16.1__9 Documentation of Statistical Methods

16.1__9.1 Statistical Analysis Plan

All statistical tests were two-tailed and were performed at significance level of 0.05, unless otherwise indicated. Computation for the statistical tests was performed with the SAS, Version 9.20 or above on a Hewlett Packard workstation using the Unix operating system. For the analysis of variance (ANOVA), SAS procedure GLM with type III sums of squares was utilized. SAS procedure PROC UNIVARIATE and PROC MEANS were used to obtain summary statistics. SAS procedure PROC FREQ was used for analysis of categorical variables. SAS procedure PROC LIFETEST was used for survival analysis.

Data Sets Analyzed

Subjects who took at least one dose of navitoclax were included in the efficacy, safety, and pharmacokinetics summaries.

All 29 subjects enrolled and treated in the Phase 1 portion of the study were analyzed for safety, efficacy, and pharmacokinetics. All 31 subjects enrolled and treated in the Phase 2 portion of the study were analyzed for safety, and efficacy while 25 subjects who had at least one PK result for any visit were included in PK analysis.

Demographic Variables

All baseline summary statistics are based on characteristic prior to the first dose of navitoclax. Descriptive statistics were provided for baseline characteristics and demographic variables for the Phase 1 and the Phase 2 portions of the study separately. Age, height, and weight (female, male, and together), Beta-2 microglobulin, baseline lymphocytes were summarized with means, medians, standard errors, standard deviations, and ranges. Frequencies and percentages were provided for gender and race, ethnicity, age ranges, nicotine and alcohol use, bulky lymphadenopathy (nodes >5 cm), CD38, IGVH, ZAP70, staging - Binet, staging - RAI, and protocol version.

Medical History

Following analysis was provided for each portion of the study. Medical history data was summarized and presented using primary MedDRA system organ classes (SOCs) and preferred terms (PTs). The number and percentage of subjects experiencing events were summarized by dose and overall.

Previous Treatment and Concomitant Medications

A prior medication was defined as any medication taken prior to the first dose of navitoclax. A concomitant medication was defined as any medication that started prior to the first dose of navitoclax and continued to be taken after the first dose of navitoclax or any medication that started after the first dose of Navitoclax, but not after the last dose of navitoclax. Following analysis was provided for each portion of the study. The number and percentage of subjects who have taken medications were summarized per subjects and by generic drug name for prior medications, concomitant medication. The number and percentage of subjects who have taken 1, 2, 3, 4, 5, 6 and above prior medications and concomitant medications were also summarized.

For summaries of concomitant medications, if an incomplete start date was collected for a medication, the medication was assumed to be a concomitant medication unless there was evidence that confirms that the medication was not a concomitant medication (e.g., the medication end date was prior to the first dose of navitoclax).

A subject who reports the use of two or more medications was counted only once in the summary of "Any Concomitant Medication." A subject who reports two or more uses of the same medication was counted only once in the total for the associated generic drug name. Similar rules apply to prior medications as well.

Drug Exposure and Compliance

Following analysis was provided for each portion of the study. The duration of exposure to navitoclax were summarized. Duration of exposure is defined for each subject as (last dose date – first dose date) + 1. Duration of exposure was summarized using the

following statistics: sample size (N), mean, standard deviation, median, minimum, and maximum. Similar analyses were provided for time on study data. Time on study is defined for each subject as (last visit date – first dose date) + 1. In addition, the number and percentage of subjects exposed to navitoclax were summarized for the following categories of exposure duration: 1, 2, 3, 4, 5, and 6 or more cycles.

The compliance based on investigator opinion for each subject was provided in the data listing.

Pharmacokinetic Analyses

Tabulations and Summary Statistics

Plasma concentrations of navitoclax and pharmacokinetic parameter values were tabulated for each subject and each dose level, and summary statistics were computed for each sampling time and each parameter.

