Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Inotuzumab ozogamicin

Proprietary Product Name: Besponsa

Sponsor: Pfizer Australia Pty Limited

July 2019

TGA Health Safety Regulation

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- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
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- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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Contents

Common abbreviations

Abbreviation	Meaning
Δ	Delta (difference)
AcBut	4-(4'-Acetylphenoxy)butanoic acid, a bifunctional linker
ACM	Advisiory Committee on Medicines
ADA	Antidrug antibody/antibodies
ADC	Antibody drug conjugate
ADR	Adverse drug reaction
AE	Adverse event
AEoSI	Adverse event of special interest
AIHW	Australian Institute of Health and Welfare
ALL	Acute lymphoblastic leukaemia
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
ARDS	Acute respiratory distress syndrome
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
ARTG	Australian Register of Therapeutic Goods
AST	Aspartate aminotransferase
AUC	Area under the curve
BCR-ABL	Breakpoint cluster region Abelson
BCRP	Breast cancer resistance protein
BSA	Body surface area
CER	Clinical evaluation report
CD22	Cluster of differentiation-22
CHOP	Cyclophosphamide, doxorubicin hydrochloride, vincristine and prednisone

Abbreviation	Meaning
CI	Confidence interval
CL	Clearance
C_{max}	Maximal plasma concentration
CMI	Consumer Medicines Information
CNS	Central nervous system
CR	Complete response
CRi	Complete response with incomplete haematologic recovery
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CU	Compassionate use
CV	Coefficient of variance
C_{avg}	Average plasma concentration
CU	Compassionate use
CVP	Cyclophosphamide, vincristine and prednisone
CYP	Cytochrome P450
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DLT	Dose limiting toxicity
DMH	Dimethylhydrazide
DoR	Duration of remission
EAC	Endpoint Adjudication Committee
ECG	Electrocardiogram
ECL	Electrochemiluminescent
ECOG	Eastern Cooperative Oncology Group
ELISA	Enzyme linked assay
EMA	European Medicines Agency

Abbreviation	Meaning
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer, core quality of life questionnaire(30 questions)
EQ-VAS	EuroQoL visual analogue scale
EQ-5D-3L	EuroQoL 5 dimension questionnaire (3 level version)
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration (United States)
FLAG	Fludarabine, cytarabine, granulocyte-colony stimulating factor
GCP	Good Clinical Practice
GCSF	Granulocyte colony stimulating factor
GGT	Gamma-glutamyl transpeptidase
GLP	Good Laboratory Practice
GVHD	Graft versus host disease
h	Hour(s)
HEAB	Hepatic Events Adjudication Board
HIDAC	High-dose cytarabine
HR	Hazard ratio
HSCT	Haematopoietic stem cell transplant
Hyper-CVAD	Cyclophosphamide, vincristine, doxorubicin, dexamethasone (part A); methotrexate and cytarabine (part B)
IC_{50}	Half maximal inhibitory concentration
ICH	International Conference on Harmonisation
InO	Inotuzumab ozogamicin
ILD	Interstitial lung disease
IP	Intraperitoneal
IV	Intravenous
Inv Choice	Investigator's choice of chemotherapy

Abbreviation	Meaning
ITT	Intent-to-treat
ITT218	Intent-to-treat for the initial 218 patients randomised
IV	Intravenous
IVRS	Interactive Voice Response System
K_D	Dissociation constant
LC/MS/MS	High-performance liquid chromatography tandem mass spectrometric method
LFT	Liver function test
LLOQ	Lower limit of quantitation
LOEL	Lowest observable effect level
LSLV	Last Subject Last Visit
mAb	Monoclonal antibody
MATE	Multidrug and toxin extrusion protein
Max	Maximum
MDACC	MD Anderson Cancer Center (University of Texas, USA)
MDR1	Multi-drug resistance protein 1
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
mITT	Modified intent-to-treat
MRD	Minimal residual disease
MRP	Multidrug resistance associated protein
MTD	Maximum tolerated dose
MXN/Ara-C	Mitoxantrone + cytarabine
n/N	Number of patients
N-Ac	N-acetyl
NCI CTCAE v3.0	National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0

Abbreviation	Meaning
NHL	Non-Hodgkin's lymphoma
NOEL	No observable effect level
NYHA	New York Heart Association
OAT	Organic anion transporter
OATP	Organic anion-transporting polypeptide
OCT	Organic cation transporter
OECD	Organisation for Economic Co-operation and Development
OS	Overall survival
p	p-value
PD	Pharmacodynamic
PFS	Progression-free survival
P-gp	P-glycoprotein
Ph-	Philadelphia chromosome–negative
Ph+	Philadelphia chromosome-positive
PK	Pharmacokinetic(s)
PIP	Paediatric Investigation Plan
popPK	Population pharmacokinetics
PP218	Patients among the initial 218 patients randomized who met the criteria for PP Population
PRO	Patient reported outcome
PSUR	Post-safety update report
PT	Prothrombin time
PTS	Post-transplant survival
PROs	Patient-reported outcomes
QoL	Quality of life
QRS	Beginning of Q to the end of the S wave

Abbreviation	Meaning
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RMST	Restricted mean survival time
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
sCSR	Supplemental clinical study report
SD	Standard deviation
SOC	System Organ Class
SOS	Sinusoidal obstruction syndrome
SPM	Second primary malignancy
TEAEs	Treatment-emergent adverse events
TKI	Tyrosine kinase inhibitor
TLS	Tumour lysis syndrome
UGT	Uridine diphosphate-glucuronosyltransferase
ULN	Upper limit of normal
UK	United Kingdom
US	United States (of America)
v	Version
VAD/CVAD	Vincristine, adriamycin, and dexamethasone/cyclophosphamide, vincristine, adriamycin, and dexamethasone
VOD	Venoocclusive disease
WBC	White blood cell

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Decision:	Approved
Date of decision:	11 May 2018
Date of entry onto ARTG:	17 May 2018
ARTG number:	288135
, *Black Triangle Scheme*	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia
Active ingredient:	Inotuzumab ozogamicin
Product name:	Besponsa
Sponsor's name and address:	Pfizer Australia Pty Ltd 38-42 Wharf Road West Ryde NSW 2114
Dose form:	Powder for injection
Strength:	1 mg
Container:	vial
Pack size:	1
Approved therapeutic use:	*Besponsa is indicated for the treatment of adults with relapsed or refractory CD22 positive B cell precursor acute lymphoblastic leukaemia (ALL)*
Route of administration:	Intravenous infusion
Dosage:	The dosing regimen consists of 4 week cycles in which doses are in 3 divided doses on Days 1, 8 and 15, for up to 6 cycles. For full details please see the Product Information.

Product background

This AusPAR describes the application by Pfizer Australia Pty Ltd (the sponsor) to register Besponsa, inotuzumab ozogamicin 1 mg powder for injection vial for the following indication:

> *Besponsa is indicated for the treatment of adults with relapsed or refractory B cell precursor acute lymphoblastic leukaemia (ALL).*

Inotuzumab ozogamicin is an antibody drug conjugate (ADC) The pharmacological activity as well as toxicity of inotuzumab ozogamicin is attributable to the calicheamicin component.

Inotuzumab antibody binds to the cluster of differentiation 22 (CD22) antigen, which is located on the vast majority of mature human B cells, as well as on a high proportion of malignant cells in acute lymphoblastic leukaemia (ALL) and a number of other B cell cancers. Binding to CD22 on B cells is followed by internalisation and trafficking to lysosomes, where the acidic conditions favour hydrolysis of the calicheamicin derivative. B cell lines treated with the ADC showed induction of double strand DNA breaks, consistent with the proposed mechanism of action for calicheamicin, ultimately leading to induction of apoptosis and cell death.

Treatment of relapsed or refractory ALL is still a major clinical challenge and there is no universally accepted treatment protocol for these patients. The European Society for Medical Oncology (ESMO) guidelines (2016)[1] indicate that allogeneic stem cell transplantation (SCT) is the only known curative option for patients with ALL and that treatment of the disease with a curative aim involves achievement of complete response (CR) followed by allogeneic SCT.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 17 May 2018.

International regulatory status

At the time the TGA considered this application; a similar application had been approved and was under consideration in the countries as shown in Table 1.

Table 1: International regulatory status (as at 6 April 2018)

Country	Key dates	Indication
United States of America	Rolling submission from 21 January 2016 Approved 17 August 2017	*Besponsa is indicated for the treatment of adults with relapsed or refractory B cell precursor acute lymphoblastic leukemia (ALL).*
European Union (centralised procedure)	Submitted 14 April 2016 Approved 29 June 2017	*Besponsa is indicated as monotherapy for the treatment of adults with relapsed or refractory CD22 positive B cell precursor acute lymphoblastic leukaemia (ALL). Adult patients with Philadelphia chromosome positive (Ph+) relapsed or refractory B*

[1] The European Society for Medical Oncology (ESMO) guidelines (2016) at https://www.esmo.org/Guidelines

Country	Key dates	Indication
		cell precursor ALL should have failed treatment with at least 1 tyrosine kinase inhibitor (TKI).
Canada	Submitted 30 March 2017 Under evaluation	
Switzerland	Submitted 30 August 2016 Approved 10 July 2017	*Besponsa is indicated for the treatment of adult patients with relapsed or refractory CD22 positive B cell precursor ALL (acute lymphoblastic leukaemia). Adult patients with Philadelphia chromosome-positive (Ph+) relapsed or refractory B cell precursor ALL should have failed treatment with at least one tyrosine kinase inhibitor (TKI).*

Orphan drug designation

Inotuzumab ozogamicin (Besponsa) was designated as an orphan drug by the Therapeutic Goods Administration (TGA), Delegate of the Secretary, on 9 January 2017. The indication was for the treatment of B cell acute lymphoblastic leukaemia (ALL).

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration time line

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for submission PM-2017-01455-1-4

Description	Date
Submission dossier accepted and first round evaluation commenced	1 June 2017
First round evaluation completed	21 November 2017
Sponsor provides responses on questions raised in first round evaluation	19 January 2018
Second round evaluation completed	9 February 2018
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	23 February 2018
Sponsor's pre-Advisory Committee response	13 March 2018

Description	Date
Advisory Committee meeting	6 April 2018
Registration decision (Outcome)	11 May 2018
Completion of administrative activities and registration on ARTG	17 May 2018
Number of working days from submission dossier acceptance to registration decision*	195

*Statutory timeframe for standard applications is 255 working days

Evaluations included under quality findings and nonclinical findings incorporate both the first and second round evaluations.

III. Quality findings

Drug substance (active ingredient)

The manufacture of inotuzumab ozogamicin begins with the reaction of 2 drug substance intermediates: inotuzumab and activated calicheamicin derivative. Activated calicheamicin derivative is prepared from N-acetyl calicheamicin and an activated linker, and is produced by microbial fermentation followed by synthetic modification.

Inotuzumab

Inotuzumab is a recombinant humanised monoclonal antibody (hinge-mutated immunoglobulin gamma-4 with kappa light chains, IgG4κ), specific for human antigen CD22, and is produced by mammalian (Chinese hamster ovary) cells. The two identical heavy chains and two identical light chains, are covalently linked with four inter-chain disulphide bonds. The complete, confirmed amino acid sequence of inotuzumab was provided.

Activated calicheamicin derivative

N-acetyl (N-Ac)-γ-calicheamicin dimethylhydrazone

Calicheamicin is a cytotoxic anti-tumour antibiotic isolated from the bacterium *Micromonospora echinospora* ssp *calichensis*. Calicheamicin has an unusual, complex, cyclic enediyne with methytrisulfide and arylglycoside functionality.

Calicheamicin is converted to a derivative and linked to a monoclonal antibody by a disulfide link.

The calicheamicin is bound to the antibody via a linker that forms an amide bond with the antibody and a disulfide bond with the calicheamicin. The linker also contains an internal hydrazone bond that is acid-labile. After hydrolysis, the antibody is left with a small amide residue (4-(4-acetylphenoxy)-butyrate) on the linked lysine.

Calicheamicin is converted to a mono-*N*-acetyl derivative and linked to a monoclonal antibody by conversion of the reactive trisulfide into a disulfide link. The activated calicheamicin derivative structure (molecular weight of approximately d 1779.76 Da)..

Inotuzumab ozogamicin is a CD22-targeted antibody-drug conjugate (ADC). The antibody is a humanised immunoglobulin G, subtype 4 (IgG4) antibody (hinge-mutated immunoglobulin gamma-4 with kappa light chains, IgG4κ), inotuzumab, which specifically recognises human CD22. The small molecule, *N*-acetyl (*N*-Ac)-γ-calicheamicin dimethylhydrazide (DMH), is a cytotoxic semisynthetic natural product that is significantly more potent than conventional cytotoxic chemotherapeutic agents. *N*-Ac-γ-calicheamicin DMH is covalently attached to the antibody via a linker.

Conjugation occurs when calicheamicin reacts with un-protonated, accessible amine groups on the protein to form stable amide bonds. Conjugation leads to the formation of some undesired aggregated protein and removed by HIC chromatography followed by ultrafiltration.

Drug substance (inotuzumab ozogamicin)

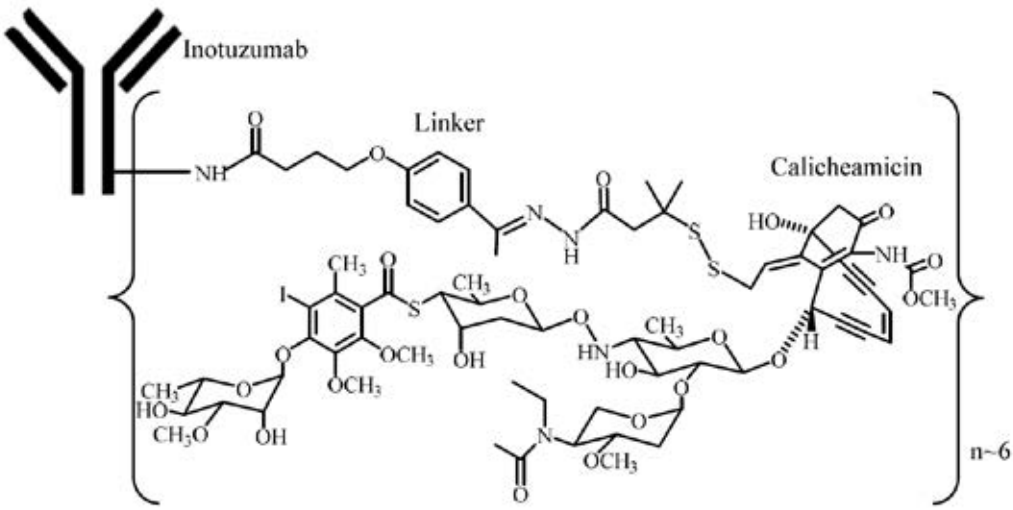
Synthesis of the drug substance (active pharmaceutical ingredient (API)) inotuzumab ozogamicin involves:

- γ-calicheamicin is made by fermentation, isolated and converted to N-acetyl calicheamicin;
- N-acetyl calicheamicin is synthetically coupled to t activated (N-hydroxysuccinimide ester) linker;
- (manufacture of the antibody is discussed separately);
- the activated calicheamicin derivative is conjugated with the inotuzumab antibody to form the API inotuzumab ozogamicin.

In the API, inotuzumab is covalently linked to a calicheamicin, a cytotoxic agent. The antibody is covalently bonded to N-acetyl-γ-calicheamicin dimethyl hydrazide (NAc-γ-calicheamicin DMH). The linker is a relatively complex chain attached via a sterically stabilised disulfide to the calicheamicin residue (sterically stabilised through 2 methyls on the adjoining carbon), and via an amide to lysines of the antibody. The linker includes a hydrazone residue. The hydrazone is hydrolysed in acidic conditions to *'calicheamicin'* (actually NAc-γ-calicheamicin DMH).

The chemical structure of the drug substance inotuzumab ozogamicin is below. The average number of calicheamicin derivative molecules conjugated to each inotuzumab molecule is approximately 6, with a distribution from 2 to 8.

Figure 1: Inotuzumab ozogamicin



Inotuzumab ozogamicin consists of a recombinant, humanized, IgG4 antibody covalently bonded (conjugated) to a semi-synthetic derivative of calicheamicin. Inotuzumab ozogamicin is a conjugate of the two intermediates: inotuzumab (G544 antibody) and activated calicheamicin derivative. The antibody chosen for development of inotuzumab was selected to target CD22, which is expressed on B cells. Calicheamicin is a potent cytotoxin that once conjugated to the anti-CD22 monoclonal antibody allows target-directed therapy. The calicheamicin is bound to the antibody via a linker, which forms an amide bond with the antibody and forms a disulphide bond with the calicheamicin. The linker also contains an internal hydrazone bond, which is acid-labile.

Upon binding to its target, the conjugate is internalized by endocytosis. Hydrolysis of the linker can occur in the acidic environment of lysosomes of the tumour cell. Following hydrolytic cleavage of the linker, the calicheamicin acts as a DNA minor groove binding cytotoxin which causes cell death by inducing double strand DNA breaks. The structure of the linker was designed to achieve the best balance between release in the tumour cell and stability in circulation, thereby enhancing toxicity to tumour cells while minimizing exposure of unconjugated calicheamicin in circulation.

The manufacturing process and control procedures and tests were described.

Drug product

Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product.

Based on the data provided, the proposed storage condition for the inotuzumab ozogamicin drug product of 24 months at 2 to 8 °C (protect from light), is justified.

In-use stability data have also been submitted. The following in-use condition is recommended:

> *'Reconstituted solution should be used immediately or after being refrigerated (2-8°C) for up to 4 hours. Protect from light. Do not freeze.'*

Stability studies have been conducted in accordance with relevant International Conference on Harmonisation (ICH) guidelines and Australian Regulatory Guidelines for Prescription Medicines (ARGPM).

No temperature excursion during shipping is permitted. Any batch exposed to temperature excursions outside the proposed shelf life storage conditions may not be supplied, and should be quarantined until a subsequent variation application has been determined.

Quality summary and conclusions

There are no objections to the registration of this product from sterility; endotoxin, container safety and viral safety related aspects.

With respect to quality matters, the Product Information (PI), Consumer Medicines Information (CMI) and labels are acceptable.

IV. Nonclinical findings

Introduction

General comments

Inotuzumab ozogamicin (Besponsa) is an antibody drug conjugate (ADC) proposed to be used for the treatment of adults with relapsed or refractory B cell precursor acute lymphoblastic leukaemia (ALL). In the European Union (EU), it was approved (June 2017) with the following indication:

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

In the United States of America (USA), it was approved (August 2017) with the following indication:

> *Besponsa is a CD22-directed antibody-drug conjugate (ADC) indicated for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).*

The cytotoxic component is the same as in gemtuzumab ozogamicin, a CD33-targeting ADC for the treatment of CD33-positive acute myeloid leukaemia. Gemtuzumab ozogamicin was initially approved by the US Food and Drug Administration (FDA) through an accelerated approval process, but was subsequently withdrawn owing to safety and efficacy concerns. However, it has since (September 2017) been approved by the FDA at a lower dosing schedule and for a different patient population.[2]

The nonclinical dossier included studies to investigate safety pharmacology and toxicology that were designed and conducted in accordance with relevant ICH and Organisation for Economic Co-operation and Development (OECD) guidelines. Pivotal safety pharmacology, tissue cross reactivity and toxicology studies were conducted in accordance with Good Laboratory Practice (GLP) guidelines.

Pharmacology

Primary pharmacology

Inotuzumab ozogamicin is an antibody drug conjugate (ADC) targeting human CD22. The antibody component of inotuzumab ozogamicin is a humanised immunoglobulin G that recognises CD22, a B cell specific transmembrane glycoprotein that is expressed on the cell surface of the vast majority of mature human IgM+ IgD+ B cells. CD22 is also expressed on a high proportion of malignant cells in ALL, as well as a number of other B cell cancers, including non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukaemia, hairy cell leukaemia, marginal zone lymphoma, diffuse large B cell lymphoma, follicular lymphoma and mantle cell lymphoma.[3] Thus, CD22 is a suitable antigen for targeting with ADC therapies for B cell malignancies.

[2] https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm574518.htm
[3] Shor, B. et al (2015). Pre-clinical and clinical development of inotuzumab ozogamicin in haematological malignancies. *Molecular Immunology* 67**:** 107-116.

In vitro studies with inotuzumab demonstrated specific and saturable binding of the antibody to human B cell lines and normal human B cells from human blood (dissociation constant (K_D) = 130 pM), but not to B cells in whole blood from mouse, rat, rabbit or cynomolgus monkey. Inotuzumab did not bind to granulocytes, monocytes or T cells in whole blood from human or any other species examined. Following binding to CD22 on B cells and ALL and NHL cell lines, inotuzumab was shown to be internalised and trafficked to lysosomes. Owing to the lack of cross-species reactivity for inotuzumab, the toxicology studies will only be useful for assessing target-independent toxicities associated with conjugated and unconjugated calicheamicin.

The cytotoxic component of the ADC is N-acetyl-γ-calicheamicin, which is covalently linked to inotuzumab by an acid cleavable linker composed of the condensation product of 4-(4'-acetylphenoxy)-butanoic acid (Ac-But) and 3-methyl-3-mercaptobutane hydrazide (known as dimethylhydrazide, DMH). Calicheamicin is a member of the enediyne family of anti-tumour antibiotics. A common structural feature of the calicheamicins is a 'warhead' triggered for rearrangement through reduction of a sulfur-sulfur bond by free thiols, in particular glutathione at the concentrations normally present intracellularly. It is proposed that following binding and internalisation of the ADC the calicheamicin derivative is hydrolysed in the acidic conditions of the cytoplasmic endosomes and lysosomes. Calicheamicin ultimately enters the nucleus of the cell, where it binds to the minor groove of DNA and causes double-strand DNA breaks, which leads to induction of apoptosis and cell death.[4,5]

The binding affinity of inotuzumab to B cells was unaffected by conjugation to calicheamicin (K_D for ADC = 150 pM). Inotuzumab ozogamicin exhibited specific and concentration-dependent cytotoxicity against CD22+ B cell origin cancer cell lines, while the unconjugated antibody had no effect on viability of CD22+ cells (at up to 100 μg/mL). A dose-dependent induction of double strand DNA breaks following treatment of B cell lines with the ADC provided was consistent with the proposed mechanism of action. Correspondingly (and as expected for an IgG4 isotype), there was no evidence of complement- or antibody-dependent cytotoxicity following treatment of a B cell line with inotuzumab or inotuzumab ozogamicin. In summary, the in vitro data support the proposed mechanism of action of the ADC.

The anti-tumour activity of inotuzumab ozogamicin was demonstrated in B cell ALL and lymphoma xenografts in immunocompromised mice, including large and small subcutaneously (SC) implanted tumours as well as in systemically disseminated tumour models. Although most of the animal studies used the intra peritoneal (IP) route, the (clinical) intravenous (IV) route was shown to be equally efficacious in a mouse lymphoma model. Neither unconjugated inotuzumab nor the unconjugated calicheamicin had any anti-tumour activity. Inotuzumab ozogamicin dose-dependently inhibited growth of SC implanted xenografts of Reh ALL cells in nude mice, with complete regression observed in mice treated with inotuzumab ozogamicin doses of 160 μg/kg (calicheamicin equivalents; three IP doses every four days; Q4D x 3), equivalent to 6.57 mg/m^2 of inotuzumab antibody. In a disseminated model of ALL, inotuzumab ozogamicin treatment at a dose of 3.3 mg/m^2 was associated with 100% survival.

The anti-tumour effects of inotuzumab ozogamicin were more sustained compared with CHOP, CVP;[6] or rituximab in inhibiting B cell lymphoma xenografts. Inotuzumab ozogamicin was also shown to be effective in treating resistant or relapsed tumours

[4] Ellestad, G. (2011). Structural and conformational features relevant to the anti-tumour activity of calicheamicin-Ɣ. *Chirality* 23: 660-671

[5] Dedon, P.C. (1996). Mechanisms of target selection by DNA-damaging chemicals: studies with enediyne anticancer drugs. *International Archives of Occupational and Environmental Health* 68**:** 408-414.

[6] CHOP = cyclophosphamide 40 mg/kg IP, doxorubicin HCl 3.3 mg/kg IP, vincristine 0.5 mg/kg IP and prednisone 0.2 mg/kg PO; CVP = cyclophosphamide, vincristine, prednisone

following CHOP or rituximab treatment. Combination treatment with CHOP or CVP was more effective than single agent treatment, while combination with rituximab enhanced survival only when treatment was commenced early in tumour development.

Secondary pharmacodynamics and safety pharmacology

In tissue cross reactivity studies, inotuzumab stained human tissues with known CD22 expression, including lymphocytes in lymph node, spleen, tonsil, gut associated lymphoid tissue (GALT), mononuclear cell infiltrates and whole blood. Unexpectedly, inotuzumab also stained the stromal fibres in the dermis of the skin, mammary gland, and uterine cervix of humans. The clinical significance of this is uncertain, but it may indicate the potential for additional off target toxicity in these tissues.

Inotuzumab did not cross react with a limited selection of tissues samples from mouse, rat, rabbit, dog, cynomolgus and rhesus monkey (blood vessel endothelium, bone marrow, small intestine, kidney, liver, lymph node, spleen and skeletal muscle, but excluding skin, mammary gland and uterine cervix).

Specialised safety pharmacology studies revealed no remarkable effects on the central nervous system (CNS) or respiratory systems of rats (relative exposures based on dose per unit of body surface area, (BSA), up to 11). A study of cardiovascular effects in conscious cynomolgus monkeys found toxicologically insignificant increases in mean blood pressure, and no effects on PR, QRS, QT or QTc intervals;[7] (relative exposures based on dose per unit of BSA up to 10). The half maximal inhibitory concentration (IC_{50}) for N-acetyl-Ɣ-calicheamicin DMH inhibition of hERG currents was greater than 6.77 µM, which is approximately 540 times greater than the clinical maximal plasma concentration (C_{max}).[8]

Pharmacokinetics

Owing to the lack of cross-species reactivity for inotuzumab the disposition of inotuzumab ozogamicin and its cytotoxic component in the nonclinical species (rat and monkey) is primarily non-target related. The disposition of inotuzumab ozogamicin in these species following IV administration was characterised by low plasma clearance (1.52 mL/h/kg and 1.14 mL/h/kg in rat and monkey, respectively), apparent volume of distribution (0.082 and 0.062 L/kg, respectively) consistent with no extravascular distribution, and mean terminal elimination half-life of the order of 50 to 60 h in both species. In comparison, plasma clearance in humans was lower (0.476 mL/h/kg, assuming a 70 kg body weight), the terminal elimination half-life was much longer (approximately 12 days, or 288 h) and the apparent volume of distribution was 0.17 L/kg.

Exposure to inotuzumab ozogamicin and the unconjugated antibody increased with dose, and the systemic exposure of the antibody (based on AUC values) was higher than the conjugate in both species. In monkeys, serum unconjugated calicheamicin concentrations were below quantifiable limits at all time points. Most of the circulating material in rat plasma was associated with the conjugated antibody, with only minimal amounts of de-conjugated calicheamicin-associated radioactivity detected.

Repeat dose toxicokinetic studies in rats and monkeys revealed no sex-related differences in exposure. Increases in exposure were approximately dose-proportional in rats, but not in monkeys, where exposure increased more rapidly than dose. Anti-drug antibodies (ADAs) were detected in approximately 10 to 13% of rats dosed with inotuzumab ozogamicin, but they were not detected in the monkey studies.

[7] PR = pulse rate, QRS = Beginning of Q to the end of the S wave, QT = QT interval or QTc = QT interval corrected for heart rate

[8] Assuming a clinical mean C_{max} value for inotuzumab ozogamicin of 308 ng/mL (B1931022 supplemental CSR [sCSR], Table 14.4.3.1), a mean calicheamicin content of 73µg/mg of antibody (Module 2.6.2.1, p.7 footnote), and calicheamicin MW = 1779.76

Binding of N-Ac-γ-calicheamicin-DMH to proteins in plasma was high in humans, rabbits and cynomolgus monkeys (approximately 97%), and slightly higher values in Wistar Han rats, SD rats and mice, with fraction unbound (fu) values 0.5, 0.24 and 0.03 times the human value, respectively. Blood to plasma concentration ratios and RBC partition coefficients of *N*-Ac-γ-calicheamicin-DMH in rat, monkey and human are indicative of limited distribution in red blood cells. A distribution study in rats with radiolabelled inotuzumab ozogamicin confirmed the limited tissue distribution following IV administration, as tissue-to-plasma radioactivity AUC ratios were below unity. The ADC and its metabolites showed very limited potential to cross the blood-brain barrier.

The pathways for clearance of inotuzumab ozogamicin from plasma in the nonclinical species are expected to differ from that in humans, owing to the lack of cross-species reactivity for inotuzumab. The metabolites identified following incubation of *N*-Ac-γ-calicheamicin DMH in S9 fractions from rats, monkeys and humans were similar, and were also similar to those seen in plasma and in buffer control, suggesting that biotransformation may occur non-enzymatically. ^{3}H-N-Ac-γ-calicheamicin DMH was extensively metabolised in rats following release from IV-administered ^{3}H-inotuzumab ozogamicin. The primary metabolic pathway for ^{3}H-N-Ac-γ-calicheamicin DMH was via non-enzymatic reduction of the disulfide moiety, with hydrolysis (at the hydrazide moiety), oxidation, and adduction (with pyruvic acid) being minor metabolic pathways. Approximately 98% of circulating radioactivity remained associated with protein, and inotuzumab ozogamicin accounted for 66% of total radioactivity based on the area under the curve from dosing to infinity ($AUC_{0-\infty}$), with two unidentified higher molecular weight components accounting for the remainder. The only metabolite detected in serum from non-Hodgkin's Lymphoma patients treated with inotuzumab ozogamicin was cleaved N-Ac-γ-calicheamicin DMH. There were no unique human urinary metabolites.

Non-specific hydrolysis of the acid-labile DMH linker of inotuzumab ozogamicin in plasma could potentially reduce its efficacy and/or increase toxicity. In an ex vivo study more than 90% of drug related activity remained associated with protein following incubation with plasma from rat, monkey and human for 96 h at 37 °C, and over time ^{3}H-N-Ac-γ-calicheamicin DMH-related radioactivity is likely to become associated with plasma proteins.

Following IV administration of ^{3}H-inotuzumab ozogamicin to rats, approximately 80% of drug related radioactivity was recovered in the faeces, following excretion into the bile, with approximately 8 to 9% of the dose excreted via urine. Faecal radioactivity eliminated slowly over 504 h post-dose.

Pharmacokinetic drug interactions[9]

As discussed above, metabolism of N-Ac-γ-calicheamicin DMH is unlikely to be mediated by cytochrome P450 (CYP) or uridine diphosphate-glucuronosyltransferase (UGT) drug metabolising enzymes, and so interactions following co-administration with inhibitors or inducers of such enzymes are not anticipated. Based on in vitro data, inotuzumab ozogamicin and/or N-Ac-γ-calicheamicin DMH showed low potential for inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5, UGT1A1, UGT1A4, UGT1A6, UGT1A9 and UGT2B7 at clinically relevant concentrations. N-Ac-γ-calicheamicin DMH did not show potential to induce the activity of CYP450 enzymes.

[9] The following assumptions were made: (1) *N*-Ac-Y-calicheamicin DMH molecular weight, 1779.76; dose, 248 µg; $C_{max,}$ 0.05 ng/mL (total); free fraction, 3%; k_{deg} for CYP3A, 0.0005 min^{-1}; (2)for systemic CYP, renal uptake and efflux transporters, and hepatic efflux transporters (OAT1, OAT3, OCT2, MRP2, BCRP, P-glycoprotein, MATE1 and MATE2K): if the IC_{50} is ≤ 50 fold the unbound clinical C_{max}, an *in vivo* interaction is considered possible; (3) for hepatic uptake transporters (OCT1, OATP1B1 and OATP1B3): if the IC_{50} is ≤ 25 fold the unbound hepatic inlet concentration, an *in vivo* interaction is considered possible.

N-Ac-γ-calicheamicin DMH was shown to be a substrate for P-glycoprotein but not the breast cancer resistance protein (BCRP) efflux transporter in MDCK cells. Its uptake into human hepatocytes *in vitro* was not inhibited by the organic anion-transporting polypeptide (OATP) OATP1B1 and OATP1B3 hepatic uptake transporter inhibitor, rifamycin, indicating that it enters human hepatocytes by passive diffusion, and therefore is unlikely to be a substrate for hepatic uptake transporters.

Similarly, based on *in vitro* studies, at clinically relevant concentrations, N-Ac-γ-calicheamicin DMH is not expected to inhibit the efflux transporters P-glycoprotein (P-gp), BCRP, bile salt export pump (BSEP), multidrug resistance associated protein (MRP) 2, multidrug and toxin extrusion protein (MATE) 1, and MATE2K, or the uptake transporters OATP1B1, OATP1B3, organic cation transporter (OCT) OCT1, and the organic anion transporters (OAT) OAT1 and OAT3, and OCT2.

Toxicology

Acute toxicity

Table 3: Relative exposure in acute toxicity studies

Species Study no.	Dose (mg/m^2)	ER[1]	^C_{max} (ng/mL)	ER[2]	^$AUC_{0-\infty}$ (ng·h/mL)	ER[3]
Rat (SD) RPT-46233	2.92	3.7	8389	27	220389	2.2
	7.68	9.6	38895	126	779073	7.8
Monkey (cynomolgus) RPT-46644	4.2	5.1	17750	58	2530004 [KJP1] [KJP2]	2.5
	8.3	10.2	36300	118	5835004	5.8
	16.7 [KJP3]	20.6	65100	211	1218000	12.2
Human ALL patients steady state (Cycle 4) (population PK analysis, Module 2.5.3.1)	Max. 0.8	-	308	-	100000	-

[1] = exposure ratio based on dose per unit of BSA; [2] = exposure ratio based on inotuzumab ozogamicin C_{max}; [3] = exposure ratio based on animal AUC:human plasma AUC_{0-t}, where t = ∞ (or 336 h)[4] for animal data, or1 cycle/4 weeks for human data); ^ = data are for the sexes combined

Single dose toxicity studies were conducted in rats and monkeys using the IV route, with bolus dose administration. In clinical use, therapeutic doses based on BSA (4 to 21 times the maximum recommended human dose) are infused over one hour, and this probably accounts for the high relative exposures achieved in the single dose toxicity studies based on comparisons of C_{max} in Table 3. The maximum non-lethal doses were 7.7 mg/m^2 and 16.4 mg/m^2 in rats and monkeys, respectively (approximately 10 and 21 times the

maximum proposed clinical dose in rats and monkeys, respectively; relative exposures 126 and 211, respectively based on C_{max}, or 8 and 12, respectively based on AUC). In both species, toxicity was evident at the lowest doses administered, which was 0.77 mg/m^2 in the rat (approximately 0.4 times the maximum human dose per unit of BSA) and 4.1 mg/m^2 in the monkey (relative exposure 5 based on dose per unit of BSA; 58 based on C_{max} and 2.5 based on AUC).

In rats, treatment-associated mortalities occurred at a dose of 16.4 mg/m^2 (11 times higher than the maximum clinical dose per unit of BSA). Death was attributed to compound-related multiple organ toxicity (hepatic centrilobular necrosis, lymphoid atrophy of spleen and thymus, and bone marrow hypocellularity). Necropsy findings included hypocellularity of the bone marrow, sinus haemorrhage in the mesenteric node, lymphoid atrophy in the spleen, thymus, and mandibular or mesenteric node and gut-associated lymphatic tissue, cardiac haemorrhage, mucosal degeneration of the caecum, tubular casts in the kidneys and eosinophilic chief cells in glandular stomach. Males exhibited mammary gland atrophy, and reproductive organ toxicity (tubular degeneration in the testes, hypospermia in epididymides and prostate atrophy).

Toxicities observed in the single dose studies were generally similar to those observed in the repeat dose studies, and are described in detail below.

Repeat dose toxicity

Repeat dose toxicity studies were conducted with SD rats and cynomolgus monkeys dosed weekly with inotuzumab ozogamicin by IV bolus for up to 26 weeks (the same as the clinical route, with the same dosing interval as for the first 3 weeks of each clinical dosing cycle). Investigations with N-Ac-γ calicheamicin DMH were conducted in single- and 6-week repeat-dose studies in mice (single-dose only), rats, and dogs, and with *N*-Ac-ε-calicheamicin in single-dose studies in rats and dogs (see Appendix 1, previously evaluated studies [not included in this AusPAR]). In addition, the effect of the unconjugated anti CD22 antibody was assessed in the 4 week studies in rats and monkeys. Additional toxicity studies in monkeys included a combination study evaluating the effect of oprelvekin (Neumega) administration on inotuzumab ozogamicin-related thrombocytopenia and an investigational study using a non-binding antibody conjugated to calicheamicin to explore the mechanism of conjugated and unconjugated calicheamicin related hepatotoxicity and thrombocytopenia.

The study designs and conduct were consistent with ICH guidelines, and the pivotal studies were GLP compliant.[10,11,12,13,14,15] As already mentioned, owing to the lack of cross species reactivity for inotuzumab, the toxicology studies are only useful for assessing target independent toxicities associated with conjugated and unconjugated calicheamicin.

Relative exposure

In the toxicology and toxicokinetic study reports, doses of inotuzumab ozogamicin were expressed as calicheamicin equivalents on the basis of µg/kg of body weight. These have been converted dose equivalents of the inotuzumab antibody on the basis of mg/kg of body weight and mg/m^2 BSA. Exposure ratios have been calculated using animal and human plasma AUC_{0-t} values where t = 168 h for animals, and one cycle (4 weeks) for

[10] ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals (EMA/CPMP/ICH/286/1995)
[11] ICH guideline M3 (R2) - questions and answers (EMA/CHMP/ICH/507008/2011)
[12] ICH guideline S9 on nonclinical evaluation for anticancer pharmaceuticals (EMA/CHMP/ICH/646107/2008)
[13] ICH guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals (EMA/CHMP/ICH/731268/1998)
[14] ICH Topic S 4 Duration of Chronic Toxicity Testing in Animals (Rodent and Non Rodent Toxicity Testing; CPMP/ICH/300/95);
[15] Guideline on repeated dose toxicity (CPMP/SWP/1042/99 Rev 1 Corr*)

humans. The human reference value is the population pharmacokinetic estimate at steady state (Cycle 4). The AUC data used for animals is multiplied by four, to account for the difference in AUC measurement time period between animals and humans. The relative exposures at the highest dose were generally low multiples of the clinical exposure, with the exception of the 4 week monkey study, where the relative exposure was 24.

Table 4: Relative exposure in repeat dose toxicity studies

Species	Study duration (Study no.)	Dose (mg/m^2/cycle)	Sex	AUC0–t^ (ng·h/mL)	Exposure ratio#
Rat (SD)	4 weeks RPT-46910	0.41	M	50 700	2.0
		1.24	M	182 000	7.3
			F	160 000	6.4
			M/F	171 000	6.8
		4.07	M	619 000	25
	26 weeks Pivotal; RPT-65042	0.073	M	‡7630	0.08
		0.218	M	20 200	0.81
		0.727	M	64 000	2.6
Monkey (Cynomolgus)	4 weeks RPT-46909	0.36	M	33 000	1.3
			F	20 000	0.8
			M/F	26 500	1.1
		1.32	M	145 000	5.8
			F	92 800	3.7
			M/F	118 900	4.8
		4.20	M	628 000	25.1
			F	576 000	23.0
			M/F	602 000	24.1
	26 weeks Pivotal; RPT-65773	0.072	M	4430	0.18
			F	3230	0.13
			M/F	3 830	0.15
		0.216	M	23 200	0.93
			F	20 200	0.89

Species	Study duration (Study no.)	Dose (mg/m²/cycle)	Sex	AUC0–t^ (ng·h/mL)	Exposure ratio#
			M/F	21 700	0.91
		0.732	M	86 100	3.4
			F	95 200	3.8
			M/F	90 650	3.6
Human ALL patients	steady state (cycle 4) (population PK analysis)	0.5-0.8		100 000	–

= (4 x animal AUC): human plasma AUC_{0-t}, where t = 168 h for animal data, and 1 cycle/4 weeks for human data); ^ = data are generally at the last sampling occasion (‡Day 1 data)

Major toxicities

As already noted, the nonclinical studies are unable to inform on target-mediated toxicity. There are currently no approved agents that target CD22, but there are several monoclonal antibodies that target CD20 and deplete B cells (for example rituximab). Adverse events associated with B cell depleting agents and included in the associated Product Information documents include infusion reactions, hepatitis B reactivation, progressive multifocal leukoencephalopathy, tumour lysis syndrome, infections and myelosuppression.

In the 4 week repeat dose toxicity studies in rats and monkeys there were no lesions attributable to the antibody itself. Rats exhibited only limited (10 to 13%) ADA formation in repeat dose studies, and ADAs were not detected in monkeys. One male monkey dosed at 0.73 mg/m² in the 26 week study was euthanised prematurely in a moribund condition, and was found to be suffering from a protein losing glomerulonephritis. The characteristics of the renal histopathological changes in this animal and their time course were consistent with immune complex deposition associated with ADAs, even though no ADAs were detected in this animal. Since it is possible that the ADAs may not have been present at the time of sampling, or there may have been drug interference in the ADA assay, it is not possible to rule out renal immune complex deposition as the underlying cause of the renal findings. In general, however, the toxicity studies suggested that in common with the pharmacology, the toxicity was driven by the calicheamicin component. Many of the results suggested that there was sufficient intracellular uptake and activation of the calicheamicin moiety in non-targeted cells in these toxicity studies to produce cytotoxic consequences of DNA damage. The major target organs for inotuzumab ozogamicin were the liver, haematolymphopoietic tissues and the male and female reproductive organs, with some effects also observed on the nervous system of rats and the kidney of rats and monkeys. Decreased body weight and food consumption were evident in single and repeat dose studies.

Hepatotoxicity

Adverse hepatic effects, most notably associated with endothelial injury, were seen in rats and monkeys in both the acute and repeat dose toxicity studies, and are likely to represent early stages of hepatic veno-occlusive disease (VOD; also known as sinusoidal obstruction syndrome). Development of VOD is a known serious and potentially life-threatening consequence of treatment with calicheamicin conjugates including gemtuzumab

ozogamicin.[16] [17] Hepatic VOD was reported in clinical trials with inotuzumab ozogamicin, and detailed information on this is included in the proposed PI document. In the repeat dose studies in rats and monkeys, increases in aminotransferases were associated with sinusoidal dilatation and (in monkeys) hepatocyte atrophy associated with intervening foci of hepatocyte hypertrophy or regeneration. In rats, these changes were accompanied by angiectasis, oval cell hyperplasia, cholangiofibrosis, hepatocellular hypertrophy, karyomegaly, cellular vacuolation, fibrosis and extramedullary haematopoiesis.

