Non-Interventional Study Protocol
< B1931027>

Korean Post Marketing Surveillance study to observe safety and effectiveness of BESPONSA®

Statistical Analysis Plan
(SAP)

Version: 2.0

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

- Rationale and Background is updated according to protocol amendment 4.
- CCI
- Analysis about best overall response is added to Effectiveness analyses section.
- Analysis for publication is added to effectiveness analyses section.

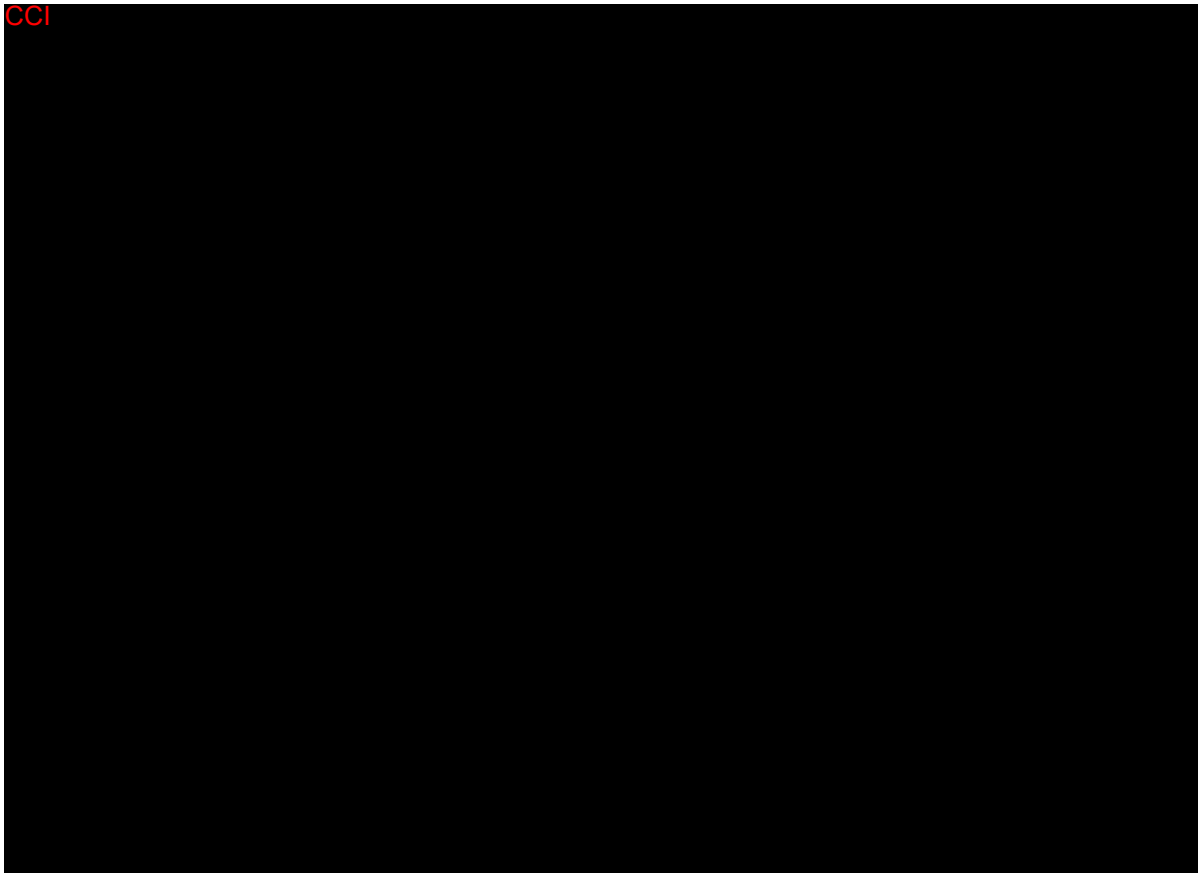
2. INTRODUCTION

Note: in this document, any text taken directly from the non-interventional (NI) study protocol is ***italicised***.

