| | |
|---|---|
| **DRUG:** | ALT-803 (also known as N-803) |
| **STUDY NUMBER(S):** | QUILT-3.032-PK |
| **PROTOCOL(S) TITLE:** | A Pharmacokinetic Sub-Study of QUILT-3.032 (CA-ALT-803-01-16): A Multicenter Clinical Trial of Intravesical Bacillus Calmette-Guerin (BCG) in Combination with ALT-803 in Patients with BCG Unresponsive High Grade Non-Muscle Invasive Bladder Cancer |
| **IND NUMBER:** | 121976 |
| **SPONSOR:** | Altor BioScience, LLC, a wholly-owned subsidiary of NantCell, Inc. (Altor BioScience) |
| **ORIGINAL PROTOCOL DATE:** | 10 June 2019 |
| **VERSION NUMBER:** | 1.0 |
| **VERSION DATE:** | 10 June 2019 |

# CLINICAL PROTOCOL APPROVAL FORM

**Protocol Title: A Pharmacokinetic Sub-Study of QUILT-3.032: A Multicenter Clinical Trial of Intravesical Bacillus Calmette-Guerin (BCG) in Combination with ALT-803 in Patients with BCG Unresponsive High Grade Non-Muscle Invasive Bladder Cancer**

**Study No: QUILT-3.032-PK**

**Original Protocol Date: 10 June 2019**

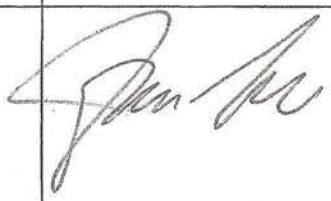
**Protocol Version No: 1.0**

**Protocol Version Date: 10 June 2019**

This study protocol was subject to critical review and has been approved by the appropriate protocol review committee of the Sponsor. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the investigational product.
- The moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and principles of GCP as described in 21 CFR parts 50, 54, 56 and 312 and according to applicable local requirements.

The Investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

| Name and Title | Signature | Date |
|---|---|---|
| Clinical Development:<br><br>Amy Rock, PhD<br>Vice-President, Clinical Development & Regulatory Affairs |  | 20 JUN 2019 |
| Medical Lead:<br><br>John Lee, MD<br>Senior Vice-President, Adult Medical Affairs |  | 6-20-19 |
| Regulatory Affairs:<br><br>Melissa Luras<br>Associate Director, Regulatory Affairs |  | 06/20/19 |

# STUDY SYNOPSIS

**Title:** A Pharmacokinetic Sub-Study of QUILT-3.032: A Multicenter Clinical Trial of Intravesical Bacillus Calmette-Guerin (BCG) in Combination with ALT-803 in Patients with BCG Unresponsive High Grade Non-Muscle Invasive Bladder Cancer

**Rationale:** ALT-803 is an IL-15-based immunostimulatory protein complex that acts as a growth and activation factor for natural killer (NK) cells and effector and memory T cells. Based on the results of animal tumor models, ALT-803 stimulated cellular immune responses are expected to exhibit potent activity against human tumor cells. The objective of this study is to establish the pharmacokinetic (PK) profile of intravesical ALT-803 administered to patients with BCG Unresponsive High Grade Non-Muscle Invasive Bladder Cancer (NMIBC).

**Target Population:** Adult Patients with BCG Unresponsive High Grade Non-Muscle Invasive Bladder Cancer

**Number of Subjects:** 12 - 20 subjects

**Objectives:**

Primary
To determine the PK profile of ALT-803 after single dose intravesical instillation of 400 µg ALT-803 plus BCG

Secondary
To determine the PK profile of ALT-803 after multiple intravesical instillations of 400 µg ALT-803 plus BCG

**Study Design:** Non-interventional PK sub-study of QUILT-3.032 (CA-ALT-803-01-16)

QUILT-3.032 (CA-ALT-803-01-16): Phase 2, open-label, single-arm, two-cohort, multicenter study of intravesical BCG plus ALT-803 (400 µg) in patients with BCG unresponsive high grade NMIBC. Patients will be enrolled into one of two study cohorts. Cohort A will enroll 80 patients who have histologically confirmed presence of BCG-unresponsive carcinoma in situ (CIS) [with or without Ta/T1 papillary disease]. Cohort B will enroll 80 patients who have histologically confirmed BCG-unresponsive high-grade Ta/T1 papillary disease. Cohort A and B are two independent study cohorts and will be separately evaluated for efficacy and safety. The study will be conducted in conformity with Good Clinical Practice (GCP). All patients treated in the study will receive via a urinary catheter in the bladder ALT-803 plus BCG, weekly for 6 consecutive weeks during the induction treatment period.