A more detailed understanding of calicheamicin-mediated hepatotoxicity in monkeys was gained in a study investigating the mechanism underlying the thrombocytopenic effect of inotuzumab ozogamicin in monkeys (the thrombocytopenic effect is discussed in more detail below). Bolus IV injections of an ADC (comprised of a humanised nonbinding IgG1 monoclonal antibody conjugated to N-Ac-γ-calicheamicin-DMH) were administered on Days 1, 22 and 43 of a 9 week study. Consistent with ADC-mediated liver specific endothelial injury, increased blood concentrations of hyaluronic acid were associated with increased serum aspartate aminotransferase (AST) and histopathological changes, and micro RNA-122 levels were markedly increased. In addition, the loss of VEGFR2 staining in endothelial cells of the midzonal and centrilobular regions, the presence of platelet staining in midzonal sinusoids, together with multifocal sinusoidal dilation and/or hepatocyte atrophy, is consistent with platelet sequestration, activation and degranulation. The increased CD34 expression observed in sinusoidal endothelial cells is a marker of sinusoidal capillarisation, which has been associated with functional impairment of the liver.[18]

Hepatic neoplasia and pre-neoplastic changes were also associated with inotuzumab ozogamicin administration in both species. In the 26 week study in rats, hepatocellular adenomas were observed following dosing at 0.73 mg/m^2, and basophilic and/or eosinophilic cell foci were associated with doses of 0.07 mg/m^2 and above. Oval cell hyperplasia was also observed in rats given single doses of 8.2 mg/m^2, and after 4 weeks at 4.1 mg/m^2 and at 0.073 mg/m^2 in the 26 week study. In the 26 week study in monkeys, a focus of hepatocellular alteration in one HD female dosed at 0.73 mg/m^2. This is an uncommon spontaneous finding in cynomolgus monkeys. Increased hepatocellular proliferative activity (positive Ki-67 staining of nuclei) was seen in both rats and monkeys dosed for 26 weeks with 0.22 and 0.072 mg/m^2 and above, respectively. The increase in proliferative activity and identification of pre-neoplastic and neoplastic lesions is likely due to an increased turnover rate in the hepatocyte population and is consistent with genotoxic and cytotoxic effects in the liver. The no observable effect levels (NOELs) for the increased proliferative activity and pre-neoplastic change in the monkey were below 0.15 and 0.9, respectively.

Haematolymphopoietic tissues

Haematological findings associated with inotuzumab ozogamicin dosing in both rats and monkeys included reduced numbers of red cells, white cells, lymphocytes and platelets, and was usually associated with reduced reticulocyte numbers. Reductions in red cell numbers were accompanied by decreases in haemoglobin concentration and haematocrit, and by increases in red cell distribution width, mean cell volume and mean cell haemoglobin, with the combined effect indicative of reduced erythropoiesis. The magnitude of these effects increased with dose and duration of treatment, with relative

[16] Tack, D.K. *et al* (2001). Development of hepatic veno-occlusive disease after Mylotarg infusion for relapsed acute myeloid leukaemia. *Bone Marrow Transplantation* 28**:** 895-897

[17] McKoy, J.M. et al (2007). Gemtuzumab ozogamicin-associated sinusoidal obstructive syndrome (SOS): An overview from the research on adverse drug events and reports (RADAR) project. *Leukemia Research* 31: 599-604

[18] Narita, M. et al (2012). Liver injury due to chemotherapy-induced sinusoidal obstruction syndrome is associated with sinusoidal capillarisation. *Annals of Surgical Oncology* 19**:** 2230-2337

exposure comparisons in both species confirming their clinical relevance. The reduction in white blood cells number was largely accounted for by reductions in lymphocyte numbers. In the 4 week repeat dose study in rats, peripheral blood lymphocyte immune typing indicated that the effect of inotuzumab ozogamicin was consistent with a differential effect of DNA damaging agents on major lymphocyte subsets, with the most pronounced effect on B-lymphocytes.[19]

Haematological findings were associated with decreased hematopoietic cellularity in the bone marrow and lymphoid depletion in the thymus, spleen, lymph nodes, and/or gut associated lymphatic tissue (GALT). Haematolymphopoietic toxicity was partially to completely reversible at the end of a 4 week non-dosing period in the 4 week studies.

Mechanism underlying the acute thrombocytopenic effect in monkeys

The acute thrombocytopenic effect was more notable in monkeys than rats, and was present 3 to 4 days after single dose administration, associated with systemic exposures (based on AUC) comparable to those anticipated in clinical use. The sponsor considered that the concomitant microscopic bone marrow hypocellularity appeared to develop at higher levels of systemic exposure, and could only partially account for the haematological changes. In addition, the rapid onset of platelet loss was considered to be more likely to be due to peripheral destruction rather than inhibition of de novo synthesis, since the normal platelet lifecycle is 6 to 8 days in monkeys.[20] Based on these considerations, the sponsor conducted a mechanistic study in cynomolgus monkeys with a non-binding ADC, which has already been discussed above in relation to calicheamicin-mediated hepatic endothelial toxicity. The study aimed to examine the hypothesis that the acute thrombocytopenic effect was secondary to liver specific endothelial injury due to the calicheamicin component of the ADC. Similar to the repeat dose studies with inotuzumab ozogamicin, platelet numbers declined reversibly after each dose, with the first dose producing the most marked effect. Recovery was more protracted after subsequent administrations of the ADC. An absence of changes in bone marrow megakaryocyte density and morphology was supportive of the hypothesis that the thrombocytopenia was not due to inhibition of platelet production. The proposed mechanism underlying the acute thrombocytopenic effect in monkeys is analogous to the effects of oxaliplatin.[21] ADC mediated liver specific endothelial injury was associated with the presence of platelet staining in midzonal sinusoids, together with multifocal sinusoidal dilation and/or hepatocyte atrophy, and is consistent with platelet sequestration, activation and degranulation in this tissue, which is likely to account for the acute thrombocytopenic effect of the calicheamicin component of inotuzumab ozogamicin.

Nerve

Peripheral and central axonal degeneration was observed in the 4 week repeat dose study in rats at doses of 1.24 mg/m^2 and above (relative exposure equal to 7, based on AUC; NOEL relative exposure = 2). It was not observed in the 26 week study, where the high dose (HD) level was 0.73 mg/m^2 (relative exposure 3), nor was it observed in the monkey studies. In the 4 week rat study with inotuzumab ozogamicin, the sciatic nerve appeared to be more sensitive than cervical spinal cord based on numbers of affected animals, while axonal degeneration of trigeminal nerve was only seen in one animal of each sex at a dose of 4.1 mg/m^2 both males and females. Of concern is the observation that axonal degeneration increased in incidence and severity at all three sites in the 4 week recovery

[19]Thompson S.C. *et al* (1987). The effect of immunosuppressive agents on lymphocyte subsets in rat peripheral blood. *International Journal of Immunopharmacology* 9: 747-759

[20] Moroni, M. et al (2011). Haematological changes as prognostic indicators of survival: similarities between Göttingen minipigs, humans and other large animal models. *PLoS ONE* 6: e25210. doi:10.1371/journal.pone.0025210

[21] Tajima, H. et al (2015). Oxaliplatin-based chemotherapy induces extravasated platelet aggregation in the liver. *Molecular and Clinical Oncology* 3**:** 555-558.

period, with additional findings reported in the lumbar spinal cord. In both the post dose and post recovery examinations, there was a low incidence of axonal degeneration seen in the protein control group (1/15 in both sexes), with a small increase in incidence and severity (2/5 males and 1/4 females). The sponsor considered this to be an incidental finding, and considers that the neural toxicity is related to the cytotoxic agent. However, it was not seen in the saline control group.

Peripheral neuropathy is a known adverse event associated with certain cytotoxic antineoplastic agents such paclitaxel. Based on the results in the 4 week rat study, there appears to be a potential for peripheral neuropathy with clinical use of inotuzumab ozogamicin. The safety margin of 2 at the NOEL in rats, and the lack of effect in monkeys (at up to24 times the clinical AUC in the 4 week study) provide some reassurance. Neural toxicity is included in the Risk Management Plan, but is not mentioned in the PI document.

Male reproductive organs

Adverse effects of inotuzumab ozogamicin on the male reproductive organs were primarily observed in the rat toxicity studies, and were consistent with the effects of N-Ac-γ calicheamicin DMH (previously evaluated). Reduced testicular and epididymal size and weight, tubular degeneration, epididymal hypospermia and atrophy of the seminal vesicles, prostate and mammary gland were associated with single doses of 8.7 mg/m^2 and repeated doses of 0.07 mg/m^2 and above. While these effects did not reverse, or were only partially reversed, in the 4 week recovery period, this is likely to be reflective of the 7 to 8 week spermatogenic cycle in this species.[22] No male reproductive effects were noted in the 26 week repeat dose study in monkeys. In the 4 week study in monkeys, retracted and vacuolated Sertoli cell cytoplasm was noted in 2 males dosed at 4.2 mg/m^2. In both studies in this species, testicular maturation was either incomplete or variable, precluding an accurate assessment of male reproductive effects. Based on the known effects of calicheamicin and the outcome of the rat studies, adverse effects on male reproductive function are clinically relevant.

Female reproductive organs

Adverse effects on female reproductive organs included reduced ovarian or uterine weight, atrophy of ovarian, uterine and vaginal epithelium and ovarian necrosis. Partial to complete reversibility was demonstrated in both species. These effects are consistent with the effects of N-Ac-γ calicheamicin DMH in rats and dogs. The only effects of treatment that was observed at clinical exposure levels (based on AUC) were reduced ovarian and uterine weight in the 4 week monkey study. The NOEL for all other effects corresponded to low multiples of the clinical exposure level.

Kidney

Calicheamicin-mediated renal toxicity was observed in the previously evaluated studies. In single dose studies in rats, renal tubular dilation, karyocytomegaly, and degeneration was observed with calicheamicin doses of 100 µg/kg and above, increased renal tubular basophilia at 300 µg/kg and renal tubular casts and necrosis of the renal cortical tubular epithelium was observed at 1000 µg/kg. With repeated dosing, the lowest observable effect level (LOEL) for karyocytomegaly was 30 µg/kg in rats. Karyocytomegaly was not observed in the single dose studies in this species with inotuzumab ozogamicin at calicheamicin equivalent doses of up to 200 µg/kg, but renal tubular proteinaceous casts were seen at 100 µg/kg and above, and also in the 4 week study at a calicheamicin dose of 50 µg/kg, with no concurrent lesions. There was an increased incidence and severity of chronic progressive nephropathy in the 26 week study in rats dosed at 10 µg/kg calicheamicin equivalents (inotuzumab ozogamicin dose 0.73 mg/m^2, relative

[22] Foster, P.M.D. (1988). Testicular Organisation and Biochemical Function. *Physiology and Toxicology of Male Reproduction* Chapter 2: 7-34. Ed. Lamb, J.C. & Foster, P.M.D. Academic Press Inc.

exposure = 3). This is a species-specific spontaneous lesion, but it was clearly exacerbated by treatment.

In the monkey, as already discussed above one male in the 26 week study was euthanased prematurely in a moribund condition, which was attributed to a protein losing glomerulonephritis, associated with the presence of urinary protein, tubular protein casts in the kidney and systemic subacute vascular inflammation. It is not possible to rule out renal immune complex deposition as the underlying cause of the renal findings in this animal, although no ADAs were detected. However, it is considered to be highly likely that this was a consequence of treatment with inotuzumab ozogamicin. The NOEL for renal effects in the rat and monkey repeat dose studies were 0.22 mg/m^2 in monkeys and 0.073 mg/m^2 in rats which were associated with clinically relevant exposures.

Other findings

In the repeat dose studies in rats and monkeys, increases in neutrophil and monocyte numbers, accompanied by increased fibrinogen was consistent with inflammation. Changes in serum proteins (decreased albumin, increased globulin, and reduced albulin/globulin ratio) were consistent with the haematology findings. Increases in activated partial thromboplastin time (APTT) andprothrombin time (PT) were observed in monkeys in single dose studies.

Genotoxicity

Genotoxicity studies with inotuzumab ozogamicin and its cytotoxic component, N-Ac-Ɣ-calicheamicin DMH, were adequate considering technical limitations, and the expectation of positive findings for mutagenicity and/or clastogenicity. Consistent with its capacity to bind in a sequence-specific manner to the minor groove of DNA, resulting in double stranded breaks, N-Ac-Ɣ-calicheamicin DMH was mutagenic in the Ames assay only in the *E.* coli strain, at concentrations of 3.09 µg/plate and above in the absence of metabolic activation, and at 12.3 µg/plate and above in its presence. Inotuzumab ozogamicin was not mutagenic in the Ames assay at the maximum feasible concentration of 7.3 µg/plate. This is well below the recommendation of 5000 µg/plate, and may be below the limits of the assay sensitivity.[23] The lack of mutagenicity in this study may also be reflective of a lack of intracellular penetration of the cytotoxic component.

Clastogenicity of *N*- Ac-Ɣ-calicheamicin DMH was demonstrated in an *in vitro* micronucleus assay in TK6 cells, and inotuzumab ozogamicin was clastogenic in the male mouse, with dose dependent increases in micronuclei formation from the lowest dose tested of 28 µg/kg (corresponding to 1.14 mg/m^2, 1.4 times the maximum human dose).

Carcinogenicity

Given the intended indication (treatment of advanced cancer) and the genotoxicity of the calicheamicin component, carcinogenicity studies with inotuzumab ozogamicin are not required, and none were conducted.[12,13,24,25]As discussed above, neoplastic and non-neoplastic changes were seen in the livers of rats and monkeys in repeat dose studies with inotuzumab ozogamicin. The increase in proliferative activity and development of pre-neoplastic and neoplastic lesions in these studies is consistent with genotoxic and cytotoxic effects of calicheamicin. Increased proliferative activity was only partially reversible in the 4 week repeat dose study in rats, as oval cell hyperplasia and a clear cell

[23] Kenyon, M. *et al* (2007). An evaluation of the sensitivity of the Ames assay to discern low-level mutagenic impurities. *Regulatory Toxicology and Pharmacology* 48**:** 75-86.
[24] EMA/CHMP/ICH/731268/1998; ICH guidelines S1 (Regulatory notice on changes to core guideline on rodent carcinogenicity testing of pharmaceuticals, EMA/CHMP/ICH/536328/2013 Rev.1)
[25] S1A (The need for carcinogenicity studies of pharmaceuticals, CPMP/ICH/140/95)

focus were reported in the recovery group. The NOEL for pre-neoplastic liver findings in the monkey was 0.22 mg/m^2, which was associated with a relative exposure of 0.9. In the rat, a NOEL for pre-neoplasia was not established, and the AUC at the LOEL of 0.073 mg/m^2 was approximately 0.1 times the clinical AUC.

Reproductive toxicity

Reproductive toxicity studies covered female fertility in rats, and embryofetal development in rats and rabbits. Animals were dosed daily by the clinical (IV) route. The study designs and their conduct were generally consistent with the relevant European Medicines Agency (EMA) guideline,[26] and they were GLP compliant. The absence of a male fertility is acceptable based on the known genotoxicity of inotuzumab ozogamicin and the demonstration of male reproductive organ toxicity in the repeat dose studies. Effects on pre and postnatal development were also not investigated, but this is appropriate given that the proposed indication is for advanced cancer.

Relative exposure

Table 5: Relative exposure in reproductive toxicity studies

Species	Study (Study no.)	Dose (mg/m^2/day)	AUC_{0-24h} (ng·h/mL)	Exposure ratio[#]
Rat (SD)	Fertility Study RPT-69733	0.011	441	0.12
		0.036	1724	0.48
		0.109	9672	2.7
	Embryofetal development Study RPT-68342	0.011	364	0.10
		0.036	1680	0.47
		0.109	6900	1.9
Rabbit (NZW)	Embryofetal development Study RPT-72134	0.015	1349	0.38
		0.044	4187	1.2
		0.145	13264	3.7
Human ALL patients	steady state (cycle 4) (population PK analysis)	0.5-0.8	†3571	–

[#] = animal:human plasma AUC_{0-24h}; †human plasma AUC_{0-24h} calculated by dividing AUC measured over a 4 week cycle by 28

Relative exposures at the high dose levels in the reproductive toxicity studies were 2-4, and are considered adequate based on the demonstration of maternal toxicity. There were no studies examining placental or lactational transfer of inotuzumab ozogamicin or its metabolites in animals.

As discussed above, inotuzumab ozogamicin had adverse effects on reproductive organs in the repeat dose studies. In male rats, these effects consisted of reduced testicular and epididymal size and weight, tubular degeneration, epididymal hypospermia and atrophy of the seminal vesicles, prostate and mammary gland, and were seen with repeated doses of 0.07 mg/m^2 and above (relative exposure 0.08). The extent of the sensitivity of reproductive organs in male monkeys to inotuzumab ozogamicin was not clearly established owing to their relative immaturity. In female animals, dosing with inotuzumab ozogamicin was associated with reduced ovarian or uterine weight, atrophy of ovarian,

[26] EMA Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: from Data to Labelling (EMEA/CHMP/203927/2005)

uterine and vaginal epithelium and ovarian necrosis. The NOEL for oestrous cycling and mating performance in the rat fertility study was 0.11 mg/m^2 (approximately 3 times the clinical exposure, based on AUC). However, this dose was associated with maternal toxicity and increased numbers of resorptions, and hence the NOEL for reproductive performance was 0.036 mg/m^2 (0.5 times the clinical exposure, based on AUC).

Maternal toxicity was observed in the embryofetal development studies in rats and rabbits at doses of 0.11 and 0.15 mg/m^2, respectively. In rats, fetal weights were decreased at doses of 0.036 mg/m^2 and above (0.5 times the clinical exposure, based on AUC), and this was associated with reduced skeletal ossification. No developmental toxicity was seen in the pivotal embryofetal study in rabbits at maternally toxic doses of up to 0.145 mg/m^2 (approximately 4 times the clinical exposure, based on AUC). In the dose range-finding study in this species, a dose of 0.44 mg/m^2 was associated with significant maternal toxicity (including mortality), increased fetal resorptions and decreased fetal body weight.

Based on the nonclinical studies, clinical use of inotuzumab ozogamicin is likely to result in impaired male and female fertility. Although no teratogenic effects were observed in the reproductive toxicity studies in rats and rabbits, based on the genotoxic potential of the calicheamicin component, treatment with inotuzumab ozogamicin it is considered likely to pose a reproductive hazard to the developing fetus.

Pregnancy classification

The sponsor has proposed Pregnancy Category D.[27] This is appropriate based on the above considerations.

Local tolerance

The sponsor did not conduct a dedicated local tolerance study. This is acceptable, since there were no macroscopic or microscopic changes noted at injection sites after 4 and 26 weeks of repeated dosing in rats and monkeys (using the same dosage formulation, route and frequency as is proposed clinically).

ImmunogenicityThe sponsor did not submit any studies on immunogenicity. As already discussed, ADA levels were measured in the 4 and 26 week repeat dose toxicity studies in rats and monkeys. Two of 20 satellite rats (10%) administered inotuzumab ozogamicin (1 animal given 4.07 mg/m^2/week) or inotuzumab antibody (1 animal) for 4 weeks tested positive for ADAs at one or more time points after initiation of dosing. No rats were positive for ADA in the 0.41 and 1.24 mg/m^2/week groups. Two of 15 (13.3%) satellite rats administered inotuzumab ozogamicin for 26 weeks tested positive for ADAs at one or more time points (2 of 5 rats at 0.073 mg/m^2/week; 0 of 5 rats each at 0.218 or 0.727 mg/m^2/week). In the 4 and 26 week repeat dose toxicity studies in monkeys, ADAs were not detected in any animals after administration of inotuzumab ozogamicin or inotuzumab antibody.

Phototoxicity

N-Ac-γ-calicheamicin DMH has significant absorbance in the UVA-UVB/visible range from 290 to 700 nm, with a molar extinction coefficient exceeding1000 L/mol/cm. On the basis of the results of a phototoxicity assay in Balb/c 3T3 cells, N-Ac-γ-calicheamicin DMH and its antibody-conjugate, inotuzumab ozogamicin, is not expected to have phototoxic potential.

[27] Pregnancy Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Blood compatibility

Inotuzumab ozogamicin and its vehicle showed no haemolytic potential in blood compatibility assays in rats, monkeys and humans, and there was no evidence of methaemoglobin formation or protein precipitation.

Impurities

The proposed specifications for inorganic impurities/degradants in the drug substance/product are below the ICH qualification thresholds.

Paediatric use

Inotuzumab ozogamicin is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Comments on the nonclinical safety specification of the risk management plan

Results and conclusions drawn from the nonclinical program for inotuzumab ozogamicin detailed in the sponsor's draft Risk Management Plan are in general concordance with those of the nonclinical evaluator.

Nonclinical summary and conclusions

- The submitted nonclinical dossier was in accordance with the relevant ICH guidelines for the nonclinical assessment of pharmaceuticals, anticancer pharmaceuticals and biological medicines (ICH M3(R2), ICH S9 and ICH S6). The overall quality of the nonclinical dossier was high. All pivotal safety-related studies (including tissue cross reactivity) were GLP compliant. Inotuzumab did not show cross-species reactivity to mouse, rat, rabbit or cynomolgus monkey B cells or other tissues, and therefore the nonclinical species are only able to provide information on non-target mediated effects of the ADC. Any possible effects associated with CD22 binding would not be revealed by the animal models used.
- The pharmacological activity as well as toxicity of inotuzumab ozogamicin is attributable to the calicheamicin component. Inotuzumab antibody binds to the CD22 antigen, which is located on the vast majority of mature human B cells, as well as on a high proportion of malignant cells in ALL and a number of other B cell cancers. Binding to CD22 on B cells and ALL and NHL cell lines was demonstrated, followed by internalisation and trafficking to lysosomes, where the acidic conditions favour hydrolysis of the calicheamicin derivative. B cell lines treated with the ADC showed induction of double strand DNA breaks, consistent with the proposed mechanism of action for calicheamicin, ultimately leading to induction of apoptosis and cell death.
- The anti-tumour activity of inotuzumab ozogamicin was demonstrated in B cell ALL and lymphoma xenografts in immunocompromised mice, including large and small SC implanted tumours as well as in systemically disseminated tumour models. Neither unconjugated inotuzumab nor the unconjugated calicheamicin had any anti-tumour activity.
- In tissue cross reactivity studies, in addition to staining human tissues with known CD22 expression, inotuzumab also stained the stromal fibres in the dermis of the skin, mammary gland, and uterine cervix of humans. The clinical significance of this is uncertain, but it may indicate the potential for additional off target toxicity in these tissues.

- Safety pharmacology studies assessed effects on the cardiovascular, respiratory and central nervous systems. No adverse effects were seen on CNS or respiratory function in rats. Increases in mean blood pressure in conscious cynomolgus monkeys were toxicologically insignificant. No significant inhibition of hERG K+ channel tail current by N-acetyl-Ɣ-calicheamicin DMH was observed at clinically-relevant concentrations. Inotuzumab ozogamicin is not predicted to prolong the QT interval in patients.
- Inotuzumab ozogamicin is stable in plasma. The pharmacokinetics of the ADC was characterised by low plasma clearance (1.1 to 1.5 mL/h/kg), an apparent volume of distribution indicating no or limited extravascular distribution, and mean terminal elimination half-life of the order of 50 to 60 h. Plasma clearance in humans was lower than in animals, and the terminal elimination half-life was much longer, most probably due to the additional effect of target-mediated drug disposition. In keeping with this hypothesis, systemic exposures were approximately one third lower in human CD22 positive tumour bearing mice compared with mice without tumours. *N*-Ac-γ-calicheamicin-DMH was approximately 97% bound to proteins in plasma.
- Biotransformation of *N*-Ac-γ-calicheamicin-DMH is primarily non-enzymatic. The main metabolic pathways is reduction at the disulfide moiety that lead to the formation of *N*-Ac-ε calicheamicin, which is of low toxicity. There were no unique human urinary metabolites. In rats, elimination is predominantly the faecal (approximately 80%) following excretion into the bile.
- *N*-Ac-γ-calicheamicin DMH is substrate for P-gp, but not for the BCRP efflux or hepatic uptake transporters. According to the Product Information document, clinically relevant interactions with P-gp inhibitors were not observed. Based on *in vitro* studies, inotuzumab ozogamicin has low potential for interactions with substrates, inhibitors or inducers of CYP450 or UGT drug metabolising enzymes. Similarly, based on *in vitro* studies, at clinically relevant concentrations *N*-Ac-γ-calicheamicin DMH is not expected to inhibit the efflux transporters P-gp, BCRP, bile salt export pump (BSEP), multidrug resistance associated protein (MRP) 2, multidrug and toxin extrusion protein (MATE) 1, and MATE2K, or the uptake transporters OATP1B1, OATP1B3, organic cation transporter (OCT1), organic anion transporter (OAT) 1, OAT3, and OCT2.
- Single and repeat dose toxicity studies were conducted with SD rats and cynomolgus monkeys dosed with inotuzumab ozogamicin by IV bolus for up to 26 weeks (weekly dosing for repeat dose studies). The relative exposures at the highest dose were generally low multiples of the clinical exposure, with the exception of the 4 week monkey study, where the relative exposure was 24. Investigations with N-Ac-γ calicheamicin DMH and *N*-Ac-ε-calicheamicin were also conducted in single and repeat dose studies (up to 6 weeks) in mice, rats and dogs.
- There were no lesions attributable to the antibody itself in the 4 week repeat dose toxicity studies in rats and monkeys. There was limited (10 to 13%) ADA formation in repeat dose studies in rats, and ADAs were not detected in monkeys. One male monkey dosed at 0.73 mg/m^2 in the 26 week study developed a protein losing glomerulonephritis. Renal immune complex deposition associated with ADA formation cannot be ruled out as the underlying cause of this finding. However, in general the toxicity was driven by the calicheamicin component, with evidence of sufficient intracellular uptake and activation of the calicheamicin moiety in non-targeted cells to produce cytotoxic consequences of DNA damage. The major target organs for inotuzumab ozogamicin were the liver, haematolymphopoietic tissues and the male and female reproductive organs, with some effects also observed on the nervous system of rats and the kidney of rats and monkeys.

- Adverse hepatic effects, most notably associated with endothelial injury in monkeys, were seen in rats and monkeys in both the acute and repeat dose toxicity studies, and are likely to represent early stages of hepatic veno-occlusive disease (VOD) in monkeys. Hepatic neoplasia and pre-neoplastic changes were also associated with inotuzumab ozogamicin administration in both species. An increase in proliferative activity and development of pre-neoplastic and neoplastic lesions is likely due to an increased turnover rate in the hepatocyte population and is consistent with genotoxic and cytotoxic effects in the liver. The NOELs for the increased proliferative activity and pre-neoplastic change in the monkey were below 0.15 and 0.9, respectively.
- Acute thrombocytopenia in monkeys appears to be a secondary effect of the liver specific endothelial injury due to the calicheamicin component of the ADC, and is characterised by platelet sequestration, activation and degranulation in this tissue. Decreases in red cell parameters and numbers of white cells, lymphocytes and reticulocytes were associated with decreased hematopoietic cellularity in the bone marrow and lymphoid depletion in the thymus, spleen, lymph nodes, and/or gut-associated lymphatic tissue (GALT). Peripheral blood lymphocyte immune-typing in rats indicated that the effect of inotuzumab ozogamicin was consistent with a differential effect of DNA damaging agents on major lymphocyte subsets, with the most pronounced effect on B lymphocytes.
- Based on the development of irreversible peripheral and central axonal degeneration in the 4 week repeat dose study in rats, there may be a potential for peripheral neuropathy with clinical use of inotuzumab ozogamicin. While this is most likely due to the cytotoxic component of the ADC, there was a low incidence of axonal degeneration seen in the protein control group, but not in the saline controls.
- Adverse male reproductive organ effects included decreased testicular weights, testicular degeneration, hypospermia, and prostatic and seminal vesicle atrophy. Testicular degeneration and hypospermia were non-reversible following a 4 week non-dosing period. Effects in females included decreased ovarian and uterine weights, and ovarian and uterine atrophy. In the chronic studies of 26 weeks duration, adverse effects on reproductive organs occurred at ≥ 0.07 mg/m^2 in male rats and at 0.73 mg/m^2 in female monkeys (approximately 0.1 and 4 times the exposure in patients at the maximum recommended dose, based on AUC, respectively).
- Consistent with the known effects of N-acetyl-ϒ-calicheamicin DMH on DNA, inotuzumab ozogamicin was clastogenic in the *in vivo* mouse micronucleus assay. Although the ADC was negative in the Ames test at the maximum feasible dose, *N*-acetyl-ϒ-calicheamicin DMH was mutagenic in this assay and was also found to be clastogenic in an *in vitro* micronucleus assay. Carcinogenicity studies with inotuzumab ozogamicin are not required, and none were conducted. The NOEL for pre-neoplastic liver findings in the monkey was 0.22 mg/m^2, (relative exposure 0.9). In the rat, the LOEL for pre-neoplasia of 0.073 mg/m^2 was approximately 0.1 times the clinical AUC. Increased proliferative activity was only partially reversible in the 4 week repeat dose study in rats.
- There were increased resorptions and reduced numbers of viable embryos in rats and rabbits following daily IV dosing of in fertility and embryofetal development studies. In rats, a maternally toxic dose of 0.109 mg/m^2/day was fetotoxic, resulting in fetal growth retardation and delayed skeletal ossification. Slight fetal growth retardation in rats also occurred at 0.036 mg/m^2/day (approximately 0.5 times the human clinical exposure based on AUC). In rabbits, increased resorptions and fetal growth retardation were associated with maternal dosing during organogenesis at the 0.436 mg/m^2 dose level.

- Based on the adverse effects on male and female reproductive organs (see above), female and male fertility is likely to be impaired by treatment with inotuzumab ozogamicin.
- Inotuzumab ozogamicin showed no phototoxic potential *in vitro*. There was no evidence of haemolytic potential, methaemoglobin formation or protein precipitation in blood compatibility assays in rats, monkeys and humans.

Conclusions and recommendation

- There were no major deficiencies in the nonclinical dossier. However, owing to a lack of cross-species specificity, the nonclinical species are only able to provide information on non-target mediated effects of the ADC.
- The primary pharmacology studies provide evidence supporting the proposed mechanism of action and potential efficacy in the treatment of human B cell malignancies.
- No clinically relevant hazards were identified in the safety pharmacology studies. In tissue cross-reactivity studies inotuzumab unexpectedly stained the stromal fibres in the dermis of the skin, mammary gland, and uterine cervix of humans. The clinical significance of this is uncertain, but it may indicate the potential for additional off target toxicity in these tissues.
- Important toxicities included hepatic endothelial injury (likely to represent early stages of hepatic VOD), hepatic neoplasia and pre-neoplasia, thrombocytopenia (secondary to hepatic endothelial toxicity), irreversible peripheral and central axonal degeneration and toxicity to haematolymphopoietic, male and female reproductive and renal tissues. These effects are all considered to be of clinical significance.
- Inotuzumab ozogamicin and its DNA reactive cytotoxic component are mutagenic and clastogenic, and may pose a carcinogenic hazard.
- The nonclinical pharmacology and toxicology data are adequate to support the approval of inotuzumab ozogamicin for the proposed indication.

The nonclinical evaluator also made recommendations with regard to the draft PI however these are beyond the scope of the AusPAR.

V. Clinical findings

A summary of the clinical findings is presented in this section.

Introduction

Inotuzumab ozogamicin is a CD22-targeted antibody-drug conjugate (ADC). The antibody, inotuzumab, is a humanised immunoglobulin G, subtype 4 (IgG4), which specifically recognises human CD22. The small molecule, N-acetyl (N-Ac)-γ-calicheamicin dimethylhydrazide (DMH), is a cytotoxic semisynthetic natural product that the sponsor states is significantly more potent than conventional cytotoxic chemotherapeutic agents. N-Ac-γ-calicheamicin DMH is covalently attached to the antibody via an acid-cleavable linker.

The dosage form is inotuzumab ozogamicin (rch) 1 mg powder for injection vial. After reconstitution with 4 mL of sterile water for injection, 1 mL of solution contains 0.25 mg inotuzumab ozogamicin.

Dosage and administration

The dosage and administration instructions for inotuzumab ozogamicin are set out in the draft PI (Section: *Dosage and Administration*). The key features are as follows:

- Besponsa should be administered in 3 to 4 week cycles.
- Recommendations are provided relating to cytoreduction therapy prior to the first dose for patients with circulating lymphoblasts. Recommendations are also provided for pre-medication with a corticosteroid, antipyretic and antihistamine.
- For patients proceeding to human stem cell transplant (HSCT), the recommended duration of treatment is 2 cycles. A third cycle should be considered for those patients who do not achieve a complete response (CR) or a complete response with incomplete haematologic recovery (CRi) and minimal residual disease (MRD) negativity after 2 cycles. For patients not proceeding to HSCT after achieving a CR or CRi and MRD negativity, additional cycles of treatment up to a maximum of 6 cycles may be administered. Patients who do not achieve a CR or CRi within 3 cycles should discontinue treatment. The recommended dosing regimens are summarised below in Table 6.

Table 6: Dosing regimen for Cycle 1 and subsequent cycles depending on response to treatment

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

Abbreviations: CR=complete remission; CRi=complete remission with incomplete haematologic recovery.
a. ± 2 days (maintain minimum of 6 days between doses).
b. Dose is based on the patient's body surface area (m^2).
c. For patients who achieve a CR or a CRi, and/or to allow for recovery from toxicity, the cycle length may be extended up to 28 days (i.e., 7-day treatment-free interval starting on Day 21).
d. CR is defined as <5% blasts in the bone marrow and the absence of peripheral blood leukaemic blasts, full recovery of peripheral blood counts (platelets ≥100 × 10^9 /L and absolute neutrophil counts [ANC] ≥1 × 10^9 /L) and resolution of any extramedullary disease.
e. CRi is defined as <5% blasts in the bone marrow and the absence of peripheral blood leukaemic blasts, incomplete recovery of peripheral blood counts (platelets <100 × 10^9 /L and/or ANC <1 × 10^9 /L) and resolution of any extramedullary disease.
f. 7-day treatment-free interval starting on Day 21.

Information on the condition being treated

Acute lymphatic leukaemia (ALL) is a heterogeneous haematological disorder characterised by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood and other organs. The clinical presentation of ALL and the signs and symptoms of recurrence are typically nonspecific, and may include fatigue, lethargy, constitutional symptoms (fevers, night sweats, and weight loss), dyspnoea, dizziness, infections, and easy bruising or bleeding. The presence of lymphadenopathy and hepatosplenomegaly on physical examination is found in approximately 20% of patients. The initial diagnosis of ALL requires demonstration of ≥ 20% bone marrow lymphoblasts.

The following data relating to the incidence of ALL has been taken from the Clinical Overview of the dossier and is based on US and European patients. However, it is considered that the data are applicable to the Australian population.

ALL represents approximately 20% of leukaemias among adults and 80% of acute leukaemias in children. The age adjusted incidence rate (2008 to 2012) of ALL in the United States (US) was 1.7 per 100,000 individuals per year, with males having a slightly higher overall rate than females (1.9/100,000 versus 1.5/100,000, respectively). In Europe, the crude incidence rate of ALL is 1.3 per 100,000 individuals. The B cell subtype accounts for approximately 75% of ALL cases in adults and approximately 88% of cases in children.

The peak incidence of ALL is in children between the ages of 0 and 4 years. The median age of diagnosis for ALL is 14 years, with approximately 58% of patients diagnosed before the age of 20 years. By contrast, approximately 26% of cases are diagnosed after 45 years of age, and approximately 11% of patients are diagnosed after 65 years of age.

Overall, approximately 20% to 30% of adult patients with ALL are Philadelphia chromosome-positive (Ph+), with the incidence exceeding 50% in patients aged 50 years or older. B cell ALL is frequently a fatal disease in adults. While the cure rates and survival outcomes for B cell ALL have improved during the last several decades, most of the improvements have occurred in younger patients, primarily among children.

Known prognostic factors associated with poor outcome after combination chemotherapy include older age, higher white blood cell (WBC) count at original diagnosis, certain cytogenetic features (for example, Ph+ or translocation (4;11)) and response to prior therapy (for example, salvage status, duration of response and persistent minimal residual disease). Overall, older adult patients have the poorest outcome, with a 5 year overall survival (OS) rate of 24.1% for patients aged 40 to 59 years and 17.7% for patients aged 60 to 69 years. Outcomes are worse in relapsed or refractory patients, with a median survival in adults of only 3 to 6 months.

The sponsor's information on the condition being treated is considered to be acceptable. Recent Australian specific data from the Australian Institute of Health and Welfare (AIHW, 2017) indicates that in 2013 there were 348 cases of ALL diagnosed in Australia with an age standardised incidence rate of 1.5/100,000 persons, with the risk being greater in males than in females (1.6/100,000 versus 1.4/100,000, respectively). The highest incidence rate was in children aged 0 to 4 years (6.8/100,000). In patients aged > 20 years, the incidence rate was higher in patients aged ≥ 65 years than in patients aged < 65 years. In patients aged ≥ 65 years categorised by age group, the incidence rates per 100,000 persons were 1.4 for patients aged 65 to 69 years, 1.1 for patients aged 70 to 74 years, 1.5 for patients aged 75 to 79 years, 2.7 for patients aged 80 to 84 years and 1.0 for patients aged 85+. In patients aged ≥ 20 years to < 65 year, the highest age specific incidence rate was in patients aged 50 to 54 years (0.9/100,000 persons). In 2014, the crude mortality rate for ALL was 0.4/100,000 persons, with the highest rates being in patients aged ≥ 55 years (0.5 to 1.8 per 100,000 persons). The mortality rates for both males and females declined in parallel from about 1980 to 2014. There were no Australian data based on the subtypes of ALL in the AIHW report.

Current treatment options

Treatment of relapsed or refractory ALL is still a major clinical challenge and there is no universally accepted treatment protocol for these patients. The European Society for Medical Oncology (ESMO) guidelines (2016) for the treatment of relapsed or refractory leukaemia in adults recommends that clinical evaluation should take into account disease specific factors (BCP-ALL, T-ALL, *ABL1* status), patient factors (age, performance status, organ function, and presence of extramedullary disease, in particular CNS disease),

previous therapy (with particular reference to prior allograft, anthracycline dose) and specific toxicities of prior treatment which might guide therapeutic selection (for example, osteonecrosis, vinca alkaloid neuropathy, and specific infectious complications such as fungal infections).[28]

The ESMO guidelines (2016) indicate that allogeneic SCT is the only known curative option for patients with ALL and that treatment of the disease with a curative aim involves achievement of CR followed by allogeneic SCT. The guidelines refer to published data from four large trials indicating that the rate of second CR in patient with relapsed disease was 44% to 45%, and that the median OS in these patients was 4.5 to 8.4 months. The guidelines refer to published data showing that following long duration of first CR (> 2 years) re-induction with a standard induction regimen (such as used for original treatment) may be used for patients who have relapsed. The guidelines comment that short first CR or primary refractory disease is a very high risk situation, and consideration should immediately be given to the availability of trials with novel agents to which the disease might be non-resistant.

The Summary of Efficacy of the submitted dossier outlines various treatment regimens for the treatment of relapsed or refractory ALL.

1. Treatment of relapsed or refractory Philadelphia-chromosome negative (Ph-) B cell ALL: There is no single, generally accepted, standard of care regimen. Treatment typically includes a variety of induction regimens. Commonly used regimens include: (1) therapies based on a backbone of vincristine, corticosteroids, and anthracyclines; (2) hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, and methotrexate and cytarabine (Hyper-CVAD); (3) cytarabine based regimens such as high-dose cytarabine (HIDAC), fludarabine plus cytarabine plus granulocyte-colony stimulating factor (FLAG) ± idarubicin, or mitoxantrone (mitoxantrone not approved in Australia for ALL) plus cytarabine (MXN/Ara-C); and (4) clofarabine (approved in Australia only for paediatric patients) or methotrexate based regimens. In addition, blinatumomob can also be used for the treatment of patients with Ph-negative B cell ALL.
2. Treatment or relapsed or refractory Ph-positive (Ph+) B cell ALL: Treatment typically includes TKIs. The ESMO guidelines recommend that patients with relapsed Ph+ B cell ALL should be offered treatment with the new generation of TKIs, according to the results of mutational analysis of their breakpoint cluster region Abelson *(BCR-ABL1)* transcripts. The guidelines comment that 'although TKIs are not without adverse events; they are, nonetheless a vastly superior option compared with repetitive treatment with myelosuppressive chemotherapy, as they preserve performance status and are better tolerated by elderly patients'. The guidelines note that there is no evidence that TKIs induce long-term survival post-relapse and that the majority of patients will require allogeneic SCT.

Clinical rationale

In its covering letter for the submission the sponsor states that 'inspite of many advances in the field of leukaemia during the past two decades, ALL remains a frequent cause of morbidity and mortality throughout the world'.

The sponsor's rationale, which is based on the significant morbidity and mortality of the disease and lack of chemotherapeutic options, is considered to be acceptable.

[28] Hoelzer D et al, 2016 Acute lymphoblastic leukaemia in adult patients: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* 2016; 27 (Supplement 5):69-82.

Formulation

The inotuzumab ozogamicin dosage strength proposed for registration is 1 mg/mL. The manufacturing process was modified from a 4 mg/vial to a 1 mg/vial dosage strength for commercial use, in part to minimise drug product wastage.

Most patients in the clinical studies received inotuzumab ozogamicin using the 4 mg/vial dosage strength rather than the 1 mg/vial dosage strength intended for commercial use. Of the 164 patients randomised to the inotuzumab ozogamicin treatment arm of Study B1931022 (the pivotal Phase III study in patients with ALL), 15 (9.1%) patients received study therapy with the 1 mg/vial dosage form of inotuzumab ozogamicin. In the supportive Phase I/II study (B1931010) in patients with ALL, all patients received inotuzumab ozogamicin with the 4 mg/vial dosage form.

