ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

BESPONSA 1 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1 mg inotuzumab ozogamicin.

After reconstitution (see section 6.6), 1 mL of solution contains 0.25 mg inotuzumab ozogamicin.

Inotuzumab ozogamicin is an antibody-drug conjugate (ADC) composed of a recombinant humanised IgG4 kappa CD22-directed monoclonal antibody (produced in Chinese hamster ovary cells by recombinant DNA technology) that is covalently linked to N-acetyl-gamma-calicheamicin dimethylhydrazide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for concentrate).

White to off-white, lyophilised cake or powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BESPONSA is indicated as monotherapy for the treatment of adults with relapsed or refractory CD22-positive B cell precursor acute lymphoblastic leukaemia (ALL). Adult patients with Philadelphia chromosome positive (Ph^+) relapsed or refractory B cell precursor ALL should have failed treatment with at least 1 tyrosine kinase inhibitor (TKI).

4.2 Posology and method of administration

BESPONSA should be administered under the supervision of a physician experienced in the use of cancer therapy and in an environment where full resuscitation facilities are immediately available. When considering the use of BESPONSA as a treatment for relapsed or refractory B cell ALL, baseline CD22 positivity of > 0% using a validated and sensitive assay is required prior to initiating treatment (see section 5.1).

For patients with circulating lymphoblasts, cytoreduction with a combination of hydroxyurea, steroids, and/or vincristine to a peripheral blast count ≤ 10,000/mm^3 is recommended prior to the first dose.

Pre-medication with a corticosteroid, antipyretic, and antihistamine is recommended prior to dosing (see section 4.4).

For patients with a high tumour burden, pre-medication to reduce uric acid levels and hydration is recommended prior to dosing (see section 4.4).
Patients should be observed during, and for at least 1 hour after the end of infusion for symptoms of infusion related reactions (see section 4.4).

<u>Posology</u>

BESPONSA should be administered in 3- to 4-week cycles.

For patients proceeding to haematopoietic stem cell transplant (HSCT), the recommended duration of treatment is 2 cycles. A third cycle may be considered for those patients who do not achieve a complete remission (CR) or complete remission with incomplete haematological recovery (CRi) and minimal residual disease (MRD) negativity after 2 cycles (see section 4.4). For patients not proceeding to HSCT, a maximum of 6 cycles may be administered. Any patients who do not achieve a CR/CRi within 3 cycles should discontinue treatment.

Table 1 shows the recommended dosing regimens.

For the first cycle, the recommended total dose of BESPONSA for all patients is 1.8 mg/m^2 per cycle, given as 3 divided doses on Days 1 (0.8 mg/m^2), 8 (0.5 mg/m^2), and 15 (0.5 mg/m^2). Cycle 1 is 3 weeks in duration but may be extended to 4 weeks if the patient achieves a CR or CRi, and/or to allow recovery from toxicity.

For subsequent cycles, the recommended total dose of BESPONSA is 1.5 mg/m^2 per cycle given as 3 divided doses on Days 1 (0.5 mg/m^2), 8 (0.5 mg/m^2), and 15 (0.5 mg/m^2) for patients who achieve a CR/CRi or 1.8 mg/m^2 per cycle given as 3 divided doses on Days 1 (0.8 mg/m^2), 8 (0.5 mg/m^2), and 15 (0.5 mg/m^2) for patients who do not achieve a CR/CRi. Subsequent cycles are 4 weeks in duration.

Table 1. Dosing regimen for Cycle 1 and subsequent cycles depending on response to treatment

	Day 1	**Day 8[a]**	**Day 15[a]**
Dosing regimen for Cycle 1			
All patients:			
Dose (mg/m^2)	0.8	0.5	0.5
Cycle length	21 days[b]		
Dosing regimen for subsequent cycles depending on response to treatment			
Patients who have achieved a CR[c] or CRi[d]:			
Dose (mg/m^2)	0.5	0.5	0.5
Cycle length	28 days[e]		
Patients who have not achieved a CR[c] or CRi[d]:			
Dose (mg/m^2)	0.8	0.5	0.5
Cycle length	28 days[e]		

Abbreviations: ANC=absolute neutrophil counts; CR=complete remission; CRi=complete remission with incomplete haematological recovery.

[a] +/- 2 days (maintain minimum of 6 days between doses).

[b] For patients who achieve a CR/CRi, and/or to allow for recovery from toxicity, the cycle length may be extended up to 28 days (i.e. 7-day treatment-free interval starting on Day 21).

[c] CR is defined as < 5% blasts in the bone marrow and the absence of peripheral blood leukaemic blasts, full recovery of peripheral blood counts (platelets ≥ 100 × 10^9/L and ANC ≥ 1 × 10^9/L) and resolution of any extramedullary disease.

[d] CRi is defined as < 5% blasts in the bone marrow and the absence of peripheral blood leukaemic blasts, incomplete recovery of peripheral blood counts (platelets < 100 × 10^9/L and/or ANC < 1 × 10^9/L) and resolution of any extramedullary disease.

[e] 7-day treatment-free interval starting on Day 21.

Dose modifications

Dose modification of BESPONSA may be required based on individual safety and tolerability (see section 4.4). Management of some adverse drug reactions may require dosing interruptions and/or dose reductions, or permanent discontinuation of BESPONSA (see sections 4.4 and 4.8). If the dose is reduced due to BESPONSA-related toxicity, the dose should not be re-escalated.

Table 2 and Table 3 show the dose modification guidelines for haematological and non-haematological toxicities, respectively. BESPONSA doses within a treatment cycle (i.e. Days 8 and/or 15) do not need to be interrupted due to neutropenia or thrombocytopenia, but dosing interruptions within a cycle are recommended for non-haematological toxicities.

Table 2. Dose modifications for haematological toxicities at the start of a treatment cycle (Day 1)

Haematological toxicity	Toxicity and dose modification(s)
Levels prior to BESPONSA treatment:	
ANC was $\geq 1 \times 10^9$/L	If ANC decreases, interrupt the next cycle of treatment until recovery of ANC to $\geq 1 \times 10^9$/L.
Platelet count was $\geq 50 \times 10^9$/L[a]	If platelet count decreases, interrupt the next cycle of treatment until platelet count recovers to $\geq 50 \times 10^9$/L[a].
ANC was $< 1 \times 10^9$/L and/or platelet count was $< 50 \times 10^9$/L[a]	If ANC and/or platelet count decreases, interrupt the next cycle of treatment until at least one of the following occurs: - ANC and platelet count recover to at least baseline levels for the prior cycle, or - ANC recovers to $\geq 1 \times 10^9$/L and platelet count recovers to $\geq 50 \times 10^9$/L[a], or - Stable or improved disease (based on most recent bone marrow assessment) and the ANC and platelet count decrease is considered to be due to the underlying disease (not considered to be BESPONSA-related toxicity).

Abbreviation: ANC=absolute neutrophil count.

[a] Platelet count used for dosing must be independent of blood transfusion.

Table 3. Dose modifications for non-haematological toxicities at any time during treatment

Non-haematological toxicity	Dose modification(s)
VOD/SOS or other severe liver toxicity	Permanently discontinue treatment (see section 4.4).
Total bilirubin > 1.5 × ULN and AST/ALT > 2.5 × ULN	Interrupt the dosing until recovery of total bilirubin to ≤ 1.5 × ULN and AST/ALT to ≤ 2.5 × ULN prior to each dose unless due to Gilbert's disease or haemolysis. Permanently discontinue treatment if total bilirubin does not recover to ≤ 1.5 × ULN or AST/ALT does not recover to ≤ 2.5 × ULN (see section 4.4).
Infusion related reaction	Interrupt the infusion and institute appropriate medical management. Depending on the severity of the infusion related reaction, consider discontinuation of the infusion or administration of steroids and antihistamines. For severe or life-threatening infusion reactions, permanently discontinue treatment (see section 4.4).
Grade ≥ 2[a] non-haematological toxicity (BESPONSA-related)	Interrupt treatment until recovery to Grade 1 or pre-treatment grade levels prior to each dose.

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal; VOD/SOS=venoocclusive disease/sinusoidal obstruction syndrome.

[a] Severity grade according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0.

Table 4 shows the dose modification guidelines depending on the duration of dosing interruptions due to toxicity.

Table 4. Dose modifications depending on duration of dosing interruption due to toxicity

Duration of dosing interruption due to toxicity	Dose modification(s)
< 7 days (within a cycle)	Interrupt the next dose (maintain a minimum of 6 days between doses).
≥ 7 days	Omit the next dose within the cycle.
≥ 14 days	Once adequate recovery is achieved, decrease the total dose by 25% for the subsequent cycle. If further dose modification is required, then reduce the number of doses to 2 per cycle for subsequent cycles. If a 25% decrease in the total dose followed by a decrease to 2 doses per cycle is not tolerated, then permanently discontinue treatment.
> 28 days	Consider permanent discontinuation of BESPONSA.

Special populations

Elderly

No adjustment to the starting dose is required based on age (see section 5.2).

Hepatic impairment

No adjustment to the starting dose is required in patients with hepatic impairment defined by total bilirubin ≤ 1.5 × upper limit of normal (ULN) and aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤ 2.5 × ULN (see section 5.2). There is limited safety information available in patients with total bilirubin > 1.5 × ULN and AST/ALT > 2.5 × ULN prior to dosing. Interrupt dosing until recovery of total bilirubin to ≤ 1.5 × ULN and AST/ALT to ≤ 2.5 × ULN prior to each dose unless due to Gilbert's syndrome or haemolysis. Permanently discontinue treatment if total bilirubin does not recover to ≤ 1.5 × ULN or AST/ALT does not recover to ≤ 2.5 × ULN (see Table 3 and section 4.4).

Renal impairment

No adjustment to the starting dose is required in patients with mild, moderate, or severe renal impairment (creatinine clearance [CL_{cr}] 60-89 mL/min, 30-59 mL/min, or 15-29 mL/min, respectively) (see section 5.2). The safety and efficacy of BESPONSA have not been studied in patients with end-stage renal disease.

Paediatric population

The safety and efficacy of BESPONSA in children aged 0 to < 18 years have not been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Method of administration

BESPONSA is for intravenous use. The infusion must be administered over 1 hour.

BESPONSA should not be administered as an intravenous push or bolus.

