BESPONSA® Injection 1 mg Special Investigation

FULL PROTOCOL

Pfizer Japan Inc.

STUDY INFORMATION

Title	BESPONSA® Injection 1 mg Special Investigation
Protocol number	B1931024
Protocol version identifier	Amended 8
Date	12 December 2023
Active substance	Inotuzumab ozogamicin (genetical recombination)
Medicinal product	BESPONSA® Injection 1 mg
Research question and objectives	The following matters will be investigated in patients receiving BESPONSA under actual conditions of use after marketing: ① Occurrence of adverse events (AEs) (including the following evaluations):Background characteristics possibly affecting the onset of liver disorder including venoocclusive liver disease (VOD)/sinusoidal obstruction syndrome (SOS), myelosuppression, infections and haemorrhage, and grade ≥3 events based on the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 as well as risk factors for early death of hematopoietic stem cell transplant (HSCT) patients after BESPONSA treatment Efficacy (hematologic remission rate and survival)
Author	PPD PPD

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
ALL	acute lymphocytic leukemia
ALT	alanine aminotransferase
AL-P	alkaline phosphatase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CNS	central nervous system
CR	complete remission
CRF	case report form
CRi	complete remission with incomplete count recovery
CTCAE	Common Terminology Criteria for Adverse Events
EC	ethics committee
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EDP	exposure during pregnancy
γ-GTP	gamma glutamyl transpeptidase
GOT	glutamic oxaloacetic transaminase
GPT	glutamic pyruvic transaminase
GVHD	graft versus host disease
HSCT	hematopoietic stem cell transplant
IRB	institutional review board
MHLW	Ministry of Health, Labour and Welfare
MRD	minimal residual disease
NIS	non-interventional study
PMDA	Pharmaceuticals and Medical Devices Agency
SAE	serious adverse event
SAP	statistical analysis plan
SOS	sinusoidal obstruction syndrome
ULN	upper limit of normal
VOD	venoocclusive disease
WHO	World Health Organization

3. RESPONSIBLE PARTIES

The Japan Good Post-marketing Study Practice officer

4. AMENDMENTS AND UPDATES

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
Amended 8	12 December 2023	Administrative revision	AMENDMENTS AND UPDATES	Addition of "Type of revision"	Change associated with the revision of the internal formats, amendment of the protocol
			LIST OF ABBREVIATIONS	Adjustment of description	Change associated with the revision of the internal formats
		Substantial revision	Planned Study Period	Change of the registration period	Because registration not necessitating creation of CRFs is terminated based on Q&A5 of Administrative Notice dated 10 August 2023.
			Study Method	Correction of description about "registration-only investigation"	
			Patient Registration	Deletion of description about "registration-only investigation"	
		Administrative revision	PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS	Adjustment of description	Change associated with the revision of the internal formats
			NAME, ADDRESS, AND OUTSOURCED OPERATIONS OF THE PERSON WHO WAS CONTRACTED WITH THE OPERATIONS	Addition of A2 Healthcare Corporation	Change of the outsource of EDC account management activities
Amended 7	11 November 2022	Administrative revision	Study information	Change from "Date of last version of protocol" to "Date of creation" Change of the division name of the author	Change associated with the revision of the internal formats, change of the organization
			LIST OF ABBREVIATIONS	Addition of items, adjustment of description	Change associated with the revision of the internal formats
			RESPONSIBLE PARTIES	Deletion of "Clinical Lead (group head)"	Change associated with the revision of the internal formats, amendment of the protocol
			AMENDMENTS AND UPDATES	Deletion of "Amendment of the	Change associated with the revision of the internal formats,

				Plan/Others," addition of the amendment	amendment of the protocol
			MILESTONES	Addition of items, postponement of the date of final report preparation	Change associated with the revision of the internal formats, delay of the investigation
			Data analysis Limitations of the research methods PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS	Adjustment of description	Change associated with the revision of the internal formats
			MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE DRUG REACTIONS	Change of terms, adjustment of description	Change associated with the revision of the internal formats
			COMMUNICATION OF ISSUES ORGANIZATIONAL SYSTEM FOR STUDY IMPLEMENTATION	Deletion	Change associated with the revision of the internal formats
			NAME, ADDRESS AND OUTSOURCED OPERATIONS OF THE PERSON WHO WAS CONTRACTED WITH THE OPERATIONS	Addition of "Monitoring" to Pfizer R&D Japan G.K.	Expansion of the scope of outsourcing
			CONTACT INFORMATION	Changes of the organization name of Pfizer R&D Japan G.K. and the name, telephone number, and e-mail address of the contact information for the EDC system	Change of the organization, change of the contact information for the EDC system
Amended 6.1	8 June 2022	Administrative revision	Cover page	Change of the company logo	Change of the logo
Amended 6	22 April 2020	Substantial revision	Duration of study	Change of the registration period	Moving on to a patient registration-only investigation
			Study procedures	Description of the moving on to a patient registration-only investigation	
			Observation period	Description of a patient from whom data should be	

