Clinical Trial Protocol

Title: **A Phase I-IIa, Multicenter, Open-Label, Multiple Dose, Safety, Tolerability and Pharmacokinetic Study of Recombinant Human Hyaluronidase (Chemophase™) in Combination with Mitomycin in Patients with Non-Muscular-Invasive Bladder Cancer**

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Sponsor: **Halozyme Therapeutics, Inc. (Halozyme)**
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1. STUDY SYNOPSIS

Protocol No.	HZ2-05-01
Study Title	A Phase I-IIa, Multicenter, Open-Label, Multiple Dose, Safety, Tolerability and Pharmacokinetic Study of Recombinant Human Hyaluronidase (Chemophase™) in Combination with Mitomycin in Patients with Non-Muscular-Invasive Bladder Cancer
Sponsor	Halozyme Therapeutics, Inc. (Halozyme) 11588 Sorrento Valley Road, Suite 17 San Diego, CA 92121 Office: [redacted]
Primary Objectives	• Determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of escalating doses of Chemophase in combination with mitomycin (mitomycin C, MMC) administered as weekly intravesical instillations for five weeks • Establish the dose of Chemophase with MMC recommended for future studies
Secondary Objectives	• Assess the pharmacokinetics of intravesical administration of MMC alone and in combination with intravesical administration of Chemophase • For those patients treated at the MTD, assess the safety and tolerability of intravesical administration of MMC with Chemophase over up to 7 additional maintenance treatments every 3 months following the initial six weekly instillations. • Observe patients for any preliminary evidence of anti-tumor activity of MMC and Chemophase when combined
Study Design	Phase I-IIa, open-label, multicenter, dose-escalation, safety, tolerability and pharmacokinetics study. Long-term follow-up information will be collected to help make a preliminary assessment of possible anti-tumor activity.
Study Medications	• Chemophase (hyaluronidase, human recombinant; rHuPH20) • Mitomycin (Mitomycin C, MMC)
Duration	Study patients will receive six (6) weekly study treatments (at Weeks 1 through 6) followed by post-treatment evaluations, at Weeks 8 and 12. The 12 patients treated at MTD will continue to receive combination therapy every three months until the end of Year 2 or until the time of documented tumor recurrence, whichever occurs first. For other patients, long-term follow-up after Week 12 will consist of disease monitoring of patients by telephone and will be performed every three (3) months beginning three months after last study treatment for two years following day 1 or until bladder tumor recurrence, whichever occurs first.
Patient Population	Patients with initial presentation or recurrence of Stage Ta, T1 or Tis, any grade, bladder cancer after TURBT

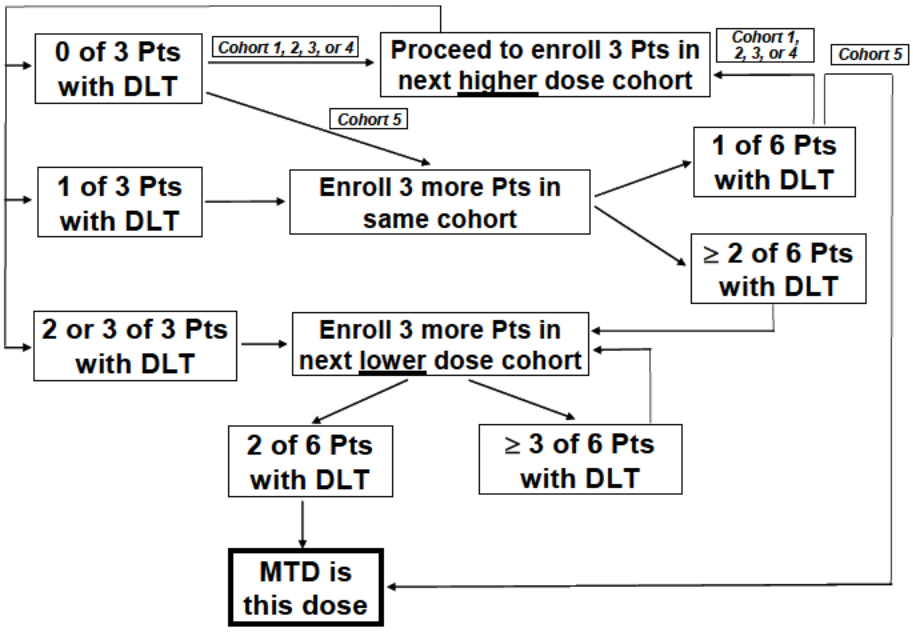
<table>
<tr><td>Planned Total Sample Size</td><td>Up to 36 evaluable patients will be enrolled. It is anticipated that no more than a total of 44 patients will need to be enrolled. An evaluable patient is one who receives all protocol-specified six weekly intravesical treatments with at least a 90-minute retention and has had MMC plasma concentration determinations and safety assessments adequate for the determination of tolerability. Patients not meeting these criteria, including those withdrawn prematurely for reasons other than toxicity, will be replaced. Groups of either 3 or 6 patients will participate in each of the five individual dose cohorts in the dose escalation phase of the study. Once the MTD has been established, 6 additional evaluable patients will be enrolled at the MTD dose level, yielding a total of 12 evaluable patients at MTD upon which to confirm safety and tolerability of the MTD regimen.</td></tr>
<tr><td>Intravesical Administration, Dose-Escalation Scheme, and Stopping Rules</td><td>
<table>
<tr><th>Cohort</th><th>Week 1 Dosing</th><th>Weekly Dosing Week 2 through Week 6</th></tr>
<tr><td>1</td><td>MMC 40 mg/20 mL</td><td>20,000 U Chemophase with MMC 40 mg/20 mL</td></tr>
<tr><td>2</td><td>MMC 40 mg/20 mL</td><td>60,000 U Chemophase with MMC 40 mg/20 mL</td></tr>
<tr><td>3</td><td>MMC 40 mg/20 mL</td><td>200,000 U Chemophase with MMC 40 mg/20 mL</td></tr>
<tr><td>4</td><td>MMC 40 mg/20 mL</td><td>400,000 U Chemophase with MMC 40 mg/20 mL</td></tr>
<tr><td>5</td><td>MMC 40 mg/20 mL</td><td>800,000 U Chemophase with MMC 40 mg/20 mL</td></tr>
</table>

A dose-limiting toxicity (DLT) is defined as either (a) plasma MMC concentration ≥ 100 ng/mL, (b) National Cancer Institute (NCI) Common Terminology Criteria (CTC) (Version 3 or current version) AE Grade 3 or higher toxicity, or (c) new, treatment-emergent diagnosis of bladder fibrosis.

Each intravesical administration will remain in the bladder for two hours after instillation. In each cohort, at Week 1 patients will receive MMC 40 mg alone (without Chemophase) in 20 mL of sterile water. If no DLT is observed prior to Week 2, this first treatment will be followed by five weekly intravesical instillations (at Weeks 2 through 6) of Chemophase at the dose specified by the assigned cohort followed by MMC 40 mg in 20 mL of sterile water.

All 3 patients within a given cohort may begin treatment simultaneously. The next higher dose cohort can be immediately opened for patient enrollment if, at the time all 3 patients in a given cohort have completed the fourth (4th) instillation of MMC (i.e., third instillation of MMC plus Chemophase), there is:
• no NCI CTC adverse event Grade 2 or higher toxicity,
• no MMC plasma concentration ≥ 100 ng/mL, and
• no new, treatment-emergent, diagnosis of bladder fibrosis.
Note that an NCI CTC adverse event Grade 2 toxicity will delay opening the next higher dose cohort to enrollment until safety data are reviewed from all six weekly instillations for all 3 patients in that cohort.

Because this study is being conducted at more than one study center, the enrollment of patients, assignment to cohorts, and opening of each sequential cohort will be controlled centrally for all study centers by Halozyme. Each time a new patient is consented for the study, the study center must</td></tr>
</table>

	immediately fax the updated Screening Log to Halozyme or its designee. In turn, Halozyme or its designee will keep all centers immediately apprised of the number of patients enrolled and patients in screening, so that new patients are not consented if there is no possibility of enrollment because there is no room for additional patients in the ongoing cohort. At the time a patient has fulfilled all eligibility criteria, the study center must fax a completed Enrollment/ Registration Form to Halozyme or its designee, in response to which Halozyme or its designee will provide authorization to dose and confirmation of the dose cohort to which the new patient will be assigned. The study center must not begin dosing any new patient or open enrollment in a new cohort without a Registration Form prior authorization from Halozyme or its designee. Flow diagram of the dose escalation schema and stopping rules:  The maximum tolerated dose (MTD) is defined as the dose level at which ≤ 2 of 6 patients experience a DLT.
Inclusion Criteria	1. Patients with initial presentation or recurrence of Stage Ta, T1 or Tis, any grade, bladder cancer after TURBT. 2. TURBT within 42 days prior to Day 1/Week 1. 3. Karnofsky Performance Status ≥ 80%. 4. Life expectancy at least 3 years. 5. Age ≥ 18 years. 6. A negative pregnancy test (if female of child-bearing potential). 7. Acceptable liver function within 7 days defined as: • Bilirubin ≤ 1.5 times upper limit of normal, and • AST (SGOT), ALT (SGPT), and Alkaline phosphatase ≤ 2.5 times upper limit of normal. 8. Acceptable renal function within 7 days defined as: • Serum creatinine ≤ 1.5 times upper limit of normal, OR • Calculated creatinine clearance ≥ 40 mL/min/1.73 m^2. 9. Acceptable hematologic status within 7 days defined as:

	• Absolute neutrophils count (ANC) ≥ 2,500 cells/mm^3, • Platelet count ≥ 150,000/mm^3, and • Hemoglobin ≥ 10.0 g/dL. 10. Urinalysis showing no clinically significant abnormalities except those attributable to bladder cancer. 11. For men and women of child-producing potential, agreement to use an effective contraceptive method during the treatment period of the study. 12. Signed, written IRB-approved informed consent.
Exclusion Criteria	1. History or previous diagnosis of bladder fibrosis. 2. Total bladder capacity estimated at cystoscopy to be < 150 mL. 3. Urinary incontinence of a severity that would compromise the ability of the patient to retain the study drug intravesical instillation for two hours. 4. Severe irritative voiding symptoms such as urgency, frequency, or nocturia. 5. Known other malignant disease except squamous or basal cell skin cancer unless the malignancy has been in complete remission off therapy for at least 5 years. 6. Major surgery, other than TURBT and diagnostic surgery, within 28 days prior to Day 1/Week 1. 7. Active, uncontrolled bacterial, viral, or fungal infections, including urinary tract infection. 8. Treatment with radiation therapy, surgery, chemotherapy, or investigational therapy within one (1) month prior to Day 1/Week 1 on study (two [2] months for nitroureas or MMC), unless given as standard treatment for bladder cancer and provided that patient is free of all treatment-related toxicities as of Day 1/Week 1. 9. Known infection with HIV. 10. Known active infection with hepatitis B or hepatitis C. 11. Serious disease (e.g., hydronephrosis, liver failure, or other conditions) that could compromise protocol objectives in the opinion of the Investigator and/or the Sponsor (Halozyme). 12. History of a hypersensitivity or idiosyncratic reaction to, or other contraindication to, mitomycin. 13. Known allergy to bee or vespid venom. 14. Known coagulation disorder or bleeding tendency. 15. Treatment with heparin or anticipation of heparin treatment during the treatment period in this study. 16. Unwillingness or inability to comply with procedures required in this protocol.

Therapy Prohibited During Study	The following therapies are prohibited from the time of enrollment through Week 12 of the study: • treatment with heparin, • any intravesical therapy except for MMC and Chemophase, and • any potentially myelosuppressive therapy. For the MTD patients who are receiving continued study drug treatments after Week 12, the following therapies are prohibited for the duration for study drug treatment: • any intravesical therapy except for MMC and Chemophase, and • any potentially myelosuppressive therapy.
Pre-Study, Standard of Care, Procedures	• Transurethral resection of bladder tumors (TURBT), with cystoscopy and estimate of bladder capacity • Intravesical standard of care therapy, if indicated • Histopathology report
Safety and Efficacy Assessments	• Signed informed consent • Karnofsky performance status • Complete medical history • Detailed urologic history • Physical examination • Vital signs • Concomitant medication assessment • Pregnancy test (women of child-bearing potential) • CBC with differential • Clinical chemistries • Urinalysis and urine dipstick evaluation • Urine biomarkers (NMP22®BladderChek® Test and UroVysion™) • Electrocardiogram, 12-lead • Adverse event collection/toxicity assessment • Blood collection for assay of levels of MMC and rHuPH20, and neutralizing antibodies to rHuPH20 • Cystoscopy, with estimate of bladder capacity, urine cytology • Long-term follow-up disease monitoring

Data Analysis	This is a Phase I-IIa study of Chemophase in humans, and is not powered for formal statistical comparisons. The sample size of 3 to 6 patients per dose cohort is standard for the determination of safety and tolerability in many initial clinical trials for oncology indications. Once the MTD has been established, 6 additional evaluable patients will be enrolled at the MTD dose level, yielding a total of 12 evaluable patients at MTD upon which to confirm safety and tolerability of the MTD regimen. It is believed that 12 patients will provide an adequate sample size to establish the tolerability of this dose regimen for subsequent clinical trials and possibly provide a preliminary estimate of anti-tumor activity. The primary endpoint in this study is the rate of toxicities observed with the combination of Chemophase and MMC. The primary statistical analysis will consist of point estimates and the 95% confidence intervals constructed around the point estimates. All safety data will be examined, such as adverse events (including overall incidence by treatment group), physical examination findings and vital signs, laboratory data, plasma MMC concentration, and ECGs. Descriptive statistics will be used to summarize all safety variables. The MTD will be determined based on DLTs. Based on the long-term follow-up monitoring, the data will be assessed for the median time to tumor recurrence, and the one-year, two-year, etc. rate of recurrence. Recurrences will be characterized with regard to the number of tumors, TNM stage, and grading. Information on tumor progression will be summarized. The data collected on the urine biomarker, comparing baseline to Week 8 values, will be summarized.
PK Assessments	Blood samples for assay of rHuPH20 (Weeks 2 & 6: predose and 1, 2, and 3 hrs postdose), MMC (Weeks 1, 2, 5 & 6: predose and 1, 2, and 3 hrs postdose) and neutralizing antibodies to rHuPH20 (Weeks 1 & 6; will only analyze Week 1 if Week 6 assay is positive).

2. STUDY SCHEDULE OF EVENTS

Schedule of Events for All Patients

Except After Week 12 for Those Patients Treated at Maximum Tolerated Dose (MTD) – See Supplemental Schedule of Events

										Until Tumor Recurrence
Week		**1**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**Q 3 Months (starting 3 mos. after last treatment) for 2 yrs from Day 1**
Day	**-28 to Day -1**	**1**	**8**	**15**	**22**	**29**	**36**	**50**		
	SCREEN	**TREATMENT**						**POSTTX**		**LONG-TERM FOLLOW-UP**
Procedures Prior to Screening[1]										
TURBT[1,2]	X									
Standard of care, possible intravesical[1] treatment at option of Investigator	X									
Histopathology report[1]	X									
Screening and Post-Screening Procedures										
Signed informed consent	X									
Karnofsky performance status	X	X	X	X	X	X	X	X	X	
Complete medical history	X									
Detailed urologic history	X									
Complete physical exam	X							X		
Interim Hx & targeted physical exam		X	X	X	X	X	X		X	
Vital signs	X	X	X	X	X	X	X	X	X	
Cystoscopy/Urine cytology[3]	X[3]								X[3]	
Pregnancy test[4]	X[4]							X[4]		
CBC with differential	X[5]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X	X	
Clinical chemistries[7]	X[5]	X	X	X	X	X	X	X	X	
Urinalysis	X[5]	X	X	X	X	X	X	X	X	
Urine dipstick evaluation[8]		X[8]	X[8]	X[8]	X[8]	X[8]	X[8]			
Urine biomarkers[9]		X[9]						X[9]		
Electrocardiogram, 12-lead	X[10]							X		
Blood collection for PK and antibodies[11]		X[11]	X[11]			X[11]	X[11]			
Intravesical MMC alone		X								
Intravesical MMC with Chemophase			X	X	X	X	X			
Adverse events/Toxicity assessment		X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	
Long-term disease monitoring[12]										X[12]

See next page for footnotes.

1. Required prior to any protocol-specified activities and before consenting patient for screening.
2. TURBT, along with cystoscopy and estimate of bladder capacity performed within Day -42 to Day -1 (i.e., TURBT must be done no more than 42 days prior to Day 1)
3. Bladder capacity will be estimated at the time of cystoscopy. For the baseline study prior to Day 1, the cystoscopy performed at the time of TURBT is acceptable. There must be a urine cytology for Screening collected more than 5 days after the TURBT and within two weeks prior to the date of enrollment in this study.
4. In women of child-bearing potential.
5. CBC, chemistries and urinalysis must be performed within 7 days prior to Day 1, Week 1.
6. CBC at these Week 1 through Week 6 visits must be performed and results known prior to each study drug administration
7. Clinical chemistries consist of sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, calcium, glucose, albumin, total protein, uric acid, phosphorus, AST, ALT, alkaline phosphatase, GGT, total bilirubin, and creatine kinase.
8. Results of urine dipstick showing no evidence of urinary tract infection must be known prior to each study drug administration.
9. Urine biomarkers consisting of the NMP22® BladderChek® Test performed in clinic on a urine specimen obtained between midnight and noon, and collected more than 5 days after cystoscopy/TURBT, and UroVysion™ sample collected in clinic and sent to central vendor for analysis.
10. 12-Lead ECG up to 42 days prior to Day 1; preoperative ECG obtained for TURBT is acceptable.
11. Blood samples sent to vendor lab for immediate processing; assays for rHuPH20 (Wks 2 & 6: predose and 1, 2, and 3 hrs postdose), MMC (Wks 1, 2, 5 & 6: predose and 1, 2, and 3 hrs postdose) and neutralizing antibodies (Wks 1 & 6; will only analyze Wk 1 if Wk 6 assay is positive).
12. Includes information collected by telephone survey (or at clinic visit) on any cystoscopy, urine cytology, bladder biopsy, tumor recurrence, and treatment administered for bladder cancer.

Note: Weekly visits are expected to occur at 7-day intervals, +/- 3 days, counting from Day 1, Week 1.

Note: For the purpose of this study, tumor recurrence is defined as a biopsy that histologically confirms the recurrence of bladder carcinoma.

Supplemental Schedule of Events for After Week 12 for Only Those Patients Treated at Maximum Tolerated Dose (MTD)
(Follow Schedule of Events for All Patients through Week 12. Activities Specific to MTD Patients are Designated by "MTD")

	Until Tumor Recurrence	
Week / **Day**	**Q 3 Months (starting 3 mos. after last treatment) for 2 yrs from Day 1**	**6 Weeks before each Q 3 Month Visit**
	LONG-TERM THERAPY AND FOLLOW-UP	
TURBT[1,2]		
Standard of care, possible intravesical[1] treatment at option of Investigator		
Histopathology report[1]		
Signed informed consent		
Karnofsky performance status		
Complete medical history		
Detailed urologic history		
Complete physical exam		
Interim Hx & targeted physical exam	**MTD**	
Vital signs	**MTD**	
Cystoscopy/Urine cytology[5]	**MTD**	
Pregnancy test[4]		
CBC with differential	**MTD**	
Clinical chemistries[7]		
Urinalysis		
Urine dipstick evaluation[8]	**MTD**[8]	
Urine biomarkers[9]		**MTD**
Electrocardiogram, 12-lead		
Blood collection for PK and antibodies[11]		
Intravesical MMC alone		
Intravesical MMC with Chemophase	**MTD**	
Adverse events/Toxicity assessment	**MTD**	
Concomitant medications	**MTD**	
Long-term disease monitoring[12]	**X**[12]	

See previous page for footnotes.

3. GLOSSARY AND ABBREVIATIONS

Abbreviations	Term
AE	Adverse event
AJCC	American Joint Committee on Cancer
ALT	Alanine transaminase (SGPT)
ANC	Absolute neutrophil count
API	Active pharmaceutical ingredient
AST	Aspartate transaminase (SGOT)
AUA	American Urological Association
BCG	Bacillus Calmette-Guérin
BUN	Blood urea nitrogen
CAP	College of American Pathologists
CAS Registry	Chemical Abstracts Service Registry
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CRF	Case report form
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
EC	Ethics Committee
ECG	Electrocardiogram
FDA	Food and Drug Administration
FISH	Florescence in situ hybridization
GCP	Good Clinical Practice
GGT	Gamma glutamyltransferase
GPI	Glycosyl-phosphatidylinositol
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IC50	Inhibition Concentration 50%
ICF	Informed consent form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ITT	Intent-to-treat
MedDRA	Medical Dictionary of Regulatory Activities
mg	Milligram
mL	Milliliter
MMC	Mitomycin C, Mitomycin
MTD	Maximum tolerated dose
NAB	Neutralizing antibody
NCI	National Cancer Institute
NMP	Nuclear matrix protein
PHI	Protected Health Information
PK	Pharmacokinetic
RBC	Red blood cells
rHuPH20	Recombinant human hyaluronidase
SAE	Serious adverse event
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvate transaminase (ALT)

SOC	System Organ Class
SPC	Summary of Product Characteristics
T24	T24 human bladder cancer cell line
TNM	Tumor Node Metastasis
TURBT	Transurethral resection of bladder tumor
ULN	Upper limit of the normal range
USAN	United States Adoptive Name
WBC	White blood cells
U.S.	United States

4. BACKGROUND AND RATIONALE

4.1. Introduction to Hyaluronidases, rHuPH20, and Chemophase™

Mammalian hyaluronidase preparations differing in source, species, and manufacturing process have been the subject of multiple investigations and regulatory approvals in Europe, the United States, and Asia. The extent of human administration of these products in the U.S. has been estimated to be in the tens of millions of patients. Additionally, patients have been treated with other regulatory-approved preparations of hyaluronidase in Europe and Asia. Collectively, this usage spans more than 50 years of clinical history in humans.