Rationale and Background

Acute lymphoblastic leukemia (ALL) is a rare, serious, and life-threatening condition with a need for improved therapies. Relapsed or refractory B-cell ALL is a fatal disease with a median survival time in adults of only approximately 3-6 months. The age adjusted incidence rate of ALL in the United States is 1.7 per 100,000 individuals per year, with approximately 6,020 new cases and 1,440 deaths estimated in 2014. While the cure rates and survival outcomes for B-cell ALL have improved during the last several decades, most of the improvements have occurred in younger patients, primarily among children. Recent improvements are largely due to advances in the understanding of the molecular genetics and pathogenesis of B-cell ALL, incorporation of risk-adapted therapy and the advent of targeted agents.

CCI



CCI [redacted]

Before the approval of BESPONSA® in Korea, this non-interventional study is designated as a Post-Marketing Surveillance (PMS) Study and is a commitment to Ministry of Food and Drug Safety (MFDS), as a part of Risk Management Plan (RMP) which is required by MFDS. The safety and effectiveness information of BESPONSA® will be gathered at minimum 100 subjects administered in the setting of routine practice in Korea during the initial 6 years after the approval.

2.1 STUDY DESIGN

This is a prospective, observational, non-interventional, multi-center study in which subjects will be administered as part of routine practice at Korean health care centers by accredited physicians. The study can be performed in Korean health care centers where BESPONSA® is prescribed to treat the relapsed or refractory B-cell precursor ALL.

All subjects enrolled should meet the usual prescribing criteria for BESPONSA® as per the local product document (LPD) and should be entered into the study at the physician's discretion.

Duration of the Study

According to MFDS re-examination regulation, the re-examination report based on collected data of 6 years must be submitted to MFDS within 3 months after the end of specified re-examination period (from the product approval date to 6 years afterwards).

The data collection period of this study is until the required subject number (100 patients) is collected. The observation period for each subject is from initiating administration of first dose of BESPONSA® to the end of the observation period of the study, which must include at least 28 calendar days following the last administration of a BESPONSA®. In case of patient that Hematopoietic Stem Cell Transplant (HSCT) after administrated BESPONSA®, follow-up until 180 days after transplantation. All the data collected during the observation period should be recorded in the case report form (CRF). In case of an adverse event/safety event recognized after the observation period ends, it should be recorded in the CRF.

Sample Size

CCI [redacted]

CCI *100 subjects will be collected during re-examination period.* CCI [redacted]

2.2 STUDY OBJECTIVES

The objectives of this study are to determine any problems or questions associated with BESPONSA® after marketing, with regard to the following clauses under conditions of general clinical practice, in compliance with the regulation "Re-examination Guideline of

New Drugs, Etc" (Ministry of Food and Drug Safety Notification 2015-79, 2015.10.30, amended).

1. *Serious adverse event/adverse drug reaction*
2. *Unexpected adverse event/adverse drug reaction that has not been reflected in the approved drug label.*
3. *Known adverse drug reaction*
4. *Non-serious adverse drug reaction*
5. *Other safety and effectiveness information*

3. INTERIM ANALYSES

As required by MFDS regulations, the periodic interim report along with RMP report would be submitted to MFDS every 6 months for the first two years and then annual report would be submitted to MFDS for the third, fourth and fifth year. The final report would be submitted in the sixth year refer to RMP milestone.
All data collected will be integrated and reported in the sixth re-examination report.

Periodic report	Surveillance period	MFDS Submission Timeline
1-1st	2019-01-03 ~ 2019-07-02	2019-09-02
1-2nd	2019-07-03 ~ 2020-01-02	2020-03-02
2-1st	2020-01-03 ~ 2020-07-02	2020-09-02
2-2nd	2020-07-03 ~ 2021-01-02	2021-03-02
3rd	2021-01-03 ~ 2022-01-02	2022-03-02
4th	2022-01-03 ~ 2023-01-02	2023-03-02
5th	2023-01-03 ~ 2024-01-02	2024-03-02
Re-examination report	2024-01-03 ~ 2025-01-02	2025-04-02

4. HYPOTHESES AND DECISION RULES

There is no formal research hypothesis for this study. The purpose of the study is to assess real-life safety and effectiveness of BESPONSA® in Korean adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) using the descriptive statistics. For the exploratory analysis, statistical tests may be performed. P-values may be provided, but no definite conclusions will be made based on p-values and no adjustments for multiplicity will be applied.

