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EMA/289046/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

BESPONSA

International non-proprietary name: inotuzumab ozogamicin

Procedure No. EMEA/H/C/004119/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Definition
ADC	antibody-drug conjugate
ADME	absorption, distribution, metabolism and excretion
ADR	adverse drug reaction
AE	adverse event or treatment-emergent adverse event
AEoSI	adverse event(s) of special interest
AEX	Anion exchange chromatography
AHO	Animal or Human Origin
ALL	acute lymphoblastic leukaemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
BCR-ABL	fusion gene that juxtaposes the Abl1 gene on chromosome 9 (region q34) to a part of the BCR gene on chromosome 22 (region q11)
BCRP	breast cancer resistance protein
BSA	body surface area
BSE	Bovine spongiform encephalopathies
C1D1	Cycle 1 Day 1
CI	confidence interval
C_{max}	maximal observed plasma concentration
CDR	Complementary Determining Region
CFU	Colony forming unit
CGE	Capillary Gel Electrophoresis
CHO	Chinese hamster ovary
CMA	Critical material attribute
control	Investigator's choice treatment arm in Study 1022: fludarabine plus cytarabine plus granulocyte-colony stimulating factor (FLAG), mitoxantrone plus cytarabine (MXN/Ara-C), or high-dose cytarabine (HIDAC)
COSY	Correlation spectroscopy
CPP	Critical process parameter
CQA	Critical quality attribute
CR	complete remission
CR/CRi	complete remission with or without haematologic recovery
CRF	case report form
CRh	complete remission with partial haematologic recovery
CRi	complete remission with incomplete haematologic recovery
CRp	complete remission without platelet recovery (or with incomplete platelet recovery)
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CU	compassionate use
CYP	cytochrome P450
DILI	drug-induced liver injury
DF	Diafiltration
DLT	dose-limiting toxicity
DMH	Dimethylhydrazide
DNA	Desoxy Nucleic Acid
DoR	duration of remission
EAC	Endpoint Adjudication Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
E-DMC	external Data Monitoring Committee
ELISA	Enzyme Linked Immuno-sorbent assay
EMA	European Medicines Agency
EOP	End of Production
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EOT	end(-)of(-) treatment

Abbreviation	Definition
EQ-5D	EuroQol-5 Dimension Questionnaire
EQ-VAS	EuroQol Visual Analogue Scale
EU	European Union
FDA	(United States) Food and Drug Administration
FISH	fluorescence in situ hybridization
FLAG	fludarabine plus cytarabine plus granulocyte-colony stimulating factor
G-CSF	granulocyte-colony stimulating factor
GGT	gamma-glutamyl transpeptidase
GLP	Good laboratory practice
GMP	Good Manufacturing Practice
G0F	Asialo, core-fucosylated, complex-type biantennary oligosaccharides with zero galactose residue
G01	Asialo, core-fucosylated, complex-type biantennary oligosaccharides with terminal galactose residue
HC	Heavy chain
HEAB	Hepatic Event Adjudication Board
hERG	the human *Ether-à-go-go*-Related Gene
HIC	Hydrophobic Interaction Chromatography
HIDAC	high-dose cytarabine
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HMMS	High Molecular Mass Species
HPLC	High-Performance Liquid Chromatography
HR	hazard ratio
HSCT	hematopoietic stem cell transplant
iCE	Imaged Capillary Isoelectric Focusing
IgG4	immunoglobulin type G, subtype 4
IIR	investigator-initiated research
IR	Infrared Radiation
ITT	intent-to-treat
IV	intravenous(ly)
LC	Light Chain
mAb	Monoclonal antibody
MCB	Master Cell Bank
MDACC	MD Anderson Cancer Center
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MRD	minimal residual disease
MS	Mass spectrometry
MS/MS	Tandem mass spectrometry
MTD	maximum tolerated dose
MXN/Ara-C	mitoxantrone plus cytarabine
N-Ac	N-acetyl
NCI	National Cancer Institute
NF	National Formulary
NHL	non-Hodgkin's lymphoma
NTU	Nephelometric turbidity unit
NMR	Nuclear magnetic resonance spectroscopy
nrCGE	non-reducing Capillary Gel Electrophoresis
OAT	organic anion transporter
OATp	organic anion transporting polypeptide
OECD	Organisation for Economic Co-operation and Development
ORR	overall remission rate
OS	overall survival
PFS	progression-free survival
P-gp	P-glycoprotein
$Ph^{+/-}$	Philadelphia chromosome positive/negative
Ph.Eur.	European Pharmacopoeia
PK	pharmacokinetic(s)
Pooled ALL Population	187 patients who received a total starting dose of 1.8 mg/m^2/cycle inotuzumab ozogamicin with a protocol-specified dose reduction upon achievement of CR/CRi (139 patients in Study 1022 and 48 patients in Study 1010)
POPPK	population pharmacokinetic(s)

