BESPONSA (INOTUZUMAB OZOGAMICIN) RISK MANAGEMENT PLAN

RMP Version number: 5.0

Data lock point for this RMP: 28 December 2024

Date of final sign off: 07 April 2026

Rationale for submitting an updated RMP (version 4.0):

A Type II variation will be submitted including an updated RMP to extent the indication to paediatric patients 1 year and older with relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukaemia.

Rationale for submitting an updated RMP (version 4.1):

On 26 March 2026, the CHMP adopted a positive opinion extending the indication of inotuzumab ozogamicin to include the treatment of paediatric patients aged ≥1 year with relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukaemia. The MAH is submitting an update to EU RMP in order to align the proposed indication for the extension to paediatric patients with the new indication adopted by the CHMP.

Rationale for submitting an updated RMP (version 5.0):

Up-version of RMP v. 4.1.

Summary of significant changes in the RMP version 4.0, version 4.1, and version 5.0:

RMP Part/Module	Major Changes RMP version 4.0	Major Changes RMP version 4.1	Major Changes RMP version 5.0
PART I Product(s) Overview	Updated to include the proposed extension of the indication and of the recommended dosing regimens to the paediatric patients 1 year and older.	Updated to align the proposed indication for the extension to the paediatric patients with the indication adopted by the CHMP.	No changes.
PART II Safety Specification			
PART II.Module SI Epidemiology of the Indication(s) and Target Population(s)	Update of the indication for the extension to the paediatric patients 1 year and older and of the epidemiology data up to the DLP 28 December 2024.	Update of the proposed indication for the extension to the paediatric patients 1 year and older in alignment with the indication adopted by the CHMP.	No changes.
PART II.Module SII Non-Clinical Part of the Safety Specification	No changes.	No changes.	No changes.
PART II.Module SIII Clinical Trial Exposure	No changes.	No changes.	No changes.

RMP Part/Module	Major Changes RMP version 4.0	Major Changes RMP version 4.1	Major Changes RMP version 5.0
PART II.Module SIV Populations Not Studied in Clinical Trials	No changes.	No changes.	No changes.
PART II.Module SV Post-Authorisation Experience	Post-Authorisation Exposure updated to the DLP of 28 December 2024.	No changes.	No changes.
PART II.Module SVI Additional EU Requirements for the Safety Specification	No changes.	No changes.	No changes.
PART II.Module SVII Identified and Potential Risks	Risks characterisation updated to the DLP of 28 December 2024. Update of the MedDRA terms for the important potential risk reproductive and developmental toxicity (post exposure during pregnancy and while breast feeding) as per MedDRA v. 27.1.	No changes.	No changes.
PART II.Module SVIII Summary of the Safety Concerns	No changes.	No changes.	No changes.
PART III Pharmacovigilance Plan (including post-authorisation safety studies)	No changes.	No changes.	No changes.
PART IV Plans for Post-Authorisation Efficacy Studies	No changes.	No changes.	No changes.
PART V Risk Minimisation Measures (including evaluation of the effectiveness of risk minimisation activities)	No changes.	No changes.	No changes.
PART VI Summary of the Risk Management Plan	Updated as per changes in PART I.	Updated as per changes in PART I.	No changes.

RMP Part/Module	Major Changes RMP version 4.0	Major Changes RMP version 4.1	Major Changes RMP version 5.0
Annex 2			
Annex 3			
Annex 4			
Annex 5			
Annex 6			
Annex 7	Annex 7 updated to include cumulative data from the safety database updated up to the DLP of 28 December 2024 for important risks Grade ≥3 and/or serious hepatotoxicity, including all VOD/SOS and Myelosuppression/cytopenia and to update the data from the		
Annex 8	Pfizer's safety database on the cases originating from the paediatric study ITCC-059 up to the DLP of 28 December 2024. Annex 8 updated to reflect the above changes.	Annex 8 updated to reflect the above changes.	Annex 8 updated to include the new RMP version.

Other RMP versions under evaluation: none.

Details of the currently approved RMP:

Version number: 3.1

Approved with procedure: EMEA/H/C/004119/II/0029

Date of approval (opinion date): 24 October 2024

QPPV name[1]: Barbara De Bernardi

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

[1] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu.

LIST OF ABBREVIATIONS

ABL	Abelson murine leukemia
ADC	Antibody-drug conjugate
ADR	Adverse drug reaction
AE	Adverse event
ALL	Acute lymphoblastic leukaemia
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
Ara-C	Cytarabine
ATC	Anatomic Therapeutic Chemical
AVDOS	Average dose
BCP	B-cell precursor
BCR	Breakpoint cluster region
CCL	creatinine clearance
CD	Cluster of differentiation
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CI	Confidence interval
CNS	Central nervous system
CL_{cr}	Creatinine clearance
CNS	Central nervous system
CR	Complete remission
CRi	Complete remission with incomplete haematologic recovery
CSF	Cerebrospinal fluid
CSR	Clinical study report
CT	Clinical trial
CTCAE	Common terminology criteria for adverse events
DCA	Data capture aid
DL	Dose level
DLP	Data Lock Point
DLT	Dose-limiting toxicity
DMH	Dimethylhydrazide
DNA	Deoxyribonucleic acid
DoR	Duration of remission
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
EM	Emerging markets
EMA	European Medicines Agency
EPAR	European Product Assessment Report
EU	European Union
FcRN	Neonatal Fc receptor for IgG

FLAG	Fludarabine/cytarabine/granulocyte colony-stimulating factor
G-CSF	Granulocyte-colony stimulating factor
GI	Gastrointestinal
GVHD	Graft versus host disease
Hyper-CVAD	Hyperfractionated-vincristine, cyclophosphamide, doxorubicin, and dexamethasone
HIDAC	High-dose cytarabine
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
(H)SCT	(Haematopoietic) stem cell transplant
HLT	High Level Term
HMA	Heads of Medicines Agencies
IARC	International Agency for Research on Cancer
IDM	International developed markets
Ig	Immunoglobulin
IgG4	Immunoglobulin type G, subtype 4
IIR	Investigator-Initiated Research
ILD	Interstitial lung disease
INN	International Non-propriety Name
IV	Intravenous
LALA	Leucémie Aiguës Lymphoblastique de l'Adulte
LOAEL	Lowest observed adverse effect level
LSLV	Last subject last visit
LVEF	Left ventricular ejection fraction
MAH	Marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
MOF	Multi-organ failure
mR3	a modified collaborative UKALL trial for relapsed and refractory ALL; InO replaces mitoxantrone; includes dexamethasone 20 mg/m^2 on Days 1-5 and 15-19 during induction
MRC	Medical Research Council
MRD	Minimal residual disease
MTD	Maximum tolerated dose
N	Number
MXN	Mitoxantrone
NA	Not applicable/ North America
NCI	National Cancer Institute
NCI ODWG	National Cancer Institute Organ Dysfunction Working Group
NEC	Not elsewhere classified
NHL	Non-Hodgkin lymphoma
NRH	Nodular regenerative hyperplasia
NSAID	Nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
O/E	Observed/expected

OS	Overall survival
QPPV	Qualified person for pharmacovigilance
PD	Pharmacodinamics
Ph^-	Philadelphia chromosome-negative
Ph^+	Philadelphia chromosome-positive
PIP	Paediatric Investigational Plan
PK	Pharmacokinetics
PL	Package leaflet
PSUR	Periodic Safety Update Report
PT	Preferred Term
QTc	Corrected QT interval
QTcF	Fridericia's correction of the QT interval
RBC	Red blood cell
RMP	Risk Management Plan
RP2D	Recommended phase 2 dose
R/R	Relapsed/refractory
SAE	Serious adverse event
SEC	Sinusoidal endothelial cells
SEER	Surveillance, Epidemiology, and End Results
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SOS	Sinusoidal obstruction syndrome
TBI	Total body irradiation
TEAE	Treatment emergent adverse event
TKI	Tyrosine kinase inhibitors
UGT	Uridine diphosphate glucuronosyltransferase
UK	United Kingdom
UKALL-R3	a historical clinical trial for relapsed and refractory ALL
ULN	Upper limit of normal
US	United States
VHR	Very High Risk
VOD	Venoocclusive disease
WBC	White blood cell
WHO	World Health Organisation

TABLE OF CONTENTS

LIST OF TABLES

PART I. PRODUCT(S) OVERVIEW

Active substance(s) **(INN or common name)**	Inotuzumab ozogamicin
Pharmacotherapeutic group(s) (ATC Code)	L01FB01
Marketing Authorisation Holder	Pfizer Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Besponsa
Marketing authorisation procedure	Centralised
Brief description of the product:	Chemical class: 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 IgG4 antibody which 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.
	Summary of mode of action: nonclinical data suggest that the anticancer activity of inotuzumab ozogamicin 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.
	Important information about its composition: inotuzumab ozogamicin is a monoclonal antibody that is manufactured using a recombinant CHO cell line that contains the DNA encoding the sequence for inotuzumab ozogamicin. Excipients include sucrose, polysorbate 80, sodium chloride, and tromethamine.
Hyperlink to the Product Information:	Please refer to Module 1.3.1 of this submission.
Indication(s) in the EEA	Current: Inotuzumab ozogamicin is indicated as monotherapy for the treatment of adults with relapsed or refractory CD22-positive B-cell precursor ALL. Adult patients with Ph+ relapsed or refractory B-cell precursor ALL should have failed treatment with at least 1 TKI.

	Proposed: Inotuzumab ozogamicin is indicated as monotherapy for the treatment of adults with relapsed or refractory CD22-positive B-cell precursor ALL. Patients with Ph^+ relapsed or refractory B-cell precursor ALL should have failed treatment with at least 1 TKI. Inotuzumab ozogamicin is indicated as monotherapy for paediatric patients 1 year and older with CD22-positive B-cell precursor ALL: in first relapse after allo-HSCT; after any first relapse in patients with VHR disease; after a second or greater relapse; and in those with refractory disease. Patients with Ph^+ disease should have exhausted relevant BCR-ABL targeting treatment options.
Dosage in the EEA	Current: Inotuzumab ozogamicin should be administered in 3-to 4-week cycles. For patients proceeding to HSCT, the recommended duration of treatment is 2 cycles. A third cycle may be considered for those patients who do not achieve a CR or complete remission with CRi and MRD negativity after 2 cycles. For patients not proceeding to HSCT, additional cycles of treatment, up to a maximum of 6 cycles, may be administered. Patients who do not achieve a CR/CRi within 3 cycles should discontinue treatment. For the first cycle, the recommended total dose of inotuzumab ozogamicin 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 inotuzumab ozogamicin 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. Dose modification of inotuzumab ozogamicin may be required based on individual safety and tolerability. Management of some adverse drug reactions may require dosing interruptions and/or dose reductions, or permanent discontinuation of inotuzumab ozogamicin. If the dose is reduced due to inotuzumab ozogamicin related toxicity, the dose should not be re-escalated. Inotuzumab ozogamicin 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. No adjustment to the starting dose is required based on age.

	No adjustment to the starting dose is required in patients with hepatic impairment defined by total bilirubin ≤ 1.5 x ULN and AST/ALT ≤ 2.5 x ULN. There is limited safety information available in patients with total bilirubin > 1.5 x ULN and AST/ALT > 2.5 x ULN prior to dosing. Interrupt dosing until recovery of total bilirubin to ≤ 1.5 x ULN and AST/ALT to ≤ 2.5 x 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 x ULN or AST/ALT does not recover to ≤ 2.5 x ULN. No adjustment to the starting dose is required in patients with mild, moderate, or severe renal impairment (CLcr 60-89 mL/min, 30-59 mL/min, or 15-29 mL/min, respectively). The safety and efficacy of inotuzumab ozogamicin have not been studied in patients with end stage renal disease. The safety and efficacy of inotuzumab ozogamicin in children (aged 0 to <18 years) have not been established. Inotuzumab ozogamicin 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, but no recommendation on a posology can be made. Inotuzumab ozogamicin is for intravenous use. The infusion must be administered over 1 hour. Inotuzumab ozogamicin should not be administered as an intravenous push or bolus. Inotuzumab ozogamicin must be reconstituted and diluted before administration.
	Proposed: Inotuzumab ozogamicin should be administered in 3-to 4-week cycles. For patients proceeding to HSCT, the recommended duration of treatment 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. For patients not proceeding to HSCT, additional cycles of treatment, up to a maximum of 6 cycles, may be administered. Patients who do not achieve a CR/CRi within 3 cycles should discontinue treatment. For the first cycle, the recommended total dose of inotuzumab ozogamicin for all patients (adults and paediatric 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 inotuzumab ozogamicin 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.

	Dose modification of inotuzumab ozogamicin may be required based on individual safety and tolerability. Management of some adverse drug reactions may require dosing interruptions and/or dose reductions, or permanent discontinuation of inotuzumab ozogamicin. If the dose is reduced due to inotuzumab ozogamicin related toxicity, the dose should not be re-escalated. Inotuzumab ozogamicin 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. No adjustment to the starting dose is required based on age. No adjustment to the starting dose is required in patients with hepatic impairment defined by total bilirubin ≤ 1.5 x ULN and AST/ALT ≤ 2.5 x ULN. There is limited safety information available in patients with total bilirubin > 1.5 x ULN and AST/ALT > 2.5 x ULN prior to dosing. Interrupt dosing until recovery of total bilirubin to ≤ 1.5 x ULN and AST/ALT to ≤ 2.5 x 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 x ULN or AST/ALT does not recover to ≤ 2.5 x ULN. No adjustment to the starting dose is required in patients with mild, moderate, or severe renal impairment (CLcr 60-89 mL/min, 30-59 mL/min, or 15-29 mL/min, respectively). The safety and efficacy of inotuzumab ozogamicin have not been studied in patients with end stage renal disease. The safety and efficacy of inotuzumab ozogamicin in paediatric patients aged < 1 year have not been established. Inotuzumab ozogamicin is for intravenous use. The infusion must be administered over 1 hour. To mitigate the risk of QT prolongation, the time of infusion should be increased to 1.5 hours in paediatric patients with a body weight < 35 kg. Inotuzumab ozogamicin should not be administered as an intravenous push or bolus. Inotuzumab ozogamicin must be reconstituted and diluted before administration.
Pharmaceutical form(s) and strengths	Current: Powder for concentrate for solution for infusion (powder for concentrate). White to off white, lyophilised cake or powder. Each vial contains 1 mg inotuzumab ozogamicin. After reconstitution, 1 mL of solution contains 0.25 mg inotuzumab ozogamicin. The required volume of the reconstituted solution needed to obtain the appropriate dose according to patient body surface area is added to an infusion container with sodium chloride 9

	mg/mL (0.9%) solution for injection, to a total nominal volume of 50 mL.
Is/will the product be subject to additional monitoring in the EU?	No

PART II. SAFETY SPECIFICATION

Module SI. Epidemiology of the Indication(s) and Target Population (s)

Indication:

Inotuzumab ozogamicin is indicated as monotherapy for the treatment of adults with relapsed or refractory CD22-positive B-cell precursor ALL. Patients with Ph^+ relapsed or refractory B-cell precursor ALL should have failed treatment with at least 1 TKI.

Inotuzumab ozogamicin is proposed to be indicated as monotherapy for paediatric patients 1 year and older with CD22-positive B-cell precursor ALL: in first relapse after allo- HSCT; after any first relapse in patients with VHR disease; after a second or greater relapse; and in those with refractory disease. Patients with Ph^+ disease should have exhausted relevant BCR-ABL targeting treatment options.

Literature search strategy

The PubMed database was searched for primary literature and review articles reporting incidence, prevalence, and mortality estimates of relapsed or refractory B-cell ALL in the general population through July 2015 and updated through 28 December 2024. When applicable, bibliographies cited by each identified paper were reviewed to identify additional relevant literature. Searches were confined to articles involving humans. Estimates primarily from the EU and US populations were included. The original search also included articles focused on important comorbidities of patients with relapsed or refractory B-cell ALL.

Epidemiologic estimates and important comorbidities are summarised for the target indication, relapsed or refractory B-cell ALL, when available. However, because literature regarding the epidemiology of the target indication with relapsed or refractory B-cell ALL is very limited, estimates of ALL epidemiology were also provided. Therefore, the type of ALL (e.g., B-cell) will be specified when known.

Incidence:

No population studies were identified that reported the incidence rate of relapsed or refractory B-cell ALL. However, the following estimates for ALL, irrespective of subtype, were available.

<u>Europe</u>

A previous study examined leukaemia subtype data available from 290 cancer registries across 68 countries worldwide using the IARC Cancer Incidence in Five Continents Volume X database.[1] The study estimated 20,684 incident ALL cases in Europe between 2003 and 2007 (Miranda-Filho, 2018). Age-standardised incidence rates across Europe ranged from 0.6 per 100,000 in both males and females in Serbia to 2.4 per 100,000 in females in Cyprus (Table 1). For 15 of the 29 countries included from Europe, the rate was 1.5 per 100,000 or greater for both males and females. This study also found geographical disparities in non-European countries, specifically Central and South America, with the highest incidences in

Ecuador (males: 2.8 per 100,000; females: 3.3 per 100,000), Costa Rica (males: 2.4 per 100,000; females: 2.3 per 100,000), and Colombia (males: 2.3 per 100,000; females: 2.1 per 100,000).

Another study using the IARC Cancer Incidence in Five Continents Volume X database reported incidence rates for childhood and adult ALL in selected countries.[2] The study found that age-standardised incidence rates for ALL in the UK, Denmark, Spain, Germany, and Italy during 2003–2007 were >3.0 per 100,000 among children aged 0-19 years but <1.0 per 100,000 among adults aged 20+ years, representing more than a threefold difference.

Table 1. Acute Lymphoblastic Leukaemia: Number of Cases and Age-Standardised Incidence Rates (per 100,000) in Europe, 2003-2007

	Male		Female	
European Country[a]	**n**	**Rate[c]**	**n**	**Rate[c]**
Central and Eastern Europe	13,170	7.7	11,720	5.1
Cyprus[b]	33	2.3	35	2.4
Czech Republic[b]	224	1.3	199	1.2
Bulgaria[b]	262	2.1	179	1.5
Belarus[b]	334	1.8	270	1.4
Poland	182	1.4	125	1.0
Slovakia[b]	186	1.9	125	1.2
Russian	121	1.8	104	1.3
Ukraine[b]	1503	1.8	1231	1.4
Northern Europe	7322	9.2	5200	6.0
Denmark[b]	180	1.8	151	1.6
Estonia[b]	26	1.0	24	1.0
Finland[b]	193	2.1	155	1.8
Ireland	161	1.9	106	1.3
Latvia[b]	38	1.2	54	1.3
Lithuania[b]	99	1.5	94	1.6
Norway[b]	175	2.0	136	1.7
Sweden[b]	293	1.8	217	1.4
United Kingdom	3553	1.8	2736	1.4
Southern Europe	11,157	8.7	8146	5.6
Croatia[b]	172	2.1	142	1.6
Italy	749	2.2	603	1.7
Serbia	72	0.6	75	0.6
Slovenia[b]	64	1.7	44	1.3
Turkey	227	2.2	175	1.7
Western Europe	14,800	9.6	10,814	6.0
Spain	354	2.0	269	1.6
Austria[b]	282	1.8	217	1.5
France	304	1.8	262	1.6
Germany	740	2.1	609	1.7
Netherlands[b]	581	1.8	510	1.6
Switzerland	104	1.6	86	1.3
Belgium[b]	292	2.0	247	1.6

Table 1. Acute Lymphoblastic Leukaemia: Number of Cases and Age-Standardised Incidence Rates (per 100,000) in Europe, 2003-2007

a. Includes countries with data available for analysing leukaemia subtype.
b. National registries.
c. Incidence rates expressed per 100,000 population and age-standardised to the world standard population.
Sources: The Cancer Incidence in Five Continents Volume X database of the IARC.
Miranda-Filho A, Piñeros M, Ferlay J et al. Epidemiological patterns of leukaemia in 184 countries: a population-based study. Lancet Haematol. 2018 Jan;5(1):e14-e24. doi: 10.1016/S2352-3026(17)30232-6.

In the paediatric population, the Global Burden of Disease database, which captures data from 204 countries and territories, estimated that the incidence of ALL in children age <14 years was 1.63 per 100,000 in Eastern Europe and 5.36 per 100,000 in Western Europe in 2021. Globally, the estimated incidence in children in 2021 was 2.3 per 100,000.[3]

In 2016-2018, there were 791 new cases of ALL in the UK: 464 (59%) in males and 327 (41%) in females, giving a male: female ratio of approximately 1.4: 1.[4] The 2016-2018 European age-standardised incidence rate was 1.1 per 100,000 (males 1.3 per 100,000 and females 0.9 per 100,000).

In 2021, for Sweden, the age standardised incidence of ALL per 100,000 (according to the population of the year 2000) was 1.6 in men and 1.2 in women.[5]

The B-cell subtype accounts for approximately 75% of ALL cases in adults and approximately 88% in children.[6,7]

US

Estimates of ALL incidence in the US come from the US SEER Program of the NCI.[8] The overall age-adjusted incidence rate in 2017-2021 was 1.8 per 100,000 individuals, with males having a slightly higher overall rate than females (2.1 per 100,000 vs. 1.6 per 100,000) (Table 2). The median age of diagnosis for ALL is 17 years, with 53.9% of patients diagnosed before the age of 20 years.

Table 2. Acute Lymphoblastic Leukaemia Age-Specific Incidence Rates per 100,000 in the US, 2015-2019

Age (Years)	Incidence Rates		
	Overall	Male	Female
All Ages	1.8	2.1	1.6
<1	1.9	1.9	2.0
1-4	7.8	8.5	7.1
5-9	3.8	4.1	3.5
10-14	2.6	2.9	2.2
15-19	2	2.6	1.3
20-24	1.2	1.5	0.8
25-29	0.9	1.1	0.6
30-34	0.8	1.0	0.6
35-39	0.9	1.0	0.7

Table 2. Acute Lymphoblastic Leukaemia Age-Specific Incidence Rates per 100,000 in the US, 2015-2019

Age (Years)	Incidence Rates		
	Overall	Male	Female
40-44	0.9	1.1	0.8
45-49	0.9	1.0	0.9
50-54	1	1.0	1.0
55-59	1.1	1.1	1.1
60-64	1.3	1.3	1.3
65-69	1.5	1.6	1.4
70-74	1.8	2.0	1.6
75-79	1.9	2.0	1.7
80-84	1.9	2.2	1.7
85+	1.5	1.7	1.3

Source: SEER 22, 2015-2019[8, 9].

Overall, in the US, 6,100 new cases of ALL (3,450 males, 2,650 females) are expected in 2025 along with 1,400 expected deaths (720 males, 680 females).[10]

From 2001 to 2007, the annual incidence rate for B-cell ALL was reported as 1.2 per 100,000 individuals.[11] A higher incidence rate was reported in males compared with females, 1.3 versus 1.1 per 100,000 person-years, respectively.

Prevalence:

No population studies were identified that reported the prevalence rate of relapsed or refractory B-cell ALL. Prevalence rates per subpopulation within the ALL category itself will vary substantially depending on the age at diagnosis, subtype of ALL, treatment and other prognostic factors.

Europe

In 2022, Orphanet, a consortium of European countries that provides, among other services, a public database of drugs with an orphan designation, along with prevalence numbers cited from various data sources (www.orpha.net),[12] cited ALL as having a prevalence rate (patients currently diagnosed and hence under treatment) of 11.0 per 100,000 persons. With the total population of the EU and UK at approximately 514.5 million,[13] a rough estimate of the number of ALL cases in the EU and UK would be 56,595 individuals as of 01 January 2022. The age and gender specific prevalence rates for Europe were not available.

US

An estimated 115,294 individuals were living with acute lymphocytic leukaemia in the US in 2021.[8] Based on estimates derived from SEER, 21.0% of total ALL cases were children aged <15 years and approximately half (53.1%) of total cases were adults aged 20-49 years, with similar patterns by gender.[14] The breakdown by age and gender is presented in Table 3 (ages <15 years was the youngest category available):

Table 3. Number of People Living with Acute Lymphoblastic Leukaemia as of 01 January 2019 (US)

Age (Years)	Overall		Male		Female	
	n	%	n	%	N	%
<15	22,615	21.0	12,068	20.5	10,547	21.6
15-19	12,802	11.9	7404	12.6	5398	11.0
20-49	57,153	53.1	31,449	53.5	25,704	52.6
50-64	11,045	10.3	5938	10.1	5107	10.5
65-74	2911	2.7	1,378	2.3	1533	3.1
75+	1094	1.0	521	0.9	573	1.2
Total	107,620		58,758		48,862	

Source: SEER*Explorer: An interactive website for SEER cancer statistics. Surveillance Research Program, National Cancer Institute. Available at: https://seer.cancer.gov/statistics-network/explorer. (Accessed 09 January 2023)

Table 4. Acute Lymphoblastic Leukaemia Prevalence Rates per 100,000 Persons by Age and Gender, as of 01 January 2019 (US)

	Prevalence Rates		
Age (Years)	Overall	Male	Female
<15	37.2	38.8	35.5
15-19	61.4	70.2	52.4
20-49	44.7	49.4	40.1
50-64	17.8	19.9	15.8
65-74	9.2	9.3	9.2
75+	5.1	5.8	4.7
Total	33.2	36.9	29.6

Rates calculated using following data sources:

1. SEER 22, 2019.[9]
2. U.S. Census Bureau, Current Population Survey, Annual Social and Economic Supplement, 2019. Internet release date: April 2020. Table 1. Population by Age and Sex: 2019. Available at: https://www.census.gov/data/tables/2019/demo/age-and-sex/2019-age-sex-composition.html. (Accessed 09 March 2023)

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Age

The median age of ALL diagnosis in the US from 2017-2021 was 17 years (females: 18 years, males: 17 years).[7] As described above, the incidence of ALL is highest in childhood with rates peaking among children aged 1-4 years. Incidence rates remain low in younger adults before gradually increasing after age 50.

In the US, the incidence of ALL is 0.7 per 100,000 for adults in their mid to late-20s to early-40s.[15] The incidence rate then begins to increase very gradually, with the peak adult rate of 2.0 per 100,000 for persons 80-84 years.

Sex

As described in the *Incidence* section above, Table 1 and Table 2 show that incidence rates for ALL were generally higher in males than females in both Europe and the US.

Race/Ethnic Origin

In the US, the majority of cases occurred among non-Hispanic Whites (44.1%) and Hispanics (39.9%), with incidence rates of 1.6 per 100,000 and 2.6 per 100,000, respectively.[9] From 2017-2021, the incidence rate of ALL in the US was greater in the Hispanic population (2.8 per 100,000) compared to the Non-Hispanic White and Non-Hispanic Black population (1.7 per 100,000, 1.1 per 100,000), respectively.[7]

Risk Factors for the Disease

In most cases the aetiology of ALL is not known, however, several risk factors for ALL have been established.[16]

Radiation Exposure

There is strong evidence that ionizing radiation exposure increases the risk of ALL. Studies show that survivors of the World War II atomic bomb blasts have substantially greater risk of acute leukaemia.[10,17] The magnitude of the risk varies according to the dose and duration of the exposure as well as to the developmental period in which the exposure occurred (preconception, *in utero*, postnatal).[17] With respect to diagnostic x-rays and risk of ALL, the results are inconsistent across studies.[17] Paternal exposure in the preconception period[17] and foetal exposure during the critical developmental period[10, 17] may increase risk to some degree, but this is not certain.

Chemical Exposure

Exposure to pesticides and hydrocarbons, particularly benzene, is linked to risk of ALL. For benzene, ALL risk appears to be imparted primarily through prenatal exposures (i.e., the preconception and *in utero* periods).[17] Numerous studies indicate that both direct and indirect exposure to pesticides are associated with childhood ALL.[18]

Race/Ethnicity

As described above, the majority of ALL cases occurred among non-Hispanics Whites and Hispanics, with incidence 62.5% greater among Hispanics than non-Hispanic Whites; see above the section *Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease*.

Gender

The incidence of ALL is slightly greater among males than females; see above the section *Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease*.

The main existing treatment options:

Currently available treatment options for the treatment of Ph^- ALL and Ph^+ ALL are summarized below.

Treatment of Relapsed or Refractory Ph^- B-Cell Acute Lymphoblastic Leukaemia

The majority subtype of B-cell ALL among adults is Ph^-.

Acceptable re-induction regimens include therapies based on a backbone of vincristine, corticosteroids, anthracyclines, ± asparaginase; Hyper-CVAD; cytarabine-based regimens such as HIDAC and fludarabine plus cytarabine plus granulocyte colony-stimulating factor (FLAG) +/- idarubicin; methotrexate-based regimens; allogeneic HSCT; and other chemotherapy regimens.[19,20]

Agents with EU approval(s) by any route (Mutual Recognition, Centralised, Decentralised, or National) relevant to the treatment of relapsed or refractory Ph^- B-cell ALL include xaluprine, clofarabine, methotrexate, cyclophosphamide, cytarabine, vincristine, daunorubicin, asparaginase, and doxorubicin. More recently, blinatumomab, a bispecific CD19-directed CD3 T-cell engager, was approved. In addition to the medications listed above, medications indicated for the palliative management of leukaemias and lymphomas in adults include corticosteroids.

