NCT # NCT00318643

Statistical Analysis Plan

Halozyme Therapeutics, Inc.

Protocol Number: HZ2-05-01

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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Approval Sheet

[redacted] Date

Halozyme Therapeutics, Inc.

[redacted] Date

Synteract, Inc.

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1. INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of data collected within the scope of Halozyme Therapeutics, Inc. Protocol Number HZ2-05-01 [A Phase I-IIa, 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]. The purpose of this plan is to provide specific guidelines from which the analysis will proceed. Any deviations from these guidelines must be substantiated by sound statistical reasoning.

2. OBJECTIVES

The primary objectives for this study are the following:

- 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 for this study include:

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

3. STUDY OVERVIEW

This is a Phase I-IIa, open-label, multicenter, dose-escalation, safety, tolerability, and pharmacokinetic study of intravesical treatment with combination of Chemophase and MMC.

Patient may be considered for enrollment in this study if they have initial presentation or recurrence of Stage Ta, T1 or Tis, any grade, bladder cancer after TURBT.

Groups of up to 6 patients will participate in each of the five individual dose cohorts in the dose escalation phase of the study. The amounts of Chemophase to be given for each of the five cohorts are as follows: 20,000 U, 60,000 U, 200,000 U, 400,000 U and 800,000 U. Once the maximum tolerated dose (MTD) has been established, 6 additional

evaluable patients will be enrolled at the MTD dose level. This will provide a total of 12 evaluable patients at MTD upon which to confirm safety and tolerability of the MTD regimen. In total, up to 36 evaluable patients will be enrolled. To reach this number, it is anticipated that no more than 44 patients will need to be enrolled.

The MTD will be determined based on number of patients experiencing a dose-limiting toxicity (DLT) at a particular dose level. A patient will be considered to have experienced a DLT if any of the following occur:

- Plasma MMC Concentration >= 100 ng/mL;
- Adverse Event (AE) with a Common Toxicity Criteria (CTC) grade greater than or equal to 3;
- New, treatment-emergent diagnosis of bladder fibrosis.

For further details on MTD determination, refer to the protocol.

Study patients will receive six weekly study treatments followed by post-treatment evaluations, at Weeks 8 and 12. In addition, the twelve patients receiving the MTD will continue to receive combination therapy every 3 months until the end of year 2 or until the time of documented tumor recurrence, whichever occurs first. Long-term follow-up information for those in the MTD cohort will be collected to help make a preliminary assessment of possible anti-tumor activity.

4. GENERAL ANALYSIS CONSIDERATIONS

Statistical analyses will be reported using summary tables, figures, and data listings. No tests for statistical significance will be performed. All analyses and tabulations will be performed using SAS® Version 8.2 on a PC platform. Continuous variables will be summarized with means, standard deviations, medians, minimums, and maximums. Categorical variables will be summarized by counts and by percentage of patients in corresponding categories. All raw data obtained from the case report forms as well as any derived data will be included in data listings.

5. ANALYSIS SETS

The following patient population sets will be used for analyses:

- The Safety Set will include all patients who received one or more doses of Chemophase. Any patient receiving MMC on study but not receiving Chemophase will be considered for safety, but assessed separately from patients receiving Chemophase for selected analysis;

- The Intent-To-Treat (ITT) Set (for anti-tumor effects) will include all patients receiving one or more doses of Chemophase with MMC. It is recognized that this definition is a modification of the rigid definition of ITT;

- The Per-Protocol Set will include all ITT patients who met the following criteria:
  - Satisfied disease-defining Inclusion Criteria #1 and #2;
  - Received at least 4 protocol-specified doses of Chemophase with MMC over an interval not exceeding 8 weeks;
  - Retained at least 4 intravesical instillations for at least 90 minutes;
  - Were monitored to the time of tumor recurrence, or at least 5 years, whichever occurs first.

Anti-tumor analysis will be performed on the ITT and Per Protocol Sets. In the event all patients in the ITT Set are also in the Per Protocol Set, analysis will only be carried out on the ITT Set.

Baseline and safety analysis will be performed on the Safety Set. Any patient who received MMC on study but not Chemophase will be considered for selected safety assessments; however, those patients will be assessed separately from patients receiving Chemophase.

6. PATIENT DISPOSITION

Patient disposition information will be summarized for all patients. Summaries will include: the number of enrolled patients, the number of patients in each analysis set, the number of patients completing the study without premature withdrawal, and the reasons for not completing the study.

7. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic variables include: age, sex, ethnicity, and race. Other baseline characteristics include: Karnofsky performance status, medical history, urologic history and bladder cancer history. Patient history endpoints to be summarized include the years since initial bladder cancer diagnosis, total number of bladder cancer occurrences, estimated bladder capacity, total number of bladder tumor treatments, total number of bladder cancer surgeries, total number of previous cystoscopies with tumor detected and without tumor detected. When applicable, demographic and baseline characteristics will be summarized.

8. STUDY DRUG ADMINISTRATION

For each visit during the study drug administration phase of the study other than Day 1, patients are expected to receive a pre-specified amount of Chemophase, MMC and sterile saline based on the cohort they are assigned to (on Day 1, patients will only receive MMC). Counts and percentages of those patients who receive the pre-specified dose of study drug as well as those who do not will be displayed by cohort and visit. Also summarized will be the instillation dwell time (end time of instillation minus post-instillation void time).

For amount of study drug and sterile saline to be administered for each cohort at each visit, refer to Table 9.3-A of the protocol.

9. PHARMACOKINETIC ANALYSES

The plasma concentrations for MMC and plasma concentrations of rHuPH20 are part of the study design, but will not be summarized in tabular form as part of the analysis plan. Concentrations will be presented in listings.

10 OTHER ANTI CANCER ANALYSES

Plasma determinations for rHuPH20 neutralizing antibodies are part of this study design, but will not be summarized in tabular form as part of this analysis plan. Plasma determinations for antibodies will be presented in listings.

All patients completing the study will have a cystoscopy performed at the Week 12 visit. For those patients being treated at MTD, cystoscopies will be performed every three months through the end of Year 2 starting 3 months after the last study drug treatment, which is anticipated to be at Week 6. Endpoints to be collected include the cystoscopy result and the estimated bladder capacity. Summaries of these endpoints will be presented by cohort.

Biomarker tests, consisting of NMP22 BladderChek tests and UroVysion tests, are to be conducted during Week 1 and Week 8 of the study. For those patients treated at MTD, these biomarker tests are also to be performed every 3 months, occurring 6 weeks before each every-three-month clinic visit. Results from these tests will be used to construct a shift table with possible results of positive, negative, no valid result and not done for the BladderChek test and negative, positive, equivocal, other and not done for the Urovysion test.

11. SAFETY ANALYSES

All patients who received Chemophase will be included in the safety analyses. Patients who receive MMC, but not Chemophase, will be summarized separately for adverse events. Analysis will consist of point estimates and the 95% confidence interval constructed around the point estimates for the overall incidence of adverse events.

11.1 Adverse Events

The adverse events considered are Treatment Emergent Adverse Events (TEAE) defined as those AEs that occurred after initial study drug dosing (first dose of MMC) and those existing AEs that worsened after initial study drug dosing. All listings and tabular summaries of AEs will be restricted to only TEAEs, except for a separate listing showing only those AEs that are pre-treatment-emergent, should any such AEs exist in the

database. Verbatim terms on case report forms will be mapped to preferred terms and system organ classes using the MedDRA dictionary (version 8.0, or a later version at the discretion of Synteract). If a patient has more than one adverse event mapped to the same preferred term, that adverse event will be reported only once in a given summary table using the highest severity and/or closest relationship to study medication. Patient incidence of adverse events will be displayed by system organ class (SOC) and preferred term. Adverse events will also be summarized by severity and relationship to each study drug (Chemophase, MMC) independently. Patient incidence of serious adverse events (including deaths) will also be displayed. Tabular summaries of AEs will list SOCs according to the internationally agreed order, and within each individual SOC the AEs will be listed in order of decreasing incidence. See Appendix D for the internationally agreed order for SOC.

11.2 Clinical Laboratory Evaluation

Descriptive statistics of clinical laboratory assessment changes will be presented for baseline and each post baseline time point. In addition, shift tables will be presented to assess abnormal laboratory values over time. In constructing shift tables, baseline results will be compared to the most abnormal post baseline result. Laboratory parameters will be classified as low, normal, high and patient counts of shifts from baseline will be presented. The designation of clinical significance will be displayed.