Abbreviation	Definition
PP	Process parameters
PRO	patient-reported outcomes
PT	(MedDRA) preferred term
PXRD	Powder X-ray diffraction
QbD	Quality by Design
QoL	quality(-)of(-)life
rCGE	Reducing Capillary Gel Electrophoresis
R-CVP	rituximab, cyclophosphamide, vincristine, and prednisone
R-GDP	rituximab, gemcitabine (and/or cisplatin), and dexamethasone
RP-HPLC	Reverse Phase High-Performance Liquid Chromatography
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SEC	Size Exclusion Chromatography
SE-HPLC	Size Exclusion High-Performance Liquid Chromatography
SOC	(MedDRA) system organ class
SOS	sinusoidal obstruction syndrome
SPR	surface plasmon resonance
TEAE	treatment-emergent adverse event
TGA	Therapeutic Goods Administration
TKI	tyrosine kinase inhibitor
TRAE	treatment-related adverse event
TSE	Transmissible spongiform encephalopathies
UF	Ultrafiltration
UGT	uridine diphosphate glucuronosyltransferase
ULN	upper limit of normal
US(A)	United States (of America)
USP	United States Pharmacopoeia
UV	Ultraviolet
VOD	Venoocclusive liver disease (single PT) or veno(-)occlusive disease
vs	Versus
VRF	Viral reduction filtration
WBC	white blood cell
WCB	Working Cell Bank
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pfizer Limited submitted on 14 April 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for BESPONSA, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 November 2014.

BESPONSA was designated as an orphan medicinal product EU/3/13/1127 on 7 June 2013 in the following condition: 'Treatment of B-cell acute lymphoblastic leukaemia'.

The applicant applied for the following indication:

'BESPONSA is indicated for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL)'.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Besponsa as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website:

ema.europa.eu/Find medicine/Human medicines/Rare disease designation.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that inotuzumab ozogamicin was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0304/2014 on the agreement of a paediatric investigation plan (PIP) and a product-specific waiver. At the time of the submission of the application, the PIP P/0304/2014 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan

medicinal products.

New active Substance status

The applicant requested the active substance inotuzumab ozogamicin contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP, which pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Robert James Hemmings Co-Rapporteur: Filip Josephson

- The application was received by the EMA on 14 April 2016.
- The procedure started on 19 May 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 5 August 2016 The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 8 August 2016 The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 18 August 2016
- During the meeting on 2 September 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 2 September 2016
- During the meeting on 15 September 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 15 September 2016
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 December 2016.
- The following GMP and GCP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:
  - A GCP inspection at three investigator sites (Japan and USA) and at the sponsor site (USA) were performed in August and October 2016.
  - A GMP inspection at the site for drug product manufacture, testing and storage (USA) was undertaken between 7–10 November 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 31 January 2017
- During the PRAC meeting on 9 February 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 9 February 2017

- During the CHMP meeting on 23 February 2017, the CHMP agreed on a list of outstanding issues to be addressed by the applicant
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 21 March 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 6 April 2017
- During the meeting on 21 April 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to BESPONSA.
- The CHMP adopted a report on similarity of BESPONSA with Blincyto, Evoltra, Sprycel, Xaluprine, Atrriance and Iclusig on 21 April 2017