5. ANALYSIS SETS/POPULATIONS

The study requires enrolling patients aged 19 years or older who are diagnosed with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) and meet all the following inclusion and exclusion criteria.

Inclusion criteria:

1. *Patients diagnosed as relapsed or refractory B-cell precursor lymphoblastic leukemia (ALL).*

2. *Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.*

Exclusion criteria:

1. *Any patients who does not agree that Pfizer and companies working with Pfizer use his/her information.*
2. *Patients to whom BESPONSA® is contraindicated as per the local labeling.*

5.1 SAFETY ANALYSIS SET

The safety analysis set includes patients who have been administered BESPONSA® at least once and evaluated with safety-related endpoints at least once.

Patients meeting any of the following criteria will be excluded in the safety analysis set.

1. Patients who received BESPONSA® prior to site initiating contract date
2. Patients who didn't receive BESPONSA®
3. Safety follow-up failure: Patients without documented evidence for whom adverse event status was evaluated(Patients with "Whether AE status was evaluated" checked as No in the eCRF OR no answer is provided to question "Whether a patient has AE" in the eCRF)
4. Patients who violated inclusion/exclusion criteria
5. Patients who violated usage
6. Patients who have enrolled twice or more (i.e. if a patient has been assigned to two or more subject ID or CRFs, only one record clarified by site will be used for analysis and the others will be excluded)

5.2 EFFECTIVENESS ANALYSIS SET

The effectiveness analysis set includes patients who have been administered BESPONSA® at least once and evaluated based upon effectiveness endpoints.

Patients meeting any of the following criteria will be excluded in the effectiveness analysis set.

1. Patients who are not included in safety analysis set
2. Patients who do not have any response evaluation

5.3 SPECIAL POPULATION SET

Patients who are included in safety analysis set or effectiveness analysis set will be categorized into the following special population set.

1. Elderly (≥65 years)
2. Hepatic disorder
3. Renal disorder

5.4 NON-SAFETY POPULATION SET

If patients excluded from safety analysis are collected, such as in off-label use cases, these patients are classified as non-safety population set and any adverse events occurring during the PMS period shall be additionally checked or separately analyzed as the per needed.

6. ENDPOINTS AND COVARIATES

6.1 SAFETY ENDPOINTS

- Adverse event, serious adverse event, adverse drug reaction or unexpected adverse event

6.2 EFFECTIVENESS ENDPOINTS

- Response evaluations at each cycle and the final evaluation:
  CR | CRi | Refractory disease | Progressive disease | Relapsed disease
- Last effectiveness†:
  †: Based on 'final effectiveness evaluation' or 'last cycle response evaluation(if the final evaluation is missing)'
  Effective (CR, CRi) |
  Ineffective (Refractory disease, Progressive disease, Relapsed disease)

6.3 OTHER ENDPOINTS

Not Applicable

6.4 COVARIATES

The demographics and baseline characteristics listed in section 8.2.1 could be considered as covariates to identify the factors that may affect safety or effectiveness.

7. HANDLING OF MISSING VALUES

There are no plans for imputation of missing values for variables; all missing values will be excluded from corresponding analyses. The impact of missing data will be evaluated as appropriate.
However, if the causality of the study drug on adverse event is missing, it will be considered 'related' and classified as adverse drug reaction(ADR).

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1 STATISTICAL METHODS

The analysis of this study is primarily descriptive. Data shall be presented by following unless otherwise specified.

8.1.1 Analysis for Continuous Data

The continuous variables will be summarized using the following parameters.