Treatment of Relapsed or Refractory Ph^+ Positive B-Cell Acute Lymphoblastic Leukaemia

In the EU, 3 TKIs have been approved for the treatment of Ph^+ B-cell ALL: imatinib, dasatinib, and ponatinib. Imatinib was approved for adult patients with relapsed or refractory Ph^+ ALL; dasatinib was approved for adult patients with Ph^+ ALL with resistance or intolerance to prior therapy; and ponatinib was approved for adult patients with ALL for whom no other TKI therapy is indicated.

Role of Haematopoietic Stem Cell Transplant

For patients with relapsed or refractory ALL eligible for HSCT, the ultimate goal of therapy is to achieve a CR prior to proceeding to a potentially curative allogeneic HSCT.

For patients with ALL refractory to primary chemotherapy or with early relapse, or in those who have a poor prognosis, allogeneic HSCT is considered the only potentially curative option. According to the LALA-94 study, which examined the outcome of patients with ALL 15 to 55 years of age in first relapse, OS at 5 years was only 8% for all relapsed patients; however, for patients who had available donors and were able to achieve a second CR and survive until they received an allogeneic HSCT (61/421), 5-year OS was 33%.[21] Likewise, outcomes from 609 patients with ALL, aged 15 to 60 years of age in first relapse enrolled in the MRC/ ECOG 2993 study showed a 23% 5-year OS for patients receiving a HLA-matched sibling allogeneic HSCT (n=42) and a 16% 5-year OS for patients receiving matched unrelated donor allogeneic HSCT (n=65), compared with 15% for autologous HSCT and 4% for chemotherapy.[22]

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Morbidity

If left untreated, ALL is usually fatal within a few weeks, depending on the level of bone marrow failure, related cytopenias, and effects of circulating blast cells and their metabolites on vital organs.[23] At diagnosis, severe anaemia (haemoglobin <8 g/dl) is present in 28%, severe granulocytopenia (neutrophils $<0.5\times10^9\ l^{-1}$) in 22%, severe thrombocytopenia (platelets $<25\times10^9\ l^{-1}$) in 30%, hyperleukocytosis (total white blood cells $>50\times10^9$/L) in 28%, and detectable circulating blast cells in 92% of cases.[23] Resulting complications include febrile neutropenia, infections, sepsis, bleeding disorder and CNS complications. Spread of leukaemic cells to the CNS is likely in untreated or ineffectively treated patients. Headache and cranial nerve or other nerve palsies are related to meningeal or extradural nerve involvement, which occurs in 5–10% of cases at presentation. The presence of lymphadenopathy, splenomegaly, and/or hepatomegaly by physical examination is found in approximately 50% of patients. Death occurs soon in untreated cases as a result of infections, hemorrhages, or a combination of both.[23]

Front-line therapy for adults with ALL results in rates of CR ranging between 78% and 93% in recent clinical trials.[24] Around 10–20% (depending on age) of patients die during induction treatment, and a further 10% are truly refractory to remission-induction therapy. In addition to these early failures, more than half of the patients who achieve a CR are expected to relapse. There is an overall chance of cure in approximately 20–40% of adult patients after initially being diagnosed with ALL.[23]

In relapsed or refractory ALL, additional complications may occur as a result of prior treatment. These complications include chemotherapy-induced organ toxicity (e.g., renal, hepatic, cardiac, pancreas, CNS) along with haematologic toxicities and consequences of serious infections. If prior ALL therapy included an allogeneic HSCT, the patient may have toxicities relating to GVHD and its continuous immunosuppressive therapy. In adults, secondary malignancies may also develop following ALL treatment.[7,23]

Mortality

Following a first relapse in adult ALL patients, only 30-45% of patients experience a second CR after salvage chemotherapy with a median survival of 5-9 months.[25] The outcome is especially poor for patients with primary refractory disease, short duration of first remission (<12 months), or relapse after HSCT. In such patients, CR occurs in 20–30% of patients, with median OS of 3–6 months.[25] The prognosis for patients who have disease that has failed multiple lines of therapy is even worse. In 609 adults with recurring ALL, all of whom were previously treated on the MRC UKALL12/ECOG2993 study, the OS at 5 years after relapse was 7% (95% CI=4%-9%). Prognosis is worse for standard risk patients with persistent detectable MRD during consolidation as this has been associated with a higher risk of relapse.[26] In comparison, the OS at 5 years of newly diagnosed patients was 38% (95% CI=36%-41%).[22]

Important co-morbidities:

Liver and Renal Dysfunction

In a retrospective study of 151 consecutive adult patients with ALL in Germany (median age of 31 years), who received allogeneic HSCT between 1995 and 2007, all patients had received initial treatment according to the German Multicenter Study Group for Adult ALL protocols. At baseline, 33 (22%) of patients had liver dysfunction (29 mild, 4 moderate or severe) and none of the patients had renal dysfunction.[27]

Diabetes

In a retrospective study of 151 consecutive adult patients with ALL in Germany (median age of 31 years), who received HSCT between 1995 and 2007, 4 (3%) patients had diabetes at the start of treatment.[27] Saillard investigated the application of a comorbidity index to predict treatment outcomes in older adults newly diagnosed with ALL in France between 1995 and 2012. A total of 89 consecutive patients, age 60 years and older, were analysed. Of these 89 patients, 9 (10%) had diabetes.[28]

Toxicities Related to Prior ALL Chemotherapy

Relapsed or refractory ALL patients experience significant toxicity from their prior chemotherapy.[7] Asparaginase is poorly tolerated in adults and may cause thrombotic/bleeding issues, pancreatitis, and/or liver toxicity acutely, or upon administration of second line therapy.[29] Prior ALL therapy often includes methotrexate and 6 mercaptopurine; both drugs commonly cause liver toxicity.[30] Anthracyclines are commonly associated with cardiac toxicity.[31] In general, ALL chemotherapies are extremely myelosuppressive and immunosuppressive both in the initial induction treatment and in conditioning regimens pre-HSCT. Conditioning regimens for allogenic HSCT cause nausea, vomiting, diarrhoea, mucositis, anorexia, end-organ toxicities such as heart, lung, kidney and liver, and are frequently associated with serious bacterial, viral and/or fungal infections.[7] Antibiotic, antifungal, and antiviral therapy used in the treatment or as prophylaxis for infections that result from immunosuppression, are often themselves associated with toxicities either acutely (e.g., amphotericin B associated with renal toxicity), or upon administration of second line treatment with resulting interaction (e.g., trimethoprim/sulfamethoxazole use increasing systemic exposure to methotrexate due to decrease renal clearance).[7] Additional late onset toxicities related to prior ALL chemotherapy include loss of active immunization, infertility, secondary cancers, and diabetes, avascular necrosis, and/or osteoporosis secondary to steroid treatment.[23]

Other Co-morbidities

Adult ALL patients are expected to experience common age-related co-morbid conditions. At diagnosis, the adult age distribution of ALL in the US SEER database was 20-34 years (24.2%), 35-44 years (13.5%), 45-54 years (14.9%), 55-64 years (18.3%), 65-74 years (16.5%), 75-84 years (9.0%), and 85+ (3.6%).[9] Common age-related conditions such as cardiovascular disease (e.g., hypertension), obesity, hepatic steatosis, tobacco, ethanol and/or illicit drug exposure, or hepatitis that are prevalent in the general adult population are present

in many adult patients prior to treatment. Saillard et al.[28] reported cardiovascular disease in 58 (65%) of 89 patients newly diagnosed with ALL. Prior other malignancy had occurred in 19 patients (21%) often requiring surgery, chemotherapy, and/or irradiation therapy. Terwey et al.[27] reported cardiovascular diseases in 6 (4%) of 151 ALL patients awaiting HSCT. Pulmonary disease was present in 47 (31%) cases (28% moderate, 3% severe). Psychiatric disturbances were reported in 11 patients (7%).[27]

Module SII. Non-Clinical Part of the Safety Specification

The nonclinical safety profile of inotuzumab ozogamicin was evaluated *in vitro* and *in vivo* in rats and cynomolgus monkeys. Rats and monkeys are considered to be relevant biological species only for potential target-independent toxicities associated with conjugated and unconjugated calicheamicin because the anti CD22-antibody (G544 antibody) component of inotuzumab ozogamicin does not bind to the target antigen CD22 in any nonclinical species. Consistent with the intended clinical route of administration, the majority of the toxicity studies were conducted using the IV route. Repeat-dose toxicity studies up to 26 weeks of duration (1 dose/week) were conducted and were considered relevant to the recommended clinical dosing regimen, (i.e., the first cycle being a 21- to 28-day cycle with 3 divided doses on Days 1, 8 and 15, followed by 28-day cycles consisting of 3 doses divided on Day 1, 8 and 15 followed by 7 treatment free days and a maximum of 6 cycles). In addition, safety pharmacology, genetic toxicity, fertility and early embryonic development, and embryo-foetal development studies were conducted.

Based on the nonclinical safety studies conducted with inotuzumab ozogamicin, the primary toxicities occurred in the liver, haematolymphopoietic tissues, and reproductive organs. Embryo-foetal effects were also identified from rat fertility and rat and rabbit embryo-foetal development studies. Other inotuzumab ozogamicin-related effects identified following repeat dosing included kidney findings in rats and monkeys, and peripheral and CNS effects in rats only. Inotuzumab ozogamicin was also identified as a clastogen and potential carcinogen. The observed findings were attributed to target-independent toxicity associated with conjugated and/or unconjugated calicheamicin. No new important target organ toxicities were observed in single and repeat-dose rat and dog studies with N-acetyl-γ-calicheamicin DMH. There was no toxicity observed in rats or monkeys administered repeat doses of G544 antibody alone, as would be expected because the G544 antibody does not bind CD22 in nonclinical species including rats and monkeys.

Table 5 describes the nonclinical key safety findings and relevance to human usage.

Table 5. Key Safety Findings and Relevance to Human Usage

Findings (From Nonclinical Studies)	Relevance to Human Usage
Liver Dose related increases in AST and/or ALT were observed in rats and monkeys following single or repeated dosing. Increases in total bilirubin were observed in monkeys after a single dose but not after repeat dosing. Microscopic changes associated with ≥4 weeks repeated administration in rats included sinusoidal dilatation with hepatocyte atrophy, hepatocyte hypertrophy and karyomegaly, and angiectasis. In monkeys, sinusoidal dilatation, hepatocyte atrophy, and hepatocellular hypertrophy were observed after 26 weeks of repeated dosing. Increases in AST and/or ALT and histopathological changes including sinusoidal dilatation with damage/loss of SECs and accompanied by sequestration of platelets along with multifocal hepatocyte hypertrophy were consistent with microvascular liver injury and were considered to represent early stages of VOD/SOS and NRH, morphologically similar to those reported in clinical trials.	Inotuzumab ozogamicin has the potential to cause elevations in liver-related laboratory tests and hepatotoxicity. Grade ≥3 and/or serious hepatotoxicity, including all VOD/SOS is an important identified risk (for further information see Module SVII.3.1).

Table 5. Key Safety Findings and Relevance to Human Usage

Findings (From Nonclinical Studies)	Relevance to Human Usage
Additional findings after repeat dosing in rats and monkeys included an altered hepatocyte focus in one monkey and preneoplastic and neoplastic lesions in rats. Liver effects occurred in studies ≥4 weeks in duration in rats and in studies 26 weeks in duration in monkeys at subtherapeutic exposures and multiples thereof. Partial to complete recovery of findings in rats was observed following a 4-week non-dosing period but slight to mild hepatocellular hypertrophy, increased single cell necrosis, and slight karyomegaly were still present. Preneoplastic and neoplastic lesions observed after 26 weeks of dosing in rats would not be expected to resolve. There were no liver-related findings in monkeys at the end of a 4-week non-dosing period in the 4-week toxicity study.	
Haematolymphopoietic Decreased platelets, RBC mass, and lymphocytes were observed in rats and/or monkeys after a single dose and/or in repeat-dose studies ≥ 4 weeks in duration. Acute decreases in platelets in monkeys were likely due to sequestration in the liver in association with microvascular liver injury. Haematological changes were in part associated with hypocellularity in the bone marrow and lymphoid organs (thymus, spleen, lymph nodes and/or gut-associated lymphoid tissue). Major haematological effects occurred at subtherapeutic exposures and multiples thereof, and were partially or fully reversible.	Inotuzumab ozogamicin has the potential to cause myelosuppression/cytopenia in humans. Myelosuppression/cytopenia is an important identified risk (for further information see Module SVII.3.1).
Reproductive and developmental toxicity (post exposure during pregnancy and while breast feeding) <u>Male Reproductive</u> Dose-related testicular degeneration associated with hypospermia and prostatic and seminal vesical atrophy was observed in rats given single or repeated-doses in studies ≥4 weeks at subtherapeutic exposures and multiples thereof. After 4 weeks of dosing in the monkey Sertoli cell vacuolation was observed. There were no male reproductive effects noted in monkeys after 26 weeks of dosing; however the male reproductive organs were immature in most animals in the repeat-dose toxicity studies and a complete assessment could not be conducted. Recovery from testicular degeneration and associated effects were not observed in rats after 4 weeks of repeat-dosing and a subsequent 4-week non-dosing period. <u>Female Reproductive</u> Atrophy of the ovaries, uterus, vagina, and mammary gland occurred in rats and/or monkeys in single and/or repeated dose studies of 4 weeks in duration. After a 4-week non-dosing period partial to full recovery was observed. After 26-weeks of dosing, the only change in monkeys was slight ovarian atrophy and there were no adverse female reproductive organ effects in rats or monkeys after 26 weeks of dosing at 2.2x and 3.1x respectively, the maximum human clinical exposure.	Inotuzumab ozogamicin has the potential to impair human male and female fertility, to adversely affect human embryo-foetal development, and to potentially affect the nursing infant. Reproductive and developmental toxicity (post exposure during pregnancy and while breast feeding) is an important potential risk (for further information, see Module SVII.3.1).

Table 5. Key Safety Findings and Relevance to Human Usage

Findings (From Nonclinical Studies)	Relevance to Human Usage
Embryo-foetal toxicity In fertility studies in female rats and embryo-foetal development studies in rats and rabbits, foetal effects, except for foetal weight decreases in rats, were only observed at maternally toxic doses. Increases in resorptions and concomitant decreases in viable embryos in a rat female fertility study were observed. In embryo-foetal development studies in rats, foetal body weights were lower and were associated with reduced foetal skeletal ossification and increased foetal incidence of short/thick humerus and misshapen scapula and/or ulna at subtherapeutic exposure and multiples thereof. The delayed skeletal ossification and other foetal morphological effects were considered reversible and a consequence of maternal toxicity and foetal growth retardation. In rabbits, lower foetal body weights and foetal mortality were observed in the presence of significant maternal toxicity in the nonpivotal embryo-foetal development study; there were no adverse foetal effects in the pivotal rabbit developmental study. There were no adverse embryo-foetal effects observed in rats or rabbits at 0.1x and 3.2x, respectively, the maximum human clinical exposure.	
Nervous System Peripheral and CNS axonal degeneration was observed following 4 weeks of repeat dosing in rats at 5.8x the maximum human clinical exposure, but not after 26 weeks of dosing at 2.2x the maximum human clinical exposure. After a 4-week non-dosing period, the severity of sciatic nerve axonal degeneration was increased and axonal degeneration of the cervical spinal cord and trigeminal nerve in the brain was still present. Additionally, following the non-dosing period, slight axonal degeneration of the lumbar spinal cord was observed. There were no nervous system effects observed in the monkey after single- or repeat-dose administration up to 26 weeks at 3.1x the maximum human clinical exposure.	Inotuzumab ozogamicin has the potential to cause neurotoxicity in humans. Neurotoxicity is an important potential risk (for further information see Module SVII.3.1).
Renal After 26 weeks of repeat dosing in rats, chronic progressive nephropathy occurred at subtherapeutic clinical exposures and margins thereof. It is unclear whether the nephropathy represents an exacerbation of a spontaneous rat-specific lesion with no relevance to humans or is a direct effect of inotuzumab ozogamicin administration. One male monkey was euthanized during the 26-week study; a protein-losing glomerulonephritis was identified as the cause of morbidity at 3.1x the maximum human clinical exposure. The glomerulonephritis was associated with protein in the urine, tubular protein casts in the kidney, and multisystemic subacute vascular inflammation. The time course and histopathological characteristics of the glomerulonephritis and vasculitis are consistent with possible immune complex deposition associated with anti-drug antibodies.	Inotuzumab ozogamicin has the potential to cause neurotoxicity in humans. Nephrotoxicity is an important potential risk (for further information see Module SVII.3.1).
Mutagenicity, Clastogenicity, and Carcinogenicity Inotuzumab ozogamicin was identified as a clastogen, but not a mutagen: N-acetyl-γ-calicheamicin DMH, the released cytotoxin, was identified as a mutagen and clastogen. It is known that γ-	Inotuzumab ozogamicin has the potential to cause secondary malignancies in humans. Second primary malignancy is

Table 5. Key Safety Findings and Relevance to Human Usage

Findings (From Nonclinical Studies)	Relevance to Human Usage
calicheamicin (the naturally occurring form of calicheamicin) is a highly potent DNA-cleaving agent that causes sequence-specific double strand cuts. Consistent with its mechanism of action, γ-calicheamicin is also a potent inducer of chromosome damage as measured by the *in vitro* micronucleus assay and the *in vitro* chromosome aberration assay. After 26 weeks of administration, hepatocellular adenomas, basophilic and/or eosinophilic altered cell foci, and oval cell hyperplasia were observed in rats at subtherapeutic exposures and multiples thereof. Oval cell hyperplasia was also observed in rats after a single dose or after 4 weeks of repeated-dose administration. A focus of hepatocellular alteration was observed in one female monkey after 26 weeks of dosing at 3.1x the maximum human clinical exposure. Foci of altered hepatocytes are uncommon spontaneous findings in cynomolgus monkeys. Although foci of altered hepatocytes are considered preneoplastic changes in laboratory rodents, the aetiology and relationship to the development of neoplasia in nonhuman primates are unknown. Preneoplastic and neoplastic lesions observed after 26 weeks of dosing in rats would not be expected to resolve. The dose where no effects were observed in monkeys and the LOAEL in rats provided subtherapeutic exposure and margins thereof.	an important potential risk (for further information see Module SVII.3.1).

ALT=alanine aminotransferase; AST=aspartate aminotransferase; DMH=dimethylhydrazide; DNA=deoxyribonucleic acid; LOAEL=lowest-observed-adverse-effect-level; RBC=red blood cell; SOS=sinusoidal obstruction syndrome; VOD=venoocclusive disease

Juvenile Animal Toxicity

The conduct of juvenile animal toxicity studies with inotuzumab ozogamicin, (where such studies can only be used to evaluate target-independent toxicity associated with the released cytotoxin N-acetyl-γ-calicheamicin DMH), would not be anticipated to provide additional information relevant to the safety or benefit risk profile of inotuzumab ozogamicin in paediatric populations beyond the data that has been presented in this risk management plan. Therefore, juvenile toxicity studies have not been conducted with inotuzumab ozogamicin.

Other Nonclinical Data

No additional nonclinical studies are considered necessary to support the use of inotuzumab ozogamicin in the intended target population.

Module SIII. Clinical Trial Exposure

This RMP focuses on the safety findings from 2 studies in adult patients with relapsed or refractory B-cell ALL: pivotal randomised Phase 3 Study B1931022 (hereinafter referred to as Study 1022[2]) and supportive Phase 1/2 Study B1931010 (hereinafter referred to as Study 1010). This RMP also summarises safety findings from 9 studies in patients with relapsed or refractory NHL treated with inotuzumab ozogamicin as a single agent, in combination with rituximab, or in combination with rituximab plus chemotherapy.

Overall, a total of 1207 adult patients were treated in Pfizer-sponsored studies (Phases 1 to 3), including 880 (72.9%) patients who received at least 1 dose of inotuzumab ozogamicin, 323 (26.8%) patients who received a comparator drug or drug regimen, and 4 (0.3%) patients who received only rituximab in studies of patients with relapsed or refractory NHL. Of the 880 patients who received at least 1 dose of inotuzumab ozogamicin in Pfizer-sponsored studies, 236 patients were from ALL studies with single-agent inotuzumab ozogamicin, 173 patients were from NHL studies with single-agent inotuzumab ozogamicin, 368 patients were from NHL studies with inotuzumab ozogamicin in combination with rituximab, and 103 patients were from the NHL study with inotuzumab ozogamicin in combination with rituximab plus multiagent chemotherapy.

ALL studies with single-agent inotuzumab ozogamicin (Studies 1022 and 1010)

Study 1022 is a randomised (1:1) open label Phase 3 study in which patients with relapsed or refractory B-cell ALL due to receive either Salvage 1 or 2 therapy[3] were randomised to receive treatment with either inotuzumab ozogamicin monotherapy or a defined investigator's choice of chemotherapy (hereinafter referred to as the "control arm" or 'control therapy').

In Study 1022, 326 patients were randomised; 307 patients were treated: 164 patients received inotuzumab ozogamicin and 143 patients received 1 of 3 standard chemotherapy regimens in the control arm. Patients in the inotuzumab ozogamicin arm received study medication on Days 1, 8, and 15 of a 21-28 day cycle for up to 6 cycles. Inotuzumab ozogamicin was administered with a starting recommended total dose of 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) and subsequent cycles as a recommended total dose of 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 achieved a CR or CRi, or 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) for patients who did not achieve a CR or CRi. Patients in the control arm were treated with fludarabine, cytarabine, and granulocyte-

[2] Across the inotuzumab ozogamicin clinical development programme each clinical study number consists of the clinical project number (e.g., 'B193') followed by a unique study number (e.g., '1003'); hence 'B1931003'. For simplicity, throughout the RMP, each protocol is referred to by just the study number (e.g., 'Study 1003'). However, the full protocol number appears in some tables.

[3] Salvage 1 is defined as morphological relapse after initial treatment or resistant disease (no CR or CRi) after initial treatment. Salvage 2 is defined as morphological relapse after Salvage 1 therapy or resistant disease (no CR or CRi) after Salvage 1.

colony stimulating factor (G-CSF) (FLAG), MXN + Ara-C, or HIDAC. FLAG dosing consisted of 5 to 6 days of cytarabine (2 g/m^2/day) and 5 days of fludarabine (30 mg/m^2/day) with G-CSF for a 28 day cycle for up to 4 cycles. Dosing with MXN + Ara-C consisted of mitoxantrone (12 mg/m^2/day) for 3 days and cytarabine (200 mg/m^2/day IV by continuous infusion over 7 days) per cycle for up to 4 cycles, with mitoxantrone dose modification based on patient age, comorbidities, and prior anthracycline use. HIDAC dosing consisted of cytarabine at 3 g/m^2 IV over 1-3 hours every 12 hours for up to 12 doses per cycle for up to 2 cycles with dose modifications for age and organ dysfunction. Of the 143 patients who received 1 of 3 standard chemotherapy regimens in the control arm: 93 patients received FLAG, 33 patients received MXN + Ara-C, and 17 patients HIDAC.

In Study 1010, a Phase 1/2 study, 72 patients received inotuzumab ozogamicin at dose levels of 1.2–1.8 mg/m^2/cycle. There were 3 parts to this study: Phase 1 dose escalation, Phase 1 dose expansion, and Phase 2:

- In the Phase 1 dose-escalation portion, 24 patients received inotuzumab ozogamicin at dose levels of 1.2 mg/m^2/cycle (N=3), 1.6 mg/m^2/cycle (N=12), and 1.8 mg/m^2/cycle (N=9). No dose reductions due to achieving CR or CRi after cycle 1 were allowed.

- In the Phase 1 dose expansion, additional experience was gained at the 1.8 mg/m^2 per 28-day for cycle; however, in contrast to the dose escalation patients, in the dose expansion part of the study a dose reduction to 1.6 mg/m^2/cycle occurred if CR or CRi was achieved (N=13).

- In the Phase 2 portion, patients were treated with a similar regiment to the Phase 1 dose expansion portion: 1.8 mg/m^2 per 28-day for cycle 1, followed by a dose reduction to 1.6 mg/m^2/cycle if CR or CRi was achieved (N=35).

NHL studies with inotuzumab ozogamicin alone or in combination with rituximab with or without chemotherapy (Studies B1931001, B1931002, B1931003, B1931004, B1931005, B1931006, B1931007, B1931008, and B1931016)

A total of 644 patients with relapsed or refractory NHL received inotuzumab ozogamicin as detailed above.

Other Considerations

- Eight (8) clinical studies in the inotuzumab ozogamicin clinical development programme have a Pfizer study number and a corresponding Wyeth study number (Wyeth is now a wholly owned subsidiary of Pfizer Inc.). For simplicity, throughout the RMP, each study is referred to using the Pfizer protocol number. Please see Annex 7 for a listing of these studies.

- Throughout this RMP, studies in which inotuzumab ozogamicin was administered as a single-agent are referred to as “single-agent studies” and studies where inotuzumab ozogamicin was administered as a component of rituximab and multiagent chemotherapy are referred to as “combination studies.”

Paediatric relapsed/refractory CD22-positive ALL study with inotuzumab ozogamicin as a single agent and in combination with chemotherapy (Study ITCC-059)

Inotuzumab ozogamicin was also being utilised in Study ITCC-059 (WI203581) "A phase I/II study of inotuzumab ozogamicin as a single agent and in combination with chemotherapy for paediatric CD22-positive relapsed/refractory acute lymphoblastic leukemia". This is a non-Pfizer Sponsored ongoing Phase 1-2, multicenter, international, single-arm, multi-cohort, open-label study in paediatric patients with R/R CD22-positive ALL, part of an approved EU PIP (EMEA-001429-PIP01-13-M06). The objectives of this study were to identify the recommended dose of inotuzumab ozogamicin administered IV either as monotherapy (Stratum 1A) or in combination with chemotherapy (Stratum 1B) for paediatric patients with R/R CD22-positive ALL, and to estimate the efficacy, safety and tolerability of the selected RP2D of monotherapy inotuzumab ozogamicin dose, and to evaluate PK and PD in this patient population.

Paediatric participants (≥1 and <18 years) with relapsed (2nd or greater relapse or first relapse after transplant)/refractory CD22-positive BCP-ALL were enrolled in this study. A total of 85 participants were assigned to treatment and 83 participants were treated. The total dose of inotuzumab ozogamicin per cycle mentioned hereafter refers to Cycle 1 mainly.

- Stratum 1A: 25 participants were treated; 12 received inotuzumab ozogamicin 1.4 mg/m^2/cycle (DL1) and 13 received inotuzumab ozogamicin 1.8 mg/m^2/cycle (DL2).

- Phase 2 Cohort: 28 participants received inotuzumab ozogamicin 1.8 mg/m^2/cycle.

- Stratum 1B: 30 participants were treated:

    - inotuzumab ozogamicin was given at an initial starting dose of 1.1 mg/m^2/cycle, combined with UKALL-R3 modified regimen 1.5 mg/m^2 on Days 3, 10, 17 and 24; oral dexamethasone 20 mg/m^2/day on Days 1-5 and 15-19, divided in 2 daily doses, and IT methotrexate prophylaxis on Days 1 and 8.

    - Due to 2 out of 4 participants at this 1.1 mg/m^2/cycle dose level experienced DLTs, the dose of inotuzumab ozogamicin was de-escalated to 0.8 mg/m^2/cycle while awaiting approval of Study ITCC-059 Protocol Amendment 4 which supported re-escalation of inotuzumab ozogamicin to 1.1 mg/m^2 during C1; 6 participants received inotuzumab ozogamicin combined with a reduced dose of dexamethasone at 10 mg/m^2/day (amended mR3). Next, 3 participants received inotuzumab ozogamicin 1.4 mg/m^2/cycle + amended mR3. Finally, 10 participants received inotuzumab ozogamicin 1.8 mg/m^2/cycle + amended mR3. A total of 19 participants were treated with the reduced dose of dexamethasone.

For the purposes of this RMP, "a completed" study signifies that the final analysis of the primary endpoint(s) has been completed and a final CSR is available; however, patients may still be in follow-up for overall survival and late safety events. "Ongoing" study signifies

that the final analysis of all the primary endpoint(s) has not been completed and a final CSR is not available.

The clinical exposure data summarised below are based upon:

- Data pooled based on indication, dosage and combination therapy for the following 11 completed Pfizer-sponsored clinical studies in patients with relapsed or refractory ALL and NHL (the safety cohorts for evaluation are presented below):
    - Study 1022 is considered to be completed. A CSR is available that reports the analysis of the primary endpoint of CR/CRi and secondary endpoints (based on the initial 218 patients randomised), and safety (based on 259 patients treated out of 279 randomised by the data cutoff of 02 October 2014). A sCSR is available reporting the analysis of the primary endpoint of OS, an updated analysis of CR/CRi, secondary endpoints, and safety based on all 326 randomised patients. A data cutoff date of 08 March 2016 was used for the sCSR.
    - Study 1010 is considered to be completed and the safety database lock date of 26 April 2016 is the data extraction date at the end of this Pfizer-sponsored clinical study with 15 January 2016 as the last subject last visit date.
    - The 9 NHL Pfizer sponsored studies (B1931001, B1931002, B1931003, B1931004, B1931005, B1931006, B1931007, B1931008, and B1931016) are considered completed and the safety data cutoff date is the data extraction date at the end of the respective Pfizer-sponsored clinical study.
- Data presented separately for the following studies:
    - ITCC-059 (WI203581); this study involved paediatric participants with R/R CD22-positive BCP-ALL and was ongoing at the DLP of this RMP, the estimated LSLV is 11 April 2025. The interim CSR was issued on 14 February 2023. This study and results from the CSR and from the safety database are presented in Annex 7.
    - B1931030; this study involved adult participants with R/R B-cell ALL eligible for HSCT and who have risk factor(s) for VOD. The study was completed and is presented in Annex 2.