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Treatment of relapsed or refractory CD22-positive B cell precursor acute lymphoblastic leukaemia (ALL)

2.1.2. Epidemiology and risk factors, screening tools/prevention

ALL represents approximately 20% of leukaemias among adults and 80% of acute leukaemias in children (Jabbour et al., 2005). In Europe, the crude incidence rate of ALL is 1.3 per 100,000 individuals (Sant et al., 2010). The B-cell subtype accounts for approximately 75% of ALL cases in adults and approximately 88% of cases in children (NCCN Guidelines, 2015).

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 (Howlader et al., 2015).

Overall, approximately 20%-30% of adult patients with ALL are Ph+, with the incidence exceeding 50% in patients aged 50 years or older (Jabbour et al., 2015, Thomas DA, 2007).

2.1.3. Biologic features

Acute lymphoblastic leukaemia (ALL) is a heterogeneous haematologic disease characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood and other organs resulting in loss of normal haematopoiesis and organ failure leading to death if left untreated (Jabbour et al., 2005).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

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, weight loss), dyspnoea, dizziness, infections, and easy bruising or bleeding (Faderl et al., 2010, Jabbour et al., 2005). 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. Patients diagnosed with B-cell ALL in routine clinical practice undergo screening for CD22 at their local laboratory.

Cure rates and survival outcomes for B-cell ALL have improved over the last decades, mainly in children and young adults who are treated according to paediatric protocols. Advances in the understanding of the molecular genetics have led to the adoption of risk adapted therapy and novel targeted agents have been developed. About 20-30% of B-cell precursor ALL is Ph+ and the development of BCR-ABL tyrosine kinase inhibitors has markedly improved prognosis. There is general agreement that for Ph+ ALL a myeloablative allogeneic stem cell transplant (HSCT) in first complete remission is the most appropriate therapy for both children and adults who are sufficiently fit and have a well-matched donor.

However prognosis remains poor in adult patients. Older adults have the poorest outcome with a 5-year OS rate of 24.1% for patients between the ages of 40 and 59 and an even lower rate of 17.7% for patients between the ages of 60 and 69 (Pulte et al. ,2014). Despite the high remission rates with first line therapy, only approximately 30 to 40% of adults achieve long-term disease-free survival, with the primary reason for failure being disease recurrence. Particular unfavourable prognostic factors include high leucocyte count (>30,000/µL), late haematological remission (>3 weeks after induction II), complex aberrant karyotype or molecular aberrations (Philadelphia chromosome positive [t9;22] or t4;11) and high minimal residual disease level after early consolidation (Moorman et al., 2007; Bruggemann et al. ,2006). Risk of relapse is highest in the first two years after achievement of complete remission. The median survival time in adults with relapsed or refractory B-cell ALL is approximately 3-6 months (O'Brien et al., 2008, Thomas et al., 1999).

2.1.5. Management

There is no standard treatment for relapsed/refractory Philadelphia chromosome negative (Ph-) ALL and a variety of chemotherapy induction regimens, including high dose cytarabine, hyper CVAD (hyper-cyclophosphamide, vincristine, doxorubicin and dexamethasone) and fludarabine/cytarabine/GCSF are administered.

Recently, Blincyto (blinatumomab), a bispecific anti-CD3/CD19 monoclonal antibody, has been approved for the treatment of adults with Ph- relapsed or refractory B-precursor ALL.

For Ph+ patients, imatinib (Glivec) was approved in 2001 for the treatment of adult and paediatric patients with newly diagnosed Ph+ ALL integrated with chemotherapy. Dasatinib (Sprycel) was approved in 2006 for the treatment of adult patients with resistance or intolerance to prior therapy. Ponatinib (Iclusig) was approved in 2013 for the treatment of adult patients with Ph+ ALL who are resistant to/ intolerant of dasatinib.