Listings will be provided for laboratory analyte values. Values outside of the normal range will be flagged as either high or low and the designation of clinical significance will be displayed.

11.3 Other Safety Analyses

Complete physical examinations will occur at screening and Week 8. In addition, targeted physical examinations will take place through the study drug administration phase of the study. Shift tables will be created for each body system to show any abnormal result both pre- and post-study drug.

Results for vital signs will be summarized by cohort for each visit. In addition, change from baseline will be presented.

Information for 12-Lead ECG will be collected at screening and Week 8. A shift table of the results for the test will be displayed along with summary statistics of QT, QTc, Heart Rate, P-R Interval and QRS.

The Karnofsky Performance Status will performed on each patient at each visit. Results will be shown by visit and cohort.

11.4 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 in this study. Concomitant medications will be linked to generic terms and ATC classes using the WHO dictionary, Version 4.3. Concomitant medication use will be presented in listings.

12 LONG-TERM FOLLOW-UP

The twelve patients receiving the MTD will continue to receive combination therapy every 3 months until the end of Year 2 or until the time of documented tumor recurrence, whichever occurs first. During this time of extended, long-term, treatment information collected on patients will include vital signs, targeted physical examinations, cystoscopy and urine cytology, urine dipsticks, hematology results, study drug administration, AE collection, concomitant medications and NMP22 BladderChek and UroVysion biomarker tests. Results for endpoints collected will be summarized in similar manner as the regular dosing portion of the study, except results will be presented for only the MTD cohort.

In addition, any patients reported to have tumor recurrences will be recorded. The data will be assessed to make Kaplan Meier estimates of time to tumor recurrence at 6, 12, 18 and 24 months as well as determine median time to tumor recurrence. All other information on tumor recurrences including number of tumors, TNM stage and grading will be shown in listings.

13. SAMPLE SIZE CALCULATION

This is a Phase I-IIa multiple dose study of Chemophase, and is neither designed nor powered for formal statistical comparisons.

APPENDIX A: LIST OF TABLES, FIGURES AND LISTINGS

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APPENDIX B: TABLE LAYOUTS

Table 1
Patient Disposition
All Patients

	20,000 U	60,000 U	200,000 U	400,000 U	800,000 U	Total
Patients Enrolled [1]	n	n	n	n	n	n
Received MMC Only	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Safety Set [2]	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
ITT Set [3]	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Per Protocol Set [4]	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Completed Study Without Premature Withdrawal						
Yes	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
No	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Reasons Patient Did Not Complete Study [5]						
Did not receive all expected instillations of study drug	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Protocol Violation	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Lost to Follow-up	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Adverse Event	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Non-compliance	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patient Decision	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Investigator Decision	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Other	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

Percentage based on number of patients enrolled.
[1] Assigned to a treatment cohort.
[2] Received at least one dose of Chemophase.
[3] Received at least one dose of Chemophase with MMC.
[4] Satisfied Inclusion Criteria 1 and 2; received at least 4 doses of Chemophase with MMC over an interval that did not exceed 8 weeks; retained at least 4 intravesical instillations for at least 90 minutes. Note: the criterion "monitored to the time of tumor recurrence, or at least 5 years, whichever occurs first" was not applied for the generation of this table.
[5] Patient may have more than one reason for not completing study.

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Table 2.1
Demographic Characteristics
Safety Set

	20,000 U (N=)	60,000 U (N=)	200,000 U (N=)	400,000 U (N=)	800,000 U (N=)	Total (N=)
Age (years) [1]						
n	n	n	n	n	n	n
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Sex						
Male	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Female	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Ethnicity						
Hispanic or Latino	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Not Hispanic or Latino	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Race						
White	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Black, of African Heritage	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Asian	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
American Indian or Alaska Native	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Native Hawaiian or Other Pacific Islander	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Other	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Multiple Races						
Combination 1	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Combination 2	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

[1] Age is calculated from the date of informed consent.
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Programmer Note Tables 2.2-2.3 will be for the ITT and Per Protocol Sets (if needed).

Table 3
Abnormal Medical History at Baseline
Safety Set

Body System	20,000 U (N=)	60,000 U (N=)	200,000 U (N=)	400,000 U (N=)	800,000 U (N=)	Total (N=)
Respiratory	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Cardiovascular	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Gastrointestinal	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Hepatic	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Endocrine/Metabolic	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Central Nervous System	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Hematopoietic/Lymphatic	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Dermatological	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Musculoskeletal	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Genitourinary/Reproductive	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Psychiatric	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Alcohol/Drug Abuse	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Drug Allergy	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Non-Drug Allergy	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
HEENT	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Other	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

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Table 4
Urologic History/ Bladder Cancer History
Safety Set

	20,000 U (N=)	60,000 U (N=)	200,000 U (N=)	400,000 U (N=)	800,000 U (N=)	Total (N=)
Years Since Initial Diagnosis [1]						
n	n	n	n	n	n	n
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Total Number of Bladder Cancer Occurrences						
n	n	n	n	n	n	n
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Most Recent Estimated Bladder Capacity (mL)						
n	n	n	n	n	n	n
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

[1] Years Since Initial Diagnosis= (Informed Consent Date- Date of Initial Bladder Cancer Diagnosis + 1)/(365.25).
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Programmer Note: Years Since Initial Diagnosis is calculated as the difference in years between the Date of Initial Bladder Cancer Diagnosis (MHSTDT) and the Date of Informed Consent (IEDT). If only the year of Initial Bladder Cancer Diagnosis is reported then calculate the difference using only the years.

Table 5
Bladder Treatments/ Surgeries/ Procedures
Safety Set

	20,000 U (N=)	60,000 U (N=)	200,000 U (N=)	400,000 U (N=)	800,000 U (N=)	Total (N=)
Total Number of Previous Bladder Tumor Treatments [1]						
n	n	n	n	n	n	n
Mean (SD)	xx.x (xx.xx)	xx.x (xx xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Total Number of Previous Bladder Surgeries						
n	n	n	n	n	n	n
Mean (SD)	xx.x (xx.xx)	xx.x (xx xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Total Number of Previous Cystoscopies With Tumors Detected						
n	n	n	n	n	n	n
Mean (SD)	xx.x (xx.xx)	xx.x (xx xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Total Number of Previous Cystoscopies Without Tumors Detected						
n	n	n	n	n	n	n
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

[1] Each “treatment” may include multiple cycles of the same treatment.
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Table 6
Study Drug Administration
Safety Set

Visit	20,000 U (N=)	60,000 U (N=)	200,000 U (N=)	400,000 U (N=)	800,000 U (N=)	Total (N=)
Week 1, Day 1	n	n	n	n	n	n
Dose of MMC Instilled						
40 mg	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Other	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Volume of MMC Instilled						
20 mL	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Other	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Dwell Time (min) [1]						
N	n	n	n	n	n	n
Mean (SD)	xx.x (xx.xx)	xx.x (xx xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

[1] Dwell Time= (Time of post-instillation voiding- end time of instillation) .
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Programmer Note Table will repeat for each day study drug is administered.

Table 6
Study Drug Administration
Safety Set

Visit	20,000 U (N=)	60,000 U (N=)	200,000 U (N=)	400,000 U (N=)	800,000 U (N=)	Total (N=)
Week 2, Day 8	n	n	n	n	n	n
Volume of Chemophase Instilled						
Expected Volume	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Other	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Units of Chemophase Instilled						
Expected Units	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Other	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Volume of Saline Instilled						
Expected Volume	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Other	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Dose of MMC Instilled						
40 mg	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Other	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Volume of MMC Instilled						
20 mL	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Other	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total Volume Instilled						
28 mL	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Other	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Dwell Time (min) [1]						
N	n	n	n	n	n	n
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

[1] Dwell Time= (Time of post-instillation voiding- end time of instillation) .
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Programmer Note Table will repeat for each day study drug is administered.

Table 7
Cystoscopy at Week 12
ITT Set

	20,000 U (N=)	60,000 U (N=)	200,000 U (N=)	400,000 U (N=)	800,000 U (N=)	Total (N=)
Result	n	n	n	n	n	n
Normal	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Abnormal, Not Clinically Significant	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Abnormal, Clinically Significant	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Estimated Bladder Capacity Volume						
n	n	n	n	n	n	n
Mean (SD)	xx.x (xx xx)	xx.x (xx.xx)	xx x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Absence of Tumor Recurrence Verified						
Yes	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
No	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Not Applicable	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

path\t_program.sas date time

Programmer Note Table using ITT Set will be renumbered to 7.1 if analysis for Per Protocol Set is needed. Table number for Per Protocol Set will be 7.2.