BESPONSA must be reconstituted and diluted before administration. For instructions on reconstitution and dilution of BESPONSA before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

- Patients who have experienced prior confirmed severe or ongoing venoocclusive liver disease/sinusoidal obstruction syndrome (VOD/SOS).
- Patients with serious ongoing hepatic disease (e.g., cirrhosis, nodular regenerative hyperplasia, active hepatitis).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hepatotoxicity, including VOD/SOS

Hepatotoxicity, including severe, life-threatening, and sometimes fatal hepatic VOD/SOS, was reported in patients with relapsed or refractory ALL receiving BESPONSA (see section 4.8). BESPONSA significantly increased the risk of VOD/SOS above that of standard chemotherapy regimens in this patient population. This risk was most marked in patients who underwent subsequent HSCT.

In the following subgroups, the reported frequency of VOD/SOS post-HSCT was ≥ 50%:
- Patients who received a HSCT conditioning regimen containing 2 alkylating agents;
- Patients aged ≥ 65 years; and
- Patients with a serum bilirubin ≥ ULN prior to HSCT.

The use of HSCT conditioning regimens containing 2 alkylating agents should be avoided. The benefit/risk should be carefully considered before administering BESPONSA to patients in whom the future use of HSCT conditioning regimens containing 2 alkylating agents is likely unavoidable.

In patients in whom the serum bilirubin is ≥ ULN prior to HSCT, HSCT post BESPONSA treatment should only be undertaken after careful consideration of the benefit/risk. If these patients do proceed to HSCT, signs and symptoms of VOD/SOS should be monitored closely (see section 4.2).

Other patient factors that appear to be associated with an increased risk of VOD/SOS after HSCT include a prior HSCT, age ≥ 55 years, a history of liver disease and/or hepatitis before treatment, later salvage lines, and a greater number of treatment cycles.

Careful consideration is required before administering BESPONSA to patients who have had a prior HSCT. No patients with relapsed or refractory ALL who were treated with BESPONSA in clinical studies had undergone HSCT within the previous 4 months.

Patients with a history of liver disease should be carefully evaluated (e.g., ultrasound scan, viral hepatitis testing) prior to treatment with BESPONSA to exclude serious ongoing hepatic disease (see section 4.3).
Due to the risk of VOD/SOS, for patients proceeding to HSCT, the recommended duration of treatment with inotuzumab ozogamicin is 2 cycles; a third cycle may be considered for those patients who do not achieve a CR or CRi and MRD negativity after 2 cycles (see section 4.2).

Signs and symptoms of VOD/SOS should be monitored closely in all patients, especially post HSCT. Signs may include elevations in total bilirubin, hepatomegaly (which may be painful), rapid weight gain, and ascites. Monitoring only total bilirubin may not identify all patients at risk of VOD/SOS. In all patients, liver tests should be monitored, including, ALT, AST, total bilirubin, and alkaline phosphatase, prior to and following each dose of BESPONSA. For patients who develop abnormal liver tests, liver tests and clinical signs and symptoms of hepatotoxicity should be monitored more frequently. For patients who proceed to HSCT, liver tests should be monitored closely during the first month post-HSCT, then less frequently thereafter, according to standard medical practice. Elevation of

liver tests may require dosing interruption, dose reduction, or permanent discontinuation of BESPONSA (see section 4.2).

Treatment should be permanently discontinued if VOD/SOS occurs (see section 4.2). If severe VOD/SOS occurs, the patient should be treated according to standard medical practice.

Myelosuppression/cytopenias

In patients receiving inotuzumab ozogamicin, neutropenia, thrombocytopenia, anaemia, leukopenia, febrile neutropenia, lymphopenia, and pancytopenia, some of which were life-threatening, have been reported (see section 4.8).

In patients receiving inotuzumab ozogamicin, complications associated with neutropenia and thrombocytopenia (including infections and bleeding/haemorrhagic events, respectively) were reported in some patients (see section 4.8).

Complete blood counts should be monitored prior to each dose of BESPONSA and signs and symptoms of infection during treatment and after HSCT (see section 5.1), bleeding/haemorrhage, and other effects of myelosuppression should be monitored during treatment. As appropriate, prophylactic anti-infectives should be administered and surveillance testing should be employed during and after treatment.

Management of severe infection, bleeding/haemorrhage and other effects of myelosuppression, including severe neutropenia or thrombocytopenia, may require a dosing interruption, dose reduction, or discontinuation of treatment (see section 4.2).

Infusion related reactions

In patients receiving inotuzumab ozogamicin, infusion related reactions were reported (see section 4.8).

Pre-medication with a corticosteroid, antipyretic, and antihistamine is recommended prior to dosing (see section 4.2).

Patients should be monitored closely during and for at least 1 hour after the end of infusion for the potential onset of infusion related reactions, including symptoms such as hypotension, hot flush, or breathing problems. If an infusion related reaction occurs, the infusion should be interrupted and appropriate medical management should be instituted. Depending on the severity of the infusion related reaction, discontinuation of the infusion or administration of steroids and antihistamines should be considered (see section 4.2). For severe or life-threatening infusion reactions, treatment should be permanently discontinued (see section 4.2).

Tumour lysis syndrome (TLS)

In patients receiving inotuzumab ozogamicin, TLS, which may be life-threatening or fatal, was reported (see section 4.8).

Pre-medication to reduce uric acid levels and hydration is recommended prior to dosing for patients with a high tumour burden (see section 4.2).

Patients should be monitored for signs and symptoms of TLS and treated according to standard medical practice.

QT interval prolongation

In patients receiving inotuzumab ozogamicin, QT interval prolongation was observed (see sections 4.8 and 5.2).

BESPONSA should be administered with caution in patients who have a history of, or predisposition to QT interval prolongation, who are taking medicinal products that are known to prolong QT interval (see section 4.5) and in patients with electrolyte disturbances. ECG and electrolytes should be obtained prior to the start of treatment and periodically monitored during treatment (see sections 4.8 and 5.2).

Increased amylase and lipase

In patients receiving inotuzumab ozogamicin, increases in amylase and lipase have been reported (see section 4.8).

Patients should be monitored for increases in amylase and lipase. Potential hepatobiliary disease should be evaluated and treated according to standard medical practice.

Immunisations

The safety of immunisation with live viral vaccines during or following BESPONSA therapy has not been studied. Vaccination with live viral vaccines is not recommended for at least 2 weeks prior to the start of BESPONSA treatment, during treatment, and until recovery of B lymphocytes following the last treatment cycle.

Excipients

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per 1 mg inotuzumab ozogamicin, that is to say essentially 'sodium-free'.

This medicinal product may be further prepared for administration with sodium-containing solutions (see sections 4.2 and 6.6) and this should be considered in relation to the total sodium from all sources that will be administered to the patient.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed (see section 5.2).

Based on *in vitro* data, coadministration of inotuzumab ozogamicin with inhibitors or inducers of cytochrome P450 (CYP) or uridine diphosphate-glucuronosyltransferase (UGT) drug metabolising enzymes are unlikely to alter exposure to N-acetyl-gamma-calicheamicin dimethylhydrazide. In addition, inotuzumab ozogamicin and N-acetyl-gamma-calicheamicin dimethylhydrazide are unlikely to alter the exposure of substrates of CYP enzymes, and N-acetyl-gamma-calicheamicin dimethylhydrazide is unlikely to alter the exposure of substrates of UGT enzymes or major drug transporters.

In patients receiving inotuzumab ozogamicin, prolonged QT interval was observed (see section 4.4). Therefore, the concomitant use of inotuzumab ozogamicin with medicinal products known to prolong QT interval or to induce Torsades de Pointes should be carefully considered. The QT interval should be monitored in case of combinations of such medicinal products (see sections 4.4, 4.8, and 5.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential should avoid becoming pregnant while receiving BESPONSA.

Women should use effective contraception during treatment with BESPONSA and for at least 8 months after the final dose. Men with female partners of childbearing potential should use effective contraception during treatment with BESPONSA and for at least 5 months after the final dose.

Pregnancy

There are no data in pregnant women using inotuzumab ozogamicin. Based on non-clinical safety findings, inotuzumab ozogamicin can cause embryo-foetal harm when administered to a pregnant woman. Studies in animals have shown reproductive toxicity (see section 5.3).

BESPONSA must not be used during pregnancy unless the potential benefit to the mother outweighs the potential risks to the foetus. Pregnant women, or patients becoming pregnant while receiving inotuzumab ozogamicin, or treated male patients as partners of pregnant women, must be apprised of the potential hazard to the fetus.

Breast-feeding

There are no data on the presence of inotuzumab ozogamicin or its metabolites in human milk, the effects on the breast-fed child, or the effects on milk production. Because of the potential for adverse reactions in breast-fed children, women must not breast-feed during treatment with BESPONSA and for at least 2 months after the final dose (see section 5.3).

Fertility

Based on non-clinical findings, male and female fertility may be compromised by treatment with inotuzumab ozogamicin (see section 5.3). There is no information on fertility in patients. Both men and women must seek advice for fertility preservation before treatment.

4.7 Effects on ability to drive and use machines

BESPONSA has moderate influence on the ability to drive and use machines. Patients may experience fatigue during treatment with BESPONSA (see section 4.8). Therefore, caution is recommended when driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

The most common (≥ 20%) adverse reactions were thrombocytopenia (51%), neutropenia (49%), infection (48%), anaemia (36%), leukopenia (35%), fatigue (35%), haemorrhage (33%), pyrexia (32%), nausea (31%), headache (28%), febrile neutropenia (26%), increased transaminases (26%), abdominal pain (23%), increased gamma-glutamyltransferase (21%), and hyperbilirubinaemia (21%).

In patients who received BESPONSA, the most common (≥ 2%) serious adverse reactions were infection (23%), febrile neutropenia (11%), haemorrhage (5%), abdominal pain (3%), pyrexia (3%), VOD/SOS (2%), and fatigue (2%).

Tabulated list of adverse reactions

Table 5 shows the adverse reactions reported in patients with relapsed or refractory ALL who received BESPONSA.

