GILEAD

## STATISTICAL ANALYSIS PLAN

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|---|---|
| **Study Title:** | A Prospective, Open-Label, Multicenter, Phase 2 Trial to Evaluate the Safety and Efficacy of the Combination of Tirabrutinib (GS-4059) and Entospletinib with and without Obinutuzumab in Subjects with Chronic Lymphocytic Leukemia |
| **Name of Test Drug:** | Tirabrutinib (GS-4059) |
| **Study Number:** | GS-US-401-2076 |
| **Protocol Version (Date):** | Amendment 4 (15 January 2019) |
| **Analysis Type:** | Final Analysis |
| **Analysis Plan Version:** | Version 2.0 |
| **Analysis Plan Date:** | 13 January 2021 |
| **Analysis Plan Author:** | PPD |

## CONFIDENTIAL AND PROPRIETARY INFORMATION

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | adverse event |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| ATC | Anatomical Therapeutic Chemical |
| BLQ | below the limit of quantitation |
| BM | bone marrow |
| BMI | body mass index |
| CCR | clinical complete response |
| CI | confidence interval |
| CLL | chronic lymphocytic leukemia |
| CPR | clinical partial response |
| CR | complete remission |
| CR/BM MRD- | complete remission with bone marrow minimal residual disease negativity ($<10^{-4}$ CLL cells present) |
| CR/PB MRD- | complete remission with peripheral minimal residual disease negativity ($<10^{-4}$ CLL cells present) |
| CRi | complete remission with incomplete recovery of the bone marrow |
| CRF | case report form |
| CSR | clinical study report |
| CTCAE | Common Toxicity Criteria for Adverse Events |
| CCI | |
| ECG | electrocardiogram |
| EOT | End of Treatment |
| FAS | Full Analysis Set |
| HLT | high-level term |
| ID | identification |
| IWCLL | International Workshop on CLL |
| IWRS | Interactive Web Response System |
| LLT | lower-level term |
| LOQ | limit of quantitation |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NLP | Natural Language Processing |
| nPR | nodular partial response |
| ORR | overall response rate |
| CCI | |
| PB | peripheral blood |
| PD | progressive disease |
| CCI | |
| PP | per protocol |

| | |
|---|---|
| PR | partial response |
| PR-L | partial response with lymphocytosis |
| PT | preferred term |
| Q1, Q3 | first quartile, third quartile |
| QRS | electrocardiographic deflection between the beginning of the Q wave and termination of the S wave representing time for ventricular depolarization |
| QT | electrocardiographic interval between the beginning of the Q wave and termination of the T wave representing the time for both ventricular depolarization and repolarization to occur |
| QTc | QT interval corrected for heart rate |
| QTcF | QT interval corrected for heart rate using Fridericia's formula |
| RR | electrocardiographic interval representing the time measurement between the R wave of one heartbeat and the R wave of the preceding heartbeat |
| SAP | statistical analysis plan |
| SD | stable disease |
| SMQ | Standardized MedDRA Queries |
| StD | standard deviation |
| SI (units) | international system of units |
| SOC | system organ class |
| TEAE | treatment-emergent adverse event |
| TFLs | tables, figures, and listings |
| CCI | |
| ULN | upper limit of normal |
| VR | ventricular rate |
| WHO | World Health Organization |

# 1.     INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the synoptic clinical study report (CSR) for Study GS-US-401-2076. This SAP is based on the study protocol amendment 4 dated 15 January 2019 and the electronic case report form (eCRF). The SAP will be finalized before database finalization. Any changes made after the finalization of the SAP will be documented in the CSR.

## 1.1.     Study Objectives

The primary objective of this study is:

- To determine the preliminary efficacy of the combination of tirabrutinib and entospletinib with obinutuzumab in subjects with relapsed or refractory chronic lymphocytic leukemia (CLL)

The secondary objective of this study is:

- To evaluate the safety and tolerability of the combination of tirabrutinib and entospletinib with and without obinutuzumab

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## 1.2.     Study Design

This is a Phase 2, prospective, open-label, multicenter trial to evaluate the safety and efficacy of the combination of tirabrutinib and entospletinib with and without obinutuzumab in subjects with relapsed or refractory CLL.

Eligible subjects will be randomized in a 1:1 manner to one of the following two arms, stratified by the presence of 17p deletion/TP53 mutation (del17p/TP53mut) in CLL cells:

- Arm A: tirabrutinib + entospletinib

- Arm B: tirabrutinib + entospletinib + obinutuzumab

With Amendment 3, randomization was discontinued. All subsequent subjects will be enrolled into Arm B.

**Duration of Treatment:**

Tirabrutinib 80 mg will be self-administered orally once daily and entospletinib 400 mg will be self-administered orally once daily. Dosing of both agents will begin on Week 1 Day 1 of the study and thereafter continue for up to 104 weeks in the absence of disease progression, unacceptable toxicity, or documentation of complete remission (CR) with bone marrow minimal residual disease (MRD) negativity (CR/BM MRD-). If CR/BM MRD- is documented on study, treatment will stop after the earlier of:

i)   an additional 3 months of therapy or

ii)  104 weeks of total treatment.

Obinutuzumab will be administered as 8 intravenous infusions of 1000 mg each over 21 weeks. A test dose of 100 mg will be administered on Week 1 Day 1. If this dose is tolerated, the remainder of the full dose may be subsequently administered on Day 1. Alternatively, the remaining 900 mg will be administered on Day 2. Subsequent infusions will be administered on Week 2 Day 1, Week 3 Day 1, Week 5 Day 1 and then every 4 weeks through Week 21.

This study will continue to monitor subjects for up to 30 days post end of treatment, or up to Week 25 should a subject discontinue treatment prior to Week 25 for reasons other than disease progression.

**Efficacy Assessment Schedule:**

Tumor response assessment per modified International Workshop on CLL (IWCLL) 2008 criteria will be performed at the Week 25 visit, with evaluation of areas affected by CLL during the screening evaluation. During the treatment phase, additional response assessment per IWCLL 2008 criteria may be performed as clinically indicated.

Clinical response based on physical exam, laboratory parameters and presence of B-symptoms will be performed every 4 weeks until Week 33 Day 1 (except for Week 25) and then every 12 weeks starting Week 33 until Week 105 following the modified IWCLL 2008 criteria, with the exception of lymphadenopathy, hepatomegaly, splenomegaly, and bone marrow.

Bone marrow MRD will be assessed at Week 25. Additional bone marrow MRD may be assessed as clinically indicated. Peripheral blood MRD will be assessed on Day 1 of Weeks 1, 13, 25, 33, 45, 105, and End of Treatment (EOT). EOT collection is not needed for subjects who complete the Week 105 visit.

The Schedule of Assessments is located in Appendix 1.

## 1.3.          Sample Size and Power

The primary goal of this study is to evaluate the efficacy of the combination of tirabrutinib and entospletinib with obinutuzumab in relapsed and refractory CLL. The primary endpoint for this study is the rate of CR (including CR and CR with incomplete recovery of the bone marrow (CRi)) at Week 25. The corresponding single-agent CR rate with BTK and SYK inhibitors in subjects with relapsed or refractory CLL is ≤5%. The 90% confidence interval (CI) corresponding to different CR rates ranging from 20% to 60% for a sample size of 30 is provided in Table 1-1. With a sample size of 30, the lower bound of the 90% CI of an observed CR rate of 20% or above will exclude 5%.

**Table 1-1.**          **90% Confidence Intervals at Different CR Rates**

| Sample Size | CR Rate | 90% Confidence Interval using Clopper-Pearson Method |
|---|---|---|
| 30 | 20% | (9.1%, 35.7%) |
| 30 | 30% | (16.6%, 46.5%) |
| 30 | 40% | (25.0%, 56.6%) |
| 30 | 50% | (33.9%, 66.1%) |
| 30 | 60% | (43.4%, 75.1%) |

With Amendment 3, randomization was discontinued. All subsequent subjects will be enrolled to Arm B. A total of approximately 6 subjects in Arm A and 30 subjects in Arm B will be enrolled, thus the total sample size for the study will be approximately 36 subjects.

# 2. TYPE OF PLANNED ANALYSIS

## 2.1. Interim Analysis

No formal interim analysis is planned.

## 2.2. Final Analysis

After all subjects have discontinued/completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized, the final analysis of the data will be performed.

## 2.3. Follow-up Analysis

No follow-up analysis is planned.

# 3.        GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of subjects in each category will be presented; for continuous variables, the number of subjects (n), mean, standard deviation (StD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

By-subject listings will be presented for all subjects in the All Enrolled Analysis Set and sorted by subject ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within the subject. The treatment group to which subjects were randomized/initially assigned will be used in the listings. Age, sex at birth, race, and ethnicity for each subject will be presented in the listings, as space permits.

## 3.1.        Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

For each analysis set, the number and percentage of subjects eligible for inclusion will be summarized by treatment group.

A listing of reasons for exclusion from analysis sets will be provided by subject.

This study was initially designed as a randomized study. With Amendment 3, randomization was discontinued, and all subsequent subjects will be enrolled into Arm B. There is no intention to compare the treatments, so intent-to-treat Analysis Set will not be used; instead, All Enrolled Analysis Set defined in Section 3.1.1 and Full Analysis Set defined in Section 3.1.2 will be used.

### 3.1.1.        All Enrolled Analysis Set

All Enrolled Analysis Set includes all subjects who received a study subject identification number in the study after screening.

### 3.1.2.        Full Analysis Set

The Full Analysis Set (FAS) includes all randomized or enrolled subjects who received at least 1 dose of any study drug with treatment group designated according to the planned treatment. This is the primary analysis set for efficacy analyses.

### 3.1.3.        Safety Analysis Set

The Safety Analysis Set includes all subjects who took at least 1 dose of study drug. This is the primary analysis set for safety analyses.

### 3.1.4. Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set will include all randomized or enrolled subjects who took at least 1 dose of study drug and have at least 1 nonmissing postdose concentration value reported by the PK laboratory. This is the primary analysis set for all PK analyses.

### 3.2. Subject Grouping

For analyses based on FAS, subjects will be grouped according to the treatment they are assigned to at randomization or enrollment. For analyses based on the Safety Analysis Set, subjects will be grouped according to the actual treatment received. The actual treatment received will differ from the treatment assigned at randomization or enrollment only when their actual treatment differs from assigned treatment for the entire treatment duration.

For the PK Analysis Set, subjects will be grouped according to the actual treatment they received.

### 3.3. Strata and Covariates

Subjects will be randomly assigned to treatment groups via the interactive web response system (IWRS) in a 1:1 ratio using a stratified randomization schedule. Stratification will be based on the presence of del17p/TP53mut in CLL cells. If there are discrepancies in stratification factor values between the IWRS and the clinical database, the values recorded in the clinical database will be used for analyses.

With Amendment 3, randomization was discontinued. All subsequent subjects were enrolled into Arm B. There is no intention to compare the treatments. No covariates will be included in efficacy analyses.

### 3.4. Examination of Subject Subgroups

Primary and secondary efficacy endpoints will be examined in the subgroups based on randomization stratification factor (either del17p or TP53mut versus neither del17p nor TP53mut) for each arm. CCI

### 3.5. Multiple Comparisons

Not applicable.

### 3.6. Missing Data and Outliers

### 3.6.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document.

For missing last dosing date of study drug, imputation rules are described in Section 4.2.1. The handling of missing or incomplete dates for CLL diagnosis is described in Section 5.3; for prior anti-cancer therapy in Section 5.4, for new anti-cancer therapy in Section 6.3.2, for death in Section 6.3.1, for AE onset in Section 7.1.5.2, and for prior and concomitant medications in Section 7.4.

### 3.6.2.        Outliers

Outliers will be identified during the data management and data analysis process, but no sensitivity analyses will be conducted. All data will be included in the data analysis.

### 3.7.          Data Handling Conventions and Transformations

The following conventions will be used for the imputation of date of birth when it is partially missing or not collected:

- If only month and year of birth is collected, then "15" will be imputed as the day of birth

- If only year of birth is collected, then "01 July" will be imputed as the day and month of birth

- If year of birth is missing, then date of birth will not be imputed. In general, age collected at Day 1 (the first dosing date of study drug) (in years) will be used for analyses and presented in listings. If age at Day 1 is not available for a subject, then age derived based on date of birth and the Day 1 visit date will be used instead. If an enrolled subject was not dosed with any study drug, the randomization or enrollment date will be used instead of the Day 1 visit date. For screen failures, the date the first informed consent was signed will be used for the age derivation. Age required for longitudinal and temporal calculations and analyses (eg, estimates of creatinine clearance, age at date of AE) will be based on age derived from date of birth and the date of the measurement or event, unless otherwise specified.

Non-PK data that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows:

- A value that is 1 unit less than the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.

- A value that is 1 unit above the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the LOQ). Values with decimal points will follow the same logic as above.

- The LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the LOQ).

If methods based on the assumption that the data are normally distributed are not adequate, analyses may be performed on transformed data or nonparametric analysis methods may be used, as appropriate.

Sparse PK concentration values that are BLQ will be presented as "BLQ" in the concentration data listing. Values that are BLQ will be treated as 0 at predose time points, and one-half the value of the LOQ at postdose time points for summary purposes. The following conventions will be used for the presentation of summary of PK concentrations:

- If at least 1 subject has a concentration value of BLQ for the time point, the minimum value will be displayed as "BLQ."

- If more than 25% of the subjects have a concentration data value of BLQ for a given time point, the minimum and Q1 values will be displayed as "BLQ."

- If more than 50% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, and median values will be displayed as "BLQ."

- If more than 75% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, median, and Q3 values will be displayed as "BLQ."

- If all subjects have concentration data values of BLQ for a given time point, all order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as "BLQ."

### 3.8.        Analysis Visit Windows

### 3.8.1.        Definition of Study Day

Study day will be calculated from the first dosing date of study drug and derived as follows:

- For postdose study days: Assessment Date    First Dosing Date + 1

- For days prior to the first dose: Assessment Date    First Dosing

Therefore, study day 1 is the day of first dose of study drug administration.

### 3.8.2.        Analysis Visit Windows

The nominal visit as recorded on the CRF will be used when data are summarized by visit. Any data relating to unscheduled visits will not be assigned to a particular visit or time point. However, the following exceptions will be made:

- An unscheduled visit prior to the first dosing of study drug may be included in the calculation of the baseline value, if applicable.

- Unscheduled visits after the first dosing of study drug will be included in determining the maximum postbaseline toxicity grade.

3.8.2.1.        Analysis Visit Windows for Primary/Secondary Efficacy Endpoints

The analysis windows for Week 25 response assessment and Week 25 MRD assessment are defined as 24×7±28 days (inclusive) starting from first dose.

### 3.8.3.        Selection of Data in the Event of Multiple Records in an Analysis Visit Window

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis would not require 1 value per analysis window.

