximately 6 months from Day 1 of previous part).
2. If not previously obtained in **part 1** or **part 2**, obtain informed consent for **part 3** at treatment exit visit or first available visit in **part 3**.
3. Only recorded in eCRF if they relate to an AE continuing from **part 1** or **part 2** or a treatment for a recurrence.
4. AEs continued from **part 1** or **part 2**, but no new AEs will be recorded.

3. INTRODUCTION AND STUDY RATIONALE

More than 74,000 new patients will be diagnosed with bladder cancer in 2015, of whom approximately 16,000 will die (Greenlee et al., 2001). Currently there are approximately 600,000 survivors of bladder cancer in the United States (Devesa et al., 1995). Non-muscle-invasive bladder cancer (NMIBC), including carcinoma in situ (Tis) as well as stages Ta (confined to urothelium) and T1 (invasive into lamina propria), accounts for approximately 70% of cases (Abel, 1988). While the primary method of non-muscle-invasive bladder tumor treatment continues to be transurethral resection, intravesical therapy has become an integral component in the management of NMIBC (Fair WR, 1993).

Superficial bladder cancer accounts for 70% to 80% of newly diagnosed bladder cancers. Recurrence rates after initial treatment range from 30% to 85%, with grade progression occurring in 10% to 30% and stage progression in 4% to 30% of cases (Abel, 1988, Devesa et al., 1995). The primary treatment for papillary bladder tumors that do not invade the muscular layer (stage Ta or T1 transitional-cell carcinoma [TCC]) is transurethral resection of the bladder tumor (TURBT). Resection, fulguration, and laser coagulation of these tumors can be performed with minimal morbidity.

Despite complete eradication of the primary tumor, approximately two-thirds of patients will develop tumor recurrences within the first 5 years of follow-up (Fair WR, 1993).

Most bladder cancers are TCCs. Low-grade tumors have less potential to progress to invasive cancers, but they have a 50% to 70% chance of recurrence. High-grade tumors have an approximately 20% higher chance of progression to muscle-invasive disease than low-grade cancers (Fair WR, 1993). This high rate of recurrence (and potentially progression) can be reduced with intravesical therapy, although no therapy has resulted in an improvement in overall survival.

The goal of intravesical therapy is to reduce disease recurrence and its progression to muscle-invasive bladder cancer. T1 tumors, which invade the lamina propria, are an indication for intravesical treatment because patients with these tumors have a 25% to 30% risk of progression to muscle-invasive disease (Lee et al., 2012). Tumor penetration into the muscularis mucosa is associated with a 54% risk of progression, compared with a 7% risk with penetration of the lamina propria (Sylvester et al., 2004). This is still considered to be a T1 cancer, but clearly it carries a worse prognosis. Carcinoma-in-situ (CIS) represents high-grade anaplasia of the surface mucosa and is virtually always associated with adjacent low-grade cancers. In only 10% of cases is it an isolated pathologic finding. The potential for development of muscle-invasive disease is 42% to 83% in cases of CIS associated with papillary tumors versus 20% to 34% when CIS is an isolated finding (Cookson et al., 2012). The risk of invasion of CIS is increased if there is widespread disease. Bacillus Calmette-Guérin (BCG) is the most effective regimen for the management of superficial disease, including CIS. In a large randomized clinical trial, the use of maintenance therapy with BCG was shown to decrease subsequent recurrences, but with some increase in side effects (Soloway, 1988). To date, BCG has not been demonstrated to prolong overall survival of patients with superficial disease.

Patients who do not respond to this agent represent a significant challenge. Clinicians need options to treat patients who do not respond to BCG. Most recommend a cystectomy, but many patients are not surgical candidates either because of comorbid conditions or because they refuse the procedure. No chemotherapy agent to date has proven to have activity equivalent to BCG, and no agent has been very successful in treating patients who do not respond to BCG. Valrubicin is an intravesical chemotherapeutic agent that possesses minimal activity, and more active alternatives are needed.

An additional matter is the level 1 evidence of reduced recurrence after a single postoperative intravesical instillation in low-grade, stage Ta disease (Sylvester et al., 2004). In addition, a single postoperative instillation is both cost effective and enhances quality-adjusted life-years (QALYs) (Lee et al., 2012). Despite these advantages, no intravesical agent is approved for immediate postoperative installation and physician adherence to National Comprehensive Cancer Network (NCCN), American Urological Association (AUA), or European Association of Urology (EAU) guidelines is marginal.

For both the BCG-recurrent NMIBC population and the immediate postoperative instillation of low- and intermediate-risk NMIBC patients, a clear need exists for more active alternatives.

4. STUDY OBJECTIVES

This is a phase 1/2a study to evaluate the safety of TSD-001, the local and systemic paclitaxel pharmacokinetic (PK) concentrations after intravesical exposure to TSD-001, and the marker lesion response rate after TSD-001 treatment in subjects with low-grade, stage Ta NMIBC.

The primary objective for **part 1** is to establish the maximum tolerated dose (MTD), defined as the dose immediately preceding the dose at which dose-limiting toxicity (DLT) occurs or when a maximum deliverable dose (MDD) is determined. The severity and frequency of adverse events (AEs) will be assessed in the weeks following TSD-001 administration, and defined according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

The secondary objectives for **part 1** are to determine the local (bladder urine) and systemic (peripheral blood) paclitaxel PK concentrations before and after intravesical exposure to TSD-001 at all doses. Blood and urine samples will be collected 15 ± 15 minutes before and 2 hours (± 10 minutes) after each instillation.

Exploratory objectives for **part 1** include evaluation of the change from baseline to Week 16 in International Prostate Symptom Score (IPSS) (men only) and Overactive Bladder Questionnaire (OAB-q) scores.

The primary objective for **part 2** is to assess the marker lesion response rate using the MTD/MDD established in part 1. For subjects in cohort 1, the assessment will occur 12 weeks (± 7 days) after Day 1 (i.e., 7 weeks [± 7 days] after last intravesical TSD-001 instillation) at the MTD/MDD established in **part 1**. Subjects in cohort 2 will have the marker lesion response rate determined 15 weeks (± 7 days) after Day 1 (i.e., 8 weeks [± 7 days] after the last intravesical instillation).

Complete marker lesion response requires no evidence of TCC on cystoscope-directed biopsy. Partial response is at least a 30% decrease in marker lesion size (Eisenhauer et al., 2009).

The secondary objectives of **part 2** are to: 1) determine the systemic (peripheral blood) paclitaxel PK concentrations before and after the third intravesical exposure to TSD-001 at the MTD/MDD; and 2) characterize the severity and frequency of AEs at the MTD/MDD following TSD-001 administration, and defined according to CTCAE.

Paclitaxel PK concentration measurements of peripheral blood during **part 2** will be obtained 2 hours (± 10 minutes) after the first intravesical instillation, and 15 minutes (± 15 minutes) before and 2 hours (± 10 minutes) after the third intravesical exposure of TSD-001 at the MTD/MDD.

Exploratory objectives of **part 2** include change from baseline to the end of the treatment part in IPSS (men only) and OAB-q scores and paclitaxel levels in voided urine samples at 24, 48, and 72 hours after the third instillation of TSD-001.

Part 1 and **2** safety assessments will be evaluated by analyzing results of AE, laboratory test, vital signs, electrocardiogram (ECG), and physical examination assessments.

The exploratory objective of **part 3** (surveillance) is to determine rates of disease-free survival of subjects exposed to TSD-001 in **part 1** or **part 2**. Cystoscopic surveillance will be performed as standard of care approximately every 3 months from last endoscopic assessment in **part 1** or

part 2 until 24 months (from initial instillation). Disease-free survival will be defined as no histological tissue diagnosis evidence of recurrence. Histological tissue diagnosis evidence is any diagnosis of urothelial carcinoma (i.e., TCC), including all grades and stages.

5. INVESTIGATIONAL PLAN

5.1. Overall Design and Plan of the Study

This is a single-arm, phase 1/2a study of intravesical proliposomal formulated paclitaxel (TSD-001) in subjects with low-grade (WHO, 2004), stage Ta, NMIBC. An enrollment of up to 21 subjects (6 in **part 1** and up to 15 in **part 2**) is planned. Any subject that receives at least two treatments in **part 1** or **part 2** is eligible for surveillance in **part 3**. Subject eligibility will be determined during the screening period based on the subject meeting all of the inclusion and none of the exclusion criteria.

Figure 1 presents a diagram depicting an overview of the study design. The study, for each subject, comprises a screening period, a six-dose escalation safety and paclitaxel PK concentration assessment (**part 1**), and a stable dosing phase assessing the marker lesion response rate, safety, and (in **part 2**) a paclitaxel PK concentration assessment after the first and third intravesical instillations. Study **part 1** will include a cystoscopy about 13 weeks (± 7 days) after TURBT. Study **part 2** cohort 1 will include a cystoscopy and biopsy (or TURBT) under general/regional anesthesia 12 weeks (± 7 days) after Day 1. **Part 2** cohort 2 will include a cystoscopy and biopsy (or TURBT) under general/regional anesthesia 15 weeks (± 7 days) after Day 1.

The study has a total of 17 planned clinic visits for **part 1** and 14 planned clinic visits (**part 2** cohort 1) or 16 planned clinic visits (**part 2** cohort 2), including office visits in each part for study drug administration and additional office visits for safety and paclitaxel concentration assessments. **Part 3** has an additional 7 planned clinic visits.

Figure 2 presents a diagram of the adaptive individual dose-escalation schedule for **part 1** and dose assignment for **part 2**. For the first 3 subjects (cohort 1) in **part 1**, study drug will be administered every 2 weeks at a starting dose of 10 mg TSD-001 and adjusted every 2 weeks for a total of 6 intravesical treatments. The study drug starting dose for the next three subjects in **part 1** (cohort 2) will be 90 mg, and increased according to the schedule (180, 270, 360, 450, 540 mg). In **part 1**, peripheral blood and urine samples will be collected for paclitaxel concentrations 15 minutes (± 15 minutes) before and 2 hours (± 10 minutes) after each instillation. Thirteen weeks (± 7 days) after TURBT, an office cystoscopy will be performed.

During **part 2**, up to 15 additional subjects with low-grade, stage Ta NMIBC will have weekly intravesical instillations of TSD-001 at the highest nontoxic dose (MTD/MDD) established in **part 1**. Paclitaxel PK concentration measurements of peripheral blood during **part 2** will be obtained 2 hours (± 10 minutes) after the first intravesical instillation, and 15 minutes (± 15 minutes) before and 2 hours (± 10 minutes) after the third instillation of TSD-001. All subjects in **part 2** will also have additional urine samples collected after their third intravesical instillation. Voided urine paclitaxel levels will be determined for urine samples taken at 24, 48, and 72 hours after instillation of TSD-001 as an exploratory endpoint. For **part 2** cohort 1, the marker lesion response assessment will be performed at Week 12 (i.e., 7 weeks [± 7 days] after the last TSD-001 intravesical instillation). For **part 2** cohort 2, the marker lesion response assessment will be performed at Week 15 (i.e., 8 weeks [± 7 days] after the last intravesical instillation). Subjects will report to the study site prepared to undergo cystoscopy and bladder

biopsy under general anesthesia. Complete marker lesion response requires no evidence of TCC on cystoscope-directed biopsy. Partial response is at least a 30% decrease in marker lesion size.

Before each of the planned intravesical treatment visits in **part 2**, the subjects will report to the study site as directed. Intravesical instillation of study drug will be performed with dwell time of 2 hours (1 hour or more will be acceptable, depending on subject's tolerability of the procedure). Subjects will be observed within the study site for any AEs during the 2-hour intravesical dwell and for 30 minutes after completing intravesical administration.

Subject questionnaires (IPSS, OAB-q) will be administered at baseline enrollment, day of last treatment, and at the end of the treatment part on Day 92 (Week 13) for **part 2** cohort 1 or Day 113 (Week 16) for **part 2** cohort 2.

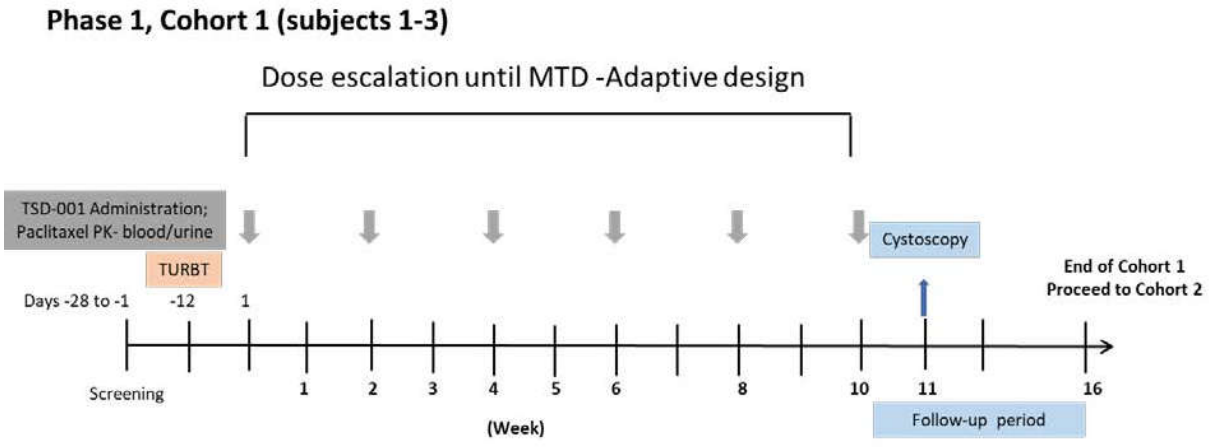
Safety analysis will be performed on data collected through Week 16 of **part 1**, Week 13 of **part 2** cohort 1, and Week 16 of **part 2** cohort 2.

Upon or after completion of **part 1** or **part 2** (treatment part) of the study, the subject may be entered into **part 3** (surveillance). In **part 3**, subjects will be followed for disease-free survival and receive cystoscopic assessments approximately every 3 months as part of standard care following treatment of low-grade NMIBC. Subjects will receive no intravesical administrations of TSD-001 during **part 3**.