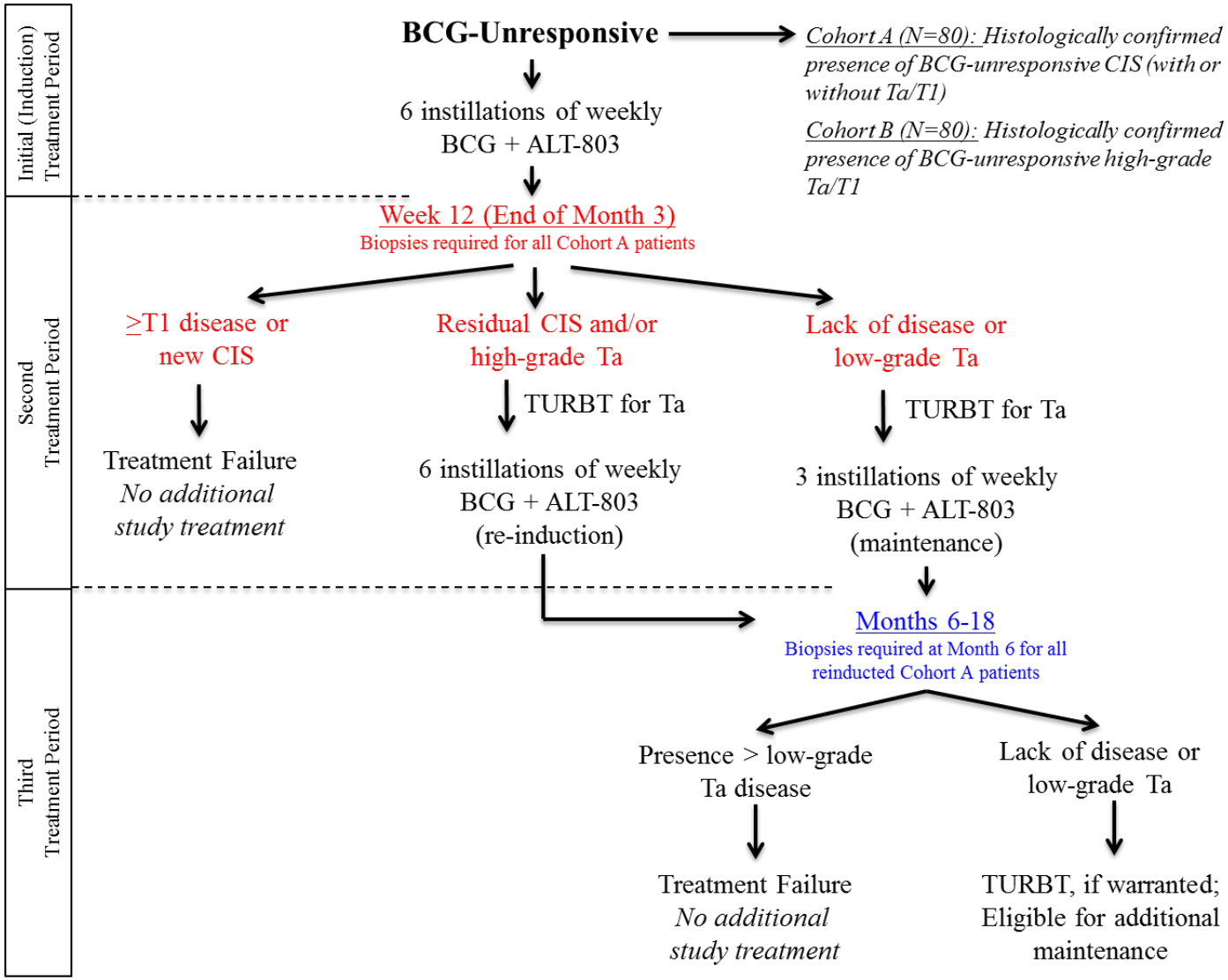
PK sub-study: Blood samples to determine serum levels of ALT-803 will be collected on study day 1 prior to dosing, and at post-bladder voiding (± 15 minutes), 24 (±2), 48 (±4), 72 (±4), 96 (±4) and 168 (±4) hours after dosing administered at study Week 1 and again at the same time points for study Week 6. Six subjects from cohort A and six subjects from cohort B will be sampled initially. Up to an additional 4 subjects from each cohort may also be sampled.