If multiple valid, nonmissing measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- For baseline, the last nonmissing value on or prior to the first dosing date of study drug will be selected, unless specified differently. If there are multiple records with the same time or no time recorded on the same day, the baseline value will be the average of the measurements for continuous data, or the measurement with the lowest severity (eg, normal will be selected over abnormal for safety electrocardiogram [ECG] findings) for categorical data.

- For postbaseline values:

    The record closest to the nominal day for that visit will be selected.

    If there are 2 records that are equidistant from the nominal day, the later record will be selected.

    If there is more than 1 record on the selected day, the average will be taken for continuous data and the worse severity will be taken for categorical data, unless otherwise specified.

# 4.         SUBJECT DISPOSITION

## 4.1.         Subject Enrollment and Disposition

A summary of subject enrollment will be provided by treatment group for each investigator and overall. The summary will present the number and percentage of subjects enrolled. For each column, the denominator for the percentage calculation will be the total number of subjects analyzed for that column.

A listing of subjects with discrepancies in the value used for stratification assignment between the IWRS and the clinical database at the time of data finalization will be provided.

A summary of subject disposition will be provided by treatment group. This summary will present the number of subjects screened, the number of subjects randomized or enrolled, the number of subjects who were randomized or enrolled but not dosed, and the number of subjects in each of the categories listed below by treatment group:

- Safety Analysis Set

- Tirabrutinib completion status

    Completed study drug dosing as specified per protocol

    Discontinued study drug dosing with reasons

- Entospletinib completion status

    Completed study drug dosing as specified per protocol

    Discontinued study drug dosing with reasons

- Obinutuzumab completion status

    Completed study drug dosing as specified per protocol

    Discontinued study drug dosing with reasons

- Study completion status

    Completed the protocol-planned duration of the study

    Discontinued the study with reasons

For the status of study drug and study completion and reasons for discontinuation, the number and percentage of subjects in each category will be provided. The denominator for the percentage calculation will be the total number of subjects in the All Enrolled Analysis Set corresponding to that column. In addition, a flowchart will be provided to depict the disposition.

The following by-subject listings will be provided by subject identification (ID) number in ascending order to support the above summary tables:

- Reasons for study drug or study discontinuation

- Reasons for screen failure (will be provided by screening ID number in ascending order)

## 4.2.        Extent of Study Drug Exposure and Adherence

Extent of exposure to study drug will be examined by assessing the total duration of exposure to study drug and the level of adherence to the study drug specified in the protocol.

### 4.2.1.        Duration of Exposure to Study Drug

Total duration of exposure to study drug will be defined as last dosing date minus first dosing date plus 1, regardless of any temporary interruptions in study drug administration, and will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks). If the last study drug dosing date is missing, the latest date among the study drug end date, clinical visit date, laboratory sample collection date, and vital signs assessment date will be used.

The total duration of exposure to study drug will be summarized using descriptive statistics. For tirabrutinib and entospletinib, the number (ie, cumulative counts) and percentage of subjects exposed will be summarized by the following time periods: ≥1 day, ≥1 week, ≥2 weeks, ≥3 weeks, ≥4 weeks, ≥6 weeks, ≥8 weeks, every 4 weeks starting from 8 weeks to 32 weeks, and then every 12 weeks starting from 32 weeks until 104 weeks (if appropriate). For obinutuzumab, the number of infusions will be summarized using descriptive statistics. Summaries will be provided by treatment group for the Safety Analysis Set.

The number and percentage of subjects who have dose reduction or interruptions, and the reasons, will be summarized by treatment.

No formal statistical testing is planned.

### 4.2.2.        Adherence to Study Drug

The total amount of study drug administered (mg) will be summarized using descriptive statistics.

For tirabrutinib and entospletinib, the presumed total number of doses administered to a subject will be determined by the data collected on the drug accountability CRF using the following formula:

Total Amount of Study Drug Administered (mg) =

$$\left(\sum \text{No. of Doses Dispensed} \times \text{strength}\right) - \left(\sum \text{No. of Doses Returned} \times \text{strength}\right)$$

The level of on-treatment adherence to the study drug regimen will be determined by the total amount of study drug administered relative to the total amount of study drug expected to be administered during a subject's actual on-treatment period based on the study drug regimen. Investigator-prescribed interruption, reductions and escalations as specified in the protocol will be taken into account. If there are treatment periods that bottles are not returned or the return information is missing, these periods will be excluded from the on-treatment adherence calculation for both total amount of study drug administered and study drug expected to be administered. If subjects never returned any bottle, the adherence will be set as missing.

The level of on-treatment adherence will be expressed as a percentage using the following formula:

$$\text{On-Treatment Adherence (\%)} = \left(\frac{\text{Total Amount of Study Drug Administered}}{\text{Study Drug Expected to be Administered on Treatment}}\right) \times 100$$

Descriptive statistics for the level of on-treatment adherence with the number and percentage of subjects belonging to adherence categories (eg, < 75% and ≥ 75%) will be provided by treatment group for the Safety Analysis Set.

A by-subject listing of study drug administration and drug accountability will be provided separately by subject ID number (in ascending order) and visit (in chronological order).

## 4.3.        Protocol Deviations

Subjects who did not meet the eligibility criteria for study entry but enrolled in the study will be summarized regardless of whether they were exempted by the sponsor or not. The summary will present the number and percentage of subjects who did not meet at least 1 eligibility criterion and the number of subjects who did not meet specific criteria by treatment group based on the All Enrolled Analysis Set. A by-subject listing will be provided for those subjects who did not meet at least 1 eligibility (inclusion or exclusion) criterion. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that subjects did not meet and related comments, if collected.

Protocol deviations occurring after subjects entered the study are documented during routine monitoring. The number and percentage of subjects with important protocol deviations by deviation reason (eg, nonadherence to study drug, violation of select inclusion/exclusion criteria)

will be summarized by treatment group for the All Enrolled Analysis Set. A by-subject listing will be provided for those subjects with important protocol deviation.

## 4.4.        Assessment of COVID-19 Impact

This study was ongoing during the novel coronavirus (2019 nCOV [COVID-19]) pandemic, and the COVID-19 pandemic has caused a disruption in the regular visit schedules for this study. Some subjects were unable to attend onsite visits due to shelter in place guidelines, site closures, or other reasons. This section provides how to handle special situations due to COVID-19 in the analysis.

Adverse events (AEs) due to COVID-19 will be included in AE analyses if applicable. A by-subject listing of Adverse Events due to COVID-19 may be provided. The COVID-19 Standardized MedDRA Queries (SMQ) with Broad Scope in Appendix 2 will be implemented.

### 4.4.1.        Study Drug or Study Discontinuation Due to COVID-19

A by-subject listing of reasons for premature study drug or study discontinuation due to COVID-19 will be created.

### 4.4.2.        Protocol Deviations Due to COVID-19

A by-subject listing will be provided for subjects with important protocol deviation related to COVID-19. A separate listing will be provided for subjects with non-important protocol deviation related to COVID-19.

### 4.4.3.        Missed and Virtual Visits Due to COVID-19

A by-subject listing of subjects with missed or virtual visits due to COVID-19 will be provided by subject ID number in ascending order .

Information regarding virtual or missed visits due to COVID-19 was collected as free text in the CRF comment fields. The determination of missing or virtual visits due to COVID-19 was done using Natural Language Processing (NLP) to search the CRF comment fields.  A detailed explanation of the algorithm is given in Appendix 3.

# 5.        BASELINE CHARACTERISTICS

## 5.1.        Demographics

Subject demographic variables (ie, age, sex, race, and ethnicity) will be summarized by treatment group and overall using descriptive statistics for age, and using number and percentage of subjects for sex, race, and ethnicity. The summary of demographic data will be provided for FAS.

A by-subject demographic listing, including the informed consent date, will be provided by subject ID number in ascending order.

## 5.2.        Other Baseline Characteristics

Other baseline characteristics include body weight (in kg), height (in cm), body mass index (BMI; in kg/m$^2$), Eastern Cooperative Oncology Group (ECOG) Performance Status, CIRS (Cumulative Illness Rating Scale), fluorescence in situ hybridization (FISH) results, TP53 mutation status, and IGHV mutation status. These baseline characteristics will be summarized by treatment group and overall using descriptive statistics for continuous variables and using number and percentage of subjects for categorical variables. The summary of baseline characteristics will be provided for FAS. No formal statistical testing is planned.

A by-subject listing of other baseline characteristics will be provided by subject ID number in ascending order.

## 5.3.        Medical History

Medical history will be collected at screening for disease-specific and general conditions (ie, conditions not specific to the disease being studied).

Disease-specific medical history will be summarized by treatment group and overall by the number and percentage of subjects with each prepopulated condition. The summary will be provided for FAS. Time since CLL diagnosis (years) will be calculated by (date of first dose of study drug    date of CLL diagnosis) / 365.25. Time since CLL diagnosis will be summarized using summary statistics for a continuous variable. Disease stage at diagnosis and at screening and cytogenetic risk group will be summarized using summary statistics for a categorical variable. No formal statistical testing is planned. A by-subject listing of disease-specific medical history will be provided by subject ID number in ascending order.

In deriving the time since CLL diagnosis, all partial dates of diagnosis and last regimen will be identified, and the partial dates will be imputed as follows:

- If day and month are missing but year is available, then the imputed day and month will be 01 Jan.

- If day is missing but the month and year are available, then the imputed day will be the first day of the month.

- Partial date will not be imputed if the year is missing.

General medical history data will not be coded, but will be listed only. A by-subject listing of general medical history will be provided by subject ID number in ascending order.

## 5.4.         Prior Anti-cancer Therapy

Number of prior regimens, time since the completion of last regimen, and time since progression in the last regimen will be summarized by treatment group using descriptive statistics based on FAS. A partial completion date will be imputed using the algorithm defined in Section 5.3.

The regimens and prior therapies that the subjects received will be summarized. The last regimen subjects received prior to study entry and the best response and PD to the last regimen will be summarized.

Number of subjects who received prior radiation therapy and surgery will be listed.

# 6.        EFFICACY ANALYSES

Efficacy analysis will be performed on FAS. The result summary will be provided by treatment group if not otherwise specified.

## 6.1.        Primary Efficacy Endpoint

### 6.1.1.        Definition of the Primary Efficacy Endpoint

The primary efficacy endpoint of this study is the rate of CR per modified IWCLL 2008 criteria {Hallek 2008} at Week 25, which is defined as the proportion of subjects who achieved CR/CRi at Week 25. Subjects who received anti-cancer therapy other than the study drug prior to achieving CR/CRi at Week 25, will be considered as nonresponders for CR/CRi and will be included in the denominator when calculating the CR rate at Week 25.

The analysis window of Week 25 response assessment is defined as 24×7±28 days (inclusive) starting from first dose. If there are multiple assessments within the analysis window, records will be chosen based on rules specified in Section 3.8.3.

### 6.1.2.        Analysis of the Primary Efficacy Endpoint

The CR rate at Week 25 and the corresponding 2-sided 90% exact CIs based on Clopper-Pearson method will be presented.

## 6.2.        Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Rate of CR with MRD negativity ($<10^4$) in bone marrow (CR/BM MRD-) at Week 25, defined as the proportion of subjects who achieved CR/CRi and also achieved BM MRD negativity at Week 25

- Rate of CR with MRD negativity ($<10^4$) in peripheral blood (CR/PB MRD-) at Week 25, defined as the proportion of subjects who achieved CR/CRi and also achieved PB MRD negativity at Week 25

- Overall response rate (ORR) at week 25, defined as the proportion of subjects who achieved CR, CRi, partial response (PR), or PR with lymphocytosis at Week 25

The response assessment definition of each response category is based on Modified IWCLL 2008 criteria and PR includes nodular partial response (nPR).

The MRD response is assessed with four-color-flow cytometry (FACS) and MRD negativity is defined as one CLL cell per 10,000 leukocytes [0.01 %], ie, $<10^4$.

The analysis window of Week 25 response assessment is defined as 24×7±28 days(inclusive) starting from first dose. If there are multiple assessments within the analysis window, records will be chosen based on rules specified in Section 3.8.3.

### 6.2.1. Rates of CR/BM MRD- and CR/PB MRD- at Week 25

Subjects who received anti-cancer therapy other than the study drug prior to achieving CR with MRD negativity at Week 25 will be considered as nonresponders and will be included in the denominators of the response rates.

The rates of CR/BM MRD- and CR/PB MRD- and the corresponding 2-sided 90% exact CIs based on Clopper-Pearson method will be presented.

### 6.2.2. ORR at Week 25

When calculating ORR at Week 25, subjects who received anti-cancer therapy other than the study drug prior to achieving responses at Week 25, will be considered as nonresponders and will be included in the denominator.

ORR at Week 25 and the corresponding 2-sided 90% exact CIs based on Clopper-Pearson method will be presented.

A by-subject listing of overall response based on modified IWCLL 2008 criteria will be provided.

A by-subject listing of BM and PB MRD results will be provided.

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## 6.4. Change From Protocol-Specified Efficacy Analyses

As understanding of clinical response and response per modified IWCLL 2008 criteria beyond week 25 are desired, the following endpoints not defined by protocol will also be analyzed:

- ORR, defined as the proportion of subjects achieving best overall response of CR, CRi, PR, or PR with lymphocytosis per Modified IWCLL 2008 criteria while on study

- Time to clinical response, defined as the interval from first dose of study drug to the date of the first clinical response which includes clinical complete response (CCR) and clinical partial response (CPR)

Clinical response assessment is a qualitative treatment response assessment based on physical exam, laboratory parameters and presence of B-symptoms performed every 4 weeks until Week 33 Day 1 and then at all scheduled visits thereafter following the modified IWCLL 2008 criteria, with the exception of lymphadenopathy, hepatomegaly, splenomegaly, and bone marrow. Clinical response categories are CCR, CPR, stable disease, and suspected progressive disease.

The date of disease progression will be the time point at which progression is first identified by relevant radiographic imaging data or clinical data.

### 6.4.1. ORR

The analysis will be performed with data collected throughout the study. Subjects, who never achieved these responses or received anti-cancer therapy other than the study drug prior to achieving responses, will be considered as nonresponders and will be included in the denominator when calculating ORR.

ORR and the corresponding 2-sided 90% exact CIs based on Clopper-Pearson method will be presented. A by-subject listing of overall response will be provided.

CCI

CCI

# 7.      SAFETY ANALYSES

## 7.1.            Adverse Events and Deaths

### 7.1.1.            Adverse Event Dictionary

Clinical and laboratory AEs will be coded using the current version of MedDRA. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be provided in the AE dataset.

### 7.1.2.            Adverse Event Severity

Adverse events are graded by the investigator as Grade 1, 2, 3, 4, or 5 according to CTCAE Version 4.03. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings. The missing category will be listed last in summary presentation.