The adverse reactions are presented by system organ class (SOC) and frequency categories, defined using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 5. Adverse reactions reported in patients with relapsed or refractory B-cell precursor ALL who received BESPONSA

MedDRA System organ class	Very common	Common
Infections and infestations	Infection (48%)[a] (includes Sepsis and Bacteraemia [17%], Fungal infection [9%], Lower respiratory tract infection [12%)], Upper respiratory tract infection [12%], Bacterial infection [1%], Viral infection [7%], Gastrointestinal infection [4%], Skin infection [4%])	
Blood and lymphatic system disorders	Febrile neutropenia (26%) Neutropenia (49%) Thrombocytopenia (51%) Leukopenia (35%) Lymphopenia (18%) Anaemia (36%)	Pancytopenia[b] (2%)
Immune system disorders		Hypersensitivity (1%)
Metabolism and nutrition disorders	Decreased appetite (12%)	Tumour lysis syndrome (2%) Hyperuricaemia (4%)
Nervous system disorders	Headache (28%)	
Vascular disorders	Haemorrhage[c] (33%) (includes Central nervous system haemorrhage [1%], Upper gastrointestinal haemorrhage [6%], Lower gastrointestinal haemorrhage [4%], Epistaxis [15%])	
Gastrointestinal disorders	Abdominal pain (23%) Vomiting (15%) Diarrhoea (17%) Nausea (31%) Stomatitis (13%) Constipation (17%)	Ascites (4%) Abdominal distension (6%)
Hepatobiliary disorders	Hyperbilirubinaemia (21%) Increased transaminases (26%) Increased GGT (21%)	VOD/SOS (3% [pre-HSCT][d])
General disorders and administration site conditions	Pyrexia (32%) Fatigue (35%) Chills (11%)	
Investigations	Increased alkaline phosphatase (13%)	ECG QT prolonged (1%) Increased amylase (5%) Increased lipase (9%)
Injury, poisoning and procedural complications	Infusion related reaction (10%)	

Adverse reactions included treatment-emergent, all-causality events that commenced on, or after Cycle 1 Day 1 within 42 days after the final dose of BESPONSA, but prior to the start of a new anticancer treatment (including HSCT).

Preferred terms were retrieved by applying the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1.

Abbreviations: ALL=acute lymphoblastic leukaemia; VOD/SOS= venoocclusive liver disease/sinusoidal obstruction syndrome; ECG=electrocardiogram; GGT=gamma-glutamyltransferase; HSCT=haematopoietic stem cell transplant.

Table 5. Adverse reactions reported in patients with relapsed or refractory B-cell precursor ALL who received BESPONSA

MedDRA System organ class	Very common	Common

[a] Infection also includes other types of infection (11%). Note: patients may have had > 1 type of infection.
[b] Pancytopenia includes the following reported preferred terms: Bone marrow failure, Febrile bone marrow aplasia, and Pancytopenia.
[c] Haemorrhage also includes other types of haemorrhage (17%). Note: patients may have had > 1 type of haemorrhage.
[d] VOD/SOS includes 1 additional patient with VOD that occurred at Day 56 with no intervening HSCT. VOD/SOS was also reported in 18 patients after a subsequent HSCT.

Description of selected adverse reactions

Hepatotoxicity, including VOD/SOS

In the pivotal clinical study (N=164), VOD/SOS was reported in 23 (14%) patients including 5 (3%) patients during study therapy or in follow-up without an intervening HSCT. Among the 79 patients who proceeded to a subsequent HSCT (8 of whom received additional salvage therapy after treatment with BESPONSA before proceeding to HSCT), VOD/SOS was reported in 18 (23%) patients. Five of the 18 VOD/SOS events that occurred post-HSCT were fatal (see section 5.1).

VOD/SOS was reported up to 56 days after the final dose of inotuzumab ozogamicin without an intervening HSCT. The median time from HSCT to onset of VOD/SOS was 15 days (range: 3-57 days). Of the 5 patients who experienced VOD/SOS during treatment with inotuzumab ozogamicin but without an intervening HSCT, 2 patients had also received an HSCT before BESPONSA treatment.

Among patients who proceeded to HSCT after BESPONSA treatment, VOD/SOS was reported in 5/11 (46%) patients who received an HSCT both prior to and after BESPONSA treatment and 13/68 (19%) patients who only received an HSCT after BESPONSA treatment.

Regarding other risk factors, VOD/ SOS was reported in 6/11 (55%) patients who received a HSCT conditioning regimen containing 2 alkylating agents and 9/53 (17%) patients who received a HSCT conditioning regimen containing 1 alkylating agent, 7/17 (41%) patients who were ≥ 55 years old and 11/62 (18%) patients who were < 55 years old, and 7/12 (58%) patients with a serum bilirubin ≥ ULN prior to HSCT and in 11/67 (16%) patients with a serum bilirubin < ULN prior to HSCT.

In the pivotal study (N=164), hyperbilirubinaemia and increased transaminases were reported in 35 (21%) and 43 (26%) patients, respectively. Grade ≥ 3 hyperbilirubinaemia and increased transaminases were reported in 9 (6%) and 11 (7%) patients, respectively. The median time to onset of hyperbilirubinaemia and increased transaminases was 73 days and 29 days, respectively.

For clinical management of hepatotoxicity, including VOD/SOS, see section 4.4.

Myelosuppression/cytopenias

In the pivotal study (N=164), thrombocytopenia and neutropenia were reported in 83 (51%) and 81 (49%) patients, respectively. Grade 3 thrombocytopenia and neutropenia were reported in 23 (14%) and 33 (20%) patients, respectively. Grade 4 thrombocytopenia and neutropenia were reported in 46 (28%) and 45 (27%) patients, respectively. Febrile neutropenia, which may be life-threatening, was reported in 43 (26%) patients.

For clinical management of myelosuppression/cytopenias, see section 4.4.

Infections

In the pivotal study (N=164), infections, including serious infections, some of which were life-threatening or fatal, were reported in 79 (48%) patients. The frequencies of specific infections were: sepsis and bacteraemia (17%), lower respiratory tract infection (12%), upper respiratory tract infection (12%), fungal infection (9%), viral infection (7%), gastrointestinal infection (4%), skin infection (4%), and bacterial infection (1%). Fatal infections, including pneumonia, neutropenic sepsis, sepsis, septic shock, and pseudomonal sepsis, were reported in 8 (5%) patients.

For clinical management of infections, see section 4.4.

Bleeding/haemorrhage

In the pivotal clinical study (N=164), bleeding/haemorrhagic events, mostly mild in severity, were reported in 54/ (33%) patients. The frequencies of specific bleeding/haemorrhagic events were: epistaxis (15%), upper gastrointestinal haemorrhage (6%), lower gastrointestinal haemorrhage (4%), and central nervous system (CNS) haemorrhage (1%). Grade 3/4 bleeding/haemorrhagic events were reported in 8/164 (5%) patients. One Grade 5 bleeding/haemorrhagic event (intra-abdominal haemorrhage) was reported.

For clinical management of bleeding/haemorrhagic events, see section 4.4.

Infusion related reactions

In the pivotal study (N=164), infusion related reactions were reported in 17 (10%) patients. All events were Grade ≤ 2 in severity. Infusion related reactions generally occurred in Cycle 1 and shortly after the end of the inotuzumab ozogamicin infusion and resolved spontaneously or with medical management.

For clinical management of infusion related reactions, see section 4.4.

Tumour lysis syndrome (TLS)

In the pivotal study (N=164), TLS, which may be life-threatening or fatal, was reported in 4/164 (2%) patients. Grade 3/4 TLS was reported in 3 (2%) patients. TLS occurred shortly after the end of the inotuzumab ozogamicin infusion and resolved with medical management.

For clinical management of TLS, see section 4.4.

QT interval prolongation

In the pivotal study (N=164), maximum increases in QT interval corrected for heart rate using the Fridericia formula (QTcF) ≥ 30 msec and ≥ 60 msec from baseline were measured in 30/162 (19%) and 4/162 (3%) patient, respectively. An increase in QTcF interval of > 450 msec was observed in 26/162 (16%) patients. No patients had an increase in QTcF interval > 500 msec. Grade 2 QT interval prolongation was reported in 2/164 (1%) patients. No Grade ≥ 3 QT interval prolongation or events of Torsades de Pointes were reported.

For periodic monitoring of ECG and electrolyte levels, see section 4.4.

Increased amylase and lipase

In the pivotal study (N=164), increases in amylase and lipase were reported in 8 (5%) and 15 (9%) patients, respectively. Increases in Grade ≥ 3 amylase and lipase were reported in 3 (2%) and 7 (4%) patients, respectively.

For periodic monitoring of increased amylase and lipase, see section 4.4.

Immunogenicity

In clinical studies of inotuzumab ozogamicin in adult patients with relapsed or refractory ALL, 7/236 (3%) patients tested positive for anti-inotuzumab ozogamicin antibodies (ADA). No patients tested positive for neutralising ADA. In patients who tested positive for ADA, no effect on clearance of BESPONSA was detected based on population-pharmacokinetic analysis. The number of patients with positive ADA was too small to assess the impact of ADA on efficacy and safety.

In clinical study ITCC-059 of inotuzumab ozogamicin in paediatric patients with relapsed or refractory ALL (N=51), the incidence of ADA against inotuzumab ozogamicin was 0%.

Paediatric population

BESPONSA has been evaluated in 53 paediatric patients ≥ 1 and < 18 years of age with relapsed or refractory CD22-positive B cell precursor ALL in Study ITCC-059 (see section 5.1).

The most common adverse reactions (> 30%) in the paediatric study ITCC-059 were thrombocytopenia (60%), pyrexia (52%), anaemia (48%), vomiting (48%) neutropenia (44%), infection (44%), haemorrhage (40%), febrile neutropenia (32%), nausea (32%), abdominal pain (32%) in the Phase 1 Cohort and pyrexia (46%), thrombocytopenia (43%), anaemia (43%), vomiting (43%), neutropenia (36%), leukopenia (36%), nausea (32%), infection (32%), transaminase increased (32%), and haemorrhage (32%) in the Phase 2 Cohort.

In the Phase 1 Cohort, 2/25 (8.0%) patients had VOD (neither received transplant) and 6/28 (21.4%) patients in the Phase 2 Cohort had VOD, with a post-HSCT VOD rate of 5/18 (27.8% [95% CI: 9.69-53.48]). In the Phase 1 Cohort, 8/25 patients (32%) and 18/28 (64%) in the Phase 2 Cohort had a follow-up HSCT. The post-HSCT non-relapse mortality rate was 2/8 (25%) and 5/18 (28%) in the Phase 1 Cohort and the Phase 2 Cohort, respectively.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In clinical studies in patients with relapsed or refractory ALL, the maximum single and multiple doses of inotuzumab ozogamicin were 0.8 mg/m^2 and 1.8 mg/m^2, respectively, per cycle, given as 3 divided doses on Days 1 (0.8 mg/m^2), 8 (0.5 mg/m^2), and 15 (0.5 mg/m^2) (see section 4.2). Overdoses may result in adverse reactions that are consistent with the reactions observed at the recommended therapeutic dose (see section 4.8).