				collected to the extent possible at the medical institution to which the patient has been transferred	
			Patient registration	Addition of the description of the moving on to a patient registration-only investigation	
Amended 5	22 May 2019	Administrative revision	Data management	Addition of the "Case report forms/Electronic data records" and "Record retention" sections	Change associated with the revision of the internal formats
			PROTECTION OF HUMAN SUBJECTS	Changes to the "Patient information," "Patient consent," and "Ethical conduct of the study" sections	
			Adverse events	Correction of description	
			Single reference safety document	Deletion	
			CONTACT INFORMATION	Change of the e-mail address in "the contact information for the EDC system"	Change of the e-mail address
			Overall	Unification of "Pfizer Japan Inc." to "Pfizer"	Unification of the term
Amended 4	1 December 2018	Administrative revision	NAME, ADDRESS, AND OUTSOURCED OPERATIONS OF THE PERSON WHO WAS CONTRACTED WITH THE OPERATIONS	Addition of Pfizer R&D Japan G.K.	Establishment of Pfizer R&D Japan G.K.
			CONTACT INFORMATION	Change of the name of the contact information for the contents of the study to "Pfizer R&D Japan G.K."	
Amended 3	25 May 2018	Administrative revision	Variables	Correction of errors in writing, adjustment of description	Errors in writing
			MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE DRUG REACTIONS	Adjustment of description	Accurate definition of the reporting period, reflection of the internal formats

Amended 2	29 March 2018	Administrative revision	NAME, ADDRESS, AND OUTSOURCED OPERATIONS OF THE PERSON WHO WAS CONTRACTED WITH THE OPERATIONS	Addition of EPS Corporation and Medidata Solutions K.K.	Determination of the contractors
			CONTACT INFORMATION	Addition of the contact information for the contents of the study and the contact information for the EDC system	Determination of the contact information
			Overall	Adjustment of description	Adjustment of description
Amended 1	14 March 2018	Substantial revision	Variables	(1) Background: Addition of "Date of confirming the initial onset" as an item not to be collected for transferred patients. (2) Clinical laboratory tests: Addition of peripheral blast cells and myeloblast cells	(1) Omission of description (2) Addition of the parameters to investigate risk factors
First version	7 March 2018	N/A	N/A	N/A	N/A

5. MILESTONES

Milestone	Planned date
Start of investigation period	Start date of releasing BESPONSA to the market
Start of data collection (registration date of the first patient)	2 July 2018
End of investigation period	5 years after the start date of releasing BESPONSA to the market*
End of data collection (release date of the database)	May 2024
Final study report	October 2024

*: See Section 8.4. "Planned Study Period."

6. RATIONALE AND BACKGROUND

BESPONSA® Injection 1 mg (nonproprietary name, inotuzumab ozogamicin [genetical recombination]) (hereinafter referred to as BESPONSA) is a chemotherapeutic targeting the CD22 antigen that is an antibody-drug conjugate composed of a CD22-specific antibody linked to calicheamicin, a cytotoxic antitumor antibiotic. In Japan, the drug was approved in January 2018 for the indication, "Relapsed or refractory CD22-positive acute lymphoblastic leukemia (ALL)."

The "BESPONSA® Injection 1 mg Special Investigation" will be conducted to understand the safety of BESPONSA when administered under actual conditions of use in ALL patients.

7. RESEARCH QUESTION AND OBJECTIVES

7.1. Safety Specifications

7.1.1. Important Identified Risks

(1) Liver disorder including venoocclusive liver disease (VOD)/sinusoidal obstruction syndrome (SOS)*

Rationale: In global Phase 3 (B1931022) and non-Japanese Phase 1/2 (B1931010) studies in patients with relapsed or refractory ALL, VOD/SOS frequently occurred, and grade ≥3 hepatotoxicity was also reported in the inotuzumab ozogamicin group. Hence, the occurrence of adverse drug reactions (ADRs) and other relevant matters after marketing will be examined in the special investigation.

(2) Myelosuppression

Rationale: In Study B1931022, myelosuppression occurred in the inotuzumab ozogamicin group, and many of these events were grade ≥3. Hence, the occurrence of ADRs and other relevant matters after marketing will be evaluated in the special investigation.

(3) Infections

Rationale: In Study B1931022, infections occurred in many patients in the inotuzumab ozogamicin group, and infections attributable to myelosuppression would be likely to frequently develop. Hence, the occurrence of ADRs and other relevant matters after marketing will be assessed in the special investigation.

(4) Hemorrhage

Rationale: In Study B1931022, hemorrhage occurred in the inotuzumab ozogamicin group, and hemorrhage attributable to myelosuppression would be likely to frequently develop. Hence, the occurrence of ADRs and other relevant matters after marketing will be examined in the special investigation.

(5) Tumor lysis syndrome

Rationale: In Study B1931022, tumor lysis syndrome occurred in the inotuzumab ozogamicin group, and many of these events were grade ≥3. Hence, the occurrence of ADRs and other relevant matters after marketing will be evaluated in the special investigation.

(6) Infusion reaction

Rationale: In Study B1931022, infusion reaction related to inotuzumab ozogamicin occurred in the inotuzumab ozogamicin group. Hence, the occurrence of ADRs and other relevant matters after marketing will be assessed in the special investigation.

(7) Pancreatitis

Rationale: In Studies B1931022 and B1931010, and Studies B1931006 and B1931008 involving subjects other than patients with relapsed or refractory ALL, pancreatitis occurred in the inotuzumab ozogamicin group. Pancreatitis may affect the benefit-risk balance of inotuzumab ozogamicin.

Hence, the occurrence of ADRs and other relevant matters after marketing will be examined in the special investigation.