Contents of the clinical dossier

The clinical dossier included a comprehensive data package for evaluation of inotuzumab ozogamicin for the proposed indication. The clinical studies included 11 sponsor-sponsored clinical trials including 1 pivotal Phase III study in patients with ALL (Study B1931022), 1 supportive Phase I/II studies in patients with ALL (Study B1931010) and 9 studies in patients with non-Hodgkin's lymphoma (NHL). There were no data in healthy volunteers. The clinical dossier was well presented and contrained the following:

- 2 sponsor-sponsored studies in patients with ALL. The data for the pivotal Phase III study included an original clinical study report (CSR), a supplementary CSR (sCSR), a Day 120 Safety Update, and an updated overall survival analysis with data as of the last subject last visit (LSLV) of 4 January 2017.
- 9 sponsor-sponsored clinical trials in patients with NHL.
- 1 population pharmacokinetic (popPK) report for ALL and NHL and a supplement to this report.
- 6 pharmacodynamic (PD) and pharmacokinetic (PK) PK/D studies providing concentration QTc analysis in patients with NHL, PK/PD analyses of QT intervals in patients with ALL and NHL, PK/PD analyses of the effects of exposure on safety and efficacy, and popPK exposure response efficacy modelling (OS and progression-free survival (PFS)) in patients with ALL.
- Safety data from investigator initiated studies (IIR).
- Safety data from compassionate use (CU) programs.
- Integrated summary of clinical efficacy, cluster terms for analysis of safety, summary of clinical safety, Day 120 safety update appendices 1 and 2.
- Reports of bioanalytical and analytical methods for the human studies.
- Literature references.

Paediatric data

No paediatric data were included in the clinical dossier. The sponsor has an agreed European Paediatric Investigation Plan (PIP), which includes a waiver for submitting data in a paediatric population from birth to less than 1 year on the grounds that the specific medicinal product does not represent a specific therapeutic benefit over existing treatments, and a deferral for starting studies in patients aged 1 to less than 18 years. The European Paediatric Committee decided that the first paediatric study should start as soon as a favourable benefit-risk relationship has been established in a controlled study in adults with ALL (Study B1931022).

The sponsor is exempt from the requirement to submit paediatric data in the USA as inotuzumab ozogamicin is designated as an orphan drug for the treatment of B cell ALL in that jurisdiction.

The lack of paediatric data is acceptable at this stage. However, the sponsor is requested to update the TGA on progress towards undertaking paediatric studies with inotuzumab ozogamicin for the treatment of ALL.

Good clinical practice

The sponsor states the studies were conducted in compliance with Good Clinical Practice (GCP) guidelines.

Pharmacokinetics

Studies providing pharmacokinetic data

The submission included 11 sponsor sponsored clinical studies comprising 2 studies in patients with acute lymphoblastic leukaemia (ALL) and 9 studies in patients with non-Hodgkin's lymphoma (NHL). All 11 clinical studies included PK information for inotuzumab ozogamicin. The 11 clinical studies with PK information are summarised in Table 7.

Table 7: Completed sponsor-sponsored clinical studies with pharmacokinetic information

Study Number (Former Wyeth Study Number [If Applicable])	Title	Dosage and Regimen (n; Treated)
Patients With Relapsed or Refractory ALL Who Received Inotuzumab Ozogamicin		
B1931022	An open-label, randomized, Phase 3 study of inotuzumab ozogamicin compared with a defined investigator's choice in adult patients with relapsed or refractory CD22-positive acute lymphocytic leukemia	• Arm 1 (n=164)[a]: Inotuzumab ozogamicin: 1.8 mg/m^2/21-28-day per cycle (0.8 mg/m^2 on Day 1 and 0.5 mg/m^2 on Days 8 and 15); subsequent reduction to 1.5 mg/m^2/28-day cycle (0.5 mg/m^2 on Days 1, 8, and 15) for patients achieving remission. • Arm 2 (n=162)[b]: FLAG, cytarabine plus mitoxantrone, or high dose cytarabine[c]
B1931010	An open-label, Phase 1/2 study of inotuzumab ozogamicin in subjects with relapsed or refractory CD22-positive acute lymphocytic leukemia	• Phase 1 (n = 37) Inotuzumab ozogamicin: 1.2 mg/m^2/28-day cycle (0.8 and 0.4 mg/m^2 on Days 1 and 15; n = 3), 1.6 mg/m^2/28-day cycle (0.8, 0.4, and 0.4 mg/m^2 on Days 1, 8, and 15; n = 12), or 1.8 mg/m^2/28-day cycle (0.8, 0.5, and 0.5 mg/m^2 on Days 1, 8, and 15; n = 22) • Phase 2 (n = 35) Inotuzumab ozogamicin: 1.8 mg/m^2/28-day cycle (0.8 mg/m^2 on Day 1 and 0.5 mg/m^2 on Days 8 and 15)
Patients With Relapsed or Refractory NHL Who Received Inotuzumab Ozogamicin		
B1931002 (3129K1-100-WW)	A Phase 1 study of inotuzumab ozogamicin administered as a single agent in subjects with B-cell NHL	• Part 1 (n = 30) Inotuzumab ozogamicin 0.4 mg/m^2/q3w (n = 2) 0.8 mg/m^2/q3w (n = 5) 1.34 mg/m^2/q3w (n = 11) 1.8 mg/m^2/q3w (n = 6) 2.4 mg/m^2/q3w (n = 6) • Part 2 (n = 49) Inotuzumab ozogamicin 1.8 mg/m^2/q4w
B1931016 (3129K1-103-JA)	A Phase 1 study of inotuzumab ozogamicin administered as a single agent in subjects with B-cell NHL	Inotuzumab ozogamicin 1.3 mg/m^2/q4w (n = 3) 1.8 mg/m^2/q4w (n = 10)
B1931007 (3129K7-2001-WW)	A Phase 2 study of inotuzumab ozogamicin in subjects with indolent NHL that is refractory to or has relapsed after rituximab and chemotherapy or radioimmunotherapy	Inotuzumab ozogamicin 1.8 mg/m^2/q4w (n = 81)

Table 7 (continued): Completed sponsor-sponsored clinical studies with pharmacokinetic information

Study Number (Former Wyeth Study Number [If Applicable])	Title	Dosage and Regimen (n; Treated)
Patients With Relapsed or Refractory NHL Who Received Inotuzumab Ozogamicin in Combination With Rituximab		
B1931005 (3129K3-1104-JA)	A Phase 1 study of inotuzumab ozogamicin administered in combination with rituximab in subjects with B-cell NHL	Inotuzumab ozogamicin 1.8 mg/m^2 on Day 2 of a q4w, plus Rituximab 375 mg/m^2 on Day 1 of a q4w (n = 10)
B1931004 (3129K3-101-WW)	A Phase 1/2 study of inotuzumab ozogamicin administered in combination with rituximab in subjects with follicular or diffuse large B-cell NHL	Inotuzumab ozogamicin 0.8 mg/m^2 on Day 2 of a q4w (n = 5) 1.3 mg/m^2 on Day 2 of a q4w (n = 3) 1.8 mg/m^2 on Day 2 of a q4w (n = 111), plus Rituximab 375 mg/m^2 on Day 1 of a q4w
B1931001 (3129K5-2005-WW)	An open-label, single-arm, Phase 2 study of inotuzumab ozogamicin plus rituximab in subjects with relapsed/refractory CD22-positive diffuse large B-cell lymphoma, eligible for autologous stem cell transplantation	Inotuzumab ozogamicin 1.8 mg/m^2 on Day 2 of a q3w, plus Rituximab 375 mg/m^2 on Day 1 of a q3w (n = 61)
B1931006 (3129K4-3301)	An open-label, randomized, Phase 3 study of inotuzumab ozogamicin administered in combination with rituximab compared to a defined investigator's choice therapy in subjects with relapsed or refractory, CD22-positive, follicular B-cell NHL	• Arm 1 (n = 15): Inotuzumab ozogamicin: 1.8 mg/m^2 on Day 2 of a q4w, plus Rituximab: 375 mg/m^2 on Day 1 of a q4w • Arm 2 (n = 13)[d]: R-CVP or R-FND
B1931008 (3129K5-3303-WW)	An open-label, randomized, Phase 3 study of inotuzumab ozogamicin administered in combination with rituximab compared with defined investigator's choice therapy in subjects with relapsed or refractory CD22-positive aggressive NHL who are not candidates for intensive high-dose chemotherapy	• Arm A: (n = 164): Inotuzumab ozogamicin: 1.8 mg/m^2 on Day 2 of a q4w, plus Rituximab: 375 mg/m^2 on Day 1 of a q4w • Arm B (n = 167)[e]: Rituximab plus bendamustine or rituximab plus gemcitabine
[illegible]	[illegible]	[illegible]
B1931003 (3129K2-1105-WW)	An open-label, Phase 1 study of R-CVP or R-GDP in combination with inotuzumab ozogamicin in subjects with CD22-positive NHL	• Arm A (n = 48): Inotuzumab ozogamicin (0.8, 1.3 mg/m^2) + R-CVP[f] • Arm B (n = 55): Inotuzumab ozogamicin (0.8 mg/m^2) + R-GDP[g]

Completed studies are studies for which a clinical study report is available; the study may be ongoing to continue safety follow-up, or in the case of B1931022, continuing to follow patients to assess overall survival.
ALL = acute lymphoblastic leukemia; CR = complete remission; CRi = complete remission with incomplete hematologic recovery; FLAG = fludarabine plus cytarabine plus granulocyte colony-stimulating factor; G-CSF = granulocyte colony-stimulating factor; HIDAC = high-dose cytarabine; n = number of subjects; NHL = non-Hodgkin's lymphoma; OS = overall survival; q3w = every 3 weeks; q4w = every 4 weeks; R-CVP = rituximab in combination with cyclophosphamide, vincristine and prednisone/prednisolone; R-FND = rituximab in combination with fludarabine, mitoxantrone, and dexamethasone; R-GDP = rituximab in combination with gemcitabine and/or cisplatin and dexamethasone.

a. The ITT population included 164 patients (164 treated patients and 109 initially randomized patients for CR/CRi analysis)
b. The ITT population included 162 patients (143 treated patients and 109 initially randomized patients for CR/CRi analysis)
c. Study B1931022 Arm B Investigator's Choice: FLAG (2.0 g/m^2/day cytarabine + 30 mg/m^2/day fludarabine + 5µg/kg/day G-CSF) administered for up to 4 cycles (1 cycle was 28 days); cytarabine plus mitoxantrone (12 mg/m^2 mitoxantrone + 200 mg/m^2/day cytarabine) administered for up to 4 cycles (1 cycle was 15 to 20 days); HIDAC (3 g/m^2 cytarabine) administered for up to 12 doses.
d. Study B1931006 Arm 2 Investigator's Choice: R-CVP (rituximab [375 mg/m^2] on Day 1, cyclophosphamide [750 mg/m2] on Day 1, vincristine [1.4 mg/m^2] on Day 1, and oral prednisone [40 mg/m^2] on Days 1 to 5) or R-FND (rituximab [375 mg/m^2] on Day 1, mitoxantrone [10 mg/m^2] on Day 2, fludarabine [25 mg/m^2] on Days 2 to 4, and oral dexamethasone [20 mg/day] on Days 1 to 5). The sequence for Arm 2 was repeated every 21 days.
e. Study B1931008 Arm 2 Investigator's Choice: Rituximab + bendamustine (rituximab [375 mg/m^2] on Day 1 of each cycle + bendamustine [120 mg/m^2] on Days 1 and 2 of each cycle every 28 days) or rituximab + gemcitabine (rituximab [375 mg/m^2] on Days 1, 8, 15 and 22 of Cycle 1 and on Day 1 for all other cycles + gemcitabine [1000 mg/m^2] on Days 1, 8 and 15 of each cycle every 28 days).
f. R-CVP: Rituximab (375 mg/m^2), cyclophosphamide (375, 550, or 750 mg/m^2), vincristine (1.4 mg/m^2), and prednisone (40 mg/m^2); rituximab, cyclophosphamide, and vincristine on Day 1, inotuzumab ozogamicin on Day 2, and prednisone on Days 1 to 5 of each 21-day cycle for a maximum of 6 cycles.
g. R-GDP: Rituximab (375 mg/m^2), gemcitabine (500 and 1000 mg/m^2) and/or cisplatin (37.5, 50, and 75 mg/m^2), dexamethasone (40 mg); rituximab, gemcitabine, and cisplatin on Day 1, inotuzumab ozogamicin on Day 2, and dexamethasone on Days 1 to 4 of each 21-day cycle for a maximum of 6 cycles.

There were no PK studies in healthy subjects. All PK information for inotuzumab ozogamicin is derived from patients with ALL or NHL. This is considered to be acceptable given that the proposed product for registration contains a cytotoxic product. The proposed PI states that '*inotuzumab ozogamicin was clastogenic in vivo in the bone marrow of male mice that received single doses ≥ 1.14 mg/m^2. This is consistent with the known induction of DNA breaks by calicheamicin and other enediyne antitumour antibiotics*'.

Single agent inotuzumab ozogamicin was administered in the 2 studies in patients with ALL (Study B1931022 (Phase III, pivotal); Study B1931010 (Phase I/II, supportive)). In these studies, the concentration of inotuzumab ozogamicin and unconjugated calicheamicin in serum were measured using validated high-performance liquid chromatography with tandem mass spectrometry (HPLC/MS/MS) methods. The dose amount of inotuzumab ozogamicin was calculated based on total protein as reported on the vials. The molecular ratio of ADC versus total protein is close to 1 (1.076). Therefore, for studies which utilised the HPLC/MS/MS analysis for inotuzumab ozogamicin reference was to either total protein or inotuzumab ozogamicin. The quantitation range based on HPLC/MS/MS was 1.00 to 500 ng/mL for inotuzumab ozogamicin and 0.0500 to 10.0 ng/mL for unconjugated calicheamicin.

In the 9 studies in patients with NHL, single agent inotuzumab ozogamicin was administered in 3 studies (Studies B1931002, B1931016, and B1931007), inotuzumab ozogamicin in combination with rituximab was administered in 5 studies (Studies B1931001, B1931004, B1931005, B1931006, and B1931008), and inotuzumab ozogamicin in combination with rituximab and chemotherapy was administered in 1 (Study B1931003). In the clinical studies in patients with NHL, concentrations of inotuzumab ozogamicin, unconjugated calicheamicin, total calicheamicin (that is, unconjugated plus conjugated calicheamicin), and total antibody in serum were measured using enzyme-linked immunosorbent assay (ELISA) methods. In the clinical studies in patients with NHL where inotuzumab ozogamicin was administered in combination with rituximab, an additional assessment was performed for detection of anti-rituximab antibodies using an ELISA.

In the two ALL studies, anti-drug antibodies (ADA) to inotuzumab ozogamicin were identified using a bridging electrochemiluminescence (ECL) assay. In the ALL studies, patients who tested positive for ADA were also tested for the presence of neutralising antibodies (nAbs) to inotuzumab ozogamicin using a cell-based assay. In the nine NHL studies, ADAs to inotuzumab ozogamicin were identified using an ELISA method. In the NHL studies, patients who tested positive for ADAs were not tested for the presence of nAbs as the assay was no available at the time these studies were conducted.

Population pharmacokinetic (popPK) analyses

In addition to the PK data from the individual studies in patients with ALL and NHL the submission also included two related popPK analyses. The initial popPK analysis (Report PMAR-EQDD-B193a-DP4-202) provided an integrated analysis of pooled data from 736 patients, comprising 205 patients with relapsed or refractory ALL (from the 2 ALL studies referred to above) and 531 patients with relapsed or refractory NHL (from the 9 NHL studies referred to above). The supplemental popPK analysis (Report MAR-EQDD-B193a-DP4-202-Supplement) provided an updated integrated analysis including data from an additional 29 patients with ALL from Study B1931022. Therefore, the supplemental popPK analysis included pooled data from a total of 765 patients comprising 234 patients with ALL and 531 patients with NHL.

Evaluator's conclusions on pharmacokinetics

- Inotuzumab ozogamicin is an antibody drug conjugate (ADC). The ADC consists of 3 components:
  - the recombinant humanised IgG4 kappa antibody inotuzumab, specific for human CD22;
  - the cytotoxic agent N-acetyl-gamma-calicheamicin that causes DNA double strand-breaks; and
  - an acid cleavable linker composed of the condensation product of 4-(4'-Acetylphenoxy)butanoic acid, a bifunctional linker (AcBut) and 3-methyl-3-mercaptobutane hydrazide (known as dimethylhydrazide) that covalently attaches N-acetyl-gamma-calicheamicin to inotuzumab.
- Validated HPLC/MS/MS methods were used to measure inotuzumab ozogamicin and unconjugated calicheamicin in serum from patients with relapsed or refractory ALL. Unconjugated calicheamicin levels were generally below the lower limit of quantitation (LLOQ) of the assay (50 pg/mL) following the inotuzumab ozogamicin treatment regimen proposed for patients with relapsed or refractory ALL (Study B1931022). Therefore, meaningful investigation of the clinical (*in vivo*) pharmacokinetics of the cytotoxic moiety of the ADC in humans was precluded. Validated ELISA methods were used to measure inotuzumab ozogamicin, total antibody, total calicheamicin, and unconjugated calicheamicin in serum pharmacokinetic samples from patients with relapsed or refractory NHL.
- The pharmacokinetics of inotuzumab ozogamicin are complex and have been reasonably well characterised based on data from patients with relapsed or refractory ALL (2 studies) or NHL (9 studies). In addition to PK data from the 11 individual clinical studies, pooled PK data were also available from an initial popPK analysis in 736 patients (ALL (n = 205), 2 studies; NHL (n = 531), 9 studies), with 7911 PK observations for inotuzumab ozogamicin and a supplemental popPK analysis including 29 additional patients with ALL. There were no PK data in healthy subjects. This is considered to be acceptable given that calicheamicin is a cytotoxic agent reported to cause DNA double strand-breaks.
- The popPK analysis demonstrated that the pharmacokinetics of inotuzumab ozogamicin were well characterised using a 2-compartment model with both linear clearance (time independent) and time-dependent clearance. Time dependent clearance predominates at the start of treatment, but its contribution to total clearance declines over time. At steady state (approximately Cycle 4), linear clearance predominates. Time dependent clearance results in increased exposure being observed over the first 3 to 4 treatment cycles (that is, clearance decreases with time), with steady state exposure being achieved after 3 to 4 cycles (that is, clearance becomes linear). The time dependent component of clearance for inotuzumab ozogamicin is consistent with target mediated drug disposition, with clearance decreasing and exposure increasing as the available receptors become saturated over the first 3 to 4 treatment cycles.
- There were no absorption studies as inotuzumab ozogamicin is administered via IV infusion. Only one strength is being proposed for registration (1 mg/ vial). In the clinical studies in patients with ALL and NHL vial strengths of 1, 3, and 4 mg/vial were used. The most commonly used strength was 4 mg/vial. No clinical bioequivalence studies were submitted comparing the three vial strengths used in the clinical program. However, such studies are not required as all strengths are administered by the IV route and, therefore, by definition are each 100% bioavailable. The sponsor

reports that an analytical study demonstrated comparability between the 1 mg/vial in a 20 mL vial and the 4 mg/vial in a 20 mL vial.

- After the first dose of 0.8 mg/m^2 on Day 1 in patients (n = 128) with relapsed or refractory ALL (Study B1931022), mean (standard deviation (SD)) inotuzumab ozogamicin concentration at the end of the 1 hour infusion (C_{max}) was 211 (232) ng/mL. The inter-subject variability for the C_{max} was high following the first dose, with a mean coefficient of variance (CV) of 110%. The mean (SD) simulated area under the concentration-time curve within the first dosing interval of 7 days (AUC_{tau}) for inotuzumab ozogamicin following the first 0.8 mg/m^2 dose was 4330 (2140) ng·h/mL, based on data from the supplemental popPK analysis for the two ALL studies; Studies B1931022 and B1931010.
- Steady-state exposure to inotuzumab ozogamicin was achieved by Cycle 4 in patients with relapsed or refractory ALL. In Study B1931022, the mean (SD) observed at the end of the 1 hour infusion (C_{max}) on Cycle 4 Day 1 was 308 (362) ng/mL, and pre-dose serum concentration (C_{trough}) was 57.9 (29.8) ng/mL on Cycle 4 Day 1. The inter-subject variability for the C_{max} was still high at steady state (Cycle 4, Day 1), with mean CV% of 118%. The mean (SD) simulated AUC_{tau} at steady state in Cycle 4 Day 1 was 29,500 (9430) ng·h/mL, based on data from the supplemental popPK analysis for the two ALL studies; Studies B1931022 and B1931010.
- The accumulation ratio ($AUC_{cycle\ 4}/AUC_{cycle\ 1}$) for inotuzumab ozogamicin was 5.30 (90% confidence interval (CI): 5.12, 5.47), based on simulated concentration data from the supplemental popPK analysis for the two ALL Studies B1931022 and B1931010 for the recommended dosing regimen of inotuzumab ozogamicin at a total dose of 1.8 g/m^2 per 21 to 28 day cycle (0.8 mg/m^2 on Day 1, and 0.5 mg/m^2 on Days 8 and 15).
- In general, PK parameters across the individual ALL and NHL studies showed moderate to high inter-subject variability. The pooled data for the two ALL studies showed that inter-individual variability for C_{max} was greater following single dose (CV = 172%) compared to multiple dose (CV = 113%), as was inter-subject variability (CV%) for C_{trough} (157% (single dose) versus 101% (multiple dose)).
- In the NHL Studies B1931002 and B1931016, inotuzumab ozogamicin was administered at single doses of 0.4, 0.8, 1.34, 1.8, and 2.4 mg/m^2 and 1.3 and 1.8 mg/m^2, respectively. Using the C_{max} and AUC_{inf} data from these two NHL studies, power models were applied to test dose proportionality for each component of inotuzumab ozogamicin. The increase in C_{max} appeared to be less than dose proportional for inotuzumab ozogamicin, total calicheamicin and total antibody within the single dose range of 0.4 to 2.4 mg/m^2. The increase in AUC_{inf} appeared to more than dose proportional for total calicheamicin and total antibody over the single dose, dose range of 0.4 to 2.4 mg/m^2, while dose ranging data for AUC_{inf} were not available for inotuzumab ozogamicin. There were no single dose proportionality assessments in patients with ALL.
- In the NHL Study B1931002, inotuzumab ozogamicin administered as multiple doses of 0.4 (n = 2), 0.8 (n = 8), 1.34 (n = 11), 1.8 (n = 6), and 2.4 (n = 6) mg/m^2 Q3W for 3 and 4 week treatment cycles were administered in Part 1 of the study (dose escalation). Using C_{max} and AUC_{tau} data, power models were applied to test dose proportionality for each component of inotuzumab ozogamicin. The increase in C_{max} appeared to be less than dose proportional for inotuzumab ozogamicin and total antibody, but appeared dose proportional for total calicheamicin within the dose range of 0.4 to 2.4 mg/m^2 Q3W. The increase in AUC_{tau} appeared to be greater than dose proportional for total antibody, but appeared to be dose proportional for total calicheamicin within the dose range of 0.4 to 2.4 mg/m^2 Q3W. There were no multiple-dose proportionality assessments in patients with ALL.

- Based on the popPK analysis, the total volume of distribution of inotuzumab ozogamicin was approximately 12 L. This result indicates that inotuzumab ozogamicin is not significantly distributed to the extravascular tissues.
- Unconjugated calicheamicin was highly bound to plasma proteins in humans (97.2%), with the geometric mean plasma unbound fraction (fu) being 0.0279. Unconjugated calicheamicin demonstrated limited distribution into red blood cell, with a blood-to-plasma partition ratio of 0.71. There was no assessment of protein binding for inotuzumab ozogamicin as such assessments are not applicable to therapeutic proteins.
- The primary metabolic pathway for inotuzumab ozogamicin was hydrolysis (at the hydrazone moiety) to release N-Ac-γ-calicheamicin DMH (that is, unconjugated calicheamicin). The primary metabolic pathway for unconjugated calicheamicin was via non-enzymatic reduction (at the disulfide moiety), with hydrolysis (at the hydrazide moiety), oxidation, and adduction (with pyruvic acid) being minor metabolic pathways. There were no metabolic studies of the inotuzumab monoclonal antibody component of the drug, with clearance of monoclonal antibodies being primarily by catabolism with the resulting amino acids being recycled into other proteins.
- There were no mass balance studies determining the excretion profile of inotuzumab ozogamicin. However, in general such studies are not a requirement for therapeutic proteins as they are primarily cleared by catabolism. In the supplementary popPK analysis, the total clearance of inotuzumab ozogamicin at steady state in patients with ALL (n = 234) was 0.0333 L/h and the terminal elimination half-life (beta t½) was 120 hours (5 days) following the first dose on Day 1 Cycle 1, and 294 hours (12.3 days) at steady state. The slow clearance and long terminal half-life of inotuzumab ozogamicin is typical of large molecular weight therapeutic proteins.
- There were no dedicated clinical studies investigating the PK of inotuzumab ozogamicin in special groups. However, the popPK analysis investigated the effects of a large number of pre-specified covariates on the PK of inotuzumab ozogamicin. The statistically significant covariates identified in the supplemental popPK analysis were:
  - baseline body surface area (BBSA) on linear clearance (CL_1), clearance associated with time-dependent clearance (CL_2), and volume of distribution in the central compartment (V_1);
  - disease and/or bioanalytical methods on CL_1 and the decay co-efficient associated with time dependent clearance (k_{des});
  - absence of concomitant rituximab on CL_1 (relevant for patients with NHL only);and
  - baseline percent of blasts in peripheral blood (BLSTPB) on k_{des} (relevant for patients with ALL only).

  However, the only clinically significant covariate on the PK of patients with ALL was baseline body surface area. The proposed dosage regimen of inotuzumab ozogamicin for the treatment of patients with ALL is based on individual patient BSA, which will account for the impact of BSA on the PK of the drug.
- Based on the supplemental popPK analysis, the covariates of age, gender, racial group, mild hepatic impairment,[29] and renal impairment had no significant effects on the PK of inotuzumab ozogamicin in patients with ALL. However, the data for moderate hepatic impairment was based on 1 patient only and there were no data for patients

[29] Clarification: the data for patients with mild hepatic impairment (B2) was badsed on data from 8 patients.

with severe hepatic impairment, while there were only limited data for patients with renal impairment as most patients had normal renal function (78.6% (184/234))

- There were no dedicated clinical drug-drug interaction (DDI) studies investigating the PK of co-administration of inotuzumab ozogamicin and other medicines. Limited data from the popPK analysis indicated that salvage line and prior radiotherapy had no clinically relevant effects on the PK of inotuzumab ozogamicin. In addition, the popPK analysis showed that concomitant administration of hydroxyurea, granulocyte-colony stimulating factors or P-glycoprotein inhibitors had no clinically relevant effects on inotuzumab ozogamicin clearance.
- There were number of in vitro human biomaterial studies investigating the potential clinical impact of co-administration of inotuzumab ozogamicin and drugs that are substrates for CYP enzymes, UGT enzymes, and transporters. Based on the reported results of these studies, it can be reasonably inferred that inotuzumab ozogamicin and/or unconjugated calicheamicin are unlikely to have clinically significant effects at relevant serum concentrations on drugs that are substrates for CYP enzymes, UGT enzymes, and transporters.
- In patients with relapsed or refractory ALL, anti-drug antibodies (ADAs) at any time (pre- and post-dose) were observed in 7 of 236 patients (3.0%), including 1 (0.4%) patient who exhibited positive ADAs de novo following treatment with inotuzumab ozogamicin. None of the 7 patients with ADAs tested positive for neutralising antibodies using a cell based assay.
- In patients with relapsed or refractory NHL, ADAs at any time (pre- and post-dose) were observed in 27 of 630 patients (4.29%), with no patients demonstrating only a positive post-dose ADA response. There were no data on neutralising antibodies in patients with NHL because the analytical method was not available at the time these studies were conducted.
- In patients with ALL, a post-hoc analysis showed that ADA status had no significant impact on the clearance of inotuzumab ozogamicin. No assessment of the impact of ADA status on efficacy was undertaken due to the limited number of ADA positive patients. An assessment of the effect on all-causality adverse events (AEs) in the 7 ADA positive ALL patients from Study B1931022 was undertaken. However, the number of ADA positive patients is too small to draw clinically meaningful conclusions relating to the impact on safety of ADAs.

Pharmacodynamics

Studies providing pharmacodynamic data

The following six analyses provided PK/PD information:

- PMAR-EQDD-B193a-DP4-205 provided PK/PD analyses of inotuzumab ozogamicin exposure with selected safety (VOD/ sinusoidal obstruction syndrome (SOS); hepatotoxicity; haematoxicity) and efficacy (CR/CRi and MRD) endpoints using pooled data from patients with ALL from Studies B1931010 and B1931022. Individual patient PK parameters estimated from the analysis described in the popPK analysis PMAR-EQDD-B193a-DP4-202 provided the exposure values used in the E-R analysis.
- PMAR-EQDD-B193a-DP4-205-Supplement provided updated PK/PD analyses of inotuzumab ozogamicin exposure for selected safety (VOD/SOS; hepatotoxicity; haematoxicity) and efficacy (CR/CRi and MRD) endpoints using pooled data from patients with ALL from Studies B1931010 and B1931022. Individual patient PK

parameters estimated from the popPK analysis described in PMAR-EQDD-B193a-DP4-202-Supplement provided the exposure values used in the E-R analysis.

- PMAR-EQDD-B193a-Regulatory Response-628 provided PK/PD analyses of ozogamicin exposure with OS and PFS using pooled data from patients with ALL from Studies B1931010 and B1931022.
- PMAR-EQDD-B193c-Other-331, PMAR-EQDD-B193c-Other-332, and PMAR-EQDDB193c- DP4-533 summarised the modelling of QT interval versus concentrations of inotuzumab ozogamicin using data from Study B1931006 (NHL), Study B1931007 (NHL), and from Studies B1931007 (NHL), B1931010 (ALL), and B1931022 (ALL), respectively. Study B1931007 in patients with relapsed or refractory NHL was included in the pooled analysis with the studies in patients with relapsed or refractory ALL to allow assessment of QT data at therapeutic as well as supra-therapeutic concentrations (PMAR-EQDDB193c- DP4-533).

Evaluator's conclusions on pharmacodynamics

Exposure-response (efficacy)

- Exposure based on the average plasma concentration (C_{avg}) of inotuzumab ozogamicin and the percentage of leukaemic blasts that were CD22 positive at baseline were found to be statistically significant predictors of CR/CRi at a significance level of 0.05 (Study PMAR-EQDD-B193a-DP4-205-Supplement). For the same C_{avg} value, the predicted probability of a response was greater in patients with ≥ 90% of CD22 positive leukaemic blasts at baseline compared to patients with < 90% of CD22 positive leukaemic blasts at baseline.
- Exposure based on the C_{avg} of inotuzumab ozogamicin was a statistically significant predictor of MRD negativity, as were baseline cytogenetics and baseline percentage of leukaemic blasts that were CD22 positive (Study PMAR-EQDD-B193a-DP4-205-Supplement).
- In the OS and PFS analyses, with and without censoring for post-study HSCT, inotuzumab ozogamicin C_{avg} was a statistically significant predictor of both OS and PFS affecting the base hazard of both efficacy endpoints (that is, higher C_{avg} increased the probability of both OS and PFS) (Study PMAR-EQDD-B193a-Regulatory Response-628). However, when CR/CRi and MRD were tested as potential prognostic factors affecting OS and PFS, along with the other pre-specified prognostic factors, inotuzumab ozogamicin exposure (C_{avg}) was no longer a statistically significant predictor of either OS or PFS survival. The supplemental popPK analysis identified C_{avg} as statistically significant predictor of CR/CRi and MRD and therefore this exposure metric correlated with these variables.
- Limited data on unconjugated calicheamicin levels in patients with ALL indicate that this exposure metric is not a significant predictor of efficacy (CR/CRi and MRD) (Study PMAR-EQDD-B193a-DP4-205).

Exposure-response (safety)

- Log(cAUCP1) was found to be a statistically significant predictor of VOD/SOS (Hepatic Events Adjudication Board (HEAB) assessed). Increasing cumulative AUC after period 1 (cAUCP1) was associated with an increased risk of VOD/SOS (HEAB assessed), and the risk was significantly greater in patients who received a HSCT during the study compared to patients who did not received a HSCT during the study (Study PMAR-EQDD-B193a-DP4-205-Supplement).
- No statistically significant E-R (safety) relationships were found for neutropenia ≥ 3 Grade or thrombocytopenia ≥ Grade 3. However, a high percentage of the total

population had baseline neutropaenia ≥ Grade 3 or baseline thrombocytopaenia ≥ Grade 3. Therefore, these patients were excluded and the percentage of the remaining population tested in the relevant E-R safety models were 62.8% (142/226) (neutropenia model) and 50.9% (119/234) (thrombocytopenia model) (Study PMAR-EQDD-B193a-DP4-205-Supplement).

- No statistically significant positive exposure-response (safety) relationships were found for elevated alanine aminotransferase (ALT) ≥ Grade 3, elevated AST ≥ Grade 3, elevated bilirubin ≥ Grade 3, hepatic events defined by a pre-specified cluster term, and Investigator reported VOD/SOS (Study PMAR-EQDD-B193a-DP4-205-Supplement).
- Limited data on unconjugated calicheamicin levels in patients with ALL indicate that this exposure metric is not a significant predictor of safety (VOD/SOS; hepatotoxicity, haematological AEs) (Study PMAR-EQDD-B193a-DP4-205).

QTc analysis

- There was no 'thorough QT/QTc' study in healthy volunteers meeting the relevant TGA adopted EU guidelines for non-arrhythmic drugs.[30] However, such a study in healthy volunteers could not be justified given that calicheamicin is a cytotoxic agent. The submitted data included a PK/PD analysis, which showed that inotuzumab ozogamicin is unlikely to be associated with clinically significant increases in QTc prolongation in patients with ALL (StudyPMAR-EQDD-B193c-DP4-533). Simulated QTcF;[31] and QTcS values showed that the median (upper 97.5th percentile) for the changes at the therapeutic C_{max} of inotuzumab ozogamicin (371 ng/mL) were 2.53 ms (4.92 ms) for QTcF and 2.70 ms (5.40 ms) for QTcS. The median (upper 97.5th percentile) for the changes at the supra therapeutic C_{max} of inotuzumab ozogamicin (569 ng/mL) were 3.87 ms (7.54 ms) for QTcF and 4.14 ms (8.28 ms) for QTcS. The simulated median changes in QTc and QTcF and associated upper 97.5th percentiles were < 10 ms at both therapeutic and supra therapeutic C_{max} levels. In addition, unconjugated calicheamicin exposure in patients with ALL is unlikely to have a significant effect on QTc prolongation.
- In an exploratory central tendency analysis in patients with ALL (Study B1931022) mean maximum QTcF changes from baseline were 16.5 ms (90% CI: 14.3, 18.7) in the inotuzumab ozogamicin arm and 10.8 ms (90% CI: 8.0, 13.6) in the control arm. The central tendency analysis of QTcF change from baseline for all data points demonstrated that the highest upper bound of the 2-sided 90% CI for QTcF was 21.1 ms (observed at Cycle 4/Day 1/1 hour) in the inotuzumab ozogamicin arm and 21.2 ms (observed at Cycle 2/Day 1/1 hour) in the control arm. The reason for the prolonged QTcF observed in Study B1931022 in both treatment arms is unknown. The sponsor stated that the finding might partly be due to the fact that patients in the study received many concomitant medications, some of which are known to prolong QT (for example, metronidazole, posaconazole, virocanazole) or cause electrolyte disturbances (for example, furosemide). In addition, many patients were reported to have electrolyte disturbances known to contribute to QT prolongation. However, given the overall frequency of concomitant medications and electrolyte disturbances, the sponsored acknowledged 'that it is not easily possible to estimate the impact that these factors may have had in prolonging QT in both arms' of Study B1931022. In summary, it is considered that the reason for QTcF prolongation observed in both treatment arms in Study B1931022 is unknown.

[30] CHMP/ICH/2/04; Note for guidance on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non antiarrhythmic drugs.
[31] QTcF = QT interval corrected for heart rate using Fridericia's formula

Dosage selection for the pivotal studies

Clinical experience with inotuzumab ozogamicin in B cell ALL started with the investigator initiated Study 2009-0872;[32] and the Pfizer sponsored Study B1931010 (submitted as a supportive efficacy and safety study).

Study 2009-0872

Study 2009-0872, an investigator initiated, Phase II study conducted at MD Anderson Cancer Center (MDACC) in the USA investigated the safety and preliminary activity of inotuzumab ozogamicin in patients with relapsed or refractory CD22 positive ALL. In this study, 90 patients were treated with single agent inotuzumab ozogamicin (49 patients received a single dose of 1.3 to 1.8 mg/m^2 every 3 to 4 weeks (single dose schedule), while 41 patients received a fractionated weekly dosing schedule of 0.8 mg/m^2 on Day 1 and 0.5 mg/m^2 on Days 8 and 15 every 3 to 4 weeks (weekly dose schedule)).

An overall response rate of 58% (52/90 patients) was reported (that is, CR (n = 17, 19%) + CRp (that is, CR + no platelet recovery; n = 27; 30%) + bone marrow CR (that is, no recovery of counts; n = 8, 9%)). Response rates were similar for the single dose and weekly-dose schedules (57% versus 59%, respectively). The median survival was 6.2 months overall, 5.0 months with the single dose schedule, and 7.3 months with the weekly-dose schedule. The median survival was 9.2 months for patients in salvage 1 (37% at 1 year), 4.3 months for patients in salvage 2, and 6.6 months for patients in salvage 3 or later. The median remission duration was 7 months.

Reversible bilirubin elevation, fever, and hypotension were observed less frequently in patients on the weekly-dose schedule. In total, 36 of 90 patients (40%) underwent allogeneic stem cell transplantation. Veno-occlusive disease was noted in 6 of 36 patients after stem cell transplantation (17%), was less frequent after the weekly schedule (7%), and with less alkylators in the preparative regimen. It was concluded that inotuzumab ozogamicin single agent therapy was highly active, safe, and convenient in patients with refractory or relapsed ALL. The weekly dose schedule appeared to be equally effective and less toxic than the single dose schedule.

Study B1931010

Study B1931010 was an open label, Phase I/II, multicentre study conducted in the US designed to evaluate the safety, PK, and preliminary efficacy of a weekly dosing regimen of inotuzumab ozogamicin in adult patients with relapsed or refractory CD22 positive ALL, while establishing a recommended Phase 2 dose (RP2D). In the Phase 1 dose escalation portion of the study, which was designed to determine the RP2D of inotuzumab ozogamicin based on both, efficacy and safety parameters, inotuzumab ozogamicin was administered on a weekly or biweekly schedule with a cumulative doses per 28 day cycle of 1.2, 1.6, and 1.8 mg/m^2/cycle. One patient (out of 9 first enrolled patients) experienced a dose limiting toxicity (DLT) of elevated lipase at the 1.8 mg/m^2 dose level. This DLT occurred after the first dose of 0.8 mg/m^2, which was the same initial dose for all 3 dose groups. In this portion of the study there were no discernible differences between the 1.6 mg/m^2 and the 1.8 mg/m^2 dose groups for Grade ≥ 3 hepatic AEs, with only 1 event of Grade 3 ALT increased being observed in each group. No cases of VOD/SOS were reported in this portion of the study. No doses higher than 1.8 mg/m^2/cycle were investigated. The maximum tolerated dose (MTD) was not reached in the Phase 1 dose escalation portion of the study.

[32] Kantarjian H et al., 2013 Results of Inotuzumab Ozogamicin, a CD22 Monoclonal Antibody, in Refractory and Relapsed Acute Lymphocytic Leukemia. *Cancer* 2013;119:2728-2736

Overall, 72 patients were enrolled and treated in Study B1931010. In the Phase 1 dose finding portion of the study, the CR/CRi rate was 66.7% (2/3 patients) for the 1.2 mg/m^2/cycle; 75.0% (9/12) for the 1.6 mg/m^2/cycle; and 88.9% (8/9 patients) for the 1.8 mg/m^2/cycle. In the Phase 1 dose expansion portion of the study, the CR/CRi rate was 46.2% (6/13) for the 1.8 mg/m^2/cycle. Based on a review of both safety and efficacy results, doses higher than 1.8 mg/m^2/cycle were not examined, the MTD was not reached, and the RP2D was determined to be 1.8 mg/m^2/cycle. However, while a MTD was not determined in this study, it had been previously determined to be 1.8 mg/m^2 every 4 weeks in patients with NHL.

In the Phase 2 portion of Study B1931010, the CR/CRi rate was 68.6% (24/35 patients) in patients treated with the 1.8 mg/m^2/cycle. The 1-sided p-value for the H0 (null hypothesis) CR/CRi rate ≤ 20% was < 0.0001. Therefore, the primary objective for the CR/CRi rate in the Phase 2 portion of the study was met as the rate was > 20%. However, dose reduction to 1.6 mg/m^2/cycle was implemented after remission based on observations from previous studies indicating that increased exposure to inotuzumab ozogamicin occurs with subsequent doses and may be related to dose delays and reductions required later in therapy. Overall, the CR/CRi rate for all doses was 68.1% (49/72), with a CR rate of 31.9% (23/72 patients) and a CRi rate of 36.1% (26/72 patients).

For the 49 patients who achieved CR or CRi (all doses), the median time to remission was 27 days while the median duration of remission (DoR) (CR + CRi) was 20.1 weeks. Of the patients who achieved CR/CRi (all doses), 83.7% patients also achieved MRD-negativity, and the median time to MRD-negativity was 29 days. The HSCT rate (all doses) was 33.3% (24/72 patients). Overall, the median PFS was 17 weeks (95%CI: 12.4, 23.6), without censoring for HSCT and the median OS was 32 weeks (95% CI: 24.7, 40.0), without censoring for HSCT.

For the total study population (n = 72), the most common all-causality treatment-emergent adverse events (TEAEs) (≥ 20%) were thrombocytopaenia (36.1%), nausea (34.7%), febrile neutropaenia (30.6%), vomiting (27.8%), and AST increased (26.4%), constipation (23.6%), pyrexia (23.6%), and neutropaenia (20.8%). These commonly reported TEAEs had also been observed in the previous investigator initiated study (Study 2009-0872). Grade 3 or 4 all-causality TEAEs occurring in 79.2% of patients were primarily haematologic events. All-causality TEAEs resulting in treatment modifications were primarily due to haematologic all-causality TEAEs (thrombocytopenia and neutropenia) and hepatic all-causality TEAEs (ALT increased, AST increased, gamma-glutamyl transpeptidase (GGT) increased, alkaline phosphatase (ALP) increased, hyperbilirubinemia, and ascites). VOD/SOS Serious adverse events (SAEs) were reported in 4 (5.6%) patients of which 2 events occurred (2/24 (8.3%)) post-HSCT. One patient met the biochemical criteria for Hy's law (drug-induced liver injury (DILI)), but the liver function test (LFT) abnormalities were due to leukaemic infiltration of the liver in a setting of rapid disease progression. Grade 5 all-causality TEAEs occurred in 12.5% of patients and included disease progression (6.9%) and pneumonia, septic shock, Stenotrophomonas sepsis, and VOD/SOS (1.4% each). Reasons for death within the active treatment phase was disease under study (8 (11.1%) patients) and other reasons (4 (5.6%) patients), including septic shock, disease progression, pneumonia, and subdural haematoma.