Model and Tests

For subjects who participated in the Phase 1, 14/21 day dosing portion of the study, an analysis was performed on pharmacokinetic variables for Cycle 1 Day 1 dose to simultaneously explore for demographic variables that explained some of the variability in pharmacokinetics and to address questions of dose proportionality and linear kinetics. An analysis was performed for dose-normalized C_{max}, T_{max}, and dose-normalized AUC_t (AUC_{0-24}). The model used for the statistical analyses included dose level. This was done by classifying subjects by dose level. Covariates such as age, body weight, BSA, gender, and formulation, as well as others that might have explained some of the variability in the population, were considered for inclusion in the model initially. However, a covariate was dropped from the model if the regression coefficient was not significant at level 0.10. The natural logarithmic transformation was employed for C_{max} and AUC_t. Within the framework of the model, tests that had good power for a trend with dose were performed on the effect of dose level.

A corresponding analysis was also performed on pharmacokinetic variables of the dose on Cycle 1 Day 14 for both the Phase 1, 14/21 and 21/21 day dosing schedules. The variables included dose-normalized C_{max}, T_{max}, and dose normalized AUC_t (AUC_{0-8}).

Exploratory Efficacy

The following exploratory efficacy analyses were performed for Phase 1 and Phase 2 of the study. Unless specified otherwise all the analyses were presented by dose levels and overall; all the response and associated data were evaluated based on NCI WG Criteria (1996), and updated IWCLL NCI WG Criteria (2008) for Phase 1, and 2, respectively.

Progression-Free Survival

The distribution of PFS was estimated using Kaplan-Meier methodology. Median time to PFS and the corresponding 95% confidence interval were estimated.

For a given subject, PFS was defined as the number of days from the date the subject started study drug to the date the subject experiences an event of disease progression, or to the date of death if disease progression was not reached. All events of disease progression were included, regardless of whether the event occurred while the subject was still taking study drug or had previously discontinued study drug. Events of death were included for subjects who had not experienced disease progression provided the death occurred within 2 cycles (42 days) of the date of the last available tumor evaluation. If a subject had not experienced an event of disease progression or death as defined above, then the subject's data was censored at the date of the last available evaluation for disease progression. The date of the last available evaluation was the date of the last study visit at which a tumor assessment was performed.

Response Rate

- Objective Response Rate (ORR)
  - Phase 1: ORR = CR + PR.
  - Phase 2: ORR = CR + CRi + PR.

- Best Response Rate
  - Phase 1: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Disease Progression (PD), and Incomplete Data (ID) were reported.
  - Phase 2: Complete Response (CR), Complete Response - incomplete bone marrow (CRi), Partial Response (PR), Stable Disease (SD), Disease Progression (PD), and Incomplete Data (ID) were reported.
- Disease Control Rate (DCR)
  - Phase 1: DCR = CR + PR + SD.
  - Phase 2: DCR = CR + CRi + PR + SD.

The exact binomial distribution was used to construct this confidence interval for the response rates, and the corresponding 95% confidence interval was constructed.

Time to Tumor Progression

Time to tumor progression for a given subject was defined as the number of days from the date the subject started study drug to the date of the subject's tumor progression. Time to tumor progression was collected up to 2 cycles (42 days) following the date of the last available tumor evaluation. All events of tumor progression were included, regardless of whether the event occurred while the subject was still taking study drug, or after the subject discontinued study drug. If a subject had not progressed, then the data was censored at the date of the last study visit at which a tumor assessment was performed.

The distribution of the time to tumor progression was estimated using Kaplan-Meier methodology. Median time to tumor progression and the corresponding 95% confidence interval were estimated.

Overall Survival

Time to death for a given subject was defined as the number of days from the date the subject started study drug to the date of the subject's death. All events of death were included, regardless of whether the event occurred while the subject was still taking study drug, or after the subject discontinued study drug. If a subject had not died, then the data was censored at the date of the last study visit, the last contact date, or the date the subject was last known to be alive, whichever was last. The date of the last study visit was determined by selecting the last available date of the following study procedures for a subject: physical examination, vital signs assessment, blood chemistry, hematology, and urinalysis collection.

The distribution of the time to death was estimated using Kaplan-Meier methodology. Median survival time and the corresponding 95% confidence interval were estimated.