The U.S. Food and Drug Administration (FDA) contracted a review of the efficacy and safety of several hyaluronidase drug products through a program known as the Drug Efficacy Study Implementation (DESI). The studies were conducted by the National Academy of Sciences and the National Research Council. The DESI review findings published in the Federal Register (September 23, 1970; 35(185):14800-1) established that hyaluronidase injection was "effective" for the following indications:

> *For use as an adjunct to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; as an adjunct in subcutaneous urography; for improving the resorption of radiopaque agents.*

The DESI review also concluded that hyaluronidase was "probably effective" for the following indications:

> *As an aid in retrobulbar and cone injection infiltrative anesthesia in ocular surgery; as an adjunct in reducing painful swelling by resorption of locally accumulated fluid; for hastening the onset of action and diffuseability of local anesthetics; in minimizing tumefaction during surgery; and for reducing postoperative edema and ecchymosis.*

The hyaluronidase drugs included in the DESI reviews included injectable hyaluronidase preparation derived from bovine testes. Replacing animal-derived slaughterhouse products with recombinant human biotechnology-developed materials potentially alleviates risks associated with animal pathogens, transmissible spongiform encephalopathies, and allergy and immunogenicity to foreign proteins.

Chemophase™ is a formulation that contains a highly purified human hyaluronidase, rHuPH20, which is a glycoprotein enzyme generated by recombinant DNA technology. PH20 is a neutral pH-active hyaluronidase enzyme that degrades hyaluronan under physiologic conditions, but is normally locked on the plasma membrane through a glycosyl-phosphatidylinositol (GPI) moiety anchor. Therefore, Halozyme developed a recombinant soluble GPI-anchor deletion mutant form of the human PH20 hyaluronidase (rHuPH20) that, in non-human primates, does not elicit gross or histologic toxicity, neutralizing antibodies, or inflammatory responses at the site of injection across a three-log therapeutic dose range.

rHuPH20is a 447-amino acid single chain polypeptide with N-linked and O-linked glycan structures. rHuPH20is synthesized in Chinese hamster ovary (CHO) cells that have been transfected with a plasmid containing the DNA sequence encoding the GPI-anchor deleted human PH20 hyaluronidase. The protein is purified through a series of chromatographic steps that results in a purified protein with high specific activity. rHuPH20 is up to 100-times more pure than slaughterhouse-derived hyaluronidases based on specific activity. rHuPH20 degrades hyaluronan by hydrolysis of the β-1,4 linkage between the C1 position of N-acetyl glucosamine and the C4 position of glucuronic acid.

4.2. Background on Non-Muscular-Invasive Bladder Carcinoma

Non-muscular-invasive transitional bladder carcinomas are those tumors that have not infiltrated beyond the lamina propria, and consist of American Joint Committee on Cancer (AJCC) TNM classifications Ta (non-invasive papillary tumor confined to the urothelium), T1 (tumor penetrating the below the basement membrane and infiltrating the lamina propria subepithelial connective tissue), and Tis (Cis, carcinoma in situ, “flat tumor”) (see Appendix A). The histology of bladder carcinoma is often characterized as Grade 1 (low, or well differentiated), Grade 2 (intermediate, or moderately differentiated), and Grade 3 (high, or poorly differentiated).

Non-muscular-invasive bladder carcinoma has a high rate of tumor recurrence within the bladder, which requires repetition of surgery and medical therapy. The rate of recurrence of superficial (non-muscular-invasive) bladder cancer is reported to range from 40% to 85% [1]. The FDA’s Oncology Drugs Advisory Committee concluded in 1988 that as a general rule, over 50% of recurring patients will have recurrence within the first year [2]. The American Urologic Association (AUA) Bladder Cancer Guidelines Panel concluded in 1999 that intravesical treatment-related reductions in the probability of recurrence were detected within the first year of observation in most studies and the observed reductions were carried forward into subsequent years [3]. With tumor recurrence comes an increased risk of tumor progression and the possibility of medical/surgical treatment complications and anesthesia complications and their effect on the patient’s quality of life.

Most non-muscular-invasive bladder cancers are initially treated with transurethral surgical resection of the bladder tumor (TURBT), and less commonly with fulguration

and/or laser therapy. Following resection, adjuvant intravesical chemotherapy or immunotherapy is commonly used to prevent recurrences and eradicate residual disease. The most commonly administered intravesical therapies are bacillus Calmette-Guérin (BCG) and mitomycin (Mitomycin C, MMC). Other intravesical agents include thiotepa, doxorubicin, epirubicin, valrubicin, and interferon.

Both intravesical BCG and intravesical MMC following TURBT have been shown in randomized clinical trials to statistically reduce the rate of tumor recurrence when compared to TURBT alone [3]. For patients with established bladder cancer of any grade, Stage Ta or T1, with or without Tis, who have not had prior intravesical therapy, the AUA includes a "Guideline" of "Intravesical instillation of either BCG or mitomycin is recommended for treatment of CIS and for treatment after endoscopic removal of T1 tumors and high-grade Ta tumors" [3]. Additionally, the AUA includes an "Option" of "Adjuvant intravesical chemotherapy or immunotherapy is an option for treatment after endoscopic removal of low-grade Ta bladder cancers." Thus, both BCG and MMC have a role in the intravesical therapy of patients. However, there remains a substantial rate to tumor recurrence after intravesical therapy, and therefore an unmet medical need for therapy that is safe and more effective in preventing tumor recurrences and also tumor progression.

BCG is widely used for intravesical immunotherapy, and has become first-line treatment for Stage Tis. The most serious side effect of BCG is sepsis, and the most common side effects are cystitis and hematuria. BCG may cause irritative voiding symptoms in about two-thirds of patients, and flu-like symptoms/systemic side effects in about one quarter of patients [3].

MMC is a purple antibiotic isolated from the broth of *Streptomyces caespitosus* and was initially investigated as an antibiotic. Later found to selectively inhibit the synthesis of DNA as an alkylating agent, MMC was studied as an anti-tumor agent. The AUA Bladder Cancer Guidelines Panel found that based on randomized clinical trials, intravesical MMC conferred about a 15% reduction in tumor recurrence compared to TURBT alone [3]. Despite the clinical trial data supporting the safety and effectiveness of MMC for bladder carcinoma, MMC has not been approved by the United States FDA for intravesical therapy of bladder cancer. The approved product label in the U.S. (see Appendix C) states that "Mitomycin for Injection is not recommended as single-agent, primary therapy. It has been shown to be useful in the therapy of disseminated adenocarcinoma of the stomach or pancreas in proven combinations with other approved chemotherapeutic agents and as palliative treatment when other modalities have failed." When used to treat bladder carcinoma in the U.S., MMC is typically administered by intravesical instillation at doses of 20 to 40 mg at a concentration of 1-2 mg/ml in a final volume of 20 to 40 ml for a residence time of 1 to 2 hours.

MMC is approved for use in Canada (see Appendix D) and the United Kingdom (see Appendix E) as a single agent "as topical therapy for superficial (no invasion beyond the lamina propria) transitional cell carcinoma of the urinary bladder. Efficacy has been demonstrated both in patients who have had no prior intravesical chemotherapy

and in those who have failed such therapy with thiotepa and other neoplastic agents." The approved dose is 20 to 40 mg in 30 to 60 mL of sterile water given intravesically once weekly for up to eight weeks. Patients are advised to abstain from liquids for 12 hours prior to therapy. The patient is catheterized, the bladder is drained, and MMC is instilled. The solution should be retained for two hours, during which time the patient may rotate positions every 15 minutes to promote maximum area of contact in the bladder. The approved dose in the U.K. for treatment of tumors is 20 to 40 mg dissolved in 20 to 40 [mL, sic] of diluent weekly or three times a week for a total of 20 doses. Mitomycin is also approved in the U.K. for prevention of recurrent superficial bladder tumors, with various doses having been used, including 20 mg in 20 mL of diluent every two weeks and 40 mg in 40 mL of diluent monthly or three monthly.

Myelosuppression is the major dose-limiting toxicity after intravenous MMC administration, and may be cumulative, occurring any time within eight weeks of onset of therapy, often with a late onset at 3 to 4 weeks, with recovery by 8 to 10 weeks. With a moderately high molecular weight of 329 daltons, MMC is not well absorbed through the bladder urothelium and therefore the risk of myelosuppression is very low. Myelosuppression has not been noted with intravesical administration [4]. In 55 patients treated with doses of 20 to 40 mg of MMC by intravesical instillation, serial plasma samples collected during and 30 minutes after therapy contained no detectable MMC at an assay limit of 10 to 100 ng/mL [5]. Based on data from intravenous administration, a serum MMC concentration of 400 ng/mL has been cited as predictive of myelosuppression [6]. Dalton et al. studied the pharmacokinetics of MMC in 10 patients after TURBT given six weekly instillations of 20 mg MMC in 40 mL water and found that at the first cycle (Treatment 1), maximal plasma concentrations of MMC during and up to four hours after instillation averaged 43 ng/mL (range 2.1 to 180.5 ng/mL) [7]. The concentrations measured at the subsequent Treatments 2, 4, and 6 were at least four-fold lower than those in Treatment 1 and in most cases were below the detection limit of 0.5 ng/mL. Thus, plasma levels were well below the 400 ng/mL level known to be predictive of myelosuppression, and MMC absorption in subsequent treatments was less than during the first treatment.

Intravesical MMC may cause irritative voiding symptoms (e.g., dysuria, frequency/nocturia) in about 35% to 42% of patients, hematuria in about 16%, and skin rash in about 13% as the most common side effects [3]. Bladder fibrosis with a reduction in bladder capacity is an uncommon but known complication of generally long-term intravesical MMC therapy, the incidence of which appears to correlate directly with the cumulative MMC dose and correlate inversely with the time interval between a second tumor resection and the first MMC instillation [8].

4.3. Rationale for Use of Chemophase in Bladder Cancer

Chemophase (recombinant human hyaluronidase, rHuPH20) is being developed as a novel chemoadjuvant to enhance the delivery of chemotherapy to tumors in patients with various solid tumor malignancies (e.g., bladder, breast, colon, lung, and prostate) that accumulate hyaluronan (also known as hyaluronic acid). Clinical trials of animal-derived,

bovine hyaluronidase PH20 in hundreds of patients have shown promise in enhancing chemotherapy regimens using adjunctive hyaluronidase in previously chemo-refractory patients. However, the animal-derived hyaluronidases have been impaired by immunologic limitations upon repeat administration.

Chemophase (recombinant human hyaluronidase) Solution for Intravesical Instillation is being specifically developed for use as an adjuvant with MMC in non-muscular-invasive bladder carcinoma following TURBT. It is envisioned that the Chemophase product would be administered with MMC as an adjuvant to increase the local penetration of MMC into residual malignant disease following TURBT. By reducing tumor recurrence rates, Chemophase adjuvant therapy with MMC could provide clinical benefit for patients by limiting repeated surgical resections and possible complications from medical and surgical treatment and anesthesia. Furthermore, reduced recurrence rates may conceivably limit the progression of disease such that the need for cystectomy or systemic chemotherapy may be delayed or eliminated.

Nonclinical pharmacology studies have shown that rHuPH20 enhances the dispersion of co-administered molecules up to 200 nm in diameter in a dose-dependent fashion, decreasing in relation to the increasing size of co-administered molecules, and rHuPH20 increases hydraulic conductivity more than ten-fold. Application of rHuPH20 to T24 human bladder tumor cells in vitro effectively removes pericellular hyaluronan and allows direct contact with tumor cell membranes, an effect confirmed to be due to degradation of hyaluronan, which rapidly regenerated upon removal of rHuPH20 from the culture media. Incubation with rHuPH20 dramatically increased the doxorubicin penetration into T24 bladder cancer multicellular tumor spheroid cores. rHuPH20 induced a dose-dependent, up to 2.5-fold change in the IC50 for MMC in T24 bladder cancer cell monolayers, and a 7.8-fold change in IC50 for spheroids, thereby increasing the sensitization of bladder tumor aggregates to MMC by increasing the penetration into the inner cellular layers.

Application of rHuPH20 to human osteosarcoma orthotopic xenograft models resulted in a significant reduction in tumor interstitial fluid pressure within one hour of administration. As increased interstitial fluid pressure is a key factor limiting bulk fluid flow in solid tumors, it is reasonable to conclude that rHuPH20 warrants testing as an adjunct to chemotherapy agents to increase the therapeutic index of those agents.

Three nonclinical toxicology studies have been conducted to assess the toxicity of co-administration of rHuPH20 with MMC. A GLP study in 60 rats of the acute intravenous administration of MMC and rHuPH20 found transient slight decreases in the weight in female animals receiving rHuPH20, but no overt toxicity following the administration of rHuPH20 alone or in combination with MMC at any dose level. A GLP study in 60 rats of the local tolerance of repeated exposure to intravesical MMC and rHuPH20 found that six weekly intravesical instillations of rHuPH20 alone at 6,000 units and MMC 0.4 mg (2 mg/mL) combined with rHuPH20 at dose levels of 0, 60, 600, and 6,000 units were well tolerated and no toxicity was observed. A GLP study in 48 New Zealand white rabbits of the tolerance of a single intravesical instillation of MMC

(8 mg/animal) and rHuPH20 (4,000, 40,000 and 160,000 units/animal) found the study drug treatment well-tolerated without evidence of test article-related toxicity. In addition, a GLP study in six rhesus monkeys of the local tolerance of repeated exposure to intravesical rHuPH20 alone (without MMC) found no toxicity.

As an adjuvant to intravesically administered MMC, animal-derived, bovine hyaluronidase has been previously studied in clinical trials in at least 43 patients with bladder carcinoma. The rationale for the adjuvant use of PH20 in this setting is that the pharmacologic activity of hyaluronidase as a spreading agent could increase the penetration of MMC into residual hyaluronan-rich bladder tumors, thereby increasing the effectiveness of MMC in killing residual malignant cells and reducing the risk of tumor recurrence.

In 1986, Maier and Baumgartner published a series of 20 patients undergoing TURBT or multiple transurethral biopsies receiving a single dose of 20 mg intravesical MMC in 20 mL distilled water, 10 of whom received intravesical bovine hyaluronidase 200,000 units added to the dissolved MMC [9]. Serum levels of MMC were assayed at 30 and 60 minutes after instillation and found to range from < 1 to 31.5 ng/mL. The systemic absorption of MMC was not affected by hyaluronidase. The mean MMC concentrations at 30 minutes were 14.2 ± 8.4 ng/mL for MMC alone and 13.4 ± 6.5 ng/mL for MMC with hyaluronidase. The respective mean concentrations at 60 minutes were 10.9 ± 7.1 ng/mL and 10.0 ± 6.4 ng/mL. The highest serum level overall, 31.5 ng/mL, was measured in a patient not given hyaluronidase. Thus, MMC concentrations in this study remained below one tenth of 400 ng/mL, the critical systemic level that is believed to be predictive of myelosuppression [6]. This study concluded that hyaluronidase at a dose of 200,000 units does not enhance the systemic absorption of MMC given as a perioperative intravesical instillation.

In 1989, Maier and Baumgartner published a larger, double-blind, randomized trial of 56 patients who had undergone TURBT and were randomized equally to multiple doses of either intravesical MMC 20 mg in 20 mL or the same dose of MMC plus 200,000 units of bovine hyaluronidase [10]. Twenty patients were Stage Ta, 27 were T1, and nine were T2. Twenty-nine patients were Grade 1, 22 were Grade 2, and five were Grade 3. Thirty-one patients were treated for primary tumors and 25 for recurrences. The treatment groups were comparable statistically. Intravesical instillations were started approximately one week after TURBT and given every two weeks for the first six months, followed by every four weeks until the end of two years (total of about 30 instillations per patient). Cystoscopy with lavage cytology follow-up was scheduled every three months for the first two years, and then biannually thereafter.

Of the 28 patients treated with MMC alone (who received a total of 788 instillations), five (17.8%) had side effects, including four with cystitis and one with skin rash. Of the 28 patients treated with MMC and hyaluronidase (who received a total of 750 instillations), four (14.2%) had side effects, including three with cystitis and one with skin rash. There was no significant alteration in white blood count during therapy.

A total of 32.1% (9/28) of MMC monotherapy patients had recurrent tumors over a median observation period of 21.1 months, compared to 7.1% (2/28) of MMC plus hyaluronidase patients over a median observation of 20.2 months ($p < 0.05$). The nine tumor recurrences in the MMC monotherapy group were detected at a mean of 11 months (range 6 to 24 months) compared to a mean of 13 months (6 and 20 months) for the two recurrences for MMC plus hyaluronidase. The nine MMC monotherapy recurrences were the same stage and grade as the primary tumor for four patients, downstaged for three, and upstaged for two. Both recurrences in the MMC plus hyaluronidase group were downstaged. This study, which consisted of a large number of exposures (about 30 per patient) over a relatively long duration (two years), concluded a significant additive benefit of hyaluronidase when given with MMC for the prevention of recurrent bladder tumors without an increase in adverse effects.

In 1992, Hobarth, Maier and Marberger published long-term follow-up of 43 patients undergoing TURBT of Ta-T1 bladder tumors treated with intravesical bovine hyaluronidase plus MMC [11]. Twenty-four patients were Stage T1 and 19 were Stage Ta. Twenty-eight patients were Grade 1, 14 were Grade 2, and one was Grade 3. Thirty-seven patients had primary tumors and six had recurrent tumors. Beginning approximately one week after TURBT, these patients received 200,000 units of hyaluronidase along with 20 mg of MMC intravesically every two weeks for six months, then every four weeks until the end of two years. The tumor recurrence rate was 25% (11/43) over a mean follow-up of 48.5 months (range 42 to 66 months). These data compared favorably to a retrospective study of 63 comparable patients who demonstrated a tumor recurrence rate of 52.5% during and after two years of intravesical MMC monotherapy. Side effect of the combination therapy were observed in a total of 14% (6/43) of patients, and consisted of bacterial cystitis (6.9%), chemocystitis (4.6%), and skin allergy (2.3%). No patients were withdrawn due to side effects. This study concluded that the considerable reduction in tumor recurrence rate observed with hyaluronidase plus MMC compared to that seen after MMC monotherapy and the absence of any evidence of an increase in local side effects justify the application of hyaluronidase in this clinical setting. The authors postulated that, like other tumor cells, malignant transitional urothelial cells might be surrounded by a halo of hyaluronan, and destruction of this protective halo by hyaluronidase would explain the local enhancement of the anti-tumor effect of MMC.

A Phase I safety, tolerability, and PK single-administration clinical trial (HZ2-05-02) of a low dose (20,000 units) of Chemophase with 40 mg MMC administered intravesically in a targeted sample size of five evaluable patients who had undergone transurethral resection of bladder tumor (TURBT) for transitional cell bladder cancer Stage Ta, T1 or Tis (any grade), were free of known bladder cancer recurrence, and were being monitored for recurrence of superficial transitional cell bladder cancer was initiated in August 2005 and completed enrollment on 2 March 2006. All five patients completed the study. There were no deaths, serious AEs, AEs judged to be possibly or more related to either study drug, moderate or severe AEs, premature withdrawals, or dose-limiting toxicities. The only three AEs reported in the study were, by MedDRA Preferred Terms, Influenza, Urinary tract infection, and Acne. All plasma samples for MMC were below the lower

limit of quantitation (10 ng/mL) and all plasma samples of PH20 were below the lower limit of quantitation (10 U/mL).

In summary, the previous human experience with bovine hyaluronidase administered as an adjunct to intravesical MMC collectively in at least 43 patients, based on two clinical trials and a larger sample size follow-up publication, demonstrated no increase in toxicity and no increase in systemic absorption of MMC, but did show a statistically significant and clinically meaningful benefit in the prevention of tumor recurrences. The bovine hyaluronidase studies are important in establishing the anticipated safety and efficacy of the investigation of Chemophase as an adjunct in the treatment of bladder cancer. The nonclinical data for rHuPH20 in various tumor models including the T24 human bladder cancer cell line and the tolerability of co-administered rHuPH20 with mitomycin in two animal species (rats and rabbits) provide additional support for the study of Chemophase as an adjunct to the treatment of bladder carcinoma. Taken together, the nonclinical findings for rHuPH20 and the human clinical trial data for bovine hyaluronidase support the rationale for the anticipated safety and the potential efficacy of Chemophase administered intravesically along with MMC for non-muscular-invasive bladder carcinoma.

5. STUDY OBJECTIVES

5.1. Primary Objectives

- Determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of escalating doses of Chemophase in combination with mitomycin (Mitomycin C, MMC) administered as weekly intravesical instillations for five weeks.

- Establish the dose of Chemophase with MMC recommended for future studies.

5.2. Secondary Objectives

- Assess the pharmacokinetics of intravesical administration of MMC alone and in combination with intravesical administration of Chemophase.

- For those patients treated at the MTD, assess the safety and tolerability of intravesical administration of MMC with Chemophase over up to 7 additional maintenance treatments every 3 months following the initial six weekly instillations.

- Observe patients for any preliminary evidence of anti-tumor activity of MMC and Chemophase when combined.