Safety Cohorts for Evaluation in the RMP

ALL Cohorts

Pooled ALL all dose levels cohort (N=236) comprised of the following:

- 164 inotuzumab ozogamicin-treated patients in Study 1022, as of the safety cutoff date of 08 March 2016, plus
- 72 patients in Study 1010 as of the database lock date of 26 April 2016.

Pooled ALL 1.8 mg/m^2 cohort (N=212) comprised of the following:

- 164 inotuzumab ozogamicin-treated patients in Study 1022, as of the safety cutoff date of 08 March 2016, plus

- 48 of the 72 patients in Study 1010 as of the database lock date of 26 April 2016. The 48 patients from Study 1010 included all patients who received 1.8 mg/m^2/cycle inotuzumab ozogamicin as a single-agent during Cycle 1, with a protocol-specified dose reduction for subsequent cycles upon achievement of CR/CRi (all patients from the dose expansion portion [N=13] plus all patients from the Phase 2 portion [N=35]).

Dose escalation ALL 1.8 mg/m^2 cohort (N=9) comprised of patients within the dose escalation phase of Study 1010 who received 1.8 mg/m^2/cycle of inotuzumab ozogamicin without a protocol-specified subsequent dose reduction regimen for patients who achieve CR/CRi. These 9 patients were not added to the pooled ALL 1.8 mg/m^2 cohort (N=212) described above as they could not be compared to this patient population; however, safety data for these 9 patients are separately described in the RMP.

In addition to the ALL cohorts noted above, data for each of the Study 1022 treatment arms is displayed for selected parameters as specified in Module SVII.3.

NHL Cohorts

- **Pooled Single-Agent NHL cohort (N=173)** comprised of patients treated with single-agent inotuzumab ozogamicin (studies 1002, 1007, and 1016)

- **Pooled Combination with rituximab NHL cohort (N=368)** comprised of patients treated with inotuzumab ozogamicin in combination with rituximab (studies 1001, 1004, 1005, 1006, and 1008)

- **Combination with chemotherapy NHL cohort (N=103)** comprised of patients treated with inotuzumab ozogamicin in combination with rituximab and multiagent chemotherapy (Study 1003).

Patients in these studies who were randomised to the inotuzumab ozogamicin containing arm but did not receive inotuzumab ozogamicin, were excluded from the data provided in this RMP.

Please see Annex 7 for an overview of inotuzumab ozogamicin RMP cohorts and their corresponding safety cutoff dates.

Exposure to inotuzumab ozogamicin in these patients is summarized in the tables below. These tables include all exposed patients in the following cohorts: Pooled ALL all dose levels cohort (N=236); Pooled ALL 1.8 mg/m^2 cohort (N=212); Pooled Single-Agent NHL cohort (N=173); Pooled Combination with rituximab NHL cohort (N=368); and Combination with Chemotherapy NHL cohort (N=103). Please see aforementioned description of these cohorts in the above section.

Table 6. Duration of Inotuzumab Ozogamicin Exposure (Safety Population)

Cohort Duration of exposure (at least)	Persons	Person-Time (Months)[a]
Pooled ALL all dose level cohort (N=236)		
<1 month	59	26.02
≥1 month to <2 months	58	84.37
≥2 months to <3 months	50	115.55
≥3 months to <4 months	32	110.23
≥4 months to <5 months	20	89.59
≥ 5 months to <6 months	14	76.85
≥6 months to <7 months	2	12.81
≥7 months to ≤8 months	0	0
>8 months	1	9.46
Total (≥1 dose)	**236**	**524.88**
Pooled ALL 1.8 mg/m^2 cohort (N=212)		
<1 month	54	23.92
≥1 month to <2 months	49	70.41
≥2 months to <3 months	49	113.28
≥3 months to <4 months	30	102.34
≥4 months to <5 months	14	62.52
≥5 months to <6 months	13	71.06
≥6 months to <7 months	2	12.81
≥7 months to ≤8 months	0	0
>8 months	1	9.46
Total (≥1 dose)	**212**	**465.81**
Pooled Single-Agent NHL cohort (N=173)		
<1 month	71	35.94
≥1 month to <2 months	25	38.60
≥2 months to <3 months	20	51.55
≥3 months to <4 months	26	91.63
≥4 months to <5 months	12	54.67
≥5 months to <6 months	8	43.96
≥6 months to <7 months	8	51.15
≥7 months to ≤8 months	2	15.05
>8 months	1	8.64
Total (≥1 dose)	**173**	**391.20**
Pooled Combination with rituximab NHL cohort (N=368)		
<1 month	131	54.05
≥1 month to <2 months	59	95.24
≥2 months to <3 months	50	132.80
≥3 months to <4 months	36	131.75
≥4 months to <5 months	41	192.49
≥5 months to <6 months	16	86.67
≥6 months to <7 months	28	183.89
≥7 months to ≤8 months	7	51.88
>8 months	0	0
Total (≥1 dose)	**368**	**928.76**
Combination with chemotherapy NHL cohort (N=103)		
<1 month	28	14.88
≥1 month to <2 months	12	18.73
≥2 months to <3 months	9	22.44
≥3 months to <4 months	44	159.34

Table 6. Duration of Inotuzumab Ozogamicin Exposure (Safety Population)

Cohort Duration of exposure (at least)	Persons	Person-Time (Months)[a]
≥4 months to <5 months	9	39.82
≥5 months to <6 months	1	5.55
≥6 months to <7 months	0	0
≥7 months to ≤8 months	0	0
>8 months	0	0
Total (≥1 dose)	**103**	**260.76**

ALL=acute lymphoblastic leukemia; N=number of patients; NHL=non-Hodgkin lymphoma

a. Person-Time represents the cumulative number of months of exposure of the patients represented in the adjacent Persons column (last dose of inotuzumab - first dose of inotuzumab + 1)/ 30.4375; duration includes the time in which a patient temporarily withdrew from the study but re-started at a later date; one month is defined as 30.4375 days. Person time is based on first total daily dose received and includes time spent at lower doses. Exposure is based on overall person-time exposure to inotuzumab ozogamicin using this definition.

Source: t_II_SIII_1_1_293_t_durexp

Table 7. Inotuzumab Ozogamicin Exposure by First Dose (Safety Population)

Cohort Starting Dose	Persons	Person-Time (Months)[a]
Pooled ALL all dose level cohort (N=236)		
1.2 mg/m^2	3	10.61
1.6 mg/m^2	12	21.95
1.8 mg/m^{2b}	9	26.51
1.8 mg/m^{2c}	212	465.81
Total	236	524.88
Pooled Single-Agent NHL cohort (N=173)		
0.4 mg/m^2	2	0.76
0.8 mg/m^2	5	5.91
1.3 mg/m^2	14	38.28
1.8 mg/m^2	146	341.36
2.4 mg/m^2	6	4.90
Total	**173**	**391.20**
Pooled Combination with rituximab NHL cohort (N=368)		
0.4 mg/m^2	0	0
0.8 mg/m^2	5	13.31
1.2 mg/m^2	0	0
1.3 mg/m^2	3	17.64
1.6 mg/m^2	0	0
1.8 mg/m^2	360	897.81
2.4 mg/m^2	0	0
Total	**368**	**928.76**
Combination with chemotherapy NHL cohort (N=103)		
0.4 mg/m^2	0	0
0.8 mg/m^2	100	256.46
1.2 mg/m^2	0	0
1.3 mg/m^2	3	4.30
1.6 mg/m^2	0	0
1.8 mg/m^2	0	0

Table 7. Inotuzumab Ozogamicin Exposure by First Dose (Safety Population)

Cohort Starting Dose	Persons	Person-Time (Months)[a]
2.4 mg/m^2	0	0
Total	**103**	**260.76**

ALL=acute lymphoblastic leukemia; N=number of patients; NHL=non-Hodgkin lymphoma

a. Person-Time represents the cumulative number of months of exposure of the patients represented in the adjacent Persons column (last dose of inotuzumab - first dose of inotuzumab + 1)/ 30.4375; duration includes the time in which a patient temporarily withdrew from the study but re-started at a later date; one month is defined as 30.4375 days. Person time is based on first total daily dose received and includes time spent at lower doses. Exposure is based on overall person-time exposure to inotuzumab ozogamicin using this definition.

b. Includes the 9 patients from the dose escalation part of Study 1010 who, although treated with the same initial 1.8 mg/m^2/cycle inotuzumab ozogamicin dose, did not follow the protocol-specified dose reduction regimen for patients who achieve CR/CRi.

c. Includes all 164 patients in Study 1022 and 48 [out of 72] patients in Study 1010 who received a total starting dose of 1.8 mg/m^2/cycle inotuzumab ozogamicin followed by a protocol-specified dose reduction for patients who achieve CR/CRi.

Source: t_II_SIII_1_2_293_t_exp_maxdose

Table 8. Inotuzumab Ozogamicin Exposure by Age Group and Gender (Safety Population)

Cohort Age group	Persons by Gender		Person-Time (Months)[a] by Gender	
	Male	**Female**	**Male**	**Female**
Pooled ALL all dose level cohort (N=236)				
Age <18 Years	0	0	0	0
18≤ Age ≤45 Years	72	45	157.60	84.73
45< Age ≤55 Years	20	13	36.47	23.85
55< Age <65 Years	25	20	46.65	57.20
Age ≥65 Years	25	16	81.12	37.26
Total	142	94	321.84	203.04
Pooled ALL 1.8 mg/m^2 cohort (N=212)				
Age <18 Years	0	0	0	0
18≤ Age ≤45 Years	65	40	141.70	69.98
45< Age ≤55 Years	19	13	35.75	23.85
55< Age <65 Years	19	19	30.26	52.80
Age ≥65 Years	22	15	76.09	35.38
Total	125	87	283.79	182.01
Pooled Single-Agent NHL cohort (N=173)				
Age <18 Years	0	0	0	0
18≤ Age ≤45 Years	12	7	36.11	9.30
45< Age ≤55 Years	25	15	63.21	28.75
55< Age <65 Years	26	23	59.99	47.97
Age ≥65 Years	35	30	78.16	67.71
Total	**98**	**75**	**237.47**	**153.72**
Pooled Combination with rituximab NHL cohort (N=368)				
Age <18 Years	0	0	0	0
18≤ Age ≤45 Years	23	16	49.18	45.21
45< Age ≤55 Years	31	19	79.80	52.73

Table 8. Inotuzumab Ozogamicin Exposure by Age Group and Gender (Safety Population)

Cohort Age group	Persons by Gender		Person-Time (Months)[a] by Gender	
	Male	**Female**	**Male**	**Female**
55< Age <65 Years	44	22	109.04	46.62
Age ≥65 Years	120	93	279.66	266.51
Total	**218**	**150**	**517.68**	**411.07**
Combination with chemotherapy NHL cohort (N=103)				
Age <18 Years	0	0	0	0
18≤ Age ≤45 Years	3	4	10.91	8.38
45< Age ≤55 Years	9	8	20.50	20.37
55< Age <65 Years	19	10	46.88	22.28
Age ≥65 Years	33	17	95.64	35.81
Total	**64**	**39**	**173.93**	**86.83**

ALL=acute lymphoblastic leukemia; N=number of patients; NHL=non-Hodgkin lymphoma

a. Person-Time represents the cumulative number of months of exposure of the patients represented in the adjacent Persons column (last dose of inotuzumab - first dose of inotuzumab + 1)/ 30.4375; duration includes the time in which a patient temporarily withdrew from the study but re-started at a later date; one month is defined as 30.4375 days. Person time is based on first total daily dose received and includes time spent at lower doses. Exposure is based on overall person-time exposure to inotuzumab ozogamicin using this definition.

Source: t_II_SIII_1_3_293_t_exp_agegen

Table 9. Inotuzumab Ozogamicin Exposure by Ethnic or Racial Origin (Safety Population)

Cohort Ethnic/Racial Origin	Persons	Person-Time (Months)[a]
Pooled ALL all dose level cohort (N=236)		
Black	6	3.45
White	167	379.83
Asian	37	83.58
Other[b]	23	45.70
Unspecified[b]	3	12.32
Total	236	524.88
Pooled ALL 1.8 mg/m^2 cohort (N=212)		
Black	5	2.96
White	147	328.44
Asian	36	79.21
Other[b]	21	42.87
Unspecified[b]	3	12.32
Total	212	465.81
Pooled Single-Agent NHL cohort (N=173)		
Black	5	5.22
White	124	290.27
Asian	41	88.44
Other[b]	3	7.26
Unspecified[b]	0	0
Total	**173**	**391.2**

Table 9. Inotuzumab Ozogamicin Exposure by Ethnic or Racial Origin (Safety Population)

Cohort Ethnic/Racial Origin	Persons	Person-Time (Months)[a]
Pooled Combination with rituximab NHL cohort (N=368)		
Black	9	20.07
White	257	699.99
Asian	68	149.16
Other[b]	33	59.50
Unspecified[b]	1	0.03
Total	**368**	**928.76**
Combination with chemotherapy NHL cohort (N=103)		
Black	2	5.82
White	55	149.49
Asian	44	100.34
Other[b]	2	5.13
Unspecified[b]	0	0
Total	**103**	**260.76**

ALL=acute lymphoblastic leukemia; N=number of patients; NHL=non-Hodgkin lymphoma

a. Person-Time represents the cumulative number of months of exposure of the patients represented in the adjacent Persons column (last dose of inotuzumab - first dose of inotuzumab + 1)/ 30.4375; duration includes the time in which a patient temporarily withdrew from the study but re-started at a later date; one month is defined as 30.4375 days. Person time is based on first total daily dose received and includes time spent at lower doses. Exposure is based on overall person-time exposure to inotuzumab ozogamicin using this definition

b. Other/Unspecified: Includes 23 patients with a reported ethnic or racial origin (i.e. Hispanic (14), Caucasian (2), Arabian, Arabic (Tunisian), Chamorro, Mauritian, Middle Eastern, Multi-racial, Native Hawaiian) and 42 patients where the ethnic or racial origin of the patient was unknown primarily due to privacy laws in Europe or the patient declined.

Source: t_II_SIII_1_4_293_t_exp_race

Table 10. Inotuzumab Ozogamicin Exposure by Special Population (Safety Population)

Cohort Special Population	Persons	Person-Time (Months)[a]
Pooled ALL all dose level cohort (N=236)		
Renal impairment[b]		
No impairment	191	419.88
Mild	29	69.55
Moderate	16	35.45
Severe	0	0
Unknown/Missing data[c]	0	0
Hepatic impairment[d]		
No impairment	168	387.78
Mild	66	135.43
Moderate	2	1.68
Severe	0	0
Unknown/Missing data[c]	0	0
Pooled ALL 1.8 mg/m^2 cohort (N=212)		
Renal impairment[b]		

Table 10. Inotuzumab Ozogamicin Exposure by Special Population (Safety Population)

Cohort Special Population	Persons	Person-Time (Months)[a]
No impairment	171	372.67
Mild	27	63.51
Moderate	14	29.63
Severe	0	0
Unknown/Missing data[c]	0	0
Hepatic impairment[d]		
No impairment	149	341.82
Mild	61	122.32
Moderate	2	1.68
Severe	0	0
Unknown/Missing data[c]	0	0
Pooled Single-Agent NHL cohort (N=173)		
Renal impairment[b]		
No impairment	72	178.30
Mild	69	156.42
Moderate	31	56.44
Severe[e]	1	0.03
Unknown/Missing data[c]	0	0
Hepatic impairment[d]		
No impairment	150	332.48
Mild	21	52.50
Moderate	0	0
Severe	1	0.03
Unknown/Missing data[c]	1	6.18
Pooled Combination with rituximab NHL cohort (N=368)		
Renal impairment[b]		
No impairment	139	362.97
Mild	147	367.41
Moderate	80	198.31
Severe[e]	2	0.07
Unknown/Missing data[c]	0	0
Hepatic impairment[d]		
No impairment	306	803.98
Mild	61	123.83
Moderate	0	0
Severe	0	0
Unknown/Missing data[c]	1	0.95
Combination with chemotherapy NHL cohort (N=103)		
Renal impairment[b]		
No impairment	58	160.36
Mild	32	72.97
Moderate	13	27.43
Severe	0	0
Unknown/Missing data[c]	0	0
Hepatic impairment[d]		
No impairment	99	257.94
Mild	4	2.83
Moderate	0	0

Table 10. Inotuzumab Ozogamicin Exposure by Special Population (Safety Population)

Cohort Special Population	Persons	Person-Time (Months)[a]
Severe	0	0
Unknown/Missing data[c]	0	0

ALL=acute lymphoblastic leukemia; N=number of patients; NHL=non-Hodgkin lymphoma

a. Person-Time represents the cumulative number of months of exposure of the patients represented in the adjacent Persons column (last dose of inotuzumab - first dose of inotuzumab + 1)/ 30.4375; duration includes the time in which a patient temporarily withdrew from the study but re-started at a later date; one month is defined as 30.4375 days. Person time is based on first total daily dose received and includes time spent at lower doses. Exposure is based on overall person-time exposure to inotuzumab ozogamicin using this definition.

b. Renal impairment: normal [creatinine clearance (CCL) ≥90mL/min], mild (60 mL/min ≤ CCL <90 mL/min), moderate (30 mL/min≤ CCL <60 mL/min), and severe (CCL <30 mL/min). CCL was calculated by Cockcroft-Gault formula at patient baseline.

c. Unknown/Missing data: Unknown or missing data to calculate baseline impairment.

d. Hepatic impairment categories determined by NCI scale at patient baseline. Normal hepatic function: total bilirubin and AST ≤ ULN; mild impairment: total bilirubin ≤ULN and AST >ULN or total bilirubin >1.0 - 1.5 x ULN and AST any level; moderate impairment: total bilirubin >1.5 - 3.0 x ULN and AST any level; severe impairment: total bilirubin >3 x ULN and AST any level.

e. No patient(s) with CCL <15 mL/min

Source: t_II_SIII_1_5_293_t_exp_splpop

Table 11. Total Number of Subjects Exposed to Inotuzumab Ozogamicin in Clinical Trials (Safety Population)

Cohorts	Persons
Pooled ALL all dose level cohort	236
Pooled Single-Agent NHL cohort	173
Pooled Combination with rituximab NHL cohort	368
Combination with chemotherapy NHL cohort	103
Total studies	**880**

ALL=acute lymphoblastic leukemia; NHL=non-Hodgkin lymphoma

Source: t_II_SIII_1_6_293_t_exp

The clinical trial exposure data for Study ITCC-059 are presented in Table 12 through Table 16.

Table 12. Duration of Inotuzumab Ozogamicin Exposure - Full Analysis Set - Protocol ITCC-059 (B193-WI203581)

Duration of Exposure	Participants	Person-Time (Months)[a]
Stratum 1A + Phase2		
< 1 month	25	11.47
1 to < 3 months	25	41.86
3 to < 6 months	3	10.58
Total person time	**53**	**63.90**
Stratum 1B (combo)		
< 1 month	16	8.05
1 to < 3 months	14	25.92
3 to < 6 months	0	0
Total person time	**30**	**33.97**

a. Person-Time represents the cumulative number of months of exposure of the participants represented in the adjacent participants column (last dose of Inotuzumab Ozogamicin- first dose of Inotuzumab Ozogamicin+ 1)/ 30.4375. Duration includes the time in which a participant temporarily withdrew from the study but re-started at a later date. One month is defined as 30.4375 days. Person time is based on first total daily dose received and includes time spent at lower doses. Exposure is based on overall person-time exposure to Inotuzumab Ozogamicin using this definition.
SDTM Creation: 22FEB2023 (16:07) Source Data: adsl Table Generation: 27FEB2023 (14:19)
(Data cutoff date - Stratum 1A: 30SEP2022 Phase2: 07OCT2022 and Stratum 1B: 21OCT2022) Output File: ./csr_cdisc2/INO_ITCC_059_SCS/exp_dur

Table 13. Inotuzumab Ozogamicin Exposure by Starting Dose Level - Full Analysis Set - Protocol ITCC-059 (B193-WI203581)

Cohort Starting Dose	Participants	Person-Time (Months)[a]
Stratum 1A + Phase2		
0.6 mg/m^2	1	0.03
0.8 mg/m^2	2	0.07
1.3 mg/m^2	1	0.26
1.4 mg/m^2	12	20.96
1.8 mg/m^2	37	42.58
Total person time	**53**	**63.90**
Stratum 1B (combination with chemotherapy)		
0.5 mg/m^2	1	0.03
0.6 mg/m^2	1	1.64
0.8 mg/m^2	6	7.92
1 mg/m^2	1	1.68
1.1 mg/m^2	7	9.95
1.3 mg/m^2	1	0.26
1.4 mg/m^2	3	2.76
1.8 mg/m^2	10	9.72
Total person time	**30**	**33.97**

Dose levels reflected the actual dosing received by participants during the first cycle of treatment. The following dose levels were administered under the study: 1.4 mg/m² and 1.8 mg/m² for Stratum 1A and Phase 2, and 0.8 mg/m², 1.1 mg/m², 1.4 mg/m², and 1.8 mg/m² for Stratum 1B. Other dose levels reported correspond to mis-dosing or study drug interruptions, reductions, or delays.

a. Person-Time represents the cumulative number of months of exposure of the participants represented in the adjacent participants column (last dose of Inotuzumab Ozogamicin- first dose of Inotuzumab Ozogamicin+ 1)/ 30.4375. Duration includes the time in which a participant temporarily withdrew from the study but re-started at a later date. One month is defined as 30.4375 days. Person time is based on first total daily dose received and includes time spent at lower doses. Exposure is based on overall person-time exposure to Inotuzumab Ozogamicin using this definition.

SDTM Creation: 22FEB2023 (16:07) Source Data: adsl Table Generation: 27FEB2023 (13:09) (Data cutoff date - Stratum 1A: 30SEP2022 Phase2: 07OCT2022 and Stratum 1B: 21OCT2022) Output File: ./csr_cdisc2/INO_ITCC_059_SCS/adsl_ec

Table 14. Inotuzumab Ozogamicin Exposure by Age Group and Gender - Full Analysis Set - Protocol ITCC-059 (B193-WI203581)

Age Group	Participants		Person Time (Months)[a]	
Stratum 1A + Phase2	**M**	**F**	**M**	**F**
1 - <2 Years	2	0	2.89	0
2 - <12 Years	18	12	23.16	11.63
12 - 17 Years	16	5	21.29	4.93
Total	36	17	47.34	16.56
Stratum 1B (combo)	**M**	**F**	**M**	**F**
1 - <2 Years	1	0	0.49	0
2 - <12 Years	12	9	14.92	7.62
12 - 17 Years	6	2	8.74	2.20
Total	19	11	24.15	9.82

a. Person-Time represents the cumulative number of months of exposure of the participants represented in the adjacent participants column (last dose of Inotuzumab Ozogamicin- first dose of Inotuzumab Ozogamicin+ 1)/ 30.4375. Duration includes the time in which a participant temporarily withdrew from the study but re-started at a later date. One month is defined as 30.4375 days. Person time is based on first total daily dose received and includes time spent at lower doses. Exposure is based on overall person-time exposure to Inotuzumab Ozogamicin using this definition.
SDTM Creation: 22FEB2023 (16:07) Source Data: adsl Table Generation: 27FEB2023 (14:19)
(Data cutoff date - Stratum 1A: 30SEP2022 Phase2: 07OCT2022 and Stratum 1B: 21OCT2022) Output File: ./csr_cdisc2/INO_ITCC_059_SCS/exp_dura

Table 15. Inotuzumab Ozogamicin Exposure by Special Population - Full Analysis Set - Protocol ITCC-059 (B193-WI203581)

Cohort Special Population	Participants	Person-Time (Months)[a]
Stratum 1A + Phase2 (N= 53)		
Renal impairment [b]		
No impairment	45	51.45
Mild	7	10.87
Moderate	1	1.58
Severe	0	0
Unknown/Missing data [c]	0	0
Hepatic impairment[d]		
No impairment	27	34.07
Mild	26	29.83
Moderate	0	0
Severe	0	0
Unknown/Missing data	0	0
Total	53	63.90
Stratum 1B (combo) (N=30)		
Renal impairment[b]		
No impairment	24	29.24
Mild	5	4.14

Table 15. Inotuzumab Ozogamicin Exposure by Special Population - Full Analysis Set - Protocol ITCC-059 (B193-WI203581)

Cohort Special Population	Participants	Person-Time (Months)[a]
Moderate	1	0.59
Severe	0	0
Unknown/Missing data[c]	0	0
Hepatic impairment[d]		
No impairment	20	22.64
Mild	10	11.33
Moderate	0	0
Severe	0	0
Unknown/Missing data[c]	0	0
Total	30	33.97

a. Person-Time represents the cumulative number of months of exposure of the participants represented in the adjacent participants column (last dose of Inotuzumab Ozogamicin- first dose of Inotuzumab Ozogamicin+ 1)/ 30.4375. Duration includes the time in which a participant temporarily withdrew from the study but re-started at a later date. One month is defined as 30.4375 days. Person time is based on first total daily dose received and includes time spent at lower doses. Exposure is based on overall person-time exposure to Inotuzumab Ozogamicin using this definition.
b. Renal impairment: normal [creatinine clearance (CCL) >=90mL/min], mild (60 mL/min =< CCL <90 mL/min), moderate (30 mL/min=< CCL <60 mL/min), and severe (CCL <30 mL/min). CCL was calculated by Cockcroft-Gault formula at participant baseline.
c. Unknown/Missing data: Unknown or missing data to calculate baseline impairment.
d. Hepatic impairment categories determined by National Cancer Institute (NCI) scale at patient participant baseline. Normal hepatic function: total bilirubin and AST =< upper limit of normal (ULN); mild impairment: total bilirubin =<ULN and AST >ULN or total bilirubin >1.0 - 1.5 x ULN and AST any level; moderate impairment: total bilirubin >1.5 - 3.0 x ULN and AST any level; severe impairment: total bilirubin >3 x ULN and AST any level.
SDTM Creation: 22FEB2023 (16:07) Source Data: adsl Table Generation: 27FEB2023 (14:19)
(Data cutoff date - Stratum 1A: 30SEP2022 Phase2: 07OCT2022 and Stratum 1B: 21OCT2022) Output File: ./csr_cdisc2/INO_ITCC_059_SCS/exp_dur_rh

Table 16. Total Number of Participants Exposed to Inotuzumab Ozogamicin in Clinical Trials - Full Analysis Set - Protocol ITCC-059 (B193-WI203581)

Cohorts	Participants
Stratum 1A + Phase2	53
Stratum 1B (combo)	30
Total participants	**83**

The clinical trial exposure data for Study B1931030 are presented in Table 17 through Table 22.

Table 17. Duration of Inotuzumab Ozogamicin Exposure - Safety Analysis Set (Protocol B1931030)

Duration of Exposure	Participants (n)	Person-Time (Months)[a]
1.2 mg/m²/cycle (N=64)		
< 1 month	9	3.78
1 to < 3 months	44	73.17
3 to < 6 months	10	40.48
6 to <9 months	1	6.01
Total person time	**64**	**123.4**
1.8 mg/m²/cycle (N=38)		
< 1 month	13	5.72
1 to < 3 months	21	40.71
3 to < 6 months	3	12.55
6 to <9 months	1	6.05
Total person time	38	65.02

a. Person-Time represents the cumulative number of months of exposure of the participants represented in the adjacent participants column (last dose of Inotuzumab Ozogamicin- first dose of Inotuzumab Ozogamicin+ 1)/ 30.4375. Duration includes the time in which a participant temporarily withdrew from the study but re-started at a later date. One month is defined as 30.4375 days. Exposure is based on overall person-time exposure to Inotuzumab Ozogamicin using this definition.
SDTM Creation: 30JUN2023 (12:51) Source Data: ADSL Output File: ./CaPS Interim Analysis/B1931030_RMP_2024/exp_dur Date of Generation: 02JAN2024 (16:25) Cutoff Date: 26MAY2023

Table 18. Inotuzumab Ozogamicin Exposure by Starting Dose Level - Full Analysis Set (Protocol B1931030)

Cohort Starting Dose	Participants	Person-Time (Months)[a]
0.6 mg/m^2	1	0.03
0.8 mg/m^2	1	0.03
0.9 mg/m^2	2	1.81
1.2 mg/m^2	61	121.6
1.3 mg/m^2	4	5.26
1.8 mg/m^2	33	59.73
Total person time	**102**	**188.5**

Dose levels reflected the actual dosing received by participants during the first cycle of treatment. The following dose levels were administered under the study: 1.2 mg/m² and 1.8 mg/m². Other dose levels reported correspond to mis-dosing or study drug interruptions, reductions.
a. Person-Time represents the cumulative number of months of exposure of the participants represented in the adjacent participants column (last dose of Inotuzumab Ozogamicin- first dose of Inotuzumab Ozogamicin+ 1)/ 30.4375. Duration includes the time in which a participant temporarily withdrew from the study but re-started at a later date. One month is defined as 30.4375 days. Exposure is based on overall person-time exposure to Inotuzumab Ozogamicin using this definition.
SDTM Creation: 30JUN2023 (12:51) Source Data: ADSL Output File: ./CaPS Interim Analysis/B1931030_RMP_2024/adsl_ec Date of Generation: 02JAN2024 (16:34) Cutoff Date: 26MAY2023

Table 19. Inotuzumab Ozogamicin Exposure by Age Group and Gender – Safety Analysis Set (Protocol B1931030)

Age Group	Participants (n)		Person Time (Months)[a]	
1.2 mg/m²/cycle (N=64)	**M**	**F**	**M**	**F**
18≤ Age <45 Years	18	15	34.27	29.08
45≤ Age <55 Years	10	5	18.86	6.31
55≤ Age <65 Years	6	5	14.52	8.15
Age ≥65 Years	2	3	3.61	8.64
Total person time	36	28	71.26	52.17
1.8 mg/m²/cycle (N=38)	**M**	**F**	**M**	**F**
18≤ Age <45 Years	14	11	22.57	13.90
45≤ Age <55 Years	3	1	2.73	1.38
55≤ Age <65 Years	1	6	2.96	16.89
Age ≥65 Years	2	0	4.60	0
Total person time	20	18	32.85	32.16

a. Person-Time represents the cumulative number of months of exposure of the participants represented in the adjacent participants column (last dose of Inotuzumab Ozogamicin- first dose of Inotuzumab Ozogamicin+ 1)/ 30.4375. Duration includes the time in which a participant temporarily withdrew from the study but re-started at a later date. One month is defined as 30.4375 days. Exposure is based on overall person-time exposure to Inotuzumab Ozogamicin using this definition.