### 7.1.3.            Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected "Related" on the AE CRF to the question of "Related to Study Treatment GS-4059", "Related to Study Treatment Entospletinib", or "Related to Study Treatment Obinutuzumab". Relatedness will always default to the investigator's choice, not that of the medical monitor. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing.

### 7.1.4.            Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definitions of SAEs that were specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Pharmacovigilance and Epidemiology Department before data finalization.

### 7.1.5.            Treatment-Emergent Adverse Events

7.1.5.1.            Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as 1 or both of the following:

- Any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug

- Any AEs leading to discontinuation of study drug

7.1.5.2.        Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent. The event is considered treatment emergent if both of the following 2 criteria are met:

- The AE onset is the same as or after the month and year (or year) of the first dosing date of study drug, and

- The AE onset date is the same as or before the month and year (or year) of the date corresponding to 30 days after the date of the last dose of study drug

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dosing date of study drug, will be considered to be treatment emergent. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of study drug will be considered treatment emergent.

In case when the AE onset date is incomplete and needs to be imputed, the following algorithm will be followed:

- If the day is missing but the month and year are available, then the imputed day will be the first day of the month or the first dosing date if they have the same month and year, whichever is later.

- If the day and month are missing but year is available, then the imputed day and month will be 01Jan or the first dosing date if they have the same year, whichever is later.

**7.1.6.        Summaries of Adverse Events and Deaths**

Treatment-emergent AEs will be summarized based on the Safety Analysis Set.

7.1.6.1.        Summaries of AE Incidence by Severity

The number and percentage of subjects who experienced at least 1 TEAE will be provided and summarized by SOC, HLT, PT, and treatment group. For the AE categories described below, summaries will be provided by SOC, PT, maximum severity, and treatment group:

- TEAEs

- TEAEs with Grade 3 or higher

- TEAEs related to tirabrutinib

- TEAEs related to entospletinib

- TEAEs related to obinutuzumab

- TEAEs related to tirabrutinib with Grade 3 or higher

- TEAEs related to entospletinib with Grade 3 or higher

- TEAEs related to obinutuzumab with Grade 3 or higher

- TE SAEs

- TE SAEs related to tirabrutinib

- TE SAEs related to entospletinib

- TE SAEs related to obinutuzumab

- TEAEs leading to discontinuation of tirabrutinib

- TEAEs leading to discontinuation of entospletinib

- TEAEs leading to discontinuation of obinutuzumab

- TEAEs leading to dose modification of tirabrutinib

- TEAEs leading to dose modification of entospletinib

- TEAEs leading to dose modification of obinutuzumab

- TEAEs leading to temporary interruption of tirabrutinib

- TEAEs leading to temporary interruption of entospletinib

- TEAEs leading to temporary interruption of obinutuzumab

- TEAEs leading to discontinuation of study

- TEAEs leading to death (note that the severity will not be shown as all the TEAEs are Grade 5)

A brief, high-level summary of AEs described above will be provided by treatment group and by the number and percentage of subjects who experienced the above AEs. This summary table will also include TEAEs with Grade 3 or 4 and all deaths.

Multiple events will be counted only once per subject in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC and then by PT in descending order of total frequency within each SOC. For summaries by severity, the most severe severity will be used for those AEs that occurred more than once in a given subject during the study.

In addition to the above summary tables, TEAEs, TEAEs of Grade 3 or higher, TE treatment-related AEs, and TE SAEs will be summarized by PT only in descending order of total frequency.

In addition, data listings will be provided for the following:

- All AEs, indicating whether the event is treatment emergent

- All AEs with Grade 3 or higher

- All SAEs

- All Deaths

- AEs leading to death

- AEs leading to discontinuation of study drug

- AEs leading to discontinuation of study

### 7.1.6.1.1.    Summary of Deaths

A summary (number and percentage of subjects) of deaths will be provided by treatment group. The summary will include the following categories:

- All deaths

- Deaths within 30 days of the last dosing of study drug

- Deaths beyond 30 days of the last dosing of study drug

The attribution of death will also be summarized.

## 7.1.7.        Adverse Events of Interest

The treatment-emergent AEs of interest (AEI) include:

| AEI | Grouped Terms |
|---|---|
| Hemorrhage/Bleeding | MST-CT Bleeding/Haemorrhage (Appendix 4) |
| Infections | SOC: Infections and infestations |
| Hypersensitivity | MST-CT Hypersensitivity (Appendix 5) |
| Cytopenia | MST: Anemia-related events, leukopenias, neutropenia, thrombocytopenias (Appendix 6) |
| Cardiac Arrhythmias | MST-CT Cardiac arrhythmia and bradycardia  narrow (Appendix 7) |
| Diarrhoea | PT: Diarrhoea |
| Rash | MST-CT Rash - specific to ONC (Appendix 8) |

The following summaries will be provided for AEIs by SOC, PT, and maximum severity:

A) TEAE

B) TEAEs leading to dose modifications or temporary interruption of study drug

C) TEAEs leading to discontinuation of study drug

A data listing of AEIs will be provided by alphabetic ascending order of AEI name, then by subject ID.

## 7.2.       Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data in Appendix 9 will be provided for the Safety Analysis Set and will include data collected up to the last dose of study drug plus 30 days for subjects who have permanently discontinued study drug. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7. Hemolized test results will not be included in the analysis, but they will be listed in by-subject laboratory listings.

A by-subject listing for laboratory test results will be provided by subject ID number and visit in chronological order for hematology, serum chemistry, and coagulation, separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on CTCAE severity grade will be flagged in the data listings, as appropriate.

No formal statistical testing is planned.

### 7.2.1.       Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment group for each laboratory test specified in the study protocol as follows:

- Baseline values

- Postbaseline maximum value

- Postbaseline minimum value

- Change and percentage change from baseline to postbaseline maximum value

- Change and percentage change from baseline to postbaseline minimum value

A baseline laboratory value will be defined as the last measurement obtained on or prior to the date/time of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the visit value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; StD values will be displayed to the reported number of digits plus 1.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3.

## 7.2.2.        Graded Laboratory Values

CTCAE Version 4.03 will be used to assign toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

### 7.2.2.1.        Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to and including the date of last dose of study drug plus 30 days for subjects who permanently discontinued study drug. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

### 7.2.2.2.        Summaries of Laboratory Abnormalities

The following summaries (number and percentage of subjects) for treatment-emergent laboratory abnormalities will be provided by lab test and treatment group; subjects will be categorized according to the most severe postbaseline abnormality grade for a given lab test:

- Graded TE laboratory abnormalities

- TE Grade 3 or 4 laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of subjects with nonmissing postbaseline values up to 30 days after last dosing date.

A by-subject listing of treatment-emergent laboratory abnormalities will be provided by subject ID number and visit in chronological order. This listing will include all test results that were collected throughout the study for the lab test of interest, with all applicable severity grades and abnormal flags displayed.

## 7.2.3.        Liver-related Laboratory Evaluations

Liver-related abnormalities after initial study drug dosing will be examined and summarized using the number and percentage of subjects who were reported to have the following laboratory test values for postbaseline measurements:

- Aspartate aminotransferase (AST): (a) > 3 times of the upper limit of reference range (ULN); (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN

- Alanine aminotransferase (ALT): (a) > 3 x ULN; (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN

- AST or ALT: (a) > 3 x ULN; (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN

- Total bilirubin: > 2 x ULN

- Alkaline phosphatase (ALP) > 1.5 x ULN

- AST or ALT > 3 x ULN and total bilirubin: (a) > 1.5 x ULN; (b) > 2 x ULN

The summary will include data from all postbaseline visits up to 30 days after the last dose of study drug. For individual laboratory tests, subjects will be counted once based on the most severe postbaseline values. For both the composite endpoint of AST or ALT and total bilirubin, subjects will be counted once when the criteria are met at the same postbaseline visit date. The denominator is the number of subjects in the Safety Analysis Set who have nonmissing postbaseline values of all relevant tests at the same postbaseline visit date. A listing of subjects who met at least 1 of the above criteria will be provided.

### 7.2.4.        Shifts Relative to the Baseline Value

Shift tables will be presented by showing change in severity grade from baseline to the worst postbaseline grade up to 30 days after last dosing date. The percentage will be based on subjects with values available at both baseline and postbaseline.

### 7.3.        Body Weight and Vital Signs

Body weight and vital signs are collected at screening and may be collected at unscheduled visits. Thus, only a by-subject listing of vital signs will be provided by subject ID number and time visit in chronological order.

### 7.4.        Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary.

### 7.4.1.        Prior Medications

Prior medications are defined as any medications taken before a subject took the first study drug.

Prior medications will be summarized by Anatomical Therapeutic Chemical (ATC) drug class Level 2 and preferred name using the number and percentage of subjects for each treatment group and overall. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered alphabetically by ATC medical class and then by preferred term in order of descending overall frequency within each ATC medical class. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medication with a start date prior to the first dosing date of study drug will be included in the prior medication summary regardless of when the stop date is. If a partial start date is entered the medication will be considered prior unless the month and year (if day is missing) or year (if day and month are missing) of the start date are after the first

dosing date. Medications with a completely missing start date will be included in the prior medication summary, unless otherwise specified.

Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

### 7.4.2.        Concomitant Medications

Concomitant medications are defined as medications taken while a subject took study drug. Use of concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) drug class Level 2 and preferred name using the number and percentage of subjects for each treatment group. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered alphabetically by ATC medical class and then by preferred term in descending overall frequency within each ATC medical class. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medications with a start date prior to or on the first dosing date of study drug and continued to be taken after the first dosing date, or started after the first dosing date but prior to or on the last dosing date of study drug will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date or the last dosing date of study drug will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of study drug or a start date after the last dosing date of study drug will be excluded from the concomitant medication summary. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified.

Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

All prior and concomitant medications (other than per-protocol study drugs) will be provided in a by-subject listing sorted by subject ID number and administration date in chronological order.

### 7.5.        Electrocardiogram Results

Electrocardiogram (ECG) analysis results are intended to identify meaningful changes in the QT interval. If potential abnormalities of interest are identified, further analyses may be conducted. Summaries of investigator assessment of ECG readings and ECG data will be provided for the Safety Analysis Set. No formal statistical testing is planned.

### 7.5.1.        Investigator Electrocardiogram Assessment

A shift table of the investigators' assessment of ECG results at worst outcome during study compared with baseline values will be presented by treatment group using the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant; or

missing. The number and percentage of subjects in each cross-classification group of the shift table will be presented. Subjects with a missing value at baseline or postbaseline will not be included in the denominator for percentage calculation. No formal statistical testing is planned.

A by-subject listing for ECG assessment results will be provided by subject ID number and visit in chronological order.

### 7.5.2.        Corrected QT Intervals

The QT interval (measured in millisecond [msec]) is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarization and repolarization of the ventricles. The QT interval is affected by heart rate, and a number of methods have been proposed to correct QT for heart rate.

Corrected QT (QTc) intervals will be derived using Fridericia's correction (QTcF) as follows:

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

where QT is measured in msec; RR = 60/Heart Rate (beats per min [bpm]) and RR is measured in seconds

The maximum postdose QTcF interval values obtained during the study will be summarized within the following categories:

- \> 450 msec

- \> 480 msec

- \> 500 msec

The maximum postdose change in QTcF interval values obtained during the study will also be summarized within the following categories:

- \> 30 msec

- \> 60 msec

### 7.5.3.        PR and QRS Intervals

The PR interval (measured in msec) is a measure of the time between the start of the P wave (the onset of atrial depolarization) and the beginning of the QRS complex (the onset of ventricular depolarization). The QRS interval measures the duration of the QRS complex. The maximum ventricular rate (VR) and PR and QRS intervals observed during the study will be categorized. The number and percentage of subjects having values in the following ranges will be presented by treatment group:

- VR > 100 bpm

- PR interval > 200 msec

- QRS interval > 110 msec

## 7.6.          Other Safety Measures

No additional safety measures are specified in the protocol.

## 7.7.          Changes From Protocol-Specified Safety Analyses

There are no deviations from the protocol-specified safety analyses.

# 8.        PHARMACOKINETIC (PK) ANALYSES

## 8.1.        PK Sample Collection

A PK sample will be collected on Week 1 Day 1 at 2 (±1) hours (inclusive) post-dose of tirabrutinib and entospletinib. At the visits on Week 5, 13, and 21, a PK sample will be collected at pre-dose (within 2 hours prior to dosing) and 1 sample will be collected at 2 (±1) hours (inclusive) post-dose of tirabrutinib and entospletinib.

## 8.2.        PK Analyses

Individual subject concentration data for tirabrutinib and entospletinib will be listed and summarized using descriptive statistics by treatment. Summary statistics (n, mean, StD, coefficient of variation [%CV], median, min, max, Q1, and Q3) will be presented for individual subject concentration data by time point by treatment. Moreover, the geometric mean and 95% CI of the natural log-transformed values will be presented.

Individual concentration data listings and summaries will include all subjects with concentration data. The sample size for each time point will be based on the number of subjects with nonmissing concentration data at that time point. The number of subjects with concentration BLQ will be presented for each time point. For summary statistics, BLQ values will be treated as 0 at predose and one-half of the lower limit of quantitation (LLOQ) for postdose time points.

The following table will be provided for each analyte by treatment:

- Individual subject concentration data and summary statistics

PK sampling details by subject, including procedures, differences in scheduled and actual draw times, and sample age will be provided in listings.

# 9.        REFERENCES

Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Dohner H, et al. Guidelines
        for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the
        International Workshop on Chronic Lymphocytic Leukemia (IWCLL) updating the
        National Cancer Institute-Working Group (NCI-WG) 1996 guidelines. Blood 2008;111
        (12):5446-56.