**Primary Endpoints:**

Serum concentration will be used to calculate the following PK parameters:

- half-life ($t_{½}$)
- apparent (extravascular) volume of distribution ($V_z/F$)
- apparent (extravascular) clearance (CL/F)
- maximum observed concentration ($C_{max}$)
- time of the observed maximum concentration ($T_{max}$)
- area under the plasma concentration curve from time 0 through the last measurable concentration ($AUC_{0-t}$)
- area under the plasma concentration curve from time 0 extrapolated to infinite time ($AUC_{0-inf}$)

## STUDY SCHEMATIC



# 10 STATISTICS

## 10.1 GENERAL PROCEDURES

A separate, detailed PK Analysis Plan will be developed for data analysis prior to study completion and data lock. Descriptive statistical methods will be used to summarize the data from this study. Unless otherwise stated, the term descriptive statistics refers to the number of subjects, mean, median, standard deviation, minimum, and maximum for continuous data, and frequencies and percentages for categorical data. No statistical testing will be performed. Results will be summarized in the final clinical study report for QUILT-3.032

## 10.2 SAMPLE SIZE

Six subjects from Cohort A and six subjects from Cohort B will be sampled initially. Up to an additional 4 subjects from each cohort may also be sampled. The maximum number of subjects enrolled will be 20.

## 10.3 PK ASSAY DESCRIPTION

The method used to detect and quantify serum IL-15 employs a Human IL-15 assay kit, supplied by R&D Systems (Minneapolis, MN). The specific assay utilized comprises a sandwich ELISA (enzyme-linked immunosorbent assay) employing two unique anti-human IL-15 monoclonal antibodies

## 10.4 PK PARAMETER ANALYSIS

The following PK parameters will be calculated from the serum concentration-time data by noncompartmental analysis (NCA) with Phoenix™ WinNonlin® Version 8.0 or higher (WinNonlin; Certara, Inc., Mountain View, California), using an extravascular administration model (as feasible):

- Apparent half-life ($t_{½}$)
- apparent (extravascular) volume of distribution ($V_z/F$)
- apparent (extravascular) clearance (CL/F)
- maximum observed concentration ($C_{max}$)
- time of the observed maximum concentration ($T_{max}$)
- area under the plasma concentration curve from time 0 through the last measurable concentration ($AUC_{0-t}$)
- area under the plasma concentration curve from time 0 extrapolated to infinite time ($AUC_{0-inf}$ or $AUC_{0-\infty}$)

The actual sampling times and nominal doses will be used in the analysis. Prior to $T_{max}$, N-803 concentrations that are BLQ (< 23.4 pg/mL) will be set to 0; BLQ concentrations after $T_{max}$ will be excluded from the analysis. Concentrations reported as "0" will be converted to BLQs prior to analysis.

The area under the curve from time zero to the last measurable concentration ($AUC_{0-t}$) will be calculated using the linear up/log down method. Log/linear regression through the last three or more time points (excluding $T_{max}$) will be used to estimate the elimination constant ($\lambda_z$). The terminal phase half-life ($t_{1/2}$) and the AUC from time zero to infinity ($AUC_{0-inf}$ or $AUC_{0-\infty}$) will be calculated using the following equations:

$$t_{1/2} = \ln (2)/\lambda_z$$

$$AUC_{0-inf} = AUC_{0-t} + C_{t,pred}/ \lambda_z,$$

where $C_{t,pred}$ is the last predicted concentration based on the exponential decline (eg, $e^{-\lambda z \cdot t}$). If any of the following are observed, the terminal phase-dependent parameters (eg, $\lambda_z$, $t_{1/2}$, $AUC_{0-inf}$, CL/F, $V_z$/F) following single dose administration will not be reported:

- $\lambda_z$ indicates a positive slope ($\lambda_z$>0)
- $T_{max}$ is one of the last three time points with measurable concentrations
- the linear regression coefficient or the goodness of fit ($R^2$) is less than 0.80

When the extrapolated area (eg, $C_{t,pred}/\lambda_z$ or AUC Extrap.) is greater than 20% of total $AUC_{0-inf}$, this suggests that there may be greater uncertainty in PK parameters dependent on the definition of the terminal phase and/or this extrapolation (eg, $\lambda_z$, $t_{1/2}$, $AUC_{0-inf}$, CL/F, $V_z$/F).

No statistical comparisons will be performed for the PK parameters. All PK parameters will be analyzed descriptively including mean, standard deviation, minimum, median, maximum and %CV, as applicable.

| | |
|---|---|
| **DRUG:** | ALT-803 (also known as N-803) |
| **STUDY NUMBER(S):** | QUILT-3.032-2.005-PK |
| **PROTOCOL(S) TITLE:** | A Pharmacokinetic Sub-Study of QUILT-3.032 (CA-ALT-803-01-16): A Multicenter Clinical Trial of Intravesical Bacillus Calmette-Guerin (BCG) in Combination with ALT-803 in Patients with BCG Unresponsive High Grade Non-Muscle Invasive Bladder Cancer and QUILT-2.005: A Study of Intravesical BCG in Combination With ALT-803 in Patients With Non-Muscle Invasive Bladder Cancer |
| **IND NUMBER:** | 121976 |
| **SPONSOR:** | Altor BioScience, LLC, a wholly-owned subsidiary of ImmunityBio, Inc. (Altor BioScience) |
| **ORIGINAL PROTOCOL DATE:** | 10 June 2019 |
| **VERSION NUMBER:** | 2.0 |
| **VERSION DATE:** | 24 February 2020 |

# CLINICAL PROTOCOL APPROVAL FORM

**Protocol Title: A Pharmacokinetic Sub-Study of QUILT-3.032: A Multicenter Clinical Trial of Intravesical Bacillus Calmette-Guerin (BCG) in Combination with ALT-803 in Patients with BCG Unresponsive High Grade Non-Muscle Invasive Bladder Cancer and QUILT-2.005: A Study of Intravesical BCG in Combination With ALT-803 in Patients With Non-Muscle Invasive Bladder Cancer**

**Study No: QUILT-3.032-2.005-PK**

**Original Protocol Date: 10 June 2019**

**Protocol Version No: 2.0**

**Protocol Version Date: 24 February 2020**

This study protocol was subject to critical review and has been approved by the appropriate protocol review committee of the Sponsor. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the investigational product.
- The moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and principles of GCP as described in 21 CFR parts 50, 54, 56 and 312 and according to applicable local requirements.

The Investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

| Name and Title | Signature | Date |
|---|---|---|
| Clinical Development:<br><br>Amy Rock, PhD<br>Vice-President, Clinical Development & Regulatory Affairs | Amy Rock | 25FEB2020 |
| Medical Lead:<br><br>John Lee, MD<br>Chief Medical Officer | John Lee | 2-24-2020 |
| Regulatory Affairs:<br><br>Melissa Luras<br>Director, Regulatory Affairs | Melissa Luras<br>Digitally signed by Melissa Luras<br>DN: cn=Melissa Luras, o=ImmunityBio, Inc., ou=Regulatory Affairs, email=melissa.luras@immunitybio.com, c=US<br>Reason: I am approving this document<br>Date: 2020.02.25 07:04:39 -07'00' | |

# STUDY SYNOPSIS

**Title:** A Pharmacokinetic Sub-Study of QUILT-3.032: A Multicenter Clinical Trial of Intravesical Bacillus Calmette-Guerin (BCG) in Combination with ALT-803 in Patients with BCG Unresponsive High Grade Non-Muscle Invasive Bladder Cancer and QUILT-2.005: A Study of Intravesical BCG in Combination With ALT-803 in Patients With Non-Muscle Invasive Bladder Cancer

**Rationale:** ALT-803 is an IL-15-based immunostimulatory protein complex that acts as a growth and activation factor for natural killer (NK) cells and effector and memory T cells. Based on the results of animal tumor models, ALT-803 stimulated cellular immune responses are expected to exhibit potent activity against human tumor cells. The objective of this study is to establish the pharmacokinetic (PK) profile of intravesical ALT-803 administered to patients with High Grade Non-Muscle Invasive Bladder Cancer (NMIBC).