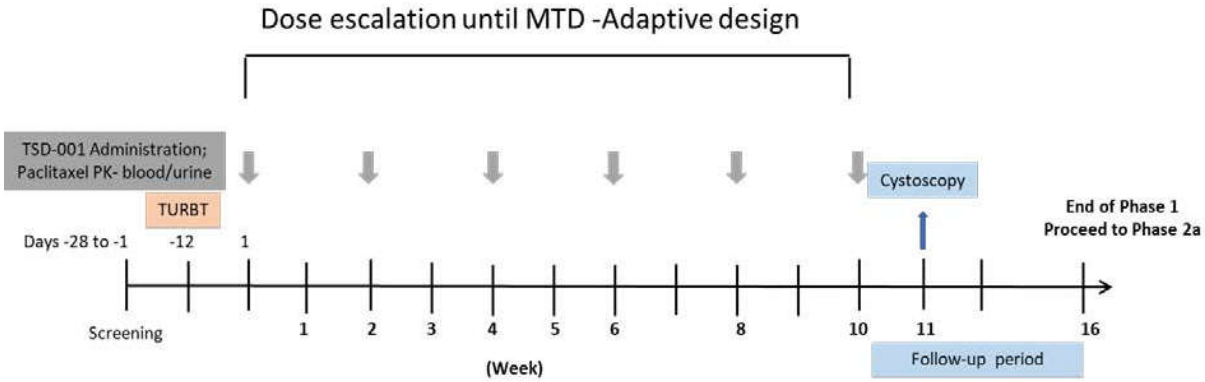
If there is evidence of recurrence upon cystoscopic examination during **part 3**, then subjects will have additional standard care. If known, the determination of grade, stage, and results of urine cytology will be recorded in the electronic case report form (eCRF). In addition, any treatments administered as part of standard care for the NMIBC recurrence will be recorded as concomitant medication(s). During **part 3**, AEs continued from **part 1** or **part 2** will be followed until resolution or stabilization but no new AEs will be recorded.

Study assessments will be performed as noted in the schedules of events provided in Section 2.

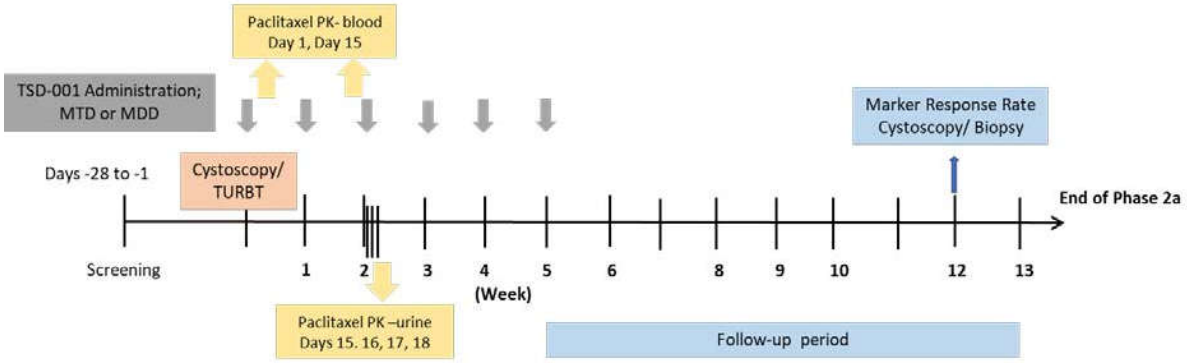
Figure 1: Overview of Study Design



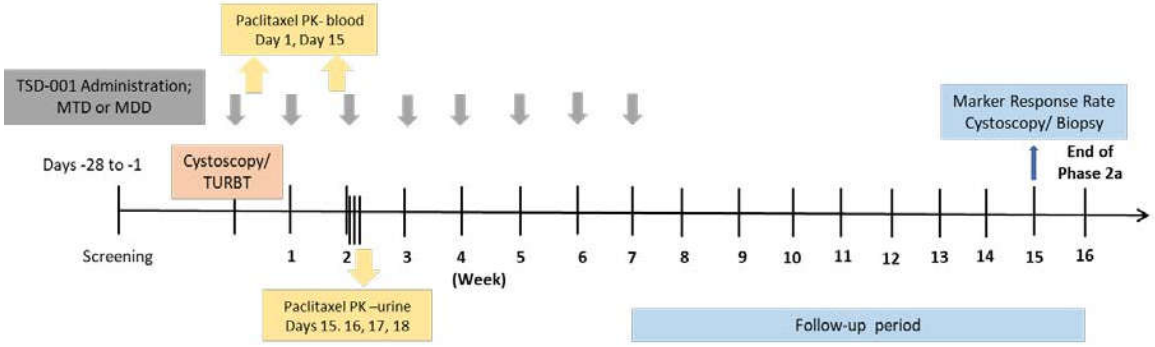
Phase 1, Cohort 2 (subjects 4-6)



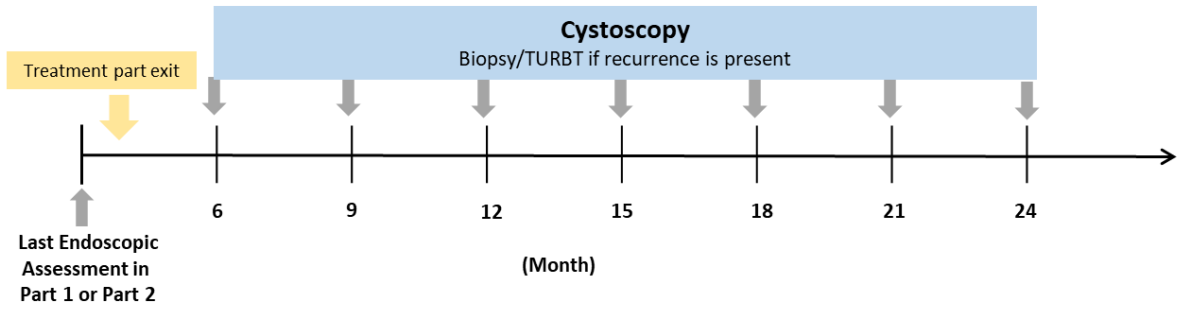
Phase 2a - Part 2 Cohort 1



Phase 2a – Part 2 Cohort 2



Surveillance – Part 3



MDD = maximum deliverable dose; MTD = maximum tolerated dose; PK = pharmacokinetics; TURBT = transurethral resection of bladder tumor

6. SELECTION OF STUDY POPULATION

6.1. Inclusion Criteria

Potential study subjects have to meet all of the following inclusion criteria to be enrolled (prior to TURBT). These criteria apply to study entry into **part 1** or **part 2**. Subjects are eligible for inclusion in **part 3** if they received at least two eligible treatments in **part 1** or **part 2** and provided informed consent to surveillance procedures.

Diagnosis and Inclusion Criteria:

1. 18 to 85 years of age at time of study enrollment.
2. Able to meet the requirements of the study; give voluntary, written informed consent; and adhere to dosing and visit schedules.
3. Has a diagnosis of low-grade (WHO, 2004) (i.e., G1 or G2 (WHO, 1973)), uni- or multifocal papillary-appearing bladder tumor, stage Ta. In part 2, a subject meets this inclusion without this histological tissue diagnosis if on cystoscopic assessment they have a solitary papillary tumor (≥ 0.5 cm and ≤ 2.0 cm in diameter).
4. For **part 1**, subject will have ≥ 1 and ≤5 tumors (prior to TURBT), none of which exceeds 3.0 cm in diameter; and for **part 2** subject will have ≥ 2 and ≤ 5 tumors (prior to TURBT), none of which exceeds 3.0 cm in diameter (resection loop ~1 cm), OR, for **part 2**, subject meets this inclusion criterion if on cystoscopic assessment they have a solitary papillary tumor (≥ 0.5 cm and ≤ 2.0 cm in diameter).
5. Subject is surgical candidate for TURBT as part of normal NMIBC treatment plan. For **part 1**, successful completion of TURBT procedure. For **part 2**, successful completion of cystoscopic assessment/TURBT procedure with one marker lesion left intact; the marker lesion should be ≥ 0.5 cm and ≤ 2.0 cm in diameter.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
7. Peripheral neuropathy grade 1 or less (NCI CTCAE Version 5.0).
8. Adequate hematological, hepatic and renal parameters; i.e., hemoglobin > 10 g/dL, creatinine < 3.5 mg/dL, bilirubin < 1.5 mg/dL, aspartate aminotransferase < 50 U/L, alanine aminotransferase < 50 U/L, and alkaline phosphatase < 130 U/L.
9. All sexually active subjects of reproductive potential are required to use or start using a reliable method of birth control at least 2 weeks prior to study enrollment, throughout the treatment part, and for at least 3 months following completion of study drug treatment. A reliable method of birth control is defined Section 7.6.
10. Females of childbearing potential must have a negative pregnancy test within 30 days prior to enrollment. Females who are postmenopausal for at least 1 year (defined as more than 12 months since last menses) or are surgically sterilized do not require this test.
11. Adequate venous access to allow collection of blood samples by venipuncture.
12. For male subjects, the digital rectal examination must not be suspicious for carcinoma of the prostate.

13. Able to retain bladder instillations for up to 120 minutes (± 15 minutes).

6.2. Exclusion Criteria

These criteria apply to study entry into **part 1** or **part 2**. Potential study subjects will be excluded if they meet one or more of the following exclusion criteria:

1. Has an active concurrent malignancy/life-threatening disease. If there is a history of prior malignancies/life-threatening diseases, the subject is to be disease free for at least 5 years. Subjects with other prior malignancies less than 5 years before study entry may still be enrolled if they have received treatment resulting in complete resolution of the cancer and currently have no clinical, radiologic, or laboratory evidence of active or recurrent disease. Subjects will not be excluded for recurrent NMIBC, basal or squamous cell skin cancers, or noninvasive cancer of the cervix.
2. Has positive urine cytology for urothelial malignancy (i.e., high-grade) at screening.
3. Has Cis or T1 transitional cell carcinoma (TCC).
4. Has BCG-refractory TCC.
5. Has an active uncontrolled infection, including a urinary tract infection, underlying medical condition (e.g., systolic blood pressure ≥ 160 mm Hg and/or diastolic blood pressure ≥ 92 mm Hg), or other serious illness that would impair the ability of the subject to receive protocol treatment.
6. Previous intravesical therapy (e.g. BCG, mitomycin C, chemotherapeutic agent) within 6 months of study entry.
7. Has participated in a previous clinical trial or used any investigational drugs, biologics, or devices within 90 days prior to study treatment or plans to use any of these during the course of the study.
8. Has had any previous exposure to paclitaxel or docetaxel in the last 5 years.
9. Has or has ever had: upper tract TCC; urethral tumor (prostatic urethra included); any invasive bladder tumor (T2 or greater); any evidence of lymph node or distant metastasis; any bladder tumor with histology other than TCC.
10. Has a tumor in a bladder diverticulum.
11. Concurrent treatment with any chemotherapeutic agent.
12. History of vesicoureteral reflux.
13. An indwelling ureteral stent.
14. Has received any pelvic radiotherapy (including external beam and/or brachytherapy).
15. Has a bleeding disorder or a screening platelet count < 100×10^9/L.
16. Has any unstable medical condition that would make it unsafe to undergo TURBT or receive instillation (e.g., presence of uncontrolled gross hematuria). Subject experienced any procedure-related adverse effect during TURBT that, in the opinion of the

investigator, would put the subject at unacceptable risk to receive intravesical treatment or participate in the study (e.g., bladder perforation).

17. Has active diagnosis of interstitial cystitis.
18. For subjects with recurrent tumor, the subject did not have at least a 6-month cystoscopically confirmed tumor-free interval between the last tumor recurrence and screening cystoscopic examination.
19. Females of childbearing potential who are nursing, pregnant, intending to become pregnant or intending to nurse during the time of the study, or who have a positive pregnancy test at baseline.
20. Currently seeking to father a child or is seeking fertility within one year of trial participation.
21. Presence of poorly controlled diabetes mellitus (glycated hemoglobin [HgbA1c] > 9.0%).
22. Clinically significant co-morbid conditions that would interfere with the subject's participation or compromise the subject's safety.
23. Any significant history of allergy and/or sensitivity to the drug products or their excipients, including any history of sensitivity to paclitaxel.
24. Undergone surgery or had a medical condition that in the judgment of the principal investigator places the subject at unacceptable risk to participate in the study.
25. Any contraindication to blood sampling.
26. Intent to have an elective surgical procedure (other than TURBT) during the course of the trial.
27. Donated blood or blood products or had a significant loss of blood within 90 days before dosing.
28. Donated bone marrow within 6 months before dosing.
29. Positive urine drug screen or history of drug or alcohol abuse in the past six months.
30. Any condition that the investigator believes would interfere with the intent of this study or would make participation not in the best interests of the subject.

7. TREATMENTS

7.1. Description of Treatment Preparation

TSD-001 is delivered sterilely, intravesically via urethral catheter. After passage of the urethral catheter, the subject's bladder will be completely emptied. Please note, as required according to the schedule of events, urine may be required for PK analysis.

The proliposomal TSD-001 lyophilized powder will be reconstituted with sterile water for injection (SWFI), mixed, and then instilled intravesically via the sterile urethral catheter under gentle plunger pressure. The catheter and attached syringe will then be removed and discarded according to usual biohazard precautions. For more information on reconstitution protocol, refer to the pharmacy manual.

The dwell time will be 2 hours (1 hour or more will be acceptable, depending on subject's tolerability of the procedure).

For more detailed information on TSD-001 and its excipients, refer to the Investigator Brochure.

7.1.1. Packaging and Labeling

Packaging and labeling will be carried out in accordance with the requirements of Annex 13 of the Good Manufacturing Practice (GMP) guidelines, ICH GCP/ISO 14155 requirements, LIPAC and vendor-approved standard operating procedures, and all applicable US laws.

7.1.2. Storage and Accountability

TSD-001 should be stored at controlled refrigerator temperature (2 to 8ºC) in the supplied packaging.

The study site must maintain accurate investigational product records, including dates and amount of study drug dispensed (subject-by-subject accounting), and accounts of any study drug accidentally or deliberately destroyed.