When the pivotal Phase III Study B1931022 was designed, only preliminary results were available from the investigator initiated Study 2009-0872 and the Pfizer sponsored Study B1931010 (Phase 1 was incomplete). However, based on the favourable preliminary results in high risk patients with relapsed or refractory ALL from these two preliminary studies, the pivotal Phase III Study (Study B1931022) was initiated to compare the safety and efficacy of inotuzumab ozogamicin 1.8 mg/m^2/cycle per cycle (dosed according to BSA) to defined Investigator's choice of chemotherapy.

Evaluator's conclusions on dose finding for the pivotal studies

The dose finding data for inotuzumab ozogamicin based on the investigator initiated Study 2009-0872 and the Pfizer sponsored Study B1931010 in high risk patients with relapsed or refractory ALL are considered to be satisfactory.

Efficacy

Studies providing efficacy data

Two open label studies provided evaluable efficacy data for the proposed indication in patients with relapsed or refractory ALL, including one pivotal Phase III Study B1931022; and one supportive Phase I/II Study B1931010. Both studies have been fully evaluated.

The pivotal Phase III Study B1931022 included patients randomised 1:1 to open label treatment with either inotuzumab ozogamicin (n = 164) or investigator's choice (n = 162) of one of three pre-defined treatment regimens. The pivotal study included the proposed dosage regimen of 1.8 mg/m^2 in cycle 1 administered at a dose of 0.8 mg/m^2 on Day 1 and 0.5 mg/m^2 on Days 8 and 15 for 21 days, with cycle lengthening to 28 days for patients who achieved a response and/or to allow recovery from toxicity, and subsequent dose reduction in responders to 1.5 mg/m^2/cycle at a dose of 0.5 mg/m^2 on Days 1, 8 and 15).

The supportive single-arm Phase I/II Study (B1931010) included a total 72 patients treated with inotuzumab ozogamicin, including 37 patients in Phase 1 (dose finding) treated with a total dose of 1.2 mg/m^2 (n = 3), 1.6 mg/m^2 (n = 12), 1.8 mg/m^2 (n = 9), 13 patients in the dose expansion cohort and 35 patients in Phase 2 treated with 1.8 mg/m^2/cycle administered at a dose of 0.8 mg/m^2 on Day 1 and 0.5 mg/m^2 on Days 8 and 15 of a 28 day cycle with a dose reduction upon achieving CR/CRi. The dose finding data from the supportive study used to define the most appropriate dose for the pivotal study.

Evaluator's conclusions on efficacy

The primary efficacy data supporting the application to register inotuzumab ozogamicin for the proposed indication was provided by one pivotal Phase III Study B1931022. Supportive efficacy data were provided by one single-arm study in a heavily pre-treated group of patients with relapsed or refractory ALL. While the efficacy data for the proposed indication is limited it is considered adequate for inotuzumab ozogamicin, a designated orphan drug for an indication consistent with that being proposed for registration.

Safety

Studies providing safety data

The submission included a Summary of Clinical Safety (SCS) which included safety analyses performed in patients who received inotuzumab ozogamicin in 11 Pfizer sponsored clinical studies as well as in investigator initiated research (IIR) studies and through compassionate use (CU) programs. The SCS focused on the safety findings from the two studies in patients with relapsed or refractory B cell ALL (that is, the pivotal randomised Phase III Study B1931022 and the supportive Phase I/II Study B1931010). The safety databases are summarised below:

Sponsor sponsored studies

A total of 1207 patients were treated in 11 Pfizer sponsored studies (Phases I to III), 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 the 2, single agent studies in patients with ALL, 307 patients were treated in the pivotal Study B1931022, including 164 patients treated with inotuzumab ozogamicin 1.8 mg/m^2/cycle reduced to 1.5 mg/m^2/cycle for responders and 143 patients treated with control, and 72 patients were treated with inotuzumab ozogamicin at dose levels of 1.2 to 1.8 mg/m^2/cycle in the supportive Study B1931010, with 48 of these patients receiving inotuzumab ozogamicin at a dose level of 1.8 mg/m^2/cycle reduced to 1.6 mg/m^2/cycle for responders. The data cut-off dates in the SCS for the pivotal and supportive studies were 8 March 2016 and 30 January 2015, respectively.

In the 9 NHL studies with inotuzumab ozogamicin alone or in combination with rituximab with or without chemotherapy, a total of 644 patients received inotuzumab ozogamicin (n = 173, single agent inotuzumab ozogamicin; n = 368, inotuzumab ozogamicin plus rituximab; n = 103, inotuzumab ozogamicin plus rituximab plus multi-agent chemotherapy). An additional 4 patients in the inotuzumab ozogamicin plus rituximab arm of the combination studies received rituximab but did not receive inotuzumab ozogamicin.

IIR and CU studies

Safety data from IIR studies and CU patients included only deaths and other serious adverse events (SAEs) obtained from the sponsor's global safety database. In the IIR studies, as of the safety data cut-off date of 30 June 2016, 307 patients had received either single agent inotuzumab ozogamicin or inotuzumab ozogamicin combined with other agents. For the CU patients, as of the safety data cut-off date of 30 June 2016, approximately 211 patients had received single agent inotuzumab ozogamicin for relapsed or refractory ALL or NHL after exhaustion of all other approved and available therapeutic options.

Day 120 safety update

The submission included a Day 120 Safety Update (SU) prepared for the FDA. This report provided updated safety information as of the data cut-off date of 1 September 2016. The safety update focussed primarily on the updated data for the 307 patients who received treatment in the pivotal Study B1931022. As all of these patients had discontinued study therapy (last patient last dose occurred on 29 April 2015) relatively few changes occurred in the safety data between the 8 March 2016 SCS cut-off date and the 1 September 2016 safety update cut-off date. The safety update provided changes in the safety data for 54 patients who were alive and in follow-up in Study B19311022 as of the 8 March 2016 safety data cut-off date for the SCS (that is, 39 patients in the inotuzumab ozogamicin arm and 15 patients in the control arm). In this 54 patient cohort, the last patient had been randomised on 23 December 2014. The Medical Dictionary for Regulatory Activities (MedDRA) (v19.0) coding dictionary was applied to the AEs and the AEs were graded according to the NCI CTCAE (v3.0).

The Day 120 SU also included updated safety data for 48 patients in Study B1931010 who received a total starting inotuzumab ozogamicin dose of 1.8 mg/m^2/cycle as a single agent; 7 of these patients remained in disease and survival follow-up between the 30 January 2015 safety data cut-off date for Study 1931010 in the SCS and the LPLV date of 15 January 2016. Of note, there were no new SAEs reported in this study after the 30 January 2015 cut-off date (SCS).

The Day 120 SU also included updated safety data (SAEs, deaths) for patients in the IIR studies (n = 323) and the CU program (n = 257), as of the 1 September 2016 cut-off date.

The approach to the evaluation of safety adopted in this clinical evaluation report (CER) has been to focus on the data from the pivotal Study B1931022 in patients with ALL. This

study provides the key safety data as it includes patients with relapsed or refractory B cell precursor ALL treated with the proposed inotuzumab ozogamicin treatment regimen (n = 164) and comparative data for control group treatment (n = 143). The evaluation of the safety data for this study is based on data from the sCSR, SCS and 120-Day SU. The safety data for Study B1931022 is consistent across all three data sources.

Patient exposure

The duration of exposure in the two ALL studies is summarised below in Table 8.

Table 8: Exposure in patients with ALL, Studies B1931022 and B1931010, safety population

	Study 1022					Study 1010 (Phase 2 + Dose Expansion Cohort)	Pooled ALL study population
		Control					
	Inotuzumab ozogamicin (N=164)	FLAG (N=93)	MXN/Ara-C (N=33)	HIDAC (N=17)	Total (N=143)	Inotuzumab ozogamicin (N=48)	Inotuzumab ozogamicin (N=212)
Duration of treatment (weeks)[a]							
Median	8.9	0.9	1.1	1.0	0.9	10.1	9.1
Min, Max	0.1, 26.4	0.4, 15.6	0.4, 8.6	0.1, 9.7	0.1, 15.6	0.1, 41.1	0.1, 41.1
Number of cycles started per patient[b]							
Mean (cycles)	2.8	1.3	1.1	1.2	1.2	2.9	2.8
Median (range)	3 (1, 6)	1 (1, 4)	1 (1, 2)	1 (1, 2)	1 (1, 4)	3 (1, 6)	3 (1, 6)
Number (%) of patients who started as last cycle							
Cycle 1	37 (22.6)	72 (77.4)	31 (93.9)	13 (76.5)	116 (81.1)	10 (20.8)	47 (22.2)
Cycle 2	40 (24.4)	16 (17.2)	2 (6.1)	4 (23.5)	22 (15.4)	12 (25.0)	52 (24.5)
Cycle 3	42 (25.6)	4 (4.3)	0	NA[d]	4 (2.8)	10 (20.8)	52 (24.5)
Cycle 4	19 (11.6)	1 (1.1)	0	NA[d]	1 (0.7)	10 (20.8)	29 (13.7)
≥Cycle 5	26 (15.9)[c]	NA[d]	NA[d]	NA[d]	NA	6 (12.5)[c]	32 (15.1)

Source: SCS, Table 4.
[a] Duration of treatment = (date of last dosing of INO - date of first dosing of INO +1)/7.
[b] Cycles are determined by dosing data captured on Dosing Record CRF page. A patient is counted once per row.
[c] Study 1022: 15 (9.1%) patients in the inotuzumab ozogamicin arm and 0 patients in the control arm initiated Cycle 6 Study 1010: 3 (6.3%) patients initiated Cycle 6.
[d] Only 4 cycles of FLAG and MXN/Ara-C, and only 2 cycles of HIDAC allowed per protocol. (These are marked as "NA" for other cycles.)

The median total dose for inotuzumab ozogamicin was 4.2 mg/m^2 (range: 0.8, 9.6 mg/m^2). The median actual dose intensity, defined as total actual exposure divided by number of cycles received, was 1.575 mg/m^2. The median relative dose intensity (RDI), defined as the actual dose intensity divided by the planned dose intensity, was 100.7%. The exposure data for inotuzumab ozogamicin reported in the Day 120 SU remained unchanged from that reported in the SCS, as all 307 patients treated in Study B1931022 had discontinued treatment at the 8 March 2016 data cut-off date for the SCS.

In Study B1931022 (pivotal), the duration of Cycle 1 was planned to be 21 days for patients receiving 1 cycle and 28 days for patients receiving more than one cycle, with a dose reduction from 1.8 mg/m^2/cycle to 1.5 mg/m^2/cycle on achieving CR/CRi. Patients in the inotuzumab ozogamicin arm received study medication on Days 1, 8, and 15 of each cycle for up to 6 cycles. The median duration of treatment was 8.9 weeks (median number of cycles = 3). In total, patients randomised to the inotuzumab ozogamicin arm received 464 cycles of therapy compared to 176 cycles for patients randomised to the control arm (2.6 x more cycles for inotuzumab ozogamicin compared to control). The maximum allowed number of cycles per protocol was 6 cycles of inotuzumab ozogamicin or 4 cycles of control. A total of 127 (77.4%) patients in the inotuzumab ozogamicin arm started > 1 cycle, 15 (9.1%) patients started at least 6 cycles, and 10 (6.1%) patients completed

6 cycles. Of note, AE frequencies were not adjusted for the longer duration of treatment in the inotuzumab ozogamicin arm.

Postmarketing data

There were no post-marketing data.

Evaluator's conclusions on safety

It is considered that the submitted data for inotuzumab ozogamicin have adequately established the safety of the drug for the treatment of the proposed indication. The safety data for inotuzumab ozogamicin is based on information from 11 sponsor sponsored clinical trials (2 ALL; 9 NHL) in which 880 patients received inotuzumab ozogamicin in single agent studies, in studies in combination with rituximab, or in a study in combination with rituximab plus multi-agent chemotherapy. In addition to the 880 patients treated with inotuzumab ozogamicin in the 11 sponsor sponsored trials, 323 patients had been treated with the drug in IIR studies and 257 patients had received the drug in CU programs as of 1 September 2016.

The key safety data for the proposed inotuzumab ozogamicin dosage regimen for patients with relapsed or refractory B-cell precursor ALL are provided by the pivotal Phase III, randomised, open label, active controlled Study B1931022. In this study, 164 patients were treated with inotuzumab ozogamicin at the dose proposed for registration and 143 patients were treated with a control regimen. Supportive safety data in patients with ALL were provided in the single arm Study B1931010 in 72 patients treated with various doses of inotuzumab ozogamicin including 42 patients treated with a dosage regimen consistent with that being proposed for registration. The safety data in the 164 patients treated with inotuzumab ozogamicin in the pivotal study is consistent with the 880 patients treated with inotuzumab ozogamicin from the 11 Pfizer studies, the IIR studies and the CU program.

In the pivotal Study B1931022, the median duration of treatment in the inotuzumab ozogamicin arm was 10 fold longer than in the control arm (8.9 weeks versus 0.9 weeks, respectively) and the median number of cycles was 3 fold higher (3 cycles versus 1 cycle, respectively). No adjustment was made in the incidence of AEs reported in patients in the two treatment arms for the greater exposure observed in the inotuzumab ozogamicin arm compared to the control arm. The maximum allowed number of cycles per protocol was 6 cycles of inotuzumab ozogamicin or 4 cycles of investigator's choice of chemotherapy (control arm). In the inotuzumab ozogamicin arm, a total of 127 (77.4%) patients started > 1 cycle, 15 (9.1%) patients started at least 6 cycles, and 10 (6.1%) patients completed 6 cycles. In the safety population, 5 (3.0%) patients in the inotuzumab ozogamicin arm were treated for ≥ 24 weeks compared to no patients in the control arm. Long-term (> 6 months) safety data for inotuzumab ozogamicin are not relevant as the recommended maximum number of cycles (21 to 28 days) for the drug is six. Treatment with inotuzumab ozogamicin is primarily designed to achieve haematological remission in ≤ 3 treatment cycles, allowing suitable responders to proceed to HSCT, and not for long term repeat dosing maintenance therapy. Based on the pivotal efficacy data most patients are expected to respond within three cycles.

In the pivotal study, TEAEs (all causality, all grades, Day 120 SU) occurred commonly in both treatment arms (99.4% (162/164), inotuzumab ozogamicin versus 100%, (143/143), control), and the majority of TEAES (all grades, SCS) were considered by the investigators to be treatment related (87.8% (144/164) inotuzumab ozogamicin versus 90.9% (130/143), control). TEAEs (all causality) reported in ≥ 20% of patients in the inotuzumab ozogamicin arm were thrombocytopaenia (49.4%), neutropenia (48.8%), anaemia (33.5%), nausea (32.3%), pyrexia (31.7%), leukopaenia (28.7%), headache

(27.4%), febrile neutropaenia (26.8%), fatigue (25.6%), AST increased (22.6%), GGT increased (21.3%) and hyperbilirubinaemia (21.3%).

In the pivotal study, TEAEs maximum Grade 3 or 4 events (Day 120 SU) occurred less frequently in the inotuzumab ozogamicin arm than in the control arm (75.0% (123/164) versus 85.3% (122/143), respectively), as did treatment related TEAEs maximum Grade 3 or 4 events (SCS) (69.5% (114/164) versus 79.0% (113/143), respectively). TEAEs maximum Grade 3 or 4 events reported in ≥ 5% of patients in the inotuzumab arm were neutropaenia (47.0%), thrombocytopaenia (40.9%), leukopaenia (26.8%), febrile leukopaenia (26.8%), anaemia (22.6%), lymphopaenia (16.5%), GGT increased (11.0%), venoocclusive disease (8.5%), hypokalaemia (6.7%), hyperbilirubinaemia (6.1%), and WBC decreased (6.1%).

Grade 5 AEs (all causality, Day 120 SU) were reported more frequently in the inotuzumab ozogamicin arm than in the control arm (15.9%, n = 26 versus 11.2%, n = 16, respectively), as were treatment related grade 5 AEs (SCS) (5.5%, n = 9 versus 2.1%, n = 3, respectively). Of particular note, in the 9 patients in the inotuzumab arm who died, 5 cases were due VOD/SOS (all after HSCT) compared to no cases of VOD/SOS leading to death in the control arm. Other treatment related grade 5 AEs in the inotuzumab ozogamicin arm were 1 each of acute respiratory distress syndrome (ARDS), intestinal ischaemia, multi-organ failure, pneumonia, and septic shock, while treatment related grade 5 AEs in the control arm were 1 each for multi-organ failure, haemorrhage intracranial, lung infection and respiratory failure.

'All deaths' (Day 120 SU), which included all deaths during treatment and in the follow-up period,[33] were reported less frequently in the inotuzumab ozogamicin arm than in the control arm (76.8% (126/164) versus 87.4% (125/143), respectively). Most deaths in both treatment arms were due to the disease under study (47.0%, n = 77 versus 69.9%, n = 100, respectively). Of note, 'all deaths' due to infection were reported more frequently in the inotuzumab ozogamicin arm than in the control arm (30.5%, n = 50 versus 17.5%, n = 25, respectively).

Post-transplantation deaths were also assessed in patients who underwent HSCT in the inotuzumab ozogamicin arm (n = 79) and the control arm (n = 35). Overall post-transplant mortality was similar in the inotuzumab ozogamicin and control arms (64.6% (51/79) versus 65.7% (23/35), respectively). The most common cause of post-transplant death was disease relapse, which was reported less frequently in the inotuzumab ozogamicin arm than in the control arm (37.3% (19/51) versus 69.6% (16/23), respectively). However, post-transplant non-relapse deaths were reported notably more frequently in patients in the inotuzumab ozogamicin arm than in the control arm (40.5% (32/79) versus 22.9% (8/35)). The most common reasons for post-transplant non-relapse deaths relative to all deaths (relapse plus non-relapse) in the inotuzumab arm (versus control, respectively) were infection (21.6% (11/51) versus 17.4% (4/23)) and VOD (9.8% (5/51) versus 0% (0/23)).

SAEs (all causality, Day 120 SU), were reported in a similar proportion of patients in the inotuzumab ozogamicin and control arms (51.8% (85/164) versus 50.3% (75/143), respectively), and SAEs reported in ≥ 2% of patients in the inotuzumab arm were VOD (14.0%), febrile neutropenia (11.6%), pneumonia (6.1%), disease progression (4.9%), pyrexia (3.0%) and sepsis (2.4%).

AEs (all causality, Day 120 SU), leading to permanent treatment discontinuation were reported notably more frequently in the inotuzumab ozogamicin arm than in the control arm (18.9% (31/164) versus 7.7% (11/143), respectively). AEs leading to permanent treatment discontinuation reported in ≥ 2 patients in the ozogamicin arm were 5 (3.0%)

[33] Clarification: all deaths including those occurring after follow-up HSCT

patients with pneumonia, 3 (0.18%) patients each with hyperbilirubinaemia and thrombocytopaenia, and 2 (1.2%) patients each with sepsis, VOD, ALT increased, and GGT increased. Similarly, AEs (all causality, Day 120 SU) resulting in temporary treatment delays were reported notably more frequently in the inotuzumab ozogamicin arm than in the control arm (43.9% (72/164) versus 11.9% (17/143), respectively). AEs (all causality, Day 120 SU) resulting in dose reduction were reported in a small number of patients in both the inotuzumab ozogamicin and control arms (n = 5, 3.0% versus n = 3, 2.1%, respectively).

The following adverse events of special interest were assessed in Study B19311022:

- hepatotoxicity, including VOD/SOS;
- myelosuppression/cytopaenia;
- infections (not considered a separate risk, but considered to be complications of myelosuppression/cytopaenias);
- haemorrhage events (not considered a separate risk, but considered to be complications of myelosuppression/cytopaenias);
- infusion related reactions;
- tumour lysis syndrome (TLS);
- interstitial lung disease (ILD);
- inflammatory gastrointestinal events;
- pancreatitis;
- second primary malignancy;
- reproductive and developmental toxicity (post exposure during pregnancy including breast feeding);
- nephrotoxicity; and
- neurotoxicity.

Matters of particular note arising from the assessment of adverse events of special interest in the inotuzumab ozogamicin arm were:

- increased risk of hepatotoxicity, including severe, life-threatening and sometimes fatal VOD/SOS;
- severe, life threatening myelosuppression/cytopenia;
- serious infections were very commonly reported, and some were life-threatening or fatal;
- infusion related reactions, including hypersensitivity, were reported very commonly; and
- pancreatic related adverse events including increased serum amylase and lipase.

Other relevant safety data are reviewed in the first round risk assessment.

First round benefit-risk assessment

First round assessment of benefits

Study B1931022

The benefits of inotuzumab ozogamicin for the treatment of patients with relapsed or refractory CD22 positive ALL, in the context of Salvage 1 or Salvage 2, has been adequately demonstrated in the pivotal study. The primary benefit of treatment with inotuzumab ozogamicin relates to the higher proportion of patients who achieved CR/CRi compared to patients treated with standard chemotherapy regimens, resulting in a higher of patients proceeding to HSCT with potentially curative outcome. However, while the proportion of patients proceeding to HSCT was higher in the inotuzumab ozogamicin arm than in the control arm, the pairwise analysis of OS did not meet the pre-specified boundary for statistical significance. In addition, the post-HSCT non-relapse mortality rate was notably higher in the inotuzumab ozogamicin arm than in the control arm, as were the 100 day and 12 month mortality rates for both post-HSCT mortality and non-relapse post-HSCT mortality.

CR/CRi (remission); primary efficacy endpoint

- In the primary analysis of CR/CRi (per endpoint adjudication committee (EAC)) based on the ITT218[34] population (n = 218) at the data cut-off date of 2 October 2014, the CR/CRi rate was statistically significantly higher in the inotuzumab ozogamicin arm compared to the control arm (80.7% (88/109) versus 29.4% (32/109), Δ = 51.4% (97.5% CI: 38.4, 64.3), p < 0.0001, 1-sided Chi square test). The difference between the two treatment arms is considered to be clinically meaningful. The results demonstrate that patients treated with inotuzumab ozogamicin have a greater chance of proceeding to potentially curative HSCT compared to patients treated with standard chemotherapy regimens.
- The difference in favour of inotuzumab ozogamicin compared to control observed in the primary analysis of CR/CRi (per EAC) in the ITT218 population as of the data cut-off date of 2 October 2014 was consistent with the findings for all pre-specified stratification factor randomisation groups (age (< 55 and ≥ 55 years), line of salvage (1 and 2), and duration of first remission (< 12 and ≥ 12 months)). Based on the pre-specified stratification factors at randomisation, the CR/CRi (per EAC) rate in patients in the inotuzumab ozogamicin arm (ITT218 population) was 80.3% (53/66) in patients aged < 55 years and 81.4% (35/43) in patients aged ≥ 55 years, 87.7% (64/73) for salvage status 1 and 66.7% (24/36) for salvage status 2, 77.5% (55/71) for patients with a first remission < 12 months and 86.8% (33/38) for patients with a first remission ≥ 12 months.
- In the supportive analysis of CR/CRi (per investigator) based on the updated data for the total intent-to-treat (ITT) population (n = 326) at the data cut-off date of 8 March 2016, the CR/CRi rate was statistically significantly higher in the inotuzumab ozogamicin arm compared to the control arm (73.2% (120/164) versus 30.9% (50/162), Δ = 42.3% (97.5% CI: 31.1, 53.5), p < 0.0001, 1-sided Chi square test). The result of the supportive analysis was consistent with the result of the primary analysis.
- In patients in the ITT inotuzumab ozogamicin arm who achieved CR/CRi (per investigator) as of the 8 March 2016 data cut-off date (n = 120), 70.8% (n = 85) achieved remission in Cycle 1, 25.8% (n = 31) achieved remission in Cycle 2 and 3.3% (n = 4) achieved remission in Cycle 3. No patients in the inotuzumab ozogamicin arm achieved CR/CRi after Cycle 3. The data indicates that patients who have not achieved

[34] ITT218 = ITT for the initial 218 patients randomized

CR/CRi after 3 treatment cycles should have treatment with inotuzumab ozogamicin discontinued.

Overall survival; primary efficacy endpoint

The primary analysis of OS was based on patients in the ITT population (n = 326) as of the 8 March 2016 data cut-off date. The analysis was undertaken when a total of 252 deaths had occurred. The stratified hazard ratio (HR) was 0.770 (97.5% CI: 0.578, 1.026), p = 0.0203 (1-sided stratified log-rank test), indicating an overall 23% reduction in the risk of death in the inotuzumab ozogamicin arm relative to the control arm. However, the difference between the two treatment arms did not reach statistical significance as the 1-sided p-value of 0.0203 exceeded the pre-specified 1-sided p-value boundary of 0.0104 (adjusted for the interim analyses). The median duration of survival was estimated to be 7.7 months (95% CI: 6.0, 9.2) in the inotuzumab arm and 6.7 months (95% CI: 4.9, 8.3) in the control arm, with an absolute difference of 1 month in favour of inotuzumab. The 1 month difference in median survival between the two treatment arms in favour of inotuzumab ozogamicin is considered to be not clinically significant.

Progression free survival (PFS); secondary efficacy endpoint

The primary analysis of PFS was based on all randomised patients in the ITT population (n = 326) as of the 8 March 2016 data cut-off date. The definition of PFS used in the study was non-standard, and included death, progressive disease (objective progression, relapsed from CR/CRi, treatment discontinuation due to global deterioration of health status), and starting new induction therapy or post-therapy HSCT without achieving CR or CRi. The duration of PFS was statistically significantly greater in the inotuzumab arm than in the control arm ($p < 0.05$), and the difference is considered to be clinically significant. The estimated mean duration of PFS was 5.0 months (95% CI: 3.7, 5.6) in the inotuzumab ozogamicin arm and 1.8 months (95% CI: 1.5, 2.2) in the control arm. The stratified HR was 0.452 (97.5% CI: 0.336, 0.609), $p < 0.0001$, 1-sided stratified log-rank test.

Other secondary efficacy endpoints

While p-values were provided for the pairwise comparisons of the other secondary efficacy endpoints it is considered that these should be considered to be nominal rather than confirmatory. No pre-specified method was described in the statistical analysis plan (SAP) for controlling the overall type 1 error of the study at 1-sided 0.025 for statistical testing of the other secondary efficacy endpoints.

Duration of remission (DoR)

The primary assessment of the DoR in patients achieving CR/CRi (per investigator) was assessed in the updated data for the ITT218 population (n = 218), as of the 8 March 2016 data cut-off date. In this analysis, the estimated median DoR was 5.4 months (95% CI: 4.2, 8.0) in the inotuzumab ozogamicin arm and 3.5 months (95% CI: 2.9, 6.6) in the control arm: stratified HR = 0.502 (95% CI: 0.303, 0.832), p = 0.0031, 1-sided stratified log-rank test. The improvement in the DoR in the inotuzumab arm compared to the control arm observed in this analysis was consistent with results in the updated data for the ITT population (n = 326) as of the 8 March 2016 data cut-off date. In this analysis, the estimated median DoR was 5.3 months (95% CI: 4.2, 7.0) in the inotuzumab ozogamicin arm and 3.6 months (95% CI: 2.9, 5.2): stratified HR = 0.597 (95% CI: 0.400, 0.890), p = 0.0052, 1-sided stratified log-rank test.

MRD-negativity

MRD was assessed by a central laboratory using flow cytometry. MRD negativity was defined as leukaemic cells comprising $< 1 \times 10^{-4}$ (< 0.01%). The primary assessment of MRD was in the ITT218 patients achieving CR/CRi (per EAC) as of the 2 October 2014. In this analysis, in patients who achieved CR/CRi (per investigator) the percentage with MRD negativity was notably higher in the inotuzumab ozogamicin arm than in the control

arm (78.4%, (69/88) versus 28.1%, (9/32), respectively), p < 0.0001, 1-sided Chi-square test). This improvement was consistent with the results in ITT patients achieving CR/CRi (per investigator) as of the 8 March 2016 data cut-off date. In this analysis, in patients who achieved CR/CRi (per investigator) the percentage with MRD-negativity was notably higher in the inotuzumab ozogamicin arm than in the control arm (76.7%, (92/120) versus 38.0% (19/50), respectively), p < 0.0001, 1-sided Chi-square test).

HSCT

The primary assessment of the HSCT rate was in the ITT population as of the 8 March 2016 data cut-off date. The percentage of patients proceeding to HSCT from the first treatment dose to any time in the study in the ITT population was greater in the inotuzumab arm than in the control arm (47.0%, n = 77 versus 20.4%, n = 33, respectively). The percentage of patients proceeding to HSCT in the interval from the first treatment dose until the start of post induction treatment was 4 fold higher in the inotuzumab ozogamicin arm than in the control arm (43.3%, n = 71 versus 11.1%, n = 18, respectively, Δ = 32.2% (95% CI: 23.2, 41.2), p < 0.0001, 1-sided Chi-square test). The percentage of patients proceeding to HSCT directly after achieving CR/CRi (per investigator) in the interval from the first treatment dose to the start of post induction therapy was higher in the inotuzumab ozogamicin arm than in the control arm (39.6%, n = 65 versus 9.9%, n = 16, respectively).

Based on the 8 March 2016 data cut-off date, the post-transplant mortality rate in the 77 patients in the inotuzumab ozogamicin arm and 33 patients in the control arm who received follow-up HSCT was similar (59.7% (46/77) versus 57.6% (19/33), respectively). However, the estimated post-HSCT 100 day mortality rate was notably higher in the inotuzumab ozogamicin arm than in the control arm (26.0% versus 6.1%, respectively), as was the estimated 12 month mortality rate (55.8% versus 36.1%), respectively.

Furthermore, the post-HSCT non relapse mortality rate was notably higher in the inotuzumab ozogamicin arm than in the control arm (39.0% versus 27.3%, respectively), as was the estimated mortality rate at the end of 100 days (20.8% versus 6.1%, respectively) and 12 months (37.7% versus 18.8%, respectively). Therefore, while the overall post-HSCT mortality rate was similar in the two treatment arms, the causes of death and timing of death were different between the arms. In the inotuzumab ozogamicin arm, more patients died due to reasons other than the disease under study (for example, infection and VOD/SOS) and had a higher 100-day and 12 month mortality rates than patients in the control arm.

Patient reported outcomes (PROs)

Based on the study EORTC QLQ-C30[35] results (ITT population), inotuzumab ozogamicin treatment was associated with significantly better post-baseline scores in physical functioning, role functioning, social functioning, and appetite loss compared to control. There were no statistically significant differences between the two treatment arms as regards the EQ-5D index and the EuroQoL visual analogue scale (EQ-VAS). Overall, treatment with inotuzumab ozogamicin is not associated with a decline in quality of life compared to control treatment.

First round assessment of risks

The risks of treatment with inotuzumab ozogamicin compared to control for the proposed indication reviewed below are based on the pivotal Phase III Study B1931022. The risks of treatment with inotuzumab ozogamicin have been reviewed based on adverse drug reaction (ADR) data, mortality data and all causality TEAE data for adverse events of

[35] EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire

special interest. Overall, the risks of inotuzumab ozogamicin have been well characterised in the submitted data. The safety data are considered to be reliable.

The criteria used to define ADRs were provided. MedDRA (v18.1) coding dictionary was applied to define the ADRs, and severity was graded according to NCI CTCAE version 3.0. Both the approved FDA and EU prescribing information documents include safety data based on the ADRs for inotuzumab ozogamicin. It should be noted that ADRs included TEAEs (all causality) that commenced on or after C1D1 within 42 days of last dose of study drug, but prior to the start of new anticancer treatment (including HSCT). Therefore, VOD after follow-up HSCT was not included as an ADR. While VOD after follow-up HSCT was not included as a defined ADR there were detailed descriptions of VOD after follow-up HSCT in the submitted safety data.

Adverse drug reactions, all grades (≥ 10%)

Adverse drug reactions (all grades) reported in ≥ 10% of patients in the inotuzumab arm versus the control arm, in descending order of frequency in the inotuzumab ozogamicin arm, are summarised below in Table 9.

Table 9: Adverse drugs reactions with an incidence of ≥ 10% in the inotuzumab ozogamicin (all grades) arm compared to control treatment, safety population

	Inotuzumab ozogamicin (n=164)			Control (n=143)		
	All	Grade 3-4	Grade 5	All	Grade 3-4	Grade 5
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Thrombocytopenia	83 (50.6)	69 (42.1)	0	87 (60.8)	85 (59.4)	0
Neutropenia	81 (49.4)	78 (47.6)	0	65 (45.5)	62 (43.4)	0
Infection	79 (48.2)	38 (23.2)	8 (4.9)	109 (76.2)	70 (49.0)	7 (4.9)
Anaemia	59 (36.0)	40 (24.4)	0	84 (58.7)	67 (46.9)	0
Leukopenia	57 (34.8)	54 (32.9)	0	61 (42.7)	60 (42.0)	0
Fatigue	57 (34.8)	8 (4.9)	0	36 (25.2)	5 (3.5)	0
Haemorrhage	54 (32.9)	8 (4.9)	1 (0.6)	40 (28.0)	7 (4.9)	0
Pyrexia	52 (31.7)	5 (3.0)	0	60 (42.0)	8 (5.6)	0
Nausea	51 (31.1)	3 (1.8)	0	66 (46.2)	0	0
Headache	46 (28.0)	3 (1.8)	0	39 (27.3)	1 (0.7)	0
Febrile neutropenia	43 (26.2)	43 (26.2)	0	76 (53.1)	76 (53.1)	0
Transaminases increased	43 (26.2)	11 (6.7)	0	18 (12.6)	7 (4.9)	0
Abdominal pain	37 (22.6)	5 (3.0)	0	33 (23.1)	1 (0.7)	0
Hyperbilirubinaemia	35 (21.3)	9 (5.5)	0	24 (16.8)	9 (6.3)	0
Gamma GT increased	35 (21.3)	17 (10.4)	0	11 (7.7)	6 (4.2)	0
Lymphopenia	30 (18.3)	27 (16.5)	0	38 (26.6)	37 (25.9)	0
Diarrhoea	28 (17.1)	1 (0.6)	0	54 (37.8)	1 (0.7)	0
Constipation	27 (16.5)	0	0	34 (23.8)	0	0
Vomiting	25 (15.2)	2 (1.2)	0	35 (24.5)	0	0
Stomatitis	21 (12.8)	3 (1.8)	0	37 (25.9)	4 (2.8)	0
ALP increased	21 (12.8)	3 (1.8)	0	10 (7.0)	0	0
Decreased appetite	19 (11.6)	2 (1.2)	0	18 (12.6)	3 (2.1)	0
Chills	18 (11.0)	0	0	16 (11.2)	0	0

Adverse drug reactions all grades (≥ 1% to < 10%)

Commonly reported ADRs (all grades) occurring in ≥ 1% to < 10% of patients in the inotuzumab ozogamicin arm (versus control), in descending order of frequency in the

inotuzumab ozogamicin arm, were (respectively): lipase increased (9.1% versus 0.7%); abdominal distension (6.1% versus 1.4%); amylase increased (4.9% versus 0.7%); hyperuricaemia (4.3% versus 0.7%); ascites (3.7% versus 0%); pancytopenia (2.4% versus 7.0%); VOD (2.4% versus 0%); infusion related reactions (2.4% versus 1.4%); TLS (2.4% versus 2.1%); and electrocardiogram (ECG) QT prolonged (1.2% versus 0.7%).

Serious adverse drug reactions

Serious ADRs (all grades) reported in ≥ 2% of patients in the inotuzumab ozogamicin arm (versus control), in descending order of frequency in the inotuzumab arm, were (respectively): infection (23.2% versus 26.6%); febrile neutropenia (11.0% versus 18.9%); haemorrhage (4.9% versus 3.5%); abdominal pain (3.0% versus 0%); pyrexia (3.0% versus 2.1%); fatigue (2.4% versus 0%); and VOD (2.4% versus 0%).

Adverse drug reactions leading to treatment discontinuation

ADRs (all grades) leading to treatment discontinuation in ≥ 2 patients in the inotuzumab arm (versus control) were (respectively): infection (n = 10, 6.1% versus n = 6, 4.2%); thrombocytopenia (n = 3, 1.8% versus 0%); transaminase increased (n = 3, 1.8% versus 0%); haemorrhage (n = 3, 1.8% versus 0%); hyperbilirubinaemia (n = 3, 1.8% versus 0%); VOD (n = 2, 1.2% versus 0%); and GGT increased (n = 2, 1.2% versus 0%).

Adverse drug reactions leading to treatment delays

ADRs (all grades) leading to treatment delays in ≥ 2% of patients in the inotuzumab arm (versus control) were (respectively): neutropenia (17.1% versus 0%); infection (10.4% versus 2.1%); thrombocytopenia (9.8% versus 0.7%); transaminase increased (5.5% versus 0.7%); febrile neutropenia (4.9% versus 1.4%); hyperbilirubinaemia (4.3% versus 0.7%); and GGT increased (4.3% versus 0%).

Adverse drug reactions leading to dose reduction

ADRs (all grades) leading to dose reduction in ≥ 2 patients in the inotuzumab arm (versus control) were (respectively): neutropenia (n = 2, 1.2% versus 0%); thrombocytopenia (n = 2, 1.2% versus 0%); and transaminase increased (n = 2. 1.2% versus 0%).

Death (Grade 5 TEAEs); data cut-off 1 September 2015

The risk of death (Grade 5 TEAEs), both all causality and treatment related, were reported more frequently in the inotuzumab ozogamicin arm than in the control arm. Grade 5 TEAEs (all causality) were reported more frequently in the inotuzumab ozogamicin arm than in the control arm (15.9% (26/164) versus 11.2% (16/143)). Treatment related Grade 5 TEAEs were reported in 9 (5.5%) patients in the inotuzumab ozogamicin arm (5 x VOD; 1 x each for ARDS, intestinal ischaemia, MOF, pneumonia, and septic shock), and 3 (2.1%) patients in the control arm (1 x each for MOF, haemorrhage intracranial, lung infection, and respiratory failure).

All deaths; data cut-off 1 September 2016

'All deaths', which included all deaths during treatment and in the follow-up period, were reported less frequently the inotuzumab ozogamicin than in the control arm (76.8% (126/164) versus 87.4% (125/143), respectively). Most deaths in both treatment were due to the disease under study (47.0%, n = 77, inotuzumab ozogamicin versus 69.9%, n = 100, control, respectively). Of note, 'all deaths' due to infection were reported more frequently in the inotuzumab ozogamicin arm than in the control arm (14.6%, n = 24 versus 9.1%, n = 13, respectively).

Post-transplant non-relapse mortality; data cut-off 1 September 2016

In patients who proceeded to HSCT, non-relapse post-transplant mortality occurred notably more frequently in patients in the inotuzumab ozogamicin arm than in the control arm (40.5% (32/79) versus 22.9% (8/35)). The estimated non-relapse post-transplant

mortality rate at the end of Day 100 was 20.3% in the inotuzumab ozogamicin arm and 5.7% in the control arm, and at the end of Month 12 was 38.0% and 14.5%, respectively. Of the total number of relapse plus non-relapse post-transplant deaths, 51 deaths occurred in 79 patients in the inotuzumab ozogamicin arm (64.6%) and 23 deaths occurred in 35 patients in the control arm (65.7%). The most common reasons for post-transplant non-relapse deaths relative to all deaths (relapse plus non-relapse) in the inotuzumab ozogamicin arm (versus control arm, respectively), were infection (21.6% (11/51 versus 17.4% (4/23)) and VOD (9.8% (5/51) versus 0% (0/23)).

Adverse events of special interest (all causality); clustered terms; data cut-off 1 September 2016

Hepatotoxicity, including VOD/SOS

Hepatotoxicity, including severe, life-threatening and sometimes fatal VOD, was a notable risk associated with inotuzumab ozogamicin treatment. Hepatotoxicity, including VOD, was reported more frequently in patients in the inotuzumab ozogamicin arm than in the control arm (all grades (50.6% versus 36.4%); Grades 3 to 4 (26.2% versus 16.1%)). Preferred term AEs (all grades) reported in ≥ 10% of patients in the inotuzumab ozogamicin arm compared to the control arm were (respectively), AST increased (22.6% versus 11.2%), GGT increased (21.3% versus 8.4%), hyperbilirubinaemia (21.3% versus 16.8%), ALT increased (15.2% versus 12.6%), VOD (14.0% versus 2.1%), and ALP increased (12.8% versus 7.0%). There were 5 (3.0%) deaths in the inotuzumab ozogamicin arm due to hepatoxicity and all were due to VOD. There were no deaths in the control arm due to hepatoxicity, including VOD.

In the inotuzumab ozogamicin treatment arm, univariate logistic regression analysis identified that greater risk of Grade ≥ 3 hepatotoxicity, including VOD/SOS was associated with baseline hepatic impairment (mild/moderate/severe versus normal function), higher salvage status (≥ 2 versus 1), prior history of liver disease (yes versus no), prior HSCT (yes versus no), and higher peripheral blast levels (> 1000 /μL versus ≤ 1000 /μL). Multivariate logistic regression analysis identified that greater risk of Grade ≥ 3 hepatotoxicity, including VOD/SOS was associated with prior HSCT (yes versus no), higher peripheral blast levels (> 1000 /μL versus ≤ 1000 /μL), and prior history of liver disease (yes versus no).

The following LFT laboratory test abnormalities (Grade 3 to 4) were reported in patients in the inotuzumab ozogamicin versus control arm, respectively: ALT increased (4.9% versus 5.7%); AST increased (5.5% versus 5.8%); ALP increased (1.2% versus 2.9%); and total bilirubinaemia (5.5% versus 6.4%).

Of note, across the ALL and NHL studies, non-VOD/SOS drug induced liver injury (DILI; Hy's law) was reported in 2 (0.2%) patients (hepatitis acute; drug induced liver injury) in the NHL combined chemotherapy study (inotuzumab ozogamicin plus chemotherapy (Study 1003)). Both patients had concomitant elevation of serum bilirubin > 2 x upper limit of normal (ULN) and transaminases of > 3 x ULN without evidence of cholestasis or other more likely aetiologies (that is, confirmed Hy's law cases). No confirmed Hy's law cases were observed in the pivotal study in either the inotuzumab ozogamicin arm or the control arm.

Patients with less than adequate liver function were excluded from the pivotal study (for example, history of chronic liver disease such as cirrhosis or chronic alcohol abuse). Therefore, the pivotal study included 230 patients with normal hepatic function, 74 patients with mild hepatic impairment, 2 patients with moderate hepatic impairment (both in the inotuzumab ozogamicin arm) and no patients with severe hepatic impairment. The number of patients with moderate or severe hepatic impairment in the pivotal study is too limited to draw meaningful conclusions relating to the safety of inotuzumab ozogamicin in these patient groups.