# 10.      SOFTWARE

SAS® Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

## 11.        SAP REVISION

| Revision Date (DD MMM YYYY) | Section | Summary of Revision | Reason for Revision |
|---|---|---|---|
| 13 Jan 2021 | 4.4 | Added the section to provide how to handle special situations due to COVID-19 in the analysis | To assess the COVID-19 impact |
| 13 Jan 2021 | 5.3 | Revised the calculation of time since CLL diagnosis | To be consistent with the calculations of similar times |

# 12.        APPENDICES

## Appendix 1. Schedule of Assessments

| | Screening | 24 Weeks | | | | | | | | | Week 25 Day 1[s] | Week 29 Day 1 | Every 12 weeks starting Week 33 until Week 105 | EOT[q] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day -28 | Week 1 Day 1 | Week 2 Day 1 | Week 3 Day 1 | Week 4 Day 1[p] | Week 5 Day 1 | Week 9 Day 1 | Week 13 Day 1 | Week 17 Day 1 | Week 21 Day 1 | | | | |
| Visit Window (days) | | 0 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±7 | ±7 | ±7 | ±7 |
| Informed Consent | X | | | | | | | | | | | | | |
| Medical and Medication History[a] | X | | | | | | | | | | | | | |
| Physical Examination[b] | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Vital Signs | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| ECOG Performance Status / B-symptoms | X | X | | | | X | X | X | X | X | X | X | X | X |
| Binet/Rai Staging | X | | | | | | | | | | | | | |
| G8 Geriatric Screening Tool[c] | | X | | | | | | | | | X | | X | X |
| 12-lead ECG[d] | X | X | | | | X | X | X | X | X | X | | | X |
| Adverse events/ Concomitant medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Tirabrutinib + entospletinib Dispensing[e] | | X | | | | X | X | X | X | X | X | X | X | |
| Tirabrutinib + entospletinib Accountability | | | | | | X | X | X | X | X | X | X | X | X |
| Obinutuzumab Administration[f] | | X | X | X | | X | X | X | X | X | | | | |

| | Screening | 24 Weeks | | | | | | | | | | Week 25 Day 1[s] | Week 29 Day 1 | Every 12 weeks starting Week 33 until Week 105 | EOT[q] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day -28 | Week 1 Day 1 | Week 2 Day 1 | Week 3 Day 1 | Week 4 Day 1[p] | Week 5 Day 1 | Week 9 Day 1 | Week 13 Day 1 | Week 17 Day 1 | Week 21 Day 1 | | | | |
| Hematology | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Chemistry[r] | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Coagulation (PT/INR, aPTT) | X | | | | | | | | | | | | | X |
| Peripheral Blood MRD[g] | | X | | | | | | X | | | X | | X | X |
| Urinalysis and Urine Chemistry | X | | | | | | | | | | | | | |
| Pregnancy Testing[h] | X | X | | | | X | X | X | X | X | X | X | X | X |
| Viral Serologies[i] | X | | | | | | | | | | | | | |
| PK sampling[j] | | X | | | | X | | X | | X | | | | |
| CCI | | | | | | | | | | | | | | |
| CLL phenotyping[l] | X | | | | | | | | | | | | | X |
| Radiographic Tumor evaluation[m] | X | | | | | | | | | | X | | | |
| Bone marrow evaluation[n] | X | | | | | | | | | | X | | | |
| Response Assessment[o] | | | | | | X | X | X | X | X | X | X | X | X |

a    Medical history includes significant past medical events (eg, prior hospitalizations or surgeries), a review of the disease under study, prior anti cancer therapies, and any concurrent medical illnesses. History of smoking in the past 30 days and CIRS score should be determined at screening.

b    Screening and End of Treatment will be complete physical examinations. Beginning at Week 1 Day 1, a modified physical examination will be a performed to monitor for any changes (eg, lymph nodes, size of the liver and spleen, lung, cardiac, abdomen, skin, neurologic, and any system clinically indicated). Weight should be measured at each PE. Height should be measured at screening only.

c    The G8 screening questionnaire will be used for assessment of subjects aged > 70 years at Week 1 Day 1 and every 6 months until EOT.

d    Subjects should be resting quietly in supine position for 5 minutes prior to ECG collection. The Investigator or qualified designee will review all ECGs.

e    Study drug is not dispensed at the Week 105 visit.

f    Obinutuzumab: 100 mg will be administered intravenously on Day 1 and 900 mg on either Day 1 or 2 (Week 1); then 1000 mg on Day 8 (Week 2), Day 15 (Week 3), and on Weeks 5, 9, 13, 17 and 21 for a total of 8 doses of 1000 mg over 21 weeks. If the 100 mg infusion on Day 1 is well tolerated, the remaining 900 mg (scheduled for Day 2) may be given on Day 1.

g    Peripheral blood MRD will be assessed on Day 1 of Weeks 1, 13, 25, 33, 45, 105, and EOT. EOT collection is not needed for subjects who complete the Week 105 visit.

h    Serum pregnancy test will be performed at screening for all women of childbearing potential. Urine pregnancy tests will be conducted prior to Week 1 Day 1 and then every 4 weeks until the EOT visit. Pregnancy kits may be provided for home testing. The results must be confirmed as negative prior to continued administration of study drug.

i    Hepatitis serology includes HBsAg, HBcAb, HCV Ab; patients with positive HBcAb and negative HBsAg should have HBV DNA PCR performed prior to treatment start to rule out occult infection, then monthly through 6 months and then at subsequent clinic visits for at least 1 year following the EOT visit. HIV testing and CMV IgG and IgM testing should be performed at screening.

j    A PK sample will be collected approximately 2 hours (± 1 hour) post dose on Week 1, Day 1. On Day 1 of Weeks 5, 13, and 21 a PK sample will be drawn at pre dose (within 2 hours prior to AM dosing) and at 2 hours (± 1 hour) post dose.

    ██████████████████████████████████████████

l    CLL immunophenotyping, karyotyping and FISH, TP53 and IgHV mutation status, CD38 and ZAP70 expression will be evaluated from peripheral blood at screening. In the event of disease progression, only FISH and TP53 will be evaluated.

m    Tumor evaluation by CT scan (preferred) or MRI of neck, chest abdomen and pelvis will be performed at screening (unless scan was already completed up to 42 days prior to first dose). At the Week 25 visit, the same type of evaluation should be performed on those body regions which showed involvement by CLL at screening. An additional CT may be obtained on protocol per investigator discretion following evidence of an improvement in clinical response if the response assessment at the Week 25 visit is less than a complete response or in the event of suspected disease progression.

n    A bone marrow evaluation is required in the screening window for subjects without radiographic evidence of disease. Bone marrow aspirate and biopsy should be performed at Week 25 for subjects fulfilling clinical response criteria for complete remission (CR) or complete remission with incomplete bone marrow recovery (CRi) per the modified IWCLL 2008 criteria. MRD should be assessed from bone marrow aspirate at the reference laboratory in Kiel; the remainder of the aspirate sample should be sent for biobanking and CCI ███████████████████████████. The analysis of the biopsy should be performed at the site's local laboratory. An additional bone marrow biopsy may be obtained on protocol per investigator discretion following evidence of an improvement in clinical response if the response assessment at the Week 25 visit is less than a complete response.

o    Qualitative treatment response assessment based on physical exam, laboratory parameters and presence of B symptoms should be performed every 4 weeks until Week 33 Day 1 and then at all scheduled visits thereafter following the modified IWCLL 2008 criteria, with the exception of lymphadenopathy, hepatomegaly, splenomegaly, and bone marrow. Assessment of response per modified IWCLL 2008 criteria should also be recorded at the completion of 24 weeks on treatment and subsequent to any CT and/or bone marrow biopsy that is repeated while on study.

p    Following evaluation of the safety data for the first 6 subjects enrolled in each treatment arm, the Safety Review Team (SRT) will determine if weekly clinical evaluation should continue for the duration of the study.

q    The EOT visit should be scheduled for approximately 30 days following discontinuation of all study treatment. For subjects that permanently discontinue all treatment prior to Week 25 Day 1, the Week 25 Day 1 visit should also be performed and may satisfy the requirement for the EOT visit if falling into the +30 days ± 7 day window from all study drug discontinuation.

r    Screening results should include creatinine clearance, and serum thymidine kinase, serum beta2 microglobulin and serum quantitative immunoglobulins.

s    The window for bone marrow assessments is  7 days or +14 days as calculated from Week 1 Day 1.

**Appendix 2.        COVID-19 SMQ with Broad Scope**

Note: The list presented below is based on MedDRA Version 23.1. The actual list will be up-versioned to the MedDRA version used at the time of database finalization.

| MedDRA Preferred Term | PT Code |
|---|---|
| Asymptomatic COVID-19 | 10084459 |
| Coronavirus infection | 10051905 |
| Coronavirus test positive | 10070255 |
| COVID-19 | 10084268 |
| COVID-19 immunisation | 10084457 |
| COVID-19 pneumonia | 10084380 |
| COVID-19 prophylaxis | 10084458 |
| COVID-19 treatment | 10084460 |
| Exposure to SARS-CoV-2 | 10084456 |
| Multisystem inflammatory syndrome in children | 10084767 |
| Occupational exposure to SARS-CoV-2 | 10084394 |
| SARS-CoV-2 antibody test positive | 10084491 |
| SARS-CoV-2 carrier | 10084461 |
| SARS-CoV-2 sepsis | 10084639 |
| SARS-CoV-2 test false negative | 10084480 |
| SARS-CoV-2 test positive | 10084271 |
| SARS-CoV-2 viraemia | 10084640 |
| Suspected COVID-19 | 10084451 |
| Antiviral prophylaxis | 10049087 |
| Antiviral treatment | 10068724 |
| Coronavirus test | 10084353 |
| Coronavirus test negative | 10084269 |
| Exposure to communicable disease | 10049711 |
| Pneumonia viral | 10035737 |
| SARS-CoV-2 antibody test | 10084501 |
| SARS-CoV-2 antibody test negative | 10084509 |
| SARS-CoV-2 test | 10084354 |
| SARS-CoV-2 test false positive | 10084602 |
| SARS-CoV-2 test negative | 10084273 |

**Appendix 3.          Determining Missing and Virtual Visits Due to COVID-19**

This appendix describes the clinical trial site collection of COVID-19 data pertaining to missed/virtual visits and the data processing algorithm used to determine which visits were missing and which visits were virtual.

Data collection
A COVID-19 supplement to the eCRF Completion Guidelines (CCG) was provided by data management to instruct clinical trial sites with respect to data entry expectations pertaining to scenarios related to the COVID-19 pandemic.  If a visit was missed, sites should enter "Visit missed due to COVID-19."  If an in-person visit was conducted virtually, sites should enter "Virtual visit due to COVID-19."

Determination of Missed and Virtual visits
NLP was used to search the CRF comment fields to identify instances of "COVID-19" (or synonyms, see the table below) and "Virtual" (or synonyms, see the table below).  The search terms are maintained in a global lookup table and can be modified to tune the NLP model.  For any comments with COVID-19 search terms, assign "Missed visit" or "Virtual visit as follows:

    i.       If COVID-19 terms are identified through NLP and the visit date is missing, then result is "Missed Visit"

    ii.      If COVID-19 and Virtual terms are identified through NLP for a visit, then result is "Virtual Visit". When there are multiple records for the same subject and the same visit, NLP will be based on multiple records to ensure 1 unique category per subject per visit

    iii.     Otherwise result is missing

**Examples of Search Terms for "COVID-19" and "Virtual" Used to Identify Missed and Virtual Visits**

| Search Terms for "COVID-19" | Search Terms for "Virtual" |
|---|---|
| COVID19 | VIRTUAL |
| CORONA | TELEMED |
| CORONAVIRUS | TELEHEALTH |
| PANDEMIC | TELEPHONE |
| OUTBREAK | REMOTE |
| CRISIS | TELEMEDICINE |
| LOCKDOWN | TELECONSULTATION |
| QUARANTINE | TELEPHONICALLY |
| SHELTER | PHONE |
| | HOME VISIT |
| | ZOOM |
| | SKYPE |

### Appendix 4.          Bleeding/Haemorrhage Medical Search Term

Note: The list presented below is based on MedDRA Version 22.0. The actual list will be up-versioned to the MedDRA version used at the time of database finalization.

| MEDDRA Preferred Term | PT Code |
|---|---|
| Abdominal wall haematoma | 10067383 |
| Haemorrhagic adrenal infarction | 10079902 |
| Eye haematoma | 10079891 |
| Spontaneous hyphaema | 10080110 |
| Anal fissure haemorrhage | 10079765 |
| Paranasal sinus haemorrhage | 10080108 |
| Peripheral artery aneurysm rupture | 10079908 |
| Aortic annulus rupture | 10079586 |
| Peripheral artery haematoma | 10081077 |
| Subgaleal haemorrhage | 10080900 |
| Von Willebrand's factor antibody | 10080829 |
| Nephritis haemorrhagic | 10029132 |
| Renal cyst haemorrhage | 10059846 |
| Renal haematoma | 10038459 |
| Renal haemorrhage | 10038460 |
| Ureteric haemorrhage | 10065743 |
| Extraischaemic cerebral haematoma | 10080347 |
| Gastrointestinal vascular malformation haemorrhagic | 10080561 |
| Abdominal wall haemorrhage | 10067788 |
| Abnormal clotting factor | 10049862 |
| Abnormal withdrawal bleeding | 10069195 |
| Acquired dysfibrinogenaemia | 10051122 |
| Acquired haemophilia | 10053745 |
| Acquired haemophilia with anti FVIII, XI, or XIII | 10056496 |
| Acquired protein S deficiency | 10068370 |
| Acquired Von Willebrand's disease | 10069495 |
| Activated partial thromboplastin time abnormal | 10000631 |
| Activated partial thromboplastin time prolonged | 10000636 |

| MEDDRA Preferred Term | PT Code |
|---|---|
| Activated partial thromboplastin time ratio abnormal | 10075284 |
| Activated partial thromboplastin time ratio fluctuation | 10075286 |
| Activated partial thromboplastin time ratio increased | 10075287 |
| Acute haemorrhagic leukoencephalitis | 10058994 |
| Acute haemorrhagic ulcerative colitis | 10075634 |
| Administration site bruise | 10075094 |
| Administration site haematoma | 10075100 |
| Administration site haemorrhage | 10075101 |
| Adrenal haematoma | 10059194 |
| Adrenal haemorrhage | 10001361 |
| Anal haemorrhage | 10049555 |
| Anal ulcer haemorrhage | 10063896 |
| Anastomotic haemorrhage | 10056346 |
| Anastomotic ulcer haemorrhage | 10002244 |
| Aneurysm ruptured | 10048380 |
| Angina bullosa haemorrhagica | 10064223 |
| Anorectal varices haemorrhage | 10068925 |
| Anti factor IX antibody positive | 10058748 |
| Anti factor V antibody positive | 10058745 |
| Anti factor VII antibody positive | 10058746 |
| Anti factor VIII antibody positive | 10049013 |
| Anti factor X activity abnormal | 10077670 |
| Anti factor X activity increased | 10077671 |
| Anti factor X antibody positive | 10058747 |
| Anti factor XI antibody positive | 10058749 |
| Anti factor XII antibody positive | 10058750 |
| Antithrombin III increased | 10051115 |
| Aortic aneurysm rupture | 10002886 |
| Aortic dissection rupture | 10068119 |
| Aortic intramural haematoma | 10067975 |