Table 8.1
NMP22 BladderChek Biomarker Test at Week 8
ITT Set
Part 1 of 2

	Baseline [1]																			
	20,000 U (N=)				60,000 U (N=)				200,000 U (N=)				400,000 U (N=)				800,000 U (N=)			
Time Point	Neg	Pos	Inv[2]	ND[3]	Neg	Pos	Inv[2]	ND[3]	Neg	Pos	Inv[2]	ND[3]	Neg	Pos	Inv[2]	ND[3]	Neg	Pos	Inv[2]	ND[3]
Week 8	n				n				n				n				n			
Negative	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Positive	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
No Valid Result (Invalid)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Not Done	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

[1] Baseline defined as measurement taken most closely prior to first study drug administration.
[2] Inv= No Valid Result (Invalid)
[3] ND= Not Done
If more than one test results is collected, the last repeated test is used.
path\t_program.sas date time

Programmer Note Table using ITT Set will be renumbered to 8.1.1 if analysis for Per Protocol Set is needed. Table number for Per Protocol Set will be 8.1.2.

Table 8.1
NMP22 BladderChek Biomarker Test at Week 8
ITT Set
Part 2 of 2

	Baseline [1]			
	Total (N=)			
Time Point	Neg	Pos	Inv[2]	ND[3]
Week 8	n			
Negative	n (%)	n (%)	n (%)	n (%)
Positive	n (%)	n (%)	n (%)	n (%)
No Valid Result (Invalid)	n (%)	n (%)	n (%)	n (%)
Not Done	n (%)	n (%)	n (%)	n (%)

[1] Baseline defined as measurement taken most closely prior to first study drug administration.
[2] Inv= No Valid Result (Invalid)
[3] ND= Not Done
If more than one test results is collected, the last repeated test is used.
path\t_program.sas date time

Programmer Note Table using ITT Set will be renumbered to 8.1.1 if analysis for Per Protocol Set is needed. Table number for Per Protocol Set will be 8.1.2.

Table 8.2
UroVysion FISH Biomarker Test at Week 8
ITT Set

	Baseline [1]																			
	__20,000 U (N=)__					__60,000 U (N=)__					__200,000 U (N=)__					__400,000 U (N=)__				
Time Point	Neg	Pos	Eq[2]	Oth[3]	ND[4]	Neg	Pos	Eq[2]	Oth[3]	ND[4]	Neg	Pos	Eq[2]	Oth[3]	ND[4]	Neg	Pos	Eq[2]	Oth[3]	ND[4]
Week 8	n					n					n					n				
Negative	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Positive	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Equivocal	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Other	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Not Done	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

[1] Baseline defined as measurement taken most closely prior to first study drug administration.
[2] Eq= Equivocal
[3] Oth= Other
[4] ND= Not Done

path\t_program.sas date time

Programmer Note Table using ITT Set will be renumbered to 8.2.1 if analysis for Per Protocol Set is needed. Table number for Per Protocol Set will be 8.2.2.

Table 8.2
UroVysion FISH Biomarker Test at Week 8
ITT Set

	Baseline [1]									
	800,000 U (N=)					Total (N=)				
Time Point	Neg	Pos	Eq[2]	Oth[3]	ND[4]	Neg	Pos	Eq[2]	Oth[3]	ND[4]
Week 8	n					n				
Negative	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Positive	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Equivocal	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Other	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Not Done	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

[1] Baseline defined as measurement taken most closely prior to first study drug administration.
[2] Eq= Equivocal
[3] Oth= Other
[4] ND= Not Done

path\t_program.sas date time

Programmer Note Table using ITT Set will be renumbered to 8.2.1 if analysis for Per Protocol Set is needed. Table number for Per Protocol Set will be 8.2.2.

Table 9.1
Treatment Emergent Adverse Events by System Organ Class [1]
Safety Set

System Organ Class / Preferred Term	20,000 U (N=)	60,000 U (N=)	200,000 U (N=)	400,000 U (N=)	800,000 U (N=)	Total [2] (N=)	Received Only MMC (N=)
Patients Experiencing at Least One Adverse Event	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
95% CI [3]	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx x, xx x)	(xx.x, xx.x)
System Organ Class 1	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Preferred Term 1	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Preferred Term 2	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
.							
.							
System Organ Class 2	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Preferred Term 1	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Preferred Term 2	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
.							
.							

[1] At each level of summation (overall, system organ class, preferred term), patients reporting more than one adverse event are counted only once.
[2] Total column does not consider patients that received only MMC.
[3] 95% Confidence Interval based on a binomial distribution.
path\t_program.sas date time

Table 9.2
Treatment Emergent Adverse Events by System Organ Class and Severity [1]
Safety Set
Part 1 of 2

	20,000 U (N=)			60,000 U (N=)			200,000 U (N=)			400,000 U (N=)			800,000 U (N=)		
System Organ Class / Preferred Term	Mild	Mod	Sev	Mild	Mod	Sev	Mild	Mod	Sev	Mild	Mod	Sev	Mild	Mod	Sev
Patients Experiencing at Least One Adverse Event	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
System Organ Class 1	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Preferred Term 1	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Preferred Term 2	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
.															
.															
System Organ Class 2	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Preferred Term 1	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Preferred Term 2	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
.															
.															

[1] At each level of summation (overall, system organ class, preferred term), patients reporting more than one adverse event are counted only once using the highest severity.
path\t_program.sas date time

Table 9.2
Treatment Emergent Adverse Events by System Organ Class and Severity [1]
Safety Set
Part 2 of 2

	Total (N=)		
System Organ Class / Preferred Term	Mild	Mod	Sev
Patients Experiencing at Least One Adverse Event	n (%)	n (%)	n (%)
System Organ Class 1	n (%)	n (%)	n (%)
Preferred Term 1	n (%)	n (%)	n (%)
Preferred Term 2	n (%)	n (%)	n (%)
.			
.			
System Organ Class 2	n (%)	n (%)	n (%)
Preferred Term 1	n (%)	n (%)	n (%)
Preferred Term 2	n (%)	n (%)	n (%)
.			
.			

[1] At each level of summation (overall, system organ class, preferred term), patients reporting more than one adverse event are counted only once using the highest severity.
path\t_program.sas date time

Table 9.3
Treatment Emergent Adverse Events by System Organ Class and Relationship to Chemophase [1]
Safety Set

	20,000 U (N=)		60,000 U (N=)		200,000 U (N=)		400,000 U (N=)		800,000 U (N=)		Total (N=)	
System Organ Class / Preferred Term	Related [2]	Not Rel [3]	Related [2]	Not Rel [3]	Related [2]	Not Rel [3]	Related [2]	Not Rel [3]	Related [2]	Not Rel [3]	Related [2]	Not Rel [3]
Patients Experiencing at Least One Adverse Event	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
System Organ Class 1	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Preferred Term 1	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Preferred Term 2	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
.												
.												
System Organ Class 2	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Preferred Term 1	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Preferred Term 2	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
.												
.												

[1] At each level of summation (overall, system organ class, preferred term), patients reporting more than one adverse event are counted only once using the closest relationship to Chemophase.
[2] Includes all events reported as “Possibly”, “Probably”, or “Related” relationship to Chemophase.
[3] Includes all events reported as “Unlikely”, or “Not Related” relationship to Chemophase.
path\t_program.sas date time

Table 9.4
Treatment Emergent Adverse Events by System Organ Class and Relationship to MMC [1]
Safety Set

	20,000 U (N=)		60,000 U (N=)		200,000 U (N=)		400,000 U (N=)		800,000 U (N=)		Total (N=)	
System Organ Class / Preferred Term	Related [2]	Not Rel [3]	Related [2]	Not Rel [3]	Related [2]	Not Rel [3]	Related [2]	Not Rel [3]	Related [2]	Not Rel [3]	Related [2]	Not Rel [3]
Patients Experiencing at Least One Adverse Event	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
System Organ Class 1	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Preferred Term 1	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Preferred Term 2	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
.												
.												
System Organ Class 2	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Preferred Term 1	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Preferred Term 2	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
.												
.												