6. STUDY DESIGN

6.1. Overview of Study Design

This is a Phase I-IIa multiple dose study of intravesical treatment with the combination of Chemophase and MMC. All patients will receive six weekly intravesical instillations of chemotherapy. The 12 patients treated at MTD will continue to receive combination therapy every three months until the end of Year 2 from Day 1 or until the time of documented tumor recurrence, whichever occurs first. For the purpose of this study, tumor recurrence is defined as a biopsy that histologically confirms the recurrence of bladder carcinoma.

All patients will be assigned to a single dose cohort, and the escalating dose cohorts will be enrolled sequentially after the safety and tolerability of the immediately preceding cohort has been ascertained.

On Day 1 of Week 1, all patients in all cohorts (Cohorts 1 through 5) will receive MMC 40 mg/20 mL monotherapy via intravesical administration. In Weeks 2 through 6, patients will receive weekly intravesical administrations of a combination of MMC and Chemophase, in cohorts with escalating doses of Chemophase while the MMC dose remains constant at 40 mg/20 mL (see **Table 6.1-A**).

Table 6.1-A. Dose Cohorts

Cohort	Week 1 Dosing	Weekly Dosing Week 2 through Week 6
1	MMC 40 mg/20 mL	20,000 U Chemophase followed by MMC 40 mg/20 mL
2	MMC 40 mg/20 mL	60,000 U Chemophase followed by MMC 40 mg/20 mL
3	MMC 40 mg/20 mL	200,000 U Chemophase followed by MMC 40 mg/20 mL
4	MMC 40 mg/20 mL	400,000 U Chemophase followed by MMC 40 mg/20 mL
5	MMC 40 mg/20 mL	800,000 U Chemophase followed by MMC 40 mg/20 mL

Post-treatment evaluations will be performed at Weeks 8 and 12. The 12 patients treated at MTD will continue to receive combination therapy every three months until the end of Year 2 from Day 1 or until the time of documented tumor recurrence, whichever occurs first. For all patients, long-term follow-up after Week 12 will consist of disease monitoring of patients by telephone (or at clinic visits for those patients still being treated at MTD) and will be performed every three months beginning three months after the last study treatment for two years and then every six months thereafter until the time of bladder tumor recurrence.

6.2. Number of Patients

Up to 36 evaluable patients will be enrolled in this study. It is anticipated that no more than a total of 44 patients will need to be enrolled to achieve this number of evaluable patients. Groups of either 3 or 6 patients will participate in each of the five individual dose cohorts in the dose escalation phase of the study. Once the MTD has been established (see Section 8.9), 6 additional evaluable patients will be enrolled at the MTD dose level, yielding a total of 12 evaluable patients at MTD upon which to confirm safety and tolerability of the MTD regimen.

An evaluable patient is one who:

- has received all protocol-specified six weekly intravesical treatments with at least a 90-minute retention, and
- has had MMC plasma concentration determinations and safety assessments adequate for the determination of safety and tolerability.

Each patient not meeting all these criteria for evaluability, including patients withdrawn prematurely for reasons other than toxicity, will be replaced by the enrollment of an additional patient.

6.3. Patient Recruitment

Patients will be recruited by each Investigator at each study center from their private practice, their institution or through referrals. Prior to consenting/enrolling patients, the Investigator will obtain Institutional Review Board (IRB) review and approval of the clinical investigation, including this protocol accompanied by the Investigator's Brochure (IB), the informed consent form, and any material provided to patients and any other advertising for study patients.

Prior to patient screening and enrollment in this study, all patients must have had transurethral resection of bladder tumor(s) (TURBT) according to standard of care within 42 days prior to Day 1/ Week 1, followed by intravesical standard of care under the judgment of the patient's physician and subsequent histopathology report following TURBT, which will be used to determine if the prospective patient meets the bladder carcinoma staging and grading eligibility criteria for this study.

A Screening Log must be maintained at each site documenting all patients screened for participation in this study and noting reasons for non-enrollment and/or ineligibility.

6.4. Treatment Summary

This study will involve one (1) intravesical dose of MMC followed by five (5) subsequent weekly intravesical dose administrations of a combination of a fixed dose of MMC preceded by the dose of Chemophase defined by the assigned dose cohort. The 12 patients treated at MTD will continue to receive combination therapy every three months until the end of Year 2 from Day 1 or until the time of documented tumor recurrence, whichever occurs first.

In each cohort, at Week 1 patients will receive MMC 40 mg alone (without Chemophase) in 20 mL of sterile water. If no dose-limiting toxicity (DLT, see Section 8.8) is observed during the course of this and subsequent study drug treatments, this first treatment will be followed by five weekly intravesical instillations (at Weeks 2 through 6) of Chemophase at the dose specified by the assigned cohort followed by MMC 40 mg in 20 mL of sterile water.

All 3 patients within a given cohort may begin treatment simultaneously. The next higher dose cohort can be immediately opened for patient enrollment if, at the time all 3 patients in a given cohort have completed the fourth (4^{th}) instillation of MMC (i.e., third instillation of MMC plus Chemophase), there is:

- no NCI CTC adverse event Grade 2 or higher toxicity,
- no MMC plasma concentration ≥ 100 ng/mL, and
- no new, treatment-emergent, diagnosis of bladder fibrosis.

Note that an NCI CTC adverse event Grade 2 toxicity will delay opening the next higher dose cohort to enrollment until safety data are reviewed from all six weekly instillations for all 3 patients in that cohort.

Because this study is being conducted at more than one study center, the enrollment of patients, assignment to cohorts, and opening of each sequential cohort will be controlled centrally for all study centers by Halozyme. Each time a new patient is consented for the study, the study center must immediately fax the updated Screening Log to Halozyme or its designee. In turn, Halozyme or its designee will keep all centers immediately apprised of the number of patients enrolled and patients in screening, so that new patients are not consented if there is no possibility of enrollment because there is no room for additional patients in the ongoing cohort.

At the time a patient has fulfilled all eligibility criteria, the study center must fax a completed Enrollment/Registration Form to Halozyme or its designee, in response to which Halozyme or its designee will provide authorization to dose and confirmation of the dose cohort to which the new patient will be assigned (see Section 8.4).

6.5. Study Duration

Study patients will receive six (6) weekly study treatments (at Weeks 1 through 6) followed by post-treatment evaluations, at Weeks 8 and 12. The 12 patients treated at MTD will continue to receive combination therapy every three months until the end of Year 2 from Day 1 or until the time of documented tumor recurrence, whichever occurs first. For all patients, long-term follow-up after Week 12 will consist of disease monitoring of patients by telephone (or at clinic visits for MTD patients continuing on study drug treatment) and will be performed every three (3) months beginning three months after last study treatment to the end of two years and 29 days following Day 1 or until bladder tumor recurrence, whichever occurs first.

7. STUDY POPULATION

7.1. Inclusion Criteria

Patients must satisfy all of the following inclusion criteria in order to be enrolled in the study.

1. Patients with initial presentation or recurrence of Stage Ta , T1 or Tis, any grade, bladder cancer after TURBT.

2. TURBT within 42 days prior to Day 1/Week 1.

3. Karnofsky Performance Status ≥ 80% (see Appendix B).

4. Life expectancy at least 3 years.

5. Age ≥ 18 years.

6. A negative pregnancy test (if female of child-bearing potential).

7. Acceptable liver function within 7 days defined as:
   - Bilirubin ≤ 1.5 times upper limit of normal, and
   - AST (SGOT), ALT (SGPT), and Alkaline phosphatase ≤ 2.5 times upper limit of normal.

8. Acceptable renal function within 7 days defined as:
   - Serum creatinine ≤ 1.5 times upper limit of normal, OR
   - Calculated creatinine clearance ≥ 40 mL/min/1.73 m^2.

9. Acceptable hematologic status within 7 days defined as:
   - Absolute neutrophils count (ANC) ≥ 2,500 cells/mm^3,
   - Platelet count ≥ 150,000/mm^3, and
   - Hemoglobin ≥ 10.0 g/dL.

10. Urinalysis showing no clinically significant abnormalities except those attributable to bladder cancer.

11. For men and women of child-producing potential, agreement to use an effective contraceptive method during the treatment period of the study.

12. Signed, written IRB-approved informed consent.

7.2. Exclusion Criteria

Patients satisfying any one or more of the following exclusion criteria must not be enrolled in this study.

1. History or previous diagnosis of bladder fibrosis.

2. Total bladder capacity estimated at cystoscopy to be < 150 mL.

3. Urinary incontinence of a severity that would compromise the ability of the patient to retain the study drug intravesical instillation for two hours.

4. Severe irritative voiding symptoms such as urgency, frequency, or nocturia.

5. Known other malignant disease except squamous or basal cell skin cancer unless the malignancy has been in complete remission off therapy for at least 5 years.

6. Major surgery, other than TURBT and diagnostic surgery, within 28 days prior to Day 1/Week 1.

7. Active, uncontrolled bacterial, viral, or fungal infections, including urinary tract infection.

8. Treatment with radiation therapy, surgery, chemotherapy, or investigational therapy within one (1) month prior to Day 1/Week 1 on study (two [2] months for nitroureas or MMC), unless given as standard treatment for bladder cancer and provided that patient is free of all treatment-related toxicities as of Day 1/Week 1.

9. Known infection with HIV.

10. Known active infection with hepatitis B or hepatitis C.

11. Serious disease (e.g., hydronephrosis, liver failure, or other conditions) that could compromise protocol objectives in the opinion of the Investigator and/or the Sponsor (Halozyme).

12. History of a hypersensitivity or idiosyncratic reaction to, or other contraindication to, mitomycin.

13. Known allergy to bee or vespid venom.

14. Known coagulation disorder or bleeding tendency.

15. Treatment with heparin or anticipation of heparin treatment during the treatment period in this study.

16. Unwillingness or inability to comply with procedures required in this protocol.

7.3. Prohibitions and Restrictions during the Study

The following therapies are prohibited from the time of enrollment through Week 12 of the study:

- treatment with heparin,
- any intravesical therapy except for MMC and Chemophase, and
- any potentially myelosuppressive therapy.

For the MTD patients who are receiving continued study drug treatments after Week 12, the following therapies are prohibited for the duration for study drug treatment:

- any intravesical therapy except for MMC and Chemophase, and
- any potentially myelosuppressive therapy.

7.4. Contraindications, Warnings and Precautions with Regard to MMC Administration

The administration of MMC in this protocol is guided in part by the approved product labeling for MMC. MMC is not approved by the United States FDA for intravesical administration but is approved for other indications. For the convenience of the Investigator, a representative U.S. package insert for MMC is provided in Appendix C and a representative Canadian package insert and United Kingdom SPC, which do allow for intravesical administration, may be found in Appendices D and E, respectively. These package inserts and SPC are current as of the date of this protocol version. It is the responsibility of the Investigator to refer to the product label that is current as of the time of treatment and management decisions.

A boxed warning in the U.S. package insert notes that MMC should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available. This boxed warning further provides information about bone marrow suppression contributing to overwhelming infections in an already immunocompromised patient, and about hemolytic uremic syndrome.

According to the U.S. package insert, MMC is contraindicated in patients who have demonstrated a hypersensitive or idiosyncratic reaction to MMC in the past. MMC is also contraindicated in patients with thrombocytopenia, coagulation disorder, or an increase in bleeding tendency due to other causes. The Canadian package insert includes the same contraindications, and adds leukopenia.

Warnings in the U.S. package insert include the need for careful and frequent observation of patients during and after MMC therapy. The U.S. package insert, specific to intravenous administration of MMC, further warns about a high incidence of myelosuppression, the need for regular monitoring of hematologic laboratory parameters, and advising patients of this potential toxicity. Patients receiving MMC should be observed for evidence of renal toxicity, and MMC should not be given to patients with a serum creatinine greater than 1.7 mg/mL. The U.S. package insert further states that bladder fibrosis/contraction has been reported with intravesical administration (not an FDA-approved route of administration), which in rare cases has required cystectomy.

The Canadian package insert adds warnings that MMC is a potent drug and should be used only by physicians experienced with cancer chemotherapeutic drugs. MMC should not be administered to any patient with a white blood cell count below 4,000/mm^3 or a platelet count less than 150,000/mm^3 or to patients with serious infections.

The safety of MMC in pregnant women has not been established, and teratological changes have been noted in animal studies of MMC. It is not known if MMC is found in human breast milk, and it is recommended that women receiving MMC not breastfeed.

The Investigator is referred to the full package insert(s) as the definitive, comprehensive, and most up-to-date guide to the administration of MMC.

8. STUDY METHODS AND PROCEDURES

8.1. Designated Laboratories: Central, Local, PK, and Biomarker Labs

A combination of a central laboratories and laboratories local to each study center will be used in this study. The central laboratories will receive and analyze all samples that are not tied to the need for an immediate evaluation of potential myelosuppression of treated patients. **At each dosing visit, intravesical dosing with study medication(s) must not be done until CBC and differential results are known, and the ANC is confirmed to be ≥ 1,500/mm^3 and the platelet count confirmed to be ≥75,000/mm^3. In addition, at each dosing visit and before any dose of study medication, a urine dipstick must be performed at the study center and the results known to not show evidence of urinary tract infection.**

It is preferable that only one local laboratory be specified and used at each individual study center. The local laboratory will receive and analyze blood drawn for a complete blood count (CBC) and differential on a "stat" basis on Week 1/Day 1, Week 2/Day 8, Week 3/Day 15, Week 4/Day 22, Week 5/Day 29, and Week 6/Day 36. For consistency,

all protocol-specified CBCs will be performed at the local laboratory, including the CBCs at Screening, Week 8 and Week 12.

Samples obtained for pharmacokinetic assays of MMC and rHuPH20and for assessment of antibodies to rHuPH20 will be sent to a separate central laboratory for analysis.

For the urine biomarkers, the NMP22® BladderChek® Test will be performed in clinic and the UroVysion™ test will be obtained in the clinic and sent to a central vendor lab for analysis.

8.2. Procedures Prior to Screening (Day -28 to Day -1)

TURBT(s) must be done on all patients no more than 42 days prior to Day 1/Week 1. Post-operatively, patients are expected to receive standard of care as determined by their physician, which may or may not include intravesical therapy with MMC. The surgical operative notes and the histopathology report (or content of information therein) from the TURBT must be available to the Investigator prior to performing any screening procedures and prior to having any patient sign the informed consent document. Cystoscopy within 42 days prior to Day 1/Week 1 (generally performed at the time of TURBT) accompanied by an estimation of bladder capacity will be used to qualify patients for this study. There must be a urine cytology during Screening collected more than 5 days after the TURBT and within two weeks prior to the date of enrollment in this study.

As noted in Section 2.0, the Schedule of Events for this study, activities taking place prior to consenting the patient (e.g., TURBT with cystoscopy and urine cytology, post-operative standard of care, and histopathology reading and report) are not protocol-specified activities, but are prerequisites before a patient can be consented for this study.

8.3. Screening Procedures (Day -28 to Day -1)

As shown in Section 2.0, Schedule of Events, the following activities are to be completed during this period.

- Verification from source documents (medical record, TURBT notes, cystoscopy notes, histopathology report) that patient meets the disease-defining criteria in Section 7.1, for (1) patient with initial presentation or recurrence of Stage Ta, T1 or Tis, any grade, bladder cancer after TURBT. The specific TNM stage will be recorded.

- Assess for exclusion criteria (see Section 7.2), including but not limited to incontinence, irritative voiding symptoms, history of bladder fibrosis, known other malignant disease, other recent surgery and therapies, active infection, concurrent serious disease, known coagulation disorder, use of or anticipated use of heparin, and willingness and ability to comply with protocol procedures.

- Informed Consent: The Investigator or one of the study staff must explain the study protocol to prospective study patients and have them read and ask questions regarding the informed consent form (ICF). This discussion must include, among other topics, the need for an effective contraception method during the treatment phase if this study. If the patient agrees to participate, they must sign and date the informed consent form and have it witnessed. Each patient must receive a copy of the signed informed consent.

- Karnofsky performance status ≥ 80% (see Appendix B).

- Complete medical history.

- Detailed urologic history. This will include a complete description of the number, estimated size and gross appearance of tumors removed at TURBT; and the area and depth of involvement of the bladder mucosa after TURBT; the anatomic location of the tumor(s); estimated bladder capacity; histopathology; tumor stage and grade; prior history of bladder cancer; etc.

- Complete physical exam.

- Vital signs (blood pressure, heart rate, respiratory rate, oral temperature, height, and weight).

- Concomitant medications. Concomitant medications taken during the time period beginning 28 days prior to initial dosing, on Day 1/Week 1, through the Week 12 assessment (and, for MTD patients continuing on study drug treatment, through the last study drug instillation) will be collected (see Section 10.8).

- Pregnancy test (if patient is female and of child-bearing potential).

- CBC with differential within 7 days of Day 1/Week 1.

- Clinical chemistries within 7 days of Day 1/Week 1. Clinical chemistries consist of sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, calcium, glucose, albumin, total protein, uric acid, phosphorus, AST, ALT, alkaline phosphatase, GGT, total bilirubin, and creatine kinase.

- Urinalysis within 7 days of Day 1/Week 1.

- Electrocardiogram. A 12-lead ECG within 42 days of Day 1/Week 1 must be available. An ECG performed within this timeframe in preparation for the TURBT is acceptable.

- Tests for HIV and hepatitis if there is suspicion or unclear history of infection with HIV or active infection with hepatitis B or hepatitis C. Patient with known

history of infection with HIV or active infection with hepatitis B or hepatitis C are not eligible for enrollment.

8.4. Patient Registration and Replacement of Patients

Because this study is being conducted at more than one study center, the enrollment of patients, assignment to cohorts, and opening of each sequential cohort will be controlled centrally for all study centers by Halozyme. Each time a new patient is consented for the study, the study center must immediately fax the updated Screening Log to Halozyme or its designee. In turn, Halozyme or its designee will keep all centers immediately apprised of the number of patients enrolled and patients in screening, so that new patients are not consented if there is no possibility of enrollment because there is no room for additional patients in the ongoing cohort.

At the time a patient has fulfilled all eligibility criteria (see Sections 7.1 and 7.2) and if there is room for a patient to be enrolled in the study, the study center must fax an updated Enrollment/Registration Form to Halozyme or its designee. Halozyme or its designee will review the information, confirm eligibility, and assign a patient identification number. Patient identification numbers will be set aside for use at each study center. Halozyme or its designee will fax a Registration Form to the clinical study center, providing authorization to dose and confirmation of the dose cohort to which the new patient will be assigned. **The study center must not begin dosing any new patient without this prior Registration Form authorization from Halozyme or its designee**.

A copy of the Screening Log and Enrollment/Registration Forms will be kept on file at Halozyme or its designee and at the study center in the Investigator Files.

If the next patient is to be enrolled as the first patient in a new, higher dose cohort, the procedures discussed in Section 8.9 must be followed.

Patients not meeting all evaluability criteria will be replaced. An evaluable patient is one who:

- has received all protocol-specified six weekly intravesical treatments, and
- has had MMC plasma concentration determinations and safety assessments adequate for the determination of safety and tolerability.

Each patient not meeting all these criteria for evaluability, including patients withdrawn prematurely for reasons other than toxicity, will be replaced by the enrollment of an additional patient. In the event that a patient withdraws from the study prematurely, every effort will be made to document the reason for termination and obtain follow-up safety data.

8.5. Patient Randomization Procedures and Blinding

No randomization or blinding will be involved, as this is an open-label non-randomized study. See Section 7.4 for patient registration procedures.

8.6. Treatment Procedures on Day 1/Week 1

As shown in Section 2.0, Schedule of Events, the following activities are to be completed on this day.

- Verification of all inclusion and exclusion criteria (see Sections 7.1 and 7.2)
- Karnofsky performance status (see Appendix B).
- Interim medical history (this history is for the interim period of time since the medical history previously performed, between Days -28 and Day -1).
- Targeted physical exam (this physical exam is targeted at observations on a review of systems and follow-up of any findings on the previous physical exam).
- Vital signs (blood pressure, pulse, oral temperature, and weight).
- Concomitant medications.
- Predose CBC with differential. The local lab will receive and analyze blood drawn for a CBC and differential on a "stat" basis. **Intravesical dosing with study medication(s) on an individual patient basis on a given treatment day must not be done until CBC and differential results are known and the ANC is confirmed to be ≥ 1,500/mm^3 and the platelet count is ≥75,000/mm^3.**
- Predose clinical chemistries. These blood samples will be drawn at the same time as the CBC and differential. Samples will be sent to the central lab for analysis.
- Predose urinalysis. A urine sample will be obtained from each patient prior to intravesical dosing with study medication and sent to the central lab for analysis.
- Predose urine dipstick analysis. In addition to the full urinalysis at Day 1, a urine dipstick analysis is performed on the day of dosing, and the results must be known with no evidence of urinary tract infection prior to study drug dosing.
- Urine biomarkers for bladder carcinoma. The NMP22® BladderChek® Test will be performed in clinic on a urine specimen obtained between midnight and noon, and collected more than five days after cystoscopy/TURBT. The UroVysion™ test will be obtained in the clinic and sent to a central vendor lab for analysis.

- Intravesical instillation of MMC (see Sections 9.1 and 9.3). All blood and urine samples must be obtained and results for CBC with differential and urine dipstick analysis must be known prior to intravesical dosing of MMC.

- Blood collection for pharmacokinetics (PK) for MMC and for antibodies. Blood samples will be drawn, sent to the appropriate laboratory, and assays performed immediately for MMC PK at the following timepoints: predose, and 1 hour, 2 hours and 3 hours after intravesical instillation of MMC. Blood will be collected predose for assessment of neutralizing antibodies, but will be analyzed only if the Week 6/Day 36 assay for antibodies is positive.