| MEDDRA Preferred Term | PT Code | MEDDRA Preferred Term | PT Code |
|---|---|---|---|
| Aortic perforation | 10075729 | Bloody discharge | 10057687 |
| Aortic rupture | 10060874 | Bloody peritoneal effluent | 10067442 |
| Aponeurosis contusion | 10075330 | Bone contusion | 10066251 |
| Application site bruise | 10050114 | Bone marrow haemorrhage | 10073581 |
| Application site haematoma | 10068317 | Brain contusion | 10052346 |
| Application site haemorrhage | 10072694 | Brain stem haematoma | 10073230 |
| Application site purpura | 10050182 | Brain stem haemorrhage | 10006145 |
| Arterial haemorrhage | 10060964 | Brain stem microhaemorrhage | 10071205 |
| Arterial intramural haematoma | 10074971 | Breast haematoma | 10064753 |
| Arterial ligation | 10003165 | Breast haemorrhage | 10006254 |
| Arterial perforation | 10075732 | Broad ligament haematoma | 10006375 |
| Arterial rupture | 10003173 | Bronchial haemorrhage | 10065739 |
| Arteriovenous fistula site haematoma | 10055150 | Bronchial varices haemorrhage | 10079163 |
| Arteriovenous fistula site haemorrhage | 10055123 | Bursal haematoma | 10077818 |
| Arteriovenous graft site haematoma | 10055152 | Capillary fragility abnormal | 10007192 |
| Arteriovenous graft site haemorrhage | 10055126 | Capillary fragility increased | 10007194 |
| Atrial rupture | 10048761 | Capillary permeability increased | 10007200 |
| Auricular haematoma | 10003797 | Cardiac contusion | 10073356 |
| Basal ganglia haematoma | 10077031 | Carotid aneurysm rupture | 10051328 |
| Basal ganglia haemorrhage | 10067057 | Carotid artery perforation | 10075728 |
| Basilar artery perforation | 10075736 | Catheter site bruise | 10063587 |
| Benign familial haematuria | 10060876 | Catheter site haematoma | 10055662 |
| Bladder tamponade | 10062656 | Catheter site haemorrhage | 10051099 |
| Bleeding time abnormal | 10049227 | Central nervous system haemorrhage | 10072043 |
| Bleeding time prolonged | 10005140 | Cephalhaematoma | 10008014 |
| Bleeding varicose vein | 10005144 | Cerebellar haematoma | 10061038 |
| Blood blister | 10005372 | Cerebellar haemorrhage | 10008030 |
| Blood fibrinogen abnormal | 10005518 | Cerebellar microhaemorrhage | 10071206 |
| Blood fibrinogen decreased | 10005520 | Cerebral aneurysm perforation | 10075394 |
| Blood thrombin abnormal | 10005818 | Cerebral aneurysm ruptured syphilitic | 10008076 |
| Blood thrombin decreased | 10005820 | Cerebral arteriovenous malformation haemorrhagic | 10008086 |
| Blood thromboplastin abnormal | 10005824 | | |
| Blood thromboplastin decreased | 10005826 | Cerebral artery perforation | 10075734 |
| Blood urine | 10005863 | Cerebral haematoma | 10053942 |
| Blood urine present | 10018870 | Cerebral haemorrhage | 10008111 |

| MEDDRA Preferred Term | PT Code | MEDDRA Preferred Term | PT Code |
|---|---|---|---|
| Cerebral haemorrhage foetal | 10050157 | Coagulation time prolonged | 10009799 |
| Cerebral haemorrhage neonatal | 10008112 | Coagulopathy | 10009802 |
| Cerebral microhaemorrhage | 10067277 | Coital bleeding | 10065019 |
| Cervix haematoma uterine | 10050020 | Colonic haematoma | 10009996 |
| Cervix haemorrhage uterine | 10050022 | Congenital coagulopathy | 10063563 |
| Chest wall haematoma | 10076597 | Congenital dysfibrinogenaemia | 10051123 |
| Choroidal haematoma | 10068642 | Conjunctival haemorrhage | 10010719 |
| Choroidal haemorrhage | 10008786 | Contusion | 10050584 |
| Chronic gastrointestinal bleeding | 10050399 | Corneal bleeding | 10051558 |
| Chronic pigmented purpura | 10072726 | Cullen's sign | 10059029 |
| Ciliary body haemorrhage | 10057417 | Cystitis haemorrhagic | 10011793 |
| Circulating anticoagulant | 10053627 | Deep dissecting haematoma | 10074718 |
| Clot retraction abnormal | 10009669 | Diarrhoea haemorrhagic | 10012741 |
| Clot retraction time prolonged | 10009675 | Dilutional coagulopathy | 10060906 |
| Coagulation disorder neonatal | 10009732 | Disseminated intravascular coagulation | 10013442 |
| Coagulation factor decreased | 10009736 | Diverticulitis intestinal haemorrhagic | 10013541 |
| Coagulation factor deficiency | 10067787 | Diverticulum intestinal haemorrhagic | 10013560 |
| Coagulation factor IX level abnormal | 10061770 | Duodenal ulcer haemorrhage | 10013839 |
| Coagulation factor IX level decreased | 10009746 | Duodenitis haemorrhagic | 10013865 |
| Coagulation factor mutation | 10065442 | Dysfunctional uterine bleeding | 10013908 |
| Coagulation factor V level abnormal | 10061771 | Ear haemorrhage | 10014009 |
| Coagulation factor V level decreased | 10009754 | Ecchymosis | 10014080 |
| Coagulation factor VII level abnormal | 10061772 | Encephalitis haemorrhagic | 10014589 |
| Coagulation factor VII level decreased | 10009761 | Endometriosis | 10014778 |
| Coagulation factor VIII level abnormal | 10061773 | Enterocolitis haemorrhagic | 10014896 |
| Coagulation factor VIII level decreased | 10009768 | Epidural haemorrhage | 10073681 |
| Coagulation factor X level abnormal | 10061774 | Epistaxis | 10015090 |
| Coagulation factor X level decreased | 10009775 | Ethanol gelation test positive | 10062650 |
| Coagulation factor XI level abnormal | 10061775 | Exsanguination | 10015719 |
| Coagulation factor XI level decreased | 10009779 | Extra axial haemorrhage | 10078254 |
| Coagulation factor XII level abnormal | 10061776 | Extradural haematoma | 10015769 |
| Coagulation factor XII level decreased | 10009783 | Extravasation blood | 10015867 |
| Coagulation factor XIII level abnormal | 10061777 | Eye contusion | 10073354 |
| Coagulation factor XIII level decreased | 10009787 | Eye haemorrhage | 10015926 |
| Coagulation time abnormal | 10009791 | Eyelid bleeding | 10053196 |

| MEDDRA Preferred Term | PT Code | MEDDRA Preferred Term | PT Code |
|---|---|---|---|
| Eyelid contusion | 10075018 | Gastroduodenal haemorrhage | 10053768 |
| Eyelid haematoma | 10064976 | Gastrointestinal angiectasia | 10078142 |
| Factor I deficiency | 10016075 | Gastrointestinal haemorrhage | 10017955 |
| Factor II deficiency | 10016076 | Gastrointestinal organ contusion | 10078655 |
| Factor III deficiency | 10052473 | Gastrointestinal polyp haemorrhage | 10074437 |
| Factor IX deficiency | 10016077 | Gastrointestinal ulcer haemorrhage | 10056743 |
| Factor V deficiency | 10048930 | Genital contusion | 10073355 |
| Factor VII deficiency | 10016079 | Genital haemorrhage | 10061178 |
| Factor VIII deficiency | 10016080 | Gingival bleeding | 10018276 |
| Factor X deficiency | 10052474 | Graft haemorrhage | 10063577 |
| Factor Xa activity abnormal | 10078667 | Grey Turner's sign | 10075426 |
| Factor Xa activity decreased | 10078676 | Haemarthrosis | 10018829 |
| Factor XI deficiency | 10016082 | Haematemesis | 10018830 |
| Factor XII deficiency | 10051806 | Haematochezia | 10018836 |
| Factor XIII deficiency | 10016083 | Haematocoele | 10018833 |
| Femoral artery perforation | 10075739 | Haematoma | 10018852 |
| Femoral vein perforation | 10075745 | Haematoma evacuation | 10060733 |
| Fibrin abnormal | 10016575 | Haematoma infection | 10051564 |
| Fibrin D dimer decreased | 10016579 | Haematosalpinx | 10050468 |
| Fibrin D dimer increased | 10016581 | Haematospermia | 10018866 |
| Fibrin decreased | 10016584 | Haematotympanum | 10063013 |
| Fibrin degradation products | 10016585 | Haematuria | 10018867 |
| Fibrin degradation products increased | 10016588 | Haematuria traumatic | 10018871 |
| Fibrinolysis abnormal | 10016604 | Haemobilia | 10058947 |
| Fibrinolysis increased | 10016607 | Haemophilia | 10061992 |
| Foetal maternal haemorrhage | 10016871 | Haemophilia A with anti factor VIII | 10056492 |
| Fothergill sign positive | 10081749 | Haemophilia A without inhibitors | 10056493 |
| Gardner Diamond syndrome | 10078888 | Haemophilia B with anti factor IX | 10056494 |
| Gastric haemorrhage | 10017788 | Haemophilia B without inhibitors | 10056495 |
| Gastric occult blood positive | 10067855 | Haemophilic arthropathy | 10065057 |
| Gastric ulcer haemorrhage | 10017826 | Haemophilic pseudotumour | 10073770 |
| Gastric ulcer haemorrhage, obstructive | 10017829 | Haemoptysis | 10018964 |
| Gastric varices haemorrhage | 10057572 | Haemorrhage | 10055798 |
| Gastritis alcoholic haemorrhagic | 10017857 | Haemorrhage coronary artery | 10055803 |
| Gastritis haemorrhagic | 10017866 | Haemorrhage foetal | 10061191 |

| MEDDRA Preferred Term | PT Code | MEDDRA Preferred Term | PT Code |
|---|---|---|---|
| Haemorrhage in pregnancy | 10018981 | Hereditary haemorrhagic telangiectasia | 10019883 |
| Haemorrhage intracranial | 10018985 | Hermansky Pudlak syndrome | 10071775 |
| Haemorrhage neonatal | 10061993 | Hyperfibrinolysis | 10074737 |
| Haemorrhage subcutaneous | 10018999 | Hyphaema | 10020923 |
| Haemorrhage subepidermal | 10019001 | Hypocoagulable state | 10020973 |
| Haemorrhage urinary tract | 10055847 | Hypofibrinogenaemia | 10051125 |
| Blood loss anaemia | 10082297 | Hypoprothrombinaemia | 10021085 |
| Haemorrhagic arteriovenous malformation | 10064595 | Hypothrombinaemia | 10058517 |
| Haemorrhagic ascites | 10059766 | Hypothromboplastinaemia | 10058518 |
| Haemorrhagic breast cyst | 10077443 | Iliac artery perforation | 10075731 |
| Haemorrhagic cerebral infarction | 10019005 | Iliac artery rupture | 10072789 |
| Haemorrhagic cyst | 10059189 | Iliac vein perforation | 10075744 |
| Haemorrhagic diathesis | 10062713 | Immune thrombocytopenic purpura | 10074667 |
| Haemorrhagic disease of newborn | 10019008 | Implant site bruising | 10063850 |
| Haemorrhagic disorder | 10019009 | Implant site haematoma | 10063780 |
| Haemorrhagic erosive gastritis | 10067786 | Implant site haemorrhage | 10053995 |
| Haemorrhagic hepatic cyst | 10067796 | Incision site haematoma | 10059241 |
| Haemorrhagic infarction | 10019013 | Incision site haemorrhage | 10051100 |
| Haemorrhagic necrotic pancreatitis | 10076058 | Increased tendency to bruise | 10021688 |
| Haemorrhagic ovarian cyst | 10060781 | Induced abortion haemorrhage | 10052844 |
| Haemorrhagic pneumonia | 10077933 | Inferior vena cava perforation | 10075742 |
| Haemorrhagic stroke | 10019016 | Infusion site bruising | 10059203 |
| Haemorrhagic thyroid cyst | 10072256 | Infusion site haematoma | 10065463 |
| Haemorrhagic transformation stroke | 10055677 | Infusion site haemorrhage | 10065464 |
| Haemorrhagic tumour necrosis | 10054096 | Injection site bruising | 10022052 |
| Haemorrhagic urticaria | 10059499 | Injection site haematoma | 10022066 |
| Haemorrhagic varicella syndrome | 10078873 | Injection site haemorrhage | 10022067 |
| Haemorrhagic vasculitis | 10071252 | Instillation site bruise | 10073630 |
| Haemorrhoidal haemorrhage | 10054787 | Instillation site haematoma | 10073609 |
| Haemostasis | 10067439 | Instillation site haemorrhage | 10073610 |
| Haemothorax | 10019027 | Internal haemorrhage | 10075192 |
| Henoch Schonlein purpura | 10019617 | International normalised ratio abnormal | 10022592 |
| Hepatic haemangioma rupture | 10054885 | International normalised ratio increased | 10022595 |
| Hepatic haematoma | 10019676 | Intestinal haematoma | 10069829 |
| Hepatic haemorrhage | 10019677 | Intestinal haemorrhage | 10059175 |

| MEDDRA Preferred Term | PT Code | MEDDRA Preferred Term | PT Code |
|---|---|---|---|
| Intestinal varices haemorrhage | 10078058 | Mesenteric haematoma | 10071557 |
| Intra abdominal haematoma | 10056457 | Mesenteric haemorrhage | 10060717 |
| Intra abdominal haemorrhage | 10061249 | Metrorrhagia | 10027514 |
| Intracerebral haematoma evacuation | 10062025 | Mouth haemorrhage | 10028024 |
| Intracranial haematoma | 10059491 | Mucocutaneous haemorrhage | 10076048 |
| Intracranial tumour haemorrhage | 10022775 | Mucosal haemorrhage | 10061298 |
| Intraocular haematoma | 10071934 | Muscle contusion | 10070757 |
| Intrapartum haemorrhage | 10067703 | Muscle haemorrhage | 10028309 |
| Intraventricular haemorrhage | 10022840 | Myocardial haemorrhage | 10048849 |
| Intraventricular haemorrhage neonatal | 10022841 | Myocardial rupture | 10028604 |
| Iris haemorrhage | 10057418 | Naevus haemorrhage | 10062955 |
| Joint microhaemorrhage | 10077666 | Nail bed bleeding | 10048891 |
| Kidney contusion | 10023413 | Nasal septum haematoma | 10075027 |
| Lacrimal haemorrhage | 10069930 | Neonatal gastrointestinal haemorrhage | 10074159 |
| Large intestinal haemorrhage | 10052534 | Nipple exudate bloody | 10029418 |
| Large intestinal ulcer haemorrhage | 10061262 | Occult blood positive | 10061880 |
| Laryngeal haematoma | 10070885 | Ocular retrobulbar haemorrhage | 10057571 |
| Laryngeal haemorrhage | 10065740 | Oesophageal haemorrhage | 10030172 |
| Lip haematoma | 10066304 | Oesophageal intramural haematoma | 10077486 |
| Lip haemorrhage | 10049297 | Oesophageal ulcer haemorrhage | 10030202 |
| Liver contusion | 10067266 | Oesophageal varices haemorrhage | 10030210 |
| Lower gastrointestinal haemorrhage | 10050953 | Oesophagitis haemorrhagic | 10030219 |
| Lower limb artery perforation | 10075730 | Optic disc haemorrhage | 10030919 |
| Lymph node haemorrhage | 10074270 | Optic nerve sheath haemorrhage | 10030941 |
| Mallory Weiss syndrome | 10026712 | Oral contusion | 10078170 |
| Mediastinal haematoma | 10049941 | Oral mucosa haematoma | 10074779 |
| Mediastinal haemorrhage | 10056343 | Osteorrhagia | 10051937 |
| Medical device site bruise | 10075570 | Ovarian haematoma | 10033263 |
| Medical device site haematoma | 10075577 | Ovarian haemorrhage | 10065741 |
| Medical device site haemorrhage | 10075578 | Palpable purpura | 10056872 |
| Melaena | 10027141 | Pancreatic contusion | 10078654 |
| Melaena neonatal | 10049777 | Pancreatic haemorrhage | 10033625 |
| Meningorrhagia | 10052593 | Pancreatitis haemorrhagic | 10033650 |
| Menometrorrhagia | 10027295 | Papillary muscle haemorrhage | 10059164 |
| Menorrhagia | 10027313 | Paranasal sinus haematoma | 10069702 |