7.1.2. Important Potential Risks

(1) Interstitial lung disease
Rationale: In Study B1931022 and Study B1931006 involving subjects other than patients with relapsed or refractory ALL, interstitial lung disease occurred in the inotuzumab ozogamicin group. Interstitial lung disease may affect the benefit-risk balance of inotuzumab ozogamicin. Thus, if it is reported in the special investigation, applicable patients will be extracted and evaluated.

(2) Inflammatory gastrointestinal events
Rationale: In Studies B1931022 and B1931010, and Studies B1931003, B1931004 and B1931008 involving subjects other than patients with relapsed or refractory ALL, inflammatory gastrointestinal events occurred in the inotuzumab ozogamicin group. Gastrointestinal mucosal inflammation and ulcers may affect the benefit-risk balance of inotuzumab ozogamicin. Thus, if they are reported in the special investigation, applicable patients will be extracted and assessed.

(3) QTc interval prolonged

Rationale: In Study B1931022, QTc interval prolonged related to inotuzumab ozogamicin occurred in the inotuzumab ozogamicin group. Thus, if it is reported in the special investigation, applicable patients will be extracted and examined.

(4) Reproductive toxicity

Rationale: While no exposure during pregnancy or lactation was reported in clinical studies, findings in the reproductive organs, and embryos and fetuses were obtained in nonclinical studies. Thus, if it is reported in the special investigation, applicable patients will be extracted and evaluated.

7.2. Research Objectives

The following matters will be investigated in patients receiving BESPONSA under actual conditions of use after marketing:

(1) Occurrence of adverse events (AEs) (including the following evaluations):
Background characteristics possibly affecting the onset of liver disorder including VOD/SOS, myelosuppression, infections and hemorrhage, and grade ≥3 events based on the CTCAE v4.0 as well as risk factors for early death of HSCT patients after BESPONSA treatment

(2) Efficacy (hematologic remission rate and survival)

8. RESEARCH METHODS

8.1. Study Design

This is a multicenter, cohort study in patients receiving BESPONSA. The investigators will complete case report forms (CRFs) based on the information required for the study that will be extracted from medical records created in daily medical practice.

8.2. Setting

All patients receiving BESPONSA will be included in this investigation.

[INDICATION]

Relapsed or refractory CD22-positive ALL

[DOSAGE AND ADMINISTRATION]

The usual dosage for adults is 0.8 mg/m^2 (body surface area) of inotuzumab ozogamicin (genetical recombination) on Day 1 and 0.5 mg/m^2 (body surface area) on Days 8 and 15 once daily by intravenous infusion over at least 1 hour followed by a treatment-free interval. The length of cycle is 21 to 28 days for Cycle 1 and 28 days for Cycles 2 and subsequent cycles. The treatment should be repeated. The number of cycles should be decided while taking account of the schedule of HSCT. The dose should be decreased as necessary according to the patient's condition.

8.3. Study Sites

The investigation will be conducted at approximately 200 sites mainly the departments of hematology and internal medicine.

8.4. Planned Study Period

The planned period of this investigation is as follows:

Study period: For 5 years from the start date of releasing BESPONSA to the market*

Registration period: From the start date of releasing BESPONSA to the market to 30 April 2020*

*: Patients starting to receive BESPONSA on or before 30 April 2020 will be registered in this investigation regardless of the registration period and CRFs will be collected.

8.5. Study Method

A central registration all-patient surveillance system will be used for this investigation. Patients applicable to the investigation will be registered until meeting the target sample size. Registration to the investigation will be made by entering information in the electronic data capture (EDC) system for post-marketing drug investigation on the Internet which will be provided by the sponsor within approximately 2 weeks after the start of BESPONSA treatment (or after concluding a contract).

The sponsor will check that patients who have started treatment with BESPONSA by 30 April 2020 have been registered using the EDC system or paper form.

After it is confirmed that the target information can be collected, patient registration and request for new CRF completion will be ended. However, the system for taking prompt measures should be maintained in preparation for the cases in which additional investigation, etc. is judged to be necessary from the viewpoint of safety measures, etc., and is instructed by the Pharmaceuticals and Medical Devices Agency or the Ministry of Health, Labour and Welfare (MHLW).

8.6. Contract

A written agreement on the implementation of this investigation should be, in principle, concluded with the head of the site before delivering BESPONSA, and then BESPONSA should be delivered. However, even if BESPONSA is given to a patient before concluding the agreement due to therapeutic priority, the patient should be registered in the investigation. If specified agreement documents are available at the sites, they should be respected.

8.7. Observation Period

Observation period: The observation period will be 52 weeks for patients not undergoing HSCT within 52 weeks after the start of BESPONSA treatment or until 52 weeks following HSCT for patients undergoing it within 52 weeks after the start of BESPONSA treatment. For a patient starting BESPONSA treatment before 30 April 2020 who is transferred to another hospital during the observation period, the conclusion of the agreement on the implementation of this investigation should be requested to the hospital to which the patient has been transferred, and data from there should be collected to the extent possible.

(1) Treatment phase

From treatment initiation to Day 28 post-treatment: Safety (e.g., AEs) and efficacy (hematologic remission and survival)

(2) Follow-up phase

From Day 29 post-treatment to Week 52 (patients who did not undergo HSCT before Week 52) or 52 weeks after HSCT (patients who underwent HSCT before Week 52): Safety (VOD/SOS) and efficacy (survival)

8.8. Variables

The following information obtained during the observation period in the investigation is defined as survey items.