- Number of subjects(n)
- Mean±Standard deviation (Mean±SD)
- Median
- Minimum and Maximum (Min, Max)

8.1.2 Analysis for Categorical Data

The categorical data will be summarized using the following parameters.

- Number of subjects(n)
- Percentage (%)
- 95% Confidence Interval (If applicable)
- Events (Events, If applicable)

8.1.3 Presentation of Statistics

The number of decimal places displayed in effectiveness and safety listings will be determined by the number of decimal places in the raw data.

- All calculated values will be rounded to two decimal places.
- A p-value will be displayed to four decimal places. If a p-value is less than 0.0001, it will be displayed as '<0.0001'.
- Unless otherwise specified, 95% confidence intervals will be calculated using the exact binomial distribution according to Clopper-Pearson's method.

8.1.4 Factorial Analyses

In order to explore the factors associated with the patient's safety and effectiveness profiles, the incidence proportion of AEs and last effectiveness rate will be analyzed by demographics and baseline characteristics factors. The Chi-square test or Fisher's exact test (depending on data counts as appropriate) will be used first to assess the impact for each background factor, and p-value will be outputted. The potentially important factors identified by Chi-square or Fisher's exact test p-values at 0.05 level will be further pooled and tested in a multivariate logistic regression model.

8.2 STATISTICAL ANALYSES

8.2.1 Demographics and baseline characteristics

8.2.1.1 Demographics and underlying disease information

- Age(years)
- Elderly(≥65 years)
- Gender: Male | Female
- Height(cm)
- Weight(kg)
- Body Surface Area(m^2, Mosteller formula)

$$= \sqrt{\frac{W \times H}{3600}} = 0.016667 \times W^{0.5} \times H^{0.5}$$

- Pregnancy: Yes | No | NA
- Breast-feeding: Yes | No | NA
- Diagnosis:

Philadelphia (+) B-cell ALL | Philadelphia (-) B-cell ALL | Unknown

- Duration of disease(day):
  BESPONSA® administration start date – First diagnosis date + 1
- Current disease status:
  Refractory | First relapsed | Second relapsed | Third or more relapsed
- Hepatic disorder: Yes | No
- Renal disorder: Yes | No

8.2.1.2 Prior treatment history of B-cell precursor lymphoblastic leukemia

All treatment drugs used in previous systemic therapy shall be divided by the order of regimen and summarized using frequency and percentage by ATC code level 1 and level 4.

- Previous systemic therapy: Yes | No | Unknown
- Number of previous systemic therapies:
  One | Two | Three | Four | More than five
- Previous hematopoietic cell transplant: Yes | No | Unknown

8.2.1.3 Medical History

All medical history shall be classified as either past or present disease based on the first BESPONSA® administration date and shall be summarized using frequency and percentage by System Organ Class(SOC) and Preferred Term (PT) of MedDRA version 22.1(or the latest version at the time of analysis).

- Past disease: Yes | No
- Present disease: Yes | No
- Veno-occlusive liver disease/Sinusoidal obstruction syndrome(VOD/SOS): Yes | No
- Hepatic disorder : Yes | No
- Severity of hepatic disorder: Mild | Moderate | Severe | Unknown
- Renal disorder: Yes | No
- Severity of renal disorder: Mild | Moderate | Severe | Unknown
- Allergic history: Yes | No

8.2.1.4 Concomitant Medication

All concomitant medication including the transfusion while BESPONSA® is being administrated shall be summarized using frequency and percentage by ATC code level 1 and level 3.

- Concomitant medication: Yes | No

8.2.1.5 Administration status of BESPONSA®

- BESPONSA® total administration period(day):
  Last administration date of last cycle – First administration date of first cycle + 1
- Total administration cycle:
  Cycle 1 | Cycle2 | Cycle3 | Cycle 4 | Cycle 5 | Cycle 6
- Total administration dose(mg)
- Administration dose(mg) per cycle

8.2.2 Safety Analyses

The safety analyses will be performed for Safety analysis set. And all adverse events (AE) will be standardized by MedDRA version 22.1 (or the latest version at the time of analysis).