| MEDDRA Preferred Term | PT Code |
|---|---|
| Parathyroid haemorrhage | 10059051 |
| Parotid gland haemorrhage | 10051166 |
| Pelvic haematoma | 10054974 |
| Pelvic haematoma obstetric | 10034248 |
| Pelvic haemorrhage | 10063678 |
| Penile contusion | 10073352 |
| Penile haematoma | 10070656 |
| Penile haemorrhage | 10034305 |
| Peptic ulcer haemorrhage | 10034344 |
| Pericardial haemorrhage | 10034476 |
| Perineal haematoma | 10034520 |
| Periorbital haematoma | 10034544 |
| Periorbital haemorrhage | 10071697 |
| Periosteal haematoma | 10077341 |
| Peripartum haemorrhage | 10072693 |
| Perirenal haematoma | 10049450 |
| Peritoneal haematoma | 10058095 |
| Peritoneal haemorrhage | 10034666 |
| Periventricular haemorrhage neonatal | 10076706 |
| Petechiae | 10034754 |
| Pharyngeal haematoma | 10068121 |
| Pharyngeal haemorrhage | 10034827 |
| Pituitary haemorrhage | 10049760 |
| Placenta praevia haemorrhage | 10035121 |
| Plasminogen activator inhibitor | 10059620 |
| Plasminogen activator inhibitor decreased | 10059619 |
| Plasminogen decreased | 10035493 |
| Plasminogen increased | 10035495 |
| Platelet factor 4 decreased | 10060220 |
| Polymenorrhagia | 10064050 |
| Post abortion haemorrhage | 10036246 |
| Post procedural contusion | 10073353 |
| Post procedural haematoma | 10063188 |
| Post procedural haematuria | 10066225 |
| Post procedural haemorrhage | 10051077 |

| MEDDRA Preferred Term | PT Code |
|---|---|
| Post transfusion purpura | 10072265 |
| Postmenopausal haemorrhage | 10055870 |
| Postpartum haemorrhage | 10036417 |
| Post traumatic punctate intraepidermal haemorrhage | 10071639 |
| Procedural haemorrhage | 10071229 |
| Proctitis haemorrhagic | 10036778 |
| Prostatic haemorrhage | 10036960 |
| Protein C increased | 10060230 |
| Protein S abnormal | 10051736 |
| Protein S increased | 10051735 |
| Prothrombin level abnormal | 10037048 |
| Prothrombin level decreased | 10037050 |
| Prothrombin time abnormal | 10037057 |
| Prothrombin time prolonged | 10037063 |
| Prothrombin time ratio abnormal | 10061918 |
| Prothrombin time ratio increased | 10037068 |
| Pulmonary alveolar haemorrhage | 10037313 |
| Pulmonary contusion | 10037370 |
| Pulmonary haematoma | 10054991 |
| Pulmonary haemorrhage | 10037394 |
| Puncture site haemorrhage | 10051101 |
| Purpura | 10037549 |
| Purpura fulminans | 10037556 |
| Purpura neonatal | 10037557 |
| Purpura non thrombocytopenic | 10057739 |
| Purpura senile | 10037560 |
| Putamen haemorrhage | 10058940 |
| Radiation associated haemorrhage | 10072281 |
| Rectal haemorrhage | 10038063 |
| Rectal ulcer haemorrhage | 10038081 |
| Renal artery perforation | 10075737 |
| Respiratory tract haemorrhage | 10038727 |
| Respiratory tract haemorrhage neonatal | 10038728 |
| Retinal aneurysm rupture | 10079121 |

| MEDDRA Preferred Term | PT Code | MEDDRA Preferred Term | PT Code |
|---|---|---|---|
| Retinal haemorrhage | 10038867 | Subarachnoid haematoma | 10076701 |
| Retinopathy haemorrhagic | 10051447 | Subarachnoid haemorrhage | 10042316 |
| Retroperitoneal haematoma | 10058360 | Subarachnoid haemorrhage neonatal | 10042317 |
| Retroperitoneal haemorrhage | 10038980 | Subchorionic haematoma | 10072596 |
| Retroplacental haematoma | 10054798 | Subchorionic haemorrhage | 10071010 |
| Ruptured cerebral aneurysm | 10039330 | Subclavian artery perforation | 10075740 |
| Russell's viper venom time abnormal | 10059759 | Subclavian vein perforation | 10075743 |
| Scleral haemorrhage | 10050508 | Subcutaneous haematoma | 10042345 |
| Scrotal haematocoele | 10061517 | Subdural haematoma | 10042361 |
| Scrotal haematoma | 10039749 | Subdural haematoma evacuation | 10042363 |
| Shock haemorrhagic | 10049771 | Subdural haemorrhage | 10042364 |
| Skin haemorrhage | 10064265 | Subdural haemorrhage neonatal | 10042365 |
| Skin neoplasm bleeding | 10060712 | Subgaleal haematoma | 10069510 |
| Skin ulcer haemorrhage | 10050377 | Subretinal haematoma | 10071935 |
| Small intestinal haemorrhage | 10052535 | Superior vena cava perforation | 10075741 |
| Small intestinal ulcer haemorrhage | 10061550 | Testicular haemorrhage | 10051877 |
| Soft tissue haemorrhage | 10051297 | Thalamus haemorrhage | 10058939 |
| Spermatic cord haemorrhage | 10065742 | Third stage postpartum haemorrhage | 10043449 |
| Spinal cord haematoma | 10076051 | Thoracic haemorrhage | 10062744 |
| Spinal cord haemorrhage | 10048992 | Thrombin time abnormal | 10051319 |
| Spinal epidural haematoma | 10050162 | Thrombin time prolonged | 10051390 |
| Spinal epidural haemorrhage | 10049236 | Thrombin antithrombin III complex abnormal | 10053972 |
| Spinal subarachnoid haemorrhage | 10073564 | Thrombin antithrombin III complex increased | 10053968 |
| Spinal subdural haematoma | 10050164 | Thrombocytopenic purpura | 10043561 |
| Spinal subdural haemorrhage | 10073563 | Thrombotic thrombocytopenic purpura | 10043648 |
| Spleen contusion | 10073533 | Thyroid haemorrhage | 10064224 |
| Splenic artery perforation | 10075738 | Tongue haematoma | 10043959 |
| Splenic haematoma | 10041646 | Tongue haemorrhage | 10049870 |
| Splenic haemorrhage | 10041647 | Tonsillar haemorrhage | 10057450 |
| Splenic varices haemorrhage | 10068662 | Tooth pulp haemorrhage | 10072228 |
| Splinter haemorrhages | 10041663 | Tooth socket haemorrhage | 10064946 |
| Spontaneous haematoma | 10065304 | Tracheal haemorrhage | 10062543 |
| Spontaneous haemorrhage | 10074557 | Traumatic haematoma | 10044522 |
| Stoma site haemorrhage | 10074508 | Traumatic haemorrhage | 10053476 |
| Stomatitis haemorrhagic | 10042132 | | |

| MEDDRA Preferred Term | PT Code | MEDDRA Preferred Term | PT Code |
|---|---|---|---|
| Traumatic haemothorax | 10074487 | Vessel puncture site haemorrhage | 10054092 |
| Traumatic intracranial haematoma | 10079013 | Vitreous haematoma | 10071936 |
| Traumatic intracranial haemorrhage | 10061387 | Vitreous haemorrhage | 10047655 |
| Tumour haemorrhage | 10049750 | Von Willebrand's disease | 10047715 |
| Ulcer haemorrhage | 10061577 | Von Willebrand's factor antibody positive | 10066358 |
| Umbilical cord haemorrhage | 10064534 | Von Willebrand's factor multimers abnormal | 10055165 |
| Umbilical haematoma | 10068712 | Vulval haematoma | 10047756 |
| Umbilical haemorrhage | 10045455 | Vulval haematoma evacuation | 10047757 |
| Upper gastrointestinal haemorrhage | 10046274 | Vulval haemorrhage | 10063816 |
| Urethral haemorrhage | 10049710 | White nipple sign | 10078438 |
| Urinary bladder haemorrhage | 10046528 | Withdrawal bleed | 10047998 |
| Urogenital haemorrhage | 10050058 | Wound haematoma | 10071504 |
| Uterine haematoma | 10063875 | Cerebral cyst haemorrhage | 10082099 |
| Uterine haemorrhage | 10046788 | Pituitary apoplexy | 10056447 |
| Vaccination site bruising | 10069484 | Haematoma muscle | 10055890 |
| Vaccination site haematoma | 10069472 | Battle's sign | 10082307 |
| Vaccination site haemorrhage | 10069475 | Puncture site bruise | 10082035 |
| Vaginal haematoma | 10046909 | Haemorrhagic cholecystitis | 10082088 |
| Vaginal haemorrhage | 10046910 | Puncture site haematoma | 10081957 |
| Varicose vein ruptured | 10046999 | Subendocardial haemorrhage | 10082459 |
| Vascular access site bruising | 10077767 | Acute haemorrhagic oedema of infancy | 10070599 |
| Vascular access site haematoma | 10077647 | Wound haemorrhage | 10051373 |
| Vascular access site haemorrhage | 10077643 | | |
| Vascular access site rupture | 10077652 | | |
| Vascular graft haemorrhage | 10077721 | | |
| Vascular pseudoaneurysm ruptured | 10053949 | | |
| Vascular purpura | 10047097 | | |
| Vascular rupture | 10053649 | | |
| Vein rupture | 10077110 | | |
| Venous haemorrhage | 10065441 | | |
| Venous perforation | 10075733 | | |
| Ventricle rupture | 10047279 | | |
| Vertebral artery perforation | 10075735 | | |
| Vessel puncture site bruise | 10063881 | | |
| Vessel puncture site haematoma | 10065902 | | |

### Appendix 5.        Hypersensitivity Medical Search Term

Note: The list presented below is based on a SMQ in MedDRA Version 22.0. The actual list will be up-versioned to the MedDRA version used at the time of database finalization.

| MedDRA Preferred Term | PT Code | MedDRA Preferred Term | PT Code |
|---|---|---|---|
| Acute respiratory failure | 10001053 | Conjunctivitis | 10010741 |
| Alveolitis | 10001889 | Conjunctivitis allergic | 10010744 |
| Anaphylactic reaction | 10002198 | Contrast media reaction | 10010836 |
| Anaphylactic shock | 10002199 | Corneal oedema | 10011033 |
| Anaphylactoid reaction | 10002216 | Cutaneous vasculitis | 10011686 |
| Anaphylaxis treatment | 10002222 | Dermatitis | 10012431 |
| Angioedema | 10002424 | Dermatitis acneiform | 10012432 |
| Application site dermatitis | 10003036 | Dermatitis allergic | 10012434 |
| Application site rash | 10003054 | Dermatitis atopic | 10012438 |
| Asthma | 10003553 | Dermatitis bullous | 10012441 |
| Asthma late onset | 10003559 | Dermatitis contact | 10012442 |
| Atopy | 10003645 | Dermatitis exfoliative | 10012455 |
| Auricular swelling | 10003800 | Dermatitis exfoliative generalised | 10012456 |
| Blepharitis allergic | 10005149 | Dermatitis herpetiformis | 10012468 |
| Blister | 10005191 | Dermatitis infected | 10012470 |
| Blood immunoglobulin A abnormal | 10005584 | Drug eruption | 10013687 |
| Blood immunoglobulin A increased | 10005586 | Drug hypersensitivity | 10013700 |
| Blood immunoglobulin E abnormal | 10005589 | Ear swelling | 10014025 |
| Blood immunoglobulin E increased | 10005591 | Eczema | 10014184 |
| Blood immunoglobulin G abnormal | 10005594 | Eczema infantile | 10014198 |
| Blood immunoglobulin G increased | 10005596 | Eczema nummular | 10014201 |
| Blood immunoglobulin M abnormal | 10005599 | Encephalopathy allergic | 10014627 |
| Blood immunoglobulin M increased | 10005601 | Eosinophil count increased | 10014945 |
| Bromoderma | 10006404 | Eosinophilia | 10014950 |
| Bronchospasm | 10006482 | Eosinophilia myalgia syndrome | 10014952 |
| Bullous impetigo | 10006563 | Eosinophilic pneumonia | 10014962 |
| Charcot Leyden crystals | 10008413 | Epidermolysis bullosa | 10014989 |
| Cheilitis | 10008417 | Epiglottic oedema | 10015029 |
| Choking | 10008589 | Erythema | 10015150 |
| Choking sensation | 10008590 | Erythema multiforme | 10015218 |
| Circulatory collapse | 10009192 | Erythema nodosum | 10015226 |
| Conjunctival oedema | 10010726 | Eye allergy | 10015907 |