Table 1. Schedule of Observation

Variables			Registration form	Booklet 1		Booklet 2
				Baseline	Treatment phase*	Follow-up phase*2
Patient background	ID number		●	○		
	Gender		●	○		
	Birth month and year (age at the start of the investigation if it is not provided)		●	○		
	Experience of participation in this investigation		●	○		
	No	(Planned) start date of BESPONSA treatment	●			
		Target disease of the investigation	●			
		Informed consent from the patient (BESPONSA treatment)*3	●			
		Informed consent from the patient (publication of the investigation results)*4	●	○		
	Yes	Patient registration number at the site from which the patient is transferred	●	○		
		Name of the site from which the patient is transferred	●	○		
	Height and weight			●		
	Target disease			●		
	Date of confirming the initial onset			●		
	Chromosomal karyotype			●		
	Medical history			●		
Treatment history at baseline (remission induction chemotherapies and HSCT from the initial onset)				●		
BESPONSA treatment record					↔	
Pregnancy status					↔	
Clinical laboratory tests (hematology, hepatic function test, renal function test, electrocardiography, pancreatic function test, bone marrow test)				●	▲	▲
ECOG PS				●	▲	▲
Treatment of the target disease after the start of BESPONSA treatment (HSCT, HSCT donor information, drug therapy, non-drug therapy)					↔	→
Prophylactic treatment for reducing infusion reactions					↔	
Prophylactic treatment for preventing and reducing tumour lysis syndrome					↔	
Clinical evaluation (hematologic remission and MRD)					↔	→

Adverse events	Any AEs			↔	
	VOD/SOS			↔	↔
Records of treatment end/discontinuation				●	
Records of investigation continuation/discontinuation				●	●
Confirmation of survival (including reasons for death)				↔	↔

*: From treatment initiation to Day 28 post-treatment
*2: From Day 29 post-treatment to Week 52 (patients who did not undergo HSCT before Week 52) or 52 weeks after HSCT (patients who underwent HSCT before Week 52)
*3: Informed consent for BESPONSA treatment should be obtained after adequately explaining the efficacy of and risks from BESPONSA to the patient.
*4: Informed consent should be obtained whenever possible for disclosing the results from this investigation at academic conferences, in papers and/or through other relevant means.
●: Data entry or items to be entered; O, If there is no change in data, data in the registration form should be used as those in the CRF.
▲: HSCT pretreatment data should be entered for patients who underwent HSCT after the initiation of BESPONSA treatment only.

8.8.1. Patient Characteristics

The following information at the start of BESPONSA treatment will be entered or recorded:

(1) ID number

(2) Gender

(3) Birth month and year (age at the start of the investigation if it is not provided)

(4) Height and weight

(5) Target disease (name of disease, WHO Classification 4th edition, relapsed or refractory)

(6) Date of confirming the initial onset

(7) Chromosomal karyotype

(8) Medical history (VOD/SOS, graft versus host disease [GVHD], hepatitis, liver disease, other diseases)

(9) Experience of participation in this investigation

(10) Patient registration number at the site from which the patient is transferred (for transferred patients)

(11) Name of the site from which the patient is transferred (for transferred patients)

(12) Informed consent from the patient (BESPONSA treatment)*

(13) Informed consent from the patient (publication of the investigation results)

Informed consent should be obtained whenever possible for disclosing the results from this investigation at academic conferences, in papers and/or through other relevant means.

(14) Target disease of the investigation*

(15) (Planned) start date of BESPONSA treatment*

*: Items to be entered in the registration form only

The following items will not be collected from transferred patients:
Informed consent from the patient (BESPONSA treatment)
Informed consent from the patient (publication of the investigation results)
Height and weight

Target disease (name of disease, WHO Classification 4th edition, relapsed or refractory)
Date of confirming the initial onset
Chromosomal karyotype
ECOG PS (baseline)
Medical history (VOD/SOS, GVHD, hepatitis, liver disease, other diseases)
Target disease of the investigation
(Planned) start date of BESPONSA treatment

8.8.2. History of Treatment for the Target Disease at Baseline

(1) Remission induction chemotherapy (remission induction chemotherapeutics, number of treatments, and response)

(2) HSCT (type of transplantation, date of transplantation, and type of pretreatment drugs)

These items will not be collected from transferred patients.

8.8.3. Targeted Drug Use Record (Actual Treatment Record)

(1) Date of dosing

(2) Single dose

(3) Number of cycles administered

8.8.4. Records of BESPONSA Treatment End/Discontinuation

(1) Whether or not the treatment is completed or discontinued

(2) Date of completion or discontinuation

(3) Reason for completion or discontinuation
(disease progression or worsening of general condition, AEs, not making another visit, remission, transfer to another hospital or department, or other)

8.8.5. Treatment for the Target Disease after the Start of BESPONSA Treatment

(1) HSCT (type of transplantation, date of transplantation, and type of pretreatment drugs)

(2) HSCT donor information (alternative donor or matched related donor)

(3) Drug therapy (name of drug, start date, and route of administration)

(4) Non-drug therapy (radiotherapy, plasma transfusion included: name of therapy and start date)

8.8.6. Prophylactic Treatment for Reducing Infusion Reactions (Presence or Absence)

8.8.7. Prophylactic Treatment for Preventing and Reducing Tumor Lysis Syndrome (Presence or Absence)

8.8.8. Clinical Laboratory Tests

(1) Hematology (red blood cell count, hemoglobin, hematocrit, white blood cell count, differential white blood count, peripheral blast cells and platelet count)

(2) Hepatic function test (AST [GOT]*, ALT [GPT]*, AL-P, γ-GTP, total bilirubin*)

*: Data on the upper limit of normal (ULN) at the site will be entered.