VOD/SOS

VOD was reported in 14% (23/164) of patients in the inotuzumab ozogamicin arm during or following treatment or following HSCT compared to 2.1% (3/143) of patients in the control arm. In the 79 patients treated with inotuzumab who proceeded to follow-up HSCT, VOD was reported in 18 (22.8%) patients. In all 164 patients treated with inotuzumab ozogamicin during study treatment or in follow-up without intervening HSCT, VOD was reported in 5 (3.0%) patients. Of the 23 patients with VOD in the inotuzumab ozogamicin arm at the data cut-off date of 1 September 2016, 10 cases had not resolved, 8 cases had resolved, and 5 cases had resulted in death (all post-HSCT).

Based on data in the SCS for patients in the inotuzumab arm who proceeded to HSCT (n = 77), VOD was reported 2 fold more frequently in patients with a prior history of liver disease and/or hepatitis than in patients without such a history (35% (7/20) versus 17.5% (10/57), respectively). One fatal case of VOD occurred in a patient with a prior history of liver disease and/or hepatitis. Therefore, it is reasonable to conclude that patients with a prior history of liver disease and/or ongoing liver disease are at an increased risk of severe, life-threatening VOD, when treated with inotuzumab ozogamicin. Consequently, in the absence of adequate safety data in patients with a prior history of moderate or severe liver disease it is recommended that treatment with inotuzumab ozogamicin be contraindicated in these patients. In addition, inotuzumab ozogamicin should be contraindicated in all patients with a prior history of VOD.

Based on the univariate logistic regression analysis (n = 79), factors associated with an increased risk of VOD post-HSCT were, exposure to dual alkylator conditioning therapy (dual versus single), exposure to busulfan containing conditioning therapy (yes versus no), number of study treatment cycles received at the time of HSCT (continuous), higher last bilirubin level prior to follow-up HSCT (≥ ULN versus < ULN), and increased age (≥ 55 years versus < 55 years). Based on the multivariate logistic regression analysis (n = 62), factors associated with an increased risk of VOD post-HSCT were, exposure to dual alkylator conditioning therapy (dual versus single), last bilirubin prior to follow-up HSCT (≥ ULN versus < ULN), and last AST or ALT prior to follow-up HSCT (> 1.5 x ULN versus ≤ 1.5 x ULN). Busulfan containing conditioning therapy and age variables were excluded from the final multivariate model due to correlation with other variables in the model.

Myelosuppression/cytopenia

Myelosuppression/cytopenias Grade 3 to 4 events were reported in 80.5% (132/164) of patients in the inotuzumab arm and 88.1% (126/143) of patients in the control arm. Grade 3 to 4 AEs reported in ≥ 20% of patients in the inotuzumab ozogamicin arm (versus control, respectively) were, neutropenia (47.0% versus 44.1%), thrombocytopenia, (40.9% versus 59.4%), leukopenia (26.8% versus 37.1%), febrile neutropenia (26.8% versus 53.8%), and anaemia (22.6% versus 44.1%). There were 2 (1.2%) patients with pancytopenia Grade 3 to 4 in the inotuzumab ozogamicin arm compared to 4 (2.8%) patients in the control arm. There was 1 (0.6%) death due to an AE in the inotuzumab ozogamicin arm (neutropenic sepsis) and no deaths due AEs in the control arm.

The following laboratory test abnormalities (Grade 3 to 4 AEs) were reported with an incidence of ≥ 50% in patients in the inotuzumab ozogamicin arm (versus control, respectively): leucocytes decreased (81.6% versus 97.9%); lymphopenia (71.2% versus 90.1%); neutrophil count decreased (85.9% versus 85.8%); and platelet count decreased (76.7% versus 98.6%).

Infections

Infection AEs (all grades) were reported notably less frequently in the inotuzumab ozogamicin arm than in the control arm (48.8% (80/164) versus 76.9% (110/143)), as

were Grade 3 to 4 AEs (23.8% (39/164) versus 50.3% (72/143), respectively). The most commonly reported infections Grade 3 to 4 AE occurring in ≥ 2% of patients in the inotuzumab ozogamicin arm (versus control, respectively) were pneumonia (4.3% versus 4.2%), bacteraemia (3.7% versus 7.0%), neutropenic sepsis (2.4% versus 4.2%) and staphylococcal bacteraemia (2.4% versus 2.1%). There were 8 (4.9%) fatal infections (Grade 5 AEs) in the inotuzumab ozogamicin arm (3 x pneumonia, 2 x sepsis, 1 x each for neutropenic sepsis, septic shock, staphylococcal sepsis, and pseudomonal sepsis), and 7 (4.9%) fatal infections (Grade 5 AEs) in the control arm (2 x sepsis, 1 x each klebsiella sepsis, lung infection, septic shock, pseudomonal pneumonia, and systemic mycosis).

Infusion related AEs

Infusion related AEs (all grades) were reported less frequently in the inotuzumab ozogamicin arm than in the control arm (32.3% (53/164 versus 44.1% (63/143)). The majority of 'infusion-related AEs' in both treatment arms were Grade 1 to 2 in severity. 'Infusion related AEs' (all grades) reported in ≥ 2% of patients in the inotuzumab ozogamicin arm (versus control, respectively) were pyrexia (12.8% versus 25.2%), chills (4.9% versus 5.6%), rash (4.9% versus 8.4%), hypotension (4.3% versus 5.6%), dizziness (2.4% versus 3.5%) and hyperhidrosis (2.4% versus 1.3%). There were no reports of anaphylaxis in either treatment arm. There were no reports of death associated with infusion related AEs in either treatment arm.

Haemorrhage AEs

Haemorrhage AEs (all grades) were reported more frequently in patients in the inotuzumab ozogamicin arm than in the control arm (33.5% (55/164) versus 29.4% (42/143)), and the majority of events were Grade 1 to 2 in severity. 'Haemorrhage AEs' (all grades) reported in ≥ 2% of patients in the inotuzumab ozogamicin arm (versus control, respectively) were epistaxis (14.6% versus 8.4%), contusion (6.1% versus 2.1%), and haematuria (2.4% versus 2.1%). Grade 3 to 4 AEs were reported in 4.9% of patients in both treatment arms, and the only event reported in ≥ 1% of patients in the inotuzumab arm (versus control, respectively) was epistaxis (1.2% versus 1.4%). Deaths due to 'haemorrhage AEs' were reported in 2 (1.2%) patients in the inotuzumab ozogamicin arm (1 x each gastrointestinal haemorrhage, intra-abdominal haemorrhage, and haemorrhagic shock) and 1 (0.7%) patient in the control arm (1 x haemorrhage intracranial).

Inflammatory GI AE events

Inflammatory GI AEs (all grades) were reported less frequently in the inotuzumab ozogamicin arm than in the control arm (17.1% (28/164) versus 28.7% (41/143)). The majority of 'inflammatory GI AEs' were Grade 1 to 2 in severity in both treatment arms. In the inotuzumab ozogamicin arm, Grade 3 AEs were reported in 4 (2.4%) patients (stomatitis; 1 x mucosal inflammation; 1 x colitis), no Grade 4 AEs were reported and 1 patient experienced a Grade 5 AE (colitis ischaemic).

Pancreatitis

Pancreatitis AEs (all grades) were reported notably more frequently in patients in the inotuzumab ozogamicin arm than in the control arm (11.0% (18/164 versus 2.1% (3/143)), as were Grade 3 to 4 AEs (4.9% (8/164) versus 0.7% (1/143)). 'Pancreatitis AEs' Grade 3 to 4 reported in ≥ 1 patient in either treatment arm (inotuzumab ozogamicin versus control, respectively) were lipase increased (n = 7, 4.3% versus n = 1, 0.7%) and amylase increased (n = 3, 1.8% versus 0%). There were no 'pancreatitis AEs' Grade 5 events reported in either treatment arm. No permanent treatment discontinuations due 'pancreatitis AEs' were reported in either treatment arm.

Pancreatic-related laboratory test abnormalities were frequently observed in both the inotuzumab ozogamicin and control arms. The results for the inotuzumab ozogamicin and control arms were (respectively), lipase increased all grades (30.4% versus 18.6%),

Grade 3 (10.8% versus 2.0%), and Grade 4 (1.4% versus 0%), and serum amylase increased all grades (13.4% versus 10.5%), Grade 3 (2.5% versus 0.9%), and Grade 4 (0% versus 0%).

Tumour lysis syndrome

Tumour lysis syndrome (TLS) AEs were reported in 4 (2.4%) patients in the inotuzumab ozogamicin arm (including 2 x Grade 3 and 1 x Grade 4) and 3 (2.1%) patients in the control arm (including 1 x Grade 3). There were no permanent treatment discontinuations or Grade 5 AEs due to TLS in patients receiving inotuzumab ozogamicin.

Second primary malignancy (SPM AEs)

There were 9 (5.5%) second primary malignancy (SPM) AEs in the inotuzumab ozogamicin arm and none in the control arm. The 'SPM AEs' (one each) in the inotuzumab arm were anogenital warts, cancer pain, chloroma, infected neoplasm, leukaemia cutis, oral neoplasm benign, skin papilloma, tumour pain, and uterine leiomyoma. The majority of events were Grade 1 to 2 severity (8/9), with the only Grade 3 AE being chloroma. There were no Grade 4 or 5 'SPM AEs'.

Neurotoxicity

Neurotoxicity AEs (all grades) were reported more frequently in patients in the inotuzumab ozogamicin arm compared to the control arm (10.4% versus 7.0%, respectively), primarily due to the increased frequency of peripheral neuropathy (3.7% versus 1.4%, respectively).

Nephrotoxicity

Nephrotoxicity AEs' were reported in a similar proportion of patients in the inotuzumab ozogamicin arm and the control arm (4.9% versus 5.6%, respectively). The only AE (all grades) reported in ≥ 2% of patients was acute kidney injury in the inotuzumab ozogamicin arm (2.4%, inotuzumab ozogamicin versus 1.4%, control).

Interstitial lung disease (ILD)

There were no AEs of interstitial lung disease (ILD) reported in Study B1931022. However, 1 patient in the inotuzumab ozogamicin arm was reported to have Grade 1 obliterative bronchiolitis and pneumonitis and 1 patient in the control arm was reported to have Grade 2 bronchiolitis.

QT interval prolongation

QT prolongation (clustered) AEs (all grades) were reported in 5 (3.0%) patients in the inotuzumab ozogamicin arm (3 x ECG QT prolonged (1 x Grade 1, 2 x Grade 2); 1 x syncope (1 x Grade 3); 1 x ventricular tachycardia (1 x Grade 2)), and 3 (2.1%) patients in the control arm (1 x ECG QT prolonged (1 x Grade 2); and 1 x each (Grade 1) syncope and ventricular tachycardia). There were no reported cases of torsade de pointes. There were no fatal AEs reported for QT prolongation. Increases from baseline in the QTcF interval of ≥ 60 ms were reported in a similar proportion of patients in the inotuzumab ozogamicin and control arms (2.5% (4/162) versus 2.4% (3/124), respectively). QTcF values > 500 ms were reported in no patients in the inotuzumab ozogamicin arm and 1 (0.8%) patient in the control arm.

In both treatment arms the mean maximum QTcF was prolonged to ≥ 10 ms (16.5 ms (90% CI: 14.3, 18.7), inotuzumab ozogamicin; 10.8 ms (90% CI: 8.0, 13.6), control), with the highest upper bound 90% CI for the mean QTcF for all time points being ≥ 20 ms in both treatment arms. The reason for QTcF prolongation in both treatment arms is unknown, but is not satisfactorily explained by the use of concomitant medications known to prolong the QT intervals and/or electrolyte disturbances.

Other risks

- In the pivotal study, in the inotuzumab ozogamicin arm AEs (all grades) were reported in 99.3% (133/134) of patients aged < 65 years and in 100% (30/30) of patients aged ≥ 65 years, while AEs Grade 3 to 4 were reported in 74.6% (100/134) and 76.7% (23/30) of patients, respectively. Both SAEs and Grade 5 AEs were reported less frequently in the inotuzumab ozogamicin arm in patients aged < 65 years than in patients aged ≥ 65 years (SAEs (48.5%, n = 65 versus 66.7%, n = 20); Grade 5 AEs (14.2%, n = 19 versus 23.3%, n = 7)). Permanent treatment discontinuations due to AEs occurred more frequently in patients in the inotuzumab ozogamicin arm aged < 65 years than aged ≥ 65 years (20.1%, n = 27 versus 10.0%, n = 3)). The interpretation of the safety data in patients aged ≥ 65 years treated with inotuzumab ozogamicin is limited by the small number of patients in this group. The univariate analysis (Day 120 SU) showed that in patients treated with inotuzumab ozogamicin who proceeded to HSCT (n = 79), age ≥ 55 years (n = 17) may significantly increase the risk of developing VOD/SOS post-HSCT compared to age < 55 years (n = 62). Based on the 77 patients in the inotuzumab ozogamicin arm who underwent HSCT (sCSR), the risk of developing VOD/VOS post-HSCT was 50% (3/6) in patients aged ≥ 65 years and 19.7% (14/71) in patients aged < 65 years.
- No notably increased risks based on gender or race were identified in patients treated with inotuzumab ozogamicin. However, safety data in Black patients were limited due to the small number of patients in this racial group treated with inotuzumab ozogamicin.
- The safety data in patients with mild renal impairment do not give rise to concern. There were no adequate safety data in patients with moderate renal impairment and no safety data in patients with severe renal impairment/ESRD.
- The safety data in patients with mild hepatic impairment suggest that inotuzumab ozogamicin should be used cautiously in these patients. There were no adequate safety data in patients with moderate or severe hepatic impairment. Treatment with inotuzumab ozogamicin is associated with notable hepatotoxicity, including life-threatening and sometimes fatal VOD. Therefore, it is recommended that inotuzumab ozogamicin be contraindicated in patients with moderate or severe hepatic impairment.
- There were no pivotal safety data in patients with cardiac disease as the pivotal study excluded patients with active heart disease (New York Heart Association (NYHA) class ≥ 3).
- Laboratory abnormalities, other than those previously discussed for haematological, hepatic and pancreatic abnormalities do not give rise to concern.
- There were no notable changes in vital signs in patients in the inotuzumab arm.

First round assessment of benefit-risk balance

The pivotal study in patients with ALL demonstrated a notably superior CR/CRi rate in the ITT218 population in the inotuzumab ozogamicin arm compared to the control arm. The majority of patients in the inotuzumab ozogamicin arm who achieved CR/CRi did so within the first 2 treatment cycles, with no patients achieving haematological remission after Cycle 3. The CR/CRi data suggest that, if considered suitable for HSCT, most patients treated with inotuzumab ozogamicin might be able to proceed to this potentially curative treatment modality. This provides a significant clinical advantage for patients treated with inotuzumab ozogamicin compared to patients treated with standard chemotherapeutic regimens.

However, while treatment with inotuzumab ozogamicin is associated with a significantly improved chance of haematological remission compared to standard chemotherapy regimens this does not translate into a statistically significant improved overall survival benefit. Furthermore, the benefits of achieving CR/CRi and then proceeding to HSCT for patients treated with inotuzumab ozogamicin are offset, at least to some extent, by the risks of hepatotoxicity, including fatal and life threatening VOD/SOS, and post-HSCT non-relapse mortality. Nevertheless, on balance it is considered that the benefits of treatment with inotuzumab ozogamicin outweigh the risks.

For patients who achieve CR/CRi but do not proceed to HSCT a maximum of six treatment cycles are recommended, provided the patient remains in remission. These patients appear to be at a lower risk of hepatotoxicity, including fatal and life-threatening VOD/SOS, than patients achieving haematological remission and proceeding to HSCT. However, the benefit-risk balance of continuing treatment with inotuzumab ozogamicin in patients achieving CR/CRi but not proceeding to transplant is unclear. It might be clinically prudent to discontinue treatment with inotuzumab ozogamicin in these patients once a decision not to proceed to HSCT has been made. The total number of patients in the inotuzumab ozogamicin arm treated for 6 cycles was limited, with 15 (9.1%) patients starting a 6th cycle of treatment and 10 (6.1%) patients finished 6 treatment cycles. Five (5) patients who did not proceed to HSCT after inotuzumab ozogamicin treatment were still alive at 18 months. Of these 5 patients, 2 patients had received 3 cycles, 2 patients had received 4 cycles, and 1 patient had received 6 cycles.

First round recommendation regarding authorisation

It is recommended that inotuzumab ozogamicin be approved for the treatment of adults with relapsed or refractory CD-22 B cell precursor acute lymphoblastic leukaemia (ALL).

Clinical questions and second round evaluation

General

Question 1

Please provide information on progress towards undertaking studies with inotuzumab ozogamicin in a paediatric population with acute lymphoblastic leukaemia.

Sponsor's response:

Published Data for Single-Agent Inotuzumab Ozogamicin in Pediatric Patients with B cell Acute Lymphoblastic Leukemia (ALL):

Currently, there is a limited amount of published data on the use of inotuzumab ozogamicin in pediatric patients with B cell ALL.

MD Anderson Cancer Center (MDACC) Investigator-initiated Research (IIR) Study:

A single institution, Phase II, IIR study exploring the safety and efficacy of inotuzumab ozogamicin patients with relapsed or refractory B cell ALL was conducted at MDACC (Texas, United States (US)). The study enrolled 6 patients who were 18 years of age or younger.[36] In the publication by Rytting M et al, 2014;[37] the results of 5 children (4 to 15 years of age) enrolled on this MDACC IIR study were described. Three of the 5 children

[36] Kantarjian H et al, 2013. Results of inotuzumab ozogamicin, a CD22 monoclonal antibody, in refractory and relapsed acute lymphocytic leukemia. *Cancer* 2013; 119: 2728-2736
[37] Rytting M et al, 2014. Initial experience with CMC-544 (inotuzumab ozogamicin) in pediatric patients with relapsed B cell acute lymphoblastic leukemia. *Pediatr Blood Cancer* 2014; 61: 369-372

received 1.3 mg/m^2 inotuzumab ozogamicin given once every 3 weeks; 1 of these patients had a dose escalation to 1.8 mg/m^2 for the second course. Two patients received the weekly schedule of inotuzumab ozogamicin as described above. All children received at least 2 courses of inotuzumab ozogamicin. One patient achieved a complete remission (CR), 2 patients achieved bone marrow morphologic remission with incomplete platelet count recovery (CRp), and 2 patients had no response. Toxicities included fever, sepsis and liver enzyme elevation. Three patients proceeded to a hematopoietic stem cell transplant (HSCT) following inotuzumab ozogamicin therapy. One of the transplanted patients developed venoocclusive disease (VOD) following receipt of an unrelated donor HSCT; the VOD resolved after therapy with defibrotide.

Compassionate access:

Inotuzumab ozogamicin has also been used in the compassionate access setting. Clinical findings from 34 children and young adults (aged 2.3 to 21.4 years (median 11.7)) with multiply relapsed B cell ALL, treated with inotuzumab ozogamicin through the sponsor's compassionate access program, were recently presented at the American Society Clinical Oncology (ASCO) annual meeting.[38] Patients were heavily pretreated in 1st-5th relapse; 28 patients were refractory to their preceding regimen. Thirteen patients had received a prior HSCT. Patients received 1 to 4 cycles (3 weekly doses) of inotuzumab ozogamicin. Of the 29 patients with > 5% bone marrow blasts at baseline, 18 (62%) patients achieved a CR of whom 13 achieved minimal residual disease (MRD) negativity; 15 patients proceeded to HSCT, and 5 proceeded to chimeric antigen receptor (CAR) T-cell therapy. Grade 1 to 4 liver toxicity was reported in 32% of patients; findings were primarily asymptomatic elevations in transaminases/bilirubin. No VOD developed during inotuzumab ozogamicin treatment, but VOD was reported in 8/15 patients who proceeded to allogeneic HSCT after inotuzumab ozogamicin therapy; 1 event was fatal while the others recovered. There was a higher incidence of VOD in patients who had received a prior HSCT (6/8 patients) versus no prior HSCT (2/7 patients). Grade 3/4 infections were reported in 34% of patients.

Ongoing Trials of Inotuzumab Ozogamicin in Pediatric Patients with B cell ALL:

There are 2 ongoing pediatric studies with inotuzumab ozogamicin.

- *ITCC-059 Study*

The ITCC-059 Study is a clinical research collaboration (CRC) trial sponsored by the Innovative Therapies for Children with Cancer (ITCC) pediatric consortium through Erasmus Medical Center in the Netherlands. This study is being conducted in fulfillment of the Paediatric Investigational Plan (PIP) which was approved on 24 November 2014 by the European Medicines Agency's (EMA) Paediatric Committee (PDCO).[39] This ongoing study is investigating weekly inotuzumab ozogamicin as a single agent with the goal of establishing the recommended dose of inotuzumab ozogamicin when given as a single agent to pediatric patients ≥ 1 year of age with relapsed or refractory B cell ALL. In the second part of this study, inotuzumab ozogamicin will be combined with a standard ALL re-induction chemotherapy regimen (the UKALL-R3 regimen) to determine a recommended dose of inotuzumab ozogamicin in combination with this regimen in pediatric patients with second or greater relapsed or refractory B cell ALL.

In order to fulfil the PIP, a randomized open label superiority trial will subsequently be conducted in order to evaluate the safety and efficacy of inotuzumab ozogamicin (based on the dose determined in the ITCC-059 study) added to a modified UKALL-R3 regimen in

[38] Bhojwani D et al, 2017. Inotuzumab ozogamicin in pediatric patients with relapsed/refractory acute lymphoblastic leukemia (R/R ALL). *J Clin Oncol* 2017; 35:10512
[39] Paediatric Investigational Plan (PIP) for inotuzumab ozogamicin: EMA PDCO opinion and decision: http://www.ema.europa.eu/ema/index.jsp?curl = pages/

children and adolescents with early first relapse of B cell ALL.

- *AALL 1621 Study*

The AALL 1621 Study is an IIR sponsored by the Children's Oncology Group (COG) in the US investigating inotuzumab ozogamicin at a starting dose of 1.8 mg/m^2/cycle using the weekly schedule in pediatric patients ≥ 1 year of age with relapsed or refractory B cell ALL. As of 30 October 2017, 16 of the planned 56 patients have been enrolled (Pfizer's INSPIRE Tracking System (Accessed 9 November 2017)).

Clinical evaluator's comment

The sponsor's response is satisfactory.

Pharmacokinetics

Question 2

In the Summary of Clinical Pharmacology, the value given for mean AUC_{tau} *of 4350 ng.hr/mL in Study Cycle 4 Day of Dose 94 (Table 16) appears to be incorrect. The source table from which the value is taken (PMAR-EQDD-B193a-DP4-202-Supplement, Table 14) indicates that the value is 43500 ng.hr/mL. Please comment on this apparent discrepancy.*

Sponsor's response

The simulated mean for area under the curve (AUC_{tau}) for Cycle 4 Day 92 is 43500 ng.hr/mL. The mean AUC_{tau} for Cycle 4 Day 92 is incorrect. (The sponsor provided a corrected Table 16).

Clinical evaluator's comment

The sponsor's response is satisfactory. However, the quality evaluator should be asked to comment on the response.

Question 3

It was reported that there are 19 chiral centres on the activated calicheamicin derivative structure and two possible E-Z isomerisation sites. During the studies aimed at identifying the various impurities in activated calicheamicin derivative it was reported that an interconverting isomer of activated calicheamicin derivative was being separated from the main HPLC peak under the conditions used for the analysis and release of the material. Please comment on the clinical significance of the identified interconverting isomer of activated calicheamicin derivative.

Sponsor's response

The presence of the interconverting isomers in the activated calicheamicin derivative is not clinically significant for one or both of the following reasons:

- The inotuzumab ozogamicin administered to the patient contains an invariant ratio of isomers of the calicheamicin derivative. Since the isomers are interconverting and the time needed to reach equilibrium is relatively short, their ratio is thermodynamically controlled. Based upon the literature cited in the quality module, the equilibration of the isomers does not require nucleophilic attack on the hydrazide; therefore, the equilibration proceeds irrespective of the medium in which the calicheamicin derivative is contained (that is, including both organic and aqueous solvents). Therefore, given the amount of time involved in the manufacturing of the activated calicheamicin derivative and the inotuzumab ozogamicin drug substance and drug product, equilibrium is consistently achieved.
- The point of isomerization is removed during the delivery of the active calicheamicin molecule to cellular DNA. The origin and fate of the isomers is described in the quality

module. The isomeric moiety is the hydrazide portion of the linker which is hydrolyzed when inotuzumab ozogamicin enters the tumor cell. This hydrolysis removes the point of isomerism; therefore, the same calicheamicin molecule, after being further reduced and without isomeric potential, interacts with DNA, and leads to cell death.

Clinical evaluator's comment

The sponsor's response is satisfactory.

Question 4

In the synopsis for the population modelling analysis report (PMAR-EQDD-B193a-Regulatory Response-162a), in the paragraphs discussing the results for the PFS analysis under Tables S7 and S9 reference is made to predictors of survival associated with a lower risk of death. The same issue arises in the discussion of the results for the PFS analysis in Section 7 of the report. However, as the data refer to PFS analyses should the references be to predictors of progression free survival with a lower risk of progression free events rather than predictors of survival associated with a lower risk of death?

Sponsor's response

In the clinical module, PMAR-EQDD-B193a-Regulatory Response-628, in the paragraphs discussing the results for the PFS analysis under Tables S7 and S9 and in the discussion of the results for the PFS analysis in Section 7 of the report, the data should be referencing to predictors of progression free survival (PFS) with a lower risk of PFS events rather than predictors of survival associated with a lower risk of death. (The sponsor provided corrected text for discussion of PFS analysis under Tables S7 and S9 and in Section 7 of the PPK analysis report).

Clinical evaluator's comment

The sponsor's response is satisfactory.

Question 5

In the PK/PD Study PMAR-EQDD-B193c-DP4-533, it is not clear why the changes from baseline in the QTcF and QTcS at therapeutic and supra-therapeutic C_{max} levels were summarised using the median and 2.5th to 97.5th percentiles. The sponsor is requested to summarise the results using mean changes in QTcF and QTcS with 90% confidence intervals at therapeutic and supra-therapeutic C_{max} levels.

Sponsor's response

In the clinical module, PMAR-EQDD-B193c-DP4-533, summary statistics were reported as the median and 95% confidence interval (CI) since the data were slightly skewed and the median was considered the most appropriate measure of central tendency. However, as shown in Table 10 (see below), the mean, median, and geometric mean (summary statistic for log-normally distributed data) were similar.

Table 10: Simulated changes in QTcF and QTcS

	Median (msec)	Mean (msec)	Mean 90% CI (msec)	Geometric Mean (msec)	Geometric Mean 90% CI (msec)
Therapeutic C_{max}					
QTcF Model	2.53	2.71	1.13, 4.75	2.46	2.40, 2.52
QTcS Model	2.70	2.91	1.11, 5.07	2.61	2.55, 2.68
Supratherapeutic C_{max}					
QTcF Model	3.87	4.16	1.74, 7.29	3.77	3.68, 3.86
QTcS Model	4.14	4.47	1.71, 7.78	4.01	3.90, 4.11

Source: Epharmacology Artifact ID RA 14061483

C_{max}: maximum plasma concentration; CI: confidence interval; msec: milliseconds; QTcF: QT interval corrected using Fridericia's formula; QTcS: QT interval corrected using population-specific formula.

Clinical evaluator's comment

The sponsor's response is satisfactory.

Efficacy

Question 6

In Study B1931022, the control arm consisted of investigator's choice of FLAG, MXN/Ara-C or HiDAC regimens. Please comment on the place of the three control regimens in current Australian clinical practice for the treatment of relapsed and refractory CD22 positive ALL, including Ph+ disease.

Sponsor's response

In the treatment of patients with relapsed and refractory B cell ALL, there is no single standard of care. Given this, and as agreed with regulators as well as global ALL key opinion leaders, patients in the control arm were randomized to receive 1 of 3 predefined cytarabine-based chemotherapy regimens: fludarabine + cytarabine + granulocyte-colony stimulating factor (FLAG), mitoxantrone + cytarabine (MXN/Ara-C), or high-dose cytarabine (HIDAC). Reported remission rates with these regimens vary from 32% to 83.3%.[40,41,42,43,44;] Of note, tyrosine kinase inhibitors (TKIs) were not included in the control regimens because patients with Philadelphia chromosome positive (Ph+) B cell ALL would have already been expected to have progressed after standard treatment with TKIs.

Based on feedback from hematologists in Australia, cytarabine-based regimens, such as FLAG, MXN/Ara-C, and HIDAC, are standardly used in current clinical practice for the treatment of relapsed and refractory CD22 positive B cell ALL, including in patients with Ph+ disease. Therefore, the comparators used in the control arm of Study B1931022 are applicable in Australia for patients with relapsed or refractory B cell ALL.

Clinical evaluator's comment

The sponsor's response is satisfactory.

[40] Montillo M, et al. Treatment of relapsed adult acute lymphoblastic leukemia with fludarabine and cytosine arabinoside followed by granulocyte colony-stimulating factor (FLAG-GCSF). *Leuk Lymphoma* 1997; 25: 579-583

[41] Liso V, et al. Mitoxantrone and continuous infusion of cytosine arabinoside in refractory and relapsed acute lymphoblastic leukemia. *Acta Haematol* 1992; 87: 54-57.

[42] Herzig RH, et al. High-dose cytosine arabinoside therapy for refractory leukemia. *Blood* 1983; 62: 361-369

[43] Advani AS, et al. Response to high dose cytarabine (HIDAC) as first salvage for relapsed acute lymphocytic leukemia in patients receiving HIDAC as initial therapy. *Blood* 2011;118:Abstr 2594

[44] Specchia G, et al. FLAG-IDA in the treatment of refractory/relapsed adult acute lymphoblastic leukemia. *Ann Hematol* 2005; 84: 792-795

Question 7

Please provide a summary of the cumulative incidence of post-transplant mortality and post-transplant non-relapse mortality for patients with follow-up HSCT in the ITT population using the updated survival data of 4 January 2017 LSLV. The data should be presented in the same format as Table 64, page 275, supplemental CSR

Sponsor's response

Table 11 (see below) summarises post-transplant mortality and non-relapse mortality for all patients with follow-up HSCT in the ITT population using the updated survival data as of 4 January 2017 last subject last visit (LSLV).

Table 11: Study B1931022 Cumulative incidence of post-transplant mortality and non-relapse mortality for patients with follow-up HSCT; ITT population (4 January 2017 LSLV)

	Inotuzumab Ozogamicin (N=164)	Defined Investigator's Choice of Chemotherapy (N=162)
Number of patients who underwent follow-up transplant, n (%)	79 (48.2)	36 (22.2)
Post-transplant mortality		
Number of patients with post-transplant mortality[a], n (%)	53 (67.1)	25 (69.4)
Estimated mortality rate at end of Day 100 (95% CI)	25.32 (17.14, 36.44)	5.56 (1.42, 20.43)
Estimated mortality rate at end of Month 12 (95% CI)	56.96 (46.42, 67.99)	34.27 (21.08, 52.47)
Estimated mortality rate at end of Month 24 (95% CI)	63.29 (52.80, 73.76)	72.26 (55.82, 86.63)
Estimated mortality rate at end of Month 36 (95% CI)	68.91 (57.15, 80.02)	77.81 (60.54, 91.26)
Post-transplant non-relapse mortality		
Number of patients with post-transplant non-relapse mortality adjusting for competing risks[a, b], n (%)	31 (39.2)	8 (22.2)
Estimated mortality rate at end of Day 100 (95% CI)	20.25 (12.19, 29.77)	5.56 (0.97, 16.50)
Estimated mortality rate at end of Month 12 (95% CI)	36.71 (26.14, 47.31)	14.13 (5.04, 27.75)
Estimated mortality rate at end of Month 24 (95% CI)	37.97 (27.27, 48.60)	23.17 (10.62, 38.55)
Estimated mortality rate at end of Month 36 (95% CI)	42.13 (29.05, 54.64)	23.17 (10.62, 38.55)

Source: Module 5, Section 5.3.5.1, Study B1931022 sCSR (04 January 2017 LSLV), Table 14.2.2.8.3; Module 5, Section 5.3.5.1, Study B1931022 sCSR (04 January 2017 LSLV), Table 14.2.2.8.4.

Defined Investigator's choice was 1 of the defined chemotherapy regimens (FLAG, MXN/Ara-C, or HIDAC).

Abbreviations: CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete hematologic recovery; FLAG=fludarabine + cytarabine + G-CSF; G-CSF=granulocyte-colony stimulating factor; HIDAC=high-dose cytarabine; HSCT=hematopoietic stem cell transplant; ITT=intent-to-treat; MXN/Ara-C=mitoxantrone + cytarabine; n=number of patients that met the criteria; N=number of patients.

a. Number of patients with post-transplant was used for percent calculation.

b. Competing risk was defined as death due to relapse from CR/CRi after follow-up transplant, or death where the mechanism of death was disease progression or relapse. Events that occurred after competing risk were not included in the calculation of cumulative incidence rate.

As of 8 March 2016 cut-off, the number of patients with post-transplant mortality was 46 (59.7%) patients in the inotuzumab ozogamicin arm and 19 (57.6%) patients in the control arm. The number of patients with post-transplant non-relapse mortality was 30 (39.0%) patients in the inotuzumab ozogamicin arm, and 9 (27.3%) patients in the control arm.

As of 4 January 2017 LSLV, the number of patients with post-transplant mortality was 53 (67.1%) patients in the inotuzumab ozogamicin arm and 25 (69.4%) patients in the control arm. The number of patients with post-transplant non-relapse mortality was 31 (39.2%) patients in the inotuzumab ozogamicin arm and 8 (22.2%) patients in the control arm.

The number of patients with post-transplant non-relapse mortality in the control arm decreased from 9 to 8 patients between the 8 March 2016 cut-off and 4 January 2017 LSLV. The reason for this was due to a change in the reason for cause of death for 2 patients (considered to have died due to relapse of disease instead of non-relapse) and

there was 1 additional patient with non-relapse death.Overall, the conclusions regarding post-transplant mortality and post-transplant non-relapse mortality for patients with follow-up HSCT in the ITT population using the updated survival data of 4 January 2017 LSLV remain the same as those based on the 8 March 2016 cut-off. As of the 4 January 2017 LSLV, there was a higher post-HSCT non-relapse mortality rate in patients in the inotuzumab ozogamicin arm compared to the Investigator's choice of chemotherapy arm, resulting in a higher Day 100 post-HSCT mortality rate. However, as previously noted, the overall post-HSCT mortality rate (including both non-relapse mortality as well as relapse related mortality) was similar in the inotuzumab ozogamicin arm and Investigator's choice of chemotherapy arm (67% and 69%, respectively).

Clinical evaluator's commen

The sponsor's response is satisfactory. In the updated data, the overall risk of post-transplant relapse related mortality in patients who underwent HSCT was similar in the inotuzumab ozogamicin arm and in the control arm (67.1% versus 69.7%, respectively), but the 100 day relapse related mortality rate was higher in the inotuzumab ozogamicin arm than in the control arm (25.32% versus 5.56%, respectively).

The overall risk of post-transplant non-relapse mortality in patients who underwent HSCT was higher in the inotuzumab ozogamicin arm than in the control arm (39.2% versus 22.2%, respectively), and 100 day non-relapse related mortality rate was higher in the inotuzumab ozogamicin arm than in the control arm (20.25% versus 5.56%, respectively). In Study B1931022, the most common causes of post-HSCT non-relapse mortality included VOD and infections in the inotuzumab ozogamicin arm (Day 120 Safety Update). VOD was reported in 18 (22.8%) of the 79 patients in the inotuzumab ozogamicin arm, who underwent HSCT, and 5 of these patients experienced a fatal VOD event. In the inotuzumab ozogamicin arm, among patients with ongoing VOD at time of death, 6 patients died due to multi-organ failure (MOF) or infection (3 patients died due to MOF, 2 patients died due to infection, and 1 patient died due to MOF and infection).

The updated draft PI includes a boxed warning and a precautionary statement relating to the increased risk of post-HSCT non-relapse mortality in patients treated with inotuzumab ozogamicin.

Question 8

It is noted that the updated number of patients in the Investigator's choice of chemotherapy arm who proceeded to HSCT is given as 35 in the US label and 36 in the LSLV (4 January 2017) data. Please comment on this apparent discrepancy.

Sponsor's response

The approved USPI reflects the Study B1931022 data from the total number of patients in the inotuzumab ozogamicin arm and Investigator's choice of chemotherapy arm that proceeded to hematopoietic HSCT as of the BLA Day 120 Safety Update (that is, cut-off date of 1 September 2016); at that time, 35 patients in the Investigator's choice of chemotherapy arm had proceeded to hematopoietic HSCT.

As of Study B1931022 last subject last visit date (LSLV; 4 January 2017), 36 patients in the Investigator's choice of chemotherapy arm had proceeded to hematopoietic stem cell transplant (HSCT). Although the FDA was made aware of this updated data during BLA review, the Agency did not request the USPI to be updated to reflect this change.

Clinical evaluator's comment

The sponsor's response is satisfactory.

Question 9

Please discuss the benefits and risks of treatment with inotuzumab ozogamicin in patients who achieve a CR/CRi but do not proceed to HSCT. The benefit-risk balance of continuing treatment with inotuzumab ozogamicin in these patients is unclear. Does the sponsor consider that it might be clinically prudent to discontinue treatment with inotuzumab ozogamicin in these patients once a decision not to proceed to HSCT has been made?

Sponsor's response

Efficacy:

In the inotuzumab ozogamicin arm of Study B1931022, all responding patients first achieved remission (complete remission (CR) or complete remission with incomplete hematologic recovery (CRi)) within 1 to 3 cycles; no responding patient first achieved remission after Cycle 3.

Table 12 (see below) shows duration of response (DoR) and overall survival (OS), by maximum cycle received, for patients in the inotuzumab ozogamicin arm of Study B1931022 who achieved CR/CRi and did not undergo follow-up HSCT (as of the 08 March 2016 data cut-off date). Although not statistically significant, responders who received a maximum of 4 to 6 cycles had numerically higher median DoR and OS compared to responders who received a maximum of 1 to 3 cycles (median DoR of 4.2 and 2.5 months, respectively, and median OS of 8.0 and 5.3 months, respectively). Five (5) responders who did not proceed to HSCT after inotuzumab ozogamicin treatment were still alive at 18 months. Of these 5 patients, 2 patients had received 3 cycles and had DoR of 57 and 128 days, 2 patients had received 4 cycles and had DoR of 332 and 488 days, and 1 patient had received 6 cycles and had DoR of 317 days.

Table 12: Study B1931022 Duration of response and overall survival for patients who achieved CR/CRi but did not undergo follow up HSCT by maximum number of treatment cycles received (ITT population, inotuzumab ozogamicin arm) (8 March 2016 data cut-off)

	Inotuzumab Ozogamicin, Maximum Number Cycles Received		Unstratified hazard ratio (97.5% CI)	One-sided unstratified log rank p-value
	1 to 3 Cycles N=18	4 to 6 Cycles N=33		
Duration of Response (month), median (95% CI)	2.5 (1.6, 2.8)	4.2 (3.6, 8.0)	4.726 (2.310, 9.667)	1.0000
Overall Survival (month), median (95% CI)	5.3 (3.4, 9.4)	8.0 (6.7, 13.1)	1.750 (0.829, 3.695)	0.9558

Source: Module 5, Section 5.3.5.1, Table 530.188.10, Module 5, Section 5.3.5.1, Table 530.188.12
CI = confidence interval; CR/CRi = complete remission/complete remission with incomplete hematologic recovery; HSCT = hematopoietic stem cell transplant; ITT = intent-to-treat.

Safety

In order to determine whether more cycles of inotuzumab ozogamicin treatment resulted in increased toxicity in Study B1931022, an analysis of safety (based on 8 March 2016 data cut-off date) according to treatment cycle was undertaken. Patients could receive up to 6 cycles of treatment, though it was recommended that patients proceeding to HSCT be treated with 2 cycles or the fewest number of cycles to achieve CR/CRi (if CR/CRi not achieved after 2 cycles). Reasons for discontinuation of inotuzumab ozogamicin treatment included complete response (39.0%), adverse events (16.5%), objective progression or relapse (14.6%) and resistant disease (11.0%).

Table 13 shows the frequency of all-causality Grade ≥ 3 treatment emergent adverse events (TEAEs) occurring in > 1 patient according to the treatment cycle started. The frequency of all-causality Grade ≥ 3 TEAEs was similar among the patients who started

Cycles 1 through 6 for most of the individual TEAEs. In general, individual Grade ≥ 3 TEAEs did not appear to increase with increasing number of cycles. A few Grade ≥ 3 TEAEs did trend higher in patients treated with more than 3 cycles of inotuzumab ozogamicin (for example, thrombocytopenia, and neutropenia).