- Adverse events/toxicity assessment. Assessment for AEs will commence after the initial exposure to MMC at this visit, and continue during the study (see Sections 10.1 through 10.6).

8.7. Treatment Procedures Week 2 through Week 6

As shown in Section 2.0, Schedule of Events, the following activities are to be completed on the clinic visit days at each of these weekly visits.

- Karnofsky performance status (see Appendix B).

- Interim medical history (this history is for the interim period of time since the previous medical history).

- Targeted physical exam (this physical exam is targeted at observations on a review of systems and follow-up of any findings on the previous physical exam).

- Vital signs (blood pressure, pulse, oral temperature, and weight).

- Concomitant medications.

- Predose CBC with differential. The local lab will receive and analyze blood drawn for a CBC and differential on a "stat" basis. **Intravesical dosing with study medication(s) on an individual patient basis on a given treatment day must not be done until CBC and differential results are known and the ANC is confirmed to be ≥ 1,500/mm^3 and the platelet count is ≥75,000/mm^3.**

- Predose clinical chemistries. These blood samples will be drawn at the same time as the CBC and differential. Samples will be sent to the central lab for analysis.

- Predose urine dipstick analysis. A urine dipstick analysis is performed on the day of dosing, and the results must be known with no evidence of urinary tract infection prior to study drug dosing.

- Intravesical instillation of MMC with the appropriate dose of Chemophase (see Sections 9.1 through 9.3). All blood and urine samples must be obtained and results for CBC with differential and urine dipstick analysis must be known prior to intravesical dosing of Chemophase and MMC.

- Blood collection for pharmacokinetics (PK) for MMC and rHuPH20 and for antibodies. Blood samples will be drawn, sent to vendor laboratory, and assays performed immediately for MMC and rHuPH20 PK on the following schedule:

  - Week 2/Day 8: Both MMC and rHuPH20 at predose, and 1, 2 and 3 hours postdose after intravesical instillation of MMC.

  - Week 5/Day29: MMC only at predose, and 1, 2 and 3 hours postdose after intravesical instillation of MMC.

  - Week 6/Day 36: Both MMC and rHuPH20 at predose, and 1, 2 and 3 hours postdose after intravesical instillation of MMC.

  - Week 6/Day 36: Blood collected for neutralizing antibodies at 3 hours postdose after intravesical instillation of MMC.

  - The plasma concentration of MMC must be known to be < 100 ng/mL for a given patient prior to the next intravesical dosing of study medications (see **Section 8.8**).

- Adverse events/toxicity assessment (see Sections 10.1 through 10.6).

8.8. Dose-Limiting Toxicity (DLT)

A dose-limiting toxicity (DLT) is defined as any of the following:

- plasma MMC concentration ≥ 100 ng/mL,

- National Cancer Institute (NCI) Common Terminology Criteria (CTC) (Version 3 or current version) adverse event Grade 3 or higher toxicity (see **http://ctep.cancer.gov/reporting/ctc.html**) [12], or

- new, treatment-emergent diagnosis of bladder fibrosis.

8.9. Escalation to Next Dose Cohort, Stopping Rules, and Determination of MTD

In each cohort, at Week 1, patients will receive MMC 40 mg in 20 mL of sterile water alone (without Chemophase). If no dose-limiting toxicities (DLTs) are observed (see Section 8.8) during this and subsequent study drug treatments, this will be followed by five weekly instillations (Week 2 through Week 6) of the specified dose of Chemophase followed by MMC 40 mg in 20 mL as long as no DLTs are observed with the previous instillations.

A flow diagram of the dose escalation schema and stopping rules is provided in Figure 8.9-A. If at any time during the study, 1 of the 3 patients in a given cohort experiences a DLT, an additional 3 patients will be enrolled in that same cohort before consideration of enrolling the next higher dose cohort.

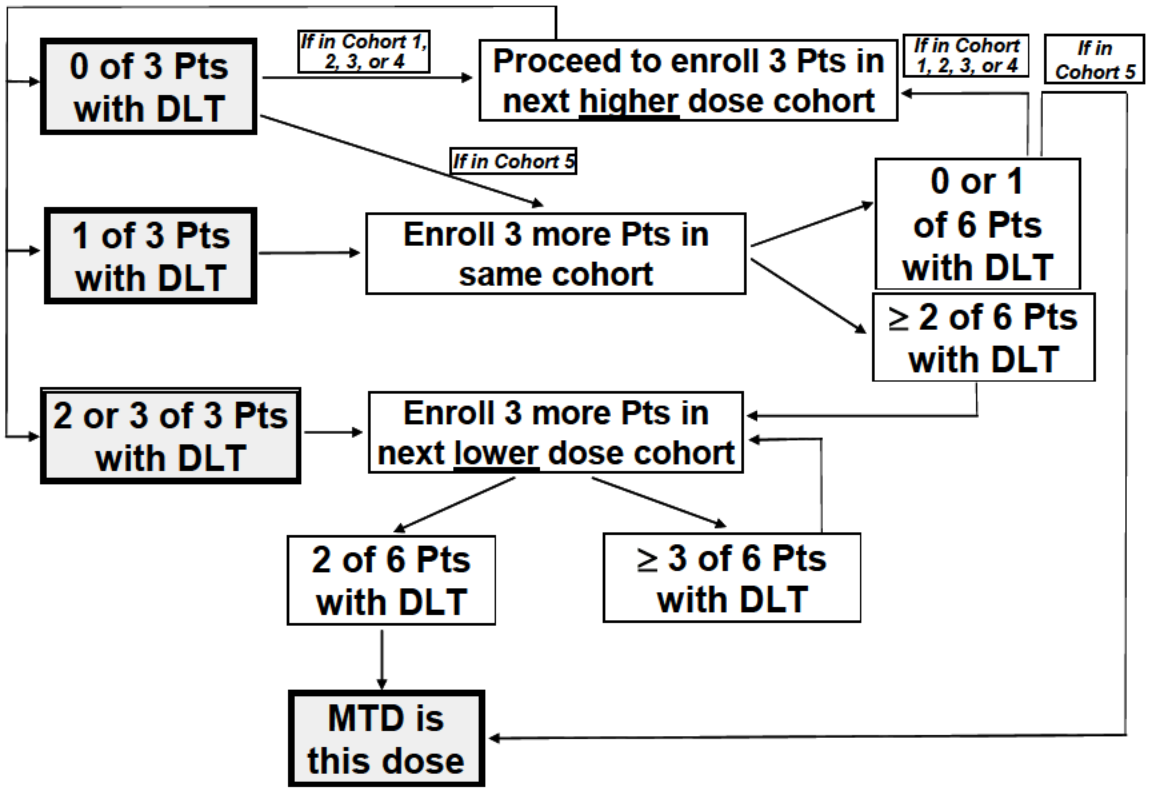
If 2 or more out of 3 patients, or 2 or more out of 6 patients, in a given cohort experience a DLT, that dose will be declared not tolerated and 3 additional patients will be enrolled in the next lower dose cohort.

If 0 or 1 patient at the highest cohort studied to date experiences a DLT, 3 additional patients will be enrolled at that same dose.

If the dose in a given cohort is found to be not tolerated after dosing has begun in the next higher dose cohort, all patients in that next higher dose cohort will be immediately dose reduced to the highest dose cohort that has not been determined to be intolerable.

The maximum tolerated dose (MTD) is defined as the dose level at which ≤ 2 of 6 patients experience a DLT.

Figure 8.9-A. Flow Diagram of Dose Escalation Schema



See Section 8.8 for definition of DLT.

All 3 patients within a given cohort may begin treatment simultaneously. If there is (1) no NCI CTC adverse event Grade 2 or higher toxicity, (2) no MMC plasma concentration ≥ 100 ng/mL, and (3) no new, treatment-emergent diagnosis of bladder fibrosis, after all 3 patients in a given cohort have completed the fourth (4^{th}) instillation of MMC (i.e., third instillation of MMC plus Chemophase), the new higher dose cohort can be opened for patient enrollment (provided there is authorization from Halozyme or its designee in the form of a faxed Registration Form to open enrollment in the next higher dose cohort, as discussed in Section 8.4). Note that an NCI CTC adverse event Grade 2 toxicity will delay opening the next higher dose cohort to enrollment until safety data are reviewed from all six weekly instillations for all 3 patients in that cohort. Once the highest dose cohort is reached or the cohort suspected to be the MTD determined, after this dose has been tolerated without a DLT by at least two of the first three patients through their fourth (4^{th}) instillation of MMC (i.e., third instillation of MMC plus Chemophase), the remaining nine patients for the MTD cohort may be enrolled without any pause.

The study center must not begin dosing any new patient or open enrollment in a new cohort without a Enrollment/Registration Form prior authorization from Halozyme or its designee (see Section 8.4).

8.10. Premature Termination of Treatment/Withdrawal of Patients

The Investigator must guard the patient's welfare and should discontinue study drug treatment at any time that this action appears to be in the patient's best interest. Patients may discontinue study drug treatment and may withdraw or be removed from the study at any time. Possible reasons for such actions may include, but are not limited to, the following:

- Dose-limiting toxicity, as defined in Section 8.8.
- Clinical need for concomitant or ancillary therapy that is not permitted during the study (e.g., intravesical therapy other than study medications) (see Section 7.3).
- Unrelated intercurrent illness that in the judgment of the Investigator will significantly affect assessments of clinical status.
- Pregnancy (see Section 10.7).
- General or specific changes in the patient's condition that in the judgment of the Investigator render the patient unacceptable for further study drug treatment.
- Patient's request to withdraw.
- Unwillingness or inability to comply with study requirements.

It is the right and duty of the Investigator to interrupt the treatment of any study patient whose health or well-being may be threatened by continuation in this study. Such patients should have study drug treatment discontinued, rather than be continued under a modified treatment regimen that is not within the specifications of this protocol.

Once a study patient has received MMC or Chemophase under this protocol, the patient must be followed for safety as required in the protocol (see Section 10). In the event that a study patient withdraws from the study prematurely, every effort will be made to document the reason for premature termination and obtain follow-up safety data. The specific reason for and date of the premature discontinuation will be documented in the CRFs. The date of the last dose of study medications will also be documented.

Should the enrollment rate lag or significant numbers of clearly non-eligible and/or non-evaluable patients be entered in the study, Halozyme may elect to terminate the study. Halozyme also has the right to terminate the study at any time for non-adherence to protocol, unavailability of the Investigator or his or her study staff for Halozyme or its designated monitoring personnel, or for administrative reasons, at any time.

8.11. Post-Treatment Procedures at Week 8

As shown in Section 2.0, Schedule of Events, the following activities are to be completed on the Week 8 clinic visit day.

- Karnofsky performance status (see Appendix B).

- Complete physical exam

- Vital signs (blood pressure, pulse, oral temperature, and weight).
- Concomitant medications.
- Pregnancy test if female patient of child-bearing potential.
- CBC with differential.
- Clinical chemistries.
- Urinalysis.
- 12-Lead electrocardiogram.
- Urine biomarkers for bladder carcinoma. The NMP22® BladderChek® Test will be performed in clinic on a urine specimen obtained between midnight and noon, and collected more than five days after cystoscopy/TURBT. The UroVysion™ test will be obtained in the clinic and sent to a central vendor lab for analysis.
- Adverse events/toxicity assessment (see Sections 10.1 through 10.6).

8.12. Post-Treatment Procedures at Week 12

As shown in Section 2.0, Schedule of Events, the following activities are to be completed at the Week 12 clinic visit day.

- Karnofsky performance status (see Appendix B).
- Interim medical history (this history is for the interim period of time since the previous medical history).
- Targeted physical exam (this physical exam is targeted at observations on a review of systems and follow-up of any findings on the previous physical exam).
- Vital signs (blood pressure, pulse, oral temperature, and weight).
- Concomitant medications.
- Cystoscopy with bladder tumor assessment, accompanied by urine cytology and estimate of bladder capacity.
- CBC with differential.
- Clinical chemistries.

- Adverse events/toxicity assessment (see Sections 10.1 through 10.6).

8.13. Long-Term Maintenance Therapy and Follow-Up (Following Week 12)

Long-term follow-up for disease monitoring for all patients will start 3 months after the last of the weekly study drug treatments for every study patient and be performed every three (3) months for two (2) years after Day 1 or until the time of first bladder tumor recurrence if earlier (see Section 2.0, Schedule of Events). For the purpose of this study, tumor recurrence is defined as a biopsy that histologically confirms the recurrence of bladder carcinoma. It is expected that patients will be receiving standard of care according to the judgment of the Investigator and/or the patient's other physician(s).

For all patients NOT treated at the MTD, there are no protocol-required activities during this 2years term except for first recurrence status and survival.

The 12 patients treated at MTD will continue to receive combination therapy at the same dose as during their six weekly treatments every three months until the end of Year 2 or until the time of documented tumor recurrence, whichever occurs first. Thus, they are intended to receive up to seven maintenance treatments in addition to the six initial weekly treatments. The maintenance treatments are intended to immediately follow the standard of care clinic evaluations and cystoscopies for monitoring of tumor recurrence. As shown in Section 2.0, Schedule of Events, the following activities are to be completed every three months after the Week 12 clinic visit to the end of 2 years from Day 1 for those patients still being treated at MTD.

- Interim medical history (this history is for the interim period of time since the previous medical history).
- Targeted physical exam (this physical exam is targeted at observations on a review of systems and follow-up of any findings on the previous physical exam).
- Vital signs (blood pressure, pulse, oral temperature, and weight).
- Concomitant medications.
- Cystoscopy (standard of care for monitoring of tumor recurrence), with urine cytology and estimate of bladder capacity.
- Predose CBC with differential. The local lab will receive and analyze blood drawn for a CBC and differential on a "stat" basis. **Intravesical dosing with study medication(s) on an individual patient basis on a given treatment day must not be done until CBC and differential results are known and the ANC is confirmed to be ≥ 1,500/mm^3 and the platelet count is ≥ 75,000/mm^3.**

- Predose urine dipstick analysis. A urine dipstick analysis is performed on the day of dosing, and the results must be known with no evidence of urinary tract infection prior to study drug dosing.

- After completion of cystoscopy and if no clinical contraindication, intravesical instillation of MMC with the defined MTD dose of Chemophase. Hematology and urine samples must be obtained and results for CBC with differential and urine dipstick analysis must be known prior to intravesical dosing of Chemophase and MMC.

- Adverse events/toxicity assessment (see Sections 10.1 through 10.6).

Also as shown in Section 2.0, Schedule of Events, the following activities are to be completed 6 weeks before the every-three-month visits after the Week 12 clinic visit for those patients still being treated at MTD.

- Urine biomarkers for bladder carcinoma. The NMP22® BladderChek® Test will be performed in clinic on a urine specimen obtained between midnight and noon, and collected more than five days after cystoscopy/TURBT. The UroVysion™ test will be obtained in the clinic and sent to a central vendor lab for analysis. If either biomarker results are suggestive of tumor recurrence, it is anticipated that the patient will be brought back for a clinic evaluation as soon as possible, and undergo cystoscopic evaluation, if indicated.

9. STUDY MEDICATIONS AND ADMINISTRATION

9.1. Mitomycin (Mitomycin C, MMC)

9.1.1. Supply of MMC

Commercially available MMC will be obtained through Halozyme and provided to the Investigator for this study. For the convenience of the Investigator, a representative U.S. package insert for MMC is provided in Appendix C, and a representative Canadian package insert and United Kingdom SPC for MMC are provided in Appendices D and E, respectively, current as of the date of this protocol version. It is the responsibility of the Investigator to refer to the appropriate product label that is current as of the time of treatment and management decisions.

As noted in the U.S. package insert, MMC for injection is a sterile dry mixture of mitomycin and mannitol, which, when reconstituted in sterile water, provides a solution. MMC is supplied in individually-boxed vials of 5 mg, 20 mg, and 40 mg strengths. For this clinical trial, MMC will be supplied in 40 mg vials. Each 40 mg vial of MMC contains mannitol 80 mg. Each vial will be labeled with the study protocol number and the statement "Caution: New Drug – Limited by Federal Law to Investigational Use." The label will designate a space for the study center to enter the patient identification

number and initials. MMC vials will be supplied to each study center as bulk drug supply, and will not be labeled in advance to a specific patient identification number.

9.1.2. Storage and Stability of MMC

As noted in a representative U.S. package insert (see Appendix C), unreconstituted MMC should be stored at a controlled room temperature of 15ºC to 30ºC (59ºF to 86ºF), and is stable for the lot life indicated on the package. Excessive heat (over 40ºC) should be avoided. All MMC supplies must be kept in a secure area with access limited to authorized clinical investigation personnel.

When reconstituted for injection with sterile water to a concentration of 0.5 mg per mL, MMC is stable for 14 days refrigerated or 7 days at room temperature. Reconstituted solution should be protected from light.

9.1.3. Procedures for Proper Handling and Disposal of MMC

As noted in a representative U.S. package insert (see Appendix C), procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published (see References 1-7 in Appendix C). There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Anyone exposed to MMC should be cautioned to avoid contact with the skin. Study patients should be instructed to wash hands and genitals after voiding intravesically administered MMC. Towels or washcloths used by study patients should be thoroughly washed after use.

Vials and any unused portions of vials must be handled in a manner consistent with the safe management of non-infectious biohazard material. For accidental spills, wear protective gloves and avoid physical contact during removal. Use normal clean-up procedures for liquid spillage and wash thoroughly with water.

9.1.4. Preparation of MMC for Intravesical Instillation

The reconstituted MMC for intravesical instillation will be aseptically prepared at the clinical study centers or designated pharmacies. For use in this clinical trial, 20 mL of sterile water will be added to one 40 mg vial of MMC, resulting in a concentration of 2 mg/mL. The reconstituted MMC can be shaken to dissolve. If the MMC does not dissolve immediately, it can be allowed to stand at room temperature until a solution is obtained. For this clinical trial, MMC should be reconstituted no more than 24 hours before intravesical administration and stored a room temperature. The reconstituted MMC will not be admixed with the Chemophase solution for instillation (see Section 9.2.3), but rather will be instilled following instillation of the Chemophase solution and the sterile saline. The reconstituted MMC will then be delivered to the catheter for intravesical instillation (see Section 9.3).

All MMC vials supplied for this study, both used and unused, must be retained for drug accountability. The patient ID number and initials, and date of preparation, should be written in ink on the vial label. See Section 12.5 regarding drug accountability.

9.2. Chemophase (rHuPH20)

9.2.1. Formulation and Supply of Chemophase

The rHuPH20 active pharmaceutical ingredient (API) in Chemophase is a frozen solution at 1 mg/mL, pH 6.8, in 10 mM Hepes and 130 mM sodium chloride. The rHuPH20 drug substance will be supplied by Halozyme in 1.0 mL and 5.0 mL Type I glass vials with a Type I bromobutyl rubber serum stopper, both with a concentration of approximately 100,000 U/mL (see Section 9.2.3). Each vial will be labeled with the study protocol number and the statement "Caution: New Drug – Limited by Federal Law to Investigational Use." The labels will designate a space for the study center to enter in ink the date the vial was first opened. Chemophase vials will be supplied to each study center as bulk drug supply, and will not be labeled in advance to a specific patient identification number.

The Chemical Abstracts Index Name for rHuPH20 is 36-482-Hyaluronoglucosaminidase PH20 (human). The CAS Registry Number is [757971-58-7]. The USAN name is hyaluronidase (human recombinant).

9.2.2. Storage and Stability of Chemophase

Chemophase must be stored frozen. The recommended storage condition for the Chemophase API solution is -20 ± 5° C. All Chemophase supplies must be kept in a secure area with access limited to authorized clinical investigation personnel.

Vials of Chemophase must be thawed (see Section 9.2.3) prior to removal of Chemophase for dosing, but any remaining material in the vial will be immediately re-frozen at -20 ± 5° C. A given vial may be thawed, fluid withdrawn, and then frozen up to a total of five times, or over a maximum elapsed time of 12 months (or longer, as may be amended from time to time by the Sponsor based on additional stability data), whichever occurs first, after which the vial may not be used for any further dosing. The vial labels will designate a space for the study center to record in ink the "date opened."

9.2.3. Preparation of Chemophase for Intravesical Instillation

The solution of Chemophase for intravesical instillation will be aseptically prepared at the clinical study centers or designated pharmacies. For this clinical trial, Chemophase should be prepared no more than 24 hours before intravesical administration. In preparation for patient dosing, the Chemophase vial should be removed the freezer and allowed to thaw either in the refrigerator for at least several hours (typically overnight) or at room temperature for at least one hour but not more than 24 hours. Chemophase should

be protected from bright light and heat. Thaw only enough vials to prepare the required dose.

After the vial is completely thawed, the volume of solution appropriate for the dose of Chemophase to which the patient is assigned will be drawn into a syringe. The size and graduation markings of the syringe that is used should be appropriate for measuring volumes to the nearest 0.1 mL. The specific activity of Chemophase is anticipated to range from 100,000 to 120,000 units/mL. The volume of Chemophase to be instilled is based on an average of 110,000 units/mL (see Table 9.2-A). As shown in Table 9.2-A, the total volume of Chemophase drawn from the vial also provides for up to 0.2 mL hold-up volume due to filtering through the syringe filter.