SDTM Creation: 30JUN2023 (12:51) Source Data: ADSL Output File: ./CaPS Interim Analysis/B1931030_RMP_2024/exp_dura Date of Generation: 02JAN2024 (16:27) Cutoff Date: 26MAY2023

Table 20. Inotuzumab Ozogamicin Exposure by Racial Origin and Gender – Safety Analysis Set (Protocol B1931030)

Cohort Racial Origin	Participants (n)		Person Time (Months)[a]	
1.2 mg/m²/cycle (N=64)	**M**	**F**	**M**	**F**
Black or African American	0	0	0	0
White	28	23	50.20	38.51
Asian	7	4	20.57	11.27
Missing	0	0	0	0
Not reported	1	1	0.49	2.40
Total person time	36	28	71.26	52.17
1.8 mg/m²/cycle (N=38)	**M**	**F**	**M**	**F**
Black or African American	0	0	0	0
White	13	12	25.30	24.67
Asian	6	5	5.26	6.93
Missing	0	1	0	0.56
Not reported	1	0	2.30	0
Total person time	20	18	32.85	32.16

a. Person-Time represents the cumulative number of months of exposure of the participants represented in the adjacent participants column (last dose of Inotuzumab Ozogamicin- first dose of Inotuzumab Ozogamicin+ 1)/ 30.4375. Duration includes the time in which a participant temporarily withdrew from the study but re-started at a later date. One month is defined as 30.4375 days. Exposure is based on overall person-time exposure to Inotuzumab Ozogamicin using this definition.
SDTM Creation: 30JUN2023 (12:51) Source Data: ADSL Output File: ./CaPS Interim Analysis/B1931030_RMP_2024/adsl_rc Date of Generation: 02JAN2024 (16:27) Cutoff Date: 26MAY2023

Table 21. Inotuzumab Ozogamicin Exposure by Special Population - Full Analysis Set (Protocol B1931030)

Cohort Special Population	Participants (n)	Person-Time (Months)[a]
Renal impairment [b]		
1.2 mg/m²/cycle (N=64)		
Normal	53	108.3
Mild	9	13.47
Moderate	2	1.71
Severe	0	0
Unknown/Missing data[c]	0	0
Total	64	123.4
1.8 mg/m²/cycle (N=38)		
Normal	29	45.80
Mild	8	17.31
Moderate	1	1.91
Severe	0	0
Unknown/Missing data	0	0
Total	38	65.02

Table 21. Inotuzumab Ozogamicin Exposure by Special Population - Full Analysis Set (Protocol B1931030)

Cohort Special Population	Participants (n)	Person-Time (Months)[a]
Hepatic impairment[d]		
1.2 mg/m²/cycle (N=64)		
Normal	45	89.49
Mild	19	33.94
Moderate	0	0
Severe	0	0
Unknown/Missing data	0	0
Total	64	123.4
1.8 mg/m²/cycle (N=38)		
Normal	27	50.79
Mild	11	14.23
Moderate	0	0
Severe	0	0
Unknown/Missing data	0	0
Total	38	65.02

a. Person-Time represents the cumulative number of months of exposure of the participants represented in the adjacent participants column (last dose of Inotuzumab Ozogamicin- first dose of Inotuzumab Ozogamicin+ 1)/ 30.4375. Duration includes the time in which a participant temporarily withdrew from the study but re-started at a later date. One month is defined as 30.4375 days. Exposure is based on overall person-time exposure to Inotuzumab Ozogamicin using this definition.
b. Renal impairment: normal [creatinine clearance (CCL) ≥90mL/min], mild (60 mL/min ≤ CCL <90 mL/min), moderate (30 mL/min ≤ CCL <60 mL/min), and severe (CCL <30 mL/min). CCL was calculated at baseline using the Cockcroft-Gault formula.
c. Unknown/Missing data: Unknown or missing data to calculate baseline impairment.
d. Hepatic impairment categories are determined by the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) scale at participant baseline. Normal hepatic function: total bilirubin and AST≤ upper limit of normal (ULN); mild impairment: total bilirubin ≤ULN and AST >ULN or total bilirubin >1.0 - 1.5 x ULN and AST any level; moderate impairment: total bilirubin >1.5 - 3.0 x ULN and AST any level; severe impairment: total bilirubin >3 x ULN and AST any level.
SDTM Creation: 30JUN2023 (12:51) Source Data: ADSL Output File: ./CaPS Interim Analysis/B1931030_RMP_2024/exp_dur_rh Date of Generation: 02JAN2024 (16:48) Cutoff Date: 26MAY2023

Table 22. Total Number of Participants Exposed to Inotuzumab Ozogamicin in Clinical Trials - Full Analysis Set (Protocol B1931030)

Cohorts	Participants
1.2 mg/m²/cycle	64
1.8 mg/m²/cycle	38
Total participants	**102**

SDTM Creation. Source Data: ADSL Output File: ./CaPS Interim Analysis/B1931030_RMP_2024/adsl_count Date of Generation: 02JAN2024 (16:27) Cutoff Date: 26MAY2023

Module SIV. Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Table 23. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Criterion	Reason for Exclusion	Missing Information (Yes/No)	Rationale (if Not Included as Missing Information)
Isolated extramedullary relapse (i.e., testicular or CNS)	To ensure uniformity of the clinical trial population and to exclude patients with confounders potentially impacting interpretation of clinical trial results. Certain types of extramedullary disease are not expected to respond to inotuzumab ozogamicin because of the lack of penetration of the blood brain and blood testes barrier (inotuzumab ozogamicin penetration in CNS tissues was <2% of that in plasma based on preclinical animal studies) as well as theoretical concerns.	No	Based on what was observed in ALL and NHL studies with inotuzumab ozogamicin therapy[a], although in some circumstances additional therapy may be needed, there is no reason to hypothesize a different benefit-risk profile for patients who have isolated extramedullary relapse.
Burkitt's or mixed phenotype acute leukaemia based on the World Health Organisation (WHO) 2008 criteria	To ensure uniformity of the clinical trial population and to exclude patients with confounders potentially impacting interpretation of clinical trial results.	No	Based on what was observed in ALL and NHL studies with inotuzumab ozogamicin therapy there is no reason to hypothesize a different safety profile for inotuzumab ozogamicin in other cancers.
Active CNS leukaemia, as defined by unequivocal morphologic evidence of lymphoblasts in the CSF, use of CNS-directed local treatment for active disease within the prior 28 days, symptomatic CNS leukaemia (i.e., cranial nerve palsies or other significant neurologic dysfunction) within 28 days. Prophylactic intrathecal medication is not a reason for exclusion.	To ensure uniformity of the clinical trial population and to exclude patients with confounders potentially impacting interpretation of clinical trial results. Certain locations of haematologic malignancies (e.g., CNS) are not expected to respond to inotuzumab ozogamicin because of the lack of penetration (inotuzumab ozogamicin penetration in CNS tissues was <2% of that in plasma	No	There is no reason to hypothesize an unfavorable benefit-risk profile for inotuzumab ozogamicin in patients who have CNS leukaemia.

Table 23. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Criterion	Reason for Exclusion	Missing Information (Yes/No)	Rationale (if Not Included as Missing Information)
	based on preclinical animal studies).		
Prior chemotherapy within 2 weeks before randomisation with the following exceptions: • To reduce the circulating lymphoblast count or palliation: i.e., steroids, hydroxyurea or vincristine; • For ALL maintenance: mercaptopurine, methotrexate, vincristine, thioguanine and/or TKIs. Patients must have recovered from acute non haematologic toxicity (to ≤ Grade 1) of all previous therapy prior to enrolment.	To reduce the risk of overlapping toxicities, including potential for more prolonged/pronounced myelosuppression and infectious complications.	No	There is no reason to hypothesize an unfavorable benefit-risk profile for inotuzumab ozogamicin in patients who have had prior chemotherapy within 2 weeks before randomisation.
Prior monoclonal antibody treatment within 6 weeks of randomisation, with the exception of rituximab which must be discontinued at least 2 weeks prior to randomisation	To reduce the risk of neutralizing cross-reactivity or overlapping toxicities given the long half-life characteristics of monoclonal antibodies.	No	Based on what was observed in ALL and NHL studies with inotuzumab ozogamicin therapy there is no reason to hypothesize a different benefit-risk profile for patients who have received prior monoclonal antibodies within 6 weeks of randomisation.
Prior HSCT or other anti-CD22 immunotherapy ≤4 months before randomisation. Patients must have completed immunosuppression therapy for treatment of GvHD prior to enrolment. At randomisation, patients must not have ≥Grade 2 acute GvHD, or extensive chronic GvHD.	To reduce the risk of overlapping toxicities secondary to treatment with inotuzumab ozogamicin versus ongoing or late toxicities associated with a recent HSCT or those who recently received other anti-CD22 immunotherapy.	No	**Prior HSCT ≤4 months before treatment:** Prior HSCT is one of the patient factors that appear to be associated with an increased risk of VOD/SOS after HSCT Product labeling will state the following: "Careful consideration is required before administering inotuzumab ozogamicin to patients who have had a prior HSCT. No patients with relapsed or refractory ALL who were treated with inotuzumab ozogamicin, in clinical trials had undergone HSCT within the previous 4 months.

Table 23. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Criterion	Reason for Exclusion	Missing Information (Yes/No)	Rationale (if Not Included as Missing Information)
			Prior other anti-CD22 immunotherapy ≤4 months before treatment: Prior use of anti-CD22 immunotherapy is not expected to have any impact on the toxicity or efficacy of inotuzumab ozogamicin if CD22 remains expressed on the B cells. Therefore, the Applicant has no reason to hypothesize an unfavourable benefit-risk profile for inotuzumab ozogamicin in patients with prior other anti-CD22 immunotherapy ≤4 months before treatment. **Patients must not have Grade 2 acute GVHD or extensive chronic GVHD and must have completed immunosuppression therapy for treatment of GVHD before treatment:** The Applicant acknowledges that active GVHD is likely to increase the risk of any therapy. However, the Applicant has no data to consider this risk would be worse for inotuzumab ozogamicin than other therapies. GVHD should be controlled before any treatment if possible. If the patient has liver GVHD, this would qualify as active hepatic disease. In the label, patients with serious ongoing hepatic disease are contraindicated from treatment with inotuzumab ozogamicin.
Peripheral absolute lymphoblast count ≥10,000 /uL (treatment with hydroxyurea and/or steroids/vincristine is permitted within 2 weeks of	To ensure uniformity of the clinical trial population, to exclude patients with confounders potentially impacting interpretation of clinical	No	Based on what was observed in ALL and NHL studies with inotuzumab ozogamicin therapy there is no reason to hypothesize a different benefit-risk profile in patients with

Table 23. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Criterion	Reason for Exclusion	Missing Information (Yes/No)	Rationale (if Not Included as Missing Information)
randomisation to reduce the WBC count).	trial results, and to reduce risk of adverse outcomes. Patients with higher peripheral blast counts at baseline could have a higher target mediated drug clearance, however the effect is not considered clinically significant. Patients with increased blast counts may be at higher risk for infusion reactions or tumour lysis syndrome.		higher absolute lymphoblast counts.
Known systemic vasculitides (e.g., Wegener's granulomatosis, polyarteritis nodosa, systemic lupus erythematosus), primary or secondary immunodeficiency (such as HIV infection or severe inflammatory disease).	To ensure uniformity of the clinical trial population and to exclude patients with confounders potentially impacting the interpretation of clinical trial results.	No	Based on what was observed in ALL and NHL studies with inotuzumab ozogamicin therapy there is no reason to hypothesize a different safety profile in patients who have known systemic vasculitides (e.g., Wegener's granulomatosis, polyarteritis nodosa, and systemic lupus erythematosus), primary or secondary immunodeficiency.
Current or chronic hepatitis B or C infection as evidenced by hepatitis B surface antigen and anti-hepatitis C antibody positivity, respectively, or known seropositivity for HIV. HIV testing may need to be performed in accordance with local regulations or local practice.	To reduce the risk of hepatic toxicity. Hepatotoxicity is a known adverse effect of inotuzumab ozogamicin; patients with current or chronic hepatitis B or C or HIV infection treated with inotuzumab ozogamicin may experience prolonged/pronounced hepatic toxicities.	No	There is no reason to hypothesize an unfavorable benefit-risk profile for inotuzumab ozogamicin in patients with a current or chronic hepatitis B or C infection or known seropositivity for HIV.
Major surgery within ≤4 weeks before randomisation	To ensure uniformity of the clinical trial population and to exclude patients with confounders potentially impacting the interpretation of clinical trial results.	No	Based on what was observed in ALL and NHL studies with inotuzumab ozogamicin therapy there is no reason to hypothesize a different benefit-risk profile in patients who have had major surgery within ≤ 4 weeks before randomisation.
Unstable or severe uncontrolled medical	To ensure uniformity of the clinical trial population	No	There is no reason to hypothesize an unfavorable

Table 23. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Criterion	Reason for Exclusion	Missing Information (Yes/No)	Rationale (if Not Included as Missing Information)
condition (e.g., unstable cardiac function or unstable pulmonary condition).	and to exclude patients with confounders potentially impacting the interpretation of clinical trial results.		benefit-risk profile for inotuzumab ozogamicin in patients with an unstable or severe uncontrolled medical condition (e.g., unstable cardiac function or unstable pulmonary condition).
Concurrent active malignancy other than non-melanoma skin cancer, in situ of the cervix, or localized prostate cancer that has been definitely treated with radiation or surgery. Patients with previous malignancies are eligible provided that they have been disease free for ≥2 years.	To ensure uniformity of the clinical trial population and to exclude patients with confounders potentially impacting the interpretation of clinical trial results.	No	Based on what was observed in ALL and NHL studies with inotuzumab ozogamicin therapy there is no reason to hypothesize a different benefit-risk profile in patients who have a concurrent active malignancy other than non-melanoma skin cancer, in situ of the cervix, or localized prostate cancer that has been definitely treated with radiation or surgery.
Cardiac function, as measured by LVEF that is < 45%, or the presence of New York Heart Association (NYHA) Stage III or IV congestive heart failure.	To ensure uniformity of the clinical trial population, to exclude patients with confounders potentially impacting interpretation of clinical trial results, and to reduce the risk of adverse outcomes.	No	Based on what was observed in ALL and NHL studies, and in preclinical studies with inotuzumab ozogamicin, there is no reason to hypothesize a different benefit-risk profile in patients who have significantly diminished cardiac function, as measured by LVEF, that is less than 45%, or the presence of NYHA stage III or IV congestive heart failure.
Patients with active heart disease (NYHA class ≥3 as assessed by history and physical examination).	To ensure uniformity of the clinical trial population, to exclude patients with confounders potentially impacting interpretation of clinical trial results, and to reduce the risk of adverse outcomes.	No	Based on what was observed in ALL and NHL studies with inotuzumab ozogamicin therapy there is no reason to hypothesize a different benefit-risk profile in patients who have active heart disease (NYHA class ≥3 as assessed by history and physical examination).
Fridericia's correction of the QT interval (QTcF) >470 msec (based on the average of 3 consecutive ECG).	To reduce the risk of clinically significant cardiac arrhythmias such as Torsades de Pointes.	No	Based on what was observed in ALL and NHL clinical studies and nonclinical studies with inotuzumab ozogamicin therapy, there is no reason to hypothesize a different benefit-

Table 23. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Criterion	Reason for Exclusion	Missing Information (Yes/No)	Rationale (if Not Included as Missing Information)
			risk profile in patients with QTc prolongation.
Myocardial infarction ≤6 months before randomisation.	To ensure uniformity of the clinical trial population, to exclude patients with confounders potentially impacting interpretation of clinical trial results and reduce the risk of adverse outcomes.	No	Based on what was observed in ALL and NHL studies with inotuzumab ozogamicin therapy, there is no reason to hypothesize a different benefit-risk profile in patients with a recent myocardial infarction.
History of clinically significant ventricular arrhythmia, or unexplained syncope not believed to be vasovagal in nature or chronic bradycardic states such as atrial block or higher degrees of atrioventricular block unless a permanent pacemaker has been implanted.	To reduce the risk of clinically significant cardiac arrhythmias and to ensure uniformity of the clinical trial population, to exclude patients with confounders potentially impacting interpretation of clinical trial results and reduce the risk of adverse outcomes.	No	Based on what was observed in ALL and NHL studies with inotuzumab ozogamicin therapy, there is no reason to hypothesize a different benefit-risk profile in patients with key arrhythmia risk factors.
Uncontrolled electrolyte disorders that can compound the effects of a QTc prolonging drug (e.g., hypokalaemia, hypocalcaemia, hypomagnesaemia)	To ensure uniformity of clinical trial population, exclude patients with confounders potentially impacting the interpretation of clinical trial results, and to reduce the risk of clinically significant cardiac arrhythmias.	No	Based on what was observed in ALL and NHL studies with inotuzumab ozogamicin therapy, there is no reason to hypothesize a different benefit-risk profile in patients with key arrhythmia risk factors.
History of chronic liver disease (e.g., cirrhosis) or suspected alcohol abuse in situations where patients do not have ongoing liver disease (e.g., cirrhosis, nodular regenerative hyperplasia, active hepatitis)	To ensure uniformity of clinical trial population, exclude patients with confounders potentially impacting the interpretation of clinical trial results, and reduce the risk of hepatic toxicities.	Yes	Patients with serious ongoing hepatic disease (e.g., cirrhosis, nodular regenerative hyperplasia, active hepatitis) are contraindicated from receiving inotuzumab ozogamicin. However, depending on an individual patient's prior treatment, medical history, and alternative treatment options, inotuzumab ozogamicin may still represent a treatment option for patients with a history of hepatic disease or suspected alcohol abuse in situations where patients do not have serious

Table 23. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Criterion	Reason for Exclusion	Missing Information (Yes/No)	Rationale (if Not Included as Missing Information)
			ongoing hepatic disease (e.g., cirrhosis, nodular regenerative hyperplasia, active hepatitis).
History of hepatic VOD/SOS posttransplant situations with a history of resolved VOD/SOS	To ensure uniformity of clinical trial population, exclude patients with confounders potentially impacting the interpretation of clinical trial results, and most importantly to reduce the risk of VOD since hepatotoxicity, including VOD was a known risk for inotuzumab ozogamicin.	Yes	In product labelling, patients who have experienced prior confirmed severe or ongoing VOD/SOS are contraindicated. However, the Applicant does not consider that all patients with prior VOD/SOS should be excluded because the risk of VOD/SOS for these patients may depend on when they recovered from VOD/SOS and how severe the VOD/SOS was. The Applicant considers that inotuzumab ozogamicin should not be contraindicated in patients with a history of mild or moderate VOD/SOS, assuming the patient recovered and has no evidence of chronic or continuing hepatic disease. These individual patient(s) may have no available alternative treatment options.
Administration of live vaccine ≤6 weeks before randomisation	To ensure uniformity of clinical trial population, exclude patients with confounders potentially impacting interpretation of clinical trial results, and to reduce the risk of systemic dissemination of vaccine-related infection.	No	Based on what was observed in ALL and NHL studies with inotuzumab ozogamicin therapy, there is no reason to hypothesize a different benefit-risk profile in patients who have received a live vaccine ≤ 6 weeks before randomisation will differ from that defined in the clinical trial programme.
Evidence of uncontrolled current serious active infection (including sepsis, bacteraemia, fungemia) or patients with a recent history (within 4 months) of deep tissue infections such as fasciitis or osteomyelitis.	To ensure uniformity of clinical trial population, exclude patients with confounders potentially impacting interpretation of clinical trial results, and to reduce the risk of serious infections. Serious infections, including pneumonia and sepsis, some of which were life-threatening or fatal, had	No	There is no reason to hypothesize an unfavorable benefit-risk profile for inotuzumab ozogamicin in patients with an uncontrolled current serious active infection (including sepsis, bacteraemia, and fungemia) or patients with a recent history (within 4 months) of deep tissue infections such as fasciitis or osteomyelitis.

Table 23. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Criterion	Reason for Exclusion	Missing Information (Yes/No)	Rationale (if Not Included as Missing Information)
	been reported in NHL studies.		
Participation in other studies involving investigational drug(s) (Phase 1-4) within 2 weeks from randomisation to end of treatment visit.	To ensure uniformity of clinical trial population, exclude patients with confounders potentially impacting the interpretation of clinical trial results.	No	Based on what was observed in ALL and NHL studies with inotuzumab ozogamicin therapy, there is no reason to hypothesize a different benefit-risk profile in patients who participated in other studies involving investigational drug(s).

ALL=acute lymphoblastic leukaemia; CD22=cluster of differentiation 22; CI=confidence interval; CNS=central nervous system; CSF=cerebrospinal fluid; ECG=electrocardiogram; GVHD=graft vs host disease; HIV=human immunodeficiency virus; HSCT=haematopoietic stem cell transplant; LVEF=left ventricular ejection fraction; MRD=minimal residual disease; NHL=non-Hodgkin lymphoma; NYHA=New York Heart Association; QTc=corrected QT interval; QTcF=Fridericia's correction of the QT interval; SOS=sinusoidal obstruction syndrome; VOD=venoocclusive disease; WBC=white blood cell; WHO=World Health Organisation

a. ALL Studies 1010 and 1022; NHL Studies 1001, 1002, 1003, 1004, 1005, 1006, 1007, 1008, 1016

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

Table 24. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

Ability to Detect Adverse Reactions	Limitation of Trial Programme	Discussion of Implications for Target Population
Which are uncommon or rare ADRs	As of 26 April 2016, approximately 880 subjects/ patients received inotuzumab ozogamicin given either as a single-agent or as a component of combination therapy in Pfizer-sponsored clinical studies. As of 30 June 2016, 307 patients from investigator-initiated research (IIR) studies and approximately 211 patients from compassionate use received inotuzumab ozogamicin.	Common events (occurring in >1/100 patients) may be identified; however, uncommon or rare ADRs may have not been observed in clinical trials.
Limited range of populations	Hispanic and Black patients have been underrepresented in clinical studies of inotuzumab ozogamicin. Therefore, it is not known whether the AE profile in those (and other) racial and/or ethnic groups is different from that seen in White and Asian patients.	The implications of the relative lack of knowledge about the safety profile of inotuzumab ozogamicin in Hispanic and Black patients are unknown. However, based on a population PK analysis in patients with relapsed or refractory ALL, race and ethnic origin was not identified as a significant factor affecting inotuzumab ozogamicin clearance.
Due to prolonged exposure	Generally, dosing of inotuzumab ozogamicin has been limited to a maximum of 6 cycles for ALL. Of the 880 subjects/patients who have been exposed to inotuzumab ozogamicin in Pfizer-sponsored studies, 9 patients received 7-8 months of therapy and 2 patients received >8 months of therapy, therefore, there is little experience with dosing beyond 8 cycles. In ALL studies[a], dosing was limited to 6 cycles.	Studies using prolonged exposure of inotuzumab ozogamicin are not currently planned. The implications of not having long-term data are not expected to have a major impact in this patient population because this treatment is designed for induction (short term) therapy and not for long term dosing. Based on data from Study 1022, most patients are expected to respond within 3 cycles.
Due to cumulative effects	Generally, dosing has been limited to a maximum of 6 cycles. Of the 880 subjects/patients who have been exposed to inotuzumab ozogamicin in Pfizer-sponsored studies, 9 patients received 7-8 months of therapy and 2 patients received >8 months of therapy therefore, there is little data on cumulative effects.	The implication of not having cumulative effect data are expected not to have a major impact in this patient population because this treatment is designed for induction (short term) therapy and not for long-term repeat dosing.

Table 24. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

Ability to Detect Adverse Reactions	Limitation of Trial Programme	Discussion of Implications for Target Population
Which have a long latency	Since the period of observation for patients treated with inotuzumab ozogamicin may be confounded by subsequent HSCT or by initiation of subsequent chemotherapy and/or radiation therapy; the information regarding potential AEs with a long latency is limited.	Implications of not having data on long latency on inotuzumab ozogamicin therapy are expected to not have a major impact.
That are dose related	In the Phase I ALL dose escalation part of Study 1010, doses of inotuzumab ozogamicin ranging from 1.2 mg/m^2/cycle to 1.8 mg/m^2/cycle were evaluated; however, doses above 1.8 mg/m^2/cycle were not evaluated in ALL studies. In NHL studies[b] doses above 1.8 mg/m^2/cycle were evaluated and a MTD was established as 1.8 mg/m^2/cycle.	Acknowledging the different dosing regimens of inotuzumab ozogamicin used in ALL studies (divided/weekly dosing as opposed to once monthly dosing in NHL studies) as well as decreased bone marrow function in patients with ALL, based on the observed DLTs with inotuzumab ozogamicin treatment in NHL, there is a potential for increased risk of haematologic and hepatic toxicities above the recommended dosing for inotuzumab ozogamicin.

ADR=adverse drug reactions; ALL=acute lymphoblastic leukaemia; AE=adverse event; DLT=dose-limiting toxicity; HSCT=haemopoietic stem cell transplant; IIR=investigator-initiated research; MTD=maximum tolerated dose; NHL=non-Hodgkin lymphoma

a. ALL Studies 1010 and 1022
b. NHL Studies 1001, 1002, 1003, 1004, 1005, 1006, 1007, 1008, 1016

SIV.3. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 25 lists the patient populations that have been under-represented in the inotuzumab ozogamicin clinical development programme.

Table 25. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	Inotuzumab ozogamicin is genotoxic and can cause embryo-foetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women using inotuzumab ozogamicin. No pregnancies were reported in female patients or in the partners of male patients during the clinical ALL or NHL studies.
Breastfeeding women	

Table 25. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
	Based on 5 times the inotuzumab ozogamicin half-life (i.e., 61.5 days) plus an additional 180 days for women and an additional 90 days for men, effective contraception for females of childbearing potential during treatment with inotuzumab ozogamicin would be at least 241.5 days (i.e., 8 months) after the last dose, and effective contraception for men with female partners of childbearing potential during treatment with inotuzumab ozogamicin would be at least 151.5 days (i.e., 5 months) after the last dose. There are no data on the presence of inotuzumab ozogamicin or its metabolites in human milk, the effects on the breast-fed children, or the effects on milk production in women treated with inotuzumab ozogamicin. There is a potential risk of exposure to the breast-fed child if breast-feeding occurs during treatment with inotuzumab ozogamicin and for at least 2 months after the final dose (based on 5 times the inotuzumab ozogamicin half-life (i.e., 61.5 days).
Patients with relevant comorbidities:	
• Patients with hepatic impairment	No formal PK studies of inotuzumab ozogamicin have been conducted in patients with hepatic impairment. For available exposure of hepatic impaired participants in the 11 completed Pfizer-sponsored clinical studies in patients with relapsed or refractory ALL and NHL reported in Module SIII, in studies ITCC-059 (WI203581) and B1931030, please refer to Table 10, Table 15 and Table 21, respectively. 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). 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. No adjustment to the starting dose is required when administering inotuzumab ozogamicin to patients with mild hepatic impairment.
• Patients with renal impairment	No formal PK studies of inotuzumab ozogamicin have been conducted in patients with renal impairment. For available exposure of renal impaired participants in the 11 completed Pfizer-sponsored clinical studies in patients with relapsed or refractory ALL and NHL reported in Module SIII, in studies ITCC-059 (WI203581) and B1931030, please refer to Table 10, Table 15 and Table 21, respectively.