About the product

Inotuzumab ozogamicin is an antibody-drug conjugate (ADC) composed of a CD22 directed monoclonal antibody that is covalently linked to N acetyl gamma calicheamicin dimethylhydrazide. Inotuzumab is a

humanised immunoglobulin class G subtype 4 (IgG4) antibody that specifically recognises human CD22. The small molecule, N acetyl gamma calicheamicin, is a cytotoxic product. N acetyl gamma calicheamicin is covalently attached to the antibody via an acid-cleavable linker. Nonclinical data suggest that the anticancer activity of inotuzumab ozogamicin is due to the binding of the ADC to CD22 expressing tumour cells, followed by internalisation of the ADC-CD22 complex, and the intracellular release of N acetyl gamma calicheamicin dimethylhydrazide via hydrolytic cleavage of the linker. Activation of N acetyl gamma calicheamicin dimethylhydrazide induces double-stranded DNA breaks, subsequently inducing cell cycle arrest and apoptotic cell death (SmPC, section 5.1).

The applicant requested the approval for the following indication: Besponsa is indicated for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL).

The final indication following CHMP review of this application is: 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) (SmPC section 4.1).

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

For the first cycle, the recommended total dose of BESPONSA for all patients is 1.8 mg/m2 per cycle, given as 3 divided doses on Days 1 (0.8 mg/m^2), 8 (0.5 mg/m^2), and 15 (0.5 mg/m^2). Cycle 1 is 3 weeks in duration, but may be extended to 4 weeks if the patient achieves a CR or CRi, and/or to allow recovery from toxicity.

For subsequent cycles, the recommended total dose of BESPONSA is 1.5 mg/m2 per cycle given as 3 divided doses on Days 1 (0.5 mg/m2), 8 (0.5 mg/m2), and 15 (0.5 mg/m2) for patients who achieve a CR/CRi or 1.8 mg/m^2 per cycle given as 3 divided doses on Days 1 (0.8 mg/m^2), 8 (0.5 mg/m^2), and 15 (0.5 mg/m^2) for patients who do not achieve a CR/CRi. Subsequent cycles are 4 weeks in duration (SmPC, section 4.2).

Type of Application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment based on the following grounds:

It was not considered that sufficient data have been submitted to substantiate the request for accelerated assessment of inotuzumab ozogamicin. It was not certain that the data from studies intended to be submitted show a significant and meaningful clinical benefit over approved treatments in this setting. The incidence of hepatic VOD requires careful assessment and possibly follow-up in the post-authorisation setting. Overall survival data would be required before inotuzumab ozogamicin can be considered of major interest from the point of view of public health and therapeutic innovation.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as powder for concentrate for solution for infusion containing 1 mg of inotuzumab ozogamicin as active substance. After reconstitution, the solution contains 0.25 mg inotuzumab ozogamicin per mL. Other ingredients are: sucrose, polysorbate 80, sodium chloride and tromethamine. The product is available in Type I amber glass vial with chlorobutyl rubber stopper and crimp seal with flip off cap.

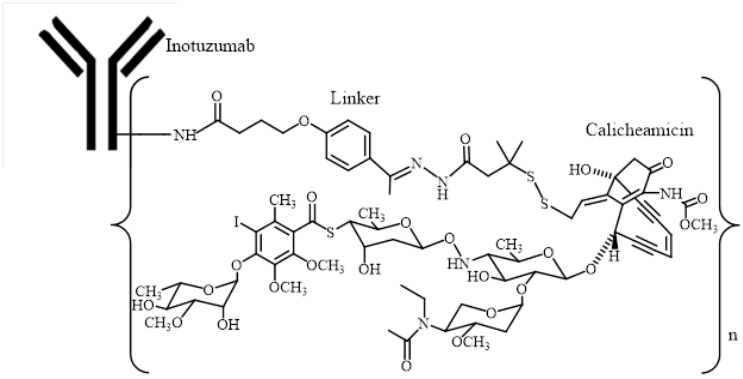
Although this dossier is not considered a Quality by Design application, certain elements of an enhanced approached were applied as described in the relevant sections below.