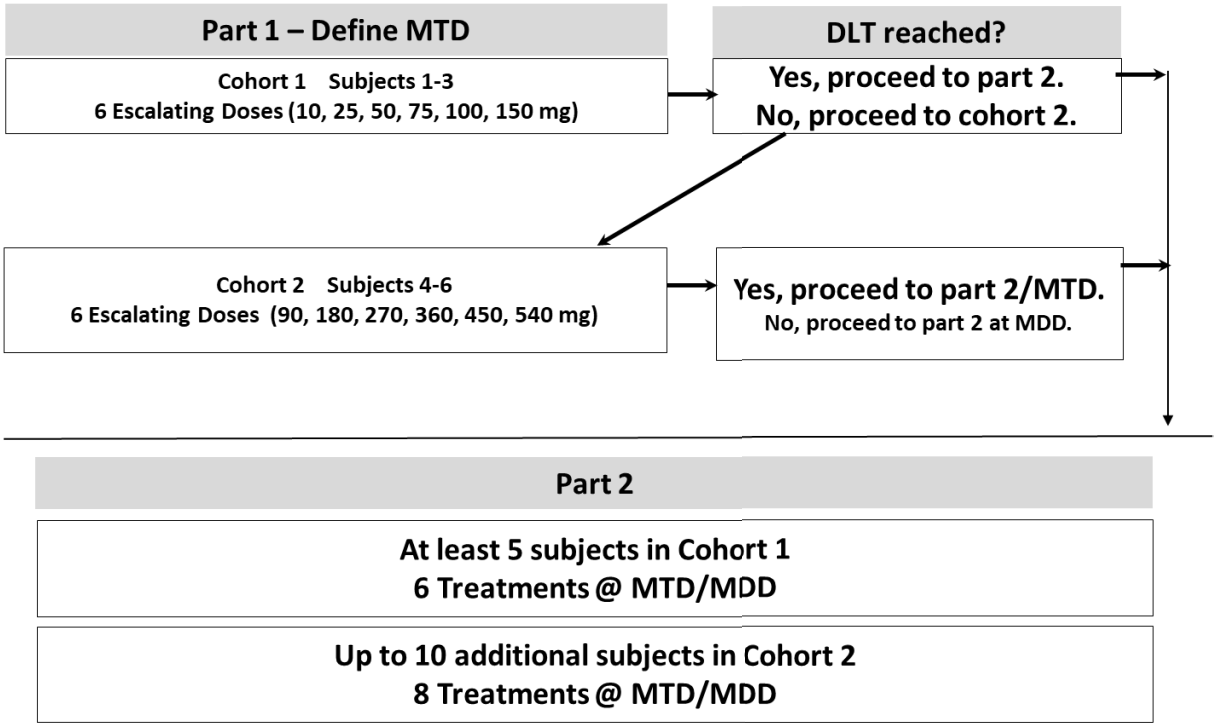
Unless otherwise notified, all study drug products including the empty packaging, if applicable, must be saved for study drug accountability. During and at the end of the study, reconciliation must be made between the amount of study drug supplied, dispensed, and returned for destruction. Any discrepancies in remaining study drug will be recorded and the investigator notified if any discrepancies are found. A written explanation will be provided for any discrepancies and the remaining supplies will be returned to a designated location for destruction.

7.2. Study Drug Dosing Rules

For **part 1,** intravesical administration of TSD-001 will begin no sooner than 12 days (±2 days) after TURBT. For this phase 1 trial, an adaptive titration design with an intra-subject dose escalation scheme will be used to establish the MTD. Figure 2 presents the study drug dosing rules and a diagram of the adaptive individual dose-escalation schedule for **part 1** and dose assignment for **part 2**. Additional information on the dose escalation and de-escalation plan is included below and in Appendix 4.

Figure 2: Diagram of the Adaptive Accelerated Individual Dose-escalation Schedule for Part 1 and Dose Assignment for Part 2:

TD-001: Phase 1/2a Dose Escalation



DLT = dose-limiting toxicity; MDD = maximum deliverable dose; MTD = maximum tolerated dose

Part 1:

For the first 3 subjects (cohort 1) enrolled, the initial dose will be 10 mg in SWFI. If DLT does not develop, intravesical instillation 14 days later will be titrated up according to the schedule (25, 50, 75, 100, 150 mg in SWFI) until DLT (defined as any grade 3 or 4 toxicity or prolonged [greater than 14 days] grade 2 toxicity) is observed.

If no DLT is observed in the first 3 subjects after titration, cohort 2 (subjects 4, 5, and 6) will start dosing at 90 mg and then every 14 days at the following doses: 180, 270, 360, 450, 540 mg or until DLT is observed.

If DLT is observed in the first 3 subjects after titration, cohort 2 (subjects 4, 5, and 6) will not be required in the study design. Enrollment will continue to **part 2** of the study (up to 15 additional subjects).

If no DLT is observed in the first 6 subjects after titration, then 360 mg will be the dose recommended for **part 2** of the study, as this paclitaxel concentration is substantially higher than the half-maximal inhibitory concentration (IC_{50}) observed in bladder cancer cell lines exposed to TSD-001. Additional subjects may be enrolled at the discretion of the sponsor to determine appropriate DLT and MTD.

The concentration of paclitaxel in TSD-001 will vary as a function of urine production over the 2-hour intravesical dwell time. The MDD, therefore, will be defined by DLT (i.e., MTD) or per protocol (i.e., the highest conforming dose instilled per the adaptive accelerated titration design).

The primary endpoint in this phase 1 trial is to define the MTD, which is defined as the dose immediately preceding the dose at which DLT occurs or when a MDD is determined in the dose escalation scheme described below without any DLT.

The MTD or MDD will be the recommended dose for the phase 2 study described below.

Part 2:

In **part 2**, the dose will be selected as the MTD (highest nontoxic dose) or MDD established in **part 1** and provided weekly via the intravesical route.

During **part 2**, up to 15 additional subjects will receive intravesical instillations of TSD-001 via urethral catheterization of the urinary bladder at the MTD or MDD established in **part 1** at weekly intervals. Subjects in **part 2** cohort 1 will receive 6 weekly instillations and subjects in **part 2** cohort 2 will have 8 weekly instillations. TSD-001 will be retained in the bladder for 2 hours (1 hour or more will be acceptable, depending on subject's tolerability of the procedure).

The deceleration plan for dose titration following study-related low-grade toxicity is detailed in Appendix 4.

Part 3:

In **part 3**, subjects will be followed for disease-free survival after participation in the treatment part of the study (**part 1** or **part 2**). Subjects in **part 3** will receive cystoscopic assessments approximately every 3 months as part of part of standard care following treatment of low-grade NMIBC.

Subjects will receive no intravesical administrations of TSD-001 during **part 3**.

7.3. Method of Assigning Subjects to Part, Cohort, and Dosing Levels

Subjects will be assigned on Day 1 into the next available study part, cohort, and starting dosing level based on a central dose assignment list kept by LIPAC. Screening may be opened or closed in coordination with participating investigators in order to ensure screened subjects will have the next available dose assignment. Accordingly, subjects may be in screening during completion of the previous cohort and be planned to enter the next available cohort assignment. Additionally, subjects that start treatment in **part 2** cohort 1 will be re-assigned to cohort 2 prior to completion of treatment administration visits (i.e., Week 5) after institutional review board (IRB) written approval of the **part 2** cohort 2 schedule and the associated protocol version.

Subjects will be entered into **part 3** (surveillance) upon or after completion of their **part 1** or **part 2** visits and informed consent to surveillance procedures. Subjects who receive at least two treatments in **part 1** or **part 2** may be entered into **part 3.**

7.4. Blinding

Not applicable to this single-arm study.

7.5. Prior/Concomitant Medication and Therapy

All medications taken by subjects during the course of the study will be recorded. Continuation of existing medications is allowed with the exception of the prohibited medications defined below, provided the use of these medications remains stable during the study. During the treatment period, subjects should contact the investigator if they need to take a new drug or make changes to the drugs they were taking upon study entry. The investigator must discuss these changes in medication with the Medical Monitor as specified in the study manual.

Changes in medications and new medications should only be recorded in the eCRF during the surveillance portion (**part 3**) of the study if they relate to an AE continuing from **part 1** or **part 2** or a treatment for a recurrence.

The following drugs are prohibited within 6 months before the first dose of study drug and during the treatment period:

- Any intravesical immunotherapy or chemotherapy (e.g., BCG or mitomycin C)
- Systemic chemotherapy, biological therapy, or immunotherapy (e.g., cisplatin, bevacizumab)

7.6. Reliable Methods of Birth Control

A reliable method of birth control is required for women of childbearing potential. Women of childbearing potential are defined as any female who has experienced menarche and who is NOT permanently sterile or postmenopausal. Postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause. Reliable birth control is defined as one of the following:

- oral or injectable contraceptives
- intrauterine device
- contraceptive implants
- tubal ligation
- a double-barrier method (diaphragm with spermicidal foam or jelly, or a condom)
- abstinence
- vasectomy
- hysterectomy.

7.7. General and Dietary Restrictions

Consumption of foods, beverages, or supplements containing the following substances will be prohibited as indicated:

- Alcohol: No more than 3 units per day of alcoholic beverages from the beginning of screening through the end of the study. A unit is defined as 4 oz. of wine, 8 oz. of beer, or 1.5 oz. of hard liquor.

- Marijuana (cannabinoids)
- Illicit drugs (e.g., cocaine, opiates, barbiturates, amphetamines, and benzodiazepines).

7.8. Treatment Compliance

Treatment compliance will be documented by the study site personnel on the instillation and dwell time eCRF. Deviations from the planned treatment procedures should be documented for Sponsor review.

8. STUDY PROCEDURES

8.1. Screening

When a potentially eligible candidate is identified (e.g., from among the outpatients coming to the site for diagnostic visits or after TURBT), the investigator or designated healthcare professional will ask the prospective subject about his/her willingness to be included in the clinical study. The prospective subject is to be informed verbally and in writing about the nature, risks, benefits, and expectations of participating in the clinical study and a copy of the subject informed consent form (ICF) is to be provided in the appropriate language. All prospective subjects will have the study explained in non-technical terms and will be informed of the study restrictions. Prior to study initiation, acknowledgement of the receipt of this information and the subject's informed consent will be obtained in writing as described in Section 14.4. The subject will be given a copy of the ICF. The ICF is to be signed by the subject and countersigned by the attending investigator prior to proceeding with any study-related procedures.

Subjects will have to meet all inclusion criteria and no exclusion criteria before being enrolled in the study. Subjects that do not meet eligibility criteria may be rescreened if inclusion criteria are met and no exclusion criteria are met in the second screening period.

The following procedures will be performed during the screening period:

- Collection of demographic data
- Determination of eligibility (meeting all inclusion and no exclusion criteria)
- Documentation of medical and surgical history
- Glycated hemoglobin (HgbA1c) determination
- Weight (kilograms) and height (centimeters) measurements
- Drug and alcohol screens
- Urinalysis with pH
- Urine pregnancy test for women of childbearing potential
- 12-lead ECG
- Vital signs
- Physical examination
- Clinical laboratory tests (hematology, serum chemistry)
- Cystoscopic assessment (to be completed during screening or within 30 days prior to start of screening as part of standard care)
- IPSS (men only) and OAB-q

Any subject not meeting enrollment inclusion criteria and/or meeting enrollment exclusion criteria will be considered a screen failure. For both study **part 1** and **part 2**, subject screening will be completed ≤ 28 days prior to Study Day 1. A schedule of events for the screening visit and Study Day 1 are provided in Section 2 and Table 1.

8.1.1. TURBT

Transurethral resection of a bladder tumor (TURBT) with pathology confirming low-grade, stage Ta TCC of the bladder is necessary before study enrollment in **part 1**. For **part 1**, eligible subjects must have low-grade, stage Ta NMIBC (transitional cell histology) with no more than 5 tumors, none of which can be larger than 3.0 cm in diameter. As a guide for tumor size, use the resection loop (~1 cm) as a guide. For **part 1**, all visible tumors must be surgically removed, there must not be any evidence of CIS, and urine cytology must be negative for cancer. Furthermore, the subject will be ineligible for study enrollment if bladder perforation occurs during TURBT. For **part 1**, it is possible for prospective subjects to be identified after TURBT. If a prospective subject is identified after TURBT, please ensure the screening procedures are completed in the 12 days (± 2 days) prior to Day 1 and all eligibility criteria are met.

For **part 2,** two different subject presentations may be eligible.

First, for subjects with multiple tumors, TURBT will occur after enrollment into the study on Day 1. Eligible subjects must have low-grade, stage Ta NMIBC (transitional cell histology) with at least 2 and no more than 5 tumors, none of which can be larger than 3.0 cm in diameter. For subjects that undergo TURBT, a final pathology report confirming low-grade, stage Ta NMIBC is required for additional subject treatments (intravesical administrations 2 through final). Furthermore, the subject will be ineligible for study treatment if bladder perforation occurs during TURBT.

Second, subjects are eligible if on cystoscopic assessment they have a solitary papillary tumor ($\geq$ 0.5 cm and $\leq$ 2.0 cm in diameter), and negative urine cytology. The cystoscopic assessment should be completed during screening or within 30 days prior to start of screening (as part of standard care). For subjects with identified solitary tumors the cystoscopic assessment is not required to be performed again on Day 1.

For all subjects there must be no evidence of CIS, urine cytology must be negative for cancer, and there should be no uncontrolled gross hematuria. The tumors must be papillary. As a guide for tumor size, the resection loop is ~ 1 cm. For **part 2**, the tumor selected to be the marker lesion should be approximately 1 cm (use resection loop as guide for size) but may be $\geq$ 0.5 cm (5 mm) and $\leq$ 2.0 cm in diameter, and appear papillary. Sessile, invasive-appearing tumors should not be selected as the marker lesion tumor.

8.1.2. Marker Lesion (for Part 2)

Marker lesion is a term used to designate a single bladder tumor deliberately left unresected for later application of a studied agent or chemo-resection (Gofrit et al., 2010). In this study, the later application is the intravesical instillation of the study drug, TSD-001. The use of this marker lesion method provides clear opportunity to observe the effect of the agent on the tumor in a measurable fashion.

Marker lesion studies have been used for the evaluation of anticancer therapies as early as the early 1980s. They are most appropriate for subjects with multiple, noninvasive, low-grade tumors representing low to intermediate risk (Gofrit et al., 2010).