**Target Population:** Adult Patients with High Grade Non-Muscle Invasive Bladder Cancer

**Number of Subjects:** 12 - 20 subjects

**Objectives:**

Primary
To determine the PK profile of ALT-803 after single dose intravesical instillation of 400 µg ALT-803

Secondary
To determine the PK profile of ALT-803 after multiple intravesical instillations of 400 µg ALT-803

**Study Design:** Non-interventional PK sub-study of QUILT-3.032 (CA-ALT-803-01-16) and QUILT-2.005 (CA-ALT-803-01-14)

QUILT-3.032 (CA-ALT-803-01-16): Phase 2, open-label, single-arm, three-cohort, multicenter study of intravesical BCG plus ALT-803 (400 µg) in patients with BCG unresponsive high grade NMIBC. Patients will be enrolled into one of three study cohorts. Cohort A will enroll 80 patients who have histologically confirmed presence of BCG-unresponsive carcinoma in situ (CIS) [with or without Ta/T1 papillary disease]. Cohort B will enroll 80 patients who have histologically confirmed BCG-unresponsive high-grade Ta/T1 papillary disease. Cohort C will enroll up to 23 patients who also have histologically confirmed presence of BCG-unresponsive CIS [with or without Ta/T1 papillary disease]. Patients in Cohorts A and B will receive ALT-803 plus BCG combination treatment. Patients in Cohort C will receive ALT-803 alone. Enrollment of Cohort C will start once the enrollment of Cohort A is complete. Cohorts A, B, and C are independent study cohorts and will be

separately evaluated for efficacy and safety. The study will be conducted in conformity with Good Clinical Practice (GCP). All patients treated in the study will receive via a urinary catheter in the bladder ALT-803 plus BCG or ALT-803 alone, weekly for 6 consecutive weeks during the induction treatment period.

QUILT-2.005 (CA-ALT-01-14): This is a phase 2b, randomized, two-cohort, open-label, multicenter study of intravesical ALT-803 plus BCG versus BCG alone, in BCG naïve patients with high-grade NMIBC. Patients will be enrolled into one of two study cohorts and randomized into two arms to be treated with either ALT-803 plus BCG or BCG alone. Cohort A will initially enroll 366 patients who have histologically confirmed CIS (with or without Ta/T1 papillary disease). Cohort B will initially enroll 230 patients who have histologically confirmed high-grade papillary Ta/T1 disease only. Cohorts A and B are two independent study cohorts and will be evaluated separately for efficacy.