(3) Renal function test (BUN, creatinine)

(4) Electrocardiography (QT, QTc)

(5) Pancreatic function test (amylase, lipase)

(6) Bone marrow test (myeloblast)

8.8.9. Records of investigation discontinuation

For patients who withdraw from the investigation during the observation period, enter the date of discontinuation. For the main reason for discontinuation, i.e., why the investigation cannot be continued, select one of the following options.

(Not making another visit, death, transfer to another hospital or department, or other)

8.8.10. ECOG PS (Eastern Cooperative Oncology Performance Status)

(1) Date of assessment

(2) Assessment results

8.8.11. Clinical Evaluation

8.8.11.1. Hematologic Remission

Response will be assessed according to the following response criteria, and the best overall response during the observation period will be entered. However, if subsequent treatment for the target disease is started or HSCT is performed, the best overall response before the start of the subsequent treatment or HSCT, whichever is earlier, will be entered.

Response criteria

1. CR
   - No peripheral blasts or extramedullary disease (no lymphadenopathy, splenomegaly, or skin/gum infiltration/testicular mass/CNS involvement)
   - Trilineage hematopoiesis (TLH) and <5% blasts
   - Absolute neutrophil count (ANC) >1,000/μL
   - Platelets >100,000/μL
   - No recurrence for 4 weeks
2. CRi (CR with incomplete count recovery)
   - Recovery of platelets but <100,000/μL or ANC is <1,000/μL
3. Progressive disease (PD)
   - Increase of at least 25% in the absolute number of peripheral blood or bone marrow blasts or development of extramedullary disease
4. Relapsed disease
   - Reappearance of blasts in the blood or bone marrow (>5%) or in any extramedullary site after CR
5. Inevaluable

8.8.11.2. Minimal Residual Disease (MRD)

If a MRD test gives a negative result during the observation period, the earliest date will be entered. However, if subsequent treatment for the target disease is started or HSCT is performed, MRD will be assessed before the start of the subsequent treatment or HSCT, whichever is earlier.

8.8.12. Confirmation of Survival

The following information will be entered to assess the overall survival during a period from the start date of BESPONSA treatment to the end date of the observation period:
Result of confirmation of survival at the end of the observation period, date of confirming the survival status if the patient is alive, date of death if the patient died (when the date of death is unknown, the last date of confirming survival), reason for death

8.8.13. Pregnancy Status (female only)

The pregnancy status during the period from the start date of BESPONSA treatment to the end date of the observation period in the treatment phase (Day 28 post-treatment) will be entered.

8.8.14. Adverse Events

Pertinent to safety assessment, the status of AEs during the period from the start of BESPONSA treatment to the end date of the observation period in the treatment phase (Day 28 post-treatment) will be confirmed, and the following information will be entered. For VOD/SOS, events during a period from the start of BESPONSA treatment to the end date of the observation period in the follow-up phase will be entered. When an AE is observed, the investigator should take an appropriate therapeutic action and promptly notify it to the sponsor. When the AE is related to BESPONSA, its course should be followed up until the AE or its sequelae resolve or become stable to the extent that is acceptable for the investigator and sponsor.

Also, further investigation should be separately conducted, if deemed necessary by sponsor for patients who experienced a serious adverse reaction, an unexpected adverse reaction or other adverse reactions not listed in the package insert.

(1) Presence/absence of AE
(2) Name of AE
(3) Date of occurrence
(4) CTCAE v4.0 Grade (worst grade)
(5) Intervention
(6) Seriousness
(7) Outcome at the present
(8) Causal relationship

Note: An AE is any and all unfavorable event (including clinically significant abnormal laboratory change) occurring in a patient after starting BESPONSA treatment regardless of causal relationship. A serious adverse event (SAE) is any unfavorable medical occurrence that results in death, is life-threatening, requires (or prolongs) hospitalization, causes persistent or significant disability/incapacity, results in congenital anomalies or birth defects, or is other conditions which represent significant health

hazards.

8.9. Data Sources

In this investigation, the investigators will extract necessary information from the medical records in accordance with the protocol.

8.10. Study Size

8.10.1. Planned Sample Size

The subjects are patients who received BESPONSA. The planned number of patients is 176 patients with relapsed or refractory CD22-positive ALL to be analyzed for safety. Considering patients to be excluded and dropouts, 200 enrolled patients will be collected.

8.10.2. Rationale

A total of 176 patients was chosen as the number of patients evaluable for risk factors related to the onset of VOD/SOS. The incidence of VOD/SOS was 12.3% (26/212 patients) in clinical studies (Studies B1931022 and B1931010).

A sample size enabling to evaluate the effect of risk factors related to the onset of VOD/SOS, which were identified in clinical studies, under actual conditions of use, and to search other risk factors was selected. Assuming the true incidence of 12.3% in all patients, a true relative risk associated with the onset of events in subgroups of 3.0 (equivalent to the incidence in the high and low risk groups being assumed to be 18.5% and 6.2%, respectively), and a ratio of the patients in each group being 1:1, when defining a probability of detecting a statistically significant relative risk as power, a sample size of 176 patients would provide power of 80.4% in a (two-sided) chi square test with a significance level of 0.1.