Table 25. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
	Based on population pharmacokinetic analysis in 765 patients, the clearance of inotuzumab ozogamicin in patients with mild renal impairment (CLcr 60 89 mL/min; n=237), moderate renal impairment (CLcr 30 59 mL/min; n=122), or severe renal impairment (CLcr 15 29 mL/min; n=4) was similar to patients with normal renal function (CLcr ⩾ 90 mL/min; n=402). Inotuzumab ozogamicin has not been studied in patients with end stage renal disease. No adjustment to the starting dose is required when administering inotuzumab ozogamicin to patients with mild, moderate, or severe renal impairment.
• Patients with cardiovascular disease	Studies of inotuzumab ozogamicin for treatment of ALL excluded those patients with impaired cardiac function; therefore, the safety and efficacy of inotuzumab ozogamicin has not been established in patients with this relevant co-morbidity.
• Immunocompromised patients	Not included in the clinical development programme.
• Patients with a disease severity different from inclusion criteria in clinical trials	**Salvage Status** In the Study 1022, enrolled patients were due to receive either Salvage 1 or Salvage 2 therapy. More heavily pretreated individuals are likely to represent patients with more persistent/resistant disease, more persisting chemotherapy-related toxicities, and/or may have more toxicities with subsequent therapies, compared to salvage 1 or 2 patients. The activity of inotuzumab ozogamicin in more resistant disease could be different from the efficacy profile observed in the Study 1022 clinical trial population. Number of prior relapses has been a factor associated with poorer outcomes in relapsed/refractory B-cell ALL patients.[26] Similarly, inotuzumab ozogamicin treatment in heavily pretreated patients could show different safety outcomes compared to those observed in the Study 1022 clinical trial population. Although not included in Study 1022, safety and efficacy data for more heavily pretreated patients is available from Study 1010. Of the 72 enrolled patients in this study, 16 were Salvage 1, 29 were Salvage 2, and 27 were Salvage 3, 4, 5, or higher. In an efficacy analysis by salvage line (1, 2 or 3+) for patients enrolled in Study 1010, salvage status did not appear to be a significant determinant of remission rate (CR/CRi rates of 75%, 62% and 70% for Salvage 1, 2 and 3+ patients, respectively). This indicates that even multiple relapsed/refractory ALL patients can respond to treatment with inotuzumab ozogamicin. In Study 1022, Grade >3 and higher hepatotoxicity adverse events were more frequently reported in Salvage 2 compared to Salvage 1 patients (41.2% versus 23.4%, respectively). Therefore, while patients who have been heavily pretreated (e.g., patients in later lines of therapy) may have additional toxicity due to prior therapies, patients in later lines (Salvage 3+) have responded to

Table 25. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
	treatment with inotuzumab ozogamicin and subsequently proceeded to HSCT. **Higher Baseline Peripheral Blast Counts** As an antibody drug conjugate, disposition of inotuzumab ozogamicin following IV administration is influenced by interaction with CD22-positive B-lymphocytes, and in part to binding with neonatal FcRN.[32] Interaction of protein therapeutics with their cognate targets is generally associated with target-mediated disposition. For inotuzumab ozogamicin, this process was characterised in the population PK analysis using both a linear- and a time-dependent component of clearance. Reduced exposure resulting from higher clearance in some patients could reduce efficacy. In addition, patients with higher blast counts could have a higher risk for certain toxicities, including infusion reactions and tumour lysis syndrome. However, in study 1022, higher baseline peripheral blast count was associated with a lower risk of grade 3 and higher hepatotoxicity and while infusion reactions and tumour lysis syndrome were reported, there were no grade 5 events and no discontinuations due to infusion reactions or tumour lysis syndrome. Furthermore, based on a subgroup analysis of patients with a baseline peripheral blast count >1,000/mL, patients in the inotuzumab ozogamicin arm also had a statistically significant higher CR/CRi rate than the control arm. As such, although there is a theoretical reduced benefit-risk in patients with higher baseline peripheral blast counts, this was not observed among patients enrolled in Study 1022. In Study 1022, eligibility required peripheral absolute lymphoblast counts <10,000/mL. In order to reduce white blood cell counts, the protocol allowed cytoreduction with hydroxyurea and/or steroids/vincristine within 2 weeks of randomisation. Among the first 218 subjects randomised in Study 1022, approximately 28% and 17% of inotuzumab ozogamicin and control arm subjects, respectively, received cytoreductive therapy within 2 weeks prior to randomisation. Higher baseline peripheral blast counts have been reported to be a prognostic factor associated with poor outcome in ALL patients with relapsed or refractory ALL.[33]
Population with relevant different ethnic origin	Hispanic (N=14) and Black (N=22) patients (see Table 9), have been underrepresented in clinical studies with inotuzumab ozogamicin, therefore, it is not known whether the safety profile in those (and other) racial and/or ethnic groups is different from that seen in White and Asian patients. However, the general safety profile of these underrepresented racial and/or ethnic groups is similar to the overall safety profile for inotuzumab ozogamicin, although the small number of patients available for analysis makes it difficult to compare safety profiles of these individual racial

Table 25. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
	and/or ethnic groups to the overall safety profile for inotuzumab ozogamicin.
Subpopulations carrying relevant genetic polymorphisms	*In vitro*, N-acetyl-γ-calicheamicin DMH was primarily metabolised via non-enzymatic reduction and hydrolysis. Therefore, polymorphisms or genes encoding drug metabolising enzymes, including cytochrome P450s and uridine diphosphate glucuronosyltransferase (UGT) isoforms, are not expected to substantially impact drug clearance.[34] No known polymorphism impacting a response to inotuzumab ozogamicin has been reported.
Paediatric patients	Inotuzumab ozogamicin was developed as monotherapy for the treatment of adults with relapsed or refractory CD22-positive B-cell precursor ALL. Adult patients with Ph+ relapsed or refractory B-cell precursor ALL should have failed treatment with at least 1 TKI. Patients <18 years have not been studied; therefore, the safety and efficacy of inotuzumab ozogamicin in patients <18 years of age have not been established. However, as of 30 June 2016, approximately 52[4] paediatric patients have received inotuzumab ozogamicin in compassionate access/named patient access programmes and IIR studies. Ages ranged from 2 to 17 years with a mean of 11.3 years and a median of 11.0 years (n=51). Based on this limited data and taking into consideration the difficulties in comparing clinical trial data to data obtained from compassionate access/named patient access programmes and IIR studies, the safety profile of inotuzumab ozogamicin in these paediatric patients appears similar to the safety profile in adult patients. The SAEs reported for these paediatric patients are the same overall pattern of SAEs reported for adult patients, e.g., mostly febrile neutropenia, fever, and infection. There were 2 events of VOD/SOS reported in children and each occurred after a follow-up HSCT; one event of VOD was fatal, however, overall the frequency of VOD/SOS in this limited analysis was not higher than that reported in adults. Refer to Annex 7 for the frequency of VOD/SOS occurring during treatment with inotuzumab ozogamicin in studies 1022 and 1010. Two Clinical Research Collaboration studies include paediatric patients with relapsed or refractory B-cell ALL, as described in the approved inotuzumab ozogamicin Paediatric Investigational Plan (PIP). These include: • Study ITCC-059 (WI203581): a Phase 1/2 study in children ages 1 to <18 years who experience a second or later relapse will first evaluate single-agent inotuzumab ozogamicin; a Phase 2 expansion cohort will further evaluate the safety and

[4] The number of paediatric patients who have received inotuzumab ozogamicin is estimated as age was not reported in some Compassionate Access/Named Patient Access programmes and IIR studies.

Table 25. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
	preliminary efficacy of the established MTD of single-agent inotuzumab ozogamicin. Finally, a Phase 1 cohort will evaluate the safety and preliminary efficacy of inotuzumab ozogamicin combined with a modified UKALLR3 regimen (no mitoxantrone to be administered).[35] The first subject was enrolled in this study in January 2017 (refer to Table 16). • Study B1931036: a randomised Phase 2 study investigating standard relapsed or refractory ALL therapy (modified UKALLR3 regimen) with or without inotuzumab ozogamicin in patients aged 1 to < 18 years who experience a first early relapse of B-cell ALL. This study is planned to start after the Phase 1/2 study above is completed.
Elderly patients	In Study 1022, 30/164 (18.3%) patients treated with inotuzumab ozogamicin were ≥65 years of age. Overall, the frequency of AEs, SAEs, and permanent discontinuations due to AEs was similar among patients <65 versus ≥65 years of age though the number of patients ≥65 years of age from which to make this comparison was relatively small (30/164 [18.3%]). There were no noteworthy age-related haematology or clinical chemistry differences for patients <65 years versus ≥65 years of age. Low-grade electrolyte abnormalities were observed but there were no significant differences between the age groups. The liver-related laboratory test abnormalities results were numerically higher in the inotuzumab ozogamicin arm compared with the control arm yet there were no consistent differences in liver-related test abnormalities between the age groups. Moreover, a multivariate analysis examining the association between baseline patient characteristics and post-SCT VOD/SOS showed that there was a statistically significant association between patients aged 55 and older with post-HSCT VOD/SOS, indicating that older patients may be at higher risk for post-HSCT VOD/SOS. Please refer to Table 8 and Table 19 for exposure information in the elderly participants in the 11 completed Pfizer-sponsored clinical studies in patients with relapsed or refractory ALL and NHL reported in Module SIII and study B1931030, respectively.

Module SV. Post-Authorisation Experience

SV.1. Post-Authorisation Exposure

Cumulatively through 28 December 2024, it is estimated that 15,132 patients worldwide were exposed to inotuzumab ozogamicin commercially since the product was first approved.

SV.1.1. Method Used to Calculate Exposure

The cumulative estimate of the number of patients worldwide who were exposed to the commercial formulation of inotuzumab ozogamicin is based on sales of vials of inotuzumab ozogamicin extracted from the shipments data.[5]

For the cumulative period through 28 December 2024, global market experience information is based on vials sold from 01 January 2019 through 28 December 2024.
The cumulative sales of 128,619 vials have been divided by AVDOS 8.5 vials to obtain the patient exposure of 15,132 patients.
The estimated exposure data by age group and gender are not available.

Cumulative estimated exposure for North America, IDM countries and EM countries based on shipments data from 01 January 2019 through 28 December 2024 is summarised in Table 26.

Table 26. Cumulative Estimated Exposure for Inotuzumab Ozogamicin in North America, IDM and EM Countries

Region Mapping	Total Vials	Total Patients
North America[a]	54,594	6423
IDM[b]	56,519	6649
EM[c]	17,506	2060
Total	**128,619**	**15,132**

a. Including Canada, Puerto Rico and US.
b. Including Albania, Australia, Austria, Belarus, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Japan, Kosovo, Latvia, Lithuania, Macedonia, Netherlands, New Zealand, Norway, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Slovenia, South Korea, Spain, Sweden, Switzerland, Turkey, Ukraine, United Kingdom.
c. Including Arab Emirates, Argentina, Brazil, Chile, China, Colombia, Egypt, Hong Kong, India, Kuwait, Lebanon, Mexico, Oman, Paraguay, Saudi Arabia, Singapore, Taiwan.

[5] These data do not include early access programs/compassionate use, donation programs, the Pfizer Accord program, and patient assistance programs. They are available starting from 01 January 2019.

Module SVI. Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

The potential for patient-initiated misuse is unlikely; patients do not self-administer inotuzumab ozogamicin, the product is prescribed by oncology specialists and generally administered in a haematology clinic/hospital setting, and access to inotuzumab ozogamicin is restricted to healthcare professionals. Additionally, inotuzumab ozogamicin does not have characteristics that would make it attractive for illegal use. There is no data available on the potential for drug abuse or dependence with inotuzumab ozogamicin or elevation of mood with inotuzumab ozogamicin use. Finally, based on results of tissue distribution studies using [^{3}H] inotuzumab ozogamicin in male Sprague-Dawley rats after a single IV dose of 1.88 mg/m^2, 62.8 µCi/kg, minimal penetration of an intact blood brain barrier to CNS tissues is anticipated as radioequivalents in the brain were <2% of those in plasma.

Module SVII. Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

Not applicable as this is not an initial version of the RMP.

SVII.1.1. Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk: Grade ≥3 and/or Serious Hepatotoxicity, including all VOD/SOS

Risk-benefit impact: Inotuzumab ozogamicin is contraindicated in patients who have experienced prior confirmed severe or ongoing VOD/SOS and patients with serious ongoing hepatic disease (e.g., cirrhosis, nodular regenerative hyperplasia, active hepatitis).

Important Identified Risk: Myelosuppression / Cytopenia

Risk-benefit impact: in addition to the haematologic abnormalities resulting from relapsed or refractory ALL, such patients may have additional haematopoietic susceptibility to cytotoxic therapies if there is pre-existing bone marrow suppression (e.g., due to prior chemotherapy, prior HSCT, radiation, other therapies), or may experience side effects of other concomitant medications or procedures.

Important Potential Risk: Interstitial lung disease

Risk-benefit impact: Factors that could potentially be associated with an increased risk of developing ILD/pneumonitis may include a history of pre-existing pulmonary disease, prior or concomitant treatment with medications with known pulmonary toxicity [antibiotics (e.g., nitrofurantoin, amphotericin B, minocycline); chemotherapy (e.g., bleomycin, methotrexate, cyclophosphamide); antiarrhythmics (e.g., amiodarone), and tamoxifen], and other treatments

or circumstances, including radiation therapy, immune suppression resulting in pneumonia (bacterial, viral, fungal, or protozoal), a predisposition to allergic pulmonary disease, autoimmune diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis, etc.), occupational exposure (e.g., smoke, dust, silicone, asbestos), or other factors.

Important Potential Risk: Inflammatory Gastrointestinal Events

Risk-benefit impact: Patients receiving therapy for refractory leukemia, particularly those receiving anti-leukemic therapy, are susceptible to GI inflammation, including gastritis, colitis and/or typhlitis.

Important Potential Risk: Pancreatitis

Risk-benefit impact: Factors that could potentially be associated with an increased risk of developing pancreatitis include a variety of medications, (e.g., prior exposure to asparaginase, antibiotics, immunosuppressive agents, anti-hypertensives, aminosalicylates, diuretics, proton-pump inhibitors, steroids, anaesthetics, antibiotics), alcohol abuse, hepatobiliary disorders (e.g., obstruction of the common bile duct, idiopathic biliary sludge, common bile duct tumour infiltration), post-operative trauma and instrumentation (e.g., endoscopic retrograde cholangiopancreatography), hypercalcaemia, parenchymal tumour infiltration, and infection.

Important Potential Risk: Second Primary Malignancy

Risk-benefit impact: Patients with prior or ongoing malignancies and those exposed to aggressive chemotherapy, radiation or other significant immunosuppressive therapies may be at higher risk for development of additional malignancies.

Important Potential Risk: Reproductive and Developmental Toxicity (post exposure during pregnancy and while breast feeding)

Risk-benefit impact: Based on findings in animals and the known mechanism of action of inotuzumab ozogamicin, male and female fertility may be compromised by treatment with inotuzumab ozogamicin and inotuzumab ozogamicin treatment can cause foetal harm when administered to a pregnant woman. The risks to breastfeeding are not known.

Important Potential Risk: Neurotoxicity

Risk-benefit impact: Factors that could potentially be associated with an increased risk of neurotoxicity include chemotherapy, drug abuse, heavy metal exposure, pesticides, solvents, organic or organometal compounds, certain foods and food additives, radiation exposure, and cosmetics.

Important Potential Risk: Nephrotoxicity

Risk-benefit impact: Factors that could potentially be associated with an increased risk of nephrotoxicity include drugs, advanced age, haemodynamic status, and underlying disease.

Missing information: Use in patients with moderate or severe hepatic impairment

Risk-benefit impact: No formal pharmacokinetic studies of inotuzumab ozogamicin have been conducted in patients with hepatic impairment.

Missing information: Use in patients with severe renal impairment

Risk-benefit impact: No formal pharmacokinetic studies of inotuzumab ozogamicin have been conducted in patients with renal impairment.

Missing information: Use in Hispanic and Black patients

Risk-benefit impact: Based on a population pharmacokinetic analysis, age, race, and gender did not significantly affect inotuzumab ozogamicin disposition.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

The important identified and potential risks have been determined based on the safety and tolerability of inotuzumab ozogamicin in the clinical development programme with the characterisation of these risks based primarily on the data from Study 1022 conducted in patients with relapsed-refractory B-cell ALL and supportive data from Study 1010 in patients with relapsed-refractory B-cell ALL, with additional supplementation of safety data from 9 clinical studies of inotuzumab ozogamicin in patients with relapsed or refractory NHL and data from the nonclinical development programme. Please see Annex 7 for a list of the included inotuzumab ozogamicin clinical studies. Additionally, available data from gemtuzumab ozogamicin, another ADC with a similar drug design and mechanism of action, has been included in the overall risk assessment for inotuzumab ozogamicin.

The reported TEAE for patients with relapsed or refractory B-cell ALL and NHL were used to characterise the frequency, severity and nature, and seriousness and outcomes of each important risk.

For all the important risks, TEAEs (hereinafter referred to in the RMP as SAEs or AEs) included all causality SAEs or AEs that commenced on or after the Cycle 1 Day 1 (hereinafter Cycle=C, Day=D, i.e., C1D1) but within 42 days of last dose in ALL studies and within 56 days of last dose in NHL studies and prior to new anti-cancer treatment in both ALL and NHL studies. The post-dosing follow-up interval is 42 days for ALL studies to allow additional time beyond the usual 28 day dosing follow up period to capture delayed events. The post-dosing follow up interval for NHL is also longer than the usual 28 day dosing follow up period to capture delayed events; however, the follow up period in NHL studies was extended to 56 days, as denoted in the NHL clinical trial protocols, because NHL patients do not usually go to transplant, thus a longer time interval seemed appropriate.

In addition, any VOD/SOS event that began within 2 years after the randomisation date regardless of causal attribution to study therapy in ALL studies and any VOD event that

began at any time on or after C1D1 regardless of causal attribution to study therapy in NHL studies. Across the ALL and NHL Pfizer-sponsored studies, all VOD/SOS events were reported as SAEs regardless of severity. For the ALL studies, all events of VOD/SOS were required to be reported for up to 2 years post-randomisation. In the NHL studies, the time requirement beyond the study treatment period for VOD/SOS reporting was not specified.

In addition, selected laboratory abnormalities reported in ALL studies that commenced on or after C1D1 but within 42 days of last dose and prior to new anti-cancer treatment, were also used to characterise the following important identified and potential risks: Grade ≥3 and/or serious hepatotoxicity, including all VOD/SOS, myelosuppression/ cytopenias, pancreatitis, and nephrotoxicity.

Of note, hereinafter, when stated, the acronym hepatotoxicity- VOD/SOS will refer to Grade ≥3 and/or serious hepatotoxicity, including all VOD/SOS; however, the risk term Grade ≥3 and/or serious hepatotoxicity, including all VOD/SOS will be used when naming the important identified risk (e.g., section heading, table captions).

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Important identified risks for inotuzumab ozogamicin include Grade ≥3 and/or serious hepatotoxicity, including all VOD/SOS and myelosuppression/cytopenia.

Important potential risks for inotuzumab ozogamicin include interstitial lung disease, inflammatory gastrointestinal events, pancreatitis, second primary malignancy, reproductive and developmental toxicity (post exposure during pregnancy and while breast feeding), neurotoxicity, and nephrotoxicity.

Cumulative post-marketing data through 28 December 2023 are presented in the sections below (MedDRA version 26.1).

Important Identified Risks

Table 27. Grade ≥3 and/or Serious Hepatotoxicity, including all VOD/SOS

Potential mechanisms	In nonclinical studies, hepatotoxicity was observed for ADCs that bind or do not bind the target antigen, indicating that hepatotoxicity was target-independent. Increases in AST and/or ALT and histopathological changes, including sinusoidal dilation with damage/loss of SECs (accompanied by sequestration of platelets) along with multifocal hepatocyte hypertrophy, were considered to be the primary important liver findings in cynomolgus monkeys. These findings were consistent with microvascular liver injury and were considered to represent early stages of SOS and NRH, morphologically similar to those reported in clinical trials.
Evidence source	Inotuzumab ozogamicin clinical and nonclinical studies.
Characterisation of the risk	**Clinical data** <u>Frequency</u> All causality events of hepatotoxicity-VOD/SOS occurred in 18.9% (95% CI: 13.6 - 24.1) of patients in pooled ALL studies, 15.0 % (95% CI: 9.7 - 20.4) of patients in pooled single-agent NHL studies; 13.3% (95% CI: 9.8 - 16.8) of patients in pooled NHL studies with inotuzumab ozogamicin in combination with rituximab, and 9.7%

Table 27. Grade ≥3 and/or Serious Hepatotoxicity, including all VOD/SOS

	(95% CI: 4.0 - 15.4) in the one NHL study with inotuzumab ozogamicin in combination with rituximab plus chemotherapy[6] (refer to Annex 7 for further details). Seriousness/outcomes and severity Clinical data on seriousness and outcomes, and an overview of severity of the relevant events from clinical data ranging from Grade 1 to Grade 4 are provided in Annex 7. **Cumulative data from the safety database** CT Cases Cumulatively through 28 December 2024, out of the 2123 CT cases received by the MAH, there were 194 cases (9.1%) containing 215 relevant events; the events' data are presented in Annex 7. Non-CT cases In the post-marketing experience, since first approval and through 28 December 2024, out of the 2658 non-CT cases received by the MAH, there were 564 cases (21.2%) containing 657 relevant events. Distribution of event by seriousness and clinical outcome is provided in Annex 7. **Background Incidence/Prevalence** The background incidence/prevalence for hepatic or hepatobiliary disorders among relapsed refractory B-cell precursor ALL patients is not available as there is no unexposed target population. After diagnosis, patients are treated and any untreated patients have a very short survival. Incidence of VOD/SOS after HSCT While there are generally accepted diagnostic criteria for identifying VOD, there is no accepted standard for laboratory, imaging or histologic tests for VOD/SOS.[36] Additionally, there is a lack of prospective, large multi-centre clinical trials that include specific diagnostic criteria for confirming the diagnosis of VOD/SOS, by contrast the relevant clinical studies tend to be small, and risk factors for VOD/SOS are variably distributed across treatment arms. As a result, the reported VOD/SOS incidence rates vary widely, especially in the early literature, ranging from 0 to 70%.[36] The vast majority of VOD/SOS cases occurred in a setting of HSCT.[36] With the introduction of intravenous busulfan-based regimens, the growing use of reduced-intensity conditioning in past decades, the reduced incidence of hepatitis C in HSCT patients, improved patient selection for HSCT, and better supportive care, the reported incidence of VOD/SOS appears to have declined significantly.[36] However, the more recently reported VOD/SOS incidence rates (1993-2010) still vary widely most likely due to difference in pre-HSCT patient characteristics, conditioning regimens, GVHD prophylaxis, donor source[37], and supportive care available.[36,38] The reported incidence of VOD/SOS in children is 5-40%.[39] In adults, reported incidence rates range from 0% with reduced-intensity conditioning, to 38% with cyclophosphamide, TBI at one center,[36] and up to 54% in studies involving greater than 100 patients.[40] The reported incidence of VOD/SOS after allogeneic HSCT is 10-15%

[6] Source: t_II_SVII_1_1_2_293_t_ae_hep_ci

Table 27. Grade ≥3 and/or Serious Hepatotoxicity, including all VOD/SOS

	following myeloablative conditioning, and as low as 5% or less with non-myeloablative or reduced conditioning regimens. Patient Outcome and Mortality of VOD/SOS The clinical presentation of VOD/SOS ranges from a mild reversible disease to a severe syndrome often associated with MOF.[37] The mortality rate of VOD/SOS varies according to its severity, with MOF being the cause of death in two thirds of patients with VOD/SOS. Severe VOD/SOS, defined as situations where liver damage did not resolve before day 100 or the patient died, whichever occurred first, accounts for 18-27% of cases.[41] Severe VOD/SOS is one of the most common causes of early death after allogeneic HSCT, with a mortality rate as high as 80-100% by day +100 post-HSCT in adults and slightly lower mortality in children and patients treated with defibrotide.[36,37,38] In nonsevere VOD/SOS, reported in 50-80% of VOD/SOS cases, the patient typically improves within 17-25 days after onset.[41] The VOD/SOS mortality ranged from 3% up to 64% in large (>100 patients) studies.[42] Incidence of VOD/SOS outside the setting of HSCT While allogeneic stem cell transplantation and stem cell transplantation are the most common causes of VOD/SOS in the Western Hemisphere, VOD/SOS has also been described in association with chemotherapeutic agents (e.g., actinomycin D, mithramycin, dacarbazine, cytosine arabinoside, 6-thioguanine, and azathioprine), therapy for AML with monoclonal anti-CD33 antibody gemtuzumab ozogamicin, combination therapy and radiation used in abdominal areas (e.g., such as in children with Wilms tumour), and after liver transplantation.[43,44] Refer to Annex 7 for further details on Background incidence/prevalence.
Risk factors and risk groups	Inotuzumab ozogamicin is contraindicated in patients who have experienced prior confirmed severe or ongoing VOD/SOS and patients with serious ongoing hepatic disease (e.g., cirrhosis, nodular regenerative hyperplasia, active hepatitis). 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. Based on multivariate analysis in Study 1022, patient factors that were significantly associated with an increased risk of VOD/SOS after a HSCT included the use of HSCT conditioning regimens containing 2 alkylating agents and serum bilirubin ≥ULN prior to HSCT. Based on univariate analysis in Study 1022, other patient factors that appeared to be associated with an increased risk of VOD/SOS after a HSCT include a prior HSCT, age ≥55 years, a history of hepatic disease and/or hepatitis before treatment, later salvage lines, and a greater number of treatment cycles.
Preventability	Product labeling contraindicates the following patients: • Patients who have experienced prior confirmed severe or ongoing VOD/SOS. • Patients with serious ongoing hepatic disease (e.g., cirrhosis, nodular regenerative hyperplasia, active hepatitis). Product labeling indicates/recommends the following: • the reported frequency of VOD/SOS post-HSCT was ≥50% in the following patients: patients who received a HSCT conditioning regimen containing 2

Table 27. Grade ≥3 and/or Serious Hepatotoxicity, including all VOD/SOS

	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 and the benefit/risk should be carefully considered before administering inotuzumab ozogamicin 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, aHSCT post inotuzumab ozogamicin treatment should only be undertaken after careful consideration of the benefit/risk and that if these patients do proceed to HSCT, signs and symptoms of VOD/SOS should be closely monitored; • 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 hepatic disease and/or hepatitis before treatment, later salvage lines, and a greater number of treatment cycles; • careful consideration is required before administering inotuzumab ozogamicin to patients who have had a prior HSCT. No patients with relapsed or refractory ALL who were treated with inotuzumab ozogamicinin clinical trials had undergone HSCT within the previous 4 months; • patients with a history of hepatic disease should be carefully evaluated (e.g., ultrasound scan, viral hepatitis testing) prior to treatment with inotuzumab ozogamicin to exclude serious ongoing hepatic disease; • patients proceeding to HSCT, the recommended duration of treatment is 2 cycles, with a maximum of 3 cycles, to reduce the risk of VOD/SOS; • signs and symptoms of VOD/SOS should be monitored closely in all patients, especially post HSCT; • in all patients, liver tests should be monitored, including, ALT, AST, total bilirubin, and alkaline phosphatase, prior to and following each dose of inotuzumab ozogamicin; • in 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 inotuzumab ozogamicin; • treatment should be permanently discontinued if VOD/SOS occurs and if severe VOD/SOS occurs, the patients should be treated according to standard medical practice.
Impact on the risk-benefit balance of the product	Patients who have experienced prior confirmed severe or ongoing VOD/SOS and patients with serious ongoing hepatic disease (e.g., cirrhosis, nodular regenerative hyperplasia, active hepatitis) should not be treated with inotuzumab ozogamicin. Inotuzumab ozogamicin significantly increased the risk of VOD/SOS above that of standard chemotherapy regimens in patients with relapsed or refractory ALL. This risk was most marked in patients who underwent subsequent HSCT. Patients should be informed that 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.

Table 27. Grade ≥3 and/or Serious Hepatotoxicity, including all VOD/SOS

	The use of HSCT conditioning regimens containing 2 alkylating agents should be avoided. The benefit/risk should be carefully considered before administering inotuzumab ozogamicin 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 inotuzumab ozogamicin 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. 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 hepatic disease and/or hepatitis before treatment, later salvage lines, and a greater number of treatment cycles. Careful consideration is required before administering inotuzumab ozogamicin to patients who have had a prior HSCT. No patients with relapsed or refractory ALL who were treated with inotuzumab ozogamicin, in clinical trials had undergone HSCT within the previous 4 months. Patients with a history of hepatic disease should be carefully evaluated (e.g., ultrasound scan, viral hepatitis testing) prior to treatment with inotuzumab ozogamicin to exclude serious ongoing hepatic disease. For patients proceeding to HSCT, the recommended duration of treatment is 2 cycles, with a maximum of 3 cycles, to reduce the risk of VOD/SOS. 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. In all patients, liver tests should be monitored, including, ALT, AST, total bilirubin, and alkaline phosphatase, prior to and following each dose of inotuzumab ozogamicin. 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 inotuzumab ozogamicin. Treatment should be permanently discontinued if VOD/SOS occurs. If severe VOD/SOS occurs, the patient should be treated according to standard medical practice.
Public health impact	The public health impact of inotuzumab ozogamicin-related serious hepatotoxicity is predominantly determined by the frequency of hospitalizations due to life-threatening complications (e.g., hepatic failure, VOD/SOS). From the individual point of view, VOD/SOS has a significant impact. However, from a public health point of view, it would appear to be of low impact because of the relatively low frequency of VOD/SOS in the population as a whole.
MedDRA terms	**Grade ≥3 AEs and/or SAEs encoded to MedDRA PTs within the following SMQs:** Cholestasis and jaundice of hepatic origin (SMQ narrow), Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ narrow), Hepatitis, noninfectious (SMQ narrow), Liver related investigations, signs and symptoms (SMQ narrow and broad). **Grade ≥3 AEs and/or SAEs encoded to the following MedDRA PTs:** Hepatic vein occlusion, Hepatic vein thrombosis, Portal vein thrombosis, Budd-Chiari syndrome, Chronic graft versus host disease in liver, Acute graft versus host disease in liver.