Adverse events which causality is missing or not 'unlikely' will be considered as adverse drug reaction (ADR).

8.2.2.1 Adverse event

The following adverse events shall be summarized by SOC and PT using the number of subjects(n), percentage (%), number of events, and 95% confidence interval of percentage.

- AE·ADR
- Serious AE·ADR
- Unexpected AE·ADR
- Unexpected serious AE·ADR

The following characteristics of adverse events shall be summarized by SOC and PT using the number of event and percentage(%).
If missing is found, the number of event and percentage(%) of missing will be presented at the bottom of each characteristics.

- Severity: G1 | G2 | G3 | G4 | G5
- Action:
  Withdrawn (temporarily or permanently, or delayed) | Dose reduced | Dose increased | Dose not changed | Unknown | Not applicable
- SAE Category:
  Results in death | Is life-threatening |
  Requires inpatient hospitalization or prolongation of hospitalization |
  Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions) |

Results in congenital anomaly/birth defect |
Is important medical event (if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above)

- Outcome:
  Recovered | Recovered with sequelae |
  Recovering | Not recovered | Unknown
- Causality of AE to the study drug:
  Certain | Probable/likely | Possible | Unlikely |
  Conditional/unclassified | Unassessable/unclassifiable
- Other causality of AE:
  Disease under the study | Other disease |
  Concomitant treatment drug or non-drug | Others

8.2.2.2 Factor analysis for adverse events

To identify factors that may be associated with AEs, AEs according to the background factors in section 8.2.1 and special population set in section 5.3 shall be summarized using the number of subjects(n), percentage(%), number of events and the 95% confidence interval of percentage. In addition, to explore the factors that affect the occurrence of AE, univariate analyses based on a Chi-square test or Fisher's exact test(when cells with an expected frequency of less than 5 exceed 20% of total cells) and logistic regression shall be used to assess the impact of each background factor on the AE occurrence and p-value will be provided.

For the final re-examination report, potentially significant factors(p-value<0.05) identified in the univariate analyses will be further explored in a multiple logistic regression model. For final models, odds ratio, 95% confidence interval of odds ratio and p-value will be provided for each factor. If there is no potential significant factor identified in the univariate analyses, multivariate analysis with logistic regression will not be applied.

8.2.2.3 Adverse event in special population set

Adverse events reported from special population set in section 5.3 shall be summarized by SOC and PT using the number of subjects(n), percentage(%), number of events and 95% confidence interval of percentage.

8.2.3 Effectiveness Analyses

The effectiveness analyses will be performed for Effectiveness analysis set.

8.2.3.1 Response evaluations

The following response evaluations after each cycle and the final effectiveness evaluation shall be summarized using the number of subjects(n) and percentage (%).

- Response:
  CR | CRi | Refractory disease | Progressive disease | Relapsed disease
- Effective: CR, CRi
- Ineffective: Refractory disease, Progressive disease, Relapsed disease

8.2.3.2 Last effectiveness

In order to identify last effectiveness of BESPONSA®, the 'effectiveness' is judged as follows based on the final effectiveness evaluation or the last cycle response evaluation(if the final evaluation is missing) and summarized by the number of subjects(n), percentage(%) and 95% confidence interval of percentage.

- Effective: CR, CRi
- Ineffective: Refractory disease, Progressive disease, Relapsed disease

8.2.3.3 Factor analysis of last effectiveness

To identify factors that may be associated with last effectiveness, last effectiveness according to the background factors in section 8.2.1 and special population set in section 5.3 shall be summarized using the number of subjects(n), percentage(%) and 95% confidence interval of percentage. In addition, to explore the factors that affect last effectiveness, univariate analyses based on a Chi-square test or Fisher's exact test (when cells with an expected frequency of less than 5 exceed 20% of total cells) and logistic regression shall be used to assess the impact of each background factor on the last effectiveness and p-value will be provided.