For **part 2**, the first methodology to be followed for this study is for subjects with $\geq$ 2 and $\leq$ 5 tumors to have all but one of these tumors resected using standard resection (e.g., electric

loop) procedures via cystoscopy. One marker tumor will be left intact, untouched because any damage to the supply of blood may cause involution. As any resection of the marker tumor would make the subject ineligible, if this occurs during the surgery, the tumor should be resected completely and the subject will be considered ineligible for treatment and withdrawn from the study.

Investigators can identify typically low grade papillary NMIBC tumors using cystoscopy. Cystoscopy correctly predicts Ta, low grade bladder tumors with an accuracy of 93%. Cystoscopy along with a negative cytology accurately predicts stage Ta, low grade NMIBC with an accuracy of 99% (Herr et al, 2002).

In addition, it has been shown that active surveillance with delayed intervention represents a safe strategy for patients with recurrent low risk bladder cancer (Gorin et al, 2015).

Of note is that the marker lesion is never biopsied; it is inferred to be histologically similar to the other synchronous tumors.

Thus, the second methodology is cystoscopic confirmation (without biopsy) of a solitary papillary bladder tumor. This methodology is consistently dependent on excluding subjects with positive urine cytology for urothelial malignancy (i.e., high-grade) or uncontrolled gross hematuria. The marker lesion for both methodologies should appear papillary and be ≥ 0.5 cm and ≤ 2.0 cm in diameter.

8.2. Study Procedures/Visits

Once the screening procedures are completed, the subject will be prepared for Study Day 1.

8.2.1. Enrollment

On Study Day 1, the following study procedures will be conducted prior to study drug preparations:

- Urinalysis with pH based on voided urine sample
- Urine pregnancy test for women of childbearing potential
- Vital signs (blood pressure, heart rate, respiratory rate, body temperature)
- Documentation of any changes to previously recorded prior and/or concurrent medications
- Final determination of subject eligibility for enrollment and treatment

8.2.2. Treatment

Treatment preparation instructions from Section 7.1 should be followed to prepare TSD-001 proliposomal formulation diluted with SWFI.

The proliposomal TSD-001 lyophilized powder will be reconstituted with SWFI, mixed, and then instilled intravesically via the sterile urethral catheter under gentle plunger pressure. The catheter and attached syringe will then be removed and discarded according to usual biohazard precautions.

If there is any evidence of an active, untreated urinary tract infection, the treatment should be postponed.

If the protocol requires a predose peripheral venous blood or urine sample, it should be obtained 15 minutes before intravesical instillation of TSD-001.

For **part 1**, administration of TSD-001 will occur approximately 2 weeks after TURBT, after enrollment on Day 1.

For **part 2**, the subject will be enrolled prior to TURBT (for subjects not meeting solitary tumor requirements). For these subjects, the first study administration of TSD-001 will begin immediately (≤ 120 minutes) following TURBT, either with the subject still anesthetized in the operating room or in a post-surgery recovery suite. Subjects not undergoing TURBT (i.e., solitary tumor subjects) will be treated as scheduled and a second cystoscopic assessment is not required on Day 1. Peripheral venous blood samples and scheduled urine samples should also be taken during the protocol-required time periods.

In **part 2**, if the subject needs to be moved after TURBT and the initial instillation of TSD-001, care should be taken to maintain time records to ensure compliance with protocol-required time of instillation and subsequent blood and urine sampling.

For **part 1** and **part 2**, TSD-001 is sterilely administered intravesically via urethral catheter. After passage of the catheter, the subject's bladder will be completely emptied and 2 separate aliquots saved for measurement of paclitaxel concentration based on the schedule of events (Table 1, Table 2, and Table 3).

The instillation should remain in the subject bladder for 1 to 2 hours (60 to 120 minutes). **The patient should be encouraged to maintain the instillation as close to 120 minutes as possible.** During instillation and when physically able, the subject should change position every 15 minutes with at least two 15-minute periods in the prone (facedown) position.

At 2 hours (± 10 minutes) after specified instillations, a peripheral venous blood sample should be collected (via venipuncture) following the sample aliquot time point instructions (see Section 2, Schedule of Events). At the completion of specified instillations, the subject should void normally into a collection device. Procedures outlined in the lab manual include addition of an additive (Tween) to the urine sample, and then duplicate aliquots should be collected for urine PK assessment according to the PK sample time point instructions (see Section 2, Schedule of Events). Urine pH should be measured using pH test strips in the pre- and post-instillation urine samples. Select sites will make observations on urine appearance (turbidity and precipitation). The volume of the post-installation void(s) should also be measured and recorded. Any deviations from the required dwell time should be recorded in the eCRF.

In **part 2**, additional urine samples (24, 48, and 72 hours post instillation) should be collected after the third instillation only (see Section 2, Schedule of Events).

Each subject will have multiple instillations of study drug. In **part 1**, subjects will have 6 instillations, 2 weeks apart beginning on Day 1. Subjects in **part 2** cohort 1 will have 6 instillations, 1 week apart beginning on Day 1. Subjects in **part 2** cohort 2 will have 8 instillations, 1 week apart beginning on Day 1. Urine pH should be measured in the pre- and post-instillation urine samples as outlined in the Schedule of Events (Section 2).

For more detailed information on TSD-001 and its excipients, refer to the Investigator Brochure.

8.2.3. Other Study Procedures

Study procedures should be conducted as outlined in Table 1, Table 2, Table 3, and Table 4. All laboratory samples should be collected and analyzed per Section 9.3.2.

For **part 1**, once the last instillation takes place on Week 10 visit (Day 71), an additional follow-up visit will occur at Week 11 (Day 78). Visit windows should be followed to keep visits within the required time frames.

On the Week 11 (Day 78 ± 2 days) visit, the final cystoscopy procedure will be conducted. This scheduled event will occur as usually performed for bladder tumor follow-up cystoscopy.

For **part 2**, all subjects will have additional post-treatment visits 24, 48, and 72 hours after the third intravesical treatment. Voided urine samples will be collected at these time points after the third treatment for these subjects to measure the amount of post-instillation paclitaxel levels in the voided urine. Vital signs should also be measured along with any changes to concurrent medications and recording any AEs.

For **part 2** cohort 1 subjects, once the last instillation takes place on the Week 5 visit (Day 36), additional follow-up visits will occur at Week 6 (Day 43) and Week 9 (Day 64). On the Week 12 (Day 85 ± 7 days) visit, the final cystoscopy procedure and biopsy will be conducted (or TURBT if a bladder tumor lesion is present).

Subjects in **Part 2** cohort 2 will have the last instillation on Week 7 visit (Day 50). Additional follow-up visits will occur at Week 9 (Day 64) and Week 12 (Day 85). On the Week 15 (Day 106 ± 7 days) visit, the final cystoscopy procedure and biopsy will be conducted (or TURBT if a bladder tumor lesion is present).

Visit windows should be followed to keep visits within the required time frames. At the time of final cystoscopic assessment, a urine sample for cytology will also be obtained. The subject should receive general/regional anesthesia in preparation for the cystoscopy and bladder biopsy.

For **part 2**, the marker lesion should be viewed and measured following normal diagnostic cystoscopy procedures. If no residual tumor is noted at the final cystoscopic assessment, the site of the marker lesion must be biopsied. If residual tumor is noted, TURBT of any remaining tumor tissue should be performed.

In addition, any tumor biopsy samples should be collected and sent for pathology examination.

8.3. Exit/Withdrawal from Part 1/Part 2

Subjects may be discontinued from study treatment at any time. Subjects are also free to discontinue their participation in the study at any time, without prejudice to further treatment outside of the study procedures.

At the scheduled treatment exit visit (end of **part 1** or end of **part 2**), all procedures from the treatment exit visit should be completed.

If the subject discontinues study treatment early (less than all protocol-required treatments), they should be followed for the remaining schedule of assessments as outlined in the Schedule of

Events (Section 2). In this case, any remaining treatment visits should have all procedures conducted except for administration of study treatment and collection of samples for paclitaxel levels. If the subject is in **part 1** of the study, a final cystoscopy should be performed 13 weeks (± 7 days) after TURBT. If the subject is in **part 2** cohort 1 of the study, a final cystoscopy and biopsy should be performed 12 weeks (± 7 days) after Day 1. If the subject is in **part 2** cohort 2 of the study, a final cystoscopy and biopsy should be performed 15 weeks (± 7 days) after Day 1. A treatment exit visit should be performed as indicated in the schedule of assessments. If not already done, the subject should be presented with the information on the surveillance part of the study (**part 3**).

If the subject discontinues the study early and whenever possible, subjects should be seen and assessed by the investigator prior to early withdrawal. At an early withdrawal visit in **part 1** or **part 2**, all procedures from the treatment exit visit should be completed. In addition, if not already performed, a final cystoscopy, cytology, and biopsy (only for **part 2**) sample collection should be performed as described in Section 8.2.3. At an early withdrawal visit in **part 3**, no additional procedures need to be completed. In the eCRF, study completion or discontinuation will be documented with the reason for any discontinuation. Possible reasons for a subject discontinuing participation in the study include:

- AE(s) that endanger the health of subjects, making it ethically unacceptable to continue. This includes AE(s) resulting from the surgical TURBT procedures.
- Any patient with grade 3 or 4 toxicity (or prolonged [greater than 14 days] grade 2 toxicity) will be considered having experienced a DLT, which will result in discontinuation of study drug.
- Ineligible to continue, e.g., TURBT procedure does not result in marker lesion meeting requirements.
- Deterioration of the subject's clinical condition(s) that requires appropriate (standard of care) therapy/treatment during the study period as determined by the investigator.
- Significant protocol deviation
- Subject noncompliance
- Withdrawal of consent
- Lack of efficacy
- Loss to follow-up
- Death

In case of study withdrawal due to an AE, the subject is to be followed until resolution/stabilization of the AE or for 30 days. Subjects who discontinue prematurely from the study may be replaced in order to achieve study enrollment goals.

8.4. Part 3 (Surveillance) Visits

Procedures should be conducted as outlined in Table 4, per standard of care. When a subject is completing the scheduled treatment exit visit (end of **part 1** or end of **part 2**), all procedures

from the treatment exit visit should be completed. In addition, if not already completed, the investigator or designated healthcare professional will ask the subject about his/her willingness to continue in the surveillance part of the study and obtain informed consent.

Cystoscopic surveillance will be performed as standard of care approximately every 3 months from last endoscopic assessment in **part 1** or **part 2** until 24 months (from initial instillation). Upon or after completion of **part 1** or **part 2** (treatment part) of the study, the subject may be entered into **part 3** (surveillance). In **part 3**, subjects will be followed for disease-free survival and receive cystoscopic assessments approximately every 3 months as part of part of standard care following treatment of low-grade NMIBC. Subjects will receive no intravesical administrations of TSD-001 during **part 3**.

If there is evidence of possible recurrence upon cystoscopic examination during **part 3,** then subjects will have additional standard care. If known, the determination of grade, stage, and results of urine cytology should be determined. In addition, any treatments administered as part of standard care for the NMIBC recurrence will be recorded as concomitant medication(s). During **part 3**, AEs continued from **part 1** or **part 2** will be followed until resolution or stabilization but no new AEs will be recorded.

8.5. Unscheduled

If a subject sees an investigator for an unscheduled clinic visit, the reason for the unscheduled visit and an assessment and recording of any AEs should be noted, if applicable. Additional evaluations should be performed as necessary, and the appropriate eCRFs should be completed.

9. EFFICACY AND SAFETY ASSESSMENTS

9.1. Methods of Assessment/Evaluations

9.1.1. Primary Endpoint

The primary endpoint of **part 1** is the MTD, defined as the dose immediately preceding the dose at which DLT occurs or when a MDD is determined. The severity and frequency of AEs will be documented following TSD-001 administration, and defined according to NCI CTCAE Version 5.0.

The primary endpoint of **part 2** is the marker lesion response rate.

9.1.2. Secondary Endpoints

The secondary endpoints of **part 1** are to determine paclitaxel PK concentrations in the urine and the peripheral blood before and after intravesical exposure to TSD-001.

Exploratory endpoints of **part 1** include evaluation of the following parameters:

- Change from baseline to Week 16 in IPSS (men only)
- Change from baseline to Week 16 in OAB-q score

The secondary endpoints of **part 2** are to:

1) Determine paclitaxel concentrations in blood at the MTD/MDD.

2) Determine the severity and frequency of AEs following intravesical administration of TSD-001 at the MTD/MDD established in **part 1**, as defined according to CTCAE, Version 5.0.

Exploratory endpoints of **part 2** include evaluation of:

- Paclitaxel levels in voided urine samples at 24, 48, and 72 hours after the third instillation of TSD-001.
- Change from baseline to the end of the treatment part in IPSS (men only)
- Change from baseline to the end of the treatment part in OAB-q score

The exploratory endpoint of **part 3** (surveillance) will be disease-free survival of subjects exposed to TSD-001 in **part 1** or **part 2**.

- The endpoint will be time to event (recurrence) after the TURBT (Day -12 in **part 1**) or after complete response or Week 12 TURBT in **part 2**. Disease-free survival will be defined as no histological tissue diagnosis evidence of recurrence.

9.2. Pharmacokinetic Parameters

Paclitaxel PK concentrations will be limited to pre-instillation (trough) and post-instillation (peak) concentration measurements of urine and plasma. The goal is to define the local and systemic exposure of the study subjects to paclitaxel (and/or its metabolites).

As per the schedule of events, a peripheral venous blood and urine sample should be obtained 15 ± 15 minutes before, and 2 hours ± 10 minutes after predetermined intravesical instillation of TSD-001 (see Section 2, Schedule of Events).

TSD-001 is sterilely administered intravesically via urethral catheter. After passage of the catheter, and as required according to the schedule of events, 2 separate duplicate aliquots of urine will be obtained for PK analysis.

At 2 hours (± 10 minutes) post-instillation per the schedule of events, a peripheral venous blood sample will be obtained at specific visits for paclitaxel concentration measurement (see Section 2, Schedule of Events).

In **part 2**, additional urine samples for paclitaxel concentration measurements should be obtained at 24, 48, and 72 hours post-instillation for the third instillation only (Section 2, Schedule of Events).

At completion of instillation, voided urine will be collected in duplicate aliquots for PK analysis according to the schedule of events. The volume of the post-installation void(s) should also be measured and recorded.