After the solution is drawn from the vial, the syringe needle will be removed and exchanged for a 0.2 micron syringe filter. This syringe filter has a hold-up volume of 0.1 to 0.2 mL, which must be taken into account when withdrawing the dose to be dispensed. Next, the plunger on the syringe is depressed and a small volume (approximately 0.1 mL) of the solution passed through the filter and discarded until the remaining volume of the solution in the syringe matches the exact volume for intravesical administration (e.g., for Cohort 1, a total of 0.4 mL is drawn into the syringe, the syringe needle replaced with the syringe filter, and the volume in the syringe is reduced to exactly 0.2 mL by expelling solution through the filter). After discarding the excess volume to reduce the remaining volume to the exact amount for intravesical instillation, the solution will then be passed through this filter as it is delivered into the catheter for intravesical instillation (see Section 9.3).

The Chemophase solution for intravesical instillation will not be admixed with the reconstituted MMC for instillation (see Section 9.1.4), but rather will be instilled prior to instillation of the reconstituted MMC and before the instillation of the amount of sterile saline needed to follow the Chemophase to add up to total of 8 mL (see Section 9.3).

Table 9.2-A. Volume of Chemophase Withdrawn from Vial for Intravesical Administration

Cohort	Units of Chemophase for Instillation	Volume of Chemophase		
		Actual mL for Instillation	Extra mL for Hold-up in Filter	Total mL Drawn into Syringe
1	20,000	**0.2**	0.2	0.4
2	60,000	**0.5**	0.2	0.7
3	200,000	**1.8**	0.2	2.0
4	400,000	**3.6**	0.2	3.8
5	800,000	**7.3**	0.2	7.5

At the initial use of vial, the date that solution was first removed from the vial will be written in ink on the vial label and the vial immediately returned to the freezer. Each time the vial is thawed and solution removed, the date will be recorded. Note that the vials are not specific to an individual patient, and more than one patient can be dosed from the same vial. As noted in Section 9.2.2, a given vial may be thawed, fluid withdrawn, and

then frozen up to a total of five times, or over a maximum elapsed time of 10 months (or longer, as may be amended from time to time by the Sponsor based on additional stability data), which occurs first, after which the vial may not be used for any further dosing.

The smallest number of vials necessary for a given intravesical instillation should be used. In general, the 1 mL-solution vials will be used for the lower doses (earlier cohorts) and the 5 mL-solution vials will be used for the higher doses (later cohorts). For example, for Cohorts 1 and 2, a 1 mL-solution vial will be used for the first, 0.2 or 0.6 mL volumes of instillation, respectively. The vial may be re-frozen and later thawed for continued use for subsequent dosing until the vial is empty. If there is insufficient volume in a given vial to complete a dose, the volume from that vial will be supplemented with volume from the next vial from the same lot number. Unless it is unavoidable in order to continue dosing of a patient without interruption, for any single instillation no patient should receive Chemophase study drug from more than one lot number. It is preferable to limit the number of lot numbers to which any given patient is exposed over the duration of that patient's total exposure to Chemophase. For Cohorts 3, 4, and 5, the 5 mL-solution vials will be used in the same manner as the 1 mL-solution vials. For planning an adequate supply of study drug, note that it is not possible to extract the full 1.0 mL from a 1 mL-solution vial, or the full 5.0 mL from a 5 mL-solution vial. Note also that allowances should be made for the 0.1 to 0.2 mL hold-up volume lost due to the syringe filter (see Table 9.2-A).

All Chemophase vials supplied for this study, both used and unused, must be retained for drug accountability. See Section 12.5 regarding drug accountability.

9.3. Dosing Schedule and Procedure for Intravesical Instillation of MMC with and without Chemophase

The only dose of MMC used in this study is 40 mg in 20 mL of Sterile Water. As shown in Table 9.3-A, the initial intravesical instillation (Day 1, Week 1) for each patient in each cohort is MMC alone (without Chemophase). For Weeks 2 through 6, the patient will receive five additional, weekly, intravesical instillations, which will consist of both Chemophase and MMC, administered sequentially in the manner described below. The 12 patients treated at MTD will continue to receive combination therapy every three months until the end of Year 2 from Day 1 or until the time of documented tumor recurrence, whichever occurs first.

Table 9.3-A. Dosing Schedule for MMC and Chemophase

Cohort	Week 1 (MMC Dose)	Volume for Instillation Week 2 through Week 6		
		(1) Chemophase Dose	(2) Sterile Saline	(3) MMC Dose
1	40 mg/20 mL	20,000 units in 0.2 mL	7.8 mL	40 mg/20 mL
2	40 mg/20 mL	60,000 units in 0.5 mL	7.5 mL	40 mg/20 mL
3	40 mg/20 mL	200,000 units in 1.8 mL	6.2 mL	40 mg/20 mL
4	40 mg/20 mL	400,000 units in 3.6 mL	4.4 mL	40 mg/20 mL
5	40 mg/20 mL	800,000 units in 7.3 mL	0.7 mL	40 mg/20 mL

1. First step of intravesical administration.
2. Second step of intravesical administration.
3. Third step of intravesical administration.

All study patients should refrain from drinking fluids for at least eight (8) hours before intravesical therapy, and also during intravesical therapy, except for sips of water needed to take medications, unless there is a medical contraindication to this eight-hour dehydration. Just prior to intravesical instillation, the patient should void completely to empty the bladder. Using sterile technique, a catheter will be inserted in the bladder and the bladder will be carefully emptied of any residual urine using the catheter. The volume of any residual urine will be recorded. If necessary to fully drain the bladder, the lower abdomen will be gently compressed and the patient may be rolled from side to side.

After the bladder is fully drained of urine and the volume of urine measured, sequential instillation of study drugs will begin. The intravesical instillation of study drug is a three-step procedure in this study, as outlined below. The three sequential steps of instillation are presented in tabular format above, in Table 9.3-A. The intermediate step, instillation of sterile saline, has been incorporated in this clinical trial for the sole reason of having the overall volume of fluid administered held constant in all patients across all cohorts. The syringes with the Chemophase and saline and the reconstituted MMC should be prepared in advance of the actual catheterization, in order to allow for no interruption in the stepwise instillation.

- First, the volume of prepared Chemophase solution (see Section 9.2.3) will be passed through the syringe filter and introduced into the sterile barrel of a syringe of at least 25 mL connected to the urinary catheter and allowed to enter the bladder by gravity flow.

- Second, immediately following the Chemophase, the volume of sterile saline solution specified in Table 9.3-A will be introduced into the sterile barrel of the syringe connected to the urinary catheter and allowed to enter the bladder by gravity flow.

- Third, immediately following the sterile saline, the prepared reconstituted 20 mL volume of MMC (see Section 9.1.3) will be shaken to mix the contents, the stopper removed from the vial, and the volume immediately poured from the vial into the sterile barrel of the syringe connected to the urinary catheter and allowed to enter the bladder by gravity flow. In order to assure that all the solutions have passed through the catheter and into the bladder, a small volume of air may be

gently pushed by syringe into the catheter. The catheter is then withdrawn from the bladder.

This procedure should ensure that all patients in all cohorts have received a total of 28 mL of intravesical volume at each dosing cycle.

Aseptic, appropriate technique must be used during administration of intravesical Chemophase, sterile saline, and MMC to avoid introducing contaminants into the urinary tract or unduly traumatizing the urinary mucosa.

After the intravesical instillation is completed, study patients will be instructed to lie on their abdomen for at least 15 minutes, after which the patient is intended to be ambulatory. Patients should retain the solution in their bladder, if possible, for a total of two (2) hours. If the solution cannot be retained in the bladder for the entire two hours, this will be noted on the CRF along with the total bladder retention time and the reasons cited for a less than two-hour retention.

During the intravesical procedure and afterwards, patients should be observed and questioned about adverse events. Two hours after intravesical instillation, patients will be instructed to empty the bladder into a urine collection container. The volume of urine voided will be measured and recorded in the CRF. A 5 mL aliquot of this urine will be frozen at -20°C and retained for possible future analysis.

Patients should be instructed to carefully clean their hands and genitalia after voiding the intravesically administered MMC. Patients may then leave the clinic if no adverse events are reported or observed that require them to remain for observation or treatment.

10. ADVERSE EVENTS AND SAFETY MONITORING

The safety parameters collected and monitored during this study include adverse events (AEs), laboratory determinations, physical examination and vital signs, 12-lead ECG, plasma concentration of MMC, and findings noted on cystoscopy.

All AEs that occur during the study should be treated appropriately to protect and ensure the patient's well-being. If such treatment constitutes a deviation from this protocol, Halozyme must be notified and the Investigator should comply with applicable Institutional Review Board (IRB)/Ethics Committee (EC) reporting requirements. If the patient is withdrawn from the study as a result of this deviation, the reason will be appropriately documented.

10.1. AE Definitions

The following definitions of terms are guided by the International Conference on Harmonization and the U.S. Code of Federal Regulations [21 CFR 312.32, effective 6 April 1998] and are included herein. The terms "serious adverse event" and "adverse event," inserted in parentheses, are commonly used terminology.

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment.

Serious adverse drug experience (serious adverse event, SAE) is any adverse drug experience (AE) occurring at any dose that results in any of the following outcomes:

- Is fatal or immediately life-threatening (life-threatening is defined as a medical event during which the patient is at immediate risk of death from the reaction as it occurred; it does not include an event that, had it occurred in a more serious form, might have caused death);

- Requires hospitalization, or prolongs existing hospitalization. Any in-patient hospital admission, regardless of duration of hospital stay, will be considered as in-patient hospitalization. Hospitalizations for procedures scheduled prior to enrollment into the study and emergency room visits do not constitute a serious AE.

- Results in persistent or significant disability/incapacity;

- Results in a congenital anomaly or birth defect; or

- Is any other Important Medical Event. Important Medical Events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient or require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in hospitalization of the patient, or the development of drug dependency or drug abuse.

Life-threatening is any adverse drug experience (adverse event) that places the patient or subject, in the view of the Investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Associated with the use of the drug means that there is a ***reasonable possibility*** that the experience (adverse event) may have been caused by the drug.

Unexpected adverse drug experience means any adverse drug experience (adverse event), the specificity or severity of which is not consistent with the current Investigator Brochure (IB).

10.2. Pre-Treatment-Emergent Adverse Events

Halozyme considers adverse events (AEs) that occur between the time the patient signs the informed consent document for the study and the time when that patient is first exposed to study drug (MMC or Chemophase in this study) as "pre-treatment-emergent" events. All known pre-treatment-emergent AEs that are serious (see Section 10.1) should be reported to Halozyme. The reason for collection of serious pre-treatment-emergent AEs is to allow for an assessment of whether or not the SAE was causally associated with any protocol-related activities. Halozyme will not collect information on pre-treatment-emergent AEs that do not meet at least one accepted criterion for a serious classification under the most rigid and comprehensive of the applicable regulatory agency criteria for this study. Events occurring after first administration of study drug will be considered treatment-emergent AEs and will be captured on the AE CRF.

10.2. Laboratory Abnormalities as Adverse Events

It is anticipated that many laboratory abnormalities observed during the course of a study will be encompassed under a reported adverse event (AE) describing a clinical syndrome (e.g., elevated BUN and creatinine in the setting of an AE of renal failure, or elevated SGOT/SGPT in the setting of an AE of hepatitis). In these cases (e.g., an AE of renal failure), the laboratory abnormality itself (e.g., elevated creatinine) does not need to be recorded as an AE.

In the absence of a reported AE identifying a clinical syndrome that encompasses the observed laboratory abnormality, that isolated laboratory abnormality itself should be reported as an AE if it is judged by the Investigator to be clinically significant for that patient.

For the purposes of this study, criteria defining a "clinically significant" laboratory abnormality are:

a) Laboratory abnormality leads to a dose-limiting toxicity (e.g., judged to be associated with study drug administration and resulting in study drug dose reduction, suspension or discontinuation), or

b) Laboratory abnormality results in any therapeutic intervention (i.e., concomitant medication or therapy), or

c) Other laboratory abnormality judged by the Investigator to be of other particular clinical relevance.

10.3. Classification of Adverse Events by Severity

The Investigator must categorize the severity of each AE according to the following guidelines. The level of severity is guided by the National Cancer Institute (NCI) Common Terminology Criteria (CTC) for adverse events, which will be provided to each study center and is available on line at http://ctep.cancer.gov/reporting/ctc.html [12].

Mild:
Grade 1 NCI Common Terminology Criteria AE; or

if not found in the Common Terminology tables, an AE that is asymptomatic or barely noticeable to the patient; not interfering with patient's daily activity performance or functioning; generally not requiring alteration or cessation of study drug administration; and/or ordinarily not needing therapeutic intervention.

Moderate:
Grade 2 NCI Common Terminology Criteria AE; or

if not found in the Common Terminology tables, an AE of sufficient severity as to possibly make the patient moderately uncomfortable; possibly influencing the patient's daily activity performance or functioning; generally not impairing the patient's ability to continue in the study; and/or possibly needing therapeutic intervention.

Severe:
Grade 3 or 4 NCI Common Terminology Criteria AE; or

if not found in the Common Terminology tables, an AE generally causing severe discomfort; significantly influencing the patient's daily activity performance or functioning; generally requiring alteration or cessation of study drug administration; life-threatening; resulting in significant disability or incapacity; and/or generally requiring therapeutic intervention.

10.4. Classification of Adverse Events by Relationship to Study Drug Administration

The relationship of each AE to the study drug administration will be assessed by the Investigator after careful consideration, and according to the following guidelines. Because there are two study drugs in this clinical trial (i.e., MMC and Chemophase), the Investigator will be expected to make his/her best assessment of the relationship of each event to each of the two study drugs. See Section 10.5 for information regarding the known toxicity profiles of MMC and Chemophase, which should guide the assessment of causality to each study drug.

No, Not Related:
This category is applicable to those AEs that are clearly due to extraneous causes (concurrent drugs, environment, etc.) and do not meet the criteria for drug relationship listed under UNLIKELY; POSSIBLY; PROBABLY; AND YES, RELATED.

Unlikely Related:
This category applies to those AEs that are judged to be unlikely to be related to the study drug administration. An AE may be considered to be PROBABLY NOT RELATED when it meets at least two (2) of the following criteria:

a) It does not follow a reasonable temporal sequence from administration of the study drug.

b) It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.

c) It does not follow a known or expected response pattern to the study drug.

d) It does not reappear or worsen when the study drug is re-administered.

Possibly Related:
This category applies to those AEs that are judged to be perhaps related to the study drug administration. An AE may be considered POSSIBLY RELATED when it meets at least one (1) of the following criteria:

a) It follows a reasonable temporal sequence from administration of the study drug.

b) It could not readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.

c) It follows a known or expected response pattern to the study drug.

Probably Related:
This category applies to those AEs that are felt with a high degree of certainty to be related to the study drug administration. An AE may be considered PROBABLY RELATED if it meets at least two (2) of the following criteria:

a) It follows a reasonable temporal sequence from administration of the study drug.

b) It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.

c) It disappears or decreases on cessation or reduction in study drug dose. There are exceptions when an AE does not disappear upon discontinuation of the drug, yet

drug relatedness clearly exists (e.g., bone marrow depression, fixed drug eruptions, tardive dyskinesia, etc.).

d) It follows a known or expected response pattern to the study drug.

Yes, Related:
This category applies to those AEs that are incontrovertibly related to study drug administration. An AE may be assigned to this category if it meets at least the first three (3) of the following criteria:

a) It follows a reasonable temporal sequence from administration of the study drug.

b) It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.

c) It disappears or decreases on cessation or reduction in study drug dose. There are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists (e.g., bone marrow depression, fixed drug eruptions, tardive dyskinesia, etc.).

d) It follows a known or expected response pattern to the study drug.

e) It reappears or worsens when the study drug is re-administered.

10.5. Known Toxicity Profiles of MMC and Chemophase

As noted in Section 10.4, the Investigator is expected to make his/her best assessment of the causal relationship of each adverse event to each of the two study drugs (i.e., MMC and Chemophase) in this clinical trial. The information summarized below is intended to be only a guide to this assessment. The Investigator should base the assessment on all available information.

10.5.1. Known Toxicity Profile of MMC

The American Urologic Association (AUA) Bladder Cancer Guidelines Panel 1999 Report on the Management of Non-Muscular-Invasive Bladder Cancer provided a summary of probability estimates of treatment complications for MMC based on its review of the literature [3]. Complications were grouped by local bladder symptoms, systemic symptoms, and other, and have been excerpted below for Table 10.5-A.

Of the 28 patients who had undergone TURBT and treated with MMC alone (who received a total of 788 intravesical instillations) in a randomized clinical trial, five (17.8%) had side effects, including four with cystitis and one with skin rash [10]. (Note: Of the 28 patients treated with MMC plus 200,000 units of bovine hyaluronidase [who received a total of 750 instillations], four [14.2%] had side effects, including three

with cystitis and one with skin rash. There was no significant alteration in white blood count during therapy.)

In a separate publication, side effects of MMC plus 200,000 units of bovine hyaluronidase combination intravesical therapy were observed in a total of 14% (6/43) of patients, and consisted of bacterial cystitis (6.9%), chemocystitis (4.6%), and skin allergy (2.3%). No patients were withdrawn due to side effects [11].

Bladder fibrosis with a reduction in bladder capacity is an uncommon but known complication of generally long-term intravesical MMC therapy, the incidence of which appears to correlate directly with the cumulative MMC dose and correlate inversely with the time interval between a second tumor resection and the first MMC instillation [8].

Table 10.5-A. Probability Estimates of Treatment Complications from Intravesical MMC

Treatment Complication	Median Probability	95% CI	G/P*
LOCAL BLADDER SYMTPOMS			
Irritative Voiding Symptoms			
Dysuria	35%	30-41%	4/456
Frequency/Nocturia	42%	26-59%	3/420
Irritative symptoms	18%	12-26%	19/1596
Pain/Cramps	10%	6-14%	1/220
Other Local Symptoms			
Local side effects	5%	3-9%	2/296
Other side effects	2%	0.3-4%	1/148
Other			
Bladder contracture	5%	2-11%	2/234
Bacterial cystitis	20%	17-23%	6/845
Hematuria	16%	7-28%	7/800
Incontinence	1%	0.4-4%	1/220
SYSTEMIC SYMPTOMS			
Flu-Like			
Arthralgia	9%	0.1-47%	2/278
Fever or Chills	3%	1-7%	5/686
Flu-like symptoms	20%	4-48%	3/498
Infectious			
Epid/Prost/Ureth infections	4%	2-9%	3/251
Hepatic changes	0.1%	0-1%	1/220
Pneumonia	0.2%	0-2%	1/148
Myelosuppression	2%	0.3-7%	2/102
Nausea/Vomiting	9%	1-26%	3/498
Skin Rash	13%	8-19%	14/992
Systemic Side Effects	3%	0.5-8%	2/296
OTHER			
Treatment Incomplete	9%	2-14%	7/683
Treatment Interruption	11%	8-16%	6/374

* G = Number of Groups/Treatment arms extracted; P = Number of Patients in those groups.

10.5.2. Known Toxicity Profile of Chemophase

Although there is an extensive body of knowledge establishing the clinical safety and tolerability of animal-derived hyaluronidases, there are no clinical data regarding the use of rHuPH20 administered intravesically. Except for the recently-initiated Phase I trial of a single administration of Chemophase and MMC, only one clinical trial has been conducted with rHuPH20 (except for trials of the *ex vivo* use of rHuPH20 to remove the cumulus matrix surrounding human oocytes for in vitro fertilization). This first exposure of rHuPH20 drug substance in humans was an investigation of the potential dermal sensitivity of an intradermal injection of Enhanze SC™ (rHuPH20 for injection) in 100 normal healthy volunteers and showed no signal of allergy or immunogenicity.

Animal-derived hyaluronidase preparations have been the subject of multiple investigations and regulatory approvals in Europe, the U.S. and Asia, and collectively encompass over 50 years of use in humans. The 11 October 2000 package insert for Wydase® (bovine hyaluronidase) lists hypersensitivity to hyaluronidase as a Contraindication. Under Adverse Events, it is stated that allergic reactions (urticaria, angioedema) are rare, and anaphylactic-like reactions following retrobulbar block or intravenous injections have occurred. The U.S. FDA has indicated that recently marketed bovine-derived preparations have a reported level of immediate hypersensitivity of less than 0.1%.

In 1998, Baumgartner et al. published a review of the literature of animal-derived hyaluronidases (Permease® 7500 IU or Neopermease® 200,000 IU) used additively to cytostastic agents in neoplastic diseases in 420 patients in a series of pilot studies [13]. Hyaluronidase was well-tolerated by multiple routes of administration, including intramuscular, intravenous, intraperitoneal, intrapleural, intrathecal, and intravesical routes of administration. Allergic reactions were noted in 4.2% (3/72) of patients treated intramuscularly, consisting of local inflammation and pain in two patients and nausea, vomiting, and circulation disturbance in a third. Allergic reactions were noted in 10% of patients treated intravenously (except for a 20% rate in astrocytoma patients), all of which were reversible and easily manageable.

Because rHuPH20 is up to 100-fold more pure than animal-derived products based on activity and contains human amino acid sequences rather than bovine, it is expected that most or all of the allergic and immunogenic problems associated with the animal-derived impurities will be avoided.

A Phase I safety, tolerability, and PK single-administration clinical trial (HZ2-05-02) of a low dose (20,000 units) of Chemophase with 40 mg MMC administered intravesically in a targeted sample size of five evaluable patients who had undergone transurethral resection of bladder tumor (TURBT) for transitional cell bladder cancer Stage Ta, T1 or Tis (any grade), were free of known bladder cancer recurrence, and were being monitored for recurrence of superficial transitional cell bladder cancer was initiated in August 2005 and completed enrollment in March 2006. All five patients completed the study. There were no deaths, serious AEs, AEs judged to be possibly or more related to either study

drug, moderate or severe AEs, premature withdrawals, or dose-limiting toxicities. The only three AEs reported in the study were, by MedDRA Preferred Terms, Influenza, Urinary tract infection, and Acne. All plasma samples for MMC were below the lower limit of quantitation (10 ng/mL) and all plasma samples of PH20 were below the lower limit of quantitation (10 U/mL).