[1] At each level of summation (overall, system organ class, preferred term), patients reporting more than one adverse event are counted only once using the closest relationship to MMC.
[2] Includes all events reported as “Possibly”, “Probably”, or “Related” relationship to MMC.
[3] Includes all events reported as “Unlikely”, or “Not Related” relationship to MMC.
path\t_program.sas date time

Table 9.5
Treatment Emergent Serious Adverse Events by System Organ Class [1]
Safety Set

System Organ Class / Preferred Term	20,000 U (N=)	60,000 U (N=)	200,000 U (N=)	400,000 U (N=)	800,000 U (N=)	Total (N=)
Patients Experiencing at Least One Adverse Event	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
95% CI	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)
System Organ Class 1	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Preferred Term 1	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Preferred Term 2	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
.						
.						
System Organ Class 2	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Preferred Term 1	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Preferred Term 2	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
.						
.						

[1] At each level of summation (overall, system organ class, preferred term), patients reporting more than one adverse event are counted only once.

path\t_program.sas date time

Table 10.1
Clinical Laboratory Results : Hematology
Safety Set
WBC (unit)

	20,000 U (N=)		60,000 U (N=)		200,000 U (N=)		400,000 U (N=)		800,000 U (N=)		Total (N=)	
	Result	Change [2]	Result	Change [2]	Result	Change [2]	Result	Change [2]	Result	Change [2]	Result	Change [2]
Baseline [1]												
n	n		n		n		n		n		n	
Mean (SD)	xx.x (xx.xx)		xx.x (xx.xx)		xx.x (xx.xx)		xx.x (xx.xx)		xx.x (xx.xx)		xx.x (xx.xx)	
Median	xx.x		xx.x		xx.x		xx.x		xx.x		xx.x	
Min, Max	xx, xx		xx, xx		xx, xx		xx, xx		xx, xx		xx, xx	
Above Normal	n (%)		n (%)		n (%)		n (%)		n (%)		n (%)	
Below Normal	n (%)		n (%)		n (%)		n (%)		n (%)		n (%)	
Week 2, Day 8												
n	n	n	n	n	n	n	n	n	n	n	n	n
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Above Normal	n (%)		n (%)		n (%)		n (%)		n (%)		n (%)	
Below Normal	n (%)		n (%)		n (%)		n (%)		n (%)		n (%)	
…	…	…	…	…	…	…	…	…	…	…	…	…
…	…	…	…	…	…	…	…	…	…	…	…	…

[1] Baseline defined as measurement taken most closely prior to first study drug administration.
[2] Change= Change from Baseline

path\t_program.sas date time

Table will repeat for each analyte for each time point.
Programmer note In most cases, baseline will be Week 1, Day 1.

Table 10.2
Clinical Laboratory Results : Chemistry
Safety Set
Sodium (unit)

	20,000 U (N=)		60,000 U (N=)		200,000 U (N=)		400,000 U (N=)		800,000 U (N=)		Total (N=)	
	Result	Change [2]	Result	Change [2]	Result	Change [2]	Result	Change [2]	Result	Change [2]	Result	Change [2]
Baseline [1]												
n	n		n		n		n		n		n	
Mean (SD)	xx.x (xx.xx)		xx.x (xx.xx)		xx.x (xx.xx)		xx.x (xx.xx)		xx.x (xx.xx)		xx.x (xx.xx)	
Median	xx.x		xx.x		xx.x		xx.x		xx.x		xx.x	
Min, Max	xx, xx		xx, xx		xx, xx		xx, xx		xx, xx		xx, xx	
Above Normal	n (%)		n (%)		n (%)		n (%)		n (%)		n (%)	
Below Normal	n (%)		n (%)		n (%)		n (%)		n (%)		n (%)	
Week 2, Day 8												
n	n	n	n	n	n	n	n	n	n	n	n	n
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Above Normal	n (%)		n (%)		n (%)		n (%)		n (%)		n (%)	
Below Normal	n (%)		n (%)		n (%)		n (%)		n (%)		n (%)	
…	…	…	…	…	…	…	…	…	…	…	…	…
…	…	…	…	…	…	…	…	…	…	…	…	…

[1] Baseline defined as measurement taken most closely prior to first study drug administration.
[2] Change= Change from Baseline

path\t_program.sas date time

Table will repeat for each analyte for each time point.
Programmer note In most cases, baseline will be Week 1, Day 1.

Table 10.3
Clinical Laboratory Results : Urinalysis
Safety Set
Specific Gravity

	20,000 U (N=)		60,000 U (N=)		200,000 U (N=)		400,000 U (N=)		800,000 U (N=)		Total (N=)	
	Result	Change [2]	Result	Change [2]	Result	Change [2]	Result	Change [2]	Result	Change [2]	Result	Change [2]
Baseline [1]												
n	n		n		n		n		n		n	
Mean (SD)	xx.x (xx.xx)		xx.x (xx.xx)		xx.x (xx.xx)		xx.x (xx.xx)		xx.x (xx.xx)		xx.x (xx.xx)	
Median	xx.x		xx.x		xx.x		xx.x		xx.x		xx.x	
Min, Max	xx, xx		xx, xx		xx, xx		xx, xx		xx, xx		xx, xx	
Above Normal	n (%)		n (%)		n (%)		n (%)		n (%)		n (%)	
Below Normal	n (%)		n (%)		n (%)		n (%)		n (%)		n (%)	
Week 2, Day 8												
n	n	n	n	n	n	n	n	n	n	n	n	n
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Above Normal	n (%)		n (%)		n (%)		n (%)		n (%)		n (%)	
Below Normal	n (%)		n (%)		n (%)		n (%)		n (%)		n (%)	
…	…	…	…	…	…	…	…	…	…	…	…	…
…	…	…	…	…	…	…	…	…	…	…	…	…

[1] Baseline defined as measurement taken most closely prior to first study drug administration.
[2] Change= Change from Baseline

path\t_program.sas date time

Table will repeat for each analyte for each time point.
Programmer note In most cases, baseline will be Week 1, Day 1.

Table 11.1
Shift Tables of Clinical Laboratory Results : Hematology
Safety Set
Part 1 of 2

	Baseline [1]														
	20,000 U (N=)			60,000 U (N=)			200,000 U (N=)			400,000 U (N=)			800,000 U (N=)		
Most Abnormal Post Baseline Result [2]	High	Normal	Low	High	Normal	Low	High	Normal	Low	High	Normal	Low	High	Normal	Low
WBC (unit)	n			n			n			n			n		
High	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Normal	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Low	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
ANC (unit)	n			n			n			n			n		
High	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Normal	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Low	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
RBC (unit)	n			n			n			n			n		
High	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Normal	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Low	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

…
…

[1] Baseline defined as measurement taken most closely prior to first study drug administration.
[2] A patient will be assigned a “High” score for post baseline result if a patient has both a high and low post baseline result.

path\t_program.sas date time

Table will repeat for each analyte.
Programmer note In most cases, baseline will be Week 1, Day 1.

Table 11.1
Shift Tables of Clinical Laboratory Results : Hematology
Safety Set
Part 2 of 2

	Baseline [1]		
	Total (N=)		
Most Abnormal Post Baseline Result [2]	High	Normal	Low
WBC (unit)	n		
High	n (%)	n (%)	n (%)
Normal	n (%)	n (%)	n (%)
Low	n (%)	n (%)	n (%)
ANC (unit)	n		
High	n (%)	n (%)	n (%)
Normal	n (%)	n (%)	n (%)
Low	n (%)	n (%)	n (%)
RBC (unit)	n		
High	n (%)	n (%)	n (%)
Normal	n (%)	n (%)	n (%)
Low	n (%)	n (%)	n (%)
…			
…			

[1] Baseline defined as measurement taken most closely prior to first study drug administration.
[2] A patient will be assigned a “High” score for post baseline result if a patient has both a high and low post baseline result.

path\t_program.sas date time

Table will repeat for each analyte.
Programmer note In most cases, baseline will be Week 1, Day 1.

Table 11.2
Shift Tables of Clinical Laboratory Results : Chemistry
Safety Set
Part 1 of 2

	Baseline [1]														
	20,000 U (N=)			60,000 U (N=)			200,000 U (N=)			400,000 U (N=)			800,000 U (N=)		
Most Abnormal Post Baseline Result [2]	High	Normal	Low	High	Normal	Low	High	Normal	Low	High	Normal	Low	High	Normal	Low
Sodium (unit)	n			n			n			n			n		
High	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Normal	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Low	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Potassium (unit)	n			n			n			n			n		
High	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Normal	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Low	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Chloride (unit)	n			n			n			n			n		
High	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Normal	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Low	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

…
…

[1] Baseline defined as measurement taken most closely prior to first study drug administration.
[2] A patient will be assigned a “High” score for post baseline result if a patient has both a high and low post baseline result.

path\t_program.sas date time

Table will repeat for each analyte.
Programmer note In most cases, baseline will be Week 1, Day 1.