For the final re-examination report, potentially significant factors(p-value<0.05) identified by in the univariate analyses will be further explored and tested in a multiple logistic regression model. For final models, odds ratio, 95% confidence interval of odds ratio and p-value will be provided for each factor. If there is no potential significant factor identified in the univariate analyses, multivariate analysis with logistic regression will not be applied.

8.2.3.4 Last effectiveness for special population set

The last effectiveness analysis for special population set is included as factor analysis of last effectiveness in this SAP 8.2.3.3.

8.2.3.5 Effectiveness(Best overall response)

In order to identify effectiveness (best overall response) of BESPONSA®, the 'effectiveness' is judged as follows based on the best overall response during evaluation and summarized by the number of subjects(n), percentage(%) and 95% confidence interval of percentage.

- Effective: CR, CRi
- Ineffective: Refractory disease, Progressive disease, Relapsed disease

8.2.3.6 Factor analysis of effectiveness based on best overall response

To identify factors that may be associated with effectiveness based on best overall response, effectiveness according to the background factors in section 8.2.1 and special population set in section 5.3 shall be summarized using the number of subjects(n), percentage(%) and 95% confidence interval of percentage. In addition, to explore the factors that affect effectiveness, univariate analyses based on a Chi-square test or Fisher's exact test (when cells with an expected frequency of less than 5 exceed 20% of total cells) and logistic regression shall be used to assess the impact of each background factor on the effectiveness and p-value will be provided.

For the final re-examination report, potentially significant factors(p-value<0.05) identified by in the univariate analyses will be further explored and tested in a multiple logistic regression model. For final models, odds ratio, 95% confidence interval of odds ratio and p-value will be provided for each factor. If there is no potential significant factor identified in the univariate analyses, multivariate analysis with logistic regression will not be applied.

8.2.3.7 Effectiveness(Best overall response) for special population set

The effectiveness(best overall response) analysis for special population set is included as factor analysis of effectiveness in this SAP 8.2.3.6.

The following clauses from 8.2.3.8 to 8.2.3.10 are analysed to prepare a manuscript for publication.

8.2.3.5 Progression-free survival (PFS)

PFS is defined as time from date of enrollment to earliest date of the following events:

- Death
- Refractory disease
- Progressive disease
- Relapsed disease

Subjects without a PFS event at time of analysis will be censored at the last valid disease assessment. In addition, subjects with documentation of an event after an unacceptably long interval (>28 weeks if there was post-baseline disease assessment, or >12 weeks if there was no post-baseline assessment) since the previous disease assessment will be censored at the time of the previous assessment (date of enrollment if no post-baseline assessment). Post-study treatment follow-up disease assessments will be included.

8.2.3.6 Overall Survival (OS)

OS is defined as the time from date of enrollment to death due to any cause. For patients last known to be alive, OS will be censored at date of completion/discontinuation.

8.2.3.7 Duration of Remission (DoR)

DoR is defined as time from date of first response in responders (CR/CRi by investigator assessment) to date of PFS event (see definition of PFS above). Responders without PFS event will be censored at the last valid disease assessment including follow-up disease assessment.

8.2.4 Non-safety population Analyses

The following adverse events from non-safety population shall be summarized by SOC and PT using the number of subjects(n), percentage(%), number of events and 95% confidence interval of percentage.

- AE·ADR
- Serious AE·ADR
- Unexpected AE·ADR
- Unexpected serious AE·ADR

8.2.5 Non-PMS Analyses

Adverse events which were reported spontaneously or collected from other clinical studies or articles shall be summarized using the number of events by PT of MedDRA version 22.1(or the latest version at the time of analysis).

- AE·ADR
- Serious AE·ADR
- Unexpected AE·ADR

- Unexpected serious AE·ADR

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10. REFERENCES

- <B1931027> Non-interventional study protocol, Amendment 4
- Ministry of Food and Drug Safety, *Re-examination Guideline of New Drugs, Etc (2020-12, 2020.12.22, amended)*