10.6. Reporting of Adverse Events

For the purpose of this study, all AEs, regardless of seriousness, severity, expectedness, or relationship to the study drug (MMC or Chemophase in this study), will be collected if the date and time of onset of the AE was after the patient's first exposure to either study drug and no later than 28 days after the last dose of study drug. There is no time limitation on the reporting of AEs that are treatment-emergent and assessed as reasonably associated with study drug (i.e., a drug-associated AE should be reported even if more than 28 days have passed since the last study drug treatment).

Events that occur prior to first study drug administration will be considered pre-treatment-emergent because the time of onset preceded the first exposure to study drug (see Section 10.2), and these observations will be captured on the patient's Medical History CRF. Events occurring after first administration of study drug will be considered treatment-emergent AEs and will be captured on the AE CRF.

Note that AEs that may be known, expected toxicities caused by MMC (see Section 10.5.1) and occurring during the study must be reported as AEs on the AE CRF.

Patients will be questioned and/or examined by the Investigator and his/her designee for evidence of AEs. The questioning of study patients with regard to the possible occurrence of AEs will be generalized such as, "How have you been feeling since your last visit?" Information gathering for AEs should generally not begin with direct solicitation from patients regarding the presence or absence of specific AEs.

All serious AEs (SAEs) occurring with any patient participating in this clinical trial must be reported to Halozyme as described in Section 10.6.1.

10.6.1. Reporting of Serious Adverse Events

CONTACT THE HALOZYME-DESIGNATED MEDICAL MONITOR IMMEDIATELY (WITHIN 24 HOURS) FOR ANY SERIOUS ADVERSE EVENT. The minimum required information for an initial report of an SAE is:

- Reporter name and contact number,
- Protocol number,
- Site and patient identification information, and
- The SAE term with a brief summary of the event including the causality assessment, if possible.

Contact the Halozyme safety personnel at:

Clinical Development and Medical Affairs
Safety Department
Halozyme Therapeutics, Inc.
San Diego, CA 92121
Phone: Office: [redacted]
or [redacted] extension [redacted]
Fax: [redacted]
After hours emergency: [redacted]

Investigators must fax the completed SAE Supplemental Report Form with as much information as is available at the time along with the completed AE CRF and with all available pertinent information within three (3) calendar days of first becoming aware of the SAE to:

Halozyme Therapeutics, Inc.
San Diego, CA 92121
Attention: Safety Department
Fax: [redacted]

A copy of the completed corresponding AE CRF matching the SAE Supplement Report Form, with as much information as is available at the time, must be faxed simultaneously with the SAE Supplemental Report Form.

10.6.2. Duration of Follow-Up of Adverse Events

Ongoing AEs and laboratory abnormalities that are considered by the Investigator to be at least POSSIBLY related to the study drug will be followed until resolved, returned to baseline, stabilized at a level acceptable to the Investigator, or later determined by the Investigator to be UNLIKELY related or not associated with study drug. Ongoing events and laboratory abnormalities that are UNLIKELY related or not associated with the study drug need only be followed until the patient's final study visit (i.e., for this study, Week 12, or earlier if the patient is withdrawn from study earlier).

10.6.3. Other Information on the Reporting of Adverse Events

Follow-up information regarding serious AEs must be provided to Halozyme promptly as it becomes known to the Investigator.

The Institutional Review Board (IRB)/Ethics Committee (EC) that approved the clinical investigation must be notified of any fatal, life-threatening and/or serious AEs regardless of cause on a timely basis, according to the IRB's/EC's established procedures (see Section 10.6.4).

A written report of all serious AEs and deaths will be submitted by the Investigator to the IRB/EC and to Halozyme. In this report, the Investigator will advise whether or not the

AE is judged to be related to the study drug administration. All such patients with AEs should be followed clinically and by the appropriate diagnostic evaluations.

All AEs, regardless of severity, and whether or not ascribed to the study drug administration, will be recorded in the appropriate section of the CRF.

10.6.4. Reporting of Safety Information to the Institutional Review Board

It is the responsibility of the Investigator to inform the study center's Institutional Review Board (IRB)/Ethics Committee (EC) of all SAEs and other safety information in accordance with applicable IRB's/EC's requirements. At the completion or early termination of the study, a final report should be made to the IRB/EC by the Investigator within the applicable IRB/EC time frames.

10.7. Pregnancy

A negative pregnancy test during screening for women of child- bearing potential and an agreement to use effective contraceptive methods during the treatment period of the study for men and women of child-bearing potential are be required for study eligibility. A pregnancy test will be repeated at Week 8 for women of child- bearing potential.

Any pregnancy in a study patient must be immediately reported to the Investigator and in turn to Halozyme (see Section 10.6.1 for contact information). Pregnancy during the study period will be reported and followed until final resolution (i.e., delivery or early termination). Any birth defect or congenital anomaly will be reported to Halozyme immediately as an SAE.

10.8. Concomitant Medications and Procedures

Any medication taken during the study, other than study drug (i.e., MMC and Chemophase), is regarded as concomitant medication. A history of current medications will be obtained from each patient during screening and recorded in the CRF. Patients must be queried regarding both prescription and over-the-counter medications that they take. Concomitant medications taken during the time period beginning 28 days prior to initial dosing, on Day 1/Week 1, through the Week 12 assessment will be collected for all patients, and through the last study drug treatment visit for the MTD patients who are continuing on study drug treatment after Week 12.

Concomitant medications will be updated at each subsequent visit according to the Schedule of Events (see Section 2), including any medication taken to treat an AE. At each study visit, patients will be asked if there has been any change in the medications they have taken since their last study visit. Changes will be recorded on the Concomitant Medications CRF.

Recording of concomitant medications will include the name of the drug, dosage, route, frequency, date of treatment, and the clinical indication for which the medication was taken.

Patients may receive medical care during the study including but not limited to antibiotics, analgesics, antipyretics, etc., when clinically indicated. Whenever possible, the patient should avoid starting any new medications during the treatment period of this study (including over-the-counter medications) unless the Investigator deems such medication medically necessary. A list of medications prohibited during the study is provided in Section 7.3 of this protocol.

11. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

11.1. Study Hypotheses

This is a study to primarily assess the safety and tolerability of Chemophase administered intravesically with MMC. The primary objective is to determine the MTD and DLTs of escalating doses of Chemophase with MMC and establish the dose of Chemophase recommended for future studies. It is anticipated, based on previous human studies using intravesical bovine hyaluronidase along with MMC, that Chemophase will be well tolerated and will not appreciably increase the systemic absorption or toxicity of MMC.

A secondary objective of this study is to observe patients for any preliminary evidence of anti-tumor activity of Chemophase and MMC when co-administered intravesically. Based on nonclinical data of rHuPH20 in various tumor cell models and on previous human studies using intravesical bovine hyaluronidase along with MMC, it is hypothesized that, compared to historical data of MMC monotherapy, Chemophase with MMC will reduce the risk of tumor recurrence. However, this early study of Chemophase in humans is neither designed nor powered to show statistical significance or otherwise confirm an anti-tumor effect of Chemophase.

In 1995, a Southwest Oncology Group Study comparing BCG to MMC intravesical therapy (weekly for six weeks, then monthly for one year) found a median time to tumor recurrence or death from any cause of 22 months for the 186 patients treated with MMC 20 mg in 20 mL water [14].

In 2001, the International Mitomycin C Consortium published a randomized clinical trial of six weekly intravesical treatments showing the median time to recurrence for 119 patients in an optimized treatment arm (MMC 40 mg, PK manipulations to decrease urine volume, and urine alkalinization) was 29.1 months (95% CI 14.0 to 44.2 months) compared to 111 patients on standard, non-optimized therapy (MMC 20 mg) who had a median time to recurrence of 11.8 months (95% CI 7.2 to 16.4 months) [15].

Urine biomarkers for bladder cancer obtained at baseline and Week 8 (and beyond Week 8 for the MTD patients who are continuing on study drug treatment) will be assessed. The NMP22® BladderChek® Test biomarker is performed in clinic on a urine

specimen obtained between midnight and noon, and collected more than five days after cystoscopy/TURBT. The UroVysion™ test biomarker will be obtained in the clinic and sent to a central vendor lab for analysis.

11.2. Patient Data Sets for Analysis

All patients randomized and receiving one or more doses of Chemophase will be included in the safety analysis data set. Any patient receiving MMC on study but not receiving Chemophase will be considered for safety, but assessed separately from patients receiving Chemophase.

A modified "intent-to-treat" (ITT) analysis data set for anti-tumor effects includes all patients receiving one or more doses of Chemophase with MMC. Patients who enter the baseline screening period but are not treated with Chemophase plus MMC will not be included in this modified ITT analysis.

A "per-protocol" analysis for anti-tumor effects will include all ITT patients who met the following criteria:

- Satisfied the disease-defining Inclusion Criteria #1 and #2 (see Section 7.1),
- Received at least four protocol-specified doses of Chemophase with MMC over an interval not exceeding 8 weeks,
- Retained at least four intravesical instillations for at least 90 minutes, and
- Were monitored to the time of tumor recurrence, or at least 5 years, whichever occurs first.

A listing of all screen failures, with the reasons for failure, will be recorded on the patient screening log. A patient listing of screen failures and a tabulation of the reasons for screen failure will be prepared.

11.3. Endpoints and Statistical Analyses

The primary endpoint in this study is the rate of toxicities observed with the combination of Chemophase and MMC. The primary statistical analysis will consist of point estimates and the 95% confidence intervals constructed around the point estimates. All safety data will be examined, such as AEs (including overall incidence by treatment group), physical examination findings and vital signs, laboratory data, plasma MMC concentration, and ECGs. Descriptive statistics will be used to summarize all safety variables. The MTD will be determined based on DLTs (see Sections 8.8 and 8.9).

All AEs and toxicities will be recorded on the appropriate CRFs and reported according to severity and assessed relationship to the study medications. The NCI CTC grading of severity for AEs (CTCAE) Version 3 or higher [12] and the latest version of MedDRA will be used for reporting and medical coding of AEs. All AEs regardless of causality will be individually listed. The incidence of patients with AEs will be tabulated by MedDRA System Organ Class (SOC), Preferred Term, grade or severity, and also

summarized by study center. SAEs will also be listed and summarized separately. AEs will also be separated into localized bladder and systemic events.

Based on the long-term follow-up monitoring, the data will be assessed for the median time to tumor recurrence and the two-year recurrence rate.
For the purpose of this study, tumor recurrence is defined as a biopsy that histologically confirms the recurrence of bladder carcinoma. Recurrences will be characterized with regard to the number of tumors, TNM stage, and grading. Information on tumor progression will be summarized. The data collected on the urine biomarker, comparing baseline to post-baseline values, will be summarized.

11.4. Sample Size Considerations

This is a Phase I-IIa multiple dose study of Chemophase in humans, and is neither designed nor powered for formal statistical comparisons. The study does not include a MMC-only control arm or other parallel control group. The sample size of 3 to 6 patients per dose cohort is standard for the determination of safety and tolerability in many initial clinical trials for oncology indications. The protocol intends a sample size of 12 evaluable patients treated at the MTD level, and it is believed that 12 patients will provide an adequate sample size to establish the tolerability of this dose regimen for the anticipated subsequent clinical trials and possibly provide a preliminary estimate of anti-tumor activity.

11.5. PK Analyses and Neutralizing Antibodies to rHuPH20

A secondary endpoint of this study is to assess the pharmacokinetics (PK) of intravesical administration of MMC alone (at Week 1) and in combination with Chemophase (subsequent weeks). Samples will be collected and assayed according to the schedule in Section 8, and according to Footnote 7 in the Schedule of Events in Section 2. Although samples will be collected for neutralizing antibodies (NABs) at Week 1 and Week 6, the Week 1 samples will be assayed only if the Week 6 sample shows evidence of NABs.

12. REGULATORY/ADMINISTRATIVE PROCEDURES AND DOCUMENTATION

12.1. Ethics

This study will be conducted under a U.S. Investigational New Drug (IND) Application. All applicable U.S. regulations governing human subject protection must be followed. All ethical and regulatory requirements necessary to comply with the principals of Good Clinical Practice (GCP) for the conduct and monitoring of clinical investigations must be followed.

To ensure ethical conduct of this clinical study, Investigators will be expected to adhere to basic principles provided from generally recognized guidelines such the Belmont Report and the International Ethical Guidelines for Biomedical Research Involving

Human Subjects. The study has been designed to involve the participation of representative patients affected by the disease under investigation. Participants must have provided written informed consent to document their voluntary participation in this study. Updated safety information will be provided to the Investigators, Institutional Review Boards (IRBs)/Ethics Committees (ECs) and patients as necessary in order that they may consider relevant and emerging information that could affect their willingness to continue participation in this study.

12.2. Institutional Review Board and Approval

In accordance with 21 CFR Parts 50 and 56, the Investigator agrees to provide the appropriate Institutional Review Board (IRB)/Ethics Committee (EC) with all appropriate material, including a copy of the protocol, informed consent form (ICF), Investigator's Brochure (IB), and any proposed advertisement for the study prior to the start of the study.

The proposed informed consent form (ICF) and any proposed advertisement must also be agreed to by the Sponsor (Halozyme). A copy of the IRB/EC approval letter of the protocol and the ICF must be supplied to Halozyme prior to consenting any patients for the study. A copy of the IRB/EC approval letter of any protocol amendments and any advertisements must be supplied to Halozyme prior to implementing these documents. The study may not begin screening or enrolling patients until the Investigator has obtained IRB/EC approval of the protocol and ICF and Halozyme has received a hardcopy documentation of each.

The Investigator will supply to Halozyme a list of the names, professions, and affiliations of IRB/EC members to demonstrate compliance with membership requirements. If the Investigator or a subinvestigator is a routine voting member of the IRB/EC, Halozyme will be provided with a statement from the IRB/EC that the Investigator/subinvestigator did not and will not vote on the subject of this investigation.

During the course of the study, the Investigator shall make timely and accurate reports to the IRB/EC on the progress of the trial, at intervals not exceeding one year, as well as satisfying any other local IRB/EC regulations regarding reporting. Copies of all reports to and correspondence with and from the IRB/EC must be provided to Halozyme. Furthermore, at the completion or early termination of the study, a final report should be made to the IRB/EC by the Investigator within the applicable IRB/EC time frames. A copy of this report will be provided to Halozyme.

Any significant changes or revisions in the study protocol or any changes that may alter patient risk must be approved by Halozyme (and may require FDA/other regulatory agency review and/or approval) and must be approved in writing by the IRB/EC prior to implementation (see Section 12.7 for protocol amendments). The Investigator must also receive a written notice of approval from Halozyme prior to initiating the revised changes to the study protocol. A protocol change intended to eliminate an apparent immediate hazard may be implemented immediately, provided that Halozyme is immediately

notified and an amendment is subsequently provided by Halozyme and approved by the IRB/EC.

It is the Investigator's obligation to maintain an IRB/EC correspondence file, and to make this available for review by Halozyme or its designated representatives as part of the study monitoring process.

12.3. Informed Consent

A copy of the proposed informed consent form (ICF) document must be submitted to Halozyme for review and comment prior to submission to the reviewing IRB/EC. The ICF must be approved by the IRB/EC and contain all elements required by all applicable federal, state, local, and institutional regulations or requirements prior to consenting a patient. Authorization to use or disclose Personal Health Information (PHI) in accordance with requirements of the Health Insurance Portability Act of 1996 (HIPAA) should be covered in the ICF or in a separate document to be signed by the patient.

The proposed ICF must contain a full explanation of the purpose and nature of the study, a description of the procedures, the possible advantages, risks, alternate treatment options, and a statement of confidentiality of patient study records, a statement regarding voluntary compensation and availability of treatment in the case of injury, an explanation of whom to contact about the research, the patient's rights, and notification that participation is voluntary and refusal will involve no penalty or loss of medical benefits. These requirements are in accordance with the U.S. Federal Regulations as detailed in the 21CFR50.25 and the Declaration of Helsinki. The ICF should also indicate by signature that the patient, or where appropriate, legal guardian/representative, permits access to relevant medical records by the Sponsor (Halozyme) and/or the Sponsor's duly appointed agent and by representatives of the U.S. Food and Drug Administration (FDA) or other applicable regulatory agency and permits their data to be used in publications.

The Investigator will be responsible for obtaining written informed consent from potential patients prior to any study specific screening and entry into the study. The research study will be completely explained to each prospective study patient. The Investigator or designee must explain that the patient is free to refuse to enter the study, and free to withdraw from it at any time for any reason. If new safety information becomes available and results in significant changes in the risk/benefit assessment, the ICF should be reviewed and updated if necessary. Under this circumstance, all patients (including those already being treated) should be informed of the new information, given a copy of the revised ICF, and be allowed to re-evaluate their consent to continue in the study.

Each patient (and/or legally authorized representative if the subject is a minor, mentally incompetent or physically incapacitated) found to be eligible for the study must have voluntarily provided written informed consent using the IRB/EC-approved ICF prior to screening procedures or enrollment in the study (i.e., before performing any protocol-dictated procedures that are not part of normal patient care). A copy of the signed and

dated ICF document will be provided to the patient, and a copy will be maintained with the patient's CRFs, or in the study documentation. The original will be retained by the Investigator along with the CRFs. The ICF must be in a language that the patient can read and understand.

12.4. Laboratory Accreditation

Any laboratory facility intended to be used for analysis of clinical laboratory samples required by this protocol must provide evidence of adequate licensure or accreditation. Reference values and/or normal ranges for the test results must be provided to Halozyme. Halozyme must be notified immediately in writing of any changes occurring in reference values during the course of the study.

All local and central laboratories used in the study must have, at a minimum, the following.

- College of American Pathologist (CAP) accreditation, and/or
- Clinical Laboratory Improvement Amendments (CLIA) accreditation
- Listing of laboratory normal reference values (for all protocol required tests)
- Laboratory license
- Curriculum vita of laboratory director may also be requested

12.5. Drug Accountability

Upon receipt of study drug(s), the Investigator, pharmacist or qualified designee is responsible for taking an inventory of the study drug(s). A record of this inventory must be kept and all usage of study drugs must be documented. All vials of study drug, both used and unused, must be retained as discussed in Sections 9.1 and 9.2.

The investigational drug (both MMC and Chemophase) is to be administered/ prescribed only by the Principal Investigator or appropriately qualified physician subinvestigators named on the Form FDA 1572. Under no circumstances will the Investigator(s) allow the investigational drug to be used other than as directed by this protocol. Although appropriate personnel may be designated to administer/dispense drug and maintain drug accountability records, the Principal Investigator is ultimately responsible for all drug accountability.

The Investigator or their designee must maintain accurate records accounting for the receipt of the investigational drug supplies and for the disposition of the drug. Documentation of the disposition of the drug should consist of a dosing record including the identification of the person to whom the drug is dosed, the quantity and the date of dosing, and any unused drug. This record is in addition to any drug accountability information recorded on the CRFs. At study end, unused drug will be reconciled with dosing records. All unused investigational drug shall be returned to Halozyme upon request unless otherwise instructed. A copy of the reconciled drug inventory record will be provided to Halozyme or its designee, and the original will be retained at the site.

12.6. Protocol Compliance and Protocol Deviations

Except for a change that is intended to eliminate an apparent immediate hazard to a study patient, the protocol shall be conducted as specified. Any such change must be reported immediately to Halozyme and to the IRB/EC.

From time to time, it is possible that Halozyme may prospectively authorize protocol deviations if the deviation is minor, and does not place patient at increased risk or the anticipated risk of potential benefit outweighs the anticipated risk of potential harm. All such protocol "waivers" must be provided *in advance* and *in writing* by Halozyme, and will be forwarded to the Investigator for filing with the patient's study records. The Investigator must notify the IRB/EC of any and all protocol deviations according to the applicable IRB/EC policy.

Written documentation of all protocol deviation must be kept in the study center file and provided to Halozyme. Examples of possible protocol deviations include, but are not limited to:

- failure to obtain/maintain approval for research,
- failure to obtain required informed consent,
- failure to collect, report or file AE reports,
- performance of an unapproved study procedure,
- performance of research at an unapproved location, and
- failure to file protocol modifications, and failure to adhere to an approved protocol.

12.7. Protocol Amendments

If the protocol is revised, protocol amendments will be prepared and must be approved by Halozyme. All protocol amendments must be submitted to the IRB/EC for review and approval prior to implementation. However, as discussed in Section 12.2, immediate implementation of a protocol amendment may be necessary if the nature of the amendment concerns the safety of patients and is required to be implemented on an urgent basis to protect the safety of patients. Any such immediate implementation of protocol amendments must be agreed to in advance and in writing by Halozyme. Hard copy documentation of IRB/EC approval must be forwarded to Halozyme.

If an amendment significantly alters the study design, increases potential risk to the subject or otherwise affects statements in the informed consent form (ICF), the ICF must be revised accordingly and submitted to the IRB/EC for review and approval (see Section 12.3). The approved ICF must be used to obtain informed consent from new patients prior to enrollment and must be used to obtain informed consent from patients already enrolled if they are potentially affected by the amendment and wish to continue participation.

12.8. Data Collection and Case Report Forms

In accordance with 21 CFR 312.62, a case report form (CRF) must be completed for each patient enrolled in the study. CRFs are an integral part of the trial and subsequent reports. All data collected for each study patient will be recorded on CRFs provided or approved by Halozyme.