Table 11.2
Shift Tables of Clinical Laboratory Results : Chemistry
Safety Set
Part 2 of 2

	Baseline [1]		
	Total (N=)		
Most Abnormal Post Baseline Result [2]	High	Normal	Low
Sodium (unit)	n		
High	n (%)	n (%)	n (%)
Normal	n (%)	n (%)	n (%)
Low	n (%)	n (%)	n (%)
Potassium (unit)	n		
High	n (%)	n (%)	n (%)
Normal	n (%)	n (%)	n (%)
Low	n (%)	n (%)	n (%)
Chloride (unit)	n		
High	n (%)	n (%)	n (%)
Normal	n (%)	n (%)	n (%)
Low	n (%)	n (%)	n (%)
…			
…			

[1] Baseline defined as measurement taken most closely prior to first study drug administration.
[2] A patient will be assigned a “High” score for post baseline result if a patient has both a high and low post baseline result.

path\t_program.sas date time

Table will repeat for each analyte.
Programmer note In most cases, baseline will be Week 1, Day 1.

Table 11.3
Shift Tables of Clinical Laboratory Results : Urinalysis
Safety Set
Part 1 of 2

	Baseline [1]														
	20,000 U (N=)			60,000 U (N=)			200,000 U (N=)			400,000 U (N=)			800,000 U (N=)		
Most Abnormal Post Baseline Result [2]	High	Normal	Low	High	Normal	Low	High	Normal	Low	High	Normal	Low	High	Normal	Low
Specific Gravity	n			n			n			n			n		
High	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Normal	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Low	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
pH	n			n			n			n			n		
High	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Normal	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Low	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

[1] Baseline defined as measurement taken most closely prior to first study drug administration.
[2] A patient will be assigned a “High” score for post baseline result if a patient has both a high and low post baseline result.

path\t_program.sas date time

Programmer note In most cases, baseline will be Week 1, Day 1. Also, only those analytes with numeric results will be considered.

Table 11.3
Shift Tables of Clinical Laboratory Results : Urinalysis
Safety Set
Part 2 of 2

	Baseline [1]		
	Total (N=)		
Most Abnormal Post Baseline Result [2]	High	Normal	Low
Specific Gravity	n		
High	n (%)	n (%)	n (%)
Normal	n (%)	n (%)	n (%)
Low	n (%)	n (%)	n (%)
pH	n		
High	n (%)	n (%)	n (%)
Normal	n (%)	n (%)	n (%)
Low	n (%)	n (%)	n (%)

[1] Baseline defined as measurement taken most closely prior to first study drug administration.
[2] A patient will be assigned a “High” score for post baseline result if a patient has both a high and low post baseline result.

path\t_program.sas date time

Programmer note In most cases, baseline will be Week 1, Day 1. Also, only those analytes with numeric results will be considered.

Table 12
Physical Examination [1]
Safety Set

	Pre-Study Drug											
	20,000 U (N=)		60,000 U (N=)		200,000 U (N=)		400,000 U (N=)		800,000 U (N=)		Total (N=)	
Post-Study Drug	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
Respiratory	n		n		n		n		n		n	
Normal	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Abnormal	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Cardiovascular	n		n		n		n		n		n	
Normal	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Abnormal	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Gastrointestinal	n		n		n		n		n		n	
Normal	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Abnormal	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
…	…	…	…	…	…	…	…	…	…	…	…	…

[1] For both pre- and post baseline results, a patient is considered normal for body system unless a result of abnormal is reported for specified body system and time interval.

path\t_program.sas date time

Table 13
Vital Signs
Safety Set
Heart Rate (unit)

	20,000 U (N=)		60,000 U (N=)		200,000 U (N=)		400,000 U (N=)		800,000 U (N=)		Total (N=)	
	Result	Change [2]	Result	Change [2]	Result	Change [2]	Result	Change [2]	Result	Change [2]	Result	Change [2]
Baseline [1]												
n	n		n		n		n		n		n	
Mean (SD)	xx.x (xx.xx)		xx.x (xx.xx)		xx.x (xx.xx)		xx.x (xx.xx)		xx.x (xx.xx)		xx.x (xx.xx)	
Median	xx.x		xx.x		xx.x		xx.x		xx.x		xx.x	
Min, Max	xx, xx		xx, xx		xx, xx		xx, xx		xx, xx		xx, xx	
Week 2, Day 8												
n	n	n	n	n	n	n	n	n	n	n	n	n
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Week 3, Day 15												
n	n	n	n	n	n	n	n	n	n	n	n	n
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
…	…	…	…	…	…	…	…	…	…	…	…	…
…	…	…	…	…	…	…	…	…	…	…	…	…

[1] Baseline defined as measurement taken most closely prior to first study drug administration.
[2] Change= Change from Baseline

path\t_program.sas date time

Table will repeat for each vital sign at each time point.
Programmer note In most cases, baseline will be Week 1, Day 1.

Table 14.1
Shift Table of 12-Lead ECG
Safety Set
Part 1 of 2

	Screening														
	20,000 U (N=)			60,000 U (N=)			200,000 U (N=)			400,000 U (N=)			800,000 U (N=)		
Week 8, Day 50	Nor[1]	Abn[2]	ACS[3]	Nor[1]	Abn[2]	ACS[3]	Nor[1]	Abn[2]	ACS[3]	Nor[1]	Abn[2]	ACS[3]	Nor[1]	Abn[2]	ACS[3]
	n			n			n			n			n		
Normal	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Abnormal, not Clinically Significant	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Abnormal , Clinically Significant	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

[1] Nor= Normal
[2] Abn= Abnormal, not Clinically Significant
[3] ACS= Abnormal, Clinically Significant

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Table 14.1
Shift Table of 12-Lead ECG
Safety Set
Part 2 of 2

	Screening		
	Total (N=)		
Week 8, Day 50	Nor[1]	Abn[2]	ACS[3]
	n		
Normal	n (%)	n (%)	n (%)
Abnormal, not Clinically Significant	n (%)	n (%)	n (%)
Abnormal , Clinically Significant	n (%)	n (%)	n (%)

[1] Nor= Normal
[2] Abn= Abnormal, not Clinically Significant
[3] ACS= Abnormal, Clinically Significant

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Table 14.2
12-Lead ECG
Safety Set

	20,000 U (N=)		60,000 U (N=)		200,000 U (N=)		400,000 U (N=)		800,000 U (N=)		Total (N=)	
	Result	Change [1]	Result	Change [1]	Result	Change [1]	Result	Change [1]	Result	Change [1]	Result	Change [1]
QT (unit)												
Screening												
n	n		n		n		n		n		n	
Mean (SD)	xx.x (xx.xx)		xx.x (xx.xx)		xx.x (xx.xx)		xx.x (xx.xx)		xx.x (xx.xx)		xx.x (xx.xx)	
Median	xx.x		xx.x		xx.x		xx.x		xx.x		xx.x	
Min, Max	xx, xx		xx, xx		xx, xx		xx, xx		xx, xx		xx, xx	
Week 8, Day 50												
n	n	n	n	n	n	n	n	n	n	n	n	n
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
QTc (unit)												
Screening												
n	n	n	n	n	n	n	n	n	n	n	n	n
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
…	…	…	…	…	…	…	…	…	…	…	…	…
…	…	…	…	…	…	…	…	…	…	…	…	…

[1] Change= Change from Baseline

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Table will repeat for each ECG parameter.