8.11. Data Management

8.11.1. Case Report Forms (CRFs) /Electronic Data Records

The CRF in this protocol refers to either a paper form or an electronic data record, or both, depending on the data collection method during this investigation.

A CRF will be completed for each patient registered in this investigation. All original completed CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator should ensure that the CRFs will be securely stored at the site in paper or encrypted electronic forms and protected by passwords or stored in a locked room to prevent access by unauthorized third parties.

The investigator will be responsible for collecting and reporting all clinical, safety, and laboratory data entered in the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized person. These signatures certify that the information recorded in the CRFs is true. Any correction made to the entries in the CRFs or source documents must be dated, initialed or stamped, and explained (if necessary) and should not obscure the original entry.

A source document is a patient's medical record that is stored at the site or owned by a physician. In this case, the information recorded in the CRF must be consistent with the information in these medical records.

8.11.2. Record Retention

The site will retain the records related to this investigation until the completion of this investigation is reported by Pfizer or until the deadline specified by the site, whichever is longer.

8.11.3. Data Collection Method

In this investigation, data will be entered in CRFs and evaluated using the EDC system for collecting post-marketing drug investigation data (hereinafter referred to as the system) on the Internet supplied by the sponsor. However, only when the EDC system cannot be used at the sites due to compelling reasons, data will be collected using paper CRFs. The investigator will complete CRFs within the investigation period after the end of the observation period for each booklet and submit them to the sponsor.

8.11.4. Patient Registration

Procedure for patient registration: The investigator will enter registration items on the patient registration screen of the system and send the data after digital signing. However, if paper CRFs are to be used, the investigator will complete the registration form provided by the sponsor, and submit the form via FAX using the toll-free number provided in the registration form.

8.11.5. Points to Consider for Completion, Revision, and Submission of Case Report Form

8.11.5.1. Data Entry

The investigator will, upon confirming the survey items, complete the CRF based on medical charts and other medical records, electronically sign the form and send it. However, if paper CRFs are to be used, after all the survey items are entered and corrected, the investigator should review the completed CRFs and the data entered in the query forms again, record his/her name and affix a seal or sign the CRFs. The CRFs and query forms should be submitted in accordance with methods specified by the sponsor.

8.11.5.2. Revision

Upon receiving the sponsor's inquiry on the contents of the CRF (query forms), the investigator will again confirm the contents of medical records described earlier, and as required, correct relevant sections and resubmit the form.

8.11.5.3. Submission

The CRFs should be submitted promptly upon completion in accordance with the procedures set out by the sponsor. However, if paper CRFs are to be used, after all the survey items are entered and corrected, the investigator should review the completed CRFs and the data entered in the query forms again, record his/her name and affix a seal or sign the CRFs. The CRFs and query forms should be submitted in accordance with methods specified by the sponsor.

8.12. Data Analysis

Summaries of data to be collected in this investigation and detailed statistical analysis methods will be described in the Statistical Analysis Plan (SAP) for this investigation, which will be dated and retained by Pfizer. The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

8.12.1. Definition of Analysis Sets

(1) A safety set will be composed of patients registered in this investigation who are confirmed to have received at least one dose of BESPONSA.

(2) An efficacy set will be separately specified in the SAP.

8.12.2. Analysis Methods

8.12.2.1. Analysis of Safety Endpoints

The occurrence of ADRs will be tabulated. In addition to an analysis using the entire safety set, analyses in subgroups stratified according to patient background characteristics will be carried out. The occurrence of liver disorder including VOD/SOS, myelosuppression, infections, hemorrhage, tumor lysis syndrome, infusion reaction, pancreatitis, interstitial lung disease, QTc interval prolonged, inflammatory gastrointestinal events and reproductive toxicity will be tabulated. For patients with special background characteristics such as children, elderly patients, pregnant women, patients with renal impairment and patients with hepatic dysfunction, the occurrence will be tabulated. Risk factors related to the development of VOD/SOS and risk factors related to early death of HSCT patients after BESPONSA treatment will be assessed.

The details of the analysis plan are specified in the SAP.

8.12.2.2. Analysis of Efficacy Endpoints

The main endpoints will be hematologic complete remission and overall survival. Exploratory analyses such as subgroup analysis by patient background characteristic will be, as necessary, performed.

The details of the analysis plan are specified in the SAP.

8.13. Quality Control

The staff responsible for medical institutions will explain the contents of the protocol, etc. to the investigator prior to the implementation of this investigation and ask the investigator to prepare CRFs based on medical records.

8.14. Limitations of the Research Methods

The following matters are considered for this investigation:

1) Since no control group is set in the investigation, there is a limit to the judgment on whether or not a risk of developing AEs and ADRs increases due to the administration of BESPONSA.

2) The consideration for confounding factors may not be adequate because the background information may not be sufficiently obtained.

3) Since this is an investigation that collects the information described in medical charts, the set data may not be collected or there may be missing information.

8.15. Other Aspects

Not applicable

9. PROTECTION OF HUMAN PARTICIPANTS

9.1. Patient Information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws. The personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

9.2. Patient Consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, or it is an information provision based on the law (even though that involves data subject to privacy laws according to applicable legal requirements), obtaining informed consent from patients by Pfizer is not required with regard to the personal information provision from the study site to Pfizer. Also, because the report of information or results collected in this study to the local regulatory authority or healthcare providers by Pfizer as needed is an information provision based on the law, obtaining informed consent from patients by Pfizer is not required.