In the event of an overdose, the infusion should be temporarily interrupted, and patients should be monitored for liver and haematological toxicities (see section 4.2). Re-initiation of BESPONSA at the correct therapeutic dose should be considered when all toxicities have resolved.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, monoclonal antibodies and antibody drug conjugates, CD22 (Clusters of Differentiation 22) inhibitors, ATC code: L01FB01.

Mechanism of action

Inotuzumab ozogamicin is an ADC composed of a CD22-directed monoclonal antibody that is covalently linked to N-acetyl-gamma-calicheamicin dimethylhydrazide. Inotuzumab is a humanised immunoglobulin class G subtype 4 (IgG4) antibody that specifically recognises human CD22. The small molecule, N-acetyl-gamma-calicheamicin, is a cytotoxic product.

N-acetyl-gamma-calicheamicin is covalently attached to the antibody via an acid-cleavable linker. Nonclinical data suggest that the anticancer activity of BESPONSA is due to the binding of the ADC to CD22-expressing tumour cells, followed by internalisation of the ADC-CD22 complex, and the intracellular release of N-acetyl-gamma-calicheamicin dimethylhydrazide via hydrolytic cleavage of the linker. Activation of N-acetyl-gamma-calicheamicin dimethylhydrazide induces double-stranded DNA breaks, subsequently inducing cell cycle arrest and apoptotic cell death.

Clinical efficacy and safety

Patients with relapsed or refractory ALL who have received 1 or 2 prior treatment regimens for ALL - Study 1

The safety and efficacy of BESPONSA in patients with relapsed or refractory CD22-positive ALL were evaluated in an open-label, international, multicentre, Phase 3 study (Study 1) in which patients were randomised to receive BESPONSA (N=164 [164 received treatment) or Investigator's choice of chemotherapy (N=162 [143 received treatment]), specifically fludarabine plus cytarabine plus granulocyte colony-stimulating factor (FLAG) (N=102 [93 received treatment]), mitoxantrone/cytarabine (MXN/Ara-C) (N=38 [33 received treatment]), or high dose cytarabine (HIDAC) (N=22 [17 received treatment]).

Eligible patients were ≥ 18 years of age with Philadelphia chromosome negative (Ph^-) or Ph^+ relapsed or refractory B-cell CD22-positive precursor ALL.

CD22 expression was assessed using flow cytometry based on bone marrow aspirate. In patients with an inadequate bone marrow aspirate sample, a peripheral blood sample was tested. Alternatively, CD22 expression was assessed using immunohistochemistry in patients with an inadequate bone marrow aspirate and insufficient circulating blasts.

In the clinical study, the sensitivity of some local tests was lower than the central laboratory test. Therefore, only validated tests with demonstrated high sensitivity should be used.

All patients were required to have ≥ 5% bone marrow blasts and to have received 1 or 2 prior induction chemotherapy regimens for ALL. Patients with Ph^+ B-cell precursor ALL were required to have failed treatment with at least 1 second or third generation TKI and standard chemotherapy. Table 1 (see section 4.2) shows the dosing regimen used to treat patients.

The co-primary endpoints were CR/CRi, assessed by a blinded independent endpoint adjudication committee (EAC), and overall survival (OS). The secondary endpoints included MRD negativity, duration of remission (DoR), HSCT rate, and progression-free survival (PFS).
The primary analysis of CR/CRi and MRD negativity was conducted in the initial 218 randomised patients and the analysis of OS, PFS, DoR, and HSCT rate was conducted in all 326 randomised patients.

Among all 326 randomised patients (ITT population), 215 (66%) patients had received 1 prior treatment regimen and 108 (33%) patients had received 2 prior treatment regimens for ALL. The median age was 47 years (range: 18-79 years), 206 (63%) patients had a duration of first remission < 12 months, and 55 (17%) patients had undergone an HSCT prior to receiving BESPONSA or Investigator's choice of chemotherapy. The 2 treatment groups were generally balanced with respect to the baseline demographics and disease characteristics. A total of 276 (85%) patients had Ph^- ALL. Of the 49 (15%) patients with Ph^+ ALL, 4 patients did not receive a prior TKI, 28 patients received 1 prior TKI, and 17 patients received 2 prior TKIs. Dasatinib was the most commonly received TKI (42 patients) followed by imatinib (24 patients).

Baseline characteristics were similar in the initial 218 patients randomised.

Of the 326 patients (ITT population), 253 patients had samples that were evaluable for CD22 testing by both local and central laboratory. By central and local laboratory tests, 231/253 (91.3%) patients and 130/253 (51.4%) patients, respectively, had ≥ 70% CD22-positive leukaemic blasts at baseline.

Table 6 shows the efficacy results from this study.

Table 6. Study 1: Efficacy results in patients ≥ 18 years of age with relapsed or refractory B-cell precursor ALL who received 1 or 2 prior treatment regimens for ALL

	BESPONSA (N=109)	**HIDAC, FLAG, or MXN/Ara-C (N=109)**
CR[a]/CRi[b]; n (%) [95% CI]	88 (80.7%) [72.1%-87.7%]	32 (29.4%) [21.0%-38.8%]
	2-sided p-value < 0.0001	
CR[a]; n (%) [95% CI]	39 (35.8%) [26.8%-45.5%]	19 (17.4%) [10.8%-25.9%]
	2-sided p-value = 0.0022	
CRi[b]; n (%) [95% CI]	49 (45.0%) [35.4%-54.8%]	13 (11.9%) [6.5%-19.5%]
	2-sided p-value < 0.0001	
MRD negativity[c] for patients achieving CR/CRi; rate[d] (%) [95% CI]	69/88 (78.4%) [68.4%-86.5%]	9/32 (28.1%) [13.7%-46.7%]
	2-sided p-value < 0.0001	
	BESPONSA (N=164)	**HIDAC, FLAG, or MXN/Ara-C (N=162)**
Median OS; months [95% CI]	7.7 [6.0 to 9.2]	6.2 [4.7 to 8.3]
	Hazard ratio [95% CI] = 0.751 [0.588-0.959] 2-sided p-value = 0.0210	
Median PFS[e, f]; months [95% CI]	5.0 [3.9-5.8]	1.7 [1.4-2.1]
	Hazard ratio [95% CI] = 0.450 [0.348-0.581] 2-sided p-value < 0.0001	
Median DoR[g]; months [95% CI]	3.7 [2.8 to 4.6]	0.0 [-,-]
	Hazard ratio [95% CI] = 0.471 [0.366-0.606] 2-sided p-value < 0.0001	

Abbreviations: ALL=acute lymphoblastic leukaemia; ANC=absolute neutrophil counts; Ara-C=cytarabine; CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete haematological recovery; DoR=duration of remission; EAC=Endpoint Adjudication Committee; FLAG=fludarabine + cytarabine + granulocyte colony-stimulating factor; HIDAC=high dose cytarabine; HSCT=haematopoietic stem cell transplant; ITT=intent-to-treat; MRD=minimal residual disease; MXN=mitoxantrone; N/n=number of patients; OS=overall survival; PFS=progression-free survival.

Table 6. Study 1: Efficacy results in patients ≥ 18 years of age with relapsed or refractory B-cell precursor ALL who received 1 or 2 prior treatment regimens for ALL

[a] CR, per EAC, was defined as < 5% blasts in the bone marrow and the absence of peripheral blood leukaemic blasts, full recovery of peripheral blood counts (platelets ≥ 100×10^9/L and ANC ≥ 1×10^9/L) and resolution of any extramedullary disease.

[b] CRi, per EAC, was defined as < 5% blasts in the bone marrow and the absence of peripheral blood leukaemic blasts, partial recovery of peripheral blood counts (platelets < 100×10^9/L and/or ANC < 1×10^9/L) and resolution of any extramedullary disease.

[c] MRD negativity was defined by flow cytometry as leukaemic cells comprising < 1×10^{-4} (< 0.01%) of bone marrow nucleated cells.

[d] Rate was defined as number of patients who achieved MRD negativity divided by the total number of patients who achieved CR/CRi per EAC.

[e] PFS was defined as the time from date of randomisation to earliest date of the following events: death, progressive disease (including objective progression, relapse from CR/CRi, treatment discontinuation due to global deterioration of health status), and start of new induction therapy or post-therapy HSCT without achieving CR/CRi.

[f] In the standard definition of PFS, defined as the time from date of randomisation to earliest date of the following events: death, progressive disease (including objective progression and relapse from CR/CRi), the HR was 0.568 (2-sided p-value=0.0002) and median PFS was 5.6 months and 3.7 months in the BESPONSA and Investigator's choice of chemotherapy arm, respectively.

[g] Duration of remission was defined as the time since first response of CR[a] or CRi[b] per Investigator's assessment to the date of a PFS event or censoring date if no PFS event was documented. Analysis was based on the ITT population with patients without remission being given a duration of zero and considered an event.

Among the initial 218 randomised patients, 64/88 (73%) and 21/88 (24%) of responding patients per EAC achieved a CR/CRi in Cycles 1 and 2, respectively, in the BESPONSA arm. No additional patients achieved CR/CRi after Cycle 3 in the BESPONSA arm.

CR/CRi and MRD negativity findings in the initial 218 randomised patients were consistent with those seen in all 326 randomised patients.

Among all 326 randomised patients, the survival probability at 24 months was 22.8% in the BESPONSA arm and 10% in the Investigator's choice of chemotherapy arm.