Table 15
Karnofsky Performance Status
Safety Set

	20,000 U (N=)		60,000 U (N=)		200,000 U (N=)		400,000 U (N=)		800,000 U (N=)		Total (N=)	
	Result	Change [2]	Result	Change [2]	Result	Change [2]	Result	Change [2]	Result	Change [2]	Result	Change [2]
Baseline [1]												
n	n		n		n		n		n		n	
Mean (SD)	xx.x (xx.xx)		xx.x (xx.xx)		xx.x (xx.xx)		xx.x (xx.xx)		xx.x (xx.xx)		xx.x (xx.xx)	
Median	xx.x		xx.x		xx.x		xx.x		xx.x		xx.x	
Min, Max	xx, xx		xx, xx		xx, xx		xx, xx		xx, xx		xx, xx	
100%	n (%)		n (%)		n (%)		n (%)		n (%)		n (%)	
90%	n (%)		n (%)		n (%)		n (%)		n (%)		n (%)	
80%	n (%)		n (%)		n (%)		n (%)		n (%)		n (%)	
70%	n (%)		n (%)		n (%)		n (%)		n (%)		n (%)	
60%	n (%)		n (%)		n (%)		n (%)		n (%)		n (%)	
50%	n (%)		n (%)		n (%)		n (%)		n (%)		n (%)	
40%	n (%)		n (%)		n (%)		n (%)		n (%)		n (%)	
30%	n (%)		n (%)		n (%)		n (%)		n (%)		n (%)	
20%	n (%)		n (%)		n (%)		n (%)		n (%)		n (%)	
10%	n (%)		n (%)		n (%)		n (%)		n (%)		n (%)	
0%	n (%)		n (%)		n (%)		n (%)		n (%)		n (%)	
Week 2, Day 8												
n	n	n	n	n	n	n	n	n	n	n	n	n
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
100%	n (%)		n (%)		n (%)		n (%)		n (%)		n (%)	…
…	…	…	…	…	…	…	…	…	…	…	…	…

[1] Baseline defined as measurement taken most closely prior to first study drug administration.
[2] Change= Change from Baseline

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Table will repeat for each available time point.
Programmer note In most cases, baseline will be Week 1, Day 1. Categories may collapsed as requested by client.

Table 16
Long-Term Follow-Up- Vital Signs
Safety Set
Heart Rate (unit)

	MTD Cohort (N=)	
	Result	Change [2]
Baseline [1]		
n	n	
Mean (SD)	xx.x (xx.xx)	
Median	xx.x	
Min, Max	xx, xx	
Month 4 ½		
n	n	n
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x
Min, Max	xx, xx	xx, xx
Month 7 ½		
n	n	n
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x
Min, Max	xx, xx	xx, xx
…	…	…
…	…	…

[1] Baseline defined as measurement taken most closely prior to first study drug administration.
[2] Change= Change from Baseline

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Table will repeat for each vital sign parameter for each long-term follow-up time point.
Programmer note In most cases, baseline will be Week 1, Day 1 and should exactly match baseline expressed in table 13 (Vital Signs).

Table 17
Long-Term Follow-Up- Targeted Physical Examination
Safety Set

Reported at least one instance of abnormality [1]:	MTD Cohort (N=)
Pre-Study Drug	
Respiratory	n (%)
Cardiovascular	n (%)
Gastrointestinal	n (%)
Hepatic	n (%)
…	
Post-Study Drug up to and including Week 12 Visit	
Respiratory	n (%)
Cardiovascular	n (%)
Gastrointestinal	n (%)
Hepatic	n (%)
…	
Post-Study Drug during Long-Term Follow-Up Starting with Month 6 until Study Discontinuation	
Respiratory	n (%)
Cardiovascular	n (%)
Gastrointestinal	n (%)
Hepatic	n (%)
…	

Patients reporting more than one abnormality for the same system will be only counted once per time period (pre-study drug/ post-study drug).

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Programmer note The first two endpoints should match up exactly with first two endpoints on table 12 (Physical Examination)

Table 18
Long-Term Follow-Up- Cystoscopy
ITT Set
Month 4 ½

	MTD Cohort (N=)
Cystoscopy	
Result	
Normal	n (%)
Abnormal, Not Clinically Significant	n (%)
Abnormal, Clinically Significant	n (%)
Estimated Bladder Capacity Volume (mL)	
n	n
Mean (SD)	xx.x (xx.xx)
Median	xx.x
Min, Max	xx, xx
…	

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Repeat table for each time point.

Table 19
Long-Term Follow-Up- Hematology
Safety Set
WBC (unit)

	MTD Cohort (N=)	
	Result	Change [2]
Baseline [1]		
n	n	
Mean (SD)	xx.x (xx.xx)	
Median	xx.x	
Min, Max	xx, xx	
Month 4 ½		
n	n	n
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x
Min, Max	xx, xx	xx, xx
Month 7 ½		
n	n	n
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x
Min, Max	xx, xx	xx, xx
…	…	…

[1] Baseline defined as measurement taken most closely prior to first study drug administration.
[2] Change= Change from Baseline

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Table will repeat for each analyte for each long-term follow-up time point.
Programmer note In most cases, baseline will be Week 1, Day 1 and should exactly match baseline expressed in table 10.1 (Hematology Results).

Table 20
Long-Term Follow-Up- Study Drug Administration
Safety Set

Visit	MTD Cohort (N=)
Month 4 ½	
Chemophase	
Units Instilled- Mean (SD)	xx.x (xx.xx)
Volume Instilled- Mean (SD)	xx.x (xx.xx)
Sterile Saline	
Volume Instilled- Mean (SD)	xx.x (xx.xx)
MMC	
Dose Instilled- Mean (SD)	xx.x (xx.xx)
Volume Instilled- Mean (SD)	xx.x (xx.xx)
Total Volume Instilled- Mean (SD)	xx.x (xx.xx)
Any Interruptions or Adjustments Due to DLTs?	
Yes	n (%)
No	n (%)
Length of Time Patient Retain Solution in their Bladder	
2 Hours	n (%)
>= 90 Minutes, < 2 Hours	n (%)
< 90 Minutes	n (%)
5 mL Urine Sample Collected and Frozen?	
Yes	n (%)
No	n (%)

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Table will repeat for each analyte for each long-term follow-up time point.

Table 21
Long-Term Follow-Up- NMP22 BladderChek Biomarker Test
Safety Set

	MTD Cohort (N=xx)
Month 3	
Negative	n (%)
Positive	n (%)
No Valid Result	n (%)
Not Done	n (%)
Month 6	
Negative	n (%)
Positive	n (%)
No Valid Result	n (%)
Not Done	n (%)
…	

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Table will repeat for each analyte for each long-term follow-up time point.

Table 22
Long-Term Follow-Up- UroVysion FISH Biomarker Test
Safety Set

	MTD Cohort (N=xx)
Month 3	
Negative	n (%)
Positive	n (%)
Equivocal	n (%)
Other	n (%)
Not Done	n (%)
Month 6	
Negative	n (%)
Positive	n (%)
Equivocal	n (%)
Other	n (%)
Not Done	n (%)
…	

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Table will repeat for each analyte for each long-term follow-up time point.

Table 23
Long-Term Follow-Up- Time to Tumor Recurrence from First Study Drug Administration (Months)
Safety Set

Category, n (%)	MTD Cohort (N=xx)
Number Patients with Tumor Recurrence	n
Number Patients Censored	n
Quartiles (95% CI):	
25th Percentile	x.x (x.x, x.x)
50th Percentile (median)	x.x (x.x, x,x)
75th Percentile	x.x (x.x, x.x)
Kaplan Meier Estimate (# at Risk)	
6 Months	x.x (n)
12 Months	x.x (n)
18 Months	x.x (n)
24 Months	x.x (n)
Range (Patients with Tumor Recurrence)	xx, xx
Range (All Patients)	xx, xx

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APPENDIX C: LISTING LAYOUTS

Listing 1
Patient Disposition
(N=)

Cohort X/ Chem Units	Patient ID	Received MMC Only?	Safety Set [1]	ITT Set [2]	Per Protocol Set [3]	Date of Study Discontinuation/ Study Termination	Completed Study?	Reason for Discontinuation [4]	Date of Investigator's Signature	Name of Investigator

[1] Received at least one dose of Chemophase.
[2] Received at least one dose of Chemophase with MMC.
[3] Satisfied Inclusion Criteria 1 and 2; received at least 4 doses of Chemophase with MMC over an interval that did not exceed 8 weeks; retained at least 4 intravesical instillations for at least 90 minutes. Note: the criterion "monitored to the time of tumor recurrence, or at least 5 years, whichever occurs first" was not applied for the generation of this table.
[4] Reasons for discontinuation include: Did not receive all expected instillations of study drug. Protocol Violation, Lost to Follow-up, Adverse Event, Non-compliance, Patient Decision, Investigator Decision, Other.
path\t_program.sas date time

Listing 2
Inclusion Criteria
(N=)

Cohort X/ Chem Units	Patient ID	Date Informed Consent Signed	Inclusion Criteria												
			1a	1b	2	3	4	5	6	7	8	9	10	11	12

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Programmer Note Inclusion criteria to be shown on separate page.