9.3. Safety Parameters

9.3.1. Adverse Events

All AEs that occur during the study after the subject has received the first dose of study drug are to be collected and reported on the eCRF. In case of study withdrawal due to an AE, the subject is to be followed until resolution/stabilization of the AE or for at least 30 days. AEs should be recorded, regardless of whether they are reported by the subject, elicited by investigator questioning, detected through physical examination, or by other means.

During **part 3**, AEs continued from **part 1** or **part 2** will be followed until resolution or stabilization but no new AEs will be recorded.

As far as possible, each AE is described by:

- duration (start and end dates)
- start/end of study medication
- severity grade (mild, moderate, severe)
- for purposes of determining DLT, the NCI CTCAE Version 5.0 will be utilized
- investigator determination of causality (relationship to the study product)
- action(s) taken (concomitant medication, change of study medication, etc.) including start and end dates of respective action
- concomitant diseases and respective medication in general
- start date, end date, and dosage of rescue medication
- outcome

9.3.1.1. Adverse Event Definition

An AE is any untoward medical occurrence (change in anatomical, physiological, or metabolic function) in a subject, which does not necessarily have any causal relationship with the product under investigation.

9.3.1.2. Serious Adverse Event Definition

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (Note: the term "life-threatening" refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event which hypothetically may cause death if it is more severe)
- requires subject hospitalization or prolongation of existing hospitalization (for the purpose of this study, a hospitalization is defined as a hospital stay of at least 8 hours and/or an overnight stay)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

  or

- other medically important condition

Events that require intervention to prevent one or more of the outcomes listed in the definition above are also to be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsion that does not result in hospitalization, or development of drug dependency or drug abuse.

However, medical judgment has to be exercised in deciding whether an event is serious in any other situations considered medically relevant.

The evaluation of the AE as serious or not serious is made independently of any attribution of causality.

Events NOT considered to be SAEs are those that require:

- elective or preplanned treatment for a pre-existing condition that is unrelated to the indication under study and does not worsen
- treatment on an emergency, outpatient basis for an event NOT fulfilling any of the definitions of serious given above and NOT resulting in hospital admission (for the purpose of this study, a hospitalization is defined as a hospital stay of at least 8 hours and/or an overnight stay)

9.3.1.3. AE Intensity

AE intensity is determined by the clinical investigator on the basis of his/her direct observations or the subject's reporting.

- Mild: causes no limitation of usual activities; the subject may experience slight discomfort
- Moderate: causes some limitation of usual activities; the subject may experience annoying discomfort
- Severe: causes inability to carry out usual activities; the subject may experience intolerable discomfort or pain.

9.3.1.4. AE Causality/Relationship

Any AE has to be judged for causality (relationship to study medication and relationship to study procedure).

The relationship of an AE to the study product is to be graded on the basis of the following:

- Probable: a reaction that follows a reasonable temporal sequence from administration of the product; that follows a known response pattern to the suspected product; that is confirmed by an improvement on stopping the product; and that cannot be reasonably explained by the subject's clinical state
- Possible: a reaction that follows a reasonable temporal sequence from administration of the product; that follows a known response pattern to the suspected drug; but that may have been produced by the subject's clinical state or other therapeutic interventions on him/her
- Unlikely: a reaction that occurs with an improbable temporal sequence from administration of the product; that can be explained by the clinical state of the subject/participant or by other therapeutic interventions or other drugs or underlying disease providing plausible explanations
- Unrelated: a reaction that occurs without a reasonable temporal sequence from administration of the product; that can be explained by the clinical state of the subject or by other therapeutic interventions on him/her and that does not improve or disappear following interruption of the product

9.3.1.5. Handling of AEs

If an AE occurs, appropriate diagnostic and therapeutic measures are to be taken and the study product has to be discontinued if appropriate. Follow-up evaluations of the subject are to be performed until the subject recovers or until the clinical investigator considers the situation to be no longer clinically significant.

If clinically significant laboratory abnormalities appear at the final visit, appropriate additional tests may to be performed to clarify the nature of any clinically significant laboratory abnormalities that occur.

Adverse events are monitored and registered on the AE form of the eCRF at each visit. In the absence of a specific diagnosis, an individual AE form must be filled in for each clinically significant sign or symptom.

Persistent AEs will be entered once in the eCRF until they are resolved or a new event has to be documented due to deterioration. These AEs will be carefully monitored; further details of

monitoring of persistent AEs will be provided in the monitoring plan. Any AE that is not resolved at the end of the study will be documented as ongoing.

For recurrent AEs, i.e., AEs of the same nature but with a different date of onset, an individual AE form must be completed for each occurrence.

Adverse events occurring after the termination of the study individually and/or of the study in total are to be reported to LIPAC even after the clinical study has been finished if, in the judgment of the investigator, there is an association between the event and the previous use of the product under investigation.

If the AE is classified as serious, the clinical investigator has also to complete the SAE report form. It is the responsibility of the investigator to send the SAE report form by fax to the Drug Safety Department of the Contract Research Organization (CRO) within one working day and to retain the original copy of the form (keeping a photocopy in the Investigator Site File). At the earliest possible date, the SAE report form has to be followed by a detailed report and any documentation that may be available, e.g., hospital case records, autopsy reports, and/or other pertinent documents. No private and/or confidential data that allow identification of study participants are to be transmitted.

All the above documents will be sent by fax to the Drug Safety Department of the CRO within one working day of receipt. The investigator will be responsible for reporting the SAE to IRBs or ethics committees; the sponsor will be responsible for reporting the SAE to the respective health authorities, according to the national regulatory requirements.

The primary person responsible for safety at LIPAC is:

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Telephone: 661-665-0505, ext. 216
Mobile: 714-401-3154

9.3.2. Laboratory Measurements and Variables

All laboratory-reported values that are outside of the reference ranges (high or low) should be reviewed by the qualified investigator(s) and recorded as clinically significant or not clinically significant. Clinically significant values should be reported as AEs (see Section 9.3.1).

Clinical laboratory parameters to be measured are summarized in Table 5.

Table 5: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	hemoglobin	white blood cell (WBC) count (with differential in %)
	hematocrit	platelet count
	red blood cell (RBC) count	
Blood Chemistry	aspartate aminotransferase (AST)	total protein
	alanine aminotransferase (ALT)	albumin
	gamma-glutamyltransferase (GGT)	albumin/globulin ratio
	lactate dehydrogenase (LDH)	direct bilirubin
	alkaline phosphatase	creatine kinase
	total bilirubin	sodium
	total cholesterol, triglycerides	potassium
	low-density lipoprotein cholesterol (LDL-C)	chloride
	high-density lipoprotein cholesterol (HDL-C)	calcium
	blood urea nitrogen	phosphate
	creatinine	magnesium
	uric acid	hemoglobin A1c
Urinalysis	pH	ketones
	specific gravity	glucose
	protein	nitrite
	occult blood	leukocyte esterase
	urobilinogen	microscopic assessment for WBC, RBC, and casts
Urine Culture	At investigator's discretion	
Urine Pregnancy Test	For women of childbearing potential	
Toxicology Screen	Urine test for use of cocaine, cannabinoids, opiates, barbiturates, amphetamines, and benzodiazepines Urine or breath test for alcohol abuse	

9.3.3. Other Safety Parameters

9.3.3.1. Vital Signs

Vital signs (sitting systolic/diastolic blood pressure, heart rate, respiratory rate, and body temperature) will be evaluated for screening (eligibility) reasons and during the course of the

study. Vital sign measurements should be separated from blood draws by a minimum of 5 minutes and preferably up to 10 minutes. Specifically, blood pressure should be recorded after 5 to 10 minutes sitting without intervention; repeat in contralateral arm for confirmation if a reading is high (e.g., systolic ≥ 140 mm Hg, diastolic ≥ 90 mm Hg).

9.3.3.2. 12-lead ECG

Standard 12-lead ECGs will be evaluated for screening (eligibility) reasons and at the end of the treatment part. PR interval, RR interval, QRS interval, QT interval, QTc interval, and heart rate will be recorded on the eCRF.

The results of ECGs are to be classified as follows:

1. normal
2. abnormal, but not clinically significant
3. abnormal and clinically significant (should be reported as an AE per Section 9.3.1)

9.4. Appropriateness of Measurements

All clinical and laboratory procedures and assessments that will be used in this study are standard and generally accepted.

10. DATA QUALITY ASSURANCE

Detailed procedures will be separately provided in the data management, monitoring, and quality plans.

10.1. Data Collection

All subject data must be reported on the eCRFs in an anonymous fashion. Subjects are identified only by a 3-digit subject number.

The investigator will be responsible for the completeness, accuracy, and legibility of the information in the eCRF and other study documents. In line with Good Documentation Practice, the source data should be accurate, legible, attributable, original, and contemporaneous. For documents other than eCRFs, only ballpoint pen is to be used and any change of data is to be done by striking out the incorrect data with a single line and dating and initialing the changes made to provide an audit trail. Corrections should be explained in writing, where applicable. Correction fluid or pencils should not be used.

The study monitors will check the eCRFs against the source documents for accuracy and validity as per the monitoring schedule, as applicable; any data recorded directly on the eCRF (that is, no prior written or electronic record of data) are also considered source data. Source data verification will include the eCRF data and drug accountability.

eCRF completion is expected at each site to ensure quality of data and subject safety. Once eCRFs are completed, they will be available for review by the monitor and the CRO's Clinical Data Management department. Completed eCRFs will be reviewed remotely for logical discrepancies. The monitor will ensure that all data queries and subsequent amendments in the eCRF documentation are made according to Good Clinical Practice (GCP) guidelines.

A copy of the eCRF is to be archived by the investigator together with the study documents, source data, and laboratory records for the time required by the national regulation.

10.1.1. Confidentiality/Property

Adequate records have to be maintained for the study, including, but not limited to, subject medical records, eCRFs, laboratory reports, worksheets, nursing notes, signed informed consent forms, product forms, SAE forms, and information regarding subject discontinuation and reasons for discontinuation. The confidentiality of each record with subject identification is to be guaranteed by the clinical investigator.

This study protocol and other study documents contain trade secrets and commercial information that is privileged and confidential. Such information is not to be disclosed unless required by laws or regulations. The investigator agrees to use this information only in conducting this study and is not allowed to use it for other purposes without written consent from LIPAC. Results obtained from this study are the property of LIPAC.

10.1.2. Retention of Records

The investigator agrees to retain copies of the eCRF data with other study documents (e.g., the protocol and any protocol amendments, the Summary of Product Characteristics, IRB approval, signed consent forms, and source documents for each subject in the study) in a secure place as

long as needed to comply with national and international regulations. These records must be made available for inspection upon reasonable request by a representative of LIPAC or regulatory authorities.

In the event an investigator retires, relocates, or for any other reason withdraws from the responsibility for maintaining records for the period of time required, custody of the records has to be transferred to another person who accepts responsibility for the records, e.g., LIPAC, an IRB, or another investigator. Notice of such transfer has to be given in writing to LIPAC. Records may not be destroyed without LIPAC's approval.

10.1.3. Routine Monitoring

For protocol monitoring and compliance, a site visit will be held prior to initiation of subject enrollment. The protocol, eCRFs, study treatment supplies, and study procedures will be explained in detail.

The purpose of monitoring is to verify the rights and well-being of human subjects are protected; that study data are accurate, complete, and verifiable with source data; and that the study is conducted in compliance with the protocol, GCP, and the applicable regulatory requirements.

A monitor assigned by the CRO will conduct regular site visits for the purpose of study monitoring.

The investigator must agree to allow the study monitor and authorized representatives of the CRO or LIPAC to inspect all eCRFs and corresponding source documents (e.g., original medical records, subject records, and laboratory raw data); to allow access to the clinical supplies, dispensing, and storage areas; and to agree to assist with their activities, if requested. The investigator should provide adequate time and space for monitoring visits and visits of other sponsor representatives.

The monitor will query any missing or spurious data with the investigator, which should be resolved in a timely manner. A monitoring log will be maintained to record each visit, the reason for the visit, the monitor's signature, and the investigator's or designee's confirmation signature.

10.1.4. Site Audits

LIPAC or its designee may carry out an audit at any time. Investigators will be given adequate notice before the audit occurs. The purpose of an audit is to confirm that the study is conducted as per protocol, GCP, and applicable regulatory requirements; that the rights and well-being of the subjects enrolled have been protected; and that the data relevant for the evaluation of the investigational product have been captured, processed, and reported in compliance with the planned arrangements. The investigator will permit direct access to all study documents, drug accountability records, medical records, and source data.

Regulatory authorities may perform an inspection of the study, even up to several years after its completion. If an inspection is announced, the investigator or the site must inform the sponsor immediately.

10.2. Database Management and Quality Control

The designated CRO will be responsible for the activities associated with the data management of this study, including the production of eCRFs, setting up a relevant database, and appropriate validation of data and resolution of queries. All data will be entered into an appropriate eCRF. Automated and manual checks will be made against the data entered into the eCRFs to ensure completeness and consistency. Resolution of queries will be implemented in the database.

AEs will be standardized for terminology and classification, using the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be classified by site of action and therapeutic and clinical characteristics using the World Health Organization drug dictionary (WHO DRUG). Versions of the dictionaries to be used will be documented in the data management plan and the statistical analysis plan (SAP).

11. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

11.1. Statistical and Analytical Plan

Maximum tolerated dose (**part 1**) will be determined by a rule-based method as follows:

- Highest dose at which no DLT (defined as grade 3 or grade 4 toxicity related to study drug), OR prolonged (more than 14 days) grade 2 toxicity, occurs
  - If no DLT occurs at any dose, the dose just before the dose at which > 33% of the study subjects experience grade 2 toxicity related to study drug.
  - Or if the MDD is determined.

The marker lesion response rate (**part 2**) will be determined by the percentage of subjects at completion cystoscopy and biopsy to have no cystoscopic or biopsy evidence of residual disease. Partial response will be determined by comparing the pretreatment marker lesion size to the post-treatment size. Partial response is at least a 30% decrease in marker lesion size.

The paclitaxel peripheral venous and urine PK samples will be collected for measurement in **part 1** at 15 (± 15) minutes pre-instillation (trough) and 2 hours (± 10 minutes) post-exposure (peak); in **part 2**, blood samples will be collected for measurement of paclitaxel levels 2 hours (± 10 minutes) after the first intravesical instillation, and 15 minutes (± 15 minutes) prior (trough) and 2 hours (± 10 minutes) after the third intravesical exposure (peak). All subjects in **part 2** will also have additional urine samples collected after their third intravesical instillation (see Section 2, Schedule of Events).