A total of 79/164 (48.2%) patients in the BESPONSA arm and 36/162 (22.2%) patients in the Investigator's choice of chemotherapy arm had a follow-up HSCT. This included 70 and 18 patients in the BESPONSA and Investigator's choice of chemotherapy arm, respectively, who proceeded directly to HSCT. In those patients who proceeded directly to HSCT, there was a median gap of 4.8 weeks (range: 1-19 weeks) between the final dose of inotuzumab ozogamicin and HSCT. The OS improvement for BESPONSA versus Investigator's choice of chemotherapy arm was seen in patients who underwent HSCT. Although there was a higher frequency of early deaths post-HSCT (at Day 100) in the BESPONSA arm, there was evidence of a late survival benefit for BESPONSA. In patients who underwent a follow-up HSCT, the median OS was 11.9 months (95% CI: 9.2, 20.6) for BESPONSA versus 19.8 months (95% CI: 14.6, 26.7) for Investigator's choice of chemotherapy. At month 24, the survival probability was 38.0% (95% CI: 27.4, 48.5) versus 35.5% (95% CI: 20.1, 51.3) for BESPONSA and Investigator's choice of chemotherapy, respectively. Furthermore, at month 24, the survival probability was 38.0% (95% CI: 27.4, 48.5) for patients who underwent a follow-up HSCT compared to 8.0% (95% CI: 3.3, 15.3) for patients who did not undergo a follow-up HSCT in the BESPONSA arm.

BESPONSA improved OS versus Investigator's choice of chemotherapy for all stratification factors including duration of first remission ≥12 months, Salvage 1 status, and age at randomisation < 55 years. There was also a trend for better OS with BESPONSA for patients with other prognostic factors (Ph^-, no prior HSCT, ≥ 90% leukaemic blasts CD22-positive at baseline, no baseline peripheral blasts, and baseline haemoglobin ≥ 10 g/dL, based on exploratory analyses). Patients with mixed-lineage leukaemia (MLL) gene rearrangements, including t (4;11), that generally have lower

CD22 expression prior to treatment, had a worse OS outcome following treatment with BESPONSA or Investigator's choice of chemotherapy.

For patient-reported outcomes, most functioning and symptom scores were in favour of BESPONSA compared to Investigator's choice of chemotherapy. Patient-reported outcomes measured using the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30), were significantly better for BESPONSA by estimated mean postbaseline scores (BESPONSA and Investigator's choice of chemotherapy, respectively) for role functioning (64.7 versus 53.4, improvement grade small), physical functioning (75.0 versus 68.1, improvement grade small), social functioning (68.1 versus 59.8, improvement grade medium), and appetite loss (17.6 versus 26.3, improvement grade small) compared to Investigator's choice of chemotherapy. There was a trend in favour of BESPONSA, improvement grade small, for estimated mean postbaseline scores (BESPONSA and Investigator's choice, respectively) in global health status/Quality of Life (QoL) (62.1 versus 57.8), cognitive functioning (85.3 versus 82.5), dyspnoea (14.7 versus 19.4), diarrhoea (5.9 versus 8.9), fatigue (35.0 versus 39.4). There was a trend in favour of BESPONSA for estimated mean postbaseline scores from the EuroQoL 5 Dimension (EQ-5D) questionnaire, (BESPONSA and Investigator's choice of chemotherapy, respectively) for the EQ-5D index (0.80 versus 0.76, minimally important difference for cancer = 0.06).

Patients with relapsed or refractory ALL who have received 2 or more prior treatment regimens for ALL - Study 2

The safety and efficacy of BESPONSA were evaluated in a single-arm, open-label, multicentre Phase 1/2 study (Study 2). Eligible patients were ≥ 18 years of age with relapsed or refractory B-cell precursor ALL.

Of 93 screened patients, 72 patients were assigned to study drug and treated with BESPONSA. The median age was 45 years (range: 20-79 years); 76.4% were Salvage status ≥ 2; 31.9% had received a prior HSCT and 22.2% were Ph^+. The most common reasons for treatment discontinuation were: disease progression/relapse (30 [41.7%)], resistant disease (4 [5.6%]); HSCT (18 [25.0%]), and adverse events (13 [18.1%]).

In the Phase 1 portion of the study, 37 patients received BESPONSA at a total dose of 1.2 mg/m^2 (N=3), 1.6 mg/m^2 (N=12), or 1.8 mg/m^2 (N=22). The recommended BESPONSA dose was determined to be 1.8 mg/m^2/cycle administered at a dose of 0.8 mg/m^2 on Day 1 and 0.5 mg/m^2 on Days 8 and 15 of a 28-day cycle with a dose reduction upon achieving CR/CRi.

In the Phase 2 portion of the study, patients had to have received at least 2 prior treatment regimens for ALL and patients with Ph^+ B-cell ALL had to have failed treatment with at least 1 TKI. Of the 9 patients with Ph^+ B-cell ALL, 1 patient had received 1 previous TKI and 1 patient had received no prior TKIs.

Table 7 shows the efficacy results from this study.

Table 7. Study 2: Efficacy results in patients ≥ 18 years of age with relapsed or refractory B-cell precursor ALL who received 2 or more prior treatment regimens for ALL

	BESPONSA (N=35)
CR[a]/CRi[b]; n (%) [95% CI]	24 (68.6%) [50.7%-83.2%]
CR[a]; n (%) [95% CI]	10 (28.6%) [14.6%-46.3%]
CRi[b]; n (%) [95% CI]	14 (40.0%) [23.9%-57.9%]
Median DoR[f]; months [95% CI]	2.2

Table 7. Study 2: Efficacy results in patients ≥ 18 years of age with relapsed or refractory B-cell precursor ALL who received 2 or more prior treatment regimens for ALL

	BESPONSA (N=35)
	[1.0 to 3.8]
MRD negativity[c] for patients achieving CR/CRi; rate[d] (%) [95% CI]	18/24 (75%) [53.3%-90.2%]
Median PFS[e]; months [95% CI]	3.7 [2.6 to 4.7]
Median OS; months [95% CI]	6.4 [4.5 to 7.9]

Abbreviations: ALL=acute lymphoblastic leukaemia; ANC=absolute neutrophil counts; CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete haematological recovery; DoR=duration of remission; HSCT=haematopoietic stem cell transplant; MRD=minimal residual disease; N/n=number of patients; OS=overall survival; PFS=progression-free survival.

[a, b, c, d, e, f] For definition, see Table 6 (with the exception that CR/CRi was not per EAC for Study 2)

In the Phase 2 portion of the study, 8/35 (22.9%) patients had a follow-up HSCT.

Paediatric population

Study ITCC-059 has been performed in compliance with the agreed Paediatric Investigation Plan (see section 4.2 for information on paediatric use).

Study ITCC-059 was a Phase 1/2 multicentre, single-arm, open-label study conducted in 53 paediatric patients ≥ 1 and < 18 years of age with relapsed or refractory CD22-positive B-cell precursor ALL to identify a recommended Phase 2 Dose (Phase 1) and to further evaluate the efficacy, safety, and tolerability of the selected BESPONSA dose as a monotherapy agent (Phase 2). The study also evaluated the Pharmacokinetics and Pharmacodynamics of BESPONSA as monotherapy (see section 5.2).

In the Phase 1 Cohort (N=25), two dose levels were examined (initial dose of 1.4 mg/m^2 per cycle and an initial dose of 1.8 mg/m^2 per cycle). In the Phase 2 Cohort (N=28), patients were treated at the initial dose of 1.8 mg/m^2 per cycle (0.8mg/m^2 on Day 1, 0.5mg/m^2 on Days 8 and 15) followed by a dose reduction to 1.5mg/m^2 per cycle for patients in remission. In both Cohorts, patients received a median of 2 cycles of therapy (range: 1 to 4 cycles). In the Phase 1 Cohort, the median age was 11 years (range: 1-16 years), and 52% of patients had second or greater relapsed B-cell precursor ALL. In the Phase 2 Cohort, the median age was 7.5 years (range: 1-17 years), and 57% of patients had second or greater relapsed B-cell precursor ALL.

Efficacy was evaluated on the basis of Objective Response Rate (ORR), defined as the rate of patients with CR+CRp+CRi. In the Phase 1 Cohort, 20/25 (80%) patients had CR, the ORR was 80% (95% CI: 59.3-93.2), and the median Duration of Response (DoR) was 8.0 months (95% CI: 3.9-13.9). In the Phase 2 Cohort, 18/28 (64%) patients had CR, the ORR was 79% (95% CI: 59.0-91.7), and the DoR was 7.6 months (95% CI: 3.3-NE). In the Phase 1 Cohort, 8/25 patients (32%) and 18/28 (64%) in the Phase 2 Cohort had a follow-up HSCT.

5.2 Pharmacokinetic properties

In patients with relapsed or refractory ALL treated with inotuzumab ozogamicin at the recommended starting dose of 1.8 mg/m^2/cycle (see section 4.2), steady-state exposure was achieved by Cycle 4. The mean (SD) maximum serum concentration (C_{max}) of inotuzumab ozogamicin was 308 ng/mL (362). The mean (SD) simulated total area under the concentration-time curve (AUC) per cycle at steady state was 100 mcg●h/mL (32.9).

Distribution

In vitro, the binding of the N-acetyl-gamma-calicheamicin dimethylhydrazide to human plasma proteins is approximately 97%. *In vitro*, N-acetyl-gamma-calicheamicin dimethylhydrazide is a substrate of P-glycoprotein (P-gp). In humans, the total volume of distribution of inotuzumab ozogamicin was approximately 12 L.

Biotransformation

In vitro, N-acetyl-gamma-calicheamicin dimethylhydrazide was primarily metabolised via nonenzymatic reduction. In humans, serum N-acetyl-gamma-calicheamicin dimethylhydrazide levels were typically below the limit of quantitation (50 pg/mL), but sporadic measurable levels of unconjugated calicheamicin up to 276 pg/mL occurred in some patients.

Elimination

Inotuzumab ozogamicin pharmacokinetics were well characterised by a 2-compartment model with linear and time-dependent clearance components. In 234 patients with relapsed or refractory ALL, the clearance of inotuzumab ozogamicin at steady state was 0.0333 L/h, and the terminal elimination half-life ($t_{½}$) at the end of Cycle 4 was approximately 12.3 days. Following administration of multiple doses, a 5.3 times accumulation of inotuzumab ozogamicin was observed between Cycles 1 and 4.

Based on a population pharmacokinetic analysis in 765 patients, body surface area was found to significantly affect inotuzumab ozogamicin disposition. The dose of inotuzumab ozogamicin is administered based on body surface area (see section 4.2).

Pharmacokinetics in specific groups of subjects or patients

Age, race and gender

Based on a population pharmacokinetic analysis, age, race and gender did not significantly affect inotuzumab ozogamicin disposition.

Hepatic impairment

No formal pharmacokinetic studies of inotuzumab ozogamicin have been conducted in patients with hepatic impairment.