Table 27. Grade ≥3 and/or Serious Hepatotoxicity, including all VOD/SOS

	All AEs encoded to the following MedDRA PTs: Venoocclusive liver disease, Venoocclusive disease.

Table 28. Myelosuppression/cytopenia

Potential mechanisms	As would be expected for an agent that selectively targets cells expressing CD22, lymphopenia has also been frequently reported as a treatment-related AE. Myelosuppression is one of the toxicities frequently associated with administration of agents that induce double-stranded DNA breaks with consequent apoptotic cell death.[45] Hence, myelosuppression associated with inotuzumab ozogamicin treatment likely reflects a combination of both target-dependent and target-independent calicheamicin exposure. In inotuzumab ozogamicin therapy in ALL, such cytotoxicity is superimposed on an already infiltrated bone marrow which has sustained microenviromental and cellular injury from prior chemotherapy and possibly total body irradiation. Infections are common in ALL patients and may induce or exacerbate myelosuppression. The major haematological changes in nonclinical studies consisted of decreases in RBC mass and lymphocytes in rats and cynomolgus monkeys and decreases in platelets in monkeys. Acute thrombocytopenia was considered due to platelet sequestration in the liver secondary to inotuzumab ozogamicin-mediated liver-specific endothelial injury; however, the mechanism for prolonged platelet effects was uncertain. <u>*Infection*</u> Infection may be a complication of myelosuppression/cytopenia superimposed on an already weak immune system due to underlying disease and previously damaged bone marrow with limited ability to respond to cytotoxic agents. Cytopenias increase the risk of bacterial, viral and fungal infections. Other risk factors for infection may include hospitalization and instrumentation, e.g., mucosal injury due to neutropenia or chemotherapy-induced mucositis, lack of skin integrity due to IVs, indwelling catheters, surgery, and other procedures, and prolonged use of antibiotics that may foster colonization by resistant organisms or fungal infections, etc. <u>*Haemorrhage*</u> Haemorrhage may be a complication of myelosuppression/cytopenia with resulting thrombocytopenia superimposed on an already damaged bone marrow with limited resiliency due to underlying disease or prior cytotoxic therapy. Other factors include platelet dysfunction due to drugs (e.g., NSAID), other mechanisms of reduction in platelets (e.g., hepatic sequestration), and coagulopathy in cases of infection and/or liver dysfunction. Intracranial haemorrhage or thrombosis is fairly common in ALL patients, usually during episodes of thrombocytopenia or following therapy with asparaginase.
Evidence source	Inotuzumab ozogamicin clinical and nonclinical studies.
Characterisation of the risk	**Clinical data** <u>Frequency</u> *Myelosuppression/Cytopenia* All causality AEs of myelosuppression/cytopenia occurred in 78.8% (95% CI: 73.3 – 84.3) of patients in pooled ALL studies and in 90.8% (95% CI: 86.4 – 95.1) of patients

Table 28. Myelosuppression/cytopenia

	in pooled single-agent NHL studies.[7] Although all causality frequency was higher for NHL, Grade 4 events were higher for ALL, likely due to a combination of the different eligibility criteria in the NHL studies (a neutrophil count of ≥1000/mm^3 and a platelet count of ≥75,000/mm^3 were required) as well as the less extensive bone marrow involvement with NHL compared to ALL. *Infection* All causality AEs of infection occurred in 45.3% (95% CI: 38.6 – 52.0) of patients in pooled ALL studies, and in 48.0% (95% CI: 40.5 – 55.4) of patients in pooled single-agent NHL studies.[8] *Haemorrhage* All causality AEs of haemorrhage occurred in 33.5% (95% CI: 27.1 – 39.8) of patients in pooled ALL studies, and in 28.3% (95% CI: 21.6 – 35.0) of patients in pooled single-agent NHL studies.[9] Seriousness/outcomes and severity Clinical data on seriousness and outcomes, and an overview of severity of the relevant events from clinical data are provided in Annex 7. **Cumulative data from the safety database** CT Cases Cumulatively through 28 December 2024, out of the 2123 CT cases received by the MAH, there were 1141 cases (53.7%) containing 1327 relevant events; the events' data are presented in Annex 7. Non-CT cases In the post-marketing experience, since first approval and through 28 December 2024, out of the 2658 non-CT cases received by the MAH, there were 883 cases (33.2%) containing 1532 relevant events. Distribution of event by seriousness and clinical outcome is provided in Annex 7. **Background Incidence/Prevalence** The background incidence/prevalence of myelosuppression/cytopenia, including infection or haemorrhage among relapsed or refractory B-cell precursor ALL patients, is not available as there is no unexposed target population. After ALL diagnosis all patients are treated, and any untreated patients have a very short survival. At diagnosis of ALL, severe anaemia (Haemoglobin <8 g/dl) is present in 28%, severe granulocytopenia (neutrophils <0.5 × 10^9/l) in 22%, severe thrombocytopenia (platelets <25 ×10^9/l) in 30%, hyperleukocytosis (total white blood cells >10 × 10^9/l in 59%, >50 × 10^9/l in 28%), and detectable circulating blast cells in 92% of cases.[23]
Risk factors and risk groups	In addition to the haematologic abnormalities resulting from relapsed or refractory ALL, such patients may have additional haematopoietic susceptibility to cytotoxic therapies if there is pre-existing bone marrow suppression (e.g., due to prior

[7] Source: t_II_SVII_2_1_293_t_ae_hem_ci (NHL) ; t_II_SVII_2_1_1_293_t_ae_hem_ci (ALL)

[8] Source: t_II_SVII_3_1_293_t_ae_inf_ci (NHL); t_II_SVII_3_1_1_293_t_ae_inf_ci (ALL)

[9] Source: t_II_SVII_14_1_293_t_ae_hemorr_ci (NHL); t_II_SVII_9_1_1_293_t_ae_hmr_ci (ALL)

Table 28. Myelosuppression/cytopenia

	chemotherapy, prior HSCT, radiation, other therapies), or may experience side effects of other concomitant medications or procedures.
Preventability	As myelosuppression/cytopenia is part of the mechanism of action of a cytotoxic agent such as calicheamicin, the goal is not specifically aimed toward preventing myelosuppression/cytopenias, but rather towards preventing or providing adequate support for severe or life-threatening myelosuppression/cytopenia. For example, measures might include use of myeloid growth factors such as G-CSF or blood product transfusion support with packed red blood cells or platelets, appropriate dose modification based on ANC and platelet count, or limiting number of cycles of therapy to the minimum needed to provide the appropriate efficacy.
Impact on the risk-benefit balance of the product	If myelosuppression/cytopenia is Grade 1 or 2, the impact on an individual patient is limited. Severe myelosuppression/cytopenia may predispose patients to serious and/or life-threatening infections, multi organ failure/septic shock and/or haemorrhage/bleeding. Depending on the type, severity and duration of the myelosuppression/cytopenia, individual patients may require significant haematologic support (e.g., red blood cell or platelet transfusions, growth factor support, and aggressive medical management of infections and haemorrhage/bleeding events).
Public health impact	The public health impact of inotuzumab ozogamicin-related myelosuppression/cytopenia is anticipated to be low.
MedDRA terms	**Myelosuppression/Cytopenia** SMQs: Haematopoietic thrombocytopenia SMQ narrow and broad; Haematopoietic leukopenia SMQ narrow; Haematopoietic erythropenia SMQ narrow and broad; Haematopoietic cytopenias affecting more than one type of blood cell SMQ narrow. **Infection** Infections and Infestations SOC. **Haemorrhage** Haemorrhage terms (excluding laboratory terms) SMQ narrow.

Important Potential Risks

Table 29. Interstitial Lung Disease

Potential mechanisms	No potential mechanism of ILD associated with inotuzumab ozogamicin is known. ILD was not observed in nonclinical studies.
Evidence source	Inotuzumab ozogamicin clinical and nonclinical studies.
Characterisation of the risk	**Clinical data** Frequency All causality AEs of ILD occurred in 0.5% (95% CI: 0.0 -2.6) of patients in pooled ALL studies and in 2.3% (95% CI: 0.6 -5.8) of patients in pooled single-agent NHL studies[10]. Seriousness/outcomes and severity Clinical data on seriousness and outcomes, and an overview of severity of the relevant events from clinical data are provided in Annex 7. **Cumulative data from the safety database** CT Cases Cumulatively through 28 December 2024, out of the 2123 CT cases received by the MAH, there were 4 cases (0.2%) containing 5 relevant events; the events' data are presented in the table below.

[10] Source: t_II_SVII_7_1_293_t_ae_ild_ci (NHL); t_II_SVII_7_1_1_293_t_ae_ild_ci (ALL)

Table 29. Interstitial Lung Disease

PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Event by Outcome N (%)				
				Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
All PTs	**5 (100)**	**5 (100)**	**2 (40)**	**2 (40)**	**-**	**1 (20)**	**1 (20)**	**1 (20)**
Pneumonitis	2 (40)	2 (100)	1 (50)	1 (50)	-	1 (50)	-	-
Diffuse alveolar damage	1 (20)	1 (100)	-	1 (100)	-	-	-	-
Lung infiltration	1 (20)	1 (100)	1 (100)	-	-	-	1 (100)	-
Pulmonary fibrosis	1 (20)	1 (100)	-	-	-	-	-	1 (100)

Non-CT cases

In the post-marketing experience, since first approval and through 28 December 2024, out of the 2658 non-CT cases received by the MAH, there were 13 cases (0.5%) containing 13 relevant events. Distribution of event by seriousness and clinical outcome is provided below.

PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Event by Outcome N (%)				
				Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
All PTs	**13 (100)**	**12 (92.3)**	**4 (30.8)**	**4 (30.8)**	**1 (7.7)**	**1 (7.7)**	**2 (15.4)**	**5 (38.5)**
Interstitial lung disease	7 (53.8)	7 (100)	2 (28.6)	1 (14.3)	1 (14.3)	-	1 (14.3)	4 (57.1)
Pneumonitis	4 (30.8)	3 (75)	1 (25)	1 (25)	-	1 (25)	1 (25)	1 (25)
Alveolitis	1 (7.7)	1 (100)	1 (100)	1 (100)	-	-	-	-
Pulmonary toxicity	1 (7.7)	1 (100)	-	1 (100)	-	-	-	-

Background Incidence/Prevalence

The background incidence/prevalence of ILD among relapsed or refractory B-cell precursor ALL patients is not available as there is no unexposed target population. After diagnosis all ALL patients are treated and any untreated patients have a very short survival.

Table 29. Interstitial Lung Disease

Risk factors and risk groups	Factors that could potentially be associated with an increased risk of developing ILD/pneumonitis may include a history of pre-existing pulmonary disease, prior or concomitant treatment with medications with known pulmonary toxicity [antibiotics (e.g., nitrofurantoin, amphotericin B, minocycline); chemotherapy (e.g., bleomycin, methotrexate, cyclophosphamide); antiarrhythmics (e.g., amiodarone), and tamoxifen], and other treatments or circumstances, including radiation therapy, immune suppression resulting in pneumonia (bacterial, viral, fungal, or protozoal), a predisposition to allergic pulmonary disease, autoimmune diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis, etc.), occupational exposure (e.g., smoke, dust, silicone, asbestos), or other factors.
Preventability	It is not known if patients may be at an increased risk of developing ILD as a result of exposure to inotuzumab ozogamicin. Thus, there are currently no known preventive measures.
Impact on the risk-benefit balance of the product	Depending on the severity, the impact of ILD on an individual patient may include the potential for permanent loss of pulmonary function. Severe ILD can be a life-threatening event or have a fatal outcome.
Public health impact	The public health impact of inotuzumab ozogamicin-related ILD is anticipated to be low.
MedDRA terms	**SMQ:** Interstitial lung disease SMQ narrow. **PT:** Graft versus host disease in lung.

Table 30. Inflammatory Gastrointestinal Events

Potential mechanisms	Cytotoxic agents are known to cause inflammatory GI events and this effect may be exacerbated by concomitant medications and other therapies in oncology patients.
Evidence source	Inotuzumab ozogamicin clinical and nonclinical studies.
Characterisation of the risk	**Clinical data** <u>Frequency</u> All causality AEs of GI inflammation occurred in 14.2% (95% CI: 9.5 - 18.8) of patients in pooled ALL studies, and in 13.9% (95% CI: 8.7 - 19.0) of patients in pooled single-agent NHL studies.[11] <u>Seriousness/outcomes and severity</u>

[11] t_II_SVII_8_1_1_293_t_ae_igi_ci; t_II_SVII_8_1_1_1_293_t_ae_nhl_ci_igi

Table 30. Inflammatory Gastrointestinal Events

Clinical data on seriousness and outcomes, and an overview of severity of the relevant events from clinical data are provided in Annex 7.

Cumulative data from the safety database

CT Cases

Cumulatively through 28 December 2024, out of the 2123 CT cases received by the MAH, there were 31 cases (1.5%) containing 32 relevant events; the events' data are presented in the table below.

PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Event by Outcome N (%)				
				Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
All PTs	**32 (100)**	**32 (100)**	**29 (90.6)**	**1 (3.1)**	**23 (71.9)**	**2 (6.3)**	**4 (12.5)**	**2 (6.3)**
Mucosal inflammation	4 (12.5)	4 (100)	4 (100)	-	4 (100)	-	-	-
Stomatitis	10 (31.3)	10 (100)	7 (70)	-	6 (60)	1 (10)	3 (30)	-
Colitis	10 (31.3)	10 (100)	10 (100)	-	7 (70)	-	1 (10)	2 (20)
Gastritis	2 (6.3)	2 (100)	2 (100)	-	2 (100)	-	-	-
Colitis ulcerative	1 (3.1)	1 (100)	1 (100)	-	-	1 (100)	-	-
Neutropenic colitis	1 (3.1)	1 (100)	1 (100)	-	1 (100)	-	-	-
Colitis ischaemic	1 (3.1)	1 (100)	1 (100)	1 (100)	-	-	-	-
Duodenitis	1 (3.1)	1 (100)	1 (100)	-	1 (100)	-	-	-
Enteritis	1 (3.1)	1 (100)	1 (100)	-	1 (100)	-	-	-
Oesophagitis	1 (3.1)	1 (100)	1 (100)	-	1 (100)	-	-	-

Non-CT cases

In the post-marketing experience, since first approval and through 28 December 2024, out of the 2658 non-CT cases received by the MAH, there were 32 cases (1.2%) containing 34 relevant events. Distribution of event by seriousness and clinical outcome is provided below.

Table 30. Inflammatory Gastrointestinal Events

	PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Event by Outcome[12] N (%)				
					Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
	All PTs	**34 (100)**	**16 (47.1)**	**4 (11.8)**	**1 (2.9)**	**11 (32.4)**	**1 (2.9)**	**1 (2.9)**	**21 (61.8)**
	Mucosal inflammation	18 (52.9)	10 (55.6)	3 (16.7)	-	4 (22.2)	-	-	14 (77.8)
	Stomatitis	5 (14.7)	2 (40)	1 (20)	-	4 (80)	1 (20)	-	1 (20)
	Colitis	1 (2.9)	1 (100)	-	1 (100)	-	-	-	-
	Mouth ulceration	3 (8.8)	-	-	-	1 (33.3)	-	-	2 (66.7)
	Colitis ulcerative	1 (2.9)	1 (100)	-	-	-	-	-	1 (100)
	Gastritis	1 (2.9)	-	-	-	-	-	-	1 (100)
	Neutropenic colitis	1 (2.9)	1 (100)	-	-	1 (100)	-	-	-
	Oral pain	2 (5.9)	-	-	-	1 (50)	-	-	1 (50)
	Oropharyngeal pain	2 (5.9)	1 (50)	-	-	-	-	1 (50)	1 (50)
	Background Incidence/Prevalence The background incidence/prevalence for of inflammatory GI events among relapsed or refractory B-cell precursor ALL patients is not available as there is no unexposed target population. After diagnosis all patients are treated and any untreated patients have a very short survival.								
Risk factors and risk groups	Patients receiving therapy for refractory leukaemia, particularly those receiving anti-leukaemic therapy, are susceptible to GI inflammation, including gastritis, colitis and/or typhlitis. Factors that could potentially be associated with an increased risk of developing inflammatory GI disease may include a history of pre-existing GI abnormalities, prior cytotoxic chemotherapy, advanced age, chronic illness, and other medications. Of note, ischemic colitis is more likely to occur in older patients, particularly those with comorbidities such as ischemic cardiac disease.								
Preventability	It is not known which patients may be at an increased risk of developing inflammatory GI events as a result of exposure to inotuzumab ozogamicin. Thus, there are currently no known preventive measures.								

[12] Multiple episodes of the same event were reported with a different outcome in some cases hence the sum of the events outcome exceeds the total number of events.

Table 30. Inflammatory Gastrointestinal Events

Impact on the risk-benefit balance of the product	If inflammatory GI events are Grade 1 or 2, the impact on an individual patient may be limited. Severe inflammatory GI event can be a life-threatening event or have a fatal outcome.
Public health impact	The public health impact of inotuzumab ozogamicin-related GI inflammation is anticipated to be low.
MedDRA terms	**SMQ:** Gastrointestinal nonspecific inflammation SMQ narrow **HLT**: Colitis (excluding infective) (all paths); Stomatitis and ulceration (all paths) **PTs**: Oral pain; Oropharyngeal pain; Mucosal inflammation.

Table 31. Pancreatitis

Potential mechanisms	In general, pancreatitis may be due to mechanical obstruction, medications, and other factors, however, no potential mechanism of pancreatitis associated with inotuzumab ozogamicin treatment is known. Pancreatitis or elevations in amylase and lipase laboratory tests were not observed in inotuzumab ozogamicin nonclinical studies.
Evidence source	Inotuzumab ozogamicin clinical and nonclinical studies.
Characterisation of the risk	**Clinical data** Frequency All causality AEs of pancreatitis occurred in 9.4% (95% CI: 5.5 – 13.4) of patients in pooled ALL studies and in 1.2% (95% CI: 0.1 – 4.1) of patients in pooled single-agent NHL studies.[13] Seriousness/outcomes and severity Clinical data on seriousness and outcomes, and an overview of severity of the relevant events from clinical data are provided in Annex 7. **Cumulative data from the safety database** CT Cases Cumulatively through 28 December 2024, out of the 2123 CT cases received by the MAH, there were 19 cases (0.9%) containing 22 relevant events; the events' data are presented in the table below.

[13] Source: t_II_SVII_10_1_293_t_ae_pan_ci (NHL); t_II_SVII_10_1_1_293_t_ae_pan_ci (ALL)

Table 31. Pancreatitis

PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Event by Outcome N (%)				
				Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
All PTs	**22 (100)**	**22 (100)**	**19 (86.4)**	**-**	**11 (50)**	**-**	**7 (31.8)**	**4 (18.2)**
Pancreatitis	13 (59.1)	13 (100)	11 (84.6)	-	8 (61.5)	-	4 (30.8)	1 (7.7)
Pancreatitis acute	5 (22.7)	5 (100)	5 (100)	-	2 (40)	-	2 (40)	1 (20)
Lipase increased	3 (13.6)	3 (100)	2 (66.7)	-	1 (33.3)	-	1 (33.3)	1 (33.3)
Amylase increased	1 (4.5)	1 (100)	1 (100)	-	-	-	-	1 (100)

Non-CT cases

In the post-marketing experience, since first approval and through 28 December 2024, out of the 2658 non-CT cases received by the MAH, there were 17 cases (0.6%) containing 18 relevant events. Distribution of event by seriousness and clinical outcome is provided below.

PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Event by Outcome N (%)				
				Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
All PTs	**18 (100)**	**11 (61.1)**	**4 (22.2)**	**-**	**6 (33.3)**	**-**	**2 (11.1)**	**10 (55.6)**
Pancreatitis	6 (33.3)	6 (100)	2 (33.3)	-	1 (16.7)	-	1 (16.7)	4 (66.7)
Pancreatitis acute	3 (16.7)	3 (100)	2 (66.7)	-	2 (66.7)	-	-	1 (33.3)
Lipase increased	2 (11.1)	-	-	-	-	-	-	2 (100)
Amylase increased	4 (22.2)	1 (25)	-	-	1 (25)	-	1 (25)	2 (50)
Pancreatic enzymes increased	2 (11.1)	-	-	-	1 (50)	-	-	1 (50)
Pancreatitis relapsing	1 (5.6)	1 (100)	-	-	1 (100)	-	-	-

Table 31. Pancreatitis

	Background Incidence/Prevalence The background incidence/prevalence of pancreatitis among relapsed or refractory B-cell precursor ALL patients is not available as there is no unexposed target population. After ALL diagnosis all patients are treated and any untreated patients have a very short survival.
Risk factors and risk groups	Factors that could potentially be associated with an increased risk of developing pancreatitis include a variety of medications, (e.g., prior exposure to asparaginase, antibiotics, immunosuppressive agents, anti-hypertensives, aminosalicylates, diuretics, proton-pump inhibitors, steroids, anaesthetics, antibiotics), alcohol abuse, hepatobiliary disorders (e.g., obstruction of the common bile duct, idiopathic biliary sludge, common bile duct tumour infiltration), post-operative trauma and instrumentation (e.g., endoscopic retrograde cholangiopancreatography), hypercalcaemia, parenchymal tumour infiltration, and infection.
Preventability	It is not known if patients may be at an increased risk of developing pancreatitis as a result of exposure to inotuzumab ozogamicin. Thus, there are currently no known preventive measures.
Impact on the risk-benefit balance of the product	If pancreatitis is Grade 1 or 2, the impact on an individual patient may be limited. Severe pancreatitis can be a life-threatening event or can have a fatal outcome.
Public health impact	The public health impact of inotuzumab ozogamicin-related pancreatitis is anticipated to be low.
MedDRA terms	**SMQ:** Acute pancreatitis SMQ narrow **PTs:** Amylase abnormal; Amylase creatinine clearance ratio abnormal; Amylase increased; Lipase abnormal; Lipase increased; Lipase urine increased; Pancreatic enzyme abnormality; Pancreatic enzymes abnormal; Pancreatic enzymes increased.

Table 32. Second Primary Malignancy

Potential mechanisms	Based on nonclinical data, inotuzumab ozogamicin is clastogenic and calicheamicin is genotoxic and clastogenic. This is consistent with the known induction of DNA breaks by calicheamicin and other enediyne antitumour antibiotics. In rats, preneoplastic lesions were observed in the liver after 4 weeks of dosing and neoplastic lesions were observed in the liver after 26 weeks of dosing. The relevance of these animal findings to humans is unknown. However, due to their mechanism of action (DNA damage), administration of an ADC containing calicheamicin may be associated with a potential risk of secondary malignancies.[46]
Evidence source	Inotuzumab ozogamicin clinical and nonclinical studies.
Characterisation of the risk	**Clinical data** Frequency

Table 32. Second Primary Malignancy

Given the broad search that identified malignant and nonmalignant tumours, the search for second primary malignancy identified all causality AEs in 5.7% (95% CI: 2.5 – 8.8) of patients in pooled ALL studies, and in 4.0% (95% CI: 1.1–7.0) of patients in pooled single-agent NHL studies. However, of these events, only 1 event of a second primary malignancy was identified (in ALL Study 1010).[14]

Seriousness/outcomes

As noted above, in ALL and single-agent NHL studies, there was only 1 event of a second primary malignancy. In ALL Study 1010, the patient experienced the SAE Acute myeloid leukaemia which did not resolve. Other than this singular event, there were no other reports of a second primary malignancy in these studies.

Severity and Nature of Risk

As noted above, in ALL and single-agent NHL studies, there was only 1 event of a second primary malignancy. In ALL Study 1010, the patient experienced Grade 4 Acute myeloid leukaemia. Other than this singular event, there were no other reports of a second primary malignancy in these studies.

Cumulative data from the safety database

CT Cases

Cumulatively through 28 December 2024, out of the 2123 CT cases received by the MAH, there were 4 cases (0.2%) containing 8 relevant events; the events' data are presented in the table below.

PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Event by Outcome N (%)				
				Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
All PTs	**8 (100)**	**8 (100)**	**4 (50)**	**-**	**-**	**-**	**8 (100)**	**-**
Second primary malignancy	4 (50)	4 (100)	2 (50)	-	-	-	4 (100)	-
Acute myeloid leukaemia	3 (37.5)	3 (100)	2 (66.7)	-	-	-	3 (100)	-
Myelodysplastic syndrome	1 (12.5)	1 (100)	-	-	-	-	1 (100)	-

[14] Source: t_II_SVII_13_1_293_t_ae_spm_ci (NHL); t_II_SVII_13_1_1_293_t_ae_spm_ci (ALL)

Table 32. Second Primary Malignancy

Non-CT cases

In the post-marketing experience, since first approval and through 28 December 2024, out of the 2658 non-CT cases received by the MAH, there were 5 cases (0.2%) containing 11 relevant events. Distribution of event by seriousness and clinical outcome is provided below.

PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Event by Outcome N (%)				
				Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
All PTs	**11 (100)**	**10 (90.9)**	**-**	**2 (18.2)**	**-**	**-**	**2 (18.2)**	**7 (63.6)**
Second primary malignancy	5 (45.5)	5 (100)	-	1 (20)	-	-	1 (20)	3 (60)
Acute myeloid leukaemia	1 (9.1)	1 (100)	-	1 (100)	-	-	-	-
Myelodysplastic syndrome	2 (18.2)	2 (100)	-	-	-	-	-	2 (100)
Colon cancer	1 (9.1)	1 (100)	-	-	-	-	1 (100)	-
Neoplasm	1 (9.1)	1 (100)	-	-	-	-	-	1 (100)
Neoplasm progression	1 (9.1)	-	-	-	-	-	-	1 (100)

Background Incidence/Prevalence

The background incidence/prevalence of secondary primary malignancy among relapsed refractory B-cell precursor ALL is not available as there is no unexposed target population. After diagnosis all patients are treated and any untreated patients have a very short survival. In a long term follow up study of patients treated for newly diagnosed acute leukaemia, a retrospective chart review was conducted in 34 patients with ALL and 67 patients with AML that had survived more than 10 years.[47] Median follow was 16 years (range 10 – 28 years). Twenty-one other malignancies were observed in 19 patients (10 ALL, 9 AML). The overall median time to development of second cancer was 10 years (range 7 months – 21 years) following ALL. The crude incidence of secondary malignancies was 21% while the 10 and 20 year cumulative incidence of secondary cancers was 8% and 27%, respectively.
In a second retrospective study,[48] 2168 adult ALL patients (median age 38 years, range: 18-93 years) diagnosed between January 1992 and December 2006 were reviewed from the SEER 13 database. A total of 35 (1.6%) patients developed 39 secondary primary malignancies, an O/E ratio of 1.43 (CI, 1.01-1.95; *P*=.04). Median follow-up time was 6.41 years (range, 6 months to 14.21 years).

Table 32. Second Primary Malignancy

	Median age of the patients who developed secondary primary malignancy was 57 years (range, 18-87 years). There was a significantly higher risk of lung and bronchial tumours and haematologic malignancies (6 AML and 2 NHL cases).
Risk factors and risk groups	Patients with prior or ongoing malignancies and those exposed to aggressive chemotherapy, radiation or other significant immunosuppressive therapies may be at higher risk for development of additional malignancies.
Preventability	Preventive measures to reduce the incidence of inotuzumab ozogamicin-related second primary malignancy have not been identified. Thus, there are currently no known preventive measures. Early detection of second primary malignancies may afford greater chances for treatment or for remission.
Impact on the risk-benefit balance of the product	The impact of a second primary malignancy on an individual patient can be a life-threatening event or have a fatal outcome.
Public health impact	The public health impact of inotuzumab ozogamicin-related second primary malignancy is anticipated to be low.
MedDRA terms	Neoplasms benign, malignant and unspecified (including cysts and polyps) SOC.

Table 33. Reproductive and Developmental Toxicity (post exposure during pregnancy and while breast feeding)

Potential mechanisms	Inotuzumab ozogamicin is clastogenic and calicheamicin is genotoxic and clastogenic. This is consistent with the known induction of DNA breaks by calicheamicin and other enediyne antitumour antibiotics. Genotoxicity and clastogenicity lead to cellular damage and cell death, particularly of rapidly dividing cells. Hence, reproductive organ toxicity and embryo-foetal toxicity observed in nonclinical studies following inotuzumab ozogamicin administration likely reflects target-independent DNA damage caused by the cytotoxin calicheamicin.
Evidence source	Inotuzumab ozogamicin nonclinical studies.
Characterisation of the risk	**Clinical data** <u>Frequency</u> Although the search for reproductive and developmental toxicity (post exposure during pregnancy and while breast feeding) identified all causality AEs in 0.9% (95% CI: 0.1 – 3.4) of patients in pooled ALL studies and in 0.6% (95% CI: 0.0–3.2) of patients in pooled single-agent NHL studies,[15] no events relevant to adult risks for reproductive and developmental toxicity (post exposure during pregnancy and while breast feeding) were identified.

[15] Source: t_II_SVII_12_1_293_t_ae_rt_ci (NHL); t_II_SVII_12_1_1_293_t_ae_rt_ci (ALL)

Table 33. Reproductive and Developmental Toxicity (post exposure during pregnancy and while breast feeding)

Seriousness/outcomes

No events relevant to adult risks were identified in the inotuzumab ozogamicin clinical programme.