Full details of the statistical analysis will be given in the SAP.

11.1.1. General Considerations

Statistical analysis of this study will be the responsibility of a CRO.

All efficacy analyses will be conducted based on the modified intent-to-treat (MITT) population as well as the PP population. All safety analyses will be conducted on the safety population. Additional exploratory analyses of the data may be conducted as appropriate.

Unless otherwise stated, all tests of significance will be performed at alpha = 0.05, two-sided. All study data, including data not appearing in tables, will be presented in by-subject data listings. All statistical analyses and data presentations (tables and data listings) will be generated using SAS version 9 or higher.

Descriptive statistics (number of subjects, mean, standard deviation, standard error of the mean, coefficient of variation, and minimum, median, and maximum values) will be presented for continuous variables by treatment group and time point (if applicable). Categorical variables will be summarized including number and percentage of subjects per category for each treatment group and time point (if applicable).

11.1.2. Handling of Missing Data

There will be no imputation of missing data.

11.1.3. Analysis Populations

Analyses will be based on the safety, MITT, PP, and PK populations.

- **Safety Population**: The safety population will include all enrolled subjects who receive at least one dose of study drug.
- **MITT Population**: The MITT population will include all enrolled subjects who receive at least one dose of study drug and have at least one post-baseline measurement of paclitaxel concentration.
- **PP Population**: The PP population will include subjects in the ITT population who have no major protocol violations. All protocol violations will be defined before hard lock of the database.
- **PK Population**: All subjects who receive study drug and complete paclitaxel PK concentration measurements.

11.1.4. Demography and Baseline Characteristics

Demography and baseline characteristics summaries will be based on the safety population.

11.1.5. Efficacy Parameters

The primary endpoint of **part 1** is the MTD, defined as the dose immediately preceding the dose at which DLT occurs or when a MDD is determined. The severity and frequency of AEs will be documented following TSD-001 administration, and defined according to NCI CTCAE Version 5.0.

The secondary endpoints of **part 1** are to determine PK parameters in the urine and the peripheral blood.

Exploratory endpoints of **part 1** include the following:

- Change from baseline to Week 16 in IPSS (men only)
- Change from baseline to Week 16 in OAB-q score

The primary endpoint of **part 2** is to determine the marker lesion response rate at the final endoscopic assessment after weekly instillations of TSD-001. The final endoscopic assessment will be 12 weeks (± 7 days) after Day 1 for subjects in **part 2** cohort 1 and 15 weeks (± 7 days) after Day 1 for subjects in **part 2** cohort 2.

The secondary endpoints of **part 2** are: 1) to determine paclitaxel concentration parameters in the peripheral blood after instillation of the MTD/MDD of TSD-001, and 2) to characterize the severity and frequency of AEs after the MTD/MDD of TSD-001 is intravesically administered weekly for 6 administrations (cohort 1) or 8 administrations (cohort 2).

Exploratory endpoints of **part 2** include the following:

- Change from baseline to the end of the treatment part in IPSS (men only)
- Change from baseline to the end of the treatment part in OAB-q score

- Paclitaxel levels in voided urine samples at 24, 48, and 72 hours after the third instillation of TSD-001.

11.1.6. Safety Parameters

Safety endpoints are:

- AEs/SAEs
- vital signs (blood pressure, pulse rate, respiratory rate, and body temperature)
- laboratory measurements
- 12-lead ECG
- physical examinations

All safety summaries will be performed on the safety population.

11.1.7. Pharmacokinetic Assessments

Paclitaxel concentrations will be limited to pre-instillation (trough) and to post-instillation (peak) concentration measurements of urine and plasma. Paclitaxel levels will also be measured in voided urine samples at 24, 48, and 72 hours after the third instillation of TSD-001. The goal is to define the local and systemic exposure of the study subjects to paclitaxel (and/or its metabolites). Paclitaxel concentrations in plasma will be monitored for evidence of systemic exposure.

11.2. Interim Analyses

Maximum tolerated dose will be determined based on a modified accelerated titration design with intra-subject escalation. The objective is to find the highest nontoxic dose, which will be the recommended dose for **part 2** of the study. Paclitaxel concentrations in plasma and other study drug findings may be used to inform the decision regarding appropriate maximum deliverable dose.

11.3. Determination of Sample Size

The study is a proof-of-concept study designed to establish the MTD in **part 1**, and to assess preliminary efficacy via a marker lesion method in **part 2**. Local and systemic paclitaxel exposure will be measured in study **part 1** and **part 2**. Given these goals, a sample size of at least 6 subjects for **part 1** and up to 15 for **part 2,** for a total of up to 21 subjects, has empirically been planned as sufficient to achieve the study goals.

12. ETHICAL AND ADMINISTRATIVE RESPONSIBILITIES

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor, its authorized US representative, and investigator abide by GCP as described in the ICH guideline E6, and in US regulations described in 21 Code of Federal Regulations (CFR) parts 50, 54, 56, and 312. Compliance with these regulations also constitutes compliance with the ethical principles that have their origins in the Declaration of Helsinki.

Details of the study administration and ethical considerations are presented in Appendix 1.

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14. APPENDICES

APPENDIX 1. STUDY ADMINISTRATION AND ETHICAL CONSIDERATIONS

14.1. Investigators and Study Administrative Structure

The investigator who is responsible for the conduct of this study, in compliance with this protocol, is identified on the protocol signature page of the protocol. The investigator will also sign the Investigator Agreement and provide it to the Sponsor or Sponsor's representative prior to receipt of investigational product and study initiation at that investigational center.

Sponsor:	LIPAC Oncology LLC 325 Sharon Park Drive, Suite 739 Menlo Park, CA 94025-6805
Clinical Project Manager:	Karl Bean, LIPAC Oncology LLC 3670 West Temple Ave., Suite 270 Pomona, CA 91768
Safety Officer:	Michael G. Oefelein, M.D., FACS LIPAC Oncology LLC 3670 West Temple Ave., Suite 270 Pomona, CA 91768

14.2. Institutional Review Board (IRB) Approval

The investigator will submit the protocol and informed consent form for IRB review. This will be appropriately documented. The protocol, any protocol amendments, the informed consent form, and all other forms of subject information related to the study and any other necessary documents will be reviewed by an IRB.

It is required that a valid IRB approves, in writing, the conduct of this clinical study, together with the informed consent form, prior to study initiation. The written approval should consist of a completed IRB approval form or written documentation from the IRB containing the same information.

Until written approval by the IRB has been received by LIPAC, no subject may undergo any procedures.

The names and qualifications of the members of the review committee will be recorded and submitted to LIPAC, together with the written approval for the conduct of the study. The members of the IRB must be independent of LIPAC and the investigator.

No deviations from, or changes of, the protocol, should be initiated without prior written IRB approval of the appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study (e.g., change of monitor[s], telephone number[s]).

14.3. Ethical Conduct of the Study

The investigator agrees that the study will be conducted according to the protocol, the Declaration of Helsinki and the principles of Good Clinical Practice (GCP), and International Conference on Harmonisation (ICH) guidelines governing clinical study conduct.

The investigator will conduct all aspects of this study in accordance with all national, state, and local laws of the pertinent regulatory authorities.

The study will be conducted in compliance with:

- the protocol
- ethical principles of the Declaration of Helsinki and its amendments
- the principles of GCP provided in the ICH Harmonised Tripartite Guidelines for GCP 1996
- all applicable national laws and regulations including, but not limited to, country-specific GCP

14.4. Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study, prior to obtaining informed consent. Specific instructions related to study conduct (e.g., visit schedule) will be provided to the subject with the informed consent form.

The investigator will obtain informed consent from each subject enrolled in the study, in accordance with the current version of the GCP guidelines and the laws and regulations of the country in which the investigation is being conducted.

The IRB must approve the informed consent form to be used by the investigator prior to its use. It is the responsibility of the investigator to assure that the subject has signed the informed consent form before any activity or treatment is undertaken. This includes, but is not limited to, the performance of diagnostic or therapeutic procedures and the administration of the investigational product.

14.5. Subject Confidentiality

Adequate records have to be maintained for the study, including but not limited to subject medical records, electronic case report form (eCRFs), laboratory reports, worksheets, nursing notes, signed informed consent forms, product forms, serious adverse event (SAE) forms, and information regarding subject discontinuation and reasons for discontinuation. The confidentiality of each record with subject identification is to be guaranteed by the clinical investigator.

This protocol and other study documents contain trade secrets and commercial information that is privileged and confidential. Such information is not to be disclosed unless required by laws or regulations. The investigator agrees to use this information only in conducting this study and is not allowed to use it for other purposes without written consent from LIPAC. Results obtained from this study are the property of LIPAC.

14.6. Study Monitoring

For protocol monitoring and compliance, an investigational center visit will be held prior to initiation of subject enrollment. The protocol, eCRFs, study supplies, and study procedures will be explained in detail.

A monitor will conduct regular investigational center visits for the purpose of study monitoring.

The investigator must agree to allow the study monitor and authorized representatives of LIPAC or LIPAC designee to inspect all eCRFs and corresponding source documents (e.g., original medical records, subject records, and laboratory raw data); to allow access to the clinical supplies, dispensing, and storage areas; and to agree to assist with their activities, if requested. The investigator should provide adequate time, availability, and space for monitoring visits.

The monitor will query any missing or spurious data with the investigator or designee, which should be resolved in a timely manner. A monitoring log will be maintained to record each visit, the reason for the visit, the monitor's signature, and the investigator's or designee's confirmation signature.

14.7. Case Report Forms and Study Records

Case report form data will be collected electronically. Subject source documents are the physician's records maintained at the investigational center. The information collected on the eCRF must match the information found on the charts.

Instructions for entering data via internet will be provided in the eCRF Completion Guidelines and training will be provided to the investigational center staff prior to initiation of the center.

Periodically, where appropriate, the Monitor or other authorized LIPAC personnel will visit the investigational center for the purpose of comparing the data on the eCRF with the source documents. The investigator agrees to make source documents available for this purpose. The eCRF should be completed as soon as possible after the data are available.

14.8. Data Monitoring Committee

Not applicable.

14.9. Termination of the Study

LIPAC reserves the right to terminate this study prematurely, either in its entirety or at a specific site, for reasonable cause provided that written notice is submitted a reasonable time in advance of the intended termination. The investigator may also terminate the study at their site for reasonable cause, after providing written notice to LIPAC a reasonable time in advance of the intended termination. Neither party requires advance notice if the study is stopped due to safety concerns. If LIPAC chooses to terminate the study for safety reasons, it will immediately notify the investigator and subsequently provide written instructions for study termination. Subjects who have not completed treatment in the study at the time of termination will be advised and offered alternative treatment, as medically necessary.

14.10. Financial Disclosure

Consistent with Title 21 CFR Part 54, all investigators will complete a Financial Disclosure Form that permits the Sponsor to demonstrate that an investigator has no personal or professional financial incentive regarding study outcome or the future approval/disapproval of an investigational drug such that the investigator's research might be biased by such incentive.

14.11. Publication and Disclosure Policy

Any formal presentation or publication of data from this study will be considered by the appropriate LIPAC personnel. For multicenter studies, it is mandatory that the first publication is based on data from all centers, analyzed as stipulated in the protocol. Investigators agree not to present data gathered from one center or a small group of centers before the full publication. In this case, LIPAC must receive copies of any intended communication in advance of publication (at least 30 working days for an abstract/oral presentation and 60 working days for a journal submission). In any case, LIPAC will review the publications/communications/abstracts for accuracy (thus avoiding potential discrepancies with submissions to health authorities), verify that proprietary, confidential information is not being inadvertently divulged, and provide any relevant supplementary information.

APPENDIX 2. INTERNATIONAL PROSTATE SYMPTOM SCORE (IPSS)

The International Prostate Symptom Score (IPSS) is a scale originally developed by the American Urological Association Measurement Committee (Barry, et al., 1992).

The IPSS is based on the answers to seven questions concerning urinary symptoms and one question concerning related quality of life. Each question concerning urinary symptoms asks the patient to choose one of six answers indicating increasing severity of the symptom. The answers are given points from 0 to 5. Total score can range from a minimum of 0 (asymptomatic) to a maximum of 35 (very symptomatic).

The questions refer to the following urinary symptoms:

Symptom

1. Incomplete emptying
2. Frequency
3. Intermittency
4. Urgency
5. Weak stream
6. Straining
7. Nocturia

Question eight refers to the patient's perceived quality of life.

The first seven questions of the IPSS are identical to the questions appearing on the American Urological Association (AUA) Symptom Index, which approximates total symptom scores as follows:

Total Score	Category
≤7	Mild
8-19	Moderate
20-35	Severe

International Prostate Symptom Score

Patient name: _____ DOB: _____ Subject #: _____ Date: _____

In the past month:	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
1. How often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5
2. How often have you had to urinate again less than 2 hours after you finished urinating?	0	1	2	3	4	5
3. How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
4. How often have you found it difficult to postpone urination?	0	1	2	3	4	5
5. How often have you had a weak urinary stream?	0	1	2	3	4	5
6. How often have you had to push or strain to begin urination?	0	1	2	3	4	5
	None	1 time	2 times	3 times	4 times	5 or more times
7. How many times did you most typically get up to urinate from the time you went to bed	0	1	2	3	4	5

at night until the time you got up in the morning?							
Total Symptom Score:							
Quality of Life Due to Urinary Symptoms	Delighted	Pleased	Mostly Satisfied	Mixed	Mostly Dissatisfied	Unhappy	Terrible
8. 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?	0	1	2	3	4	5	6

APPENDIX 3. OVERACTIVE BLADDER QUESTIONNAIRE (OAB-Q)

Overactive Bladder Questionnaire (OAB-q)

This questionnaire asks about how much you have been bothered by selected bladder symptoms during the past week. Please place a ✓ or × in the box that best describes the extent to which you were bothered by each symptom during the past week. There are no right or wrong answers. Please be sure to answer every question.