Table 13: Study B1931022 Summary of all-causality TEAEs grades ≥ 3 reported in > 1 patient by MedDRA preferred term by cycle started in inotuzumab ozogamicin arm; safety population (8 March 2016 cut-off date)

System Organ Class	Preferred Term	Cycle 1 (N=164) n (%)	Cycle 2 (N=127) n (%)	Cycle 3 (N=87) n (%)	Cycle 4 (N=45) n (%)	Cycle 5 (N=26) n (%)	Cycle 6 (N=15) n (%)
Any AEs		**132 (80.5)**	**109 (85.8)**	**78 (89.7)**	**43 (95.6)**	**26 (100.0)**	**15 (100.0)**
Blood and lymphatic system disorders	**Any**	**114 (69.5)**	**97 (76.4)**	**73 (83.9)**	**40 (88.9)**	**23 (88.5)**	**14 (93.3)**
	Anaemia	30 (18.3)	24 (18.9)	21 (24.1)	12 (26.7)	7 (26.9)	3 (20.0)
	Febrile neutropenia	37 (22.6)	31 (24.4)	20 (23.0)	8 (17.8)	7 (26.9)	3 (20.0)
	Leukopenia	40 (24.4)	35 (27.6)	22 (25.3)	11 (24.4)	5 (19.2)	3 (20.0)
	Lymphopenia	25 (15.2)	25 (19.7)	18 (20.7)	9 (20.0)	6 (23.1)	3 (20.0)
	Pancytopenia	1 (0.6)	2 (1.6)	1 (1.1)	1 (2.2)	1 (3.8)	0
	Neutropenia	63 (38.4)	62 (48.8)	45 (51.7)	25 (55.6)	15 (57.7)	7 (46.7)
	Thrombocytopenia	59 (36.0)	47 (37.0)	33 (37.9)	21 (46.7)	14 (53.8)	11 (73.3)
Gastrointestinal disorders	**Any**	**8 (4.9)**	**7 (5.5)**	**9 (10.3)**	**5 (11.1)**	**2 (7.7)**	**1 (6.7)**
	Ascites	0	0	1 (1.1)	2 (4.4)	0	0
	Gastrointestinal hemorrhage	2 (1.2)	0	0	0	0	0
	Nausea	1 (0.6)	0	2 (2.3)	1 (2.2)	0	0
	Stomatitis	2 (1.2)	2 (1.6)	1 (1.1)	1 (2.2)	0	0
	Vomiting	2(1.2)	1 (0.8)	1 (1.1)	0	0	0
General disorders and administration site conditions	**Any**	**18 (11.0)**	**9 (7.1)**	**7 (8.0)**	**5 (11.1)**	**2 (7.7)**	**1 (6.7)**
	Asthenia	2 (1.2)	0	2 (2.3)	1 (2.2)	0	0
	Disease progression	4 (2.4)	2 (1.6)	1 (1.1)	1 (2.2)	0	0
	Fatigue	3 (1.8)	2 (1.6)	1 (1.1)	0	0	0
	Pain	2 (1.2)	2 (1.6)	1 (1.1)	1 (2.2)	1 (3.8)	0
	Pyrexia	3 (1.8)	3 (2.4)	1 (1.1)	0	0	1 (6.7)
Nervous system disorders	**Any**	**3 (1.8)**	**4 (3.1)**	**2 (2.3)**	**1 (2.2)**	**0**	**0**
	Headache	2 (1.2)	3 (2.4)	2 (2.3)	0	0	0
Infections and infestations	**Any**	**28 (17.1)**	**25 (19.7)**	**20 (23.0)**	**11 (24.4)**	**7 (26.9)**	**3 (20.0)**
	Bacteraemia	4 (2.4)	5 (3.9)	3 (3.4)	1 (2.2)	0	0
	Clostridium difficile colitis	0	2 (1.6)	0	0	0	0
	Escherichia bacteraemia	1 (0.6)	1 (0.8)	1 (1.1)	2 (4.4)	1 (3.8)	0
	Herpes zoster	1 (0.6)	2 (1.6)	2 (2.3)	1 (2.2)	1 (3.8)	0
	Influenza	0	0	1 (1.1)	2 (4.4)	1 (3.8)	0
	Neutropenic sepsis	4 (2.4)	4 (3.1)	3 (3.4)	1 (2.2)	1 (3.8)	1 (6.7)
	Pneumonia	5 (3.0)	2 (1.6)	3 (3.4)	2 (4.4)	3 (11.5)	0
	Sepsis	4 (2.4)	3 (2.4)	1 (1.1)	0	0	0
	Septic shock	1 (0.6)	0	0	0	2 (7.7)	0
	Staphylococcal Bacteraemia	2 (1.2)	1 (0.8)	2 (2.3)	2 (4.4)	0	0
	Staphylococcal sepsis	1 (0.6)	2 (1.6)	0	0	0	0
	Urinary tract infection	1 (0.6)	0	2 (2.3)	1 (2.2)	1 (3.8)	0
Respiratory, thoracic and mediastinal	**Any**	**2 (1.2)**	**3 (2.4)**	**3 (3.4)**	**1 (2.2)**	**1 (3.8)**	**1 (6.7)**
	Dyspnoea	0	2 (1.6)	1 (1.1)	1 (2.2)	0	0
	Epistaxis	2 (1.2)	0	0	0	0	0
Musculoskeletal and connective tissue disorders	**Any**	**6 (3.7)**	**5 (3.9)**	**1 (1.1)**	**2 (4.4)**	**0**	**0**
	Back pain	3 (1.8)	2 (1.6)	1 (1.1)	2 (4.4)	0	0
Investigations	**Any**	**33 (20.1)**	**28 (22.0)**	**24 (27.6)**	**16 (35.6)**	**8 (30.8)**	**7 (46.7)**
	ALT increased	5 (3.0)	3 (2.4)	3 (3.4)	0	0	0
	Amylase increased	1 (0.6)	1 (0.8)	1 (1.1)	2 (4.4)	1 (3.8)	1 (6.7)
	AP increased	2 (1.2)	2 (1.6)	1 (1.1)	0	0	0
	AST increased	6 (3.7)	4 (3.1)	3 (3.4)	2 (4.4)	1 (3.8)	0
	GGT increased	11 (6.7)	9 (7.1)	8 (9.2)	6 (13.3)	2 (7.7)	3 (20.0)
	Hemoglobin decreased	4 (2.4)	1 (0.8)	1 (1.1)	1 (2.2)	0	0
	LDH increased	2 (1.2)	1 (0.8)	0	0	1 (3.8)	0
	Lipase increased	3 (1.8)	4 (3.1)	5 (5.7)	2 (4.4)	1 (3.8)	2 (13.3)
	Platelet count decreased	1 (0.6)	1 (0.8)	2 (2.3)	1 (2.2)	0	0
	WBC decreased	9 (5.5)	7 (5.5)	5 (5.7)	4 (8.9)	2 (7.7)	0
Metabolism and nutrition disorders	**Any**	**17 (10.4)**	**15 (11.8)**	**9 (10.3)**	**5 (11.1)**	**3 (11.5)**	**2 (13.3)**
	Hyperuricaemia	3 (1.8)	2 (1.6)	1 (1.1)	1 (2.2)	0	0
	Hypocalcaemia	2 (1.2)	2 (1.6)	1 (1.1)	0	0	0
	Hypokalaemia	5 (3.0)	7 (5.5)	5 (5.7)	3 (6.7)	3 (11.5)	1 (6.7)
	Hypophosphataemia	4 (2.4)	4 (3.1)	3 (3.4)	0	0	0
	Hyponatremia	2 (1.2)	0	0	0	0	0
	Tumour lysis syndrome	3 (1.8)	2 (1.6)	1 (1.1)	0	0	0
Hepatobiliary disorders	**Any**	**8 (4.9)**	**5 (3.9)**	**8 (9.2)**	**2 (4.4)**	**2 (7.7)**	**4 (26.7)**
	Hyperbilirubinaemia	5 (3.0)	0	2 (2.3)	0	0	3 (20.0)
	Venoocclusive liver disease	3 (1.8)	4 (3.1)	6 (6.9)	2 (4.4)	2 (7.7)	1 (6.7)

Source: Module 5, Section 5.3.5.1, Table 530.188.3 (08 March 2016 cutoff date).

Treatment-Emergent AEs=AEs that commenced on or after C1D1 but within 42 days after the last dose (non-related) or any time after C1D1 (treatment-related). All VOD events within 2 years after randomization date regardless of causal attribution to study therapy were included. MedDRA (v18.1) coding dictionary is applied. AEs graded according to the NCI CTCAE, v3.0.

AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; C=cycle; D=day; GGT=gamma-glutamyl transpeptidase; MedDRA=Medical Dictionary for Regulatory Activities; N/n=number of patients; NCI CTCAE=National Cancer Institute common terminology criteria for adverse events; TEAE=treatment-emergent adverse event; v=version; VOD=venoocclusive liver disease; WBC=white blood cell.

Patients who received a maximum of 6 cycles had the highest frequency of Grade ≥ 3 events within System Organ Class (SOC) Hepatobiliary Disorders (4/15 (26.7%) patients). The most common Grade ≥ 3 event within this SOC was hyperbilirubinemia (3/15 (20%) patients). While consistently increased frequency with increasing number of cycles was not observed for Grade ≥ 3 hyperbilirubinemia, the frequencies of any grade hyperbilirubinemia were highest in Cycles 3 through 6 (the frequencies of any grade hyperbilirubinemia were 7.9%, 7.1%, 9.2%, 15.6%, 38.5%, 60.0% in Cycles 1 through 6, respectively.

Venoocclusive disease/sinusoidal obstruction syndrome (VOD/SOS) was reported in each cycle category. However, for patients not proceeding to HSCT, the risk of VOD/SOS was substantially lower compared to patients who proceeded to HSCT. Among all 164 patients treated in the inotuzumab ozogamicin arm, VOD/SOS was reported in 5/164 (3%) patients during study therapy or in follow-up without an intervening HSCT: of these 5 patients, 3 patients received 1 cycle (including incomplete cycle), 1 patient received 3 cycles, and 1 patient received 6 cycles. Thus, for these 5 patients who had VOD/SOS during study therapy or in follow-up without an intervening HSCT, the risk of VOD/SOS did not increase with greater number of cycles.

Overall summary:Based on the efficacy and safety analyses summarised in this response, the sponsor considers that additional cycles of treatment up to a maximum of 6 cycles in patients not proceeding to HSCT is justified. Specifically:

- For patients who achieved CR/CRi but who were not eligible to undergo HSCT, additional cycles (up to a maximum of 6) may be beneficial to maintain the response and for survival. Additionally, among the 5 patients who did not undergo HSCT and were 18 month survivors, 3 patients had received > 3 cycles.
- The frequency of all-causality Grade ≥ 3 TEAEs was similar among patients who started Cycles 1 through 6 for most individual TEAEs. In general, individual Grade ≥ 3 TEAEs did not appear to increase with increasing number of cycles. A few Grade ≥ 3 TEAEs did trend higher in patients treated with more than 3 cycles of inotuzumab ozogamicin (for example, thrombocytopenia, neutropenia). For patients not proceeding to HSCT, the risk of VOD/SOS did not increase with greater number of cycles.

Product Information (PI):

For patients not proceeding to HSCT, the sponsor proposes the text below in the revised label. In addition, the label clearly states that patients who do not achieve a CR/CRi within 3 cycles should discontinue treatment.

> *'Recommended Dosage Regimen*
>
> *Besponsa should be administered in 3 to 4 week cycles.*
>
> *For patients proceeding to HSCT, the recommended duration of treatment with Besponsa is 2 cycles. A third cycle may be considered for those patients who do not achieve CR or CRi and MRD negativity after 2 cycles (see Precautions: Hepatotoxicity, including VOD/SOS).*
>
> *For patients not proceeding to HSCT, a maximum of 6 cycles, may be administered.*
>
> *Any patients who do not achieve a CR or CRi within 3 cycles should discontinue treatment.'*

This text aligns with the approved United States Package Insert.

Clinical evaluator's comment

The sponsor's response is satisfactory. The efficacy data showed a small increase in both the median duration of response and the median duration of overall survival in patients

who achieved CR/CRi but did no undergo follow-up HSCT treated for 4 to 6 cycles compared with 1 to 3 cycles, but the differences were not statistically significant. The safety data showed that all-causality Grade ≥ 3 TEAEs (any) increased with increasing number of cycles. However, this result should be interpreted having regard to the decreasing number of patients exposed to treatment with increasing number of cycles.

Safety

Question 10

In the pivotal Study B1931022, one patient in the inotuzumab ozogamicin arm had a prior history of VOD/SOS, which was a protocol violation. What were the safety findings in this patient?

Sponsor's response

In Study B1931022, one patient with a prior history of hepatic VOD/SOS was inadvertently enrolled on the study, At baseline, the patient had severe neutropenia (absolute neutrophil count 0) and 95% marrow blasts The patient received 2 doses of inotuzumab ozogamicin response to treatment was not assessed. The course of treatment was complicated by events including hyperbilirubinemia, ascites, cirrhosis (which was considered pre-existing since it was diagnosed radiographically 21 days after the first dose of inotuzumab ozogamicin), and infections. The patient discontinued treatment and died due to pneumonia approximately 1 month after the start of treatment. A narrative describing the patient's medical history and clinical course while on Study B1931022 is available.

Clinical evaluator's comment

The sponsor's response is satisfactory. The outcome for this patient was poor with the provided data suggesting worsening of pre-existing liver disease prior to death due to pneumonia.

Second round benefit-risk assessment

Second round assessment of benefits

After considering the responses to the clinical questions provided in the sponsor's response, the benefits of inotuzumab ozogamicin for the treatment of adults with relapsed or refractory CD22 positive B cell precursor acute lymphoblastic leukaemia (ALL) are unchanged from those identified in the first round assessment of benefits.

Second round assessment of risks

After considering the responses to the clinical questions provided in the sponsor's response, the risks of inotuzumab ozogamicin for the treatment of adults with relapsed or refractory CD22 positive B cell precursor acute lymphoblastic leukaemia (ALL) are largely unchanged from those identified in the first round assessment of risks. However, the amended proposed contraindications now allow treatment of patients with a history of less severe VOD/SOS or less serious ongoing hepatic disease to be considered, while excluding treatment of higher-risk patients with a history of severe VOD/SOS, ongoing VOD/SOS or serious ongoing hepatic disease.

Second round assessment of benefit-risk balance

The benefit-risk balance of inotuzumab ozogamicin for the treatment of adults with relapsed or refractory CD22 positive B cell precursor acute lymphoblastic leukaemia (ALL) is favourable.

Second round recommendation regarding authorisation

It is recommended that inotuzumab ozogamicin (Besponsa) be approved for the treatment of adults with relapsed or refractory CD22 positive B cell precursor acute lymphoblastic leukaemia (ALL).

VI. Pharmacovigilance findings

Risk management plan

Summary of RMP evaluation[45]

- The sponsor has submitted EU-RMP version 1.3 (dated 8 April 2017; data lock point (DLP) 26 April 2016) and ASA version 1.0 (dated 18 April 2017) in support of this application. In its response to questions, the sponsor has submitted EU-RMP version 1.5 (dated 26 April 2017; DLP 26 April 2016) and ASA version 1.1 (dated 14 December 2017).
- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below.

Table 14: Summary of Safety Concerns and their associated risk monitoring and mitigation strategies

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Grade ≥ 3 and/or serious hepatotoxicity, including all VOD/SOS	ü	–	ü	–
	Myelosuppression/cytopenia	ü	–	ü	–
Important potential risks	Interstitial lung disease	ü	–	–	–
	Inflammatory gastrointestinal events	ü	–	–	–
	Pancreatitis	ü	–	–	–

[45] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
	Second primary malignancy	ü	–	–	–
	Reproductive and developmental toxicity (post exposure during pregnancy and while breast feeding)	ü	–	ü	–
	Neurotoxicity	ü	–	–	–
	Nephrotoxicity	ü	–	–	–
Missing information	Use in patients with moderate or severe hepatic impairment	ü	–	ü	–
	Use in patients with severe renal impairment	ü	–	ü	–
	Use in Hispanic and Black patients/ Use in Aboriginal or Torres Strait Islander^	ü	–	ü**	–

**The wording in the draft PI states the following: 'Based on a population pharmacokinetic analysis, age, race, and gender did not significantly affect inotuzumab ozogamicin disposition.' This wording is identical to the wording in the SmPC. ^ ASA only (Use in Aboriginal or Torres Strait Islander)

- There are no additional pharmacovigilance or risk minimisation activities, which is acceptable as this time.
- However, inotuzumab ozogamicin should be included in the black triangle scheme for additional monitoring, similar to the EU.

New and outstanding recommendations from second round evaluation

New recommendation:

- As Besponsa is a new biological entity, it will be included in the black triangle scheme in Australia. Therefore, the PI and CMI should include the black triangle symbol and accompanying text in line with TGA advice.[46] See conditions of registration below.
- The sponsor should note the proposed wording for the condition of registration relating to the post-safety update report (PSUR) submission, which requires PSURs to be provided in line with the EU reporting schedule.

The Delegate may wish to consider if there should be information included in the draft PI regarding the following 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.

[46] See www.tga.gov.au/black-triangle-scheme-information-sponsors

Proposed wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> The Besponsa EU-Risk Management Plan (RMP) (version 1.5, dated 26 April 2017, data lock point 26 April 2016), with Australian Specific Annex (version 1.1, dated 14 December 2017), included with submission PM-2017-01455-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

The following wording is recommended for the PSUR requirement:

> An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs).
>
> Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.
>
> The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-Periodic Safety Update Report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

As Besponsa is a new biological entity it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

> 'Besponsa (Inotuzomab ozogamicin) is to be included in the Black Triangle Scheme. The PI and CMI for Besponsa must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Introduction

Background on condition being treated

The following information is taken from Freedman et al., 2017[47].

In the World Health Organization classification system for hematologic malignancies, the lymphoblastic neoplasms, which may present as leukemia and/or lymphoma, are divided into two general categories based upon lineage:

[47] Freedman A, Aster J. Clinical manifestations, pathologic features, and diagnosis of precursor B cell acute lymphoblastic leukemia/lymphoma. UpToDate article, July 2017.

- Precursor B cell lymphoblastic leukemia/lymphoma, also called precursor B cell acute lymphoblastic leukemia (precursor B cell ALL).

  is postulated to arise from precursor B cells at varying stages of differentiation. Uncertainty remains regarding the precise identity of these cells.

- Precursor T cell lymphoblastic leukemia/lymphoma (precursor T-LBL), also called precursor T cell acute lymphoblastic leukemia (precursor T cell ALL).

This is largely done because the prognosis and treatment differ between neoplasms of B and T cell lineage. These can be further divided into either lymphoblastic lymphoma or lymphoblastic leukemia:

- Clinically, a case is defined as lymphoma (LBL) if there is a mass lesion in the mediastinum or elsewhere and < 25 percent blasts in the bone marrow.
- It is classified as leukemia (ALL) if there are > 25 percent bone marrow blasts, with or without a mass lesion.

Within each lineage group, there is significant biological and clinical overlap between neoplasms diagnosed as LBL and ALL. Although some patients present with predominantly lymphomatous involvement (for example, a mediastinal mass or another defined lesion), most have or later develop marrow involvement. Similarly, patients who present with leukemia may have or may develop extramedullary tumors. Accordingly, lymphoblastic lymphoma and acute lymphoblastic leukemia should be considered the same disease with different clinical presentations.

Current treatment landscape

Treatment of relapsed or refractory ALL is still a major clinical challenge and there is no universally accepted treatment protocol for these patients. The European Society for Medical Oncology (ESMO) guidelines (2016);[1] for the treatment of relapsed or refractory leukaemia in adults recommends that clinical evaluation should take into account disease specific factors (BCP-ALL, T-ALL, ABL1 status), patient factors (age, performance status, organ function, and presence of extramedullary disease, in particular CNS disease), previous therapy (with particular reference to prior allograft, anthracycline dose) and specific toxicities of prior treatment which might guide therapeutic selection (for example, osteonecrosis, vinca alkaloid neuropathy, and specific infectious complications such as fungal infections).[28]

The ESMO guidelines (2016) indicate that allogeneic SCT is the only known curative option for patients with ALL and that treatment of the disease with a curative aim involves achievement of CR followed by allogeneic SCT. The guidelines refer to published data from four large trials indicating that the rate of second CR in patient with relapsed disease was 44% to 45%, and that the median OS in these patients was 4.5 to 8.4 months. The guidelines refer to published data showing that following long duration of first CR (> 2 years) re-induction with a standard induction regimen (such as used for original treatment) may be used for patients who have relapsed. The guidelines comment that short first CR or primary refractory disease is a very high risk situation, and consideration should immediately be given to the availability of trials with novel agents to which the disease might be non-resistant.

Australian incidence data

The most recent Australian specific data from the Australian Institute of Health and Welfare indicates that in 2013 there were 348 cases of ALL diagnosed in Australia with an age standardised incidence rate of 1.5/100,000 persons, with the risk being greater in

males than in females (1.6/100,000 versus 1.4/100,000, respectively).[48] The highest incidence rate was in children aged 0 to 4 years (6.8/100,000). In patients aged > 20 years, the incidence rate was higher in patients aged ≥ 65 years than in patients aged < 65 years. In patients aged ≥ 65 years categorised by age group, the incidence rates per 100,000 persons were 1.4 for patients aged 65 to 69 years, 1.1 for patients aged 70 to 74 years, 1.5 for patients aged 75 to 79 years, 2.7 for patients aged 80 to 84 years and 1.0 for patients aged 85+. In patients aged ≥ 20 years to < 65 year, the highest age specific incidence rate was in patients aged 50 to 54 years (0.9/100,000 persons). In 2014, the crude mortality rate for ALL was 0.4/100,000 persons, with the highest rates being in patients aged ≥ 55 years (0.5 to 1.8 per 100,000 persons). The mortality rates for both males and females declined in parallel from about 1980 to 2014. There were no Australian data based on the subtypes of ALL in the AIHW report.

Inotuzumab ozogamicin

Inotuzumab ozogamicin is a CD22 targeted antibody drug conjugate (ADC). The antibody, inotuzumab, is a humanised immunoglobulin G, subtype 4 (IgG4), which specifically recognises human CD22. The small molecule, N-acetyl (N-Ac)-γ-calicheamicin dimethylhydrazide (DMH), is a cytotoxic semisynthetic natural product that the sponsor states is significantly more potent than conventional cytotoxic chemotherapeutic agents. N-Ac-γ-calicheamicin DMH is covalently attached to the antibody via an acid-cleavable linker.

Australian regulatory status

This is the first Australian application to register inotuzumab ozogamicin.

Inotuzumab ozogamicin (Besponsa) was designated as an orphan drug by the Therapeutic Goods Administration (TGA), Delegate of the Secretary, on 9 January 2017. The indication was for the treatment of B cell acute lymphoblastic leukaemia (ALL).

Overseas regulatory status

At the time of writing this overview, Inotuzumab ozogamicin (Besponsa) was approved in the following overseas jurisdictions:

- Europe, European Medicine Agency, approved 29 June 2017:
  - *'Besponsa is indicated as monotherapy for the treatment of adults with relapsed or refractory CD22 positive B cell precursor acute lymphoblastic leukaemia (ALL). Adult patients with Philadelphia chromosome positive (Ph+) relapsed or refractory B cell precursor ALL should have failed treatment with at least 1 tyrosine kinase inhibitor (TKI)'.*
- United States of America, Food and Drug Administration (FDA), approved 17 August 2017:
  - *'Besponsa is indicated for the treatment of adults with relapsed or refractory B cell precursor acute lymphoblastic leukemia (ALL)'.*

The sponsor states that applications have been submitted to Canada, Switzerland, Singapore and New Zealand. On searching at the date of writing this overview, it was not clear if approvals have been granted in these jurisdictions.

[48] AIHW, 2017. Australian Institute of Health and Welfare (AIHW) 2017. Australian Cancer Incidence and Mortality (ACIM) books: Acute lymphoblastic leukaemia (ALL). Canberra: AIHW. <http://www.aihw.gov.au/acim-books>.

Quality

There were no objections from the quality evaluators to the approval of Besponsa inotuzumab ozogamicin 1 mg powder for injection vial. Good Manufacturing Practice (GMP) clearance was confirmed by the TGA Manufacturing Quality Branch on the 23 February 2018.

The following recommendations regarding shelf life of the drug product were agreed:

- 24 months when stored at 2°C to 8°C. Protect from light.Use reconstituted solution immediately or after being refrigerated (2 to 8°C) for up to 4 hours. Protect from light. Do not freeze.
- No temperature excursion during shipping is permitted.

The following conditions of registration were proposed:

1. Condition(s) of registration resulting from primary evaluation

   Should reprocessing (that is VRF and final filtration) be required in the future, the sponsor must submit a Category 3 application on at least one batch of the drug product manufactured at full scale prior to implementation.

2. Batch release testing & compliance with Certified Product Details (CPD)

   It is a condition of registration that all batches of Besponsa inotuzumab ozogamicin imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

   It is a condition of registration that each batch of Besponsa inotuzumab ozogamicin imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results

Nonclinical

There were no objections to approval of inotuzumab ozogamicin (Besponsa) from the nonclinical evaluators. The report concludes that the nonclinical pharmacology and toxicology data are adequate to support the approval of inotuzumab ozogamicin for the proposed indication.

The nonclinical evaluator notes the following:

- There were no major deficiencies in the nonclinical module. However, owing to a lack of cross-species specificity, the nonclinical species are only able to provide information on non-target mediated effects of the ADC.
- The primary pharmacology studies provide evidence supporting the proposed mechanism of action and potential efficacy in the treatment of human B cell malignancies.
- No clinically relevant hazards were identified in the safety pharmacology studies. In tissue cross-reactivity studies inotuzumab unexpectedly stained the stromal fibres in the dermis of the skin, mammary gland, and uterine cervix of humans. The clinical significance of this is uncertain, but it may indicate the potential for additional off target toxicity in these tissues.
- Important toxicities included hepatic endothelial injury (likely to represent early stages of hepatic VOD), hepatic neoplasia and pre-neoplasia, thrombocytopenia (secondary to hepatic endothelial toxicity), irreversible peripheral and central axonal

degeneration and toxicity to haematolymphopoietic, male and female reproductive and renal tissues. These effects are all considered to be of clinical significance.

- Inotuzumab ozogamicin and/or its DNA-reactive cytotoxic component are mutagenic and clastogenic, and may pose a carcinogenic hazard.
- Inotuzumab ozogamicin is stated as pregnancy Category D.

The nonclinical report contained a number of recommended PI changes which were accepted or justified through the sponsor's response and PI amendments.

Clinical

The clinical dossier included 11 clinical trials including a pivotal Phase III study in patients with ALL (Study B1931022), 1 supportive Phase I/II study in patients with ALL (Study B1931010) and 9 studies in patients with on-Hodgkin's lymphoma (NHL). In addition to this, the following was provided:

- 1 population pharmacokinetic (popPK) report for ALL and NHL and a supplement to this report.
- 6 PD and PK/D studies providing concentration QTc analysis in patients with NHL, PK/PD analyses of QT intervals in patients with ALL and NHL, PK/PD analyses of the effects of exposure on safety and efficacy, and popPK exposure-response efficacy modelling (OS and PFS) in patients with ALL.
- Safety data from investigator initiated studies (IIR).
- Safety data from compassionate use (CU) programs.
- Integrated summary of clinical efficacy, cluster terms for analysis of safety, summary of clinical safety, Day 120 safety update appendices 1 and 2.
- Of note, the data for the pivotal Phase III study included an original Clinical Study Report (CSR), a supplementary CSR (sCSR), a Day 120 Safety Update, and an updated overall survival analysis with data as of the last subject last visit (LSLV) of 4 January 2017.

Of note, Single agent inotuzumab ozogamicin was administered in both studies in patients with ALL and three studies in patients with NHL. Inotuzumab ozogamicin was administered in combination with other agents in the remaining studies in patients with NHL. This included combination with rituximab (5 studies) and rituximab with chemotherapy (2 studies).

Formulation

The analytical comparability study was stated to include product quality In the clinical studies in patients with ALL and NHL, vial strengths of 1, 3, and 4 mg/vial were used. The most commonly used strength was 4 mg/vial rather than the 1 mg/vial dosage strength intended for commercial use. No clinical bioequivalence studies were submitted comparing the three vial strengths used in the clinical program. However, such studies are not required as all strengths are administered by the IV route and, therefore, by definition are each 100% bioavailable. The sponsor reports that an analytical study investigating comparability between the 1 mg/vial in a 20 mL vial and the 4 mg/vial in a 20 mL vial was completedtesting and additional characterisation tests to provide an assessment of the physicochemical properties and impurity profiles of the two vials. In addition to historical data comparison of product quality tests, inotuzumab ozogamicin batches were analysed side by side to directly compare the 1 mg/vial and 4 mg/vial dosage strengths. The sponsor reports that, overall, the results indicated that the 1 mg/vial and 4 mg/vial

inotuzumab ozogamicin materials were comparable in structure (including primary structure, post-translational modifications, primary conjugation sites, and higher-order structure), biological activity, and purity. There were no objections raised by the non-clinical evaluators regarding this conclusion of comparability.

Pharmacokinetics (PK)

The PK information for inotuzumab ozogamicin is derived from patients with relapsed or refractory ALL (2 studies) or NHL (9 studies). In addition to PK data from the 11 individual clinical studies, pooled PK data were also available from an initial popPK analysis in 736 patients (ALL (n = 205), 2 studies; NHL (n = 531), 9 studies), with 7911 PK observations for inotuzumab ozogamicin and a supplemental popPK analysis including 29 additional patients with ALL. There were no PK data in healthy subjects. This is considered to be acceptable given that calicheamicin is a cytotoxic agent reported to cause DNA double strand-breaks.

A full evaluation and summary of the pharmacokinetic data, was provided in the clinical evaluation report. Key findings include the following:

- The PK parameters across the individual ALL and NHL studies showed moderate to high inter-individual and inter-subject variability (CER page 52).
  - The pooled data for the two ALL studies showed that inter-individual variability for C_{max} was greater following single dose (CV = 172%) compared to multiple dose (CV = 113%). Inter-subject variability (CV%) for C_{trough} was 157% (single dose) versus 101% (multiple dose)).
- In patients with ALL, investigation of the pharmacokinetics of the cytotoxic moiety of the ADC *in vivo* was limited as the levels of unconjugated calichaemicin generally fell below the limit of quantitation for most samples. However, data was available from patients with relapsed or refractory NHL.
- There were no single or multiple dose proportionality assessments in patients with ALL:
  - Based on data from NHL studies, post hoc power models were applied to test dose proportionality for each component of inotuzumab ozogamicin.
  - Using C_{max} and AUC_{inf} data from single doses of inotuzumab ozogamicin administered in two NHL studies, the increase in C_{max} appeared to be less than dose proportional for inotuzumab ozogamicin, total calicheamicin and total antibody with increasing dose within the single dose range of 0.4 to 2.4 mg/m^2. The increase in AUC_{inf} appeared to more than dose proportional for total calicheamicin and total antibody over the single dose, dose range of 0.4 to 2.4 mg/m^2, while dose ranging data for AUC_{inf} were not available for inotuzumab ozogamicin.
  - Using C_{max} and AUC_{tau} from multiple dosing data in one NHL study, the increase in C_{max} appeared to be less than dose proportional for inotuzumab ozogamicin and total antibody, but appeared dose proportional for total calicheamicin within the dose range of 0.4 to 2.4 mg/m^2 Q3W. The increase in AUC_{tau} appeared to be greater than dose proportional for total antibody, but appeared to be dose proportional for total calicheamicin within the dose range of 0.4 to 2.4 mg/m^2 Q3W.
- Steady-state exposure to inotuzumab ozogamicin was achieved by Cycle 4 in patients with relapsed or refractory ALL. In Study B1931022, the mean (SD) observed at the end of the 1 hour infusion (C_{max}) on Cycle 4 Day 1 was 308 (362) ng/mL, and pre-dose serum concentration (C_{trough}) was 57.9 (29.8) ng/mL on Cycle 4 Day 1. The inter-subject variability for the C_{max} was still high at steady state (Cycle 4, Day 1), with mean

CV% of 118%. The mean (SD) simulated AUC_{tau} at steady state in Cycle 4 Day 1 was 29,500 (9430) ng·h/mL, based on data from the supplemental popPK analysis for the two ALL Studies B1931022 and B1931010.

- Unconjugated calicheamicin was highly bound to plasma proteins in humans (97.2%), with the geometric mean plasma unbound fraction (fu) being 0.0279. Unconjugated calicheamicin demonstrated limited distribution into red blood cell, with a blood-to-plasma partition ratio of 0.71. There was no assessment of protein binding for inotuzumab ozogamicin as such assessments are not applicable to therapeutic proteins.
- The primary metabolic pathway for inotuzumab ozogamicin was hydrolysis (at the hydrazone moiety) to release N-Ac-γ-calicheamicin DMH (that is, unconjugated calicheamicin). The primary metabolic pathway for unconjugated calicheamicin was via non-enzymatic reduction (at the disulfide moiety), with hydrolysis (at the hydrazide moiety), oxidation, and adduction (with pyruvic acid) being minor metabolic pathways. There were no metabolic studies of the inotuzumab monoclonal antibody component of the drug, with clearance of monoclonal antibodies being primarily by catabolism with the resulting amino acids being recycled into other proteins.
- In patients with relapsed or refractory ALL, anti-drug antibodies (ADAs) at any time (pre- and post-dose) were observed in 7 of 236 patients (3.0%), including 1 (0.4%) patient who exhibited positive ADAs de novo following treatment with inotuzumab ozogamicin. None of the 7 patients with ADAs tested positive for neutralising antibodies using a cell based assay.
    - In patients with relapsed or refractory NHL, ADAs at any time (pre- and post-dose) were observed in 27 of 630 patients (4.29%), with no patients demonstrating only a positive post-dose ADA response. There were no data on neutralising antibodies in patients with NHL because the analytical method was not available at the time these studies were conducted.
    - In patients with ALL, a post-hoc analysis showed that ADA status had no significant impact on the clearance of inotuzumab ozogamicin. No assessment of the impact of ADA status on efficacy was undertaken due to the limited number of ADA positive patients. An assessment of the effect on all-causality AEs in the 7 ADA positive ALL patients from Study B1931022 was undertaken. However, the number of ADA positive patients is too small to draw clinically meaningful conclusions relating to the impact on safety of ADAs

Population PK data (popPK)

The clinical evaluator considered that the pharmacokinetics of inotuzumab ozogamicin were well characterised using a 2-compartment model with both linear clearance (time-independent) and time-dependent clearance in the popPK analysis. Of note:

- Based on the popPK analysis, the total volume of distribution of inotuzumab ozogamicin was approximately 12 L. This result indicates that inotuzumab ozogamicin is not significantly distributed to the extravascular tissues.
- The data demonstrated that the timedependent clearance predominates at the start of treatment, but its contribution to total clearance declines over time. At steady state (approximately Cycle 4), linear clearance predominates. Time-dependent clearance results in increased exposure being observed over the first 3 to 4 treatment cycles (that is, clearance decreases with time), with steady state exposure being achieved after 3 to 4 cycles (that is, clearance becomes linear). The time dependent component of clearance for inotuzumab ozogamicin is consistent with target mediated drug

disposition, with clearance decreasing and exposure increasing as the available receptors become saturated over the first 3 to 4 treatment cycles.

- After the first dose of 0.8 mg/m^2 on Day 1 in patients (n = 128) with relapsed or refractory ALL (Study B1931022), mean (SD) inotuzumab ozogamicin concentration at the end of the 1 hour infusion (C_{max}) was 211 (232) ng/mL. The inter-subject variability for the C_{max} was high following the first dose, with a mean CV of 110%. The mean (SD) simulated area under the concentration-time curve within the first dosing interval of 7 days (AUC_{tau}) for inotuzumab ozogamicin following the first 0.8 mg/m^2 dose was 4330 (2140) ng·h/mL, based on data from the supplemental popPK analysis for the two ALL Studies B1931022 and B1931010.
- The accumulation ratio (total AUC at cycle 4/total AUC at cycle 1) for inotuzumab ozogamicin in patients with relapsed or refractory ALL at the proposed dose was estimated to be 5.30 (90% CI: 5.12, 5.47) (data from the supplemental popPK analysis). The clearance of inotuzumab ozogamicin at steady state was 0.0333 L/h and the terminal half-life ($t_{1/2}$) was 12.3 days.
- There were no dedicated clinical studies investigating the PK of inotuzumab ozogamicin in special groups. However, the popPK analysis investigated the effects of a large number of pre-specified covariates on the PK of inotuzumab ozogamicin.
    - The only clinically significant covariate on the PK of patients with ALL was baseline body surface area. The proposed dosage regimen of inotuzumab ozogamicin for the treatment of patients with ALL is based on individual patient BSA, which will account for the impact of BSA on the PK of the drug.
    - Based on the supplemental popPK analysis, the covariates of age, gender, racial group, mild hepatic impairment,[29] and renal impairment had no significant effects on the PK of inotuzumab ozogamicin in patients with ALL. However, the data for moderate hepatic impairment was based on 1 patient only and there were no data for patients with severe hepatic impairment, while there were only limited data for patients with renal impairment as most patients had normal renal function (78.6% (184/234)).
- There were no dedicated clinical DDI studies investigating the PK of co-administration of inotuzumab ozogamicin and other medicines.
    - Data from the popPK analysis and a number of *in vitro* human biomaterial studies indicates that there is not likely to be clinically relevant effects on the PK of inotuzumab ozogamicin from: salvage line and prior radiotherapy; concomitant administration of hydroxyurea, granulocyte-colony stimulating factors or P-glycoprotein inhibitors; drugs that are substrates for CYP enzymes, UGT enzymes, and transporters.
- Based on a population pharmacokinetic analysis in 765 patients, body surface area was found to significantly affect inotuzumab ozogamicin disposition. However the clinical evaluator resolved that the proposed dosage regimen is based on individual patient BSA, which will account for the impact of BSA on the PK of the drug.

Overall, the clinical evaluator concludes that the pharmacokinetics of inotuzumab ozogamicin have been reasonable well characterised in the data provided.

Pharmacodynamics (PD)

A total of six studies provided PK/PD information. The full evaluation details were presented in the clinical evaluation report. Key findings of the exposure response data include the following:

- Exposure based on the C_{avg} of inotuzumab ozogamicin and the percentage of leukaemic blasts that were CD22 positive at baseline were found to be statistically significant predictors of CR/CRi at a significance level of 0.05 (Study PMAR-EQDD-B193a-DP4-205-Supplement). For the same C_{avg} value, the predicted probability of a response was greater in patients with ≥ 90% of CD22 positive leukaemic blasts at baseline compared to patients with < 90% of CD22 positive leukaemic blasts at baseline. Of note, the proposed indication in Australia now specifies CD22 positive disease.
- In the OS and PFS analyses, with and without censoring for post-study HSCT, inotuzumab ozogamicin C_{avg} was a statistically significant predictor of both OS and PFS affecting the base hazard of both efficacy endpoints (that is, higher C_{avg} increased the probability of both OS and PFS) (Study PMAR-EQDD-B193a-Regulatory Response-628). However, when CR/CRi and MRD were tested as potential prognostic factors affecting OS and PFS, along with the other pre-specified prognostic factors, inotuzumab ozogamicin exposure (C_{avg}) was no longer a statistically significant predictor of either OS or PFS survival. The supplemental popPK analysis identified C_{avg} as statistically significant predictor of CR/CRi and MRD and therefore this exposure metric correlated with these variables.
- Limited data on unconjugated calicheamicin levels in patients with ALL indicate that this exposure metric is not a significant predictor of efficacy (CR/CRi and MRD).
- There was no 'thorough QT/QTc' study in healthy volunteers meeting the relevant TGA adopted EU guidelines for non-arrhythmic drugs.[30] However, such a study in healthy volunteers could not be justified given that calicheamicin is a cytotoxic agent. The submitted data included a PK/PD analysis, which showed that inotuzumab ozogamicin is unlikely to be associated with clinically significant increases in QTc prolongation in patients with ALL. In addition, unconjugated calicheamicin exposure in patients with ALL is unlikely to have a significant effect on QTc prolongation.
- A statistically significant predictor of VOD/SOS was determined in the exposure response analysis. Increasing cumulative AUC after period 1 (cAUCP1) was associated with an increased risk of VOD/SOS (HEAB assessed), and the risk was significantly greater in patients who received a HSCT during the study compared to patients who did not received a HSCT during the study.
- In an exploratory central tendency analysis in patients with ALL (Study B1931022) mean maximum QTcF changes from baseline were 16.5 ms (90% CI: 14.3, 18.7) in the inotuzumab ozogamicin arm and 10.8 ms (90% CI: 8.0, 13.6) in the control arm. The central tendency analysis of QTcF change from baseline for all data points demonstrated that the highest upper bound of the 2 sided 90% CI for QTcF was 21.1 ms (observed at Cycle 4/Day 1/1 hour) in the inotuzumab ozogamicin arm and 21.2 ms (observed at Cycle 2/Day 1/1 hour) in the control arm. The reason for the prolonged QTcF observed in Study B1931022 in both treatment arms is unknown.
    - Although the sponsor stated that the finding might partly be due to the fact that patients in the study received many concomitant medications and many patients were reported to have electrolyte disturbances, the sponsor acknowledged: '*that it is not easily possible to estimate the impact that these factors may have had in prolonging QT in both arms*' of Study B1931022. In summary, it is considered that the reason for QTcF prolongation observed in both treatment arms in Study B1931022 is unknown.
    - A precaution regarding QT Interval Prolongation has been included in the Australian PI for Besponsa.

Efficacy

Two open label studies provided evaluable efficacy data for the proposed indication in patients with relapsed or refractory ALL, including one pivotal Phase III Study B1931022 and one supportive Phase I/II Study B1931010. A full evaluation of each study, was provided in the clinical evaluation report. The evaluator concluded that the totality of the efficacy data supports approval of inotuzumab ozogamicin for the treatment of relapse and refractory CD22 positive ALL in adults.

Study B1931022

The pivotal Phase III Study B1931022 was a randomised controlled study in 326 adult patients with relapsed or refractory CD22 positive ALL. The study randomised patients 1:1 to open label treatment with either inotuzumab ozogamicin (n = 164) or investigator's choice (n = 162) of one of three pre-defined treatment regimens. These were FLAG (n = 102), Mxn/Ara-c (n = 38), or HIDAC (n = 22). Balanced against the known lack of a single standard of care in this setting and considering the sponsor justification on the issue of compatibility of these regimens to standard treatment in Australia (provided in the sponsors response to questions), it is reasonable to consider that the results of this study are applicable to Australian patients.

The dosage regimen inotuzumab ozogamicin used in the study reflects that proposed in this submission. This consisted of 1.8 mg/m^2 in Cycle 1 administered at a dose of 0.8 mg/m^2/cycle on Day 1 and 0.5 mg/m^2 on Days 8 and 15 for 21 days, with cycle lengthening to 28 days for patients who achieved a response and/or to allow recovery from toxicity, and subsequent dose reduction in responders to 1.5 mg/m^2/cycle at a dose of 0.5 mg/m^2 on Days 1, 8 and 15).

The study included 49 (15.0%) patients who were Ph+, comprising 22 (13.4%) patients in the inotuzumab arm and 27 (16.7%) patients in the control arm. Ph+ patients were required to have failed treatment with at least one second or third generation TKI and standard multi-agent induction chemotherapy (inclusion criterion number 2). However, 3 Ph+ patients in the inotuzumab ozogamicin arm and 1 Ph+ patient in the control arm had not received prior treatment with second or third generation TKIs due to protocol violation.

The study population appears younger than the corresponding Australian patient population with ALL (mean age of total ITT population 46years with 16% aged ≥ 65 years). Subgroup analyses of the primary efficacy endpoints (CR/CRi; OS) were undertaken in patients aged < 55 years and ≥ 55 years, and no marked difference in outcome was observed between the two age groups. There was no efficacy analysis in patients aged < 65 years compared to patients aged ≥ 65 years. Overall, the median duration of treatment in the inotuzumab ozogamicin arm was 8.9 weeks (range 0.1 to 26.4) (median number of cycles started = 3) compared to 0.9 weeks (range 0.4 to 15.1) (median number of cycles started = 1) in the control arm (Study B1931022). The reasons for treatment discontinuation are discussed below.