Duration of Overall Response

The duration of overall response for a given subject was defined as the number of days from the day the criteria were met for CR, CRi or PR (whichever was recorded first) to the date that PD was objectively documented. The reference for PD was the smallest measurement recorded since the treatment started. If a subject was still responding, then the subject's data was censored at the last study visit at which a tumor assessment was performed.

The distribution of the duration of overall response was estimated using Kaplan-Meier methodology. Median duration of overall response and the corresponding 95% confidence interval were estimated.

ECOG Performance Status

For the ECOG performance scale, descriptive statistics were summarized for each assessment. In addition, a mean change from baseline to each assessment was summarized.

Safety Analyses

Safety summaries included all subjects participating in the study unless otherwise indicated. Following analysis was provided for each portion of the study.

Adverse Events

Analysis of Treatment-Emergent Adverse Events

All analyses involving AEs were treatment-emergent adverse events (TEAE) only, unless otherwise specified. TEAE were defined as any event with onset after the first dose of navitoclax and no more than 30 days after the last dose of navitoclax. Events where the onset date was the same as the navitoclax start date were assumed to be treatment-emergent, unless the navitoclax start time and the AE start time were collected and the AE start time was prior to the navitoclax start time. If an incomplete onset date was collected for an AE, the AE was assumed to be treatment-emergent unless there was evidence that confirms that the AE was not treatment-emergent (e.g., the AE end date was prior to the date of the first dose of navitoclax).

Adverse event data was summarized and presented using primary MedDRA system organ classes (SOCs) and preferred terms (PTs) according to the MedDRA 22.0 coding dictionary.

The number and percentage of subjects experiencing treatment-emergent adverse events was summarized by phase 1 or 2, day cycle (14/21 or 21/21), navitoclax dose and for the whole portion of the study for the following adverse event summaries:

- Overview of treatment emergent adverse events
- Any treatment-emergent adverse event by System Organ Class and Preferred Term.
- Subject number associated with treatment-emergent adverse event.
- Treatment-emergent adverse events by System Organ Class, Preferred Term, and maximum NCI toxicity grade (CTCAE V3.0).

- Treatment-emergent adverse events broken down by maximum relationship to study drug.
- Any treatment-emergent NCI toxicity (CTCAE V3.0) grade 3 or 4 adverse events.
- Any treatment-emergent NCI toxicity (CTCAE V3.0) grade >=3 adverse events.
- Treatment-emergent adverse events broken down by possibly or probably drug-related NCI toxicity grade >=3 adverse events
- Treatment-emergent adverse events broken down by possibly or probably drug-related NCI toxicity grade 3 or 4 adverse events
- Any treatment-emergent adverse event with possibly or probably drug-related.
- For treatment-emergent serious adverse events, analyses similar to TEAE were provided.
- Any treatment-emergent adverse event leading to discontinuation of each drug.
- Any treatment-emergent adverse event leading to each drug interruption.
- Any treatment-emergent adverse event leading to each drug reduction.
- Any treatment-emergent adverse event leading to each drug delay.
- Any treatment-emergent adverse event leading to death.
- Subject deaths occurring <= 30 days after last dose of study drug.
- Subject deaths occurring > 30 days after last dose of study drug.
- Any treatment-emergent DLT adverse events by primary MedDRA system organ class and preferred term.

Selected Adverse Events

Analysis of adverse events of safety areas of interest were conducted through the summary of MedDRA preferred terms identified using standard MedDRA queries (SMQs) and custom searches. Like TEAEs analyses, overview of selected AEs, and selected AEs by primary MedDRA system organ class and preferred term were provided. The search criteria for each of the safety areas of interest were described below.