CRFs need not be completed by the Investigator, but all entries in CRFs are the responsibility of the Investigator and entry of CRF data must be made under the supervision of the Investigator. CRF completion may be formally delegated to other study personnel. However, the Sponsor (Halozyme) must be informed in writing of the name of such persons and the scope of their authority. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of all data reported in the CRFs and all required reports for each study patient. It is the obligation of the Investigator to review each page of the CRFs and to sign the designated and appropriate CRFs as the study's authority. The Investigator is also responsible for maintaining any source documentation related to the study, including, but not limited to, any operative reports, laboratory results, radiographic films, tracings, and computer discs, files or tapes.

CRFs must be completed legibly, preferably with **black ballpoint pen**. A correction should be made by striking through the incorrect entry with a single line and entering the correct information adjacent to the incorrect entry. The correction must be initialed and dated by the person making the correction. Erasure or the use of correction fluid or film is unacceptable. Entries to the CRFs should be made only in the spaces provided, and not in the margins. Information that cannot be accommodated by the spaces provided should be entered on the comments CRF page.

For each study patient, the completed CRFs must be promptly reviewed, and required pages signed and dated by the Investigator. The original copy of all CRFs will be reviewed and retrieved by the Study Monitor representing Halozyme. The Investigator must retain a copy of all CRFs.

12.9. Study Initiation, Monitoring and Closeout Visits and Reports

Representatives of Halozyme, in conjunction with Study Monitor(s) representing Halozyme, will perform a number of on-site visits to the study center. Prior to commencement of the study, representatives of Halozyme will visit the study center to assure adequacy of facilities to conduct the protocol, and to discuss with the Investigator the general obligations regarding studies with investigational new drugs. This visit will be documented in a report. If the study center has participated in a clinical trial in conjunction with Halozyme within one year, this Pre-Study Qualification visit may be waived.

Upon satisfactory receipt of all necessary documentation (including, but not limited to, an allowed IND, the FDA Form 1572, an executed Clinical Trials Agreement, and IRB/EC approval of the protocol and informed consent form), Halozyme or its designee

monitor(s) will arrange for all study material to be delivered to the study center and for the scheduling of a mutually convenient appointment for a Study Initiation visit. Patient entry must not begin until this initiation visit by Halozyme or its designee personnel has been made. At this meeting, all personnel expected to be involved in the conduct of the study should undergo an orientation to include review of the study protocol, instruction for CRF completion, and overall responsibilities including those for drug accountability and study file maintenance. This visit will be documented in a report.

Throughout the course of the study, the Halozyme or its designee monitor(s) will make frequent contacts with the Investigator. Study Monitors representing Halozyme will visit study centers periodically throughout the trial for Routine Monitoring visits. The Study Monitor will review CRFs to verify that they are accurate, complete and verifiable from source documents. They will also verify the rights and well-being of the study patients are protected and that the study conduct is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirements. As part of the data review it is expected that source documents (e.g., hospital records, office records) will be made available for review by Halozyme or its designee monitor(s). The study and its monitors may also be similarly evaluated by auditors representing Halozyme. For these purposes, the Investigator will make CRFs, source documents and study files available when requested. A report will be generated for each monitoring visit.

At fulfillment of patient enrollment, each Investigator will be notified in writing by Halozyme. The study will be terminated and the study center closed when all completed original CRFs have been collected, all data discrepancies resolved, and drug accountability has been reconciled. A Closeout visit will be scheduled for study centers that enrolled at least one patient, during which Halozyme or its representative will review all informed consents, CRFs, drug accountability records, and other study-related documents. Halozyme or its representative will hold a final meeting with the Investigator and study staff to explain procedures for record retention, publication policy, site audit notification, and financial disclosure. A final letter to the site will record the events of this closeout visit. Study-closure activities will be documented in a report. It will be the responsibility of the Investigator to notify the IRB/EC that the study has been completed (see Section 12.11).

The Sponsor (Halozyme) has the right to terminate the study for non-adherence to protocol, unavailability of the Investigator or his or her study staff for Halozyme or its designee monitoring personnel, or for administrative reasons, at any time. In that event, Halozyme will notify each Investigator in writing that the study is to be discontinued. The Investigator will comply with the Halozyme's written instructions for study discontinuation, which will include the following:

- Date discontinuation will occur,
- Rationale for discontinuation,
- Instructions on how discontinuation is to be performed,
- Instructions for patients participating in the study, and
- Instructions for retention of study documents.

In addition to monitoring by Halozyme or its designees, the study may be audited by representatives of the Food and Drug Administration (FDA), who will also be allowed access to study documents. The Investigator should immediately notify the Clinical Research Department at Halozyme of any proposed or scheduled audits with any regulatory authorities.

12.10. Study Documentation and Retention of Records

All records of this clinical study must be retained by the Investigator, including but not limited to, the following.

- Protocol and all protocol amendments
- All signed versions of the Statement of Investigator, Form FDA 1572
- All drug accountability records
- All IRB/EC approvals, correspondence and reports
- Signed and dated informed consent forms for each patient
- Completed CRFs for each patient
- Copies of any other material distributed to patients
- Any advertisements for this study
- The Investigator's final report to the IRB/EC
- Source documents pertaining to the study, including, but not limited to, any operative reports, laboratory results, radiographic films, tracings, and computer discs, files or tapes

The period of time these documents must be maintained is governed by U.S. law and, when applicable, non-U.S., regulations. Some countries require these documents to be maintained for 15 years or longer. All records are to be retained by the Investigator for a minimum of two (2) years after the FDA has approved the new drug application, or after the Sponsor (Halozyme) has notified the Investigator in writing that all investigations of the drug have been discontinued. However, because of international regulatory requirements, Halozyme may request retention for a longer period of time. Therefore, Halozyme or its designee will inform the Investigator when these documents may be destroyed. The Investigator must obtain written approval from the Halozyme prior to destruction of any records.

The Investigator must advise Halozyme in writing if the records are to be moved to a location other than the Investigator's archives. If the Investigator leaves the institution or study center, the records shall be transferred to an appropriate designee, at the study center, who assumes the responsibility for record retention. Notice of such transfer shall be documented in writing and provided to Halozyme.

In the event of accidental loss or destruction of any study records, the Investigator will immediately notify Halozyme in writing. Halozyme or its designee must be notified in writing at least 30 days prior to the intended date of disposal of any study records related to this protocol.

12.11. Investigator's Final Report

Shortly after completion of the Investigator's participation in the study, the Investigator will submit a written report to Halozyme. This report may be a copy of the Investigator's end-of-study report to their IRB/EC, which will include, but not be limited to; notification that the study has concluded, the number of patients enrolled/ treated, and the number of adverse and serious AEs that occurred during the study. The report to the IRB/EC will be consistent with the applicable IRB/EC regulations and time frames.

12.12. Financial Disclosure

Each investigator is required to provide financial disclosure statements or certifications to Halozyme prior to study initiation. In accordance with 21 CFR 54, Investigators and all subinvestigators are required to disclose all financial interests in the Sponsor (Halozyme) in order to permit complete and accurate certification statements in an application for marketing authorization. This includes compensation affected by the outcome of a clinical study, significant equity interest in the Sponsor (Halozyme), and proprietary interest in the tested product. The investigators must promptly update this information if any relevant changes occur during the course of the investigation and over the period of one year following completion of the investigation (see 21 CFR 312.64(d)).

12.13 Disclosure of Data and Publication

All information obtained as a result of this study or during the conduct of this study will be regarded as confidential. All unpublished information relating to this drug or to the operations of the Sponsor (Halozyme), including clinical indications, formula, methods of manufacture, and any other related scientific data provided to or developed by the Investigator, is confidential and shall remain the sole property of the Sponsor (Halozyme). The Investigator agrees to use the information for the purpose of carrying out this study and for no other purpose, unless prior written permission from the Sponsor (Halozyme) is obtained. The Sponsor has full ownership of the CRFs and database resulting from this study.

Disclosures (i.e., any release of information to any third party not noted herein) of any not previously known to be public information and/or results of the investigation for publication or by oral or poster presentation shall not be made earlier than 45 days after submission of the proposed material to the Sponsor (Halozyme) for inspection, unless the Sponsor consents to earlier disclosure. Any proposed publication must be submitted to the at least 40 days prior to intended submission for publication. Publication or presentation of any study information, whether presented orally or in writing, may not be undertaken either during or after the study without Sponsor's (Halozyme's) express written approval. The Sponsor (Halozyme) may, for any reason, withhold approval for publication or presentation. If the Investigator is to be listed as an author of a publication prepared by the Sponsor (Halozyme), the Investigator will be given 40 days for review of the manuscript prior to publication. The Investigator expressly agrees that no publication

of interim, non-final, data will occur without the written authorization of the Sponsor (Halozyme). The Investigator will take appropriate cognizance of the Sponsor's (Halozyme's) suggestions before disclosure for publication or presentation consistent with protection of the Sponsor's right to its confidential data.

The Investigator agrees that results from this study may be used by the Sponsor (Halozyme) for purposes of domestic and international new drug registration, for publication, and to inform medical and pharmaceutical professionals. Regulatory authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

13. REFERENCES

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2. Draft FDA Requirements for Approval of Drugs to Treat Superficial Bladder Cancer, 19 December 1988. Draft guidance document later withdrawn by FDA.

3. Report on the management of non-muscular-invasive bladder cancer (Stages Ta, T1 and Tis). Bladder cancer guidelines panel, American Urological Association, Inc. 1999.

4. BCCancer Drug Manual, http://www.bccancer.bc.ca/HPI/DrugDatabase/DrugIndexPro/Mitomycin.htm

5. Novopharm product labeling for MMC, at www.rxmed.com

6. Reich SD, Clinical pharmacology of mitomycin C. In: Carter S, Crooke ST, editors. Mitomycin C, current status and new developments. New York: Academic;1979;243-250.

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12. Common Terminology Criteria for Adverse Events (CTCAE), National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services, http://ctep.cancer.gov/reporting/ctc.html.

13. Baumgartner G, Gomar-Höss Ch, Sakr L, Ulsperger E, Wogritsch Ch. The impact of extracellular matrix on the chemoresistance of solid tumors – experimental and clinical result of hyaluronidase as additive to cytostatic chemotherapy. Cancer Letter 1998;131:85-99.

14. Au JL-S, Badalament RA, Wientjes MG, Young DC, Warner JA, Venema PL, et al. Methods to improve efficacy of intravesical mitomycin C: Results of a randomized Phase III trial. J Nat Cancer Inst 2001;93(8):597-604.

15. Lamm DL, Blumenstein BA, Crawford ED, Crissman JD, Lowe BA, Smith JA, et al. Randomized intergroup comparison of bacillus Calmette-Guerin immunotherapy and mitomycin C chemotherapy prophylaxis in superficial transitional cell carcinoma of the bladder. Urol Oncol 1995;1:119-126.

14. APPENDICES

Appendix A. TNM Staging of Bladder Cancer

TNM DEFINITIONS

Primary tumor (T)

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- ***Ta: Noninvasive papillary carcinoma**
- ***Tis: Carcinoma *in situ*: "flat tumor"**
- ***T1: Tumor invades subepithelial connective tissue**
- T2: Tumor invades muscle
  - pT2a: Tumor invades superficial muscle (inner half)
  - pT2b: Tumor invades deep muscle (outer half)
- T3: Tumor invades perivesical tissue
  - pT3a: Microscopically
  - pT3b: Macroscopically (extravesical mass)
- T4: Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, or abdominal wall
  - T4a: Tumor invades the prostate, uterus, vagina
  - T4b: Tumor invades the pelvic wall, abdominal wall

(*Note: The suffix "m" should be added to the appropriate T category to indicate multiple lesions. The suffix "is" may be added to any T to indicate the presence of associated carcinoma in situ.)*

Regional lymph nodes (N)

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Metastasis in a single lymph node, 2 cm or less in greatest dimension
- N2: Metastasis in a single lymph node, more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, none more than 5 cm in greatest dimension
- N3: Metastasis in a lymph node, more than 5 cm in greatest dimension

Distant metastasis (M)

- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

* Acceptable stage for enrollment in this study.

AJCC STAGE GROUPINGS

Stage 0a
- ***Ta, N0, M0**

Stage 0is
- ***Tis, N0, M0**

Stage I
- ***T1, N0, M0**

Stage II
- T2a, N0, M0
- T2b, N0, M0

Stage III
- T3a, N0, M0
- T3b, N0, M0
- T4a, N0, M0

Stage IV
- T4b, N0, M0
- Any T, N1, M0
- Any T, N2, M0
- Any T, N3, M0
- Any T, any N, M1

* Acceptable stage for enrollment in this study.

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Appendix B. Karnofsky Performance Status

ECOG*	Karnofsky	Definitions
0	***100%**	Normal; no complaints; no signs or symptoms of disease.
1	***90%**	Able to carry on normal activity; minor signs or symptoms of disease.
	***80%**	Normal activity with effort; some signs or symptoms of disease.
2	**70%**	Cares for self; unable to carry on normal activity or to do active work.
	60%	Requires occasional assistance, but is able to care for most of his or her needs.
3	**50%**	Requires considerable assistance and frequent medical care.
	40%	Disabled; requires special care and assistance.
4	**30%**	Severely disabled; hospitalization is indicated although death not imminent.
	20%	Very sick; hospitalization necessary; active supportive treatment necessary.
	10%	Moribund; fatal processes progressing rapidly.
	0%	Dead.

***** ECOG = Eastern Cooperative Oncology Group

* Acceptable status for enrollment in this study.

Appendix C. United Stages Package Insert for Mitomycin

IV Fluid	Stability
5% Dextrose Injection	3 hours
0.9% Sodium Chloride Injection	12 hours
Sodium Lactate Injection	24 hours

4. **The combination** of mitomycin (5 mg to 15 mg) and heparin (1,000 units to 10,000 units) in 30 mL of 0.9% Sodium Chloride Injection is stable for 48 hours at room temperature.

Procedures For Proper Handling and Disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of he procedures recommended in the guidelines are necessary or appropriate.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solu ion and container permit.

HOW SUPPLIED

Mitomycin for Injection is supplied in the following package strengths:

NDC 55390-251-01 5 mg; individually-boxed vial
NDC 55390-252-01 20 mg; individually-boxed vial
NDC 55390-253-01 40 mg; individually-boxed vial

Store vials of unreconstituted product at controlled room temperature, 15° to 30°C (59° to 86°F).

REFERENCES

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3. National Study Commission on Cytotoxic Exposure—Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Sc.D., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
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MANUFACTURED BY:
Ben Venue Laboratories, Inc.
Bedford, OH 44146

MANUFACTURED FOR:
Bedford Laboratories™
Bedford, Ohio 44146

June 2000 MIT-P03

BEDFORD LABORATORIES™

MITOMYCIN FOR INJECTION, USP

Rx ONLY.

WARNINGS

Mitomycin should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facili ies are readily available.

Bone marrow suppression, notably hrombocytopenia and leukopenia, which may contribute to overwhelming infec ions in an already compromised patient, is he most common and severe of the toxic effects of mitomycin (see "**WARNINGS**" and "**ADVERSE REACTIONS**" Sections).

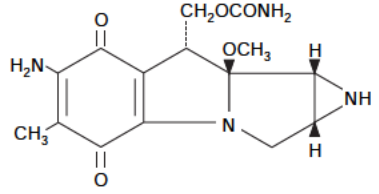
Hemolytic Uremic Syndrome (HUS) a serious complication of chemotherapy, consisting primarily of microangiopathic hemolytic anemia, thrombocytopenia, and irreversible renal failure, has been reported in patients receiving systemic mitomycin. The syndrome may occur at any time during systemic therapy with mitomycin as a single agent or in combination with other cytotoxic drugs; however, most cases occur at doses ≥ 60 mg of mitomycin. Blood product transfusion may exacerbate the symptoms associated with this syndrome.

The incidence of the syndrome has not been defined.

DESCRIPTION

Mitomycin (also known as mitomycin-C) is an antibiotic isolated from he broth of *Streptomyces caespitosus* which has been shown to have antitumor ac ivity. The compound is heat stable, has a high melting point, and is freely soluble in organic solvents.

Mitomycin for Injection is a sterile dry mixture of mitomycin and mannitol, which, when reconstituted with Sterile Water for Injection, provides a solution for intravenous administration. Each vial contains either mitomycin 5 mg and mannitol 10 mg, or mitomycin 20 mg and mannitol 40 mg, or mitomycin 40 mg and mannitol 80 mg.



$C_{15}H_{18}N_4O_5$ M.W. = 334.33

CLINICAL PHARMACOLOGY

Mitomycin selectively inhibits he synthesis of deoxyribonucleic acid (DNA). The guanine and cytosine content correlates with the degree of mitomycin-induced cross-linking. At high concentrations of the drug, cellular RNA and protein synthesis are also suppressed.

In humans, mitomycin is rapidly cleared from the serum after intravenous administration. Time required to reduce the serum concentration by 50% after a 30 mg bolus injection is 17 minutes. After injection of 30 mg, 20 mg, or 10 mg IV, the maximal serum concentrations were 2.4 mcg/mL, 1.7 mcg/mL, and 0 52 mcg/mL, respectively. Clearance is affected primarily by metabolism in the liver, but metabolism occurs in o her issues as well. The rate of clearance is inversely proportional to the maximal serum concentration because, it is thought, of saturation of the degrada ive pa hways.

Approximately 10% of a dose of mitomycin is excreted unchanged in he urine. Since metabolic pathways are saturated at relatively low doses, the percent of a dose excreted in urine increases with increasing dose. In children, excretion of intravenously administered mitomycin is similar.

Animal Toxicology: Mitomycin has been found to be carcinogenic in rats and mice. At doses approximating he recommended clinical dose in man, it produces a greater than 100% increase in tumor incidence in male Sprague-Dawley rats, and a greater than 50% increase in tumor incidence in female Swiss mice.

INDICATIONS AND USAGE

Mitomycin for Injection is not recommended as single-agent, primary therapy. It has been shown to be useful in the therapy of disseminated adenocarcinoma of the stomach or pancreas in proven combinations with other approved chemotherapeutic agents and as palliative treatment when other modalities have failed. Mitomycin is not recommended to replace appropriate surgery and/or radiotherapy.

CONTRAINDICATIONS

Mitomycin is contraindicated in patients who have demonstrated a hypersensitive or idiosyncratic reaction to it in the past.

Mitomycin is contraindicated in patients with thrombocytopenia, coagulation disorder, or an increase in bleeding tendency due to other causes.

WARNINGS

Patients being treated with mitomycin must be observed carefully and frequently during and after therapy.

The use of mitomycin results in a high incidence of bone marrow suppression, particularly thrombocytopenia and leukopenia. Therefore, the following studies should be obtained repeatedly during therapy and for at least 8 weeks following therapy: platelet count, white blood cell count, differential, and hemoglobin. The occurrence of a platelet count below 100,000/mm^3 or a WBC below 4,000/mm^3 or a progressive decline in either is an indication to withhold further therapy until blood counts have recovered above these levels.

Patients should be advised of the potential toxicity of this drug, particularly bone marrow suppression. Deaths have been reported due to septicemia as a result of leukopenia due to the drug.

Patients receiving mitomycin should be observed for evidence of renal toxicity. Mitomycin should not be given to patients with a serum creatinine greater than 1.7 mg percent.

Usage in Pregnancy: Safe use of mitomycin in pregnant women has not been established. Teratological changes have been noted in animal studies. The effect of mitomycin on fertility is unknown.

PRECAUTIONS

Acute shortness of breath and severe bronchospasm have been reported following the administration of vinca alkaloids in patients who had previously or simultaneously received mitomycin. The onset of this acute respiratory distress occurred within minutes to hours after the vinca alkaloid injection. The total number of doses for each drug has varied considerably. Bronchodilators, steroids and/or oxygen have produced symptomatic relief.

A few cases of adult respiratory distress syndrome have been reported in patients receiving mitomycin in combination with other chemotherapy and maintained at FIO_2 concentrations greater than 50% perioperatively. Therefore, caution should be exercised using only enough oxygen to provide adequate arterial saturation since oxygen itself is toxic to the lungs. Careful attention should be paid to fluid balance and overhydration should be avoided.

Bladder fibrosis/contraction has been reported with intravesical administration (not an approved route of administration), which in rare cases has required cystectomy.

Nursing Mothers: It is not known if mitomycin is found in human milk. Because many drugs are found in milk, it is recommended that women receiving mitomycin not breast feed because of the potential for serious adverse reactions from mitomycin in nursing infants.

Pediatric Use: Safety and effectiveness in pedriatric patients have not been established.

ADVERSE REACTIONS

Bone Marrow Toxicity: This was the most common and most serious toxicity, occurring in 605 of 937 patients (64.4%). Thrombocytopenia and/or leukopenia may occur anytime within 8 weeks after onset of therapy with an average time of 4 weeks. Recovery after cessation of therapy was within 10 weeks. About 25% of the leukopenic or thrombocytopenic episodes did not recover. Mitomycin produces cumulative myelosuppression.

Integument and Mucous Membrane Toxicity: This has occurred in approximately 4% of patients treated with mitomycin. Cellulitis at the injection site has been reported and is occasionally severe. Stomatitis and alopecia also occur frequently. Rashes are rarely reported. The most important dermatological problem with this drug, however, is the necrosis and consequent sloughing of tissue which results if the drug is extravasated during injection. Extravasation may occur with or without an accompanying stinging or burning sensation and even if there is adequate blood return when the injection needle is aspirated. There have been reports of delayed erythema and/or ulceration occurring either at or distant from the injection site, weeks to months after mitomycin, even when no obvious evidence of extravasation was observed during administration. Skin grafting has been required in some cases.