The two primary efficacy endpoints were CR/CRi (per EAC) and OS, with a number of secondary endpoints (that is, PFS, DoR in patients achieving CR/CRi, MRD-negativity in patients achieving CR/CRi, follow-up HSCT rate, PROs). Key efficacy results include:

- The primary analysis of the CR/CRi (per EAC) was undertaken in the first 218 patients included in the ITT population at the cut-off date of 2 October 2014 (ITT218). In this analysis, the CR/CRi was significantly greater in the inotuzumab ozogamicin arm compared to the control arm (80.7% versus 29.4%, p < 0.0001, 1-sided Chi-square test). The pre-specified sensitivity analyses for the CR/CRi (EAC) were consistent with the primary analysis.

- The result for the updated CR/CRi (per investigator) analysis in the ITT population (n = 326) at the cut-off date of 8 March 2016 was consistent with the CR/CRi for the primary efficacy analysis. In the updated ITT population, the CR/CRi (per investigator) was 73.2%, in the inotuzumab ozogamicin compared to 30.9% in the control arm ($p < 0.0001$, 1 sided Chi-square test). In the ITT population, nearly all patients in the inotuzumab arm with a CR/CRi achieved remission within the first two treatment cycles (70.8%, Cycle 1 and 25.8%, Cycle 2), and no patients achieved remission after the third cycle.
- The primary analysis of OS was undertaken in the ITT when 252 deaths had occurred (122 deaths, 74.4%, inotuzumab ozogamicin; 130 deaths, 80.2%, control). The primary OS analysis demonstrated a small survival benefit in favour of the inotuzumab ozogamicin arm compared to the control arm. However, the difference between the two treatment arms was not statistically significant based on the pre-specified stratified analysis: that is, HR = 0.770 (97.5%: 0.578, 1.026); p = 0.0203 stratified log-rank test, 1-sided. In this analysis, the p-value of 0.0203 was greater than the p-value boundary for significance of 0.0104, adjusted for alpha-spending in the interim analysis. The absolute difference in the median OS was 1 month in favour of inotuzumab ozogamicin compared to control (7.7 months versus 6.7 months, respectively). The updated results for the OS analysis in the ITT population based on data at a cut-off date of 4 January 2017 (LSLV) were consistent with the analysis undertaken at a cut-off date of 8 March 2016.
    - The sponsor considered that the assumption of proportional hazards (PH) for the two arms had not been satisfied making the calculated HR unreliable.
    - The sponsor also provided exploratory post hoc analyses of OS undertaken using restricted mean survival time (RMST) and competing risk analyses. These analyses showed a greater treatment effect for survival in patients in inotuzumab ozogamicin compared to patients in the control arm compared to the primary analysis of OS. Other exploratory post hoc analyses of OS included OS censored at HSCT date and OS censored for subsequent therapies. The results for these analyses of OS were consistent with the primary analysis of OS.
- The key secondary efficacy endpoint is considered to be PFS, as this is the only secondary efficacy endpoint for which significance testing was specifically defined in the SAP. The SAP specified that if either the CR/CRi or OS comparison was significant, then PFS between the two treatment arms was to be compared using a stratified log-rank test with significance level of 0.05. In the ITT population (updated data), the estimated HR for the PFS (inotuzumab ozogamicin versus the control arm) was 0.452 (97.5% CI: 0.336, 0.609; 1-sided $p < 0.0001$) based on the stratified analysis, and the median PFS was 3.2 months longer in the inotuzumab arm than in the control arm (5.0 versus 1.8 months, respectively). The results for the PFS are considered to be clinically meaningful. It should be noted that the pre-specified definition of PFS in this study differed from the standard definition of this endpoint, as it included starting new induction therapy or post-therapy HSCT without achieving CR/CRi in addition to death or disease progression.
- In patients achieving CR/CRi in the updated ITT population (n = 326), the percentage of patients MRD negative was greater in the inotuzumab ozogamicin arm than in the control arm, and the difference between the two arms was statistically significant (nominal). Overall, 92/120 (76.7%) achieved MRD-negativity in the inotuzumab ozogamicin arm and 19/50 (38.0%) patients achieved MRD-negativity in the control arm (1-sided $p < 0.0001$; Chi-square test), for a rate difference of 38.7%.
    - Of note, in patients with a CR, a total of 89.1% achieved MRD negative status (95% CI 77.8 to 95.9) compared to 46.2% in the control arm (95% CI 26.6 to 66.6).

- In the ITT population, there was an approximately 4 fold increase in the percentage of patients in the inotuzumab ozogamicin arm proceeding to follow-up HSCT directly after achieving CR/CRi (per investigator) without intervening induction or salvage therapy compared to patients in the control arm (39.6% versus 9.9%). Of the patients in the ITT population who proceeded to follow-up HSCT[49], the post-transplant mortality rate was similar in the inotuzumab ozogamicin arm compared to control (59.7% versus 57.6%), but the post-transplant, non-relapse mortality rate was greater in the inotuzumab ozogamicin arm than in the control arm (39.0% versus 27.3%, respectively). The higher post-transplant, non-relapse mortality in the inotuzumab ozogamicin arm compared to the control arm was largely due to infection and VOD/SOD. Furthermore, both the 100 day post-transplant mortality rate and the 100 day post-transplant, non-relapse mortality rate were higher in the inotuzumab ozogamicin arm than in the control arm.
    - In the Day 120 Safety Update (Table 15) non-relapse post-transplant mortality in patients who proceeded to HSCT was 40.5% (32/79) in patients in the inotuzumab ozogamicin arm compared to 22.9% (8/35) in the control arm. The most common reasons for post-transplant non-relapse deaths in the inotuzumab arm (versus control, respectively) were infection (21.6% (11/79) versus 17.4% (4/35)), and VOD (9.8% (5/79) versus 0% (0/35)).

[49]Clarification: the ITT population that proceeded to follow up HSCT was comprised of 77 patients in the inotuzumab ozogamicin arm versus 33 .patients in the control arm

Table 15: Summary of post-transplant survival for patients with follow-up SCT; ITT Population

	Inotuzumab Ozogamicin (N=79)	Investigator Choice (N=36)	Total (N=115)
Number of deaths	53 (67.1)	25 (69.4)	78 (67.8)
Cause of death [a]			
Disease under study	20 (37.7)	17 (68.0)	37 (47.4)
Study treatment toxicity	6 (11.3)	0	6 (7.7)
Inotuzumab	1(1.9)	0	1(1.3)
Sinusoidal Obstruction Syndrome,disseminated Mucormycosis	1(1.9)	0	1(1.3)
Veno Occlusive Disease	4(7.5)	0	4(5.1)
Unknown	1 (1.9)	0	1 (1.3)
Other	29 (54.7)	10 (40.0)	39 (50.0)
ALL Treatment Toxicity (non study drugs)	4(7.5)	2(8.0)	6(7.7)
Complications After Transplantation	0	1(4.0)	1(1.3)
Complications Associated With Transplant	1(1.9)	0	1(1.3)
Multi-Organ Failure - Follow-up Treatment Toxicity After Hyper-CVAD Salvage	1(1.9)	0	1(1.3)
Salvage Treatment Toxicity	0	1(4.0)	1(1.3)
Toxic Damage After Intrathecal Chemotherapy And Radiotherapy(2012)	1(1.9)	0	1(1.3)
Transplant Complication	1(1.9)	0	1(1.3)
Cardiac disorders	4(7.5)	1(4.0)	5(6.4)
Cardiac Arrest	2(3.8)	1(4.0)	3(3.8)
Cardiopulmonary Arrest	1(1.9)	0	1(1.3)
Ischemic Cardiac Disease And Acute Myocardial Infarction	1(1.9)	0	1(1.3)
GVHD	4(7.5)	1(4.0)	5(6.4)
Acute GVHD	1(1.9)	0	1(1.3)
GVHD	1(1.9)	0	1(1.3)
GVHD Post Transplantation	1(1.9)	0	1(1.3)
Multi-Organ Failure Secondary To Graft Versus Host Disease	1(1.9)	0	1(1.3)
Refractory Gastrointestinal, Hepatic And Cutaneous Graft Versus Host Disease	0	1(4.0)	1(1.3)
General Disorders	2(3.8)	0	2(2.6)
Multiorganic Failure	1(1.9)	0	1(1.3)
Multisystem Dysfunction	1(1.9)	0	1(1.3)
Infection	10(18.9)	4(16.0)	14(17.9)
Allogenic Trasplant Procedure (Sepsis)	1(1.9)	0	1(1.3)
Bacterial Infection	0	1(4.0)	1(1.3)
Fungal Pneumonia	1(1.9)	0	1(1.3)
Infection (Unknown)	1(1.9)	0	1(1.3)
Pneumonia	2(3.8)	1(4.0)	3(3.8)
Pneumonia And Multiorgan Failure	0	1(4.0)	1(1.3)
Pneumonia Versus Pulmonary Edema	1(1.9)	0	1(1.3)
Pseudomonas Bacteremia	1(1.9)	0	1(1.3)
Sepsis	1(1.9)	0	1(1.3)
Septic Shock	1(1.9)	1(4.0)	2(2.6)
Severe Sepsis	1(1.9)	0	1(1.3)
Other	2(3.8)	1(4.0)	3(3.8)
Acute Kidney Injury	1(1.9)	0	1(1.3)
Idiopathic Pneumonia Syndrome	0	1(4.0)	1(1.3)
MOF, Cardiopulmunary Arrest	1(1.9)	0	1(1.3)
Respiratory Disorders/Failures	3(5.7)	1(4.0)	4(5.1)
Acute Hypercarbic Respiratory Failure Leading To Cardiac Arrest	0	1(4.0)	1(1.3)
Acute Respiratory Distress Syndrome And Multi-Organ Failure	1(1.9)	0	1(1.3)
Respiratory Failure	2(3.8)	0	2(2.6)
Number censored	26 (32.9)	11 (30.6)	37 (32.2)
Reason for censorship [b]			
Completed	26 (100.0)	9 (81.8)	35 (94.6)
Subject no longer being followed for survival	0	2 (18.2)	2 (5.4)
Number of subjects with last contact date > one year prior to cutoff date [b][c]	0	2 (18.2)	2 (5.4)
Survival probability at 100 days post SCT [d] [95% CI]	74.7[63.6,82.9]	84.4[79.6,98.6]	80.9[72.4,87.0]
Survival probability at month 12 [d] [95% CI]	43.0[32.0,53.6]	65.7[47.5,78.9]	50.1[40.7,58.9]
Survival probability at month 18 [d] [95% CI]	35.2[26.5,49.8]	35.6[20.1,51.5]	38.5[29.5,47.3]
Kaplan-Meier estimates of time to event (month)			
Quartiles [95% CI] [d]			
25%	3.2[2.4,4.2]	9.9[3.4,13.4]	3.9[3.1,5.5]
50%	7.9[5.1,17.8]	15.2[11.5,19.0]	13.4[7.9,17.3]
75%	40.7[27.4,-]	25.0[17.3,-]	40.7[25.0,-]
Cox proportional hazards model			
Stratified HR[97.5%CI]/ [95%CI] [Inotuzumab Ozogamicin vs Investigator Choice] [e]	1.169[0.667,2.049]/ [0.716,1.910]		
Unstratified HR[97.5%CI]/ [95%CI] [Inotuzumab Ozogamicin vs Investigator Choice]	1.148[0.664,1.985]/ [0.711,1.854]		
One-sided Stratified log rank p-value [f]	0.7340		
One-sided Unstratified log rank p-value	0.7143		

Note: Investigator choice is one of the defined chemotherapy regimens (either FLAG (Fludarabine, Cytarabine, and G-CSF), Cytarabine with Mitoxantrone, or HIDAC).
[a] Percentage is calculated based on the number of deaths. More than one causes of death could be checked.
[b] Percentage is calculated based on the number of censored observations.
[c] Death patients were excluded.
[d] Calculated using Kaplan-Meier method.
[e] From stratified Cox proportional hazards model. The stratification factors are Duration of first remission (<12 months or >= 12 months); Salvage treatment (Salvage 1 or 2); Patient age at randomization (<55 or >=55 years). All factors are per IVRS.
[f] From one sided stratified log-rank test. The stratification factors are Duration of first remission (<12 months or >= 12 months); Salvage treatment (Salvage 1 or 2); Patient age at randomization (<55 or >=55 years). All factors are per IVRS.
Post-transplant Survival defined as date of death/last contact - date of SCT + 1
Veno Occlusive Disease includes Sinusoidal Obstruction Syndrome, Veno Occlusive Disease and Veno Occlusive Liver Disease.

- In the safety population (data cut-off date of 2 October 2014), of 259 patients who received study therapy, 116/139 patients permanently discontinued treatment in the inotuzumab ozogamicin arm and 107/120 patients permanently discontinued treatment in the control arm. The most common reasons for treatment discontinuation in the inotuzumab ozogamicin arm included 'complete response' (34.5%), AEs (15.1%), objective progression or relapse (10.8%) and resistant disease (10.1%). The most common reasons for discontinuation from study treatment in the control arm included resistant disease (40.0%), 'complete response' (15.0%) and objective progression or relapse (10.8%) (Study B1931022). As of the 8 March 2016 cut-off for the supplementary analysis (sCSR) A total of 125 (76.2%) patients in the inotuzumab ozogamicin arm had permanently discontinued the study compared to 147 (90.7%) patients in the control arm, with the number of ongoing patients being 39 (23.8%) and 15 (9.3%), respectively.
- For patients in the inotuzumab ozogamicin arm who achieved CR/CRi and did not undergo follow-up HSCT, responders who received a maximum of 4 to 6 cycles had numerically higher median DoR and OS compared to responders who received a maximum of 1 to 3 cycles (median DoR of 4.2 and 2.5 months, respectively, and median OS of 8.0 and 5.3 months, respectively) (note, not statistically significant). Five responders who did not proceed to HSCT after inotuzumab ozogamicin treatment were still alive at 18 months. Of these 5 patients, 2 patients had received 3 cycles and had DoR of 57 and 128 days, 2 patients had received 4 cycles and had DoR of 332 and 488 days, and 1 patient had received 6 cycles and had DoR of 317 days (sponsor's response to clinical questions).

Overall, the results for the study population are considered to be applicable to Australian patients with relapsed or refractory ALL who might be eligible for treatment with inotuzumab ozogamicin. The implications of these results are addressed in the discussion section below.

Study B1931010

The supportive single arm Phase I/II Study (B1931010) included a total 72 adult patients with a diagnosis of CD22 positive ALL (that is, ≥ 20% blasts CD22 positive based on local immuno-phenotyping and histopathology) who had refractory disease (defined as disease progression or no response while receiving their most recent prior anticancer therapy) or relapsed disease (defined as response to their most recent prior anticancer therapy with subsequent relapse) and, for the Phase II portion, were due to receive Salvage ≥ 2 therapy. The inclusion criteria also included patients with lymphoblastic lymphoma with bone marrow involvement with ≥ 5% lymphoblasts, and Ph+ ALL patients who had failed standard treatment with at least 1 TKI.

Phase 1 of the study included 37 patients and consisted of two parts, firstly a dose finding part designed to select the Phase II dose and a dose-expansion aimed at further evaluating the efficacy and safety of the Phase II dose. Phase II of the study included 35 patients and was designed to evaluate the efficacy of the Phase II dose of inotuzumab ozogamicin as measured by the haematologic remission rate (CR/CRi) in patients in second or later salvage setting.

Patients in Phase 2 were treated with inotuzumab ozogamicin 1.8 mg/m^2/cycle administered at a dose of 0.8 mg/m^2 on Day 1 and 0.5 mg/m^2 on Days 8 and 15 of a 28 day cycle with a dose reduction upon achieving CR/Cri. The majority of patients (85.8%) had an Eastern Cooperative Oncology Group (ECOG) status of 1 or 2, with 2 patients included with ECOG status of 3 (5.7%). The salvage status of the patients were 1 (n = 2, 5.7%), 2 (n = 16, 45.7%), 3 (n = 11, 31.4%), 4 (n = 2, 5.7%), 5 (n = 1, 2.9%), and > 5 (n = 3, 8.6%). Prior HSCT had been received by 15 (42.9%) patients in the cohort and a total of 9 Ph+ patients were included (25.7%). The clinical evaluator identified that the cohort was relatively

young, with a median age of 34 years (range: 20, 79) and only 4 (11.4%) patients were aged ≥ 65 years.

The CR/CRi response rate per investigator assessment (primary efficacy endpoint) in the Phase II (1.8 mg/m^2) cohort was 68.6% (24/35). This result met the pre-specified criteria for statistically significance, as the null hypothesis of ≤ 20% at the -1-sided 0.5 level was rejected. Of note, this result was lower than the CR/CRi response rate per investigator assessment in the ITT population in the pivotal Phase III Study (B1931022) in the inotuzumab ozogamicin arm (1.8 mg/m^2/cycle) but higher than in the control arm (that is, 73.2% (120/164) and 30.9% (50/162), respectively).

The results for the key secondary efficacy endpoints for phase 2 (treated with 1.8 mg/m^2) included: median duration of response of 3.8months (95% CI 2.2, 5.8); median PFS 3.7 months (95% CI 2.6, 4.7); post-treatment HSCT rate of 22.9%; MRD negativity in 18 of the 24 patients who achieved CR/Cri (75%); OS; 82.9% patients died, and Median OS of 6.4 months (95% CI 4.5, 7.9).

Safety

The safety data included a Summary of Clinical Safety (SCS) which included a safety analysis of 1207 patients across the 11 clinical studies, in addition to 323 patients from investigator initiated research (IIR) studies and 257 patients from compassionate use (CU) programs. A Day 120 Safety Update (SU) was also available at the time of evaluation. This report provided updated safety information as of the data cut-off date of 01 September 2016.

A total of 1207 patients were treated in the 11 clinical studies (Phases I to III), 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. The pooled ALL data included 212 patients initially treated with inotuzumab ozogamicin 1.8 mg/m^2/cycle, comprising 164 patients from the pivotal Study B1931022 and 48 patients from the supportive Study B1931010.

The clinical evaluator emphasised the safety data from the pivotal Study B1931022 which included 164 patients treated with inotuzumab ozogamicin at the dose proposed for registration and 143 patients were treated with a control regimen. The clinical evaluator concluded that the safety data for inotuzumab ozogamicin from the pivotal study is consistent with the safety data for this drug from all other safety datasets (that is, ALL Study B1931010; 9 Pfizer NHL studies; IIR studies; CU program).

In study the pivotal Study B1931022, it is important to consider that adverse event (AE) frequencies were not adjusted for the longer duration of treatment in the inotuzumab ozogamicin arm. The median duration of treatment in the inotuzumab ozogamicin arm was 10-fold longer than in the control arm (8.9 weeks versus 0.9 weeks, respectively). In total, patients randomised to the inotuzumab ozogamicin arm received 464 cycles of therapy compared to 176 cycles for patients randomised to the control arm (2.6 x more cycles for inotuzumab ozogamicin compared to control). The maximum allowed number of cycles per protocol was 6 cycles of inotuzumab ozogamicin or 4 cycles of control. A total of 127 (77.4%) patients in the inotuzumab ozogamicin arm started > 1 cycle, 15 (9.1%) patients started at least 6 cycles, and 10 (6.1%) patients completed 6 cycles. A full safety evaluation was provided in the CER. Key safety findings include:

- Similar proportions of patients in the inotuzumab ozogamicin and control arms experienced Treatment Emergent Adverse Events (TEAEs, all causality, all grades, Day 120 SU), treatment related TAEs, Serious Adverse Events (SAE's all causality, 120-Day SU) and rate of overall post-transplant mortality.

- TEAEs maximum Grade 3 or 4 events (Day 120 SU) occurred less frequently in the inotuzumab ozogamicin arm than in the control arm (75.0% (123/164) versus 85.3% (122/143), respectively), as did treatment related TEAEs maximum Grade 3 or 4 events (SCS) (69.5% (114/164) versus 79.0% (113/143), respectively).
- Grade 5 AEs (all causality, Day 120 SU) were reported more frequently in the inotuzumab ozogamicin arm than in the control arm (15.9%, n = 26 versus 11.2%, n = 16, respectively), as were treatment related Grade 5 AEs (SCS) (5.5%, n = 9 versus 2.1%, n = 3, respectively).
    - Of particular note, in the 9 patients in the inotuzumab arm who died, 5 cases were due VOD/SOS (all after HSCT) compared to no cases of VOD/SOS leading to death in the control arm. Other treatment related Grade 5 AEs in the inotuzumab ozogamicin arm were 1 each of ARDS, intestinal ischaemia, multi-organ failure, pneumonia, and septic shock, while treatment related Grade 5 AEs in the control arm were 1 each for multi-organ failure, haemorrhage intracranial, lung infection and respiratory failure.
- All deaths (Day 120 SU), which included all deaths during treatment and in the follow-up period, were reported less frequently in the inotuzumab ozogamicin arm than in the control arm (76.8% (126/164) versus 87.4% (125/143), respectively).
    - Of note, all deaths due to infection were reported more frequently in the inotuzumab ozogamicin arm than in the control arm (14.6%, n = 24 versus 9.1%, n = 13, respectively).
- Post-transplantation deaths were also assessed in patients who underwent HSCT in the inotuzumab ozogamicin arm (n = 79) and the control arm (n = 35). Overall post-transplant mortality was similar in the inotuzumab ozogamicin and control arms (64.6% (51/79) versus 65.7% (23/35), respectively).
    - However, post-transplant non-relapse deaths were reported more frequently in patients in the inotuzumab ozogamicin arm than in the control arm (40.5% (32/79) versus 22.9% (8/35)). The most common reasons for post-transplant non-relapse deaths in the inotuzumab arm (versus control, respectively) were infection (21.6% (11/51) versus 17.4% (4/23)) and VOD (9.8% (5/51) versus 0% (0/23)).
- AEs (all causality, 120-Day SU), leading to permanent treatment discontinuation were reported more frequently in the inotuzumab ozogamicin arm than in the control arm (18.9% (31/164) versus 7.7% (11/143), respectively). AEs leading to permanent treatment discontinuation reported in ≥ 2 patients in the ozogamicin arm were 5 (3.0%) patients with pneumonia, 3 (0.18%) patients each with hyperbilirubinaemia and thrombocytopenia, and 2 (1.2%) patients each with sepsis, VOD, ALT increased, and GGT increased.
- AEs (all causality, Day 120 SU) resulting in temporary treatment delays were reported more frequently in the inotuzumab ozogamicin arm than in the control arm (43.9% (72/164) versus 11.9% (17/143), respectively). AEs (all causality, Day 120 SU) resulting in dose reduction were reported in a small number of patients in both the inotuzumab ozogamicin and control arms (n = 5, 3.0% versus n = 3, 2.1%, respectively).
- The clinical evaluator reported the following matters arising from the assessment of adverse events of special interest in the inotuzumab ozogamicin arm:
    - increased risk of hepatotoxicity, including severe, life-threatening and fatal VOD/SOS:

  - § Hepatotoxicity adverse events were reported across the pooled ALL studies at a rate of 50.9% (108/212) in the inotuzumab ozogamicin arm compared to 43.3% (49/143) in the control arm.
  - § Overall, of the 880 patients exposed to inotuzumab ozogamicin in ALL or NHL studies, 34/880 (3.9%) hepatic VOD (total) SAEs were reported following treatment with inotuzumab ozogamicin, including 13.4% (22/164) in the pivotal study, 12.3% (26/212) in the pooled ALL studies.
  - § In the pivotal study, the frequency of VOD (total) in patients with pre-study HSCT versus no pre-study HSCT was 24.1% and 11.1%, respectively.
  - § Based on the 77 patients who underwent HSCT in the inotuzumab ozogamicin arm of the pivotal study, the risk of developing VOD/VOS post-HSCT was 50% (3/6) in patients aged ≥ 65 years and 19.7% (14/71) in patients aged < 65 years.
- severe, life threatening myelosuppression/cytopenia.
- serious infections were very commonly reported, and some were life threatening or fatal.
- infusion related-reactions, including hypersensitivity, were reported very commonly.
- pancreatic related adverse events including increased serum amylase and lipase.

Overall, the clinical evaluator considered that the submitted data for inotuzumab ozogamicin have adequately established the safety of the drug for the treatment of the proposed indication. A black box warning and precautions have been included in the Australian PI which includes the risks of hepatotoxicity, including severe, life threatening and fatal VOD/SOS and increased risk of post-hematopoietic stem cell transplant (HSCT) non-relapse mortality.

Clinical evaluator's recommendation

The clinical evaluator recommended that inotuzumab ozogamicin (Besponsa) be approved for the treatment of adults with relapsed or refractory CD22 positive B cell precursor acute lymphoblastic leukaemia (ALL).

A total of four outstanding PI issues were identified in the second round clinical report. These have been satisfactorily addressed by the sponsor.

Risk management plan

There were no objections to approval of the application for inotuzumab ozogamicin from the RMP evaluators.

In the second round RMP report, the evaluator requested the Delegate to consider if the important potential risks of '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' should be included in the PI. These risk are listed by the sponsor as important potential risks in the table of ongoing safety concerns in the EU-RMP Version1.5, dated 26 April 2017, data lock point 26 April 2016. The Delegate agrees with the sponsor that these risks should be included as important potential risks in the RMP and reported on within the PSUR. The clinical evaluator also agreed with this and did not suggest inclusion in the PI at this stage. In reconciling this request, the Delegate has considered the following:

- the Delegate considers the definition of an important potential risk to mean risks that are not refuted by clinical data or which are of unknown significance. There are clear mechanistic explanations for these potential risks with the use of inotuzumab ozogamicin, as discussed in detail by the sponsor in the EU-RMP Version 1.5.
- These risks have been considered by the sponsor as '*adverse events of special interest*' (AEoSI) in analysing the study from the data in patients with ALL and NHL provided in the dossier. This is appropriate.
- The RMP evaluator notes that the important identified risk of reproductive and developmental toxicity is discussed in the proposed PI under *Precautions*. This information has been reviewed and modified by the nonclinical evaluator.
- Interstitial lung disease (ILD): In the pooled data from ALL studies discussed in the Summary of Clinical Safety, there were no AE's of ILD. The sponsor noted that 1 patient in the inotuzumab ozogamicin arm was reported to have Grade 1 obliterative bronchiolitis and pneumonitis and 1 patient in the control arm reported to have Grade 2 bronchiolitis. In the pooled single agent NHL studies, ILD AE's were reported in 4 patients (2.3%). This included Grade 1 pneumonitis (n = 2), Grade 2 lung infiltration (n = 1), and Grade 4 alveolitis (n = 1)). Although ILD is clinically significant, there is insufficient data at this stage to allow for quantification of this risk for patients with relapsed or refractory ALL. The Delegate agrees with the sponsor that ongoing monitoring through the PSUR is appropriate at this stage.it is appropriate at this stage to ensure ongoing monitoring in the PSUR.
- Pancreatitis: In the pooled data from ALL studies discussed in the Summary of Clinical Safety, pancreatitis AEs were reported in 21/212 (9.9%) of pooled ALL patients, which included 18/164 (11.0%) patients from Study 1022 (Table 16). In the pooled ALL studies, Grade ≥ 3 pancreatitis AEs included: lipase increased (8 (3.8%) patients); amylase increased (4 (1.9%) patients); pancreatitis (2 (0.9%) patients: Grade 3) and pancreatitis acute (1 (0.5%; Grade 3) patients). No Grade 5 pancreatitis AEs were reported. The adverse events of lipase increased and amylase increased are included in the draft Australian PI for inotuzumab ozogamicin. The Delegate agrees with the sponsor that ongoing monitoring of the rates of pancreatitis through the PSUR is appropriate at this stage.

Table 16: Inotuzumab ozogamicin Pooled Studies B1931010 and B1931022; summary of treatment-emergent clustered pancreatitis events by MedDRA preferred term (decreasing frequency order) and maximum CTCAE Grade (All Causalities); Safety Population

	Inotuzumab Ozogamicin (N=212)							
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 3-4	Grade 3-5	Total
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AEs	5 (2.4)	5 (2.4)	7 (3.3)	4 (1.9)	0	11 (5.2)	11 (5.2)	21 (9.9)
Lipase increased	4 (1.9)	4 (1.9)	4 (1.9)	4 (1.9)	0	8 (3.8)	8 (3.8)	16 (7.5)
Amylase increased	3 (1.4)	2 (0.9)	4 (1.9)	0	0	4 (1.9)	4 (1.9)	9 (4.2)
Pancreatitis	0	0	2 (0.9)	0	0	2 (0.9)	2 (0.9)	2 (0.9)
Pancreatic pseudocyst	1 (0.5)	0	0	0	0	0	0	1 (0.5)
Pancreatitis acute	0	0	1 (0.5)	0	0	1 (0.5)	1 (0.5)	1 (0.5)
Pancreatitis necrotising	1 (0.5)	0	0	0	0	0	0	1 (0.5)

- Secondary primary malignancy: In the pooled data from ALL studies discussed in the Summary of Clinical Safety, one case of AML was reported after 3 cycles of inotuzumab ozogamicin in the setting of ALL remission in a patient receiving Salvage > 5 therapy. The patient was heavily pre-treated with chemotherapy for 7 years from initial diagnosis; however, the investigator's causal attribution to inotuzumab ozogamicin could not be excluded. No cases were reported in the pooled single agent NHL studies. Therefore, there is insufficient data at this stage to allow for quantification of this risk.

The Delegate agrees with the sponsor that ongoing monitoring through the PSUR is appropriate at this stage.

- Inflammatory gastrointestinal events:
  - Inflammatory gastrointestinal adverse events were reported in 34/212 (16.0%) patients receiving inotuzumab ozogamicin, which included 28/164 (17.1%) patients from the pivotal study. There was one case of 'colitis ischaemic' Grade 5 reported in the pivotal study. Overall, in the pooled single agent NHL Studies, Inflammatory gastrointestinal adverse events were reported in 3/173 (1.7%) patients receiving inotuzumab ozogamicin, including Gastritis (n = 2) and oesophagitis (n = 1) (Table 17). No Grade 3, 4, or 5 inflammatory gastrointestinal adverse events were reported. The sponsor states in the inotuzumab ozogamicin Risk Management Plan (dated April 2017) that '*…there is currently not enough evidence to know whether inotuzumab ozogamicin treatment could cause inflammation and ulceration of the mucous membranes lining the digestive tract in some patients*'.

Table 17: Inotuzumab ozogamicin single agent pooled Studies B1931002 and B1931007 + B1931016; summary of treatment emergent clustered inflammatory gastrointestinal adverse events by MedDRA preferred term (decreasing frequency order) and maximum CTCAE Grade (All Causalities); (Safety Population)

	NHL Single Agent Inotuzumab Ozogamicin (N=173)						
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 3-5	Total
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AEs	2 (1.2)	1 (0.6)	0	0	0	0	3 (1.7)
Gastritis	2 (1.2)	0	0	0	0	0	2 (1.2)
Oesophagitis	0	1 (0.6)	0	0	0	0	1 (0.6)

- Neurotoxicity:
  - In the pivotal study neurotoxicity adverse events were reported in 17 (10.4%) patients in the inotuzumab ozogamicin arm and 10 (7.0%) patients in the control arm (Table 18). The only AE reported with frequency ≥ 2% in the inotuzumab ozogamicin arm compared with the control arm was 'Neuropathy peripheral' (6 (3.7%) versus 2 (1.4%) patients). There were a total of 2 events of gait disturbance (1.2%, Grade 1 and Grade 3) in the inotuzumab ozogamicin arm compared with 1 (0.7%, Grade 1) event in the control arm. No other Grade 3, 4, or 5 events or permanent treatment discontinuations due to AEs were reported in the inotuzumab ozogamicin arm.

Table 18: Summary of treatment emergent clustered neurotoxicity adverse events by MedDRA preferred term (decreasing frequency order) and maximum CTCAE grade (all causalities); Safety Population

	Inotuzumab Ozogamicin (N=164)							
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 3-4	Grade 3-5	Total
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AEs	13 (7.9)	3 (1.8)	1 (0.6)	0	0	1 (0.6)	1 (0.6)	17 (10.4)
Neuropathy peripheral	5 (3.0)	1 (0.6)	0	0	0	0	0	6 (3.7)
Hypoaesthesia	2 (1.2)	1 (0.6)	0	0	0	0	0	3 (1.8)
Muscular weakness	2 (1.2)	1 (0.6)	0	0	0	0	0	3 (1.8)
Paraesthesia	3 (1.8)	0	0	0	0	0	0	3 (1.8)
Gait disturbance	1 (0.6)	0	1 (0.6)	0	0	1 (0.6)	1 (0.6)	2 (1.2)
Peripheral sensory neuropathy	2 (1.2)	0	0	0	0	0	0	2 (1.2)
Muscle atrophy	0	1 (0.6)	0	0	0	0	0	1 (0.6)
	Investigator Choice (N=143)							
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 3-4	Grade 3-5	Total
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AEs	6 (4.2)	2 (1.4)	2 (1.4)	0	0	2 (1.4)	2 (1.4)	10 (7.0)
Hypoaesthesia	2 (1.4)	0	0	0	0	0	0	2 (1.4)
Muscular weakness	1 (0.7)	0	1 (0.7)	0	0	1 (0.7)	1 (0.7)	2 (1.4)
Neuralgia	1 (0.7)	0	1 (0.7)	0	0	1 (0.7)	1 (0.7)	2 (1.4)
Neuropathy peripheral	1 (0.7)	1 (0.7)	0	0	0	0	0	2 (1.4)
Gait disturbance	1 (0.7)	0	0	0	0	0	0	1 (0.7)
Leukoencephalopathy	0	0	1 (0.7)	0	0	1 (0.7)	1 (0.7)	1 (0.7)
Paraesthesia	1 (0.7)	0	0	0	0	0	0	1 (0.7)
Peripheral sensory neuropathy	0	1 (0.7)	0	0	0	0	0	1 (0.7)
	Total (N=307)							
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 3-4	Grade 3-5	Total
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AEs	19 (6.2)	5 (1.6)	3 (1.0)	0	0	3 (1.0)	3 (1.0)	27 (8.8)
Neuropathy peripheral	6 (2.0)	2 (0.7)	0	0	0	0	0	8 (2.6)
Hypoaesthesia	4 (1.3)	1 (0.3)	0	0	0	0	0	5 (1.6)
Muscular weakness	3 (1.0)	1 (0.3)	1 (0.3)	0	0	1 (0.3)	1 (0.3)	5 (1.6)
Paraesthesia	4 (1.3)	0	0	0	0	0	0	4 (1.3)
Gait disturbance	2 (0.7)	0	1 (0.3)	0	0	1 (0.3)	1 (0.3)	3 (1.0)
Peripheral sensory neuropathy	2 (0.7)	1 (0.3)	0	0	0	0	0	3 (1.0)
Neuralgia	1 (0.3)	0	1 (0.3)	0	0	1 (0.3)	1 (0.3)	2 (0.7)
Leukoencephalopathy	0	0	1 (0.3)	0	0	1 (0.3)	1 (0.3)	1 (0.3)
Muscle atrophy	0	1 (0.3)	0	0	0	0	0	1 (0.3)

Note: Investigator Choice is one of the defined chemotherapy regimens (either FLAG (Fludarabine, Cytarabine, and G-CSF), Cytarabine and Mitoxantrone, or HIDAC).
Abbreviation: CTCAE=Common Terminology Criteria for Adverse Events; VOD=Veno-occlusive Disease.
Treatment-Emergent adverse events (TEAEs) are defined as adverse events (AEs) that commence on or after C1D1 but within 42 days of last dose and all treatment-related AEs thereafter. All VOD events within 2 years of randomization date regardless of causal attribution to study therapy are included.
Patients are counted only once per treatment in each row for individual grade columns. Maximum CTCAE grades are displayed.
MedDRA (v18.1) coding dictionary is applied. Adverse events graded according to the NCI CTCAE, version 3.0.
Cluster document version 2.1 is used for clustering.

- Nephrotoxicity:
  - Nephrotoxicity adverse events were reported in 9/212 (4.2%) pooled ALL patients, which included 8/164 (4.9%) patients from the pivotal study (Table 19, and Table 20). The laboratory abnormality 'creatinine increased' was observed in 22/212 (10.4%) patients (13 Grade 1 events, 9 Grade 2 events) (Table 21).

Table 19: Inotuzumab ozogamicin pooled Studies B1931010 and B1931022; summary of treatment emergent clustered nephrotoxicity events by MedDRA preferred term (decreasing frequency order) and maximum CTCAE Grade (all causalities); Safety Population

	Inotuzumab Ozogamicin (N=212)							
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 3-4	Grade 3-5	Total
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AEs	4 (1.9)	3 (1.4)	2 (0.9)	0	0	2 (0.9)	2 (0.9)	9 (4.2)
Acute kidney injury	2 (0.9)	2 (0.9)	1 (0.5)	0	0	1 (0.5)	1 (0.5)	5 (2.4)
Blood creatinine increased	3 (1.4)	0	0	0	0	0	0	3 (1.4)
Azotaemia	0	1 (0.5)	0	0	0	0	0	1 (0.5)
Oliguria	1 (0.5)	0	0	0	0	0	0	1 (0.5)
Urine output decreased	0	0	1 (0.5)	0	0	1 (0.5)	1 (0.5)	1 (0.5)

Table 20: Inotuzumab ozogamicin Study B1931022; summary of treatment-emergent clustered nephrotoxicity adverse events by MedDRA preferred term (decreasing frequency order) and maximum CTCAE Grade (all causalities); Safety Population

	Inotuzumab Ozogamicin (N=164)							
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 3-4	Grade 3-5	Total
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AEs	3 (1.8)	3 (1.8)	2 (1.2)	0	0	2 (1.2)	2 (1.2)	8 (4.9)
Acute kidney injury	1 (0.6)	2 (1.2)	1 (0.6)	0	0	1 (0.6)	1 (0.6)	4 (2.4)
Blood creatinine increased	3 (1.8)	0	0	0	0	0	0	3 (1.8)
Azotaemia	0	1 (0.6)	0	0	0	0	0	1 (0.6)
Oliguria	1 (0.6)	0	0	0	0	0	0	1 (0.6)
Urine output decreased	0	0	1 (0.6)	0	0	1 (0.6)	1 (0.6)	1 (0.6)
	Investigator Choice (N=143)							
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 3-4	Grade 3-5	Total
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AEs	5 (3.5)	2 (1.4)	1 (0.7)	0	0	1 (0.7)	1 (0.7)	8 (5.6)
Acute kidney injury	0	1 (0.7)	1 (0.7)	0	0	1 (0.7)	1 (0.7)	2 (1.4)
Renal failure	2 (1.4)	0	0	0	0	0	0	2 (1.4)
Azotaemia	1 (0.7)	0	0	0	0	0	0	1 (0.7)
Blood creatinine increased	1 (0.7)	0	0	0	0	0	0	1 (0.7)
Hypercreatininaemia	0	1 (0.7)	0	0	0	0	0	1 (0.7)
Oliguria	1 (0.7)	0	0	0	0	0	0	1 (0.7)
	Total (N=307)							
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 3-4	Grade 3-5	Total
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AEs	8 (2.6)	5 (1.6)	3 (1.0)	0	0	3 (1.0)	3 (1.0)	16 (5.2)
Acute kidney injury	1 (0.3)	3 (1.0)	2 (0.7)	0	0	2 (0.7)	2 (0.7)	6 (2.0)
Blood creatinine increased	4 (1.3)	0	0	0	0	0	0	4 (1.3)
Azotaemia	1 (0.3)	1 (0.3)	0	0	0	0	0	2 (0.7)
Oliguria	2 (0.7)	0	0	0	0	0	0	2 (0.7)
Renal failure	2 (0.7)	0	0	0	0	0	0	2 (0.7)
Hypercreatininaemia	0	1 (0.3)	0	0	0	0	0	1 (0.3)
Urine output decreased	0	0	1 (0.3)	0	0	1 (0.3)	1 (0.3)	1 (0.3)

Note: Investigator Choice is one of the defined chemotherapy regimens (either FLAG (Fludarabine, Cytarabine, and G-CSF), Cytarabine and Mitoxantrone, or HIDAC).
Abbreviation: CTCAE=Common Terminology Criteria for Adverse Events; VOD=Veno-occlusive Disease.
Treatment-Emergent adverse events (TEAEs) are defined as adverse events (AEs) that commence on or after C1D1 but within 42 days of last dose and all treatment-related AEs thereafter. All VOD events within 2 years of randomization date regardless of causal attribution to study therapy are included.
Patients are counted only once per treatment in each row for individual grade columns. Maximum CTCAE grades are displayed.
MedDRA (v18.1) coding dictionary is applied. Adverse events graded according to the NCI CTCAE, version 3.0.
Cluster document version 2.1 is used for clustering.

Table 21: Inotuzumab ozogamicin pooled Studies B1931010 + B1931022; summary results of labs by maximum CTCAE Grade (chemistries, all cycles); Safety Population

		Inotuzumab Ozogamicin (N=212)				
		Grade 1	Grade 2	Grade 3	Grade 4	Total
Parameter	N	n (%)	n (%)	n (%)	n (%)	n (%)
Alanine aminotransferase increased	211	77 (36.5)	20 (9.5)	8 (3.8)	0	105 (49.8)
Alkaline phosphatase increased	208	97 (46.6)	24 (11.5)	3 (1.4)	0	124 (59.6)
Aspartate aminotransferase increased	210	110 (52.4)	36 (17.1)	10 (4.8)	1 (0.5)	157 (74.8)
Blood bilirubin increased	211	33 (15.6)	34 (16.1)	11 (5.2)	1 (0.5)	79 (37.4)
Creatinine increased	211	13 (6.2)	9 (4.3)	0	0	22 (10.4)
Gamma Glutamyl Transpeptidase increased	193	57 (29.5)	44 (22.8)	29 (15.0)	1 (0.5)	131 (67.9)
Hypercalcemia	209	13 (6.2)	1 (0.5)	1 (0.5)	1 (0.5)	16 (7.7)
Hyperglycemia	207	107 (51.7)	38 (18.4)	25 (12.1)	1 (0.5)	171 (82.6)
Hyperkalemia	211	4 (1.9)	5 (2.4)	1 (0.5)	1 (0.5)	11 (5.2)
Hypermagnesemia	204	9 (4.4)	0	8 (3.9)	0	17 (8.3)
Hypernatremia	211	18 (8.5)	1 (0.5)	1 (0.5)	0	20 (9.5)
Hyperuricemia	201	28 (13.9)	0	0	6 (3.0)	34 (16.9)
Hypoalbuminemia	205	66 (32.2)	46 (22.4)	9 (4.4)	0	121 (59.0)
Hypocalcemia	209	34 (16.3)	8 (3.8)	1 (0.5)	1 (0.5)	44 (21.1)
Hypoglycemia	207	19 (9.2)	5 (2.4)	0	2 (1.0)	26 (12.6)
Hypokalemia	211	79 (37.4)	0	15 (7.1)	1 (0.5)	95 (45.0)
Hypomagnesemia	204	62 (30.4)	3 (1.5)	0	0	65 (31.9)
Hyponatremia	211	64 (30.3)	0	12 (5.7)	0	76 (36.0)
Hypophosphatemia	201	5 (2.5)	41 (20.4)	18 (9.0)	2 (1.0)	66 (32.8)
Lipase increased	163	24 (14.7)	8 (4.9)	15 (9.2)	2 (1.2)	49 (30.1)
Serum amylase increased	160	17 (10.1)	6 (3.6)	4 (2.4)	0	27 (16.1)

Abbreviation: CTCAE=Common Terminology Criteria for Adverse Events.
The number of patients with non-missing baseline and post-baseline results for a lab measurement is used to calculate percentages.
Lab results are summarized upto end of treatment + 42 days.
Version 3.0 CTCAE grading used.
Note: Inotuzumab Ozogamicin includes B1931010 patients from the Expansion Phase and Phase 2, and B1931022 patients randomized to the Inotuzumab Ozogamicin Arm.
Unplanned readings have been included in the presentation.