Identified Risks

Thrombocytopenia - PTs: 10043554 Thrombocytopenia; 10035528 Platelet count decreased

Neutropenia - PTs: 10001507 Agranulocytosis; 10016288 Febrile neutropenia; 10029354 Neutropenia; 10059482 Neutropenic infection; 10049151 Neutropenic sepsis; 10029366 Neutrophil count decreased

Lymphopenia - PTs: 10025327 Lymphopenia; 10025256 Lymphocyte count decreased

Potential Risks

Hemorrhagic Events - SMQ 20000038 Hemorrhages (Narrow)

Opportunistic Infections - SMQ 20000235 Opportunistic Infections (Broad)

Tumor Lysis Syndrome - SMQ 20000219 Tumor Lysis Syndrome (Narrow)

Hepatotoxicity - SMQ 20000006 Drug Related Hepatic Disorders – Comprehensive (Broad); SMQ 20000007 Drug Related Hepatic Disorders – Severe Events Only (Narrow)

Increased Pancreatic Enzymes - SMQ 20000022 Acute Pancreatitis (Narrow)

Cardiovascular Events - SMQs: 20000004 Cardiac Failure (Narrow); 20000130 Pulmonary Hypertension (Narrow)

Venous Thromboembolic Events - SMQ 20000084 Embolic and Thrombotic Events, Venous (Narrow)

Cerebellar Hypoplasia - PT 10008033 Cerebellar Hypoplasia

Decreased Spermatogenesis - SMQ 20000210 Fertility Disorders (Narrow; males only)

Skin Cancer or Second Malignancies - SMQs: 20000173 Skin Neoplasms, Malignant and Unspecified (Broad); 20000090 Malignancies (Broad)

Allergic Reactions - SMQ 20000021 Anaphylactic Reaction (Broad)

Drug Interactions - HLT 10022528 Interactions

Analysis of Laboratory and Vital Signs Data

The value for baseline used in laboratory and vital sign analyses is defined in the Definition of Baseline section. All laboratory and vital signs were summarized by dose and the study portion as a whole.

Analysis of Mean Changes from Baseline in Clinical Laboratory Data

Changes from baseline were analyzed for each scheduled post-baseline visit and for the final visit for lymphocyte enumeration, urinalysis, blood chemistry and hematology parameters, as well as vital sign parameters.

Laboratory tests to be summarized are included in Table 1.

Table 1. Clinical Laboratory Tests

Hematology	Chemistry	Urinalysis
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Platelet count Reticulocyte count Prothrombin time (PT) Activated partial thromboplastin time (aPTT) Mean corpuscular volume (MCV) MPV MCH MCHC	Blood Urea Nitrogen (BUN) Creatinine Total bilirubin Serum glutamic-pyruvic transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase (SGOT/AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphate Uric acid Cholesterol Total protein Glucose Triglycerides Albumin Lactate dehydrogenase (LDH) Magnesium Chloride Bicarbonate Lipase	Urine PH Urine specific gravity **Lymphocyte Enumeration** B-Lymphocytes total Natural killer cells total T-Helper cells total T-Lymphocytes total T-Suppressor cells total

Mean changes from baseline at each scheduled post-baseline visit and Final Visit was summarized with the baseline mean, visit mean, change from baseline mean, standard deviation, and minimum/maximum values.

Analyses of Shift from Baseline in Clinical Laboratory Data

For shifts relative to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE), baseline and post-baseline laboratory observations were categorized as grade 0, grade 1, grade 2, grade 3, or grade 4 according to NCI CTCAE grade version 3.0.

The baseline and final grades were defined respectively as the grade of the last measurement collected prior to the first dose of navitoclax, and as the last post-baseline

measurement collected no more than 30 days after the last dose of navitoclax. The maximum NCI toxicity grade value was the value with highest NCI toxicity grade collected after the first dose of navitoclax and within 30 days following the last dose of navitoclax. In cases where multiple values are collected on the same day, the maximum grade value was selected as the value for that day.

For each variable, shift tables were generated that cross tabulate the number of subjects with baseline values of grade 0, grade 1, grade 2, grade 3, or grade 4 versus final observations of grade 0, grade 1, grade 2, grade 3, or grade 4.

Additionally, for each variable, the number and percentage of subjects that have a baseline observation that was categorized as a grade 0, grade 1, or grade 2 and that also have a grade 3 or 4 final observation was presented. In addition to final observation, a similar set of summaries were produced for the maximum post-baseline laboratory observations.

For urinalysis, cross tabulated the number of subjects with baseline and maximum dipstick results. Similar cross tabulations were provided for baseline and final dipstick results.