Renal Toxicity: 2% of 1,281 patients demonstrated a statistically significant rise in creatinine. There appeared to be no correlation between total dose administered or duration of therapy and the degree of renal impairment.

Pulmonary Toxicity: This has occurred infrequently but can be severe and may be life-threatening. Dyspnea with a nonproductive cough and radiographic evidence of pulmonary infiltrates may be indicative of mitomycin-induced pulmonary toxicity. If other etiologies are eliminated, mitomycin therapy should be discontinued. Steroids have been employed as treatment of this toxicity, but the therapeutic value has not been determined. A few cases of adult respiratory distress syndrome have been reported in patients receiving mitomycin in combination with other chemotherapy and maintained at FIO_2 concentrations greater than 50% perioperatively.

Hemolytic Uremic Syndrome (HUS): This serious complication of chemotherapy, consisting primarily of microangiopathic hemolytic anemia (hematocrit ≤ 25%), thrombocytopenia (≤ 100,000/mm^3), and irreversible renal failure (serum creatinine ≥ 1.6 mg/dL) has been reported in patients receiving systemic mitomycin. Microangiopathic hemolysis with fragmented red blood cells on peripheral blood smears has occurred in 98% of patients with the syndrome. Other less frequent complications of the syndrome may include pulmonary edema (65%), neurologic abnormalities (16%), and hypertension. Exacerbation of the symptoms associated with HUS has been reported in some patients receiving blood product transfusions. A high mortality rate (52%) has been associated with this syndrome.

The syndrome may occur at any time during systemic therapy with mitomycin as a single agent or in combination with other cytotoxic drugs. Less frequently, HUS has also been reported in patients receiving combinations of cytotoxic drugs not including mitomycin. Of 83 patients studied, 72 developed the syndrome at total doses exceeding 60 mg of mitomycin. Consequently, patients receiving ≥ 60 mg of mitomycin should be monitored closely for unexplained anemia with fragmented cells on peripheral blood smear, thrombocytopenia, and decreased renal function.

The incidence of the syndrome has not been defined.

Therapy for the syndrome is investigational.

Cardiac Toxicity: Congestive heart failure, often treated effectively with diuretics and cardiac glycosides, has rarely been reported. Almost all patients who experienced this side effect had received prior doxorubicin therapy.

Acute Side Effects Due to Mitomycin were fever, anorexia, nausea, and vomiting. They occurred in about 14% of 1,281 patients.

Other: Headache, blurring of vision, confusion, drowsiness, syncope, fatigue, edema, thrombophlebitis, hematemesis, diarrhea, and pain. These did not appear to be dose related and were not unequivocally drug related. They may have been due to the primary or metastatic disease processes. Malaise and asthenia have been reported as part of postmarketing surveillance. Bladder fibrosis/contraction has been reported with intravesical administration (see **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION

Mitomycin should be given intravenously only, using care to avoid extravasation of the compound. If extravasation occurs, cellulitis, ulceration, and slough may result.

Each vial contains either mitomycin 5 mg and mannitol 10 mg, or mitomycin 20 mg and mannitol 40 mg, or mitomycin 40 mg and mannitol 80 mg. To administer, add Sterile Water for Injection, 10 mL 40 mL, or 80 mL, respectively. Shake to dissolve. If product does not dissolve immediately, allow to stand at room temperature until solution is obtained.

After full hematological recovery (see guide to dosage adjustment) from any previous chemotherapy, the following dosage schedule may be used at 6- to 8-week intervals:

20 mg/m^2 intravenously as a single dose via a functioning intravenous catheter.

Because of cumulative myelosuppression, patients should be fully reevaluated after each course of mitomycin, and the dose reduced if the patient has experienced any toxicities. Doses greater than 20 mg/m^2 have not been shown to be more effective and are more toxic than lower doses.

The following schedule is suggested as a guide to dosage adjustment:

Nadir After Prior Dose		Percentage of Prior Dose To be Given
Leukocytes/mm^3	Platelets/mm^3	
>4000	>100,000	100%
3000–3999	75,000–99,999	100%
2000–2999	25,000–74,999	70%
<2000	<25,000	50%

No repeat dosage should be given until leukocyte count has returned to 4000/mm^3 and platelet count to 100,000/mm^3.

When mitomycin is used in combination with other myelosuppressive agents, the doses should be adjusted accordingly. If the disease continues to progress after two courses of mitomycin, the drug should be stopped since chances of response are minimal.

Stability

1. **Unreconstituted** mitomycin stored at controlled room temperature is stable for the lot life indicated on the package. Avoid excessive heat (over 40°C).
2. **Reconstituted** with Sterile Water for Injection to a concentration of 0.5 mg per mL, mitomycin is stable for 14 days refrigerated or 7 days at room temperature. Protect reconstituted solution from light.
3. **Diluted** in various IV fluids at room temperature, to a concentration of 20 to 40 micrograms per mL:

Appendix D. Canadian Package Insert for Mitomycin

A DRUG NAME: MITOMYCIN

SYNONYM(S): Mitomycin C, MMC

COMMON TRADE NAME(S): Mutamycin® (Bristol), Mitomycin (Mayne) (Novopharm)

B MECHANISM OF ACTION AND PHARMACOKINETICS

Mitomycin is a purple antibiotic isolated from Streptomyces caespitosus. Clinical trials were begun in the United States in the late 1960's. Mitomycin is activated in vivo to a bifunctional and trifunctional alkylating agent. Binding to DNA leads to cross-linking and inhibition of DNA synthesis and function. Mitomycin is cell cycle phase-nonspecific.

Oral Absorption	Erratic	
Distribution	Detectable levels in kidney, muscles, heart, lungs, intestine and stomach, found in ascites	
	Cross blood brain barrier?	No
	Vd	16-56 L/m^2
	PPB	No information found
Metabolism	Prodrug activated in vivo, primary means of elimination is by hepatic metabolism	
	Active metabolite(s)	Yes
	Inactive metabolite(s)	Yes
Excretion	Excreted in urine, detected in bile and feces, biliary level may exceed plasma level	
	Urine	10% excreted unchanged in urine
	t ½ α	8 minutes
	t ½ β	48 minutes
	Cl	201-801 mL/min/m^2

C INDICATIONS AND STATUS

Topical
* Bladder cancer (superficial)

Systemic
* Gastric cancer (palliative)
* Colorectal cancer (palliative)

Other uses include:

Breast cancer
Cervical cancer
Head and neck cancer
Pancreatic cancer
Biliary cancer

* *Health Canada approved indication*

D ADVERSE EFFECTS

ORGAN SITE	SIDE EFFECT	ONSET		
Cardiac	Thromboembolism		E	
	Cardiac failure (rare, with prior anthracyclines)		E	
Central nervous system	Headache		E	
	Ataxia			
	Blurred vision			
	Acute encephalopathy (rare)		E	D
Dermatologic	Alopecia		E	
	Blue bands in nails (rare)		E	
	Rash	I		
	Palmar erythema with desquamation		E	
	Radiation recall reaction (rare)	I		
Extravasation hazard (refer to **Appendix 2)**	**VESICANT**	I	E	
Gastrointestinal	Nausea and vomiting	I		
	Diarrhea		E	
	Stomatitis		E	
	Anorexia		E	
Hematologic	Myelosuppression		E	
Hypersensitivity	Fever		I	
Injection site	Chemical phlebitis		I	
Pulmonary	Interstitial pneumonitis, ARDS		E	
	Acute respiratory symptoms especially with vinca's			
	Chronic fibrosis		D	

D **ADVERSE EFFECTS**

ORGAN SITE	SIDE EFFECT	ONSET
Renal/metabolic	Cystitis / fibrosis (with intravesical use, 25%)	I
	Increased BUN	
	Renal failure and hemolytic uremic syndrome (10%)	D
Reproductive	Amenorrhea	E
Other	Hypoglycaemia	
	Fatigue	

Dose-limiting side effects are underlined.
I = immediate (onset in hours to days); E = early (days to weeks);
D = delayed (weeks to months); L = late (months to years)

Myelosuppression is major dose limiting adverse effect, and may be cumulative. Onset is late at 3-4 weeks, with recovery by 8 – 10 weeks. ***Nausea and vomiting*** occur within 1-2 hours following administration. Vomiting usually subsides, but nausea may continue for 2-3 days.

The ***tissue necrosis*** that happens with ***extravasation*** may happen days to weeks after the treatment. Patients must be observed for delayed reactions and prior injection sites carefully inspected. Soft tissue ulceration distal to the injection site following uneventful injection in a peripheral vein has been reported.

Pulmonary toxicity consisting of dyspnea, non-productive cough has been reported with an incidence of 2.8-12%. Approximately 40% of patients who develop pulmonary toxicity will die of progressive pulmonary dysfunction. Threshold dose associated with pulmonary toxicity appears to be 50-60 mg/m ^{2}. Steroids may be of some benefit. Acute respiratory distress syndrome may occur with high FIO_2 concentrations or with combination chemotherapy.

A syndrome of ***renal failure and microangiopathic hemolytic anemia*** (hemolytic-uremic syndrome) has been reported in 10% of patients. This syndrome appears to have a threshold of 50-60 mg/m ^{2} and usually appears after 6 months of therapy. Patients should be monitored for development of renal failure or hemolysis.

The incidence of ***cardiotoxicity*** may be increased in patients receiving mitomycin in combination with doxorubicin or in patients who have had prior exposure to doxorubicin. No studies report cardiotoxicity in patients only receiving mitomycin. ***Genitourinary irritation*** following intravesical (bladder) administration includes dysuria, cystitis, nocturia, increased micturition and hematuria. Myelosuppression has not been noted with intravesical administration.

Mitomycin has the potential to enhance radiation injury to tissues. While often called ***radiation recall reactions***, the timing of the radiation may be before, concurrent with or even after the administration of the mitomycin. Recurrent injury to a previously radiated site may occur weeks to months following radiation.

E DOSING

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of white blood cell count. Dosage may be reduced and/or delayed in patients with bone marrow depression due to cytotoxic/radiation therapy. Patients should not be retreated until haematological recovery has occurred.

***Adults*:**
Intravenous: q4-8w: 10-20 mg/m^2
q6-8w: 2 mg/m^2/day x 5 days, stop x 2 days, repeat x 1
Intravesical: q1w: 20-40 mg in 30-60 ml SWI x 8 weeks

Dosage in myelosuppression: modify according to protocol by which patient is being treated;

Lowest Value in Preceding Course		
Leucocytes	Platelets	% previous dose
> 3000	> 75,000	100
2-3.99 X 10^3	25-74.99 X 10^3	70
< 2000	< 25,000	50

Dosage in renal failure: do not administer if creatinine > 150 μmol/L

Dosage in hepatic failure: no adjustment required

F ADMINISTRATION GUIDELINES (see Appendix 3a)

- Slow push through sidearm of free flowing IV (Normal Saline); Give 1.5mg/3mL per minute
- Doses may be mixed in 50mL minibag (Normal Saline); Infuse through sidearm of free flowing IV over 10-30 minutes

G SPECIAL PRECAUTIONS

Mitomycin is classified as ***dangerous goods*** under the Transportation of Dangerous Goods Act, and must be declared as such for the purposes of transportation (substance is considered poisonous).

Mitomycin is contraindicated in patients with thrombocytopenia, leukopenia, coagulation disorder, or an increased bleeding tendency due to other causes; with known hypersensitivity or an idiosyncratic reaction to it, or any component of its formulations.

High FIO_2 concentrations (anesthesia, oxygen therapy) should be avoided especially in patients with pulmonary toxicity.

Mitomycin has been shown to be ***carcinogenic and teratogenic*** in animal studies and should not be used in ***pregnancy***. ***Breast feeding*** is not recommended due to the potential secretion into breast milk.

H INTERACTIONS

AGENT	EFFECT	MECHANISM	MANAGEMENT
vinca alkaloids (vincristine, vinblastine, vindesine)	acute bronchospasm	unknown	caution

I RECOMMENDED CLINICAL MONITORING

Recommended Clinical Monitoring

- Clinical exam, including pulmonary, neurological and local site toxicity
- Baseline & periodic renal function tests (if failure suspected)
- Baseline and regular CBC

Suggested Clinical Monitoring

- Blood pressure at each visit
- Baseline and regular liver function tests

J REFERENCES

Cancer Drug Manual (the Manual), 1994, British Columbia Cancer Agency (BCCA)

Compendium of Pharmaceuticals and Specialties. 2004. Mutamycin®. Canadian Pharmacists Association.

Appendix E. United Kingdom Summary of Product Characteristics for Mitomycin

Kyowa Hakko UK Ltd

258 Bath Road
Slough
Berkshire SL1 4DX

Telephone:	[redacted]
Facsimile:	[redacted]
Medical Information e-mail:	medinfo@kyowa-uk.co.uk
Medical Information facsimile:	[redacted]

Document last updated on the *e*MC: **Mon 29 September 2003**

Mitomycin-C Kyowa

1. NAME OF THE MEDICINAL PRODUCT

Mitomycin-C Kyowa 2mg, 10mg, 20mg or 40 mg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Constituent Quantity per vial
Mitomycin-C 2 mg, 10 mg, 20 mg or 40 mg

3. PHARMACEUTICAL FORM

Sterile powder for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Antimitotic and Cytotoxic

Recommended for certain types of cancer in combination with other drugs or after primary therapy has failed. It has been successfully used to improve subjective and objective symptoms in a wide range of neoplastic conditions.
1. As a single agent in the treatment of superficial bladder cancer. In addition it has been shown that post-operative instillations of Mitomycin-C can reduce recurrence rates in newly diagnosed patients with superficial bladder cancer.
2. As a single agent and in combination with other drugs in metastatic breast cancer.
3. In combination with other agents in advanced squamous cell carcinoma of the uterine cervix.
4. It shows a degree of activity as part of combination therapy in carcinoma of the stomach, pancreas and lung (particularly non-small cell).
5. It shows a degree of activity as a single agent and in combination in liver cancer when given by the intra-arterial route.

6. It has a possible role in combination with other cytotoxic drugs in colo-rectal cancer.
7. It shows a degree of activity as a single agent or part of combination therapy in cancer of the head and neck.
8. It shows a degree of activity as a single agent in cancer of the prostate.
9. It has a possible role in skin cancer.
10. It has a degree of activity in leukaemia and non-solid tumours.
11. It has a possible role in sarcomas.
12. It has been successfully used in combination with surgery, pre-operatively (oesophageal squamous cell carcinoma) and post-operatively (gastric cancer).
13. It has shown to be effective when used in combination with radiotherapy.

4.2 Posology and method of administration

For parenteral use.

Intravenously, the dose should be given with great care in order to avoid extravasation. The usual dose is in the range of 4 – 10mg (0.06-0.15mg/kg) given at 1 – 6 weekly intervals depending on whether other drugs are given in combination and on bone marrow recovery. In a number of combination schedules, the dose is 10mg/m^2 of body surface area, the course being repeated at intervals for as long as required. A course ranging from 40-80mg (0.58 – 1.2mg/kg) is often required for a satisfactory response when used alone or in combination. A higher dosage course may be given when used alone or as part of a particular combination schedule and total cumulative doses exceeding 2mg/kg have been given.
For administration into specific tissues, Mitomycin-C Kyowa can be given by the intra-arterial route directly into the tumours.
Because of cumulative myelosuppression, patients should be fully re-evaluated after each course and the dose reduced if the patient has experienced any toxic effects. Doses greater than 0.6mg/kg have not been shown to be more effective and are more toxic than lower doses.
Treatment of superficial bladder tumours : In the treatment of superficial bladder tumours the usual dose is 20-40mg dissolved in 20-40 of diluent, instilled into the bladder through a urethral catheter, weekly or three times a week for a total of 20 doses. The dose should be retained by the patient for a minimum of one hour. During this one-hour period the patient should be rotated every 15 minutes to ensure that the Mitomycin-C comes into contact with all areas of the bladder urthelium.
When the bladder is emptied in the voiding process, care must be taken to ensure that no contamination occurs locally in the groin and genitalia areas.
In the prevention of recurrent superficial bladder tumours, various doses have been used. These include 20mg in 20ml of diluent every two weeks and 40mg in 40ml of diluent monthly or three monthly. The dose is instilled into the bladder through a urethral catheter.

4.3 Contraindications

Patients who have demonstrated a hypersensitive or idiosyncratic reaction to Mitomycin-C Kyowa in the past. Thrombocytopenia, coagulation disorders and increased bleeding tendency.

4.4 Special warnings and special precautions for use

Mitomycin-C Kyowa should be administered under the supervision of a physician experienced in cytotoxic cancer chemotherapy. Local ulceration and cellulitis may be caused by tissue extravasation during intravenous injection and utmost care should be taken in administration.
If extravasation occurs, it is recommended that the area is immediately infiltrated with sodium bicarbonate 8.4% solution, followed by an injection of 4mg dexamethasone. A systemic injection of 200mg of Vitamin B6 may be of some value in promoting the regrowth of tissues that have been damaged.
Mitomycin-C Kyowa should not be allowed to come into contact with the skin. If it does, it should be washed several times with 8.4% sodium bicarbonate solution, followed by soap and water. Hand creams and emollients should not be used as they may assist the penetration of the drug into the epidermal tissue.
In the event of contact with the eye, it should be rinsed several times with 8.4% sodium bicarbonate solution. It should then be observed for several days for evidence of corneal damage. If necessary, appropriate treatment should be instituted.

4.5 Interaction with other medicinal products and other forms of Interaction

Not Known.

4.6 Pregnancy and lactation

Mitomycin-C Kyowa should not normally be administrated to patients who are pregnant or to mothers who are breast-feeding. Teratological changes have been noted in animal studies.

4.7 Effects on ability to drive and use machines

Generalised weakness and lethargy have been reported on rare occasions. If affected, patients should be advised not to drive or operate machinery.

4.8 Undesirable effects

Thrombocytopenia and leucopenia resulting from myelosuppression, which is delayed and cumulative. Patients should be monitored closely during each course of treatment, paying particular attention to peripheral blood count including platelet count. No repeat dose should be given unless the leucocyte count is above 3.0×10^9/L or more and the platelet count is 90×10^9/L or more. The nadir is usually around four weeks after treatment and toxicity is usually cumulative, with increasing risk after each course of treatment. If disease progression continues after two courses of treatment, the drug should be stopped since the chances of response are minimal. Severe renal toxicity has occasionally been reported after treatment and renal function should be monitored before starting treatment and again after each course. Nausea and vomiting are sometimes experienced immediately after treatment, but these are usually mild and of short duration. Pulmonary toxicity and fever have been reported. Skin toxicity may occur in a small proportion of patients, with side effects such as alopecia (although this is less frequent and less severe than with certain other cytotoxic agents). Bleeding, rashes and mouth ulcers have been reported. General

weakness and lethargy have been reported on rare occasions. Other reported effects include anorexia, diarrhoea, stomatitis, interstitial pneumonitis, pulmonary fibrosis and microangiopathic haemolytic anaemia syndrome.

4.9 Overdose

In the unlikely event of accidental overdosage then an increase in the more common side effects should be expected, such as fever, nausea, vomiting and myelosuppression. Appropriate supportive measures should be instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mitomycin-C Kyowa is an antitumour antibiotic that is activated in the tissues to an alkylating agent which disrupts deoxyribonucleic acid (DNA) in cancer cells by forming a complex with DNA and also acts by inhibiting division of cancer cells by interfering with the biosynthesis of DNA.

5.2 Pharmacokinetic properties

In vivo

Mitomycin-C Kyowa is rapidly cleared from the serum after intravenous administration. The time required to reduce the serum concentration by 50% after a 30mg bolus injection is 17 minutes. After injection of 30mg, 20mg or 10mg intravenously, the maximal serum concentrations were 2.4 mcg/ml, 1.7 mcg/ml and 0.52mcg/ml respectively. Clearance is effected primarily by metabolism in the liver, but metabolism occurs in other tissues as well. The rate of clearance is inversely proportional to the maximal serum concentration because, it is thought, of saturation of the degradative pathways. Approximately 10% of a dose of Mitomycin-C Kyowa is excreted unchanged in the urine. Since metabolic pathways are saturated at relatively low doses, the percentage dose excreted in the urine increases with increasing dose. In children, the excretion of intravenously administered Mitomycin-C Kyowa is similar to that in adults.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included elsewhere in the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride Ph.Eur.

6.2 Incompatibilities

Not known

6.3 Shelf life

Four years from the date of manufacture.
After reconstitution, the solution is stable for 24 hours when protected from light and stored in a cool place. Do not refrigerate.

6.4 Special precautions for storage

None.

6.5 Nature and contents of container

Mitomycin-C Kyowa consists of a blue/purple crystalline powder, contained within a colourless, type I or III glass vial with a rubber stopper and an aluminium seal. The vials are packaged into cardboard cartons containing 1, 5 or 10 vials.

6.6 Instructions for use and handling

The contents of the vial should be reconstituted with Water for Injections or saline solution, at least 5 ml for the 2 mg vial, at least 10 ml for the 10 mg vial, at least 20 ml for the 20 mg vial, and at least 40 ml for the 40 mg vial.

Administrative Data

7. MARKETING AUTHORISATION HOLDER

Kyowa Hakko (UK) Ltd
258 Bath Road
Slough
Berkshire
SL1 4DX

8. MARKETING AUTHORISATION NUMBER(S)

PL12196/0001/0002/0003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26th November 1992

10. DATE OF REVISION OF THE TEXT

July 2003