Listing 3
Exclusion Criteria
(N=)

Cohort X/ Chem Units	Patient ID	Date Informed Consent Signed	Exclusion Criteria															
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16

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Programmer Note Exclusion criteria to be shown on separate page.

Listing 4
Criteria Waiver
(N=)

Cohort X/ Chem Units	Patient ID	Patient Comply with All Entry Criteria?	If No, Criteria Not Met				
			Criteria Not Met	Criteria Number	Exemption Explanation	Exemption Granted By	Date of Exemption
			Inclusion/Exclusion				

Listing 5
Demographics
(N=)

Cohort X/ Chem Units	Patient ID	Date of Birth	Day 1 Dose	Age on Day 1	Sex	Ethnicity	Race

Listing 6
Medical History
(N=)

Cohort X/ Chem Units	Patient ID	Mark if No Medical History	Site / System	Description	Year of Diagnosis / Onset	Ongoing

Listing 7
Urologic History / Bladder Cancer History
Part 1 of 3 (Cancer Recurrences)
(N=)

Cohort X/ Chem Units	Patient ID	Bladder Cancer	
		Date of Initial Diagnosis	Date of Recurrences

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Listing 7
Urologic History / Bladder Cancer History
Part 2 of 3 (Estimation of Bladder Capacity)
(N=)

Cohort X/ Chem Units	Patient ID	Bladder Capacity		
		Date of Estimation	Method of Estimation	Volume (mL)

Listing 7
Urologic History / Bladder Cancer History
Part 3 of 3 (Bladder Symptoms)
(N=)

Cohort X/ Chem Units	Patient ID	Frequent Urination?		Nighttime Urinations?		Urinary Urgency?		Urinary Incontinence?		Use Pads?	
		Yes/No	Average Urinations/Day	Yes/No	Average Urinations/Night	Yes/No	Average Urinations/Week	Yes/No	Average Urinations/Week	Yes/No	Average Pads/Day

Listing 8
Previous Bladder Tumor Treatments
(N=)

Cohort X/ Chem Units	Patient ID	Medication / Treatment	Start Date / Stop Date	Dose / Units	Route	Toxicities

Listing 9
Previous Bladder Surgeries / Cystoscopies with Tumors Detected
Part 1 of 2
(N=)

Cohort X/ Chem Units	Patient ID	Mark if None	Tumor # from CRF	Procedure Date	Procedure Type	Tumor Size (mm)	Histological Grading	Location	TNM Staging
					Surgery Cystoscopy				

Listing 9
Previous Bladder Surgeries / Cystoscopies with Tumors Detected
Part 2 of 2
(N=)

Cohort X/ Chem Units	Patient ID	Mark if None	Tumor # from CRF	Biopsy Performed?	If Yes, Biopsy Findings	Gross Appearance of Tumor	Depth of Involvement of Bladder Mucosa or Not Applicable

Listing 10
Previous Bladder Cystoscopies without Tumors
(N=)

Cohort X/ Chem Units	Patient ID	Mark if None	Cystoscopy # from CRF	Date of Procedure	Abnormal Findings

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Listing 11
Previous Bladder Fibrosis / Contracture
(N=)

Cohort X/ Chem Units	Patient ID	Mark if None	Date	Diagnosis	Etiology

Listing 12
Previous Cystometrogram
(N=)

Cohort X/ Chem Units	Patient ID	Mark if None	Test Date	Result	Test(s) Used	If Abnormal, Specify Abnormality

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Listing 13
Instillation of Chemophase and MMC
Page 1 of 2
(N=)

		Refrain From Drinking Fluids?		Pre-Instillation		Instillation				Post-Instillation		
Cohort X/ Chem Units	Patient ID	For >= 8 Hours Before Instillation	During Instillation	Fully Voided Before?	Volume Obtained by Catheter (mL)	Date	Start Time	End Time	Elapsed Time (min) [1]	Time of Voiding	Dwell Time (min) [2]	Voided Volume (mL)

[1] Elapsed Time= End Time of Instillation – Start Time of Instillation
[2] Dwell Time= Time of Voiding – End Time of Instillation

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Listing 13
Instillation of Chemophase and MMC
Page 2 of 2
(N=)

		Chemophase Instilled		Saline Instilled	MMC Instilled						
Cohort X/ Chem Units	Patient ID	Volume (mL)	Units (U)	Volume (mL)	Volume (mL)	Dose (mg)	Total Volume Instilled (mL)	Interrupt/ Adjust due to DLTs?	If Yes, Specify	Time Solution Retained [1]	Post Drug Instillation Urine Sample Collected?

[1] Possible responses for Time Solution Retained include: 2 Hours, 90 Minutes to <2 Hours, <90 Minutes
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Listing 14
Blood Collection and Results for MMC, rHuPH20 and Neutralizing Antibodies (NAB) to rHuPH20
(N=)

				Collection			Results		
Cohort X/ Chem Units	Patient ID	Visit #	Mark if Not Done	Date Drawn	Scheduled Time	Actual Time	MMC (ng/mL) or Not Done	rHuPH20 (U/mL)	Neutralizing Antibodies (NAB) to rHuPH20

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Listing 15
Urine Cytology
(N=)

Cohort X/ Chem Units	Patient ID	Visit #	Mark if Not Done	Collection Date	Diagnosis	Microscopic Description

Listing 16
Cystoscopy
(N=)

Cohort X/ Chem Units	Patient ID	Visit #	Mark if Not Done	Cystoscopy Date	Result	If Abnormal, Specify Abnormality:	Estimated Bladder Capacity (mL)	Absence of Bladder Cancer Verified?

Listing 17
Urine Dipstick
(N=)

Cohort X/ Chem Units	Patient ID	Visit #	Mark if Not Done	Collection Date	Collection Time	Do Results Indicate Possible UTI?

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Listing 18.1
NMP22 BladderChek Biomarker Test
(N=)

Cohort X/ Chem Units	Patient ID	Visit #	Mark if Not Done	Test	Collection Date	Collection Time	Result	If Invalid, Was Test Repeated?

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Programmer Note Test column will indicate whether test conducted is an initial test or a retest.

Listing 18.2
UroVysion FISH Biomarker Test
(N=)

Cohort X/ Chem Units	Patient ID	Visit #	Mark if Not Done	Test	Collection Date	Collection Time	Result

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Programmer Note Test column will indicate whether test conducted is an initial test or a retest.

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Listing 19.1
Adverse Events (Treatment-Emergent)
(N=)

									Action Taken with:		Relationship to:			
Cohort X/ Chem Units	Patient ID	Mark if None	AE #	Preferred Term/ Verbatim Term	Start Date	Stop Date	Serious ?	Severity (CTC)	MMC	Chemophase	MMC	Chemophase	Other Action	Outcome

* Treatment-Emergent Adverse Events are defined as those adverse events that occurred after initial study drug dosing and those existing AE's that worsened after initial study drug dosing. Adverse Events that occurred after the first dose of MMC but prior to first dose of Chemophase will be indicated with a "*".

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Programmer Note Abbreviations may be needed for some of the columns. If so, add a footnote to define the abbreviations.

Listing 19.2
Pre-Treatment-Emergent Adverse Events
(N=)

									Action Taken with:		Relationship to:			
Cohort X/ Chem Units	Patient ID	Mark if None	AE #	Preferred Term/ Verbatim Term	Start Date	Stop Date	Serious ?	Severity (CTC)	MMC	Chemophase	MMC	Chemophase	Other Action	Outcome

* Only Adverse Events that occurred between the time the patient signed the informed consent and prior to the first dose of MMC and Chemophase are included.

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Programmer Note Abbreviations may be needed for some of the columns. If so, add a footnote to define the abbreviations.

Listing 20
Serious Adverse Events (Treatment-Emergent)
(N=)

									Action Taken with:		Relationship to:			
Cohort X/ Chem Units	Patient ID	Mark if None	AE #	Preferred Term/ Verbatim Term	Start Date	Stop Date	Serious ?	Severity (CTC)	MMC	Chemophase	MMC	Chemophase	Other Action	Outcome

***** Treatment-Emergent Adverse Events are defined as those adverse events that occurred after initial study drug dosing and those existing AE's that worsened after initial study drug dosing. Adverse Events that occurred prior to first dose of MMC but prior to first dose of Chemophase will be indicated with a "*".

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Programmer Note Abbreviations may be needed for some of the columns. If so, add a footnote to define the abbreviations.