| MedDRA Preferred Term | PT Code | MedDRA Preferred Term | PT Code |
|---|---|---|---|
| Eye swelling | 10015967 | Oculomucocutaneous syndrome | 10030081 |
| Eyelid oedema | 10015993 | Oedema mouth | 10030110 |
| Face oedema | 10016029 | Oedema mucosal | 10030111 |
| Fixed eruption | 10016741 | Orbital oedema | 10031051 |
| Flushing | 10016825 | Oropharyngeal spasm | 10031111 |
| Generalised oedema | 10018092 | Oropharyngeal swelling | 10031118 |
| Genital rash | 10018175 | Panniculitis | 10033675 |
| Giant papillary conjunctivitis | 10018258 | Penile swelling | 10034319 |
| Gingival swelling | 10018291 | Perioral dermatitis | 10034541 |
| Henoch Schonlein purpura | 10019617 | Periorbital oedema | 10034545 |
| Hereditary angioedema | 10019860 | Pharyngeal oedema | 10034829 |
| Hypersensitivity | 10020751 | Photosensitivity reaction | 10034972 |
| Hypersensitivity vasculitis | 10020764 | Pneumonitis | 10035742 |
| Idiopathic urticaria | 10021247 | Prurigo | 10037083 |
| Immunoglobulins abnormal | 10021497 | Pruritus | 10037087 |
| Immunoglobulins increased | 10021500 | Pulmonary eosinophilia | 10037382 |
| Injection site dermatitis | 10022056 | Radioallergosorbent test positive | 10037789 |
| Injection site hypersensitivity | 10022071 | Rash | 10037844 |
| Injection site rash | 10022094 | Rash erythematous | 10037855 |
| Injection site urticaria | 10022107 | Rash follicular | 10037857 |
| Interstitial lung disease | 10022611 | Rash generalised | 10037858 |
| Laryngeal oedema | 10023845 | Rash macular | 10037867 |
| Laryngospasm | 10023891 | Rash maculo papular | 10037868 |
| Laryngotracheal oedema | 10023893 | Rash morbilliform | 10037870 |
| Lip oedema | 10024558 | Rash neonatal | 10037871 |
| Lip swelling | 10024570 | Rash papulosquamous | 10037879 |
| Mouth ulceration | 10028034 | Rash pruritic | 10037884 |
| Mucocutaneous ulceration | 10028084 | Rash pustular | 10037888 |
| Mucosa vesicle | 10028103 | Rash scarlatiniform | 10037890 |
| Mucosal ulceration | 10028124 | Rash vesicular | 10037898 |
| Multiple allergies | 10028164 | Reaction to azo dyes | 10037973 |
| Nephritis allergic | 10029120 | Reaction to colouring | 10037974 |
| Neurodermatitis | 10029263 | Reaction to food additive | 10037977 |
| Nikolsky's sign | 10029415 | Red man syndrome | 10038192 |
| Occupational dermatitis | 10030012 | Respiratory arrest | 10038669 |

| MedDRA Preferred Term | PT Code |
|---|---|
| Respiratory distress | 10038687 |
| Respiratory failure | 10038695 |
| Rhinitis allergic | 10039085 |
| Rhinitis perennial | 10039094 |
| Scrotal oedema | 10039755 |
| Scrotal swelling | 10039759 |
| Serum sickness | 10040400 |
| Serum sickness like reaction | 10040402 |
| Shock | 10040560 |
| Shock symptom | 10040581 |
| Skin erosion | 10040840 |
| Skin exfoliation | 10040844 |
| Skin necrosis | 10040893 |
| Skin reaction | 10040914 |
| Skin test positive | 10040934 |
| Sneezing | 10041232 |
| Solar urticaria | 10041307 |
| Solvent sensitivity | 10041316 |
| Status asthmaticus | 10041961 |
| Stevens Johnson syndrome | 10042033 |
| Stomatitis | 10042128 |
| Stridor | 10042241 |
| Suffocation feeling | 10042444 |
| Swelling face | 10042682 |
| Swelling of eyelid | 10042690 |
| Swollen tongue | 10042727 |
| Throat tightness | 10043528 |
| Tongue oedema | 10043967 |
| Toxic epidermal necrolysis | 10044223 |
| Tracheal obstruction | 10044291 |
| Tracheal oedema | 10044296 |
| Tracheostomy | 10044320 |
| Type I hypersensitivity | 10045240 |
| Urticaria | 10046735 |
| Urticaria cholinergic | 10046740 |

| MedDRA Preferred Term | PT Code |
|---|---|
| Urticaria contact | 10046742 |
| Urticaria papular | 10046750 |
| Urticaria physical | 10046751 |
| Urticaria pigmentosa | 10046752 |
| Urticaria vesiculosa | 10046755 |
| Vaginal ulceration | 10046943 |
| Vasculitic rash | 10047111 |
| Vulval oedema | 10047763 |
| Vulval ulceration | 10047768 |
| Wheezing | 10047924 |
| Acute generalised exanthematous pustulosis | 10048799 |
| Urticarial vasculitis | 10048820 |
| Seasonal allergy | 10048908 |
| Localised oedema | 10048961 |
| Allergic sinusitis | 10049153 |
| Gingival oedema | 10049305 |
| Rash maculovesicular | 10050004 |
| Application site eczema | 10050099 |
| Application site urticaria | 10050104 |
| Vulvovaginal ulceration | 10050181 |
| Allergic pharyngitis | 10050639 |
| Cytokine storm | 10050685 |
| Anti neutrophil cytoplasmic antibody positive vasculitis | 10050894 |
| Complement factor C3 decreased | 10050981 |
| Complement factor C4 decreased | 10050983 |
| Scleritis allergic | 10051126 |
| Allergic cystitis | 10051394 |
| Complement factor C1 decreased | 10051552 |
| Complement factor C2 decreased | 10051555 |
| Generalised erythema | 10051576 |
| Infusion related reaction | 10051792 |
| Kaposi's varicelliform eruption | 10051891 |
| Cytokine release syndrome | 10052015 |
| Iodine allergy | 10052098 |

| MedDRA Preferred Term | PT Code | MedDRA Preferred Term | PT Code |
|---|---|---|---|
| Eye oedema | 10052139 | Toxic skin eruption | 10057970 |
| Eosinophil percentage increased | 10052222 | Rash rubelliform | 10057984 |
| Circumoral oedema | 10052250 | Gastrointestinal oedema | 10058061 |
| Catheter site rash | 10052271 | Eosinophil percentage abnormal | 10058133 |
| Catheter site urticaria | 10052272 | Dermatitis psoriasiform | 10058675 |
| Laryngeal dyspnoea | 10052390 | Skin oedema | 10058679 |
| Urticaria chronic | 10052568 | Eczema vesicular | 10058681 |
| Pruritus generalised | 10052576 | Application site photosensitivity reaction | 10058730 |
| Allergic bronchitis | 10052613 | Hand dermatitis | 10058898 |
| Eosinophilic pneumonia acute | 10052832 | Stoma site rash | 10059071 |
| Eosinophilic pneumonia chronic | 10052833 | Epidermal necrosis | 10059284 |
| Epidermolysis | 10053177 | Allergic colitis | 10059447 |
| Skin swelling | 10053262 | Haemorrhagic urticaria | 10059499 |
| Injection site photosensitivity reaction | 10053396 | Laryngeal obstruction | 10059639 |
| Type IV hypersensitivity reaction | 10053613 | Infusion site rash | 10059830 |
| Type III immune complex mediated reaction | 10053614 | Alpha tumour necrosis factor increased | 10059982 |
| | | Allergic oedema | 10060934 |
| Allergic cough | 10053779 | Complement factor decreased | 10061048 |
| Streptokinase antibody increased | 10053797 | Eosinophil count abnormal | 10061125 |
| Anti insulin antibody positive | 10053814 | Immunology test abnormal | 10061214 |
| Anti insulin antibody increased | 10053815 | Mucosal erosion | 10061297 |
| Type II hypersensitivity | 10054000 | Antibody test abnormal | 10061425 |
| Allergy to fermented products | 10054929 | Antibody test positive | 10061427 |
| Allergy to vaccine | 10055048 | Arthritis allergic | 10061430 |
| Eczema weeping | 10055182 | Allergic otitis media | 10061557 |
| Allergy test positive | 10056352 | Allergy to chemicals | 10061626 |
| Encephalitis allergic | 10056387 | Reversible airways obstruction | 10062109 |
| Periorbital swelling | 10056647 | Heparin induced thrombocytopenia | 10062506 |
| Mucocutaneous rash | 10056671 | Necrotising panniculitis | 10062579 |
| Bronchial oedema | 10056695 | Dennie Morgan fold | 10062918 |
| Palpable purpura | 10056872 | Mesenteric panniculitis | 10063031 |
| Septal panniculitis | 10056876 | Anaphylactoid shock | 10063119 |
| Palatal oedema | 10056998 | Blood immunoglobulin D increased | 10063244 |
| Allergic keratitis | 10057380 | Pruritus allergic | 10063438 |
| Scleral oedema | 10057431 | Allergic respiratory symptom | 10063527 |

| MedDRA Preferred Term | PT Code | MedDRA Preferred Term | PT Code |
|---|---|---|---|
| Allergic respiratory disease | 10063532 | Injection site eczema | 10066221 |
| Application site hypersensitivity | 10063683 | Penile oedema | 10066774 |
| Implant site rash | 10063786 | Injection site recall reaction | 10066797 |
| Implant site urticaria | 10063787 | Gleich's syndrome | 10066837 |
| Vaginal oedema | 10063818 | Contrast media allergy | 10066973 |
| Implant site dermatitis | 10063855 | Anaphylactic transfusion reaction | 10067113 |
| Implant site hypersensitivity | 10063858 | Haemolytic transfusion reaction | 10067122 |
| Antiallergic therapy | 10064059 | Immediate post injection reaction | 10067142 |
| Eosinophilic oesophagitis | 10064212 | Oculorespiratory syndrome | 10067317 |
| Lip exfoliation | 10064482 | Contact stomatitis | 10067510 |
| Vaginal exfoliation | 10064483 | Genital swelling | 10067639 |
| Penile exfoliation | 10064485 | Upper airway obstruction | 10067775 |
| Mucosal exfoliation | 10064486 | HLA marker study positive | 10067937 |
| Oral mucosal exfoliation | 10064487 | Oropharyngeal blistering | 10067950 |
| Tongue exfoliation | 10064488 | Interstitial granulomatous dermatitis | 10067972 |
| Corneal exfoliation | 10064489 | Mucosal necrosis | 10067993 |
| Exfoliative rash | 10064579 | Injection site vasculitis | 10067995 |
| Immune complex level increased | 10064650 | Anti insulin receptor antibody positive | 10068225 |
| Leukotriene increased | 10064663 | Anti insulin receptor antibody increased | 10068226 |
| Reaction to preservatives | 10064788 | Oral allergy syndrome | 10068355 |
| Asthmatic crisis | 10064823 | Capillaritis | 10068406 |
| Laryngitis allergic | 10064866 | Mechanical urticaria | 10068773 |
| Neutralising antibodies positive | 10064980 | Palisaded neutrophilic granulomatous dermatitis | 10068809 |
| Non neutralising antibodies positive | 10064982 | Vaccination site hypersensitivity | 10068880 |
| Perivascular dermatitis | 10064986 | Kounis syndrome | 10069167 |
| Infusion site dermatitis | 10065458 | Henoch Schonlein purpura nephritis | 10069440 |
| Infusion site hypersensitivity | 10065471 | Vaccination site dermatitis | 10069477 |
| Infusion site photosensitivity reaction | 10065486 | Vaccination site rash | 10069482 |
| Infusion site urticaria | 10065490 | Vaccination site exfoliation | 10069489 |
| Antiendomysial antibody positive | 10065514 | Vaccination site urticaria | 10069622 |
| Eosinophilic bronchitis | 10065563 | Vaccination site vesicles | 10069623 |
| Visceral oedema | 10065768 | Administration related reaction | 10069773 |
| Eczema vaccinatum | 10066042 | Limbal swelling | 10070492 |
| Bronchial hyperreactivity | 10066091 | Distributive shock | 10070559 |
| Allergic transfusion reaction | 10066173 | | |

| MedDRA Preferred Term | PT Code | MedDRA Preferred Term | PT Code |
|---|---|---|---|
| Immune tolerance induction | 10070581 | Transplantation associated food allergy | 10075008 |
| Respiratory tract oedema | 10070774 | Allergic otitis externa | 10075072 |
| Reactive airways dysfunction syndrome | 10070832 | Aspirin exacerbated respiratory disease | 10075084 |
| Occupational asthma | 10070836 | Administration site dermatitis | 10075096 |
| Injection related reaction | 10071152 | Administration site eczema | 10075099 |
| Administration site rash | 10071156 | Administration site hypersensitivity | 10075102 |
| Allergic hepatitis | 10071198 | Administration site urticaria | 10075109 |
| Vulvovaginal swelling | 10071211 | Allergic eosinophilia | 10075185 |
| Chronic hyperplastic eosinophilic sinusitis | 10071380 | Mouth swelling | 10075203 |
| Chronic eosinophilic rhinosinusitis | 10071399 | Airway remodelling | 10075289 |
| Vulvovaginal rash | 10071588 | Allergic gastroenteritis | 10075308 |
| Device allergy | 10072867 | Perineal rash | 10075364 |
| Incision site dermatitis | 10073168 | Allergy alert test positive | 10075479 |
| Blister rupture | 10073385 | Medical device site dermatitis | 10075572 |
| Incision site rash | 10073411 | Medical device site eczema | 10075575 |
| Implant site photosensitivity | 10073415 | Medical device site hypersensitivity | 10075579 |
| Drug reaction with eosinophilia and systemic symptoms | 10073508 | Medical device site rash | 10075585 |
| Instillation site hypersensitivity | 10073612 | Medical device site urticaria | 10075588 |
| Instillation site rash | 10073622 | Nodular rash | 10075807 |
| Instillation site urticaria | 10073627 | Administration site photosensitivity reaction | 10075961 |
| Catheter site dermatitis | 10073992 | Administration site recall reaction | 10075964 |
| Catheter site eczema | 10073995 | Administration site vasculitis | 10075969 |
| Catheter site hypersensitivity | 10073998 | Application site recall reaction | 10076024 |
| Catheter site vasculitis | 10074014 | Application site vasculitis | 10076027 |
| Allergy to immunoglobulin therapy | 10074079 | Infusion site recall reaction | 10076085 |
| Pathergy reaction | 10074332 | Medical device site photosensitivity reaction | 10076137 |
| Drug provocation test | 10074350 | Medical device site recall reaction | 10076140 |
| Palatal swelling | 10074403 | Vaccination site eczema | 10076161 |
| Stoma site hypersensitivity | 10074509 | Vaccination site photosensitivity reaction | 10076186 |
| Immune thrombocytopenic purpura | 10074667 | Vaccination site recall reaction | 10076188 |
| Noninfective conjunctivitis | 10074701 | Vaccination site vasculitis | 10076191 |
| Infusion site eczema | 10074850 | Intestinal angioedema | 10076229 |
| Infusion site vasculitis | 10074851 | Documented hypersensitivity to administered product | 10076470 |
| Caffeine allergy | 10074895 | | |

| MedDRA Preferred Term | PT Code |
|---|---|
| Mast cell degranulation present | 10076606 |
| Dialysis membrane reaction | 10076665 |
| Asthma chronic obstructive pulmonary disease overlap syndrome | 10077005 |
| Vessel puncture site rash | 10077117 |
| Allergy to surgical sutures | 10077279 |
| Immune mediated adverse reaction | 10077665 |
| Vessel puncture site vesicles | 10077813 |
| Eosinophilic granulomatosis with polyangiitis | 10078117 |
| Symmetrical drug related intertriginous and flexural exanthema | 10078325 |
| Nasal crease | 10078581 |
| Oropharyngeal oedema | 10078783 |
| Allergic reaction to excipient | 10078853 |
| Allergic stomatitis | 10079554 |
| Therapeutic product cross reactivity | 10079645 |
| Reaction to excipient | 10079925 |
| Vulvovaginitis allergic | 10080783 |
| Procedural shock | 10080894 |
| Hereditary angioedema with C1 esterase inhibitor deficiency | 10080955 |
| Vernal keratoconjunctivitis | 10081000 |
| Hypersensitivity myocarditis | 10081004 |
| Acquired C1 inhibitor deficiency | 10081035 |
| Scrotal exfoliation | 10081178 |
| Childhood asthma | 10081274 |
| Atopic cough | 10081492 |
| Circumoral swelling | 10081703 |
| Hypersensitivity pneumonitis | 10081988 |
| Human anti hamster antibody increased | 10082107 |
| Human anti hamster antibody positive | 10082109 |
| Pharyngeal swelling | 10082270 |
| Urticarial dermatitis | 10082290 |
| Immune mediated pneumonitis | 10082452 |