2.2.2. Active Substance

Inotuzumab ozogamicin consists of a recombinant, humanized, IgG4 antibody covalently bonded to a semi-synthetic derivative of gamma calicheamicin. Inotuzumab ozogamicin is a conjugate of the two intermediates: inotuzumab and the activated calicheamicin derivative.

The antibody chosen for development of inotuzumab was selected to target CD22 expressed on B cells involved in acute lymphoblastic leukemia (ALL).

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 disulfide bond with the calicheamicin. The linker also contains an internal hydrazone bond, which is acid-labile.



Manufacture, process controls and characterisation

Wyeth Pharmaceuticals Division of Wyeth Holdings Corporation, a subsidiary of Pfizer Inc., Pearl River, NY, USA, is responsible for the manufacture, testing, and storage of the active substance inotuzumab ozogamicin and of the finished product, Besponsa. The MAH is Pfizer Limited, Sandwich UK.

In the manufacture of Besponsa two separate intermediate materials are used, the **activated calicheamicin derivative** and the monoclonal antibody **inotuzumab** (G544 antibody).

The manufacture, characterisation, control and stability of the two intermediates (the **activated calicheamicin derivative** and **inotuzumab** (G544 antibody)) and the active substance **inotuzumab ozogamicin** are described below in three separate sections.

Intermediate activated calicheamicin

General Information (Intermediate activated calicheamicin)

Full characterisation using various methods including infrared radiation (IR), ultraviolet (UV), mass spectrometry (MS), nuclear magnetic resonance spectroscopy (NMR) has been carried out. The results demonstrate that the activated calicheamicin derivative has the expected structure. The activated calicheamicin derivative is a white to off white powder, amorphous solid, exhibits no crystalline properties, hygroscopic and is not soluble in water or aqueous solutions.

Description of manufacturing process and process controls *(Intermediate activated calicheamicin)*

Starting from a working cell bank, fermentation of *M. echinospora* strain produces γ-calicheamicin, which is isolated as a solution in the antifoam used in the fermentation. The γ-calicheamicin solution is used to produce N-acetyl calicheamicin. Lastly, the activated linker is added to N-acetyl calicheamicin to produce the intermediate activated calicheamicin derivative:

The activated calicheamicin intermediate is transferred into glass bottles prior to drying and subsequent storage at the recommended storage temperature.

Control of Materials *(Intermediate activated calicheamicin)*

Information regarding the starting materials for the synthesis of the intermediate activated calicheamicin are provided. Sufficient information is provided about the cell banking system used and regarding testing of Master Cell Bank (MCB) and Working Cell Bank (WCB). The banks are monitored according to a pre-approved stability protocol.

Control of critical steps and intermediates *(Intermediate activated calicheamicin)*

The control strategy, critical attributes, critical process parameters, acceptance ranges of the manufacturing process of the activated calicheamicin derivative, including its purification and isolation have been discussed. Acceptable Ranges have been set for each process parameter/ in-process tests (critical and non-critical).

Process validation *(Intermediate activated calicheamicin)*

The process validation of the calicheamicin oil, N-acetyl calicheamicin, and activated calicheamicin derivative manufacturing processes has been completed. Process validation results demonstrate product and process control, as well as effectiveness and consistency of the manufacturing processes.

Characterisation *(Intermediate activated calicheamicin)*

The structure and characteristics of the activated calicheamicin derivative have been determined using several physico-chemical analyses inluding by IR, UV, MS, NMR . The results demonstrate that the activated calicheamicin derivative has the expected structure.

Specification *(Intermediate activated calicheamicin)*

Specification tests and limits are provided and are overall considered acceptable.

Analytical methods *(Intermediate activated calicheamicin)*
All analytical methods have been described clearly and appropriately validated in line with ICH requirements.

Batch analysis *(Intermediate activated calicheamicin)*

Batch analysis data generated with the current manufacturing process have been tested in accordance with specification provided. All batches met the specification criteria.