In this study, Pfizer will collect information that cannot identify specific patients from the institutions. The results of this study, which are prepared not to identify specific patients, may be reported to Pfizer Inc., which is the corporate parent of the sponsor of this study, or group companies, or regulatory authorities in other countries, as needed, or published it as a presentation at academic conferences or manuscript for the purpose of providing proper use information for this drug. If this information falls under personal information of the Personal Information Protection Act, these actions may not be based on the laws or regulations, and therefore, may correspond to provision to the third party and using the information for purposes other than business that requires consent from the patient. Therefore, the study institutions will obtain written or verbal consent from the patients to be included in this study so that Pfizer can use the results of this study to report to Pfizer Inc., group companies or regulatory authorities in other countries, or to present it at academic conferences or publish manuscript, etc. Whether consent is obtained from patients or not is described in the CRF. The original of the written informed consent form should be retained by the study investigator.

In general, the investigator must obtain consent from a patient personally. However, if the investigator determines that a patient's decisional capacity is so limited that he or she cannot reasonably be consulted or he or she is a minor, consent is obtained from legally acceptable representative or parent(s).

9.3. Institutional Review Board (IRB)/Ethics Committee (EC)

In this investigation, the review by the Institutional Review Board (IRB)/Ethics Committee (EC) is not essential.

9.4. Ethical Conduct of the Study

This investigation is within the scope of the "Ministerial Ordinance on Good Post-marketing Study Practice for Drugs" (MHLW Ordinance No. 171 dated December 20, 2004) and will be conducted in accordance with legal and regulatory requirements, as well as scientific objectives, values, and rigor.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE DRUG REACTIONS

10.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) serious adverse events (SAEs); (2) non-serious AEs (as applicable); and (3) scenarios involving exposure to a Pfizer product, including exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure. These events are defined in the section "Definitions of Safety Events".

Safety event	Recorded on the CRFs	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE	All	All
Non-serious AE	All	None
Scenarios involving exposure to a Pfizer product, including exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE) involving exposure to a Pfizer product Note: Any associated AE is reported together with the exposure scenario.

For each AE, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE (see section "Serious Adverse Events" below).

Safety events listed in the table above must be reported to Pfizer within 24 hours of awareness of the event by the investigator **regardless of whether the event is determined by the investigator to be related to this drug**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately,

irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.

For those safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information relevant to the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

10.2. Reporting Period

For each patient, the period of safety event reporting in CRF (see the table above) begins at the time of the patient's first dose of BESPONSA, and lasts through the end of the observation period (this refers to the end date of observation period in the treatment phase) of the study, but the reporting period to Pfizer Safety must include at least 28 calendar days following the last dose of BESPONSA; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. If a patient was receiving BESPONSA on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation period.

During the VOD/SOS reporting period, all VOD/SOS occurred before the end date of the observation period in the follow-up phase shall be reported as SAEs regardless of the causal relationship and severity.

If the investigator becomes aware of a SAE occurring at any time after completion of the study (this refers to the end date of the observation period in the treatment phase) and s/he considers the SAE to be related to BESPONSA, the SAE also must be reported to Pfizer Safety.

10.3. Causality Assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each AE. For AEs with a causal relationship to BESPONSA, follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that BESPONSA caused or contributed to an AE. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether BESPONSA caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that BESPONSA did not cause the event, this should be clearly documented on the CRF and the NIS AEM Report Form.

10.4. Definitions of Safety Events

10.4.1. Adverse Events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an AE);
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breastfeeding;
- Medication error;
- Occupational exposure.

Abnormal test findings

The criteria for determining whether an abnormal test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in BESPONSA dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

10.4.2. Serious Adverse Events

A SAE is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute AEs);

- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as a SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as a SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as a SAE with severity Grade 5.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance (PV) personnel. Such cases are also considered for reporting as product defects, if appropriate.

Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (e.g., patient has no place to sleep)
- Administrative admission (e.g., for yearly exam)
- Optional admission not associated with a precipitating medical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality)

10.4.3. Scenarios Necessitating Reporting to Pfizer Safety within 24 Hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to BESPONSA (e.g., environmental exposure), or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to BESPONSA (maternal exposure).

An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed, either due to treatment or environmental exposure to BESPONSA prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

For exposure during pregnancy in studies of pregnant women, data on the exposure to BESPONSA during pregnancy, are not reportable unless associated with SAEs or non-serious AEs.

As a general rule, prospective and retrospective exposure during pregnancy reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed , with the exception of those studies conducted in pregnant women (as described above), for which data on the exposure are not reportable unless associated with SAEs or non-serious AEs.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with BESPONSA, this information must be submitted to Pfizer, irrespective of whether an AE has occurred, using the NIS AEM Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to BESPONSA, in a pregnant woman (e.g., a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AEM Report Form and the EDP Supplemental Form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (e.g., induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product.

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

Exposure during breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (e.g., vitamins) is administered in accord with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

Medication error

A medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (e.g., inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);

- Confusion with regard to invented name (e.g., trade name, brand name).

The investigator must submit the following medication errors to Pfizer, irrespective of the presence of an associated AE/SAE:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.

- Medication errors that do not involve a patient directly (e.g., potential medication errors or near misses). When a medication error does not involve patient exposure to the product, the following minimum criteria constitute a medication error report:
  - An identifiable reporter;
  - A suspect product;
  - The event medication error.