Based on a population pharmacokinetic analysis in 765 patients, the clearance of inotuzumab ozogamicin in patients with hepatic impairment defined by National Cancer Institute Organ Dysfunction Working Group (NCI ODWG) category B1 (total bilirubin ≤ ULN and AST > ULN; N=133) or B2 (total bilirubin > 1.0-1.5 × ULN and AST any level; N=17) was similar to patients with normal hepatic function (total bilirubin/AST ≤ ULN; N=611) (see section 4.2). In 3 patients with hepatic impairment defined by NCI ODWG category C (total bilirubin > 1.5-3 × ULN and AST any level) and 1 patient with hepatic impairment defined by NCI ODWG category D (total bilirubin > 3 × ULN and AST any level), inotuzumab ozogamicin clearance did not appear to be reduced.

Renal impairment

No formal pharmacokinetic studies of inotuzumab ozogamicin have been conducted in patients with renal impairment.

Based on population pharmacokinetic analysis in 765 patients, the clearance of inotuzumab ozogamicin in patients with mild renal impairment (CL_{cr} 60-89 mL/min; N=237), moderate renal impairment (CL_{cr} 30-59 mL/min; N=122), or severe renal impairment (CL_{cr} 15-29 mL/min; N=4) was

similar to patients with normal renal function (CL_{cr} ≥ 90 mL/min; N=402) (see section 4.2). Inotuzumab ozogamicin has not been studied in patients with end-stage renal disease (see section 4.2).

Paediatric population

At the adult recommended dose, the median exposure in paediatric patients with ALL (aged ≥1 and < 18 years) was 25% higher than those in adults. The clinical relevance of the increased exposure is unknown.

Cardiac electrophysiology

Population pharmacokinetic/pharmacodynamic evaluation suggested a correlation between increasing inotuzumab ozogamicin serum concentrations and prolongation of QTc intervals in ALL and non-Hodgkin's lymphoma (NHL) patients. The median (upper bound of the 95% CI) for the change in QTcF at a supratherapeutic C_{max} concentration was 3.87 msec (7.54 msec).

In a randomised clinical study in patients with relapsed or refractory ALL (Study 1), maximum increases in QTcF interval of ≥ 30 msec and ≥ 60 msec from baseline were measured in 30/162 (19%) and 4/162 (3%) patients in the inotuzumab ozogamicin arm, respectively, versus18/124 (15%) and 3/124 (2%) in the Investigator's choice of chemotherapy arm, respectively. Increases in QTcF interval of > 450 msec and > 500 msec were observed in 26/162 (16%) and none of the patients in the inotuzumab ozogamicin arm versus 12/124 (10%) and 1/124 (1%) patients in the Investigator's choice of chemotherapy arm, respectively (see section 4.8).

5.3 Preclinical safety data

Repeated dose toxicity

In animals, the primary target organs included the liver, bone marrow and lymphoid organs with associated haematological changes, kidney, and nervous system. Other observed changes included male and female reproductive organ effects (see below) and preneoplastic and neoplastic liver lesions (see below). Most effects were reversible to partially reversible except for effects in the liver and nervous system. The relevance of the irreversible animal findings to humans is uncertain.

Genotoxicity

Inotuzumab ozogamicin was clastogenic *in vivo* in the bone marrow of male mice. This is consistent with the known induction of DNA breaks by calicheamicin. N-acetyl-gamma-calicheamicin dimethylhydrazide (the cytotoxic agent released from inotuzumab ozogamicin) was mutagenic in an *in vitro* bacterial reverse mutation (Ames) assay.

Carcinogenic potential

Formal carcinogenicity studies have not been conducted with inotuzumab ozogamicin. In toxicity studies, rats developed oval cell hyperplasia, altered hepatocellular foci, and hepatocellular adenomas in the liver at approximately 0.3 times the human clinical exposure based on AUC. In 1 monkey, a focus of hepatocellular alteration was detected at approximately 3.1 times the human clinical exposure based on AUC at the end of the 26-week dosing period. The relevance of these animal findings to humans is uncertain.

Reproductive toxicity

Administration of inotuzumab ozogamicin to female rats at the maternally toxic dose (approximately 2.3 times the human clinical exposure based on AUC) prior to mating and during the first week of gestation resulted in embryo-foetal toxicity, including increased resorptions and decreased viable embryos. The maternally toxic dose (approximately 2.3 times the human clinical exposure based on

AUC) also resulted in foetal growth retardation, including decreased foetal weights and delayed skeletal ossification. Slight foetal growth retardation in rats also occurred at approximately 0.4 times the human clinical exposure based on AUC (see section 4.6).

Inotuzumab ozogamicin is considered to have the potential to impair reproductive function and fertility in men and women based on non-clinical findings (see section 4.6). In repeat dose toxicity studies in rats and monkeys, female reproductive findings included atrophy of ovaries, uterus, vagina, and mammary gland. The no observed adverse effect level (NOAEL) for the effects on female reproductive organs in rats and monkeys was approximately 2.2 and 3.1 times the human clinical exposure based on AUC, respectively. In repeat dose toxicity studies in rats, male reproductive findings included testicular degeneration, associated with hypospermia, and prostatic and seminal vesicle atrophy. The NOAEL was not identified for the effects on male reproductive organs, which were observed at approximately 0.3 times the human clinical exposure based on AUC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Polysorbate 80
Sodium chloride
Tromethamine

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

5 years.

Reconstituted solution

BESPONSA contains no bacteriostatic preservatives. The reconstituted solution must be used immediately. If the reconstituted solution cannot be used immediately, it may be stored for up to 4 hours in a refrigerator (2 °C-8 °C). Protect from light and do not freeze.

Diluted solution

The diluted solution must be used immediately or stored at room temperature (20 °C-25 °C) or in a refrigerator (2 °C-8 °C). The maximum time from reconstitution through the end of administration should be ≤ 8 hours, with ≤ 4 hours between reconstitution and dilution. Protect from light and do not freeze.

6.4 Special precautions for storage

Store in a refrigerator (2 °C-8 °C).
Do not freeze.
Store in the original carton in order to protect from light.

For storage conditions after reconstitution and dilution, see section 6.3.

6.5 Nature and contents of container

Type I amber glass vial with chlorobutyl rubber stopper and crimp seal with flip off cap containing 1 mg of powder.

Each carton contains 1 vial.

6.6 Special precautions for disposal and other handling

Instructions for reconstitution, dilution, and administration

Use appropriate aseptic technique for the reconstitution and dilution procedures. Inotuzumab ozogamicin (which has a density of 1.02 g/mL at 20°C) is light sensitive and should be protected from ultraviolet light during reconstitution, dilution, and administration.

The maximum time from reconstitution through the end of administration should be ≤ 8 hours, with ≤ 4 hours between reconstitution and dilution.

Reconstitution

- Calculate the dose (mg) and number of vials of BESPONSA required.
- Reconstitute each 1 mg vial with 4 mL of water for injection, to obtain a single-use solution of 0.25 mg/mL of BESPONSA.
- Gently swirl the vial to aid dissolution. Do not shake.
- Inspect the reconstituted solution for particulates and discolouration. The reconstituted solution must be clear to slightly cloudy, colourless, and essentially free of visible foreign matter. If particles or discolouration are observed, do not use.
- BESPONSA contains no bacteriostatic preservatives. The reconstituted solution must be used immediately. If the reconstituted solution cannot be used immediately, it may be stored in a refrigerator (2 °C-8 °C) for up to 4 hours. Protect from light and do not freeze.

Dilution

- Calculate the required volume of the reconstituted solution needed to obtain the appropriate dose according to patient body surface area. Withdraw this amount from the vial(s) using a syringe. Protect from light. Discard any unused reconstituted solution left in the vial.
- Add the reconstituted solution to an infusion container with sodium chloride 9 mg/mL (0.9%) solution for injection, to a total nominal volume of 50 mL. The final concentration should be between 0.01 and 0.1 mg/mL. Protect from light. An infusion container made of polyvinyl chloride (PVC) (di(2-ethylhexyl)phthalate [DEHP]- or non-DEHP-containing), polyolefin (polypropylene and/or polyethylene), or ethylene vinyl acetate (EVA) is recommended.
- Gently invert the infusion container to mix the diluted solution. Do not shake.
- The diluted solution must be used immediately, stored at room temperature (20 °C-25 °C), or in a refrigerator (2 °C-8 °C). The maximum time from reconstitution through the end of administration should be ≤ 8 hours, with ≤ 4 hours between reconstitution and dilution. Protect from light and do not freeze.

Administration

- If the diluted solution is stored in a refrigerator (2 °C-8 °C), it must be allowed to equilibrate at room temperature (20 °C-25 °C) for approximately 1 hour prior to administration.
- Filtration of the diluted solution is not required. However, if the diluted solution is filtered, polyethersulphone (PES)-, polyvinylidene fluoride (PVDF)-, or hydrophilic polysulphone (HPS)-based filters are recommended. Do not use filters made of nylon or mixed cellulose ester (MCE).

- Protect the intravenous bag from light using an ultraviolet light-blocking cover (i.e., amber, dark brown, or green bags or aluminium foil) during infusion. The infusion line does not need to be protected from light.
- Infuse the diluted solution for 1 hour at a rate of 50 mL/h at room temperature (20 °C-25 °C). Protect from light. Infusion lines made of PVC (DEHP or non-DEHP-containing), polyolefin (polypropylene and/or polyethylene), or polybutadiene are recommended.

Do not mix BESPONSA or administer as an infusion with other medicinal products.

Table 8 shows the storage times and conditions for reconstitution, dilution, and administration of BESPONSA.

Table 8. Storage times and conditions for reconstituted and diluted BESPONSA solution

← Maximum time from reconstitution through the end of administration ≤ 8 hours[a] →		
Reconstituted solution	**Diluted solution**	
	After start of dilution	**Administration**
Use reconstituted solution immediately or after being stored in a refrigerator (2 °C-8 °C) for up to 4 hours. Protect from light. Do not freeze.	Use diluted solution immediately or after being stored at room temperature (20 °C-25 °C) or in a refrigerator (2 °C-8 °C). The maximum time from reconstitution through the end of administration should be ≤ 8 hours, with ≤ 4 hours between reconstitution and dilution. Protect from light. Do not freeze.	If the diluted solution is stored in a refrigerator (2 °C-8 °C), bring it to room temperature (20 °C-25 °C) for approximately 1 hour prior to administration. Administer diluted solution as a 1-hour infusion at a rate of 50 mL/h at room temperature (20 °C-25 °C). Protect from light.