Reference materials *(Intermediate activated calicheamicin)*

A reference standard has been established for activated calicheamicin derivative.

Stability *(Intermediate activated calicheamicin)*

The stability of primary batches of activated calicheamicin derivative was evaluated under the long term and accelerated conditions.

Intermediate inotuzumab

General Information *(Intermediate inotuzumab)*

Inotuzumab is an IgG4 kappa monoclonal antibody with two identical heavy (H) chains and two identical light (L) chains, covalently linked with four inter-chain disulfide bonds.

The N-linked glycosylation consensus sequence, NST, in the CH2 region is essentially fully occupied with asialo, core-fucosylated, complex-type biantennary oligosaccharides with zero and one terminal galactose residues, abbreviated as G0F and G1F, respectively. The C-terminal K is encoded by the H chain expression vector cDNA sequence, but is observed only at low levels in the mature, secreted form of inotuzumab, presumably due to processing by CHO cellular proteases. Therefore, the penultimate G residue is the predominant H chain C-terminus in inotuzumab. The theoretical molecular masses of the predominant N-linked glycoforms, assuming C-terminal G residues in both H chains, and full disulfide bond connectivity, are on average 14.9 KDa.

Description of manufacturing process and process controls *(Intermediate inotuzumab)*

The inotuzumab intermediate manufacturing process has been adequately described.

The manufacturing process for inotuzumab intermediate uses a recombinant CHO cell line that contains the DNA encoding the sequence for inotuzumab. Cells from the WCB are thawed, and the culture is progressively expanded. The culture is then harvested and clarified to remove cells and debris. After this harvest step, the product is processed by chromatographic steps and membrane filtration steps. The ranges of critical process parameters and the routine in-process controls along with acceptance criteria are described for each step. The inotuzumab intermediate manufacturing process is considered acceptable.

The process description is acceptable.

Inotuzumab intermediate is filled into containers and is stored under appropriate conditions.

Control of materials *(Intermediate inotuzumab)*

Sufficient information on raw materials used in the manufacturing process of inotuzumab intermediate has been submitted. The applicant has provided a list of all material used in the manufacture of inotuzumab intermediate and has described their control. Raw materials conform to United States Pharmacopoeia (USP) specifications, or National Formulary (NF); this is acceptable for an intermediate. Where no Pharmacopoeial standard is applied, materials have an in-house specification, and the acceptance criteria are given. The composition of cell culture media is fully listed and acceptable documents have been provided for raw materials of biological origin used.

The establishment of MCB and WCB have been set up in conditions free of Animal or Human Origin (AHO) substances.

Sufficient information is provided about the cell banking system used and regarding testing of MCB and WCB. The history and details of cell line establishment are given. Establishment of the cell bank follows ICH Q5A and Q5D and the approach for the preparationand testing, is acceptable. Homogeneity of the cell line was demonstrated. Genetic stability has been demonstrated for cells at and beyond the limit of cell age.

The adventitious agents' analysis of the MCB is sufficient and further characterisation carried out on the EOP cells is considered adequate.

Control of critical steps and intermediates *(Intermediate inotuzumab)*

A comprehensive overview of the control strategy throughout the inotuzumab intermediate manufacturing process is given to ensure the process produces inotuzumab intermediate with the desired quality. Acceptable ranges are provided.

Process validation *(Intermediate inotuzumab)*

Validation data from fermentation and purification batches at commercial scale were presented, and these were in compliance and overall appropriate data were submitted. The batch genealogy with the individual batch processing records was also set out. The overall approach and the results gained in the process validation are acceptable.

Process controls *(Intermediate inotuzumab)*

The control strategy has been described and includes various elements to control the quality of the product. These includes, testing of quality and material attributes and process parameters, testing of raw materials, Good Manufacturing Practice (GMP) aspects etc. The definition of attributes and parameters and the principles of the control strategy are identical to all parts of the molecule and the finished product. The designation of the process parameters for the upstream process is acceptable.