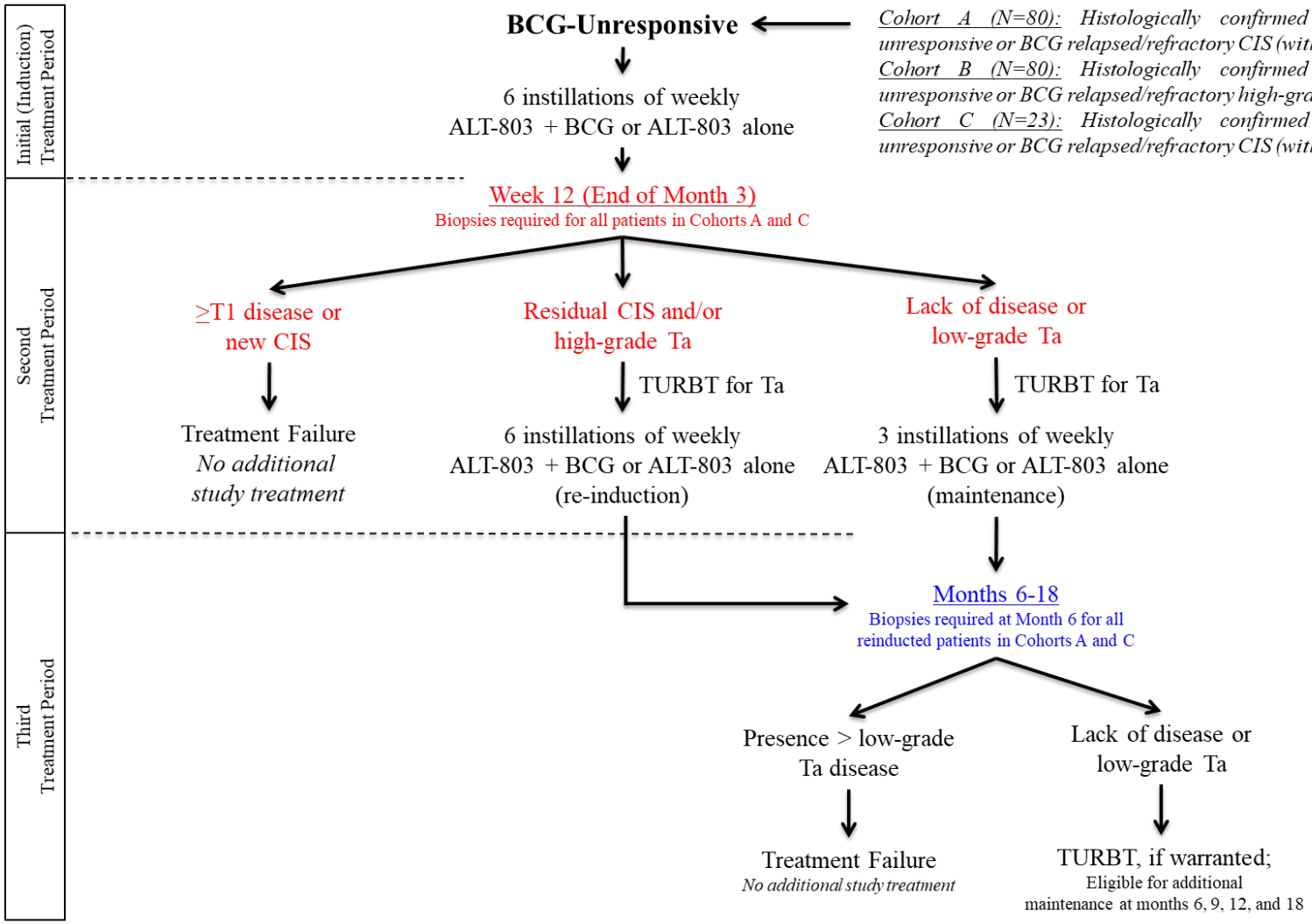
PK sub-study: Blood samples to determine serum levels of ALT-803 will be collected on study day 1 prior to dosing, and at post-bladder voiding (+ 15 minutes), 24 (±2), 48 (±4), 72 (±4), 96 (±4) and 168 (±4) hours after dosing administered at study Week 1 and again at the same time points for study Week 6. Six subjects from either cohort A (either study) or cohort C (QUILT 3.032) and six subjects from cohort B (either study) will be sampled initially. Up to an additional 4 subjects for each cohort may also be sampled. Patients enrolled in QUILT 2.005 must have been randomized to receive ALT-803 plus BCG to be eligible for the PK sub-study.