[a] With ≤ 4 hours between reconstitution and dilution.

Disposal

BESPONSA is for single use only.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1200/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 June 2017
Date of latest renewal: 16 February 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Wyeth Pharmaceutical Division of Wyeth Holdings LLC,
401 North Middletown Road,
Pearl River, New York (NY) 10965
United States (USA)

Name and address of the manufacturer responsible for batch release

Pfizer Service Company BV
Hoge Wei 10
B-1930, Zaventem
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF MEDICINAL PRODUCT

BESPONSA 1 mg powder for concentrate for solution for infusion
inotuzumab ozogamicin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 1 mg of inotuzumab ozogamicin.
After reconstitution each vial contains 0.25 mg/mL of inotuzumab ozogamicin.

3. LIST OF EXCIPIENTS

Sucrose
Polysorbate 80
Sodium chloride
Tromethamine

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
1 vial
1 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after reconstitution and dilution.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1200/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

BESPONSA 1 mg powder for concentrate
inotuzumab ozogamicin
Intravenous use after reconstitution and dilution.

2. METHOD OF ADMINISTRATION

Single use only.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

BESPONSA 1 mg powder for concentrate for solution for infusion
inotuzumab ozogamicin

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What BESPONSA is and what it is used for

The active substance in BESPONSA is inotuzumab ozogamicin. This belongs to a group of medicines that target cancer cells. These medicines are called antineoplastic agents.

BESPONSA is used to treat adults with acute lymphoblastic leukaemia. Acute lymphoblastic leukaemia is a cancer of blood where you have too many white blood cells. BESPONSA is intended for the treatment of acute lymphoblastic leukaemia for adult patients who have previously tried other treatments and for whom those treatments have failed.

BESPONSA acts by attaching to cells with a protein called CD22. Lymphoblastic leukaemia cells have this protein. Once attached to the lymphoblastic leukaemia cells, the medicine delivers a substance into the cells that interferes with the cells' DNA and eventually kills them.

2. What you need to know before you are given BESPONSA

Do not use BESPONSA if you

- are allergic to inotuzumab ozogamicin or any of the other ingredients of this medicine (listed in section 6).
- have previously had severe venoocclusive disease (a condition in which the blood vessels in the liver become damaged and blocked by blood clots) which was confirmed or have ongoing venoocclusive disease.
- have serious ongoing liver disease, e.g., cirrhosis (a condition in which the liver does not function properly due to long-term damage), nodular regenerative hyperplasia (a condition with signs and symptoms of portal hypertension that can be caused by chronic use of medicines), active hepatitis (a disease characterised by inflammation of the liver).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before you are given BESPONSA if you:

- have a history of liver problems or liver diseases or if you have signs and symptoms of a serious condition called hepatic venoocclusive disease, a condition in which the blood vessels in the liver become damaged and blocked by blood clots. Venoocclusive disease may be fatal and is associated with rapid weight gain, pain in the upper right side of your abdomen (belly), increase in the size of the liver, build-up of fluid causing abdominal swelling, and blood tests showing increases in bilirubin and/or liver enzymes (that may result in yellowing of the skin or eyes). This condition may occur during treatment with BESPONSA or after subsequent treatment with a stem cell transplant. A stem cell transplant is a procedure to transplant another person's stem cells (cells which develop into new blood cells) into your bloodstream. This procedure may take place if your disease responds completely to treatment.
- have signs or symptoms of a low number of blood cells known as neutrophils (sometimes accompanied with fever), red blood cells, white blood cells, lymphocytes, or a low number of blood components known as platelets; these signs and symptoms include developing an infection or fever or bruising easily or getting frequent nose bleeds.
- have signs and symptoms of an infusion related reaction, such as fever and chills or breathing problems during or shortly after the BESPONSA infusion.
- have signs and symptoms of tumour lysis syndrome, which may be associated with symptoms in the stomach and intestines (for example, nausea, vomiting, diarrhoea), heart (for example, changes in the rhythm), kidney (for example, decreased urine, blood in urine), and nerves and muscles (for example, muscular spasms, weakness, cramps), during or shortly after the BESPONSA infusion.
- have a history of, or tendency to have, QT interval prolongation (a change in electrical activity of the heart that can cause serious irregular heart rhythms), are taking medicines that are known to prolong QT interval, and/or have abnormal electrolyte (e.g., calcium, magnesium, potassium) levels.
- have elevations in amylase or lipase enzymes that may be a sign of problems with your pancreas or liver and gallbladder or bile ducts.

Tell your doctor, pharmacist or nurse immediately if you became pregnant during the period of treatment with BESPONSA and for up to 8 months after finishing treatment.

Your doctor will take regular blood tests to monitor your blood counts during treatment with BESPONSA. See also section 4.

During treatment, especially in the first few days after starting treatment, your white blood cell count may be severely lowered (neutropenia), which may be accompanied by fever (febrile neutropenia).

During treatment, especially in the first few days after starting treatment, you may have raised liver enzymes. Your doctor will take regular blood tests to monitor your liver enzymes during treatment with BESPONSA.

Treatment with BESPONSA may prolong QT interval (a change in electrical activity of the heart that can cause serious irregular heart rhythms). Your doctor will take an electrocardiogram (ECG) and blood tests to measure electrolytes (e.g., calcium, magnesium, potassium) before the first dose of BESPONSA and repeat these tests during treatment. See also section 4.

Your doctor will also monitor for signs and symptoms of tumour lysis syndrome after you receive BESPONSA. See also section 4.

Children and adolescents

BESPONSA should not to be used in children and adolescents under 18 years of age because limited data are available in this population.

Other medicines and BESPONSA

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription and herbal medicines.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or nurse for advice before taking this medicine.

Contraception

You must avoid becoming pregnant or fathering a child. Women must use effective contraception during treatment and for at least 8 months after the final dose of treatment. Men must use effective contraception during treatment and for at least 5 months after the final dose of treatment.

Pregnancy

The effects of BESPONSA in pregnant women are not known, but based on its mechanism of action BESPONSA may harm your unborn baby. You should not use BESPONSA during pregnancy, unless your doctor thinks that it is the best medicine for you.

Contact your doctor immediately if you or your partner becomes pregnant during the period of treatment with this medicine.

Fertility

Men and women should seek advice regarding fertility preservation before treatment.

Breast-feeding

If you need treatment with BESPONSA, you must stop breast-feeding during treatment and for at least 2 months after treatment. Talk to your doctor.

Driving and using machines

If you feel unusually tired (this is a very common side effect of BESPONSA), you should not drive or use machines.

BESPONSA contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per 1 mg inotuzumab ozogamicin, that is to say essentially ‘sodium-free.’

3. How BESPONSA is given

Always use this medicine exactly as your doctor, pharmacist, or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.

How BESPONSA is given

- Your doctor will decide on the correct dose.
- A doctor or nurse will give you BESPONSA through a drip in your vein (intravenous infusion) which will run for 1 hour.
- Each dose is given weekly and each treatment cycle is 3 doses.

- If the medicine works well and you are going to receive a stem cell transplant (see section 2), you may receive 2 cycles or a maximum of 3 cycles of treatment.
- If the medicine works well, but you are not going to receive a stem cell transplant (see section 2), you may receive up to a maximum of 6 cycles of treatment.
- If you do not respond to the medicine within 3 cycles, your treatment will be stopped.
- Your doctor may change your dose, interrupt, or completely stop treatment with BESPONSA if you have certain side effects.
- Your doctor may lower your dose based on your response to treatment.
- Your doctor will do blood tests during the treatment to check for side effects and for response to treatment.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist, or nurse.

Medicines given before treatment with BESPONSA

Before your treatment with BESPONSA, you will be given other medicines (pre-medications) to help reduce infusion reactions and other possible side effects. These may include corticosteroids (e.g., dexamethasone), antipyretics (medicines to reduce fever), and antihistamines (medicines to reduce allergic reactions).

Before your treatment with BESPONSA, you may be given medicines and be hydrated to prevent tumour lysis syndrome from occurring. Tumour lysis syndrome is associated with a variety of symptoms in the stomach and intestines (for example, nausea, vomiting, diarrhoea), heart (for example, changes in the rhythm), kidney (for example, decreased urine, blood in urine), and nerves and muscles (for example, muscular spasms, weakness, cramps).

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some of these side effects may be serious.

Tell your doctor immediately if you have signs and symptoms of any of the following serious side effects:

- infusion related reaction (see section 2); signs and symptoms include fever and chills or breathing problems during or shortly after the BESPONSA infusion.
- venoocclusive liver disease (see section 2); signs and symptoms include rapid weight gain, pain in the upper right side of your abdomen, increase in the size of the liver, accumulation of fluid causing abdominal swelling, and increases in bilirubin and/or liver enzymes (that may result in yellowing of the skin or eyes).
- low number of blood cells known as neutrophils, (sometimes accompanied with fever), red blood cells, white blood cells, lymphocytes, or low number of blood components known as platelets (see section 2); signs and symptoms include developing an infection or fever or bruising easily or getting nose bleeds on a regular basis.
- tumour lysis syndrome (see section 2); this may be associated with a variety of symptoms in the stomach and intestines (for example, nausea, vomiting, diarrhoea), heart (for example, changes in the rhythm), kidney (for example, decreased urine, blood in urine), and nerves and muscles (for example, muscular spasms, weakness, cramps).
- QT interval prolongation (see section 2); signs and symptoms include a change in electrical activity of the heart that can cause serious irregular heart rhythms. Tell your doctor if you have symptoms, such as dizziness, lightheadedness or fainting.

Other side effects may include:

Very common: may affect more than 1 in 10 people

- Infections
- Reduced number of white blood cells which may result in general weakness and a tendency to develop infections
- Reduced number of lymphocytes (a type of white blood cells) which may result in a tendency to develop infections
- Reduced number of red blood cells which may result in fatigue and shortness of breath
- Decreased appetite
- Headache
- Bleeding
- Pain in the abdomen
- Vomiting
- Diarrhoea
- Nausea
- Mouth inflammation
- Constipation
- Raised bilirubin level which may result in a yellowish colour in the skin, eyes, and other tissues
- Fever
- Chills
- Fatigue
- High levels of liver enzymes (which can be indicators of liver injury) in the blood

Common: may affect up to 1 in 10 people

- Reduction in the number of various types of blood cells
- Excess of uric acid in the blood
- Excessive accumulation of fluid in the abdomen
- Swelling of the abdomen
- Changes in heart rhythm (may show on electrocardiogram)
- Abnormally high levels of amylase (an enzyme needed for digestion and conversion of starch into sugars) in the blood
- Abnormally high levels of lipase (an enzyme needed to process dietary fat) in the blood
- Hypersensitivity

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store BESPONSA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial label and carton after EXP. The expiry date refers to the last day of that month.