During the past week, how bothered were you by. . .	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**A great deal**	**A very great deal**
1. Frequent urination during the daytime hours?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
2. An uncomfortable urge to urinate?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
3. A sudden urge to urinate with little or no warning?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
4. Accidental loss of small amounts of urine?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
5. Nighttime urination?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
6. Waking up at night because you had to urinate?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
7. An uncontrollable urge to urinate?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
8. Urine loss associated with a strong desire to urinate?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

The above questions asked about your feelings about individual bladder symptoms. For the following questions, please think about your overall bladder symptoms in the past week and how these symptoms have affected your life. Please answer each question about how often you have felt this way to the best of your ability. Please place a ✓ or × in the box that best answers each question.

Overactive Bladder Questionnaire (OAB-q)

During the past week, how often have your bladder symptoms . . .	None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
9. Made you carefully plan your commute?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
10. Caused you to feel drowsy or sleepy during the day?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
11. Caused you to plan “escape routes” to restrooms in public places?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
12. Caused you distress?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
13. Frustrated you?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
14. Made you feel like there is something wrong with you?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
15. Interfered with your ability to get a good night’s rest?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
16. Caused you to decrease your physical activities (exercising, sports, etc.)?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
17. Prevented you from feeling rested upon waking in the morning?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
18. Frustrated your family and friends?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
19. Caused you anxiety or worry?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
20. Caused you to stay home more often than you would prefer?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
21. Caused you to adjust your travel plans so that you are always near a restroom?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
22. Made you avoid activities away from restrooms (i.e., walks, running, hiking)?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

Overactive Bladder Questionnaire (OAB-q)

During the past week, how often have your bladder symptoms . . .	None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
23. Made you frustrated or annoyed about the amount of time you spend in the restroom?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
24. Awakened you during sleep?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
25. Made you worry about odor or hygiene?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
26. Made you uncomfortable while traveling with others because of needing to stop for a restroom?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
27. Affected your relationships with family and friends?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
28. Caused you to decrease participating in social gatherings, such as parties or visits with family or friends?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
29. Caused you embarrassment?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
30. Interfered with getting the amount of sleep you needed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
31. Caused you to have problems with your partner or spouse?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
32. Caused you to plan activities more carefully?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
33. Caused you to locate the closest restroom as soon as you arrive at a place you have never been?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

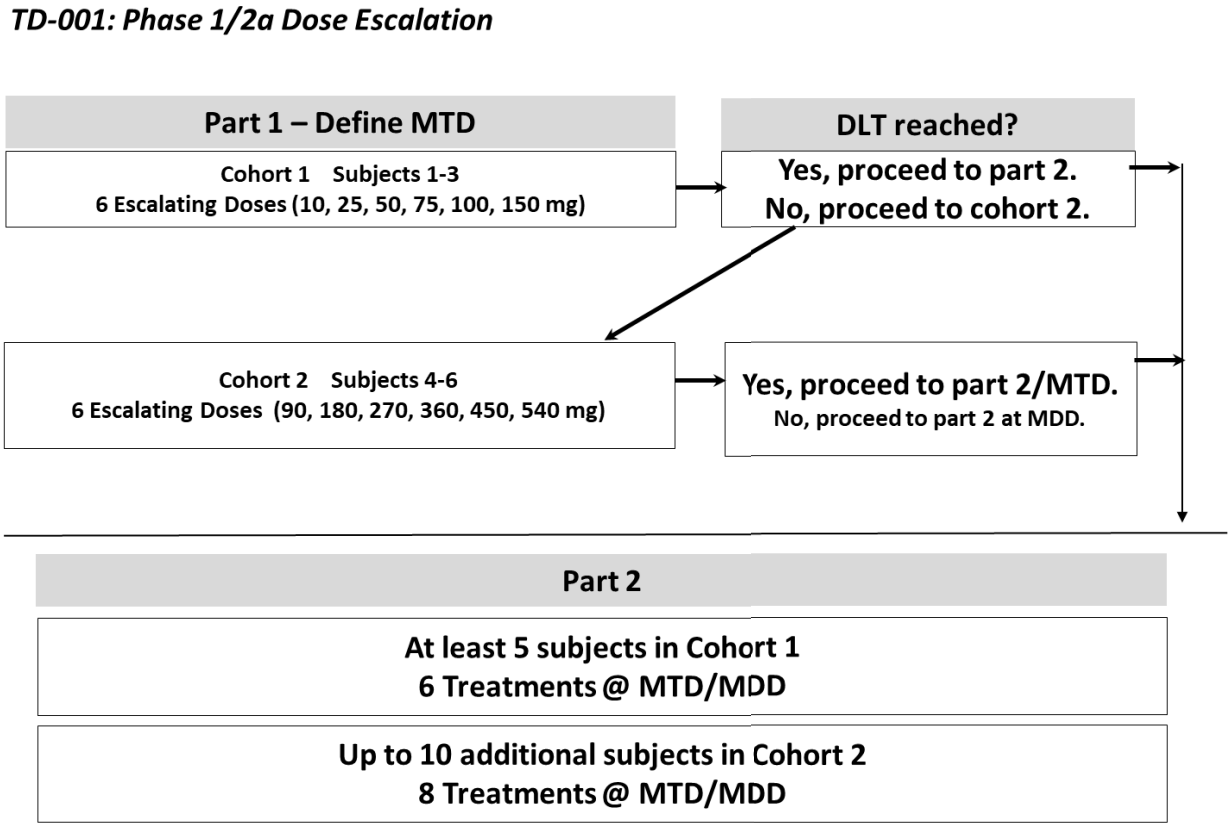
APPENDIX 4. DOSE ESCALATION RULES

Part 1. If a grade 2 toxicity is observed, the intravesical instillation may be delayed (up to 14 days) and the intravesical dose will be reduced to half the difference between the last 2 doses, and the subject can be re-exposed to study drug at the discretion of the investigator. For example, if a subject receives 180 mg of TSD-001 with no toxicity, but grade 2 toxicity occurs when the dose is increased to 270 mg, then the subject may be re-exposed at 225 mg dose. Any patient with grade 3 or 4 toxicity (or prolonged [greater than 14 day delay] grade 2 toxicity) will be considered having experienced a DLT, which will result in discontinuation of study drug.

Part 2. If any grade 2 CTCAE toxicity is observed, the intravesical instillation may be delayed (up to 14 days) and the intravesical dose will be reduced by 25% from the MTD/MDD established in part 1. For example, if grade 2 toxicity is observed after exposure to the MTD/MDD of 360 mg, then the next dose would be 270 mg, and may be delayed for up to 14 days. Any patient with grade 3 or 4 toxicity (or prolonged grade 2 toxicity) will be considered having experienced a DLT, which will result in discontinuation of study drug.

If no DLT develops in **part 1** cohort 1, then **part 1** cohort 2 (subjects 4, 5, and 6) will start with 90 mg and increase every 2 weeks up to 540 mg or until DLT is reached.

Figure 3: Diagram of the Adaptive Accelerated Individual Dose-escalation Schedule for Part 1 and Dose Assignment for Part 2



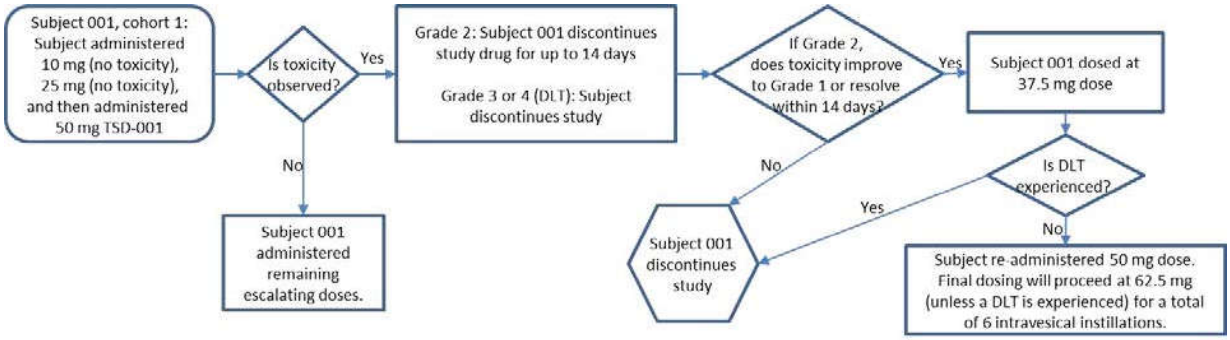
Deceleration Dose Titration Plan upon Study-related Low-grade Toxicity:

Dose-limiting toxicity is defined by any toxic effects potentially related to drug that are considered unacceptable and limit further dose escalation. Symptoms of local toxicity will be monitored throughout study treatment. Any patient with evidence of CTCAE grade 3 or 4 toxicity (or prolonged, greater than 14 days, grade 2 toxicity) will be considered to have experienced a DLT and will immediately discontinue study drug. If no grade 3 or 4 CTCAE toxicity (or prolonged grade 2 toxicity) is observed, MTD will be defined as the dose just before the dose at which > 33% of the study subjects experience grade 2 CTCAE toxicity related to study drug, or when the MDD is reached. If no DLT is observed in the first 6 subjects after titration, then 360 mg will be the dose recommended for part 2 of the study, as this paclitaxel concentration is substantially higher than the half-maximal inhibitory concentration (IC_{50}) observed in bladder cancer cell lines exposed to TSD-001.

If a CTCAE grade 2 local toxicity develops in either **part 1** or **part 2** of the study, treatment of the subject will be delayed for no longer than 14 days and resumed only if the toxicity resolves to grade 1 or less. Subsequent dose escalation in patients who experience grade 2 toxicities which improve to grade 1 or resolve within 14 days would proceed at half the magnitude of dose escalation specified in the protocol for a total of up to 6 intravesical instillations. For example, if study subject 001 had grade 2 toxicity in **part 1** cohort 1 after exposure to the 50-mg dose, the subject would postpone study drug administration and be reassessed after a delay of no longer than 14 days; if the toxicity improved to grade 1 or resolved within a period of 14 days, the subject would be eligible for exposure to 37.5 mg TSD-001 (see dose escalation example for **part 1** cohort 1 below).

Alternatively, if the study subject who experiences a grade 2 related toxicity following TSD-001 treatment does not improve or resolve after an up to 14-day delay following the last exposure of study drug, he or she would not be exposed to additional TSD-001 intravesical treatments.

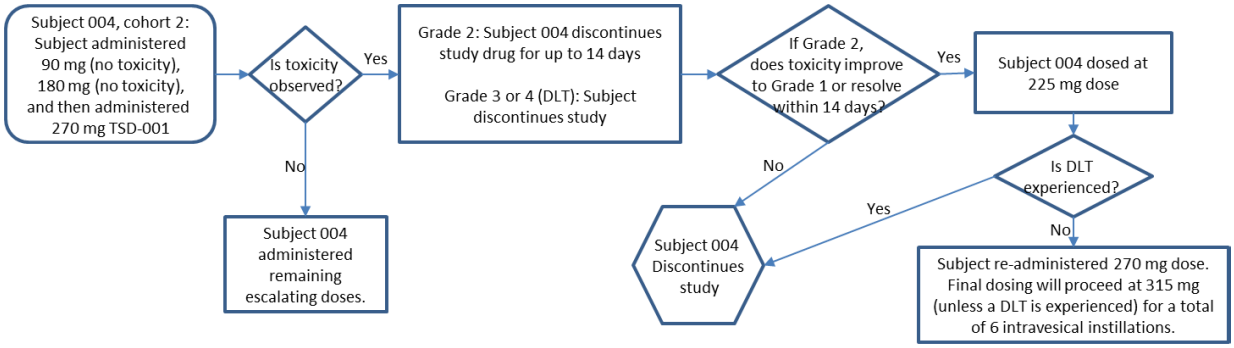
Dose escalation example – Part 1 Cohort 1:



As an additional example (#2), if study subject 004 (cohort 2) experiences moderate dysuria (grade 2) at 270 mg TSD-001, the next dose for that subject would be delayed up to 14 days if the severity of the toxicity resolves or lessens to grade 1; subject 004 can be re-exposed to TSD-001 at the 225 mg dose level. If the initial grade 2 toxicity does not improve to grade 1 or resolve within a 14-day delay, the subject will discontinue study participation. Subsequent

dosing of the subject will be at one-half the magnitude of the protocol-specified increase in dose for up to 6 intravesical instillations as described above in example for **part 1** cohort 1 (see dose escalation example for **part 1** cohort 2 below).

Dose escalation example – Part 1 Cohort 2:



PROTOCOL AMENDMENT SUMMARY OF CHANGES
A Phase 1/2a Pilot Study of intravesical TSD-001 for Treatment of Low-Grade, Stage Ta, Non-Muscle Invasive Bladder Cancer

Study Number:	**TD-001**
Indication:	**Non-Muscle Invasive Bladder Cancer (NMIBC)**
Sponsor:	**LIPAC Oncology LLC** **325 Sharon Park Drive, Suite 739** **Menlo Park, CA 94025**
Initial Version	**26 Sep 2016**
Revision #1 (V2.0)	**28 Feb 2017**
Revision #2 (V3.0)	**20 Mar 2018**
Revision #3 (V4.0)	**17 Oct 2018**
Revision #4 (V5.0)	**05 Apr2019**
Revision #5 (V6.0)	**18 Jul 2019**
Revision #6 (V7.0)	***04FEB2020***

Significant Changes to the protocol from Version 6.0 to Version 7.0
Verbiage and content changes are similar in certain sections of the protocol. All affected sections are listed in the first column for similar changes.

Protocol Section(s)	Version 6.0	Version 7.0
Header, Title Page, synopsis,	Sponsor listed as "TesoRx Pharma, LLC"	Sponsor updated to "LIPAC Oncology LLC" with accompanying address: 325 Sharon Park Drive, Suite 739 Menlo Park, CA 94025-6805
protocol throughout,	"TesoRx"	"LIPAC"
14.1. Investigators and Study Administrative Structure		Updated LIPAC Oncology LLC (Sponsor) address as above. Address for Dr. Michael Oefelein (Chief Medical Officer) and Karl Bean (Clinical Project Manager) remains as Pomona, CA address.
Synopsis and protocol	Part 2 contained no cohorts.	Part 2, Cohort 1 and Cohort 2 are introduced. Part 2 Cohort 1 is the same schedule of events as Protocol v6.0 Part 2 Schedule of Events. Part 2 Cohort 2 adds two treatment visits, extends total treatment period by 3 weeks and adds two additional visits.
Synopsis: Study Duration		"**Part 2 Cohort 2** – up to 20 weeks (up to 4-week screening period, 7-week treatment period, and 9-week follow-up period)."
Synopsis: Methodology, 5.1. Overall Design and Plan of the Study	"The study has a total of 17 planned clinic visits for **part 1** and 14 planned clinic visits for **part 2.**"	"The study has a total of 17 planned clinic visits for **part 1** and 14 planned clinic visits for **part 2** cohort 1 subjects and 16 planned clinic visits for **part 2** cohort 2 subjects."