**Primary Endpoints:**

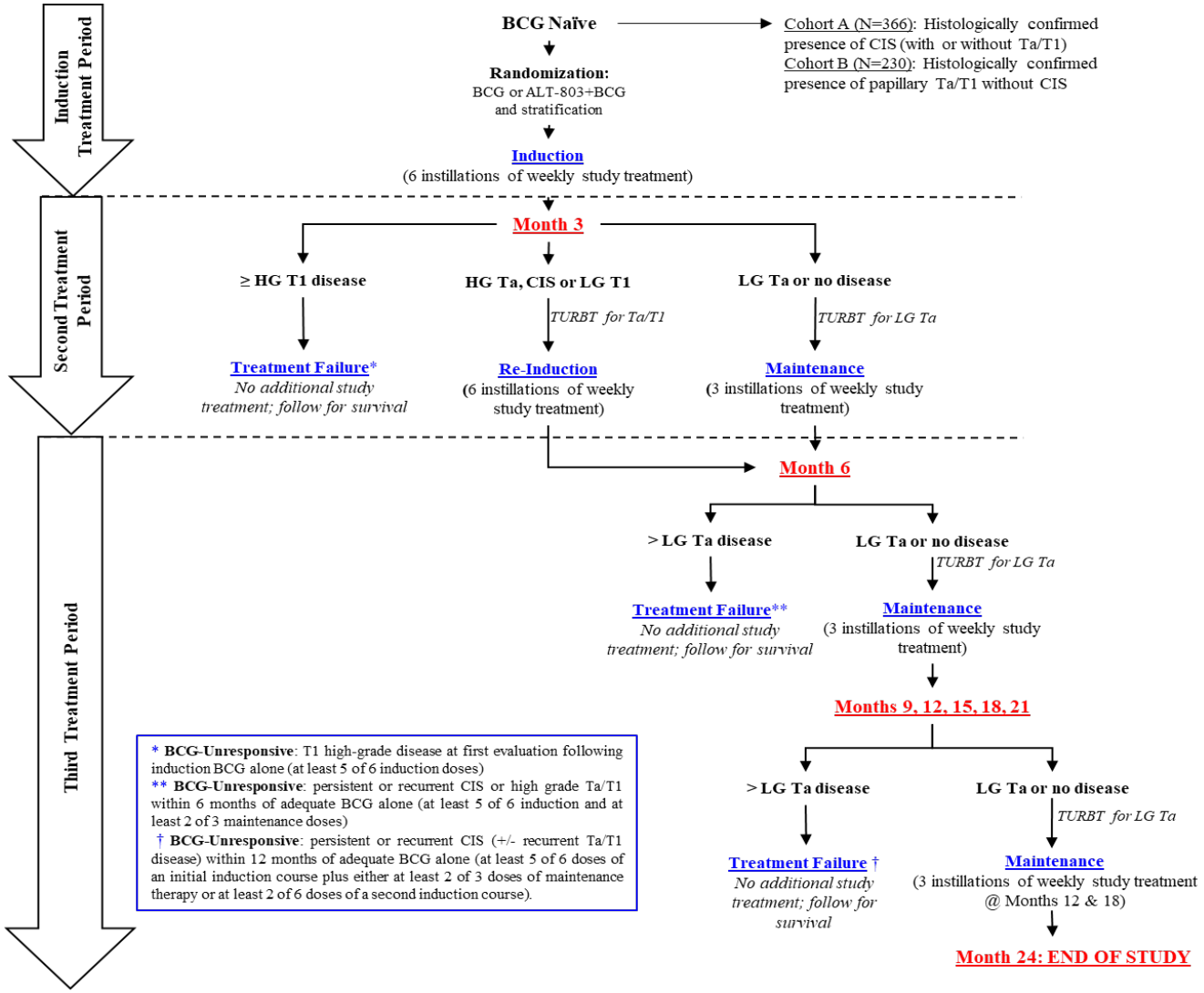
Serum concentration will be used to calculate the following PK parameters:

- half-life ($t_{½}$)
- apparent (extravascular) volume of distribution ($V_z/F$)
- apparent (extravascular) clearance (CL/F)
- maximum observed concentration ($C_{max}$)
- time of the observed maximum concentration ($T_{max}$)
- area under the plasma concentration curve from time 0 through the last measurable concentration ($AUC_{0-t}$)
- area under the plasma concentration curve from time 0 extrapolated to infinite time ($AUC_{0-inf}$)

## STUDY SCHEMATIC: QUILT-3.032



## STUDY SCHEMATIC: QUILT-2.005



## 4.2 SCHEDULE OF ASSESSMENTS

### Table 2: Schedule of Assessments

| TESTS & PROCEDURES | Screen | Initial (Induction) Treatment Period | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Week | | 1 | | | | | | | 2 | 3 | 4 | 5 | 6 | | | | | | 7 |
| Study Day | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 15 | 22 | 29 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 |
| Blood sampling for ALT-803 PK* | | X | X | X | X | X | | | X** | | | | X | X | X | X | X | | | X** |
| *Blood sampling for PK will be collected prior to ALT-803 dose and at post-bladder voiding (+15 minutes), 24 (±2 hours), 48 (±4 hours), 72 (±4 hours), 96 (±4 hours) and 168 (±4 hours) hours after dosing administered at weeks 1 and 6. | | | | | | | | | | | | | | | | | | | |
| **Pre-dose only. | | | | | | | | | | | | | | | | | | | |