Overdose, Misuse, Extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

Lack of Efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

Occupational Exposure

Reports of occupational exposure to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The information collected in this investigation will be used for reporting to the MHLW, the Pharmaceuticals and Medical Devices Agency (PMDA), and the parent company (Pfizer inc. in the United States), or its group companies or overseas regulatory authorities, and reexamination application (including Periodic Safety Update Report) for BESPONSA, reevaluation application, creation of data for providing information on the proper use of BESPONSA, preparation of articles, and activities to provide information, etc. In addition, Pfizer may publish the investigation results at www.clinicaltrials.gov (ClinicalTrials.gov) or at academic conferences or in papers, etc. for the purpose of providing information on the proper use of BESPONSA as necessary.

The data on patients collected in this investigation will be reported to the MHLW based on the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. In such cases, information including the drug name, adverse reaction name, gender, age (age group), etc. for the data on the relevant patients may be disclosed in a patient list in "Pharmaceuticals and Medical Devices Safety Information" by the MHLW, and "Website for Providing Pharmaceuticals and Medical Devices Information (http://www.info.pmda.go.jp)." Furthermore, the collected patient data will be disclosed when disclosure is requested to the MHLW based on the "Act on Access to Information Held by Administrative Organs" (Act No. 42 of May 14, 1999). In all of these cases, however, information such as the names of the investigators and the names of the institutions will not be reported, and therefore, will not be published or disclosed.

Pfizer will be notified of any prohibition or restriction imposed (e.g., clinical study termination) by the applicable regulatory authority in each area of the world. When becoming aware of new information that may influence the evaluation of benefits and risks of a Pfizer product, the investigator shall promptly notify the Pfizer of the information.

12. NAME, AND ADDRESS OF CONTRACTOR AS WELL AS SCOPE OF WORK CONTRACTED

Name: Pfizer R&D Japan G.K.
Address: 3-22-7 Yoyogi, Shibuya-ku, Tokyo
Scope of work contracted: Operations related to the planning of this investigation, the drafting of the protocol, the operation of this investigation, monitoring, etc.

Name: EPS Corporation
Address: 2-23 Shimomiyabicho, Shinjuku-ku, Tokyo
Scope of work contracted: Operations for this investigation such as registration reception, establishment of the post-marketing surveillance data collection system (EDC), data management activities, and tabulation and analysis operations, excluding operations to manage the post-marketing study

Name: Medidata Solutions
Address: 2-7-2 Marunouchi, Chiyoda-ku, Tokyo
Scope of work contracted: Activities related to the establishment and operations of the post-marketing surveillance data collection system (EDC)

Name: A2 Healthcare Corporation
Address: 1-4-1- Koishikawa, Bunkyo-ku, Tokyo
Scope of work contracted: Activities related to EDC account management, etc.

13. ADDITIONAL MEASURES THAT MAY BE IMPLEMENTED BASED ON THE SURVEY RESULTS AND CRITERIA FOR DETERMINATION OF THE INITIATION

At milestones, the risk management plan (RMP) including the following items should be reviewed:

1) To evaluate whether or not there are new safety specifications;

2) To examine whether or not it is necessary to plan additional pharmacovigilance activities and to establish a risk minimization plan for a new safety specification; and

3) To consider whether or not it is necessary to amend the additional pharmacovigilance activity plan and the details of risk minimization activities for the current safety specifications.

14. SCHEDULED TIMING OF MILESTONES AND THEIR RATIONALES FOR EVALUATION OF STUDY IMPLEMENTATION STATUS AND RESULTS AND REPORTING TO THE PMDA

Scheduled timing is at the time of submitting Periodic Safety Update Report, the time of terminating registration (at the time of preparing the 5th or 6th Periodic Safety Update Report), the time of ending the investigation (at the time of preparing the 9th or 10th Periodic Safety Update Report) and the time of preparing reexamination application data.

15. OTHER NECESSARY MATTERS

1) Amendment of the full protocol

Based on the new knowledge to be obtained according to the progress of this investigation, the need for amendment of the protocol will be examined and the protocol will be amended if necessary. Also, the need for amendment of the protocol will be examined and the protocol will be amended even if the partial change in the dosage and administration or indication is approved during the reexamination period (except the case when the reexamination period is newly designated), etc.

2) Actions to be taken for any problem or issue

In the cases where the onset of any serious and unknown ADRs is suggested, a significant increase in the frequency of ADRs is observed, any problem is found in the efficacy and safety of the drug compared to those prior to the approval, the onset of a different kind of ADR is suggested, etc., the amendment of the package insert and implementation of new post-marketing surveillance should be considered.

16. CONTACT INFORMATION

16.1. Contact Information for the Contents of the Study

Name	PMS Affairs, Pfizer R&D Japan G.K.
Address	Shinjuku Bunka Quint Building, 3-22-7 Yoyogi, Shibuya-ku, Tokyo 151-8589
Fax	03-5309-9186
E-mail address	BES_PMS@pfizer.com

16.2. Contact Information for the EDC System

Name	Medidata, Help Desk
Open hours	Weekdays: 9:00 to 20:00 (excluding Saturdays, Sundays, national holidays, and year-end and New Year holidays)
Tel	PPD (dedicated Pfizer dial)
E-mail address	japanhelpdesk@mdsol.com