Severity and Nature of Risk

No events relevant to adult risks were identified in the inotuzumab ozogamicin clinical programme.

Cumulative data from the safety database

CT Cases

Cumulatively through 28 December 2024, there were no cases reporting events indicative of reproductive or developmental toxicity.

Non-CT cases

In the post-marketing experience, since first approval and through 28 December 2024, out of the 2658 non-CT cases received by the MAH, there were 2 cases (0.1%) containing 2 relevant events. Distribution of event by seriousness and clinical outcome is provided below.

PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Event by Outcome N (%)				
				Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
All PTs	**2 (100)**	**1 (50)**	**-**	**-**	**1 (50)**	**-**	**1 (50)**	**-**
Amenorrhea	1 (50)	-	-	-	-	-	1 (100)	-
Premature menopause	1 (50)	1 (100)	-	-	1 (100)	-	-	-

Background Incidence/Prevalence

No published epidemiologic studies are available on the incidence or prevalence of reproductive toxicity among relapsed refractory B-cell precursor ALL patients in the unexposed target population.
In a long term follow up study of patients treated for newly diagnosed acute leukemia, a retrospective chart review was conducted in 34 patients with ALL and 67 patients with AML that had survived more than 10 years following treatment.[47] The article combined the results for AML and ALL unless otherwise specified. Median follow up was 16 years (range 10 – 28 years). Twenty-six out of 31(84%) women under the age of 40 years resumed normal menstruation following completion of therapy. Five patients that had not received total body irradiation prior to haematopoietic stem cell transplant. Following treatment for acute leukemia there were 42 pregnancies

Table 33. Reproductive and Developmental Toxicity (post exposure during pregnancy and while breast feeding)

	resulting in 36 live births from 24 women 15 female patients (6 ALL) and nine partners of male patients (ALL 3). One child that died soon after birth was anencephalic with several organ abnormalities; another child was born with chromosome 15 abnormality including autism (the reference did not specify the results (AML vs. ALL) any further).
Risk factors and risk groups	Based on findings in animals and the known mechanism of action of inotuzumab ozogamicin, male and female fertility may be compromised by treatment with inotuzumab ozogamicin and inotuzumab ozogamicin treatment can cause foetal harm when administered to a pregnant woman. The risks to breastfeeding are not known.
Preventability	Given the known toxicities in animals, appropriate warnings are needed regarding fertility preservation, risks to the foetus, use in pregnancy, need for effective contraception, restrictions on when to breastfeed, and recommendation on seeking advice of health care professionals if pregnancy occurs during use.
Impact on the risk-benefit balance of the product	The impact of a reproductive toxicity on an adult patient can include infertility. If a foetus is exposed to inotuzumab ozogamicin *in utero*, the impact of developmental toxicity could be significant including foetal malformations and foetal death. There is no information regarding the effects on the breast-fed infant, or the effect on milk production.
Public health impact	The public health impact of reproductive and developmental toxicities related to inotuzumab ozogamicin is anticipated to be low.
MedDRA terms	**SMQs:** Termination of pregnancy and risk of abortion SMQ narrow; Fertility disorders SMQ narrow and broad; Foetal disorders SMQ narrow and broad; Neonatal disorders SMQ narrow and broad; Congenital, familial, and genetic disorders SMQ narrow. **PTs:** Pregnancy of partner; Foetal exposure via father; Foetal exposure during pregnancy; Maternal exposure during pregnancy.

Table 34. Neurotoxicity

Potential mechanisms	Neurotoxicity was observed in nonclinical studies in the absence of binding to the target antigen indicating that the toxicity was target-independent. In rats, sensory neuropathy involving both cranial and peripheral nerves was observed and was likely a primary cytotoxic effect of calicheamicin on cell bodies in ganglia with subsequent axonal degeneration. The relevance of these findings to patients is not known.
Evidence source	Inotuzumab ozogamicin clinical and nonclinical studies.
Characterisation of the risk	**Clinical data** Frequency

Table 34. Neurotoxicity

All causality AEs of neurotoxicity occurred in 10.4% (95% CI: 6.3 – 14.5) of patients in pooled ALL studies and in 12.1% (95% CI: 7.3 - 17.0) of patients in pooled single-agent NHL studies.[16]

Seriousness/outcomes

Clinical data on seriousness and outcomes, and an overview of severity of the relevant events from clinical data are provided in Annex 7.

Cumulative data from the safety database

CT Cases

Cumulatively through 28 December 2024, out of the 2123 CT cases received by the MAH, there were 17 cases (0.8%) containing 19 relevant events; the events' data are presented in the table below.

PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Event by Outcome N (%)				
				Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
All PTs	**19 (100)**	**19 (100)**	**15 (78.9)**	**-**	**10 (52.6)**	**1 (5.3)**	**7 (36.8)**	**1 (5.3)**
Muscular weakness	9 (47.4)	9 (100)	7 (77.8)	-	5 (55.6)	-	3 (33.3)	1 (11.1)
Neuropathy peripheral	5 (26.3)	5 (100)	3 (60)	-	1 (20)	-	4 (80)	-
Gait disturbance	2 (10.5)	2 (100)	2 (100)	-	2 (100)	-	-	-
Sensory loss	1 (5.3)	1 (100)	1 (100)	-	-	1 (100)	-	-
Neurotoxicity	2 (10.5)	2 (100)	2 (100)	-	2 (100)	-	-	-

[16] Source: t_II_SVII_16_1_293_t_ae_neur_ci (NHL); t_II_SVII_16_1_1_293_t_ae_neur_ci (ALL)

Table 34. Neurotoxicity

Non-CT cases

In the post-marketing experience, since first approval and through 28 December 2024, out of the 2658 non-CT cases received by the MAH, there were 27 cases (1.0%) containing 36 relevant events. Distribution of event by seriousness and clinical outcome is provided below.

PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Event by Outcome N (%)				
				Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
All PTs	**36 (100)**	**20 (55.6)**	**3 (8.3)**	**3 (8.3)**	**7 (19.4)**	**-**	**10 (27.8)**	**16 (44.4)**
Muscular weakness	4 (11.1)	2 (50)	1 (25)	-	2 (50)	-	1 (25)	1 (25)
Neuropathy peripheral	4 (11.1)	3 (75)	-	-	-	-	2 (50)	2 (50)
Hypoaesthesia	5 (13.9)	1 (20)	-	-	-	-	1 (20)	4 (80)
Neurotoxicity	3 (8.3)	3 (100)	-	-	-	-	-	3 (100)
Gait disturbance	2 (5.6)	-	-	-	-	-	1 (50)	1 (50)
Leukoencephalopathy	3 (8.3)	3 (100)	-	1 (33.3)	-	-	1 (33.3)	1 (33.3)
Sensory loss	2 (5.6)	-	-	-	-	-	1 (50)	1 (50)
Dysaesthesia	2 (5.6)	1 (50)	-	-	2 (100)	-	-	-
Areflexia	1 (2.8)	-	-	-	-	-	1 (100)	-
Cranial nerve disorder	1 (2.8)	-	-	-	-	-	-	1 (100)
Demyelinating polyneuropathy	1 (2.8)	1 (100)	-	-	1 (100)	-	-	-
Guillain-Barre syndrome	1 (2.8)	1 (100)	-	-	-	-	1 (100)	-
Motor dysfunction	2 (5.6)	2 (100)	1 (50)	-	1 (50)	-	-	1 (50)
Paraesthesia	1 (2.8)	-	-	-	1 (100)	-	-	-
Peripheral sensory neuropathy	1 (2.8)	-	-	-	-	-	1 (100)	-
Polyneuropathy	1 (2.8)	1 (100)	-	-	-	-	-	1 (100)
Progressive multifocal leukoencephalopathy	2 (5.6)	2 (100)	1 (50)	2 (100)	-	-	-	-

Table 34. Neurotoxicity

	Background Incidence/Prevalence The background incidence/prevalence of neurotoxicity among relapsed refractory B-cell precursor ALL patients is not available as there is no unexposed target population. After diagnosis all patients are treated and any untreated patients have a very short survival.
Risk factors and risk groups	Factors that could potentially be associated with an increased risk of neurotoxicity include chemotherapy, drug abuse, heavy metal exposure, pesticides, solvents, organic or organometal compounds, certain foods and food additives, radiation exposure, and cosmetics.
Preventability	It is not known if patients may be at an increased risk of developing neurotoxicity events as a result of exposure to inotuzumab ozogamicin. Thus, there are currently no known preventive measures.
Impact on the risk-benefit balance of the product	If neurotoxicity is mild, the impact on an individual patient may be limited. Severe neurotoxicity can be a life-threatening event or have a fatal outcome.
Public health impact	The public health impact of inotuzumab ozogamicin-related neurotoxicity is anticipated to be low.
MedDRA terms	**SMQs:** Demyelination SMQ narrow and broad; Peripheral neuropathy SMQ narrow and broad. **HLT:** Cranial Nerve Disorder NEC (all paths).

Table 35. Nephrotoxicity

<table>
<tr><td>Potential mechanisms</td><td>Animal studies demonstrated chronic progressive nephropathy (rats) and glomerulonephritis (1 monkey); the relevance of these findings to patients is not known.</td></tr>
<tr><td>Evidence source</td><td>Inotuzumab ozogamicin clinical and nonclinical studies.</td></tr>
<tr><td>Characterisation of the risk</td><td>
Clinical data

Frequency

All causality AEs of nephrotoxicity occurred in 4.2% (95% CI: 1.5 – 7.0) of patients in pooled ALL studies and in 8.7% (95% CI: 4.5–12.9) of patients in pooled single-agent NHL studies.[17]

Seriousness/outcomes

Clinical data on seriousness and outcomes, and an overview of severity of the relevant events from clinical data are provided in Annex 7.

Cumulative data from the safety database

CT Cases

Cumulatively through 28 December 2024, out of the 2123 CT cases received by the MAH, there were 46 cases (2.2%) containing 48 relevant events; the events' data are presented in the table below.
<table>
<tr><th rowspan="2">PT</th><th rowspan="2"># of Events (% of Total PTs)</th><th rowspan="2"># Serious Events (% of PT)</th><th rowspan="2"># Events with Criterion of Hospitalization (% of PT)</th><th colspan="5">Distribution of Event by Outcome N (%)</th></tr>
<tr><th>Fatal</th><th>Resolved / Resolving</th><th>Resolved with Sequelae</th><th>Not Resolved</th><th>Unknown / No Data</th></tr>
<tr><td>All PTs</td><td>48 (100)</td><td>48 (100)</td><td>42 (87.5)</td><td>5 (10.4)</td><td>27 (56.3)</td><td>1 (2.1)</td><td>10 (20.8)</td><td>5 (10.4)</td></tr>
<tr><td>Acute kidney injury</td><td>31 (64.6)</td><td>31 (100)</td><td>28 (90.3)</td><td>3 (9.7)</td><td>16 (51.6)</td><td>1 (3.2)</td><td>8 (25.8)</td><td>3 (9.7)</td></tr>
<tr><td>Renal failure</td><td>11 (22.9)</td><td>11 (100)</td><td>9 (81.8)</td><td>1 (9.1)</td><td>8 (72.7)</td><td>-</td><td>1 (9.1)</td><td>1 (9.1)</td></tr>
<tr><td>Blood creatinine increased</td><td>5 (10.4)</td><td>5 (100)</td><td>4 (80)</td><td>-</td><td>3 (60)</td><td>-</td><td>1 (20)</td><td>1 (20)</td></tr>
<tr><td>Anuria</td><td>1 (2.1)</td><td>1 (100)</td><td>1 (100)</td><td>1 (100)</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
</table>
</td></tr>
</table>

[17] Source: t_II_SVII_17_1_293_t_ae_neph_ci (NHL); t_II_SVII_17_1_1_293_t_ae_neph_ci (ALL)

Table 35. Nephrotoxicity

<u>Non-CT cases</u>

In the post-marketing experience, since first approval and through 28 December 2024, out of the 2658 non-CT cases received by the MAH, there were 46 cases (1.7%) containing 54 relevant events. Distribution of event by seriousness and clinical outcome is provided below.

PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Event by Outcome N (%)				
				Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
All PTs	**54 (100)**	**40 (74.1)**	**13 (24.1)**	**5 (9.3)**	**13 (24.1)**	**-**	**2 (3.7)**	**34 (63)**
Acute kidney injury	13 (24.1)	13 (100)	6 (46.2)	1 (7.7)	6 (46.2)	-	-	6 (46.2)
Renal failure	12 (22.2)	12 (100)	3 (25)	2 (16.7)	-	-	-	10 (83.3)
Blood creatinine increased	6 (11.1)	-	-	-	3 (50)	-	-	3 (50)
Blood urea increased	7 (13)	1 (14.3)	-	-	2 (28.6)	-	1 (14.3)	4 (57.1)
Renal impairment	8 (14.8)	7 (87.5)	4 (50)	1 (12.5)	2 (25)	-	1 (12.5)	4 (50)
Anuria	2 (3.7)	2 (100)	-	-	-	-	-	2 (100)
Nephropathy toxic	3 (5.6)	3 (100)	-	1 (33.3)	.-	-	-	2 (66.7)
Proteinuria	2 (3.7)	1 (50)	-	-	-	-	-	2 (100)
Protein urine present	1 (1.9)	1 (100)	-	-	-	-	-	1 (100)

Background Incidence/Prevalence

The background incidence/prevalence of nephrotoxicity among relapsed refractory B-cell precursor ALL patients is not available as there is no unexposed target population. After diagnosis all patients are treated and any untreated patients have a very short survival.

Risk factors and risk groups	Factors that could potentially be associated with an increased risk of nephrotoxicity include drugs, advanced age, haemodynamic status, and underlying disease.
Preventability	It is not known if patients may be at an increased risk of developing nephrotoxicity events as a result of exposure to inotuzumab ozogamicin. Thus, there are currently no known preventive measures.
Impact on the risk-benefit	If nephrotoxicity is mild, the impact on an individual patient may be limited. Severe nephrotoxicity can be a life-threatening event or have a fatal outcome.

Table 35. Nephrotoxicity

balance of the product	
Public health impact	The public health impact of inotuzumab ozogamicin-related nephrotoxicity is anticipated to be low.
MedDRA terms	Acute renal failure SMQ narrow and broad.

SVII.3.2. Presentation of the Missing Information

Table 36. Use in patients with moderate or severe hepatic impairment

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

Population in need of further characterisation:
Based on a population pharmacokinetic analysis in 765 patients, the clearance of inotuzumab ozogamicin in patients with hepatic impairment defined by 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). 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.

No adjustment to the starting dose is required when administering inotuzumab ozogamicin to patients with mild hepatic impairment.

Table 37. Use in patients with severe renal impairment

Evidence source:
No formal pharmacokinetic studies of inotuzumab ozogamicin have been conducted in patients with renal impairment. Inotuzumab ozogamicin has not been studied in patients with end-stage renal disease.

Population in need of further characterisation:
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 ($CL_{cr} \geq$ 90 mL/min; n=402). Inotuzumab ozogamicin has not been studied in patients with end-stage renal disease.

No adjustment to the starting dose is required when administering inotuzumab ozogamicin to patients with mild, moderate, or severe renal impairment.

Table 38. Use in Hispanic and Black patients

Evidence source:
Hispanic and Black patients have been underrepresented in clinical studies with inotuzumab ozogamicin.

Population in need of further characterisation:
Hispanic (N=14) and Black (N=22) patients have been underrepresented in clinical studies with inotuzumab ozogamicin, therefore, it is not known whether the safety profile in those (and other) racial and/or ethnic groups is different from that seen in White and Asian patients. However, the general safety profile of these underrepresented racial and/or ethnic groups is similar to the overall safety profile for inotuzumab ozogamicin, although the small number of patients available for analysis makes it difficult to compare safety profiles of these individual racial and/or ethnic groups to the overall safety profile for inotuzumab ozogamicin.

Module SVIII. Summary of the Safety Concerns

Table 39. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Grade ≥3 and/or serious hepatotoxicity, including all VOD/SOS Myelosuppression/cytopenia
Important potential risks	Interstitial lung disease Inflammatory gastrointestinal events Pancreatitis Second primary malignancy Reproductive and developmental toxicity (post exposure during pregnancy and while breast feeding) Neurotoxicity Nephrotoxicity
Missing information	Use in patients with moderate or severe hepatic impairment Use in patients with severe renal impairment Use in Hispanic and Black patients

SOS=sinusoidal obstruction syndrome; VOD=venoocclusive disease

PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond ADRs reporting and signal detection:

- **Specific adverse reaction follow-up questionnaires for safety concerns:**

To obtain structured follow-up information for the important identified risk Grade ≥3 and/or serious hepatotoxicity, including all VOD/SOS, a Hepatic Events DCA containing specific questions for hepatic events was created.

- **Other forms of routine pharmacovigilance activities for safety concerns:**

None.

III.2. Additional Pharmacovigilance Activities

None.

III.3. Summary Table of Additional Pharmacovigilance Activities

III.3.1. Ongoing and Planned Additional Pharmacovigilance Activities

None.

PART IV. PLANS FOR POST AUTHORIZATION EFFICACY STUDIES

None.

PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

RISK MINIMISATION PLAN

V.1. Routine Risk Minimisation Measures

Table 40. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
Important Identified Risks	
Grade ≥3 and/or serious Hepatotoxicity, including all VOD/SOS	Routine risk communication: SmPC Section 4.2 *Posology and method of administration*, Section 4.3, *Contraindications*, Section 4.4, *Special warnings and precautions for use*, and Section 4.8 *Undesirable effects.* PL Section 2. *What you need to know before you are given BESPONSA*, 3. *How BESPONSA is given*, 4. *Possible side effects.* Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for hepatotoxicity, including VOD/SOS, monitoring is included SmPC section 4.4. How to detect signs and symptoms of hepatic venoocclusive disease in PL section 2.
Myelosuppression/Cytopenia	Routine risk communication: SmPC Section 4.2 *Posology and method of administration*, Section 4.4, *Special warnings and precautions for use*, and Section 4.8 *Undesirable effects.* PL Section 2. *What you need to know before you are given BESPONSA*, and 4. *Possible side effects.* Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for myelosuppression/cytopenias monitoring is included SmPC section 4.4. How to detect signs and symptoms of myelosuppression / cytopenia in PL sections 2 and 4.
Important Potential Risks	
Interstitial Lung Disease	None.
Inflammatory Gastrointestinal Events	None.
Pancreatitis	None.
Second Primary Malignancy	None.
Reproductive and Developmental Toxicity (post exposure during pregnancy and while breast feeding)	Routine risk communication: SmPC Section 4.6 *Fertility, pregnancy and lactation*, and Section 5.3 *Preclinical safety data.* PL Section 2. *What you need to know before you are given BESPONSA.*
Neurotoxicity	None.

Table 40. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
Nephrotoxicity	None.
Missing Information	
Use in patients with moderate or severe hepatic impairment	Routine risk communication: SmPC Section 4.2 *Posology and method of administration*, and Section 5.2 *Pharmacokinetic properties.* PL Section 2. *What you need to know before you are given BESPONSA.*
Use in patients with severe renal impairment	Routine risk communication: SmPC Section 4.2 *Posology and method of administration*, and Section 5.2 *Pharmacokinetic properties.*
Use in Hispanic and Black patients	Routine risk communication: SmPC Section 5.2 *Pharmacokinetic properties.*

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3. Summary of Risk Minimisation Measures

Table 41. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Grade ≥3 and/or serious hepatotoxicity, including all VOD/SOS	Routine risk minimisation measures: SmPC Sections 4.2, 4.3, 4.4, and 4.8. PL Sections 2, 3 and 4. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: DCA for hepatic events. Additional pharmacovigilance activities: None.
Myelosuppression/ cytopenia	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, and 4.8. PL Sections 2, and 4. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Table 41. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Potential Risks		
Interstitial lung disease	Routine risk minimisation measures: None. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Inflammatory gastrointestinal events	Routine risk minimisation measures: None. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Pancreatitis	Routine risk minimisation measures: None. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Second primary malignancy	Routine risk minimisation measures: None. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Reproductive and developmental toxicity (post exposure during pregnancy and while breast feeding)	Routine risk minimisation measures: SmPC Sections 4.6, and 5.3. PL Section 2. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Neurotoxicity	Routine risk minimisation measures: None. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Nephrotoxicity	Routine risk minimisation measures: None. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Missing Information		
Use in patients with moderate or severe hepatic Impairment	Routine risk minimisation measures: SmPC Sections 4.2, and 5.2. PL Section 2.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.

Table 41. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: None.	Additional pharmacovigilance activities: None.
Use in patients with severe renal impairment	Routine risk minimisation measures: SmPC Sections 4.2, and 5.2. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Use in Hispanic and Black patients	Routine risk minimisation measures: SmPC Section 5.2. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Besponsa (inotuzumab ozogamicin)

This is a summary of the risk management plan (RMP) for Besponsa. The RMP details important risks of Besponsa, how these risks can be minimised, and how more information will be obtained about Besponsa's risks and uncertainties (missing information).

Besponsa's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Besponsa should be used.

This summary of the RMP for Besponsa should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Besponsa's RMP.

I. The Medicine and What It Is Used For

Besponsa is authorised as monotherapy for the treatment of adults with relapsed or refractory cluster of differentiation-22 (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) (see SmPC for the full indication). It contains inotuzumab ozogamicin as the active substance and it is given by infusion.

Besponsa is proposed as monotherapy for the treatment of paediatric patients 1 year and older with CD22-positive B-cell precursor ALL: in first relapse after allo-haematopoietic stem cell transplant (HSCT); after any first relapse in patients with Very High Risk (VHR) disease; after a second or greater relapse; and in those with refractory disease. Patients with Ph^+ disease should have exhausted relevant BCR-ABL targeting treatment options.

Further information about the evaluation of Besponsa’s benefits can be found in Besponsa’s EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine’s webpage https://www.ema.europa.eu/en/medicines/human/EPAR/besponsa.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Besponsa, together with measures to minimise such risks and the proposed studies for learning more about Besponsa 's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;

- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status - the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Besponsa is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Besponsa are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Besponsa. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table 42. List of Important Risks and Missing Information

Important identified risks	Grade ≥3 and/or serious hepatotoxicity, including all VOD/SOS Myelosuppression/cytopenia
Important potential risks	Interstitial lung disease Inflammatory gastrointestinal events Pancreatitis Second primary malignancy Reproductive and developmental toxicity (post exposure during pregnancy and while breast feeding) Neurotoxicity Nephrotoxicity
Missing information	Use in patients with moderate or severe hepatic impairment Use in patients with severe renal impairment Use in Hispanic and Black patients

Abbreviations: SOS=sinusoidal obstruction syndrome; VOD=venoocclusive disease.

II.B Summary of Important Risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Table 43. Important Identified Risk: Grade ≥3 and/or serious hepatotoxicity, including all VOD/SOS

Evidence for linking the risk to the medicine	Inotuzumab ozogamicin clinical and nonclinical studies.
Risk factors and risk groups	Inotuzumab ozogamicin is contraindicated in patients who have experienced prior confirmed severe or ongoing VOD/SOS and patients with serious ongoing hepatic disease (e.g., cirrhosis, nodular regenerative hyperplasia, active hepatitis). In the following subgroups, the reported frequency of VOD/SOS post-haematopoietic stem cell transplant (HSCT) was ≥50%: patients who received a HSCT conditioning regimen containing 2 alkylating agents, patients aged ≥65 years, and patients with a serum bilirubin ≥ upper limit of normal (ULN) prior to HSCT. Based on multivariate analysis in Study 1022, patient factors that were significantly associated with an increased risk of VOD/SOS after a HSCT included the use of HSCT conditioning regimens containing 2 alkylating agents and serum bilirubin ≥ULN prior to HSCT. Based on univariate analysis in Study 1022, other patient factors that appeared to be associated with an increased risk of VOD/SOS after a HSCT include a prior HSCT, age ≥55 years, a history of hepatic disease and/or hepatitis before treatment, later salvage lines, and a greater number of treatment cycles.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, 4.3, 4.4, and 4.8. PL Sections 2, 3 and 4. Additional risk minimisation measures: None.

Table 44. Important Identified Risk: Myelosuppression/cytopenia

Evidence for linking the risk to the medicine	Inotuzumab ozogamicin clinical and nonclinical studies.
Risk factors and risk groups	In addition to the haematologic abnormalities resulting from relapsed or refractory ALL, such patients may have additional haematopoietic susceptibility to cytotoxic therapies if there is pre-existing bone marrow suppression (e.g., due to prior chemotherapy, prior HSCT, radiation, other therapies), or may experience side effects of other concomitant medications or procedures.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, and 4.8. PL Sections 2, and 4. Additional risk minimisation measures: None.

Table 45. Important Potential Risk: Interstitial Lung Disease

Evidence for linking the risk to the medicine	Inotuzumab ozogamicin clinical and nonclinical studies.
Risk factors and risk groups	Factors that could potentially be associated with an increased risk of developing interstitial lung disease (ILD)/pneumonitis may include a history of pre-existing pulmonary disease, prior or concomitant treatment with medications with known pulmonary toxicity [antibiotics (e.g., nitrofurantoin, amphotericin B, minocycline); chemotherapy (e.g., bleomycin, methotrexate, cyclophosphamide); antiarrhythmics (e.g., amiodarone), and tamoxifen], and other treatments or circumstances, including radiation therapy, immune suppression resulting in pneumonia (bacterial, viral, fungal, or protozoal), a predisposition to allergic pulmonary disease, autoimmune diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis, etc.), occupational exposure (e.g., smoke, dust, silicone, asbestos), or other factors.
Risk minimisation measures	Routine and additional risk minimisation measures: None.

Table 46. Important Potential Risk: Inflammatory Gastrointestinal Events

Evidence for linking the risk to the medicine	Inotuzumab ozogamicin clinical and nonclinical studies.
Risk factors and risk groups	Patients receiving therapy for refractory leukaemia, particularly those receiving anti-leukaemic therapy, are susceptible to GI inflammation, including gastritis, colitis and/or typhlitis. Factors that could potentially be associated with an increased risk of developing inflammatory GI disease may include a history of pre-existing GI abnormalities, prior cytotoxic chemotherapy, advanced age, chronic illness, and other medications. Of note, ischemic colitis is more likely to occur in older patients, particularly those with comorbidities such as ischemic cardiac disease.
Risk minimisation measures	Routine and additional risk minimisation measures: None.

Table 47. Important Potential Risk: Pancreatitis

Evidence for linking the risk to the medicine	Inotuzumab ozogamicin clinical and nonclinical studies.
Risk factors and risk groups	Factors that could potentially be associated with an increased risk of developing pancreatitis include a variety of medications, (e.g., prior exposure to asparaginase, antibiotics, immunosuppressive agents, anti-hypertensives, aminosalicylates, diuretics, proton-pump inhibitors, steroids, anaesthetics, antibiotics), alcohol abuse, hepatobiliary disorders (e.g., obstruction of the common bile duct, idiopathic biliary sludge, common bile duct tumour infiltration), post-operative trauma and instrumentation (e.g., endoscopic retrograde cholangiopancreatography), hypercalcaemia, parenchymal tumour infiltration, and infection.
Risk minimisation measures	Routine and additional risk minimisation measures: None.

Table 48. Important Potential Risk: Second Primary Malignancy

Evidence for linking the risk to the medicine	Inotuzumab ozogamicin clinical and nonclinical studies.
Risk factors and risk groups	Patients with prior or ongoing malignancies and those exposed to aggressive chemotherapy, radiation or other significant immunosuppressive therapies may be at higher risk for development of additional malignancies.
Risk minimisation measures	Routine and additional risk minimisation measures: None.

Table 49. Important Potential Risk: Reproductive and Developmental Toxicity (Post Exposure During Pregnancy and While Breast Feeding)

Evidence for linking the risk to the medicine	Inotuzumab ozogamicin nonclinical studies.
Risk factors and risk groups	Based on findings in animals and the known mechanism of action of inotuzumab ozogamicin, male and female fertility may be compromised by treatment with inotuzumab ozogamicin and inotuzumab ozogamicin treatment can cause foetal harm when administered to a pregnant woman. The risks to breastfeeding are not known.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.6, and 5.3. PL Section 2. Additional risk minimisation measures: None.

Table 50. Important Potential Risk: Neurotoxicity

Evidence for linking the risk to the medicine	Inotuzumab ozogamicin clinical and nonclinical studies.
Risk factors and risk groups	Factors that could potentially be associated with an increased risk of neurotoxicity include chemotherapy, drug abuse, heavy metal exposure, pesticides, solvents, organic or organometal compounds, certain foods and food additives, radiation exposure, and cosmetics.
Risk minimisation measures	Routine and additional risk minimisation measures: None.

Table 51. Important Potential Risk: Nephrotoxicity

Evidence for linking the risk to the medicine	Inotuzumab ozogamicin clinical and nonclinical studies.
Risk factors and risk groups	Factors that could potentially be associated with an increased risk of nephrotoxicity include drugs, advanced age, haemodynamic status, and underlying disease.
Risk minimisation measures	Routine and additional risk minimisation measures: None.

Table 52. Missing Information: Use in Patients with Moderate or Severe Hepatic Impairment

Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, and 5.2. PL Section 2. Additional risk minimisation measures: None.