Detailed listings of data for subjects experiencing NCI CTCAE grade 3 to 4 blood chemistry and hematology values were provided. Listings were also provided for urinalysis values with dipstick results of 2+ or higher. All measurements collected, regardless of the number of days after the last dose of navitoclax, were included in these listings.

The NCI CTCAE grade 3 criteria are given in Table 2 and Table 3 below.

Table 2. Criteria for Potentially Clinically Significant Laboratory Values – Chemistry Variables

		Definition of Potentially Clinically Significant Current (Version 3) Grade 3	
Chemistry Variables	**Units**	**Low**	**High**
Total bilirubin	mcmol/L		> 3.0 × ULN
Albumin	g/L	< 20	
Aspartate amino transaminase (AST/SGOT)	U/L		> 5.0 × ULN
Alanine amino transferase (ALT/SGPT)	U/L		> 5.0 × ULN
Alkaline phosphatase	U/L		> 5.0 × ULN
Creatinine	mcmol/L		> 3.0 × ULN
Sodium	mmol/L	< 130	> 155
Potassium	mmol/L	< 3.0	> 6.0
Total calcium	mmol/L	< 1.75	> 3.1
Glucose	mmol/L	< 2.2	> 13.9
Inorganic Phosphate	mmol/L	< 0.6	
Bicarbonate	mmol/L	< 11	
Cholesterol	mmol/L		> 10.34
Triglycerides	mmol/L		> 5.0 × ULN
Magnesium	mmol/L	< 0.4	> 1.23

Table 3. Criteria for Potentially Clinically Significant Laboratory Values – Hematology Variables

Hematology Variables	**Units**	**Definition of Potentially Clinically Significant Current (Version 3) Grade 3**
Hemoglobin	g/L	< 80
White blood cell count	10^9/L	< 2
Neutrophils	10^9/L	< 1
Lymphocytes	10^9/L	< 0.5
Platelets	10^9/L	< 50

Assessment of Mean Changes from Baseline in Vital Signs Variables

Analyses of mean change from baseline in continuous vital signs variables which are measured longitudinally were performed (systolic blood pressure, diastolic blood pressure, heart rate, weight, and temperature). For each change from baseline analysis, the following summary statistics were presented: sample size, baseline mean, visit mean, and the mean, standard deviation, and minimum/maximum of the changes from baseline. The baseline and visit means were calculated for each visit for subjects who have both a baseline and visit value.

Assessment of Potentially Clinically Significant Vital Signs Values

For selected vital signs variables, a listing of all observations collected was generated for subjects that had at least one post-baseline observation meeting pre-defined criteria for potentially clinically significant values. The number and percentage of subjects who have at least one post-baseline observation meeting the pre-defined criteria for potentially clinically significant values was provided for each variable.

Pre-defined criteria for potentially clinically significant vital signs values are given in Table 4 below based on CTCAE criteria:

Table 4. Criteria for Potentially Clinically Significant Laboratory Values – Vital Signs Variables

Vital Signs Variables	Criterion	Definition of Potentially Clinically Significant
Systolic blood pressure	High	Value > 150 mmHg
Diastolic blood pressure	High	Value > 100 mmHg
Heart Rate	Low	Value ≤ 50 bpm
	High	Value ≥ 120 bpm
Temperature	Low	Value ≤ 36°C
	High	Value ≥ 38.5°C

Analysis Conventions

Definition of Baseline

The baseline value was defined as the last non-missing measurement collected before the first dose of navitoclax.

Definition of Final Observation

The final observation (Final Visit) was defined as the last non-missing observation collected within 30 days following the last dose of navitoclax.

Definition of Rx Days (Days Relative to the First Dose of navitoclax)

Rx Days were calculated for each time point relative to the first dose date of navitoclax. They were defined as the number of days between the day of the first dose of navitoclax and the specific time point. Rx days were negative values when the time point of interest was prior to the first navitoclax dose day. Rx days were positive values when the time point of interest was after the first navitoclax dose day. The day of the first dose of navitoclax was defined as Rx Day 1, while the day prior to the first navitoclax dose was defined as Rx Day –1 (there is no Rx Day 0).