Protocol Section(s)	Version 6.0	Version 7.0
Synopsis, Study Duration:, Methodology:, 8.4. Part 3(Surveillance) Visits	 **"Part 3** – cystoscopic surveillance every 3 months for up to 24 months from initial instillation." "Subjects who receive at least two treatments in **part 1** or **part 2** may receive further cystoscopic surveillance in **part 3**." "Procedures should be conducted as outlined in Table 3."	Clarified that Part 3 procedures are performed as standard-of-care. **"Part 3** – Standard-of-care cystoscopic surveillance every 3 months for up to 24 months from initial instillation." "Subjects who receive at least two treatments in **part 1** or **part 2** may be followed further with standard-of-care cystoscopic surveillance in **part 3**." "Procedures should be conducted as outlined in Table 4, per standard of care."
Synopsis 4. Study Objectives, 5.1. Overall Design and Plan of the Study 9.1.2. Secondary Endpoints, 11.1.5. Efficacy Parameters	**Part 2** last visit described as Week 13 for exploratory objective related to IPSS and OAB-q. "Exploratory objectives of **part 2** include change from baseline to Week 13 in IPSS (men only) and OAB-q scores and paclitaxel levels in voided urine samples at 24, 48, and 72 hours after the third instillation of TSD-001." "Subject questionnaires (IPSS, OAB-q) will be administered on Day 1, Day 36 (Week 5), and Day 92 (Week 13)." "Exploratory endpoints of **part 2** include evaluation of: • Change from baseline to Week 13 in IPSS (men only) • Change from baseline to Week 13 in OAB-q score"	**Part 2** last visit described as "the end of the treatment part" to include both **Part 2** cohort 1 (Week 13) and **Part 2** cohort 2 (Week 16). "Exploratory objectives of part 2 include change from baseline to the end of the treatment part in IPSS (men only) and OAB-q scores and paclitaxel levels in voided urine samples at 24, 48, and 72 hours after the third instillation of TSD-001." "Subject questionnaires (IPSS, OAB-q) will be administered at baseline enrollment, day of last treatment, and at the end of the treatment part on Day 92 (Week 13) for **part 2** cohort 1 or Day 113 (Week 16) for **part 2** cohort 2." "Exploratory endpoints of **part 2** include evaluation of: • Change from baseline to the end of the treatment part in IPSS (men only) • Change from baseline to the end of the treatment part in OAB-q score"

Protocol Section(s)	Version 6.0	Version 7.0
Synopsis 4. Study Objectives		Added descriptions of histological tissue diagnosis evidence. "Histological tissue diagnosis evidence is identification of any urothelial carcinoma (i.e., transitional cell carcinoma [TCC]), including all grades and stages." "Histological tissue diagnosis evidence is any diagnosis of urothelial carcinoma (i.e., TCC), including all grades and stages."
Synopsis: Methodology:	Description of **Part 2**: "**Part 2** of the study will enroll an additional 10 subjects with low-grade, stage Ta TCC of the bladder who will receive weekly TSD-001 for 6 weeks at the highest nontoxic dose established in **part 1** of the study."	"**Part 2** cohort 1 of the study will enroll at least 5 subjects with low-grade, stage Ta TCC of the bladder who will receive weekly TSD-001 for 6 administrations at the highest nontoxic dose established in **part 1** of the study. **Part 2** cohort 2 of the study will enroll up to 10 subjects with low-grade, stage Ta TCC of the bladder who will receive weekly TSD-001 for 8 administrations at the highest nontoxic dose established in **part 1** of the study."
Synopsis, Schedule of Events (Table 2 and 3), 4. Study Objectives, 5.1. Overall Design and Plan of the Study, 8.3 Exit/Withdrawal from Part 1/Part 2, 11.1.5. Efficacy Parameters	Subjects in Part 2: "the marker lesion response rate will be determined 12 weeks (± 7 days) after Day 1 (i.e., 7 weeks [± 7 days] after the last intravesical instillation), via cystoscopy, cytology, and biopsy under general/regional anesthesia."	Subjects in **part 2** cohort 1: "the marker lesion response rate will be determined 12 weeks (± 7 days) after Day 1 (i.e., 7 weeks [± 7 days] after the last intravesical instillation), via cystoscopy, cytology, and biopsy under general/regional anesthesia." For **Part 2** cohort 2 **s**ubjects: "the marker lesion response rate will be determined 15 weeks (± 7 days) after Day 1 (i.e., 8 weeks [± 7 days] after the last intravesical instillation)."

Protocol Section(s)	Version 6.0	Version 7.0
Synopsis: Methodology:, 4. Study Objectives, 5.1. Overall Design and Plan of the Study, 11.1. Statistical and Analytical Plan	 "The marker lesion response rate (**part 2**) will be determined by the percentage of subjects at completion cystoscopy and biopsy to have negative cytology and no cystoscopic or biopsy evidence of residual disease."	Add description of marker lesion assessment, determination of complete and partial response, for all Part 2 subjects: "Complete marker lesion response requires no evidence of TCC on cystoscope-directed biopsy. Partial response is at least a 30% decrease in marker lesion size (Eisenhauer et al., 2009)." "The marker lesion response rate (**part 2**) will be determined by the percentage of subjects at completion cystoscopy and biopsy to have no cystoscopic or biopsy evidence of residual disease. Partial response will be determined by comparing the pretreatment marker lesion size to the post-treatment size. Partial response is at least a 30% decrease in marker lesion size."
Synopsis: Methodology:, Test Product, Dose, and Mode of Administration:	 "During **part 2**, an additional 10 subjects will receive intravesical instillations of TSD-001 via sterile urethral catheterization of the urinary bladder at the MTD/MDD established in **part 1** at weekly intervals for 6 consecutive weeks."	Clarification that subjects in **part 2** cohort 1 will follow previous **part 2** schedule of events including 6 treatments. **Part 2** cohort 2 will have 8 treatments. "Subjects in **part 2** cohort 1 will receive intravesical instillations of TSD-001 via sterile urethral catheterization of the urinary bladder at the MTD/MDD established in **part 1** at weekly intervals for 6 consecutive weeks. Subjects in **part 2** cohort 2 will receive intravesical instillations of TSD-001 at weekly intervals for 8 consecutive weeks." "For subjects in **part 2** cohort 2, the MTD or MDD will be administered every 7 days for 8 consecutive administrations."

Protocol Section(s)	Version 6.0	Version 7.0
Synopsis, 6.1. Inclusion Criteria 3-5, 8.1.1. TURBT, 8.1.2. Marker Lesion (for Part 2)	Marker lesion size criteria was > 0.5 cm and ≤ 2.0 cm in diameter.	Marker lesion size criteria updated to ≥ 0.5 cm and ≤ 2.0 cm in diameter.
Synopsis, 6.2. Exclusion Criteria 2, 8.1.2 Marker Lesion	Excluded if "Has positive urine cytology for urothelial malignancy at screening."	Excluded if "Has positive urine cytology for urothelial malignancy (i.e., high-grade) at screening."
Synopsis, 5.1. Overall Design and Plan of the Study, 11.3. Determination of Sample Size	An enrollment of approximately 16 subjects is planned, with 6 subjects in **part 1** and 10 subjects in **part 2** Given these goals, a sample size of at least 6 subjects for **part 1** and at least 10 for **part 2,** for a total of at least 16, has empirically been planned as sufficient to achieve the study goals.	An enrollment of up to 21 subjects is planned, with 6 subjects in **part 1** and up to 15 additional subjects in **part 2** (at least 5 in cohort 1 and up to 10 in cohort 2). Given these goals, a sample size of at least 6 subjects for **part 1** and up to 15 for **part 2,** for a total of up to 21 subjects, has empirically been planned as sufficient to achieve the study goals.
Synopsis, Appendix 4. Dose Escalation Rules	Existing references to 'cohort 1' and 'cohort 2' refer to **Part 1** cohort 1 and **Part 1** cohort 2.	Added "**part 1**" to Dose Escalation references to distinguish from **part 2** cohort 1 and cohort 2.

Protocol Section(s)	Version 6.0	Version 7.0
Synopsis: Criteria for Evaluation 9.1.2. Secondary Endpoints	"The endpoint will be a time to event (recurrence) after the last instillation of TSD-001."	Clarified starting point for time to event (recurrence) endpoint. "The endpoint will be a time to event (recurrence) after the TURBT (Day -12 in Part 1) or after complete response or Week 12 TURBT in Part 2." "The exploratory endpoint of **part 3** (surveillance) will be disease-free survival of subjects exposed to TSD-001 in **part 1** or **part 2**. • The endpoint will be time to event (recurrence) after the TURBT (Day -12 in **part 1**) or after complete response or Week 12 TURBT in **part 2**. Disease-free survival will be defined as no histological tissue diagnosis evidence of recurrence."
2. Schedule of Events		Inserted Table 3: **Part 2 Cohort 2 Schedule of Assessments** including additional treatment visits (in comparison to cohort 1) at Week 6 and Week 7. Follow-up visits at Week 9 and Week 12. Marker lesion assessment at Week 15 visit. End of treatment part visit at Week 16.
2. Schedule of Events, Table 4: Surveillance Schedule of Assessments (Part 3), 5.1. Overall Design and Plan of the Study, 7.5. Prior/Concomitant Medication & Therapy 8.4. Part 3 (Surveillance) Visits, 9.3.1. Adverse Events	1. Only recorded in eCRF if they relate to an AE continuing from **part 1** or **part 2**, a treatment for a recurrence, or a reported SAE. 2. AEs continued from **part 1** or **part 2**, but no new AEs will be recorded. New AEs only recorded if they meet the definition of a SAE. New AEs should be recorded during the surveillance portion (**part 3**) of the study only if they meet the definition of a SAE.	Removed collection of SAEs from Part 3. 1. Only recorded in eCRF if they relate to an AE continuing from **part 1** or **part 2** or a treatment for a recurrence. 2. AEs continued from **part 1** or **part 2**, but no new AEs will be recorded.

Protocol Section(s)	Version 6.0	Version 7.0
5.1. Overall Design and Plan of the Study 8.3 Exit/Withdrawal from Part 1/Part 2 8.4. Part 3 (Surveillance) Visits 9.3.1. Adverse Events	"During **part 3**, AEs continued from **part 1** or **part 2** will be followed but no new AEs will be recorded." "In case of study withdrawal due to an AE, the subject is to be followed until resolution of the AE or for 30 days." "During **part 3**, AEs continued from **part 1** or **part 2** will be followed but no new AEs will be recorded." "In case of study withdrawal due to an AE, the subject is to be followed until resolution of the AE or for at least 30 days. During **part 3**, AEs continued from **part 1** or **part 2** will be followed but no new AEs will be recorded."	Clarified collection of AEs in **Part 3.** **"**During **part 3**, AEs continued from **part 1** or **part 2** will be followed until resolution or stabilization but no new AEs will be recorded." "In case of study withdrawal due to an AE, the subject is to be followed until resolution/ stabilization of the AE or for 30 days." "During **part 3**, AEs continued from **part 1** or **part 2** will be followed until resolution or stabilization but no new AEs will be recorded." "In case of study withdrawal due to an AE, the subject is to be followed until resolution/stabilization of the AE or for at least 30 days. During **part 3**, AEs continued from **part 1** or **part 2** will be followed until resolution or stabilization but no new AEs will be recorded."
5.1. Overall Design and Plan of the Study – Figure 1: Overview of Study Design		Updated to include new figures for Part 2 Cohort 1 and Part 2 Cohort 2.
7.2. Study Drug Dosing Rules - Figure 2 Appendix 4. Dose Escalation Rules		Updated to show **Part 2** cohort 1 with at least 5 subject, 6 treatments each. Updated to show **Part 2** cohort 2 with up to 10 additional subjects, 8 treatments each.

Protocol Section(s)	Version 6.0	Version 7.0
7.3. Method of Assigning Subjects to Part, Cohort, and Dosing Levels		Added additional direction: "Additionally, subjects that start treatment in **part 2** cohort 1 will be re-assigned to cohort 2 prior to completion of treatment administration visits (i.e., Week 5) after institutional review board (IRB) written approval of the **part 2** cohort 2 schedule and the associated protocol version."
8.1. Screening		Added previously missing direction on cystoscopic assessment: "Cystoscopic assessment (to be completed during screening or within 30 days prior to start of screening as part of standard care)"
8.2.2. Treatment		Added direction: "During instillation and when physically able, the subject should change position every 15 minutes with at least two 15-minute periods in the prone (facedown) position."
8.2.3. Other Study Procedures	A urine sample for cytology will also be obtained. … If no residual tumor is noted, the site of the marker lesion must be biopsied.	Subjects in Part 2 cohort 2 will have the last instillation on Week 7 visit (Day 50). Additional follow up visits will occur at Week 9 (Day 64) and Week 12 (Day 85). On the Week 15 (Day 106 ± 7 days) visit, the final cystoscopy procedure and biopsy will be conducted (or TURBT if a bladder tumor lesion is present). At the time of final cystoscopic assessment, a urine sample for cytology will also be obtained. If no residual tumor is noted at the final cystoscopic assessment, the site of the marker lesion must be biopsied.

Protocol Section(s)	Version 6.0	Version 7.0
9.3.1.5 Handling of AEs	Michael G. Oefelein, MD, FACS Michael@tesorx.com	Michael G. Oefelein, MD, FACS Michael@lipaconcology.com
9.3.2. Laboratory Measurements and Variables -Table 5	Table 4: Protocol-Required Safety Laboratory Assessments	Now referenced as Table 5: Protocol-Required Safety Laboratory Assessments
9.3.3.2. 12-lead ECG	Standard 12-lead ECGs will be evaluated for screening (eligibility) reasons and at the end of the study.	Standard 12-lead ECGs will be evaluated for screening (eligibility) reasons and at the end of the treatment part.
13. References		Added: "Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47."