Recommended condition/s of registration

The RMP evaluator recommended the following conditions of registration:

- The Besponsa EU-Risk Management Plan (RMP) (version 1.5, dated 26 April 2017, data lock point 26 April 2016), with Australian Specific Annex (version 1.1, dated 14 December 2017), included with submission PM-2017-01455-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs). Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter. The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-Periodic Safety Update Report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report
- Besponsa (inotuzumab ozogamicin) is to be included in the Black Triangle Scheme. The PI and CMI for Besponsa must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

Risk-benefit analysis

Delegate's considerations

The pivotal evidence of efficacy of inotuzumab ozogamicin is based on the results of a randomised, open label, controlled Phase III study in 326 adult patients with relapsed or refractory CD22 positive ALL. This study compared inotuzumab ozogamicin to investigator's choice of chemotherapy. In the analysis of the primary endpoint of complete response or complete response with incomplete haematological recovery (Cr/CRi) per EAC in the first 218 patients enrolled who received inotuzumab ozogamicin, the CR/CRi was significantly greater in the inotuzumab ozogamicin arm compared to the control arm (80.7% versus 29.4%, $p < 0.0001$). The pre-specified sensitivity analyses for the CR/CRi (EAC) were consistent with the primary analysis. Further data updates were also consistent with this trend. In the updated ITT population dated 8 March 2016, the CR/CRi (per investigator) was 73.2%, in the inotuzumab ozogamicin compared to 30.9% in the control arm ($p < 0.0001$, 1-sided Chi-square test). In the ITT population, nearly all patients in the inotuzumab arm with a CR/CRi achieved remission within the first two treatment cycles (70.8%, Cycle 1 and 25.8%, Cycle 2), and no patients achieved remission after the third cycle.

The increased CR/CRi in the inotuzumab ozogamicin arm compared to the control arm is of clinical significance as it provides a greater opportunity for patients treated with inotuzumab ozogamicin to proceed to potentially curative HSCT. In the ITT population, there was an approximately 4 fold increase in the percentage of patients in the inotuzumab ozogamicin arm proceeding to follow-up HSCT directly after achieving CR/CRi (per investigator) without intervening induction or salvage therapy compared to patients in the control arm (39.6% versus 9.9%). However, this finding did not translate into a statistically significant overall survival benefit in patients in the inotuzumab arm compared to the control arm. Although the primary OS analysis demonstrated a small survival benefit in favour of the inotuzumab ozogamicin arm compared to the control arm,

the difference between the two treatment arms was not statistically significant based on the pre-specified stratified analysis (HR = 0.770 (97.5%: 0.578, 1.026); p = 0.0203, boundary for significance was 0.0104. The updated results for the OS analysis in the ITT population (data at a cut-off date of 4 January 2017 LSLV) were consistent with the analysis undertaken at a cut-off date of 8 March 2016. Of importance, the post-HSCT non-relapse mortality rate was higher in the inotuzumab ozogamicin arm than in the control arm (primarily due to higher rates of VOD/SOD and infection), as was both the 100 day and 12 month mortality rates for post-HSCT mortality and non-relapse post-HSCT mortality. This risk has been included in a black box warning in the proposed Australian PI.

Secondary endpoints of the pivotal study did demonstrate clinically meaningful results. The median PFS in the inotuzumab arm was 3.2 months longer than in the control arm (5.0 versus 1.8 months, respectively) with estimated HR of 0.452 (97.5% CI: 0.336, 0.609; 1-sided p < 0.0001). Other pre-specified endpoints in this study which support treatment with inotuzumab ozogamicin compared to control (based on updated data at a cut-off of 8 March 2016) include: Duration of remission in patients with CR/CRi (per investigator) (ITT218) of 5.4 months (95% CI: 4.2, 8.0) in the inotuzumab ozogamicin arm and 3.5 months (95% CI: 2.9, 6.6) in the control arm. Other notable statistically significant results include the percentage of patients with CR/CRi, (per investigator) achieving MRD negativity. This was markedly greater in the inotuzumab ozogamicin arm (76.7%) than in the control arm (38.0%). The follow-up HSCT rate prior to the start of another induction therapy regardless of CR/CRi status was also higher in the inotuzumab ozogamicin arm (43.3%) than in the control arm (11.1%).

For patients who achieved CR/CRi and did not undergo follow-up HSCT, a numerically higher median duration of response and the median overall survival were demonstrated in patients treated for 4 to 6 cycles compared with 1 to 3 cycles, although this was not statistically significant. The safety data showed that all-causality Grade ≥ 3 TEAEs (any) increased with increasing number of cycles. However, as noted by the clinical evaluator, this result should be interpreted having regard to the decreasing number of patients exposed to treatment with increasing number of cycles. In the Delegate's opinion, the PI document contains appropriate information regarding treatment of this group, stating: '*For patients not proceeding to HSCT, a maximum of 6 cycles may be administered. Patients who do not achieve a CR or CRi within 3 cycles should discontinue treatment.*'

In the pivotal study, the median duration of treatment in the inotuzumab ozogamicin arm was 10 fold longer than in the control arm (8.9 weeks versus 0.9 weeks, respectively). The median duration for FLAG 0.9 was weeks (range 0.4 to 15.1), median duration for Mxn/Ara-c was 1.1 weeks (range 0.4 to 8.6) and median duration HIDAC was 1.0 weeks (range 0.6 to 9.7) (Study B1931002). The most common reason for treatment discontinuation in the inotuzumab ozogamicin arm was 'complete response' (34.5%) compared to 'resistant disease' (40.0%) in the control arm. It is not clear if the treatment duration of 0.9 weeks for the chemotherapy treatments chosen is an expected outcome, however this is important to consider this context when interpreting of the results from the pivotal study. The Advisory Committee on Medicines (ACM) has been asked to provide specific comment on this issue.

Patient reported outcomes for global health status/quality of life, functioning, and symptoms were generally in favour of patients in the inotuzumab ozogamicin arm compared to patients in the control arm. Overall conclusions regarding superior tolerability compared to standard of care cannot be clearly made based on this data alone. Of note, adverse events resulting in temporary treatment delays were reported notably more frequently in the inotuzumab ozogamicin arm than in the control arm (43.9% versus 11.9% respectively). Since multiple reasons may have contributed to the decision to

permanently discontinue study therapy, this is less direct in the current setting as a potential indicator of patient tolerability.

The safety data for inotuzumab ozogamicin is based on a total of 880 patients with relapsed or refractory B cell ALL from the clinical studies, in addition of 323 patients exposed through IIR studies and 257 patients from compassionate use programmes. Common adverse events (≥ 20% in the pivotal study) included thrombocytopenia, neutropenia, infection, anaemia, leukopenia, fatigue, haemorrhage, pyrexia, nausea, headache, febrile neutropenia, increased transaminases, abdominal pain, hyperbilirubinemia, and increased gamma-glutamyltransferase.

Key findings identified in the safety profile for inotuzumab ozogamicin include the rate of VOD/SOS. In the pivotal study, VOD was reported at a significantly increased rate compared to the control arm. This risk was most pronounced in patients who underwent subsequent HSCT (22.8% of patients). VOD/SOS was reported 2 fold more frequently in patients with a prior history of liver disease and/or hepatitis than in patients without such a history. Increased frequency of VOD/SOS was also associated with 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. Of note, VOD was noted amongst the most common reasons for post-transplant non-relapse deaths in the inotuzumab arm.

Although the risks of VOD/SOS and post-transplant non-relapse mortality are clinically significant, this must be balanced against the evidence supporting use of inotuzumab ozogamicin in this heavily pre-treated population with poor prognosis. It is reasonable to consider that the risks of VOD/SOS and post-transplant non-relapse mortality can be adequately considered by clinicians as part of an individual patient risk/benefit assessment. The sponsor has agreed to include a black box warning regarding the risk of hepatotoxicity, including fatal and life-threatening hepatic venoocclusive disease. Furthermore, additional contraindications regarding prior VOD/SOS and serious ongoing hepatic disease have been included in the proposed Australian PI.

Proposed indication

The wording of the indication recommended by the clinical evaluator is as follows:

> '*Besponsa is indicated for the treatment of adults with relapsed or refractory CD22-positive B cell precursor acute lymphoblastic leukaemia (ALL)*'.

This wording is in line with the approved indication in the United States, however the European Medicines Agency approved the additional phrase '*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)*.'

Both the pivotal efficacy Study B1931022 and supportive efficacy Study B1931010 included adult patients with Philadelphia chromosome positive (Ph+) relapsed or refractory B cell precursor ALL who had failed treatment with at least 1 tyrosine kinase inhibitor (TKI). A total of 4 Ph+ patients in the pivotal study did not meet this inclusion criteria (3 in the inotuzumab ozogamicin arm and in the control arm). Therefore including the phrase '*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)'* directly reflects the efficacy data currently available. However, it must be noted that a number of uncertainties remain regarding the optimum treatment recommendations for patients with Ph+ ALL. As discussed by Larson et al 2017[50] tyrosine kinase inhibitors (TKI's) should be considered alongside first line therapy, however many questions remain, including the preferred TKI to combine with chemotherapy, the optimal

[50] Larson, R. Induction therapy for Philadelphia chromosome negative acute lymphoblastic leukemia in adults. UpToDate article. 12 January 2017.

scheduling of this TKI with chemotherapy, and the role for hematopoietic cell transplantation after remission is achieved. Furthermore, it is also not possible to accurately determine how treatment with inotuzumab ozogamicin in patients with relapsed or refractory Ph+ ALL who have *not* failed at least 1 TKI compares to current treatment options available to this group, or if there is any risk of disadvantage. Although this is uncertain, it is clear that treatment options in this group must be considered in the context of the induvial patient scenario. Therefore it is the Delegate's opinion that the indication for inotuzumab ozogamicin in Australia state:

> '*Besponsa is indicated for the treatment of adults with relapsed or refractory CD22-positive B cell precursor acute lymphoblastic leukaemia (ALL)'*.

However, the Delegate would appreciate ACM opinion on this issue.

Overall in the Delegate's opinion, the data presented support a favourable risk-benefit balance of inotuzumab ozogamicin for the treatment of adult patients with relapsed or refractory CD22 positive B cell precursor acute lymphoblastic leukaemia (ALL).

Questions for sponsor

1. Please provide an update of the overseas regulatory status for Besponsa, including any further approvals, withdrawals, rejections or delays.
2. Please provide a comment regarding the shorter duration of treatment in the control arm of this study. Is this an expected treatment duration for the clinical setting and treatment types chosen?
3. Given the increased rate of Inflammatory gastrointestinal adverse events in the pooled ALL data compared to the pooled NHL studies, in addition to the rate of reporting above 10%, please include this under the *Adverse Events* section of the PI or provide a compelling justification for exclusion
4. In light of the above data, (neurotoxicity) please include '*peripheral neuropathy*' under the *Adverse Events* section of the PI or provide a compelling justification for exclusion.
5. In light of the above data, (nephrotoxicity) please include '*creatinine increased*' under the *Adverse Events* section of the PI or provide a compelling justification for exclusion.

Conclusion

Inotuzumab ozogamicin is a CD22 targeted antibody-drug conjugate (ADC). In the pivotal efficacy study, an increased rate of CR/CRi was demonstrated in the inotuzumab ozogamicin arm compared to the control arm. This is of clinical significance as it provides a greater opportunity for patients treated with inotuzumab ozogamicin to proceed to potentially curative HSCT. In the ITT population, there was an approximately 4 fold increase in the percentage of patients in the inotuzumab ozogamicin arm proceeding to follow-up HSCT directly after achieving CR/CRi (per investigator) without intervening induction or salvage therapy compared to patients in the control arm. However, this finding did not translate into a statistically significant overall survival benefit in patients in the inotuzumab arm compared to the control arm.

The post-HSCT non-relapse mortality rate was higher in the inotuzumab ozogamicin arm than in the control arm. This was primarily due to higher rates of VOD/SOS and infection. In the pivotal study, the risk of VOD/SOS was most pronounced in patients who underwent subsequent HSCT. VOD/SOS was reported 2 fold more frequently in patients with a prior history of liver disease and/or hepatitis than in patients without such a history. Increased frequency of VOD/SOS was also associated with 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.

A black box warning has been added to the Australian PI regarding the risks of hepatotoxicity, including fatal and life threatening hepatic venoocclusive disease and the increased risk of post-haematopoietic stem cell transplant (HSCT) non-relapse mortality.

Proposed action

Subject to the advice of the ACM, the Delegate had no reason to say, at this time, that the application for Inotuzumab ozogamicin should not be approved for registration.

Request for ACM advice

The committee is requested to provide advice on the following specific issues:

1. Can the committee comment on the acceptability of the proposed wording of indication in Australia. Of note, both efficacy studies included patients with Ph+ ALL who had failed at least 1 TKI (see discussion section of overview).
2. In the pivotal study, the median duration of treatment in the control arm was 0.9 weeks. Is this an expected treatment duration in the context of the treatments chosen and this clinical setting?
3. Is the committee satisfied that the proposed PI adequately captures the safety profile of inotuzumab ozogamicin?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Introduction

Inotuzumab ozogamicin was granted orphan drug designation by the Therapeutic Goods Administration (TGA) on 9 January 2017 for the treatment of B cell precursor acute lymphoblastic leukaemia (ALL). The present application submitted by the sponsor seeks registration of inotuzumab ozogamicin for the following indication:

> *Besponsa is indicated for the treatment of adults with relapsed or refractory CD22-positive B cell precursor acute lymphoblastic leukaemia (ALL).*

The sponsor agrees with the Delegate's preliminary assessment that the data presented support a favourable risk-benefit balance of inotuzumab ozogamicin for the treatment of adult patients with relapsed or refractory CD22-positive B cell precursor ALL. There were no objections to the approval of Besponsa raised by the quality evaluators, the nonclinical evaluators, or the RMP evaluators throughout the evaluation phase, and the clinical evaluator recommended that Besponsa be approved for the above indication.

The Delegate has sought advice from the advisory committee on medicines (ACM) on three specific issues in the Delegate's Overview; Request for ACM's Advice which are shown below. In this pre-ACM response, the sponsor has provided comments addressing each of these issues. In addition, the questions raised within the body of the Delegate's overview directed to the sponsor have been addressed.

The matters being addressed are indicated in bold italic type.

Advice sought

The committee is requested to provide advice on the following specific issues.

1. Can the committee comment on the acceptability of the proposed wording of indication in Australia. Of note, both efficacy studies included patients with Ph+ ALL who had failed at least 1 TKI (see discussion section of overview).

The sponsor agrees with the Delegate's opinion that the indication wording should be identical to that recommended by the clinical evaluator and accepted by the sponsor in response to the first round clinical evaluation report, as follows:

> *Besponsa is indicated for the treatment of adults with relapsed or refractory CD22-positive B cell precursor acute lymphoblastic leukaemia (ALL).*

With the exception of 'CD22 positive' which was not required by the United States (US) Food and Drug Administration (FDA), this indication wording is identical with that included in the United States Prescribing Information (USPI).

In Study B1931022, the protocol inclusion criteria stipulated that 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).

The sponsor acknowledges that this is indicative of the patient population likely to be treated in Australia as first-line standard of care for adult patients with Ph+ B cell precursor ALL includes the use of TKIs (normally in combination with chemotherapy). Therefore, in the indication statement in the PI, the sponsor does not consider it necessary to specify that Ph+ patients should have failed treatment with at least one TKI.

The sponsor agrees with the Delegate that in the relapsed or refractory setting, all patients with Ph+ Bcell precursor ALL should be treated on a case by case basis with treatment options being considered in the context of the individual patient scenario; in any given patient, the absence of previously failed treatment with at least 1 TKI should not preclude use of Besponsa as an available treatment option.

2. In the pivotal study, the median duration of treatment in the control arm was 0.9 weeks. Is this an expected treatment duration in the context of the treatments chosen and this clinical setting?

The Delegate also raised the following related question to the sponsor:

> *Please provide a comment regarding the shorter duration of treatment in the control arm of this study. Is this an expected treatment duration for the clinical setting and treatment types chosen?*

The treatment duration for the control arm chemotherapy used in the pivotal study, Study B1931022, was as expected for patients with relapsed or refractory B cell ALL in the clinical setting. The shorter duration of treatment in the control arm compared to the inotuzumab ozogamicin arm reflects the fact that more patients were discontinuing early due to the lack of a clinical benefit in the control arm.

The main goal of therapy for patients with relapsed or refractory B cell ALL is to achieve complete remission/complete remission with incomplete haematologic recovery (CR/CRi) and proceed to a potentially curative haematopoietic stem cell transplant (HSCT) as quickly as possible.

The most commonly used regimen in Study B1931022 was fludarabine + cytarabine + granulocyte-colony stimulating factor (FLAG); this regimen is administered every day for approximately 5 to 6 days per cycle. Patients who have progressive disease after 1 cycle would be expected to stop treatment and receive an alternative therapy. Patients who achieve remission after 1 to 2 cycles would be expected to proceed to potentially curative HSCT.

Although in Study B1931022, the protocol stipulated duration of study treatment in the control arm was up to 4 cycles of FLAG or mitoxantrone + cytarabine (MXN/Ara-C) or up to 2 cycles of high dose cytarabine (HIDAC), patients responding to chemotherapy were expected to achieve remission within 1 to 2 cycles of treatment and patients not responding to chemotherapy were expected to proceed to alternative therapy.

In Study B1931022, the median duration of treatment was 8.9 weeks (median number of cycles started = 3; range 0.1 to 26.4 weeks) for patients who received inotuzumab ozogamicin and 0.9 weeks (median number of cycles started = 1, range 0.1 to 15.6 weeks) for patients who received control arm therapy (Module 5, Section 5.3.5.1, Study B1931022 sCSR (08 March 2016 cut-off), Table 22).

Table 22: Inotuzumab ozogamicin Study B1931022; summary of subject evaluation groups; ITT Population

	Inotuzumab Ozogamicin	Investigator Choice	Total
Number (%) of Subjects	164	162	326
Randomized	164	162	326
Treated	164(100.0)	143(88.3)	307(94.2)
Completed treatment [b]	10(6.1)	1(0.6)	11(3.4)
Completed study [a]	0	0	0
Discontinued study [c]	125(76.2)	128(79.0)	253(77.6)
Ongoing at date of cut-off [d]	39(23.8)	15(9.3)	54(16.6)
Analyzed for Safety [e]	164	143	307
Adverse events [f]	163(99.4)	143(88.3)	306(93.9)
Laboratory data	164(100.0)	143(88.3)	307(94.2)

Note: Investigator Choice is one of the defined chemotherapy regimens (either FLAG (Fludarabine, Cytarabine, and G-CSF), Cytarabine and Mitoxantrone, or HIDAC).
[a] Completed study: completed study is followed for 5 years for survival or 2 years from randomization of the last patient and did not pass away.
[b] Completed treatment: patients that received the maximum number of doses allowed per protocol.
[c] Discontinued Study: Includes all discontinuation reasons, including death,lost to follow up,withdrawal by subject,other, except completed study.
[d] Ongoing at date of cut-off: patients who have not discontinued study or completed study.
[e] Analysis for Safety includes all randomized subjects who received at least 1 dose of a test article (either Inotuzumab or Investigator Choice).
[f] Adverse Events: Includes patients with any adverse event.

This shorter duration of treatment in the control arm reflects the fact that more patients were discontinuing early due to the lack of a clinical benefit compared to the inotuzumab ozogamicin arm, including achieving CR/CRi. The CR/CRi rate (per Investigator's assessment, as of the 8 March 2016 data cut-off date) was 73.2% (95% CI: 65.7 to 79.8%) in the inotuzumab ozogamicin arm and 30.9% (95% CI: 23.9 to 38.6%) in the control arm (rate difference = 42.3% (97.5% CI: 31.1 to 53.5%), Chi-square test 1-sided p-value < 0.0001; Module 5, Section 5.3.5.1, Study B1931022 sCSR (8 March 2016 cut-off), Table 23).

Table 23: Inotuzumab ozogamicin Study B1931022; summary of best overall response by stratification factors per Interactive Voice Response System (IVRS), Investigator Assessment; ITT Population

	Inotuzumab Ozogamicin (N=164)	Investigator Choice (N=162)	Rate Difference	p-value[a]
All Subjects				
Complete Remission [CR]	55 (33.5)	26 (16.0)		
Complete Remission with incomplete count recovery [CRi]	65 (39.6)	24 (14.8)		
Partial response [PR]	3 (1.8)	3 (1.9)		
Resistant disease [RD]	30 (18.3)	77 (47.5)		
Progressive disease [PD]	5 (3.0)	5 (3.1)		
Death during aplasia	0	0		
Not Evaluable (NE)	6 (3.7)	27 (16.7)		
CR/CRi Rate	120 (73.2)	50 (30.9)	42.3	<.0001
95% CI for rate and 97.5% CI for Rate Difference	(65.7, 79.8)	(23.9, 38.6)	(31.1,53.5)	
CR Rate	55 (33.5)	26 (16.0)	17.5	0.0001
95% CI for rate and 97.5% CI for Rate Difference	(26.4, 41.3)	(10.8, 22.6)	(7.0,28.0)	
CRi Rate	65 (39.6)	24 (14.8)	24.8	<.0001
95% CI for rate and 97.5% CI for Rate Difference	(32.1, 47.6)	(9.7, 21.2)	(14.2,35.4)	
Duration of First Remission: < 12 Months	109	107		
Complete Remission [CR]	36 (33.0)	14 (13.1)		
Complete Remission with incomplete count recovery [CRi]	40 (36.7)	18 (16.8)		
Partial response [PR]	2 (1.8)	1 (0.9)		
Resistant disease [RD]	23 (21.1)	49 (45.8)		
Progressive disease [PD]	4 (3.7)	4 (3.7)		
Death during aplasia	0	0		
Not Evaluable (NE)	4 (3.7)	21 (19.6)		
CR/CRi Rate	76 (69.7)	32 (29.9)	39.8	<.0001
95% CI for rate and 97.5% CI for Rate Difference	(60.2, 78.2)	(21.4, 39.5)	(25.8,53.8)	
CR Rate	36 (33.0)	14 (13.1)	19.9	0.0003
95% CI for rate and 97.5% CI for Rate Difference	(24.3, 42.7)	(7.3, 21.0)	(7.5,32.4)	
CRi Rate	40 (36.7)	18 (16.8)	19.9	0.0005
95% CI for rate and 97.5% CI for Rate Difference	(27.7, 46.5)	(10.3, 25.3)	(6.7,33.0)	
Duration of First Remission: >= 12 Months	55	55		
Complete Remission [CR]	19 (34.5)	12 (21.8)		
Complete Remission with incomplete count recovery [CRi]	25 (45.5)	6 (10.9)		
Partial response [PR]	1 (1.8)	2 (3.6)		
Resistant disease [RD]	7 (12.7)	28 (50.9)		
Progressive disease [PD]	1 (1.8)	1 (1.8)		
Death during aplasia	0	0		
Not Evaluable (NE)	2 (3.6)	6 (10.9)		
CR/CRi Rate	44 (80.0)	18 (32.7)	47.3	<.0001
95% CI for rate and 97.5% CI for Rate Difference	(67.0, 89.6)	(20.7, 46.7)	(28.6,65.9)	
CR Rate	19 (34.5)	12 (21.8)	12.7	0.0690
95% CI for rate and 97.5% CI for Rate Difference	(22.2, 48.6)	(11.8, 35.0)	(-6.3,31.8)	
CRi Rate	25 (45.5)	6 (10.9)	34.5	<.0001
95% CI for rate and 97.5% CI for Rate Difference	(32.0, 59.4)	(4.1, 22.2)	(16.9,52.3)	
Salvage Treatment: Salvage 1	108	107		
Complete Remission [CR]	43 (39.8)	19 (17.8)		
Complete Remission with incomplete count recovery [CRi]	40 (37.0)	13 (12.1)		
Partial response [PR]	3 (2.8)	3 (2.8)		
Resistant disease [RD]	18 (16.7)	54 (50.5)		
Progressive disease [PD]	2 (1.9)	4 (3.7)		
Death during aplasia	0	0		
Not Evaluable (NE)	2 (1.9)	14 (13.1)		
CR/CRi Rate	83 (76.9)	32 (29.9)	46.9	<.0001
95% CI for rate and 97.5% CI for Rate Difference	(67.8, 84.4)	(21.4, 39.5)	(33.5,60.4)	
CR Rate	43 (39.8)	19 (17.8)	22.1	0.0002
95% CI for rate and 97.5% CI for Rate Difference	(30.5, 49.7)	(11.0, 26.3)	(8.6,35.5)	
CRi Rate	40 (37.0)	13 (12.1)	24.9	<.0001
95% CI for rate and 97.5% CI for Rate Difference	(27.9, 46.9)	(6.6, 19.9)	(12.3,37.5)	

Table 23 (continued): Inotuzumab ozogamicin Study B1931022; summary of best overall response by stratification factors per IVRS, Investigator Assessment; ITT Population

	Inotuzumab Ozogamicin (N=164)	Investigator Choice (N=162)	Rate Difference	p-value[a]
Salvage Treatment: Salvage 2	56	55		
Complete Remission [CR]	12 (21.4)	7 (12.7)		
Complete Remission with incomplete count recovery [CRi]	25 (44.6)	11 (20.0)		
Partial response [PR]	0	0		
Resistant disease [RD]	12 (21.4)	23 (41.8)		
Progressive disease [PD]	3 (5.4)	1 (1.8)		
Death during aplasia	0	0		
Not Evaluable (NE)	4 (7.1)	13 (23.6)		
CR/CRi Rate	37 (66.1)	18 (32.7)	33.3	0.0002
95% CI for rate and 97.5% CI for Rate Difference	(52.2, 78.2)	(20.7, 46.7)	(13.3,53.4)	
CR Rate	12 (21.4)	7 (12.7)	8.7	0.1118
95% CI for rate and 97.5% CI for Rate Difference	(11.6, 34.4)	(5.3, 24.5)	(-7.2,24.6)	
CRi Rate	25 (44.6)	11 (20.0)	24.6	0.0028
95% CI for rate and 97.5% CI for Rate Difference	(31.3, 58.5)	(10.4, 33.0)	(5.5,43.8)	
Patient Age at Randomization: < 55 Years	104	103		
Complete Remission [CR]	39 (37.5)	15 (14.6)		
Complete Remission with incomplete count recovery [CRi]	39 (37.5)	14 (13.6)		
Partial response [PR]	3 (2.9)	3 (2.9)		
Resistant disease [RD]	16 (15.4)	50 (48.5)		
Progressive disease [PD]	2 (1.9)	3 (2.9)		
Death during aplasia	0	0		
Not Evaluable (NE)	5 (4.8)	18 (17.5)		
CR/CRi Rate	78 (75.0)	29 (28.2)	46.8	<.0001
95% CI for rate and 97.5% CI for Rate Difference	(65.6, 83.0)	(19.7, 37.9)	(33.1,60.6)	
CR Rate	39 (37.5)	15 (14.6)	22.9	<.0001
95% CI for rate and 97.5% CI for Rate Difference	(28.2, 47.5)	(8.4, 22.9)	(9.7,36.1)	
CRi Rate	39 (37.5)	14 (13.6)	23.9	<.0001
95% CI for rate and 97.5% CI for Rate Difference	(28.2, 47.5)	(7.6, 21.8)	(10.9,37.0)	
Patient Age at Randomization: >= 55 Years	60	59		
Complete Remission [CR]	16 (26.7)	11 (18.6)		
Complete Remission with incomplete count recovery [CRi]	26 (43.3)	10 (16.9)		
Partial response [PR]	0	0		
Resistant disease [RD]	14 (23.3)	27 (45.8)		
Progressive disease [PD]	3 (5.0)	2 (3.4)		
Death during aplasia	0	0		
Not Evaluable (NE)	1 (1.7)	9 (15.3)		
CR/CRi Rate	42 (70.0)	21 (35.6)	34.4	<.0001
95% CI for rate and 97.5% CI for Rate Difference	(56.0, 81.2)	(23.6, 49.1)	(19.1,53.7)	
CR Rate	16 (26.7)	11 (18.6)	8.0	0.1481
95% CI for rate and 97.5% CI for Rate Difference	(16.1, 39.7)	(9.7, 30.9)	(-9.1,25.1)	
CRi Rate	26 (43.3)	10 (16.9)	26.4	0.0009
95% CI for rate and 97.5% CI for Rate Difference	(30.6, 56.8)	(8.4, 29.0)	(8.3,44.4)	

Note: Investigator Choice is one of the defined chemotherapy regimens (either FLAG (Fludarabine, Cytarabine, and G-CSF), Cytarabine and Mitoxantrone, or HIDAC).
CR is defined as a disappearance of leukemia as indicated by <5% marrow blasts and the absence of peripheral blood leukemic blasts, with recovery of hematopoiesis defined by absolute neutrophil count (ANC) >= 1000/µl and platelets >= 100,000/µl.
Absence of extramedullary disease (CI) status is required.
CRi is defined as CR except with absolute neutrophil count (ANC) <1000/µl and/or platelets <100,000/µl.
[a] One-sided p-value based on Chi-Square test or Fisher's exact test (if any cell count is < 5).
Duration of First Remission, Salvage Treatment, and Age at Randomization are based on IVRS data.
Not Evaluable category contains Indeterminate Hematologic disease status and those with no post baseline measures.
Patient 11861002 received maintenance ponatinib 9 days before the first and only disease assessment of CR after the last dose of cytarabine/mitoxantrone and is included as a CR.

In the control arm, 82/143 (57.3%) patients discontinued treatment due to disease progression/relapse or resistant disease (Module 5, Section 5.3.5.1, Study B1931022 sCSR (8 March 2016 cut-off), Table 24). In contrast, the most common reason for treatment discontinuation in the inotuzumab ozogamicin arm was 'complete response' (39.0% versus 14.7% in the inotuzumab ozogamicin and control arms, respectively) (Module 5, Section 5.3.5.1, Study B1931022 sCSR (8 March 2016 cut-off); Table 24).

Table 24: Inotuzumab ozogamicin Study B1931022; summary of discontinuations from Treatment Phase; Safety Population

		Investigator Choice				
	Inotuzumab Ozogamicin (N=164) n(%)	FLAG (N=93) n(%)	Cytarabine and mitoxantrone (N=33) n(%)	High dose cytarabine (N=17) n(%)	Total (N=143) n(%)	Total (N=307) n(%)
Discontinued from Treatment (subjects)	164 (100.0)	93 (100.0)	33 (100.0)	17 (100.0)	143 (100.0)	307 (100.0)
Reasons for Discontinuation						
Completed	10 (6.1)	0	0	1 (5.9)	1 (0.7)	11 (3.6)
Objective progression or relapse	24 (14.6)	12 (12.9)	7 (21.2)	1 (5.9)	20 (14.0)	44 (14.3)
Global deterioration of health status	2 (1.2)	1 (1.1)	1 (3.0)	2 (11.8)	4 (2.8)	6 (2.0)
Adverse event(s)	27 (16.5)	3 (3.2)	5 (15.2)	2 (11.8)	10 (7.0)	37 (12.1)
Subject died	7 (4.3)	4 (4.3)	1 (3.0)	1 (5.9)	6 (4.2)	13 (4.2)
Complete response	64 (39.0)	12 (12.9)	9 (27.3)	0	21 (14.7)	85 (27.7)
Resistant disease	18 (11.0)	46 (49.5)	7 (21.2)	9 (52.9)	62 (43.4)	80 (26.1)
Protocol violation	2 (1.2)	0	0	0	0	2 (0.7)
Lost to follow-up	0	0	0	0	0	0
Subject refused continued treatment for reason other than AE	1 (0.6)	6 (6.5)	2 (6.1)	1 (5.9)	9 (6.3)	10 (3.3)
Study terminated by sponsor	0	0	0	0	0	0
Other	9 (5.5)	9 (9.7)	1 (3.0)	0	10 (7.0)	19 (6.2)

Note: Investigator Choice is one of the defined chemotherapy regimens (either FLAG (Fludarabine, Cytarabine, and G-CSF), Cytarabine and Mitoxantrone, or HIDAC).
Completed is considered as discontinuation per CRF.

Patients in the control arm received more active post-study systemic therapies (84 (51.9%)), including novel therapies (for example, blinatumomab, inotuzumab ozogamicin, and TKIs than patients in the inotuzumab ozogamicin arm (49 (29.9%)) due to the significantly lower CR/CRi rate in the control arm (Module 5, Section 5.3.5.1, Study B1931022 sCSR, Table 25). Including all follow-up systemic ALL therapies (induction, conditioning, maintenance, intensification or consolidation), blinatumomab was administered to 9 (5.5%) patients in the inotuzumab ozogamicin arm and 20 (12.3%) patients in the control arm. TKIs were administered to 4 (2.4%) patients in the inotuzumab ozogamicin arm and 16 (9.9%) patients in the control arm.

Table 25: Inotuzumab ozogamicin Study B1931022; Follow-up systemic therapy (induction therapy); ITT Population

	Inotuzumab Ozogamicin (N=164)	Investigator Choice (N=162)
Follow-up Systemic Therapy (Induction therapy)		
No	115 (70.1)	78 (48.1)
Yes	49 (29.9)	84 (51.9)
# of Regimens		
1	36 (22.0)	63 (38.9)
2	11 (6.7)	11 (6.8)
>=3	2 (1.2)	10 (6.2)
Follow-up Systemic Therapy (Induction therapy) Agents		
Blinatumomab	7 (4.3)	17 (10.5)
BLINATUMOMAB	7 (4.3)	17 (10.5)
CAR-T	1 (0.6)	1 (0.6)
IMMUNOSTIMULANTS	1 (0.6)	1 (0.6)
Chemotherapy	46 (28.0)	64 (39.5)
ASPARAGINASE	2 (1.2)	4 (2.5)
BORTEZOMIB	1 (0.6)	4 (2.5)
CISPLATIN	1 (0.6)	0
CLOFARABINE	4 (2.4)	8 (4.9)
CYCLOPHOSPHAMIDE	16 (9.8)	25 (15.4)
CYTARABINE	24 (14.6)	30 (18.5)
DAUNORUBICIN	2 (1.2)	8 (4.9)
DOXORUBICIN	8 (4.9)	11 (6.8)
EPIRUBICIN	1 (0.6)	1 (0.6)
ETOPOSIDE	4 (2.4)	14 (8.6)
FLUDARABINE	12 (7.3)	6 (3.7)
GEMCITABINE	0	1 (0.6)
HYDROXYCARBAMIDE	1 (0.6)	0
IDARUBICIN	9 (5.5)	4 (2.5)
IFOSFAMIDE	2 (1.2)	3 (1.9)
IFOSFAMIDE W/MESNA	0	1 (0.6)
MERCAPTOPURINE	0	5 (3.1)
METHOTREXATE	10 (6.1)	31 (19.1)
MITOXANTRONE	4 (2.4)	7 (4.3)
PEGASPARGASE	5 (3.0)	8 (4.9)
PIRARUBICIN	1 (0.6)	0
TEMOZOLOMIDE	1 (0.6)	0
TENIPOSIDE	0	1 (0.6)
TOPOTECAN	0	1 (0.6)
VINBLASTINE	0	1 (0.6)
VINCRISTINE	24 (14.6)	31 (19.1)
VINDESINE	1 (0.6)	3 (1.9)
VINORELBINE	0	1 (0.6)
Growth Factors	5 (3.0)	0
FILGRASTIM	3 (1.8)	0
GRANULOCYTE COLONY STIMULATING FACTOR	2 (1.2)	0
Inotuzumab Ozogamicin	0	6 (3.7)
INOTUZUMAB	0	6 (3.7)
Steroids	19 (11.6)	26 (16.0)
DEXAMETHASONE	14 (8.5)	17 (10.5)
HYDROCORTISONE	0	1 (0.6)
METHYLPREDNISOLONE	1 (0.6)	0
PREDNISOLONE	3 (1.8)	2 (1.2)
PREDNISONE	3 (1.8)	7 (4.3)
TKIs	3 (1.8)	10 (6.2)
BOSUTINIB	0	2 (1.2)
DASATINIB	2 (1.2)	4 (2.5)
NILOTINIB	1 (0.6)	0
PONATINIB	0	6 (3.7)
Others	4 (2.4)	15 (9.3)
ANTINEOPLASTIC AGENTS	0	2 (1.2)
FOLINIC ACID	1 (0.6)	2 (1.2)
INVESTIGATIONAL DRUG	0	4 (2.5)
MESNA	1 (0.6)	1 (0.6)
RITUXIMAB	3 (1.8)	7 (4.3)

Note: Investigator Choice is one of the defined chemotherapy regimens (either FLAG (Fludarabine, Cytarabine, and G-CSF), Cytarabine and Mitoxantrone, or HIDAC).
Maximum Regimen number is displayed.

3. Is the committee satisfied that the proposed PI adequately captures the safety profile of inotuzumab ozogamicin?

The sponsor considers that the PI adequately captures the safety profile of inotuzumab ozogamicin.

The most important safety issue associated with inotuzumab ozogamicin is venoocclusive liver disease/sinusoidal obstruction syndrome (VOD/SOS).

In accordance with the clinical evaluator's request, in addition to the proposed information in the precautions section highlighting patients considered to be at highest risk of VOD/SOS, a boxed warning was added to the PI. The boxed warning highlights the risk of hepatotoxicity including fatal and life threatening VOD and the higher rate of

post-HSCT non-relapse mortality (primarily due to higher rates of mortality due to VOD/SOS and infections) observed in the inotuzumab ozogamicin arm of the pivotal study.

In addition to the boxed warning, the sponsor agreed to include the following contraindications:

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

These contraindications align the PI with the approved European Union (EU) Summary of Product Characteristics (SmPC).

Overall, the sponsor considers that the boxed warning, contraindications, and precautions sections of the PI highlight the most important safety issues associated with inotuzumab ozogamicin.

Comments addressing the changes to the PI requested by the Delegate were provided in the sponsor's response.

Foreign regulatory status

The Delegate also requested the sponsor provide an update of the overseas regulatory status for Besponsa, including any further approvals, withdrawals, rejections or delays, which were provided in the sponsor's response.

Conclusion

Relapsed or refractory B cell precursor ALL is a serious life threatening condition for which limited effective therapeutic options are available with the only potentially curative treatment option being HSCT. As such, treatment of adult patients with this condition remains a major clinical challenge for Australian physicians.

The sponsor agrees with the Delegate's position that the data presented support a favourable benefit/risk profile of inotuzumab ozogamicin for the treatment of adult patients with relapsed or refractory CD22-positive B cell precursor ALL, and considers Besponsa to be a valuable addition to the armamentarium available to physicians and patients.

Advisory Committee Considerations[51]

The Advisory Committee on Medicines (ACM), taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Besponsa inotuzumab ozogamicin (rch) powder for injection to have an overall positive benefit-risk profile for the indication;

> *Besponsa is indicated for the treatment of adults with relapsed or refractory CD22-positive B cell precursor acute lymphoblastic leukaemia (ALL).*

[51] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

The dose and dosage form submitted for registration of Besponsa inotuzumab ozogamicin is a powder for injection in a vial containing 1 mg which, after reconstitution with 4 mL of sterile water for injection, contains 0.25 mg inotuzumab ozogamicin in 1 mL of solution.

Subject to the advice of the ACM, the Delegate had no reason to say, at this time, that the application for Inotuzumab ozogamicin should not be approved for registration.

Proposed conditions of registration

The ACM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/ Consumer Medicine Information (CMI) amendments

The ACM agreed with the Delegate to the proposed amendments to the PI and CMI.

Specific advice

The ACM advised the following in response to the Delegate's specific questions on the submission:

1. ***Can the committee comment on the acceptability of the proposed wording of indication in Australia. Of note, both efficacy studies included patients with Ph+ ALL who had failed at least 1 TKI (see discussion section of overview).***

The committee agreed with the Delegate that the proposed wording for the indication in Australia is acceptable:

> *'Besponsa is indicated for the treatment of adults with relapsed or refractory CD22-positive B cell precursor acute lymphoblastic leukaemia (ALL)'.*

2. ***In the pivotal study, the median duration of treatment in the control arm was 0.9 weeks. Is this an expected treatment duration in the context of the treatments chosen and this clinical setting?***

The ACM answered that, due to the nature of the disease being a rapidly progressive malignancy for patients, 0.9 weeks is an expected median treatment duration in the context of the treatments chosen and the clinical setting. Noting; that the main reason for discontinuation was treatment failure on the control arm.

3. ***Is the committee satisfied that the proposed PI adequately captures the safety profile of Inotuzumab ozogamicin?***

Yes, the committee is satisfied that the proposed PI adequately captures the safety profile of Inotuzumab ozogamicin and in particular agreed with The Black Box warning proposed in the PI version: Besponsa draft PI 28 March 2017 (Cat 1).

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Besponsa inotuzumab ozogamicin (rch) 1 mg powder for injection vial indicated for:

> *'Besponsa is indicated for the treatment of adults with relapsed or refractory CD22 positive B cell precursor acute lymphoblastic leukaemia (ALL).'*

Specific conditions of registration applying to these goods

- Should reprocessing (that is VRF and final filtration) be required in the future, the sponsor must submit a Category 3 application on at least one batch of the drug product manufactured at full scale prior to implementation.
- Batch release testing and compliance with Certified Product Details (CPD)
  - It is a condition of registration that all batches of Besponsa inotuzumab ozogamicin imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
  - It is a condition of registration that each batch of Besponsa inotuzumab ozogamicin imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results
- Besponsa (inotuzomab ozogamicin) is to be included in the Black Triangle Scheme. The PI and CMI for Besponsa must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Besponsa EU-Risk Management Plan (RMP) (version 1.5, dated 26 April 2017, data lock point 26 April 2016), with Australian Specific Annex (version 1.1, dated 14 December 2017), included with submission PM-2017-01455-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Beponsa approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi> .

Therapeutic Goods Administration

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