Listing 21
Reference Range Lab Normals – Hematology

				Age		Lab (Both or Male)		Lab (Female)		
Site ID	Lab ID	Date Effective	Lab Test	Low	High	Low	High	Low	High	Units

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Programmer Note Order the lab tests in the same order as on the CRF.

Listing 22
Reference Range Lab Normals – Chemistry

			Age		Lab (Both or Male)		Lab (Female)		
Site ID	Date Effective	Lab Test	Low	High	Low	High	Low	High	Units
COVANCE									

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Programmer Note Order the lab tests in the same order as on the CRF.

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Listing 23
Reference Range Lab Normals – Urinalysis

					Age		Lab (Both or Male)		Lab (Female)		
Site ID	Test Code	Lab Test	Occu Seq	Date Effective	Low	High	Low	High	Low	High	Units
COVANCE											

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Programmer Note Order the lab tests in the same order as on the CRF.

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Protocol Number: HZ2-05-01

Listing 24
Hematology Results
(N=)

Cohort X/ Chem Units	Patient ID	Lab Test	Visit #	Lab ID	Mark if Not Done	Collection Date	Collection Time	Result [1]	Unit	Abnormal, not CS	Abnormal and CS

CS = Clinically Significant.
[1] H indicates a value above the normal range. L indicates a value below the normal range.

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Programmer Note Put an "H" next to results that are above the normal range. Put an "L" next to results that are below the normal range. Sort the lab tests in the same order as on the CRF.

Listing 25
Chemistry Results
(N=)

Cohort X/ Chem Units	Patient ID	Lab Test	Visit #	Lab ID	Mark if Not Done	Collection Date	Collection Time	Result [1]	Unit	Abnormal, not CS	Abnormal and CS
				COVANCE							

CS = Clinically Significant.
[1] H indicates a value above the normal range. L indicates a value below the normal range.

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Programmer Note Put an "H" next to results that are above the normal range. Put an "L" next to results that are below the normal range. Sort the lab tests in the same order as on the CRF.

Listing 26
Urinalysis Results
(N=)

Cohort X/ Chem Units	Patient ID	Lab ID	Lab Test	Visit #	Lab ID	Mark if Not Done	Collection Date	Collection Time	Result [1]	Unit	Abnormal, not CS	Abnormal and CS
					COVANCE							

CS = Clinically Significant.
[1] H indicates a value above the normal range. L indicates a value below the normal range.

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Programmer Note Put an "H" next to results that are above the normal range. Put an "L" next to results that are below the normal range. Sort the lab tests in the same order as on the CRF.

Listing 27
Physical Examination
(N=)

Cohort X/ Chem Units	Patient ID	Visit #	Mark if Not Done	Exam Date	New, Changed or Resolved Abnormality?	PE #	System	Description of Abnormality	Clinically Significant?

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Programmer Note For System', add footnotes to explain abbreviations as needed.
If Physical Exam was not done, put "Not Done" for Exam Date '.
Sort System by System code #.

Listing 28
Vital Signs and Karnofsky Performance Status
(N=)

							Blood Pressure (mmHg)		Temperature			Weight		Height		
Cohort X/ Chem Units	Patient ID	Visit #	Mark if Not Done	Date of Vital Collected	Heart Rate (bpm)	Respiration (breaths/min)	Systolic	Diastolic	Result	Unit	Coll. Type Oral Aural	Result	Units	Result	Units	Karnofsky Score

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Programmer Note If vitals were not done put "Not Done" for Date.

Listing 29
12-Lead ECG
(N=)

Cohort X/ Chem Units	Patient ID	Visit #	Mark if Not Done	ECG Date	Result	If Abnormal, CS, Specify:	QT (msec)	QTc (msec)	HR (bpm)	P-R Interval (msec)	QRS (msec)

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Listing 30
Pregnancy
(N=)

Cohort X/ Chem Units	Patient ID	Visit #	Mark if Not Done	Date	Reason, If Not Done	Result

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Listing 31
Concomitant Medications
(N=)

Cohort X/ Chem Units	Patient ID	Mark if None	Con Med #	Medication	Dose	Unit	Route	Regimen	Date of Day 1	Start Date	Stop Date	Indication	Given for AE?	If Yes, AE #s

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Programmer Note If there are no concomitant medications put "NONE" for Medication'.
Add footnotes to explain abbreviations as needed.

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Listing 32
Procedures
(N=)

Cohort X/ Chem Units	Patient ID	Mark if None	Procedure #	Procedure	Date	Findings / Results	Related to AE?	If Yes, AE #s

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Programmer Note If there are no procedures put "NONE" for Procedure'.

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Listing 33
Comments
(N=)

Cohort X/ Chem Units	Patient ID	Mark if None	Comment #	Pertains to Visit Date	CRF Page	Comment

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Programmer Note If there are no comments put "NONE" for Comment #'.

Listing 34
Death Report
(N=)

Cohort X/ Chem Units	Patient ID	Date of Death	Date Death Reported to Site	Primary Cause	Autopsy Performed?	Comments	Investigator Signed?	Date of Signature

Listing 35
Tumor Recurrence
(N=)

Cohort X/ Chem Units	Patient ID	Mark if None	Procedure Date	Procedure Type	Tumor Size (mm)	Histopathological Grading	Tumor Location	TNM Staging	Biopsy Performed?	If Yes, Biopsy Findings	Gross Appearance of Tumor	Involvement of Bladder Mucosa, or NA

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Listing 36
Long-Term Follow-Up
Part 1 of 5
(N=)

						Bladder Cancer Treatments				
Cohort X/ Chem Units	Patient ID	Contact/ Visit Date	Method of Contact	Patient Status at Contact	Source of Information	Treatment	Mark if None	Start Date	Stop Date	Ongoing?

Listing 36
Long-Term Follow-Up
Part 2 of 5
(N=)

			NMP22 BladderChek Test		
Cohort X/ Chem Units	Patient ID	Contact/ Visit Date	Mark if None	Collection Date/Time	Result

Listing 36
Long-Term Follow-Up
Part 3 of 5
(N=)

			UroVysion FISH Biomarker Test		
Cohort X/ Chem Units	Patient ID	Contact/ Visit Date	Mark if None	Collection Date/Time	Result

Listing 36
Long-Term Follow-Up
Part 4 of 5
(N=)

			Cystoscopy				Urine Cytologies				Bladder Biopsies		
Cohort X/ Chem Units	Patient ID	Contact/ Visit Date	Mark if None	Date	Result	If Abnormal, Specify Abnormality	Mark if None	Date	Diagnosis	Microscopic Description	Mark if None	Date	Findings

Listing 36
Long-Term Follow-Up
Part 5 of 5
(N=)

			Tumor Recurrence		
Cohort X/ Chem Units	Patient ID	Contact/ Visit Date	Mark if None	Date Confirmed	Investigator Signed?

Listing 37
Utility Database Panel for Dose-Limiting Toxicities (DLTs)
(N=)

Cohort X/ Chem Units	Patient ID	Mark if No DLT	Date Reported	Adverse Event Considered to be DLT? If so, Name Adverse Event	PK Lab Assessment of MMC Level Considered to be DLT?	Treatment Emergent Bladder Fibrosis?	Reason Given for Discontinuation on Termination Page

Protocol defined DLTs are AEs with a CTC grade greater than or equal to 3, Plasma MMC Concentration >=100 ug/mL and Diagnosis of treatment-emergent bladder fibrosis.

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APPENDIX D: INTERNATIONALLY AGREED ORDER FOR SOC

Infections and infestations
Neoplasms benign and malignant (including cysts and polyps)
Blood and the lymphatic system disorders
Immune system disorders
Endocrine disorders
Metabolism and nutrition disorders
Psychiatric disorders
Nervous system disorders
Eye disorders
Ear and labyrinth disorders
Cardiac disorders
Vascular disorders
Respiratory, thoracic and mediastinal disorders
Gastrointestinal disorders
Hepato-biliary disorders
Skin and subcutaneous tissue disorders
Musculoskeletal, connective tissue and bone disorders
Renal and urinary disorders
Pregnancy, puerperium and perinatal conditions
Reproductive system and breast disorders
Congenital and familial/genetic disorders
General disorders and administration site conditions
Investigations
Injury and poisoning
Surgical and medical procedures
Social circumstances

This list is from an EMEA Guideline, ‘A Guideline on Summary of Product Characteristics’, October 2005.

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

Approval Sheet

[redacted] 1/17/08
Date

Halozyme Therapeutics, Inc.

[redacted] 1/31/08
Date

Synteract, Inc.