## Appendix 6.        Cytopenia Medical Search Term

Note: The list presented below is based on MedDRA Version 22.0. The actual list will be up-versioned to the MedDRA version used at the time of database finalization.

| MEDDRA Preferred Term | PT Code |
|---|---|
| Acquired amegakaryocytic thrombocytopenia | 10076747 |
| Megakaryocytes decreased | 10027119 |
| Mononuclear cell count decreased | 10082036 |
| Platelet count decreased | 10035528 |
| Platelet maturation arrest | 10035537 |
| Platelet production decreased | 10035540 |
| Platelet toxicity | 10059440 |
| Thrombocytopenia | 10043554 |
| Febrile neutropenia | 10016288 |
| Neutropenia | 10029354 |
| Neutrophil count decreased | 10029366 |
| Agranulocytosis | 10001507 |
| Autoimmune neutropenia | 10055128 |
| Transfusion related alloimmune neutropenia | 10081503 |
| Granulocytopenia | 10018687 |
| Idiopathic neutropenia | 10051645 |
| Neutropenic colitis | 10062959 |
| Neutropenic infection | 10059482 |
| Neutropenic sepsis | 10049151 |
| Neutrophil count abnormal | 10061313 |
| Band neutrophil count decreased | 10057950 |
| Band neutrophil percentage decreased | 10059130 |
| Neutrophil percentage abnormal | 10058134 |
| Neutrophil percentage decreased | 10052223 |
| Granulocyte count decreased | 10018681 |
| Granulocytes abnormal | 10018685 |
| Anaemia macrocytic | 10002064 |
| Aplasia pure red cell | 10002965 |
| Aplastic anaemia | 10002967 |
| Erythroblast count decreased | 10058505 |

| MEDDRA Preferred Term | PT Code |
|---|---|
| Erythroid maturation arrest | 10015279 |
| Erythropenia | 10015287 |
| Hypoplastic anaemia | 10021074 |
| Microcytic anaemia | 10027538 |
| Proerythroblast count decreased | 10060229 |
| Red blood cell count decreased | 10038153 |
| Reticulocyte count decreased | 10038790 |
| Reticulocytopenia | 10038795 |
| Anaemia | 10002034 |
| Anaemia neonatal | 10002068 |
| Erythroblast count abnormal | 10058508 |
| Erythropoiesis abnormal | 10049467 |
| Foetal anaemia | 10077577 |
| Haematocrit abnormal | 10049221 |
| Haematocrit decreased | 10018838 |
| Haemoglobin abnormal | 10018879 |
| Haemoglobin decreased | 10018884 |
| Leukoerythroblastic anaemia | 10053199 |
| Normochromic anaemia | 10029782 |
| Normochromic normocytic anaemia | 10029783 |
| Normocytic anaemia | 10029784 |
| Proerythroblast count abnormal | 10060227 |
| Red blood cell count abnormal | 10038151 |
| Reticulocyte count abnormal | 10038788 |
| Reticulocyte percentage decreased | 10059921 |
| Autoimmune aplastic anaemia | 10071576 |
| Bicytopenia | 10058956 |
| Bone marrow failure | 10065553 |
| Cytopenia | 10066274 |
| Febrile bone marrow aplasia | 10053213 |
| Full blood count decreased | 10017413 |

| MEDDRA Preferred Term | PT Code |
|---|---|
| Gelatinous transformation of the bone marrow | 10078097 |
| Pancytopenia | 10033661 |
| Panmyelopathy | 10050026 |

### Appendix 7. Cardiac arrhythmia Medical Search Term

Note: The list presented below is based on MedDRA Version 22.0. The actual list will be up-versioned to the MedDRA version used at the time of database finalization.

| MEDDRA Preferred Term | PT Code | MEDDRA Preferred Term | PT Code |
|---|---|---|---|
| Accelerated idioventricular rhythm | 10049003 | Cardiac fibrillation | 10061592 |
| Neonatal bradyarrhythmia | 10082054 | Cardiac flutter | 10052840 |
| Neonatal tachyarrhythmia | 10082055 | Chronotropic incompetence | 10068627 |
| Congenital supraventricular tachycardia | 10082343 | Conduction disorder | 10010276 |
| Frederick's syndrome | 10082089 | Defect conduction intraventricular | 10012118 |
| Accessory cardiac pathway | 10067618 | Electrocardiogram delta waves abnormal | 10014372 |
| Adams Stokes syndrome | 10001115 | Electrocardiogram PQ interval prolonged | 10053656 |
| Agonal rhythm | 10054015 | Electrocardiogram PQ interval shortened | 10075328 |
| Anomalous atrioventricular excitation | 10002611 | Electrocardiogram PR prolongation | 10053657 |
| Arrhythmia | 10003119 | Electrocardiogram PR shortened | 10014374 |
| Arrhythmia neonatal | 10003124 | Electrocardiogram QRS complex prolonged | 10014380 |
| Arrhythmia supraventricular | 10003130 | Electrocardiogram QT prolonged | 10014387 |
| Arrhythmogenic right ventricular dysplasia | 10058093 | Electrocardiogram repolarisation abnormality | 10052464 |
| Atrial conduction time prolongation | 10064191 | Electrocardiogram U wave present | 10057913 |
| Atrial fibrillation | 10003658 | Electrocardiogram U wave inversion | 10062314 |
| Atrial flutter | 10003662 | Electrocardiogram RR interval prolonged | 10067652 |
| Atrial parasystole | 10071666 | Electrocardiogram U wave abnormality | 10055032 |
| Atrial tachycardia | 10003668 | Extrasystoles | 10015856 |
| Atrioventricular block | 10003671 | Foetal arrhythmia | 10016847 |
| Atrioventricular block complete | 10003673 | Foetal heart rate disorder | 10061158 |
| Atrioventricular block first degree | 10003674 | Foetal tachyarrhythmia | 10077575 |
| Atrioventricular block second degree | 10003677 | Heart alternation | 10058155 |
| Atrioventricular conduction time shortened | 10068180 | Heart block congenital | 10019263 |
| Atrioventricular dissociation | 10069571 | Heart rate irregular | 10019304 |
| Atrioventricular node dispersion | 10077893 | Junctional ectopic tachycardia | 10074640 |
| Bifascicular block | 10057393 | Lenegre's disease | 10071710 |
| Bradyarrhythmia | 10049765 | Long QT syndrome | 10024803 |
| Brugada syndrome | 10059027 | Long QT syndrome congenital | 10057926 |
| Bundle branch block | 10006578 | Lown Ganong Levine syndrome | 10024984 |
| Bundle branch block bilateral | 10006579 | Nodal arrhythmia | 10029458 |
| Bundle branch block left | 10006580 | | |
| Bundle branch block right | 10006582 | | |

| MEDDRA Preferred Term | PT Code |
|---|---|
| Nodal rhythm | 10029470 |
| Pacemaker generated arrhythmia | 10053486 |
| Pacemaker syndrome | 10051994 |
| Parasystole | 10033929 |
| Paroxysmal arrhythmia | 10050106 |
| Paroxysmal atrioventricular block | 10077503 |
| Pulseless electrical activity | 10058151 |
| Reperfusion arrhythmia | 10058156 |
| Rhythm idioventricular | 10039111 |
| Sinoatrial block | 10040736 |
| Sinus arrest | 10040738 |
| Sinus arrhythmia | 10040739 |
| Sinus bradycardia | 10040741 |
| Sinus node dysfunction | 10075889 |
| Sinus tachycardia | 10040752 |
| Sudden cardiac death | 10049418 |
| Supraventricular extrasystoles | 10042602 |
| Supraventricular tachyarrhythmia | 10065342 |
| Supraventricular tachycardia | 10042604 |
| Tachyarrhythmia | 10049447 |
| Torsade de pointes | 10044066 |
| Trifascicular block | 10044644 |
| Ventricular arrhythmia | 10047281 |
| Ventricular asystole | 10047284 |
| Ventricular dyssynchrony | 10071186 |
| Ventricular extrasystoles | 10047289 |
| Ventricular fibrillation | 10047290 |
| Ventricular flutter | 10047294 |
| Ventricular parasystole | 10058184 |
| Ventricular pre excitation | 10049761 |
| Ventricular tachyarrhythmia | 10065341 |
| Ventricular tachycardia | 10047302 |
| Wandering pacemaker | 10047818 |
| Withdrawal arrhythmia | 10047997 |
| Wolff Parkinson White syndrome | 10048015 |

| MEDDRA Preferred Term | PT Code |
|---|---|
| Wolff Parkinson White syndrome congenital | 10049291 |
| Bradycardia | 10006093 |

## Appendix 8.          Rash Medical Search Term

Note: The list presented below is based on MedDRA Version 22.0. The actual list will be up-versioned to the MedDRA version used at the time of database finalization.

| MedDRA Preferred Term | PT Code |
|---|---|
| Acute generalised exanthematous pustulosis | 10048799 |
| Angina bullosa haemorrhagica | 10064223 |
| Autoimmune dermatitis | 10075689 |
| Blister | 10005191 |
| Blister rupture | 10073385 |
| Butterfly rash | 10067982 |
| Cervical bulla | 10050019 |
| Dermatitis exfoliative | 10012455 |
| Dermatitis exfoliative generalised | 10012456 |
| Dermatosis | 10048768 |
| Drug eruption | 10013687 |
| Drug reaction with eosinophilia and systemic symptoms | 10073508 |
| Eosinophilic pustular folliculitis | 10052834 |
| Epidermolysis | 10053177 |
| Epidermolysis bullosa | 10014989 |
| Eruptive pseudoangiomatosis | 10068095 |
| Erythema multiforme | 10015218 |
| Erythema nodosum | 10015226 |
| Erythrosis | 10056474 |
| Exfoliative rash | 10064579 |
| Fixed eruption | 10016741 |
| Flagellate dermatitis | 10075467 |
| Interstitial granulomatous dermatitis | 10067972 |
| Lichenoid keratosis | 10064000 |
| Macule | 10025421 |
| Mucocutaneous rash | 10056671 |
| Mucocutaneous ulceration | 10028084 |
| Mucosa vesicle | 10028103 |
| Necrolytic migratory erythema | 10060821 |
| Neurodermatitis | 10029263 |

| MedDRA Preferred Term | PT Code |
|---|---|
| Oculomucocutaneous syndrome | 10030081 |
| Oral mucosal blistering | 10030995 |
| Oropharyngeal blistering | 10067950 |
| Palmar plantar erythrodysaesthesia syndrome | 10033553 |
| Palmoplantar pustulosis | 10050185 |
| Palpable purpura | 10056872 |
| Papule | 10033733 |
| Paraneoplastic rash | 10074687 |
| Pemphigoid | 10034277 |
| Pemphigus | 10034280 |
| Penile blister | 10052898 |
| Prurigo | 10037083 |
| Rash | 10037844 |
| Rash erythematous | 10037855 |
| Rash follicular | 10037857 |
| Rash generalised | 10037858 |
| Rash macular | 10037867 |
| Rash maculo papular | 10037868 |
| Rash maculovesicular | 10050004 |
| Rash morbilliform | 10037870 |
| Rash papular | 10037876 |
| Rash papulosquamous | 10037879 |
| Rash pruritic | 10037884 |
| Rash pustular | 10037888 |
| Rash rubelliform | 10057984 |
| Rash scarlatiniform | 10037890 |
| Rash vesicular | 10037898 |
| Seborrhoeic dermatitis | 10039793 |
| Skin disorder | 10040831 |
| Skin plaque | 10067723 |
| Skin reaction | 10040914 |

| MedDRA Preferred Term | PT Code |
|---|---|
| Skin toxicity | 10059516 |
| Stevens Johnson syndrome | 10042033 |
| Symmetrical drug related intertriginous and flexural exanthema | 10078325 |
| Toxic epidermal necrolysis | 10044223 |
| Toxic erythema of chemotherapy | 10074982 |
| Toxic skin eruption | 10057970 |
| Umbilical erythema | 10055029 |
| Urticarial vasculitis | 10048820 |
| Vaginal exfoliation | 10064483 |
| Vasculitic rash | 10047111 |
| Viral rash | 10047476 |
| Skin lesion inflammation | 10081154 |
| Target skin lesion | 10081998 |
| Plethoric face | 10081808 |
| Vulvovaginal rash | 10071588 |

## Appendix 9.            List of Laboratory Tests for Safety Summary

| Serum Chemistry | Hematology |
| --- | --- |
| Sodium<br>Potassium<br>Chloride<br>Glucose<br>Blood urea nitrogen or urea<br>Creatinine[a]<br>ALT<br>AST<br>GGT<br>Cholesterol<br>Triglycerides<br>Uric Acid<br>Alkaline phosphatase<br>Total and direct bilirubin<br>Total protein<br>Albumin<br>Calcium<br>Magnesium<br>Phosphate<br>LDH<br>Amylase<br>Lipase | WBC<br>RBC<br>Hemoglobin<br>Hematocrit<br>Platelet Count<br>Neutrophils (ANC)<br>Lymphocytes<br>Monocytes<br>Basophils<br>Eosinophils |
| | **Coagulation** |
| | PT/INR<br>aPTT |

a    Estimated creatinine clearance/glomerular filtration rate will be calculated based on the Cockroft Gault formula
ALT    alanine aminotransferase; aPTT    activated partial thromboplastin time; AST    aspartate aminotransferase; BUN    blood urea nitrogen; GGT    gamma glutamyltransferase; INR    international normalized ratio; LDH    lactate dehydrogenase; PT    prothrombin time; RBC    red blood cell; WBC    white blood cell

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| PPD | Clinical Research eSigned | 19-Jan-2021 18:42:16 |