Unopened vial

- Store in a refrigerator (2 °C-8 °C).

- Store in the original carton in order to protect from light.
- Do not freeze.

Reconstituted solution

- Use immediately or store in a refrigerator (2 °C-8 °C) for up to 4 hours.
- Protect from light.
- Do not freeze.

Diluted solution

- Use immediately or store at room temperature (20 °C-25 °C) or in a refrigerator (2 °C-8 °C). The maximum time from reconstitution through the end of administration should be ≤ 8 hours, with ≤ 4 hours between reconstitution and dilution.
- Protect from light.
- Do not freeze.

This medicine should be inspected visually for particulate matter and discolouration prior to administration. If particles or discolouration are observed, do not use.

Do not throw away any medicines via wastewater or household waste. Ask your doctor how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What BESPONSA contains

- The active substance is inotuzumab ozogamicin. Each vial contains 1 mg inotuzumab ozogamicin. After reconstitution, 1 mL of solution contains 0.25 mg inotuzumab ozogamicin.
- The other ingredients are sucrose, polysorbate 80, sodium chloride, and tromethamine (see section 2).

What BESPONSA looks like and contents of the pack

BESPONSA is a powder for concentrate for solution for infusion (powder for concentrate).

Each pack of BESPONSA contains:

- 1 glass vial containing a white to off-white lyophilised cake or powder.

Marketing Authorisation Holder

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

Manufacturer

Pfizer Service Company BV
Hoge Wei 10
B-1930, Zaventem
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments. This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only. For full information on dosage and dose modifications please refer to the Summary of Product Characteristics.

Method of administration

BESPONSA is for intravenous use. The infusion must be administered over 1 hour.

Do not administer BESPONSA as an intravenous push or bolus.

BESPONSA must be reconstituted and diluted before administration.

BESPONSA should be administered in 3- to 4-week cycles.

For patients proceeding to a haematopoietic stem cell transplant (HSCT), the recommended duration of treatment is 2 cycles. A third cycle may be considered for those patients who do not achieve a CR/CRi and MRD negativity after 2 cycles. For patients not proceeding to HSCT, a maximum of 6 cycles, may be administered. Any patients who do not achieve a CR/CRi within 3 cycles should discontinue treatment (see Summary of Product Characteristics section 4.2).

The table below shows the recommended dosing regimens.

For the first cycle, the recommended total dose for all patients is 1.8 mg/m^2 per cycle, administered as 3 divided doses on Days 1 (0.8 mg/m^2), 8 (0.5 mg/m^2), and 15 (0.5 mg/m^2). Cycle 1 is 3 weeks in duration, but may be extended to 4 weeks if the patient achieves a CR or CRi, and/or to allow recovery from toxicity.

For subsequent cycles, the recommended total dose is 1.5 mg/m^2 per cycle administered as 3 divided doses on Days 1 (0.5 mg/m^2), 8 (0.5 mg/m^2), and 15 (0.5 mg/m^2) for patients who achieve a CR/CRi or 1.8 mg/m^2 per cycle given as 3 divided doses on Days 1 (0.8 mg/m^2), 8 (0.5 mg/m^2), and 15 (0.5 mg/m^2) for patients who do not achieve a CR/CRi. Subsequent cycles are 4 weeks in duration.

Dosing regimen for Cycle 1 and subsequent cycles depending on response to treatment

	Day 1	**Day 8[a]**	**Day 15[a]**
Dosing regimen for Cycle 1			
All patients:			

Dosing regimen for Cycle 1 and subsequent cycles depending on response to treatment

	Day 1	Day 8[a]	Day 15[a]
Dose (mg/m^2)	0.8	0.5	0.5
Cycle length	21 days[b]		
Dosing regimen for subsequent cycles depending on response to treatment			
Patients who have achieved a CR[c] or CRi[d]:			
Dose (mg/m^2)	0.5	0.5	0.5
Cycle length	28 days[e]		
Patients who have not achieved a CR[c] or CRi[d]:			
Dose (mg/m^2)	0.8	0.5	0.5
Cycle length	28 days[e]		

Abbreviations: ANC=absolute neutrophil counts; CR=complete remission; CRi=complete remission with incomplete haematological recovery.

[a] +/- 2 days (maintain a minimum of 6 days between doses).

[b] For patients who achieve a CR/CRi, and/or to allow for recovery from toxicity, the cycle length may be extended up to 28 days (i.e. 7-day treatment-free interval starting on Day 21).

[c] CR is defined as < 5% blasts in the bone marrow and the absence of peripheral blood leukaemic blasts, full recovery of peripheral blood counts (platelets ≥ 100 × 10^9/L and ANC ≥ 1 × 10^9/L) and resolution of any extramedullary disease.

[d] CRi is defined as < 5% blasts in the bone marrow and the absence of peripheral blood leukaemic blasts, incomplete recovery of peripheral blood counts (platelets < 100 × 10^9/L and/or ANC < 1 × 10^9/L) and resolution of any extramedullary disease.

[e] 7-day treatment-free interval starting on Day 21.

Instructions for reconstitution, dilution, and administration

Use appropriate aseptic technique for the reconstitution and dilution procedures. Inotuzumab ozogamicin (which has a density of 1.02 g/mL at 20 °C) is light sensitive and should be protected from ultraviolet light during reconstitution, dilution, and administration.

The maximum time from reconstitution through the end of administration should be ≤ 8 hours, with ≤ 4 hours between reconstitution and dilution.

Reconstitution:

- Calculate the dose (mg) and number of vials of BESPONSA required.
- Reconstitute each 1 mg vial with 4 mL of water for injection, to obtain a single-use solution of 0.25 mg/mL of BESPONSA.
- Gently swirl the vial to aid dissolution. Do not shake.
- Inspect the reconstituted solution for particulates and discolouration. The reconstituted solution must be clear to slightly cloudy, colourless, and essentially free of visible foreign matter. If particles or discolouration are observed, do not use.
- BESPONSA contains no bacteriostatic preservatives. The reconstituted solution must be used immediately. If the reconstituted solution cannot be used immediately, it may be stored in a refrigerator (2 °C-8 °C) for up to 4 hours. Protect from light and do not freeze.

Dilution:

- Calculate the required volume of the reconstituted solution needed to obtain the appropriate dose according to patient body surface area. Withdraw this amount from the vial(s) using a syringe. Protect from light. Discard any unused reconstituted solution left in the vial.
- Add the reconstituted solution to an infusion container with sodium chloride 9 mg/mL (0.9%) solution for injection, to a total nominal volume of 50 mL. The final concentration should be between 0.01 and 0.1 mg/mL. Protect from light. An infusion container made of polyvinyl chloride (PVC) (di(2-ethylhexyl)phthalate [DEHP]- or non-DEHP-containing), polyolefin (polypropylene and/or polyethylene), or ethylene vinyl acetate (EVA) is recommended.

- Gently invert the infusion container to mix the diluted solution. Do not shake.
- The diluted solution must be used immediately, stored at room temperature (20 °C-25 °C) or in a refrigerator (2 °C-8 °C). The maximum time from reconstitution through the end of administration should be ≤ 8 hours, with ≤ 4 hours between reconstitution and dilution. Protect from light and do not freeze.

Administration:

- If the diluted solution is stored in a refrigerator (2 °C-8 °C), it must be allowed to equilibrate at room temperature (20 °C-25 °C) for approximately 1 hour prior to administration.
- Filtration of the diluted solution is not required. However, if the diluted solution is filtered, polyethersulphone (PES)-, polyvinylidene fluoride (PVDF)-, or hydrophilic polysulphone (HPS)-based filters are recommended. Do not use filters made of nylon or mixed cellulose ester (MCE).
- Protect the intravenous bag from light using an ultraviolet light-blocking cover (i.e., amber, dark brown, or green bags or aluminium foil) during infusion. The infusion line does not need to be protected from light.
- Infuse the diluted solution for 1 hour at a rate of 50 mL/h at room temperature (20 °C-25 °C). Protect from light. Infusion lines made of PVC (DEHP or non-DEHP-containing), polyolefin (polypropylene and/or polyethylene), or polybutadiene are recommended.

Do not mix BESPONSA or administer as an infusion with other medicinal products.

The storage times and conditions for reconstitution, dilution, and administration of BESPONSA are shown below.

Storage times and conditions for reconstituted and diluted BESPONSA solution

← **Maximum time from reconstitution through the end of administration ≤ 8 hours[a]** →		
Reconstituted solution	**Diluted solution**	
	After start of dilution	**Administration**
Use reconstituted solution immediately or after being stored in a refrigerator (2 °C-8 °C) for up to 4 hours. Protect from light. Do not freeze.	Use diluted solution immediately or after being stored at room temperature (20 °C-25 °C) or in a refrigerator (2 °C-8 °C). The maximum time from reconstitution through the end of administration should be ≤ 8 hours, with ≤ 4 hours between reconstitution and dilution. Protect from light. Do not freeze.	If the diluted solution is stored in a refrigerator (2 °C-8 °C), bring it to room temperature (20 °C-25 °C) for approximately 1 hour prior to administration. Administer diluted solution as a 1-hour infusion at a rate of 50 mL/h at room temperature (20 °C-25 °C). Protect from light.

[a] With ≤4 hours between reconstitution and dilution.

Storage conditions and shelf life

Unopened vials

5 years.

Reconstituted solution

BESPONSA contains no bacteriostatic preservatives. The reconstituted solution must be used immediately. If the reconstituted solution cannot be used immediately, it may be stored in a refrigerator (2 °C-8 °C) for up to 4 hours. Protect from light and do not freeze.

Diluted solution

The diluted solution must be used immediately or stored at room temperature (20 °C-25 °C) or in a refrigerator (2 °C-8 °C). The maximum time from reconstitution through the end of administration should be ≤ 8 hours, with ≤ 4 hours between reconstitution and dilution. Protect from light and do not freeze.