# 10 STATISTICS

## 10.1 GENERAL PROCEDURES

A separate, detailed PK Analysis Plan will be developed for data analysis prior to study completion and data lock. Descriptive statistical methods will be used to summarize the data from this study. Unless otherwise stated, the term descriptive statistics refers to the number of subjects, mean, median, standard deviation, minimum, and maximum for continuous data, and frequencies and percentages for categorical data. No statistical testing will be performed. Results will be summarized in the final clinical study reports for QUILT-3.032 and QUILT 2.005.

## 10.2 SAMPLE SIZE

Six subjects from Cohort A and six subjects from Cohort B will be sampled initially. Up to an additional 4 subjects from each cohort may also be sampled. The maximum number of subjects enrolled will be 20.

## 10.3 PK ASSAY DESCRIPTION

The method used to detect and quantify serum IL-15 employs a Human IL-15 assay kit, supplied by R&D Systems (Minneapolis, MN). The specific assay utilized comprises a sandwich ELISA (enzyme-linked immunosorbent assay) employing two unique anti-human IL-15 monoclonal antibodies

## 10.4 PK PARAMETER ANALYSIS

The following PK parameters will be calculated from the serum concentration-time data by noncompartmental analysis (NCA) with Phoenix™ WinNonlin® Version 8.0 or higher (WinNonlin; Certara, Inc., Mountain View, California), using an extravascular administration model (as feasible):

- Apparent half-life ($t_{½}$)
- apparent (extravascular) volume of distribution ($V_z/F$)
- apparent (extravascular) clearance (CL/F)
- maximum observed concentration ($C_{max}$)
- time of the observed maximum concentration ($T_{max}$)
- area under the plasma concentration curve from time 0 through the last measurable concentration ($AUC_{0-t}$)
- area under the plasma concentration curve from time 0 extrapolated to infinite time ($AUC_{0-inf}$ or $AUC_{0-\infty}$)

The actual sampling times and nominal doses will be used in the analysis. Prior to $T_{max}$, N-803 concentrations that are BLQ (< 23.4 pg/mL) will be set to 0; BLQ concentrations after $T_{max}$ will be excluded from the analysis. Concentrations reported as "0" will be converted to BLQs prior to analysis.

The area under the curve from time zero to the last measurable concentration ($AUC_{0-t}$) will be calculated using the linear up/log down method. Log/linear regression through the last three or more time points (excluding $T_{max}$) will be used to estimate the elimination constant ($\lambda_z$). The terminal phase half-life ($t_{1/2}$) and the AUC from time zero to infinity ($AUC_{0-inf}$ or $AUC_{0-\infty}$) will be calculated using the following equations:

$$t_{1/2} = \ln(2)/\lambda_z$$

$$AUC_{0-inf} = AUC_{0-t} + C_{t,pred}/\lambda_z,$$

where $C_{t,pred}$ is the last predicted concentration based on the exponential decline (eg, $e^{-\lambda z \cdot t}$). If any of the following are observed, the terminal phase-dependent parameters (eg, $\lambda_z$, $t_{1/2}$, $AUC_{0-inf}$, CL/F, $V_z$/F) following single dose administration will not be reported:

- $\lambda_z$ indicates a positive slope ($\lambda_z$>0)
- $T_{max}$ is one of the last three time points with measurable concentrations
- the linear regression coefficient or the goodness of fit ($R^2$) is less than 0.80

When the extrapolated area (eg, $C_{t,pred}/\lambda_z$ or AUC Extrap.) is greater than 20% of total $AUC_{0-inf}$, this suggests that there may be greater uncertainty in PK parameters dependent on the definition of the terminal phase and/or this extrapolation (eg, $\lambda_z$, $t_{1/2}$, $AUC_{0-inf}$, CL/F, $V_z$/F).

No statistical comparisons will be performed for the PK parameters. All PK parameters will be analyzed descriptively including mean, standard deviation, minimum, median, maximum and %CV, as applicable.

[redacted]