Table 53. Missing Information: Use in Patients with Severe Renal Impairment

Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, and 5.2. Additional risk minimisation measures: None.

Table 54. Missing Information: Use in Hispanic and Black patients

Risk minimisation measures	Routine risk minimisation measures: SmPC Section 5.2. Additional risk minimisation measures: None.

II.C Post-Authorisation Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorisation

None.

II.C.2 Other Studies in Post-Authorisation Development Plan

None.

PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN

Annex 2 - Tabulated summary of planned, on-going, and completed pharmacovigilance study programme

Annex 3 - Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan

Annex 4 - Specific Adverse Drug Reaction Follow-Up Forms

Annex 5 - Protocols for proposed and on-going studies in RMP Part IV

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if applicable)

Annex 7 - Other Supporting Data (Including Referenced Material)

Annex 8 - Summary of Changes to the Risk Management Plan over Time

REFERENCES

1 Miranda-Filho A, Piñeros M, Ferlay J et al. Epidemiological patterns of leukaemia in 184 countries: a population-based study. Lancet Haematol. 2018 Jan;5(1):e14-e24. doi: 10.1016/S2352-3026(17)30232-6.

2 Katz AJ, Chia VM, Schoonen WM et al. Acute lymphoblastic leukemia: an assessment of international incidence, survival, and disease burden. Cancer Causes Control. 2015 Nov;26(11):1627-42.

3 Global, regional, and national burden of acute lymphoblastic leukemia in children: Epidemiological trends analysis from 1990 to 2021 - ScienceDirect.

4 Cancer Research UK, http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-all/incidence#heading-Zero. Accessed 09 January 2023.

5 The Swedish Health and Welfare Statistical Database, https://sdb.socialstyrelsen.se/if_can/val_eng.aspx. Accessed 09 January 2023.

6 American Cancer Society. How is acute lymphocytic leukemia classified? Available: http://www.cancer.org/cancer/leukemia-acutelymphocyticallinadults/detailedguide/leukemia-acute-lymphocytic-classified. Accessed 09 January 2023.

7 National Comprehensive Cancer Network. Acute Lymphoblastic Leukemia. In: NCCN Clinical Practice Guidelines in Oncology. Version 2.2015. Fort Washington, PA: National Comprehensive Cancer Network; 2015: 103 pages.

8 SEER. SEER Cancer Stat Facts: Acute Lymphocytic Leukemia. National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/statfacts/html/alyl.html. Accessed 05 February 2025.

9 SEER*Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program, National Cancer Institute. [Cited 09 January 2023]. Available at: https://seer.cancer.gov/statistics-network/explorer.

10 American Cancer Society. What are the key statistics about acute lymphocytic leukemia? Available: http://www.cancer.org/cancer/leukemia-

acutelymphocyticallinadults/detailedguide/leukemia-acute-lymphocytic-key-statistics. 16 January 2025.

[11] Dores GM, Devesa SS, Curtis RE, et al. Acute leukemia incidence and patient survival among children and adults in the United States, 2001-2007. Blood 2012;119(1):34-43.

[12] Orphanet. Prevalence and incidence of rare diseases: Bibliographic data. Orphanet Report Series, Rare Diseases collection; January 2022, Number 1: Diseases listed in alphabetical order. Available: http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf.

[13] Eurostat. Eurostat: Main Population Indicators. Data last updated 12 January 2022. Available: https://ec.europa.eu/eurostat/databrowser/view/DEMO_GIND__custom_4591883/default/table?lang=en. Accessed: 09 March 2023.

[14] National Cancer Institute. SEER Fast Stats. Available: http://seer.cancer.gov/faststats/. 30 June 2015.

[15] Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2012, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2012/, based on November 2014 SEER data submission, posted to the SEER web site, April 2015.

[16] Crump C, Sundquist J, Sieh W, et al. Perinatal and familial risk factors for acute lymphoblastic leukemia in a Swedish national cohort. Cancer 2015;121(7):1040-7.

[17] Belson M, Kingsley B, Holmes A. Risk factors for acute leukemia in children: a review. Environ Health Perspect. 2007;115(1):138-45.

[18] Bailey HD, Fritschi L, Infante-Rivard C, et al. Parental occupational pesticide exposure and the risk of childhood leukemia in the offspring: findings from the childhood leukemia international consortium. Int J Cancer. 2014;135(9):2157-72.

[19] Gökbuget N, Hoelzer D. Treatment of adult acute lymphoblastic leukemia. Hematol (Am Soc Hematol Educ Program) 2006:133-41.

[20] O'Brien S, Thomas D, Ravandi F, et al. Outcome of adults with acute lymphocytic leukemia after second salvage therapy. Cancer 2008;113(11):3186-91.

[21] Tavernier E, Boiron JM, Huguet F, et al. Outcome of treatment after first relapse in adults with acute lymphoblastic leukemia initially treated by the LALA-94 trial. Leukemia 2007;21(9):1907-14.

[22] Fielding AK, Richards SM, Chopra R, et al. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG2993 study. Blood 2007;109(3):944-50.

[23] Bassan R, Gatta G, Tondini C, et al. Adult acute lymphoblastic leukaemia. Crit Rev Oncol Hematol. 2004;50(3):223-61.

[24] Oriol A, Vives S, Hernandez-Rivas, et al. Outcome after relapse of acute lymphoblastic leukemia in adult patients included in four consecutive risk-adapted trials by the PETHEMA Study Group. Haematologica 2010;95(4):589-96.

[25] Topp MS, Gökbuget N, Stein AS, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. Lancet Oncol 2015;16(1):57-66.

[26] Brüggemann M, Raff T, Flohr T, Gökbuget N, et al. Clinical significance of minimal residual disease quantification in adult patients with standard-risk acute lymphoblastic leukemia. Blood 2006;107(3):1116-23.

[27] Terwey TH, Hemmati PG, Martus P, et al. A modified EBMT risk score and the hematopoietic cell transplantation-specific comorbidity index for pre-transplant risk assessment in adult acute lymphoblastic leukemia. Haematologica 2010;95(5):810-8.

[28] Saillard C, Etienne A, Charbonnier, et al. Evaluation of comorbidity indexes in the outcome of elderly patients treated for acute lymphoblastic leukemia. Leuk Lymphoma 2014 ;55(9):2211-2.

[29] Kumar K, Kaur J, Walia S, et al. L-asparaginase: an effective agent in the treatment of acute lymphoblastic leukemia. Leuk Lymphoma. 2014 Feb;55(2):256-62.

[30] Schmiegelow K, Nielsen SN, Frandsen TL, et al. Mercaptopurine/Methotrexate maintenance therapy of childhood acute lymphoblastic leukemia: clinical facts and fiction. J Pediatr Hematol Oncol 2014;36(7):503-17.

[31] Vandecruys E, Mondelaers V, De Wolf D, et al. Late cardiotoxicity after low dose of anthracycline therapy for acute lymphoblastic leukemia in childhood. J Cancer Surviv 2012 ;6(1):95-101.

[32] Lobo ED, Hansen RJ, Balthasar JP. Antibody pharmacokinetics and pharmacodynamics. J Pharm Sci 2004;93(11):2645-68.

[33] Kantarjian HM, Thomas D, Ravandi F, et al. Defining the course and prognosis of adults with acute lymphocytic leukemia in first salvage after induction failure or short first remission duration. Cancer 2010;116(24):5568-74. doi: 10.1002/cncr.25354. Epub 24 Aug 2010.

[34] Sim SC1, Kacevska M, Ingelman-Sundberg M. Pharmacogenomics of drug-metabolizing enzymes: a recent update on clinical implications and endogenous effects. Pharmacogenomics J 2013;13(1):1-11.

[35] Parker C, Waters R, Leighton C, et al. Effect of mitoxantrone on outcome of children with first relapse of acute lymphoblastic leukaemia (ALL R3): an open-label randomised trial. Lancet 2010; 376(9757):2009-17.

[36] Johnson DB, Savani BN. How can we reduce hepatic veno-occlusive disease-related deaths after allogeneic stem cell transplantation? Exp Hematol. 2012;40(7):513-7.

[37] Richardson PG, Soiffer RJ, Antin JH, et al. Defibrotide for the treatment of severe hepatic veno-occlusive disease and multiorgan failure after stem cell transplantation: a multicenter, randomized, dose-finding trial. Biol Blood Marrow Transplant. 2010;16(7):1005-17.

[38] Ho VT, Revta C, Richardson PG. Hepatic veno-occlusive disease after hematopoietic stem cell transplantation: update on defibrotide and other current investigational therapies. Bone Marrow Transplant. 2008;41(3):229-37.

[39] Cesaro S, Pillon M, Talenti E, et al. A prospective survey on incidence, risk factors and therapy of hepatic veno-occlusive disease in children after hematopoietic stem cell transplantation. Haematologica. 2005;90(10):1396-404.

[40] Hasegawa S, Horibe K, Kawabe T, et al. Veno-occlusive disease of the liver after allogeneic bone marrow transplantation in children with hematologic malignancies: incidence, onset time and risk factors. Bone Marrow Transplant. 1998;22(12):1191-7.

[41] Carreras E, Granena A, Rozman C. Hepatic veno-occlusive disease after bone marrow transplant. Blood Rev. 1993;7(1):43-51.

[42] Carreras E, Bertz H, Arcese W, et al. Incidence and outcome of hepatic veno-occlusive disease after blood or marrow transplantation: a

prospective cohort study of the European Group for Blood and Marrow Transplantation. European Group for Blood and Marrow Transplantation Chronic Leukemia Working Party. Blood. 1998;92(10):3599-604.

[43] Kumar S, DeLeve LD, Kamath PS, et al. Hepatic veno-occlusive disease (sinusoidal obstruction syndrome) after hematopoietic stem cell transplantation. Mayo Clinic Proc. 2003;78(5):589-98.

[44] DeLeve LD, Shulman HM, McDonald GB. Toxic injury to hepatic sinusoids: sinusoidal obstruction syndrome (veno-occlusive disease). Semin Liver Dis. 2002;22(1):27-42.

[45] Prokop A, Wrasidlo W, Lode H, et al. Induction of apoptosis by enediyne antibiotic calicheamicin II proceeds through a caspase-mediated mitochondrial amplification loop in an entirely Bax-dependent manner. Oncogene 2003;22(57):9107-20.

[46] Vega-Stromberg, T. Chemotherapy-induced Secondary Malignancies. J. Infus Nurs 2003;26:353-61.

[47] Micallef IN, Rohatiner AZ, Carter M, Boyle M, Slater S, Amess JA, et al. Long-term outcome of patients surviving for more than ten years following treatment for acute leukaemia. Br J Haematol. 2001;May;113(2):443-5.

[48] Ghimire KB, Shah BK. Second primary malignancies in adult acute lymphoblastic leukemia: a US population-based study. Blood 2014;124(12):2000-1.

ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Table of contents

Follow-up forms

Hepatic Events Data Capture Aid

Inotuzumab Ozogamicin Hepatic Events Data Capture Aid

Instructions for use:

Select questions as needed to obtain any DCA-defined information described below that was not included in the initial report.

AER/Manufacturer Report #: _____

Suspect product: _____

Reported event term prompting special follow-up activities: _____

Hepatic Events Follow-up Questions

Please provide additional details on a separate page if needed, and reference the question number.

1. Is the reported adverse event a:

☐ New event

☐ Recurrence *(Please specify details of the prior events)*

☐ Exacerbation of existing condition *(please provide details)*

Details:

2. Please provide: name, e-mail address, postal address, and telephone number of any specialist to whom the patient was referred for further evaluation of the reported adverse event(s) *(if applicable based on local privacy regulations):*

3. Please mark whether the patient experienced any of the following signs / symptoms:

☐ Rash	☐ Pruritus	☐ Purpura
☐ Fever	☐ Joint Pain	☐ Abdominal distension
☐ Abdominal Pain	☐ Nausea	☐ Vomiting
☐ Coma	☐ Ascites	☐ Asthenia
☐ Asterixis / "Flapping"	☐ Jaundice	☐ Hepatomegaly
☐ Splenomegaly	☐ Weight gain *(please specify)*_____	

☐ Hepatic encephalopathy

☐ Sepsis *(if yes, describe time to onset and course of the event [e.g., progression and outcome])*_____

☐ Multi-organ failure *(if yes, include time to onset and the course [e.g., progression and outcome])*_____

☐ Other signs / symptoms *(including those related to infections, please specify)* _____

4. Was hepatic function test monitoring (e.g., AST, ALT, Bilirubin) done at the following times?

- **Routine LFTs <u>in year prior to start of drug</u>:**
  ☐ Unknown ☐ No ☐ Yes

If Yes, please provide details of monitoring below and record relevant results in the laboratory data section.

Details:

- **Baseline at start of therapy** ☐ Unknown ☐ No ☐ Yes

If Yes, please provide details of monitoring below and record relevant results in the laboratory data section.

Details:

- **During therapy:** ☐ Unknown ☐ No ☐ Yes

If Yes, please provide details of monitoring below and record relevant results in the laboratory data section:

Details:

- **After therapy:** ☐ Unknown ☐ No ☐ Yes

If Yes, please provide details of monitoring below and record relevant results in the laboratory data section:

Details:

5. Please mark whether the patient was taking any of the following medications / substances at the time of the adverse event or within two weeks prior to the onset of the adverse event: *(Please provide details - specify the products generic names, dates off administration, and dosage)*

- ☐ Antibiotics
- ☐ Anti-arrhythmic drugs
- ☐ ACE inhibitors
- ☐ Potassium supplements
- ☐ Protease inhibitors
- ☐ Retroviral agents
- ☐ Anticoagulants
- ☐ Diuretics
- ☐ Beta blockers
- ☐ Angiotensin II receptor antagonists
- ☐ Potassium-sparing diuretics
- ☐ PDE5 inhibitors
- ☐ Vitamin K antagonists
- ☐ Cyclosporin A
- ☐ Oral contraceptives
- ☐ Dietary supplements
- ☐ Over-the-counter drugs
- ☐ Herbal preparations
- ☐ Recreational drugs (e.g., cocaine, crack cocaine, heroin, methamphetamines)
- ☐ Cytotoxic chemotherapy
- ☐ Disease modifying drugs (e.g. DMARD medications for the treatment of rheumatoid arthritis)
- ☐ Other heart or blood pressure medications
- ☐ Products for the treatment of pulmonary arterial hypertension
- ☐ Other *(please specify)* _____
- ☐ None

Details:

6. Please mark whether the patient had prior to start of therapy any of the following: *(Please provide details and indicate whether ongoing condition or whether occurred in the past)*

- ☐ Hepatic dysfunction
- ☐ Hepatobiliary disease or dysfunction
- ☐ Elevated liver function tests
- ☐ Elevated bilirubin
- ☐ Jaundice
- ☐ Cirrhosis
- ☐ Fatty liver
- ☐ Pancreatitis
- ☐ Gallstones
- ☐ Gall bladder disease
- ☐ Bile duct obstruction
- ☐ Viral hepatitis
- ☐ Congenital heart disease
- ☐ Drug-induced liver toxicity *(please specify drug)* _____
- ☐ Recent travel to other countries *(please specify)*
- ☐ Other *(please specify)* _____
- ☐ Alcohol use *(If checked, complete question 8)*
- ☐ Parasitic diseases
- ☐ Mycobacterium Avium Complex infection
- ☐ Other non-viral suspected liver infections
- ☐ Cytomegalovirus infection
- ☐ Ischemic hepatitis
- ☐ Cystic fibrosis
- ☐ Granulomatosis
- ☐ Sickle cell anemia
- ☐ Connective tissue disease
- ☐ Lactic acidosis syndrome
- ☐ Blood product transfusions
- ☐ Renal impairment
- ☐ Gilbert's disease
- ☐ Metabolic disease
- ☐ Diabetes mellitus (Type I or II)
- ☐ Heart failure
- ☐ Hypertension
- ☐ Hypertriglyceridemia
- ☐ Portal hypertension
- ☐ Veno-occlusive disease
- ☐ Atherosclerotic / vascular disease
- ☐ Transplant
- ☐ Contact with jaundiced patient
- ☐ Epstein–Barr virus infection
- ☐ Substance abuse/Drug abuse (e.g., recreational/illicit drug use)
- ☐ Alternative medication use (e.g., herbal supplements and vitamins)
- ☐ None
- ☐ Valvular heart disease
- ☐ Primary malignancy
- ☐ Liver metastases
- ☐ Hepatoma
- ☐ Auto-immune disorder
- ☐ Immune reconstitution disease
- ☐ HIV infection
- ☐ Sepsis
- ☐ Drug toxicity *(please specify)* _____
- ☐ Vitamin deficiency *(please specify)* _____

Details:

7. Did the patient have a family history of liver disease? *(i.e., genetic conditions)*

☐ Unknown ☐ No ☐ Yes *(please provide details)*

Details:

8. If "Alcohol use" checked above, please answer the following:

How often does the patient drink beverages containing alcohol? _____ *(e.g., monthly, 2-4 times a week, more than 5 times a week, etc)*

How many drinks on a typical day when patient is drinking?: _____ *(e.g., less than 1 drink, 2 or 3 drinks, more than 3 drinks, etc)*

Please specify the type/brand of alcohol patient typically drinks: _____ *(e.g., beer)*

If this drinking history is more than one year, please specify duration: _____

9. Were any of the following laboratory tests / procedures performed? Please specify results with date(s) of test, results with units, and reference ranges. If a test was administered multiple times, please enter the date(s) of test, units, and reference ranges for each test in chronological order.

Laboratory Test / Procedure	Date Performed (DD-MMM-YYYY)	Results with units if applicable	Reference Ranges if applicable
☐ AST			
☐ ALT			
☐ GGT			
☐ Total bilirubin			
☐ Conjugated bilirubin			
☐ Total protein			
☐ Albumin			
☐ Prothrombin time (PT)			
☐ Partial thromboplastin time (PTT)			
☐ International normalized ratio (INR)			
☐ Clotting time			
☐ Alkaline phosphatase			
☐ Hepatitis A serology			
☐ Hepatitis B serology			
☐ Hepatitis C serology			
☐ Cytomegalovirus (CMV) serology			
☐ Epstein Barr serology			
☐ Other serology			
☐ Eosinophil count			
☐ Amylase			
☐ Lipase			
☐ Other pancreatic enzymes tests			
☐ Serum or plasma concentrations for any concomitant drugs			
☐ Liver ultrasound			
☐ Liver biopsy			
☐ Abdominal X-ray			
☐ Abdominal CT			
☐ Abdominal endoscopic retrograde cholangiopancreatography (ERCP)			
☐ Serum ceruloplasmin			
☐ Serum copper			
☐ Serum alpha 1-antitrypsin			
☐ Serum alpha-fetoprotein			
☐ Serum ammonia			
☐ Other relevant lab data *(please specify)*			

Additional Follow-up Questions for Inotuzumab Ozogamicin

Please provide additional details on a separate page if needed, and reference the question number.

10. Additional Medical History *Please mark all that apply:*

Inflammatory hepatic disease

☐ Alcoholic hepatitis date (mm/dd/yyyy) _____
☐ Non-alcoholic steatohepatitis (NASH) (mm/dd/yyyy) _____
☐ N/A
☐ Unknown

Fibrotic hepatic disease

☐ Nodular Regenerative Hyperplasia (mm/dd/yyyy) _____
☐ Lobular fibrosis (mm/dd/yyyy) _____
☐ Extramedullary hematopoiesis with sinusoidal fibrosis (mm/dd/yyyy) _____
☐ N/A
☐ Unknown

Cholestatic disorders :

☐ Jaundice caused by:
- ☐ Intrahepatic cholestasis ☐ Sepsis
- ☐ GVHD
- ☐ N/A
- ☐ Unknown

☐ **Prior liver biopsy**: ☐ Yes ☐ No
If yes, Date: _____ Findings: _____

☐ **Prior liver irradiation:** (mm/dd/yyyy) _____Dose_____

☐ **Prior suspected or proven VOD/SOS?** ☐ Yes ☐ No
If yes,(mm/dd/yyyy): _____

11. Did total bilirubin exceed 2 mg/dL (>34 umol/L) following Inotuzumab Treatment?

☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes,
Date of increase: _____>2 mg/dL (>34 µmol /L) _____
Peak total bilirubin value _____ mg/dL or µmol /L
Date of Peak Value (dd/mmm/yyyy) _____

Was elevated bilirubin and any other hepatic dysfunction associated with severe infection (such as sepsis/septic shock, pneumonia, etc.)?
☐ Yes ☐ No *If yes, please elaborate*

12. Was an abdominal ultrasound performed to evaluate potential hepatic VOD/SOS?

☐ Yes ☐ No ☐ Unknown ☐ N/A

If Yes, please indicate if any of the following were found (please attach ultrasound results/report and provide details)
☐ Hepatomegaly
☐ Abnormal portal flow
☐ Attenuated hepatic vein flow
☐ Reversal of hepatic vein flow
☐ Gallbladder wall edema
☐ Ascites ☐ mild ☐ moderate ☐ severe
Was therapeutic paracentesis required to manage ascites? ☐ Yes ☐ No
If yes, ☐ once ☐ twice ☐ 3 or more times____

☐ Increased Resistive Indices (RI) *(please specify RI values)*
Other Details: _____

13. Was a wedge hepatic vein pressure gradient assessed?

☐ Yes ☐ No ☐ Unknown ☐ N/A

If Yes, please provide results:

14. Was there evidence of concurrent pleural effusion during hepatic dysfunction?

☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, please quantify:

15. Did the patient develop symptomatic peripheral edema during hepatic dysfunction?

☐ Yes ☐ No ☐ Unknown ☐ N/A

16. Please specify any weight change:

Baseline weight _____ ☐ lbs ☐ kg
Peak weight _____ ☐ lbs ☐ kg
Peak change from baseline *(%)* _____
Date of Peak Value *(dd/mmm/yyyy)* _____
☐ N/A ☐ Unknown
Height _____in or_____cm

17. Did ALT increase ≥2.5 upper limits of normal (ULN) following Inotuzumab Treatment?

☐ Yes ☐ No ☐ Unknown ☐ N/A

If Yes:

Date of increase >2.5 x ULN) _____

Peak value _____ IU; upper limit of normal: ___IU

Date of Peak Value (dd/mmm/yy) _____

18. Did serum creatinine double from baseline during hepatic event?

☐ Yes ☐ No ☐ Unknown ☐ N/A

If Yes:

Baseline value: _____mg/dl

Peak value: _____mg/dl; upper limit of normal: ___IU

Date of Peak Value (dd/mmm/yyyy) _____

Was dialysis required? Yes___No____

19. Was right upper quadrant abdominal pain of liver origin reported?

☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, please specify:

Start date (dd/mmm/yyyy) _____

Stop date (dd/mmm/yyyy) _____

Required treatment for this pain *(please specify)* _____

20. Prior to this event hepatotoxic chemotherapy and general timeframe of exposure

Mark all that apply:

☐ High dose cytarabine

☐ High dose methotrexate

☐ High dose cyclophosphamide

☐ Asparaginase

☐ Mitoxantrone

☐ Anthracycline (total dose_____ mg/m^2

☐ Topoisomerase II inhibitors

☐ Prolonged 6-MP and/or methotrexate

☐ Tyrosine kinase inhibitor(s) *(please specify)* _____

☐ Abdominal irradiation

☐ Unknown ☐ N/A

How many HSCTs has this patient received?

☐ Unknown ☐ N/A ☐ 1 ☐ 2 ☐ 3 ☐ more than 3

History of liver failure/severe liver toxicity from any cause? ☐ Yes ☐ No *If yes, please provide date and presumed etiology:*

Was any chemotherapy administered after Besponsa therapy but before HSCT conditioning therapy? ☐ Yes ☐ No *If yes, please provide details:*

21. HSCT #1: Date: _____

Donor:

- ☐ Autologous HSCT
- ☐ Matched related donor
- ☐ Mismatched related/haploidentical donor
- ☐ Matched unrelated donor
- ☐ Mismatched unrelated donor

Conditioning:

- ☐ Myeloablative
- ☐ Non-myeloablative/reduced intensity

Check all conditioning agents that apply:

- ☐ BCNU or other nitrosourea
- ☐ Cyclophosphamide
- ☐ Etoposide
- ☐ Busulfan ☐ IV ☐ Oral ☐ Pharmacokinetic targeted dosing
- ☐ Fludarabine
- ☐ Other: _____
- ☐ Melphalan
- ☐ Cytarabine
- ☐ Clofarabine
- ☐ Thiotepa

Was total body radiation (TBI) included?

☐ Unknown ☐ N/A ☐ No ☐ Yes – *if yes, please indicate below:*

Date: _____Total Dose: _____Gray

Fractionated? ☐ Yes ☐ No

GVHD prophylaxis: _____

Was sirolimus prescribed post HSCT? ☐ Yes ☐ No

If yes, Start date: _____; Stop date: _____

VOD prophylaxis: ☐ Yes ☐ No ☐ Unknown

If yes, please specify:

Was post HSCT cyclophosphamide given? ☐ Yes ☐ No

HSCT #2: Date: _____

Donor:

- ☐ Autologous HSCT
- ☐ Matched related donor
- ☐ Mismatched related/haploidentical donor
- ☐ Matched unrelated donor
- ☐ Mismatched unrelated donor

Conditioning:

- ☐ Myeloablative
- ☐ Non-myeloablative/reduced intensity

Check all conditioning agents that apply:

- ☐ BCNU or other nitrosourea
- ☐ Cyclophosphamide
- ☐ Etoposide
- ☐ Busulfan ☐ IV ☐ Oral ☐ Pharmacokinetic targeted dosing
- ☐ Fludarabine
- ☐ Other: _____
- ☐ Melphalan
- ☐ Cytarabine
- ☐ Clofarabine
- ☐ Thiotepa

Was total body radiation (TBI) included?

☐ Unknown ☐ N/A ☐ No ☐ Yes – *if yes, please indicate below:*

Total Dose: _____**Gray**

Fractionated? ☐ Yes ☐ No

GVHD prophylaxis: _____

Was sirolimus prescribed post HSCT? ☐ Yes ☐ No;

If yes, Start date: _____; Stop date: _____

VOD prophylaxis: ☐ Yes ☐ No ☐ Unknown

If Yes please specify:

Was post HSCT cyclophosphamide given? ☐ Yes ☐ No

If patient received 3 or more HSCTs, please see end of this section for additional space

22. Did total bilirubin exceed 2 mg/dL (>34 µmol /L) prior to conditioning therapy?

☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes,

Date of increase: _____>2 mg/dL (>34 µmol /L) _____

Peak total bilirubin value _____ mg/dL or µmol /L

Date of Peak Value (dd/mmm/yyyy) _____

Was elevated bilirubin and any other hepatic dysfunction associated with severe infection (such as sepsis/septic shock, pneumonia, etc)?

☐ Yes ☐ No If yes, please elaborate

23. Concomitant drugs of interest used during conditioning therapy.

Please mark all that apply:

- ☐ Itraconazole
- ☐ Other azole(s), please list: _____
- ☐ Norethisterone

24. Diagnosis *(if applicable)*

Was hepatic VOD/SOS diagnosed?

☐ Unknown ☐ N/A ☐ No ☐ Yes –

If yes, please provide: Date (dd/mmm/yyyy) of diagnosis: _____

Number of days after last dose of **Inotuzumab Ozogamicin** to diagnosis: _____

Number of days from HSCT to diagnosis: _____

VOD/SOS diagnosis was based on *(mark all that apply):*

- ☐ Clinical scenario *(please list criteria):*
- ☐ Abnormal wedge hepatic vein pressure gradient *(please specify)*
- ☐ Radiographic findings *(please describe):*
- ☐ Liver biopsy showed *(please describe)*
- ☐ Autopsy showed *(please describe)*

25. Was there prior or concurrent evidence of GVHD?

☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, ☐ acute or ☐ chronic GVHD? Timeframe in relation to hepatic dysfunction? _____

GVHD: organs involved (check all that apply)

☐ Gastrointestinal tract ☐ Skin ☐ Liver

☐ Eyes ☐ Lungs ☐ Other organ(s): _____

GVHD treatment(s):_____

_____

26. Was there evidence of transfusion-refractory thrombocytopenia with no detectable cause?

☐ Yes ☐ No ☐ Unknown ☐ N/A

27. Did the patient experience any of the following concurrent with this hepatic event (check all that apply):

☐ Respiratory distress

If yes, was intubation/assisted ventilation required? ☐ Yes ☐ No

If yes, for how many days? _____

☐ Cardiovascular compromise requiring inotropic support

☐ Hepatic Encephalopathy

☐ Renal failure

☐ Admission to an intensive care unit (ICU) for management of hepatic failure?

If yes, for how many days? _____

☐ Unknown

☐ N/A

28. Outcome of the hepatic event?

☐ Resolved without intervention; Date of resolution: _____

☐ Resolved with intervention *(please specify)*

Defibrotide? ☐ No ☐ Yes Date administered _____

Ursodeoxycholic acid? ☐ No ☐ Yes Date administered _____

If other intervention(s) (list) were provided please list with dates:_____

☐ Event persisted ☐ Event Persisted for >100 days (post HSCT)

☐ Hepatic event was ongoing at time of death, but it was not the cause of death

☐ Hepatic event was the primary cause of death

☐ Hepatic event was a contributing cause of death

Version History

Version	Version Date	Summary of Revisions
1.0	03-Oct-2022	Existing DCA converted to latest DCA format which includes questions relevant to product-event (or medical concept) pair.

ANNEX 6. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.