For the downstream process characterisation, the proposed designation of the process parameters is generally acceptable.

Characterisation *(Intermediate inotuzumab)*

The applicant has employed a range of orthogonal analytical methods to characterise inotuzumab at the level of primary, posttranslational modifiations, charge and size heterogeneity, higher molecular structure and

biological activity. The results demonstrate that inotuzumab has the expected structure and target binding properties. In addition, stress testing of inotuzumab is performed to help determine the intrinsic stability of the protein. The resulting degradation of inotuzumab is monitored by appropriate analytical methods and the most prevalent degradation products were characterized.

Specification *(Intermediate inotuzumab)*

The tests and specification limits, which are based on clinical experience, are accepted.

Analytical methods *(Intermediate inotuzumab)*

The applicant is using standard analytical assays for the release test of the antibody intermediate. A binding Enzyme Linked Immuno-sorbent Assay (ELISA) is used to determine the biological activity of inotuzumab. The procedures have been adequately set out and the validation of the analytical methods is acceptable.

Batch analysis *(Intermediate inotuzumab)*

In support of the specifications, the applicant has presented batch analytical data for all inotuzumab batches produced so far. All batches met the specifications in place at the time of release.

Reference materials *(Intermediate inotuzumab)*

The reference standard qualification is described acceptably.

Stability *(Intermediate inotuzumab)*

The reported data up to 36 months show a completely unchanged analytical profile, at -80°C. Overall, it is considered that a shelf-life of 60 month could be acceptable for the mAb intermediate .

Manufacture, process controls and characterisation *(Inotuzumab ozogamicin)*

Description of manufacturing process and process controls

The inotuzumab ozogamicin active substance manufacturing process has been adequately described. The two active substance intermediates are used to initate the conjugation reaction. The entire content of the reactor is diluted and purified. The pooled product of the chromatography step is buffer-exchanged in UF/ DF operation. The ranges of critical process parameters and the routine in-process controls, along with acceptance criteria, are described for each step. The active substance manufacturing process is considered acceptable.

The inotuzumab ozogamicin active substance is filled in sterile bags, compliant with Ph. Eur. and food contact legislation (EC Regulation No 1183/2012 replacing No 10/2011), and stored at appropriate storage conditions.

Control of materials

A consolidated active substance 3.2.S.2.2 scheme depicting all GMP steps from starting materials, source materials to the final API arising from each of the process streams, (including the MAb), has been provided. Sufficient information on raw materials used in the active substance manufacturing process has been submitted in the intermediate sections (inotuzumab and activated calicheamicin derivative).

Control of critical steps and intermediates

A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the inotuzumab ozogamicin active substance manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests.

Process validation

The validation of the inotuzumab ozogamicin active substance manufacturing process has been completed. The validation study is acceptable.

Several changes were initiated to enhance manufacturing (conjugation reaction, purification, scale up and storage conditions).

Characterisation

The analytical techniques and methodologies applied for inotuzumab ozogamicin characterization are capable of evaluating primary structure, post-translational modifications, charge and size heterogeneity, conjugation sites, extent of calicheamicin derivative conjugation, higher order structure, and biological activity. The results demonstrate that inotuzumab ozogamicin has the expected structure and biological activity.

Specification (Inotuzumab ozogamicin)

The updated specification for the Inotuzumab ozogamicin active substance has been provided and includes tests for characteristics, identity, purity, biological activity and product related impurities. Limits reflect the clinical experience and are considered acceptable.

Analytical methods

All analytical methods are adequately described and validated in accordance with ICH guidelines.

Batch analysis

Batch data have been provided as well as information on lots destiny (e.g. clinical, non-clinical use), site, process, and date of manufacture.

Reference materials

The primary and working reference materials have been characterized with regard to identity, purity, and potency.

Stability (Inotuzumab ozogamicin)

The shelf life for inotuzumab ozogamicin is based on 18 months of real time stability on primary stability batches, generated at the -55 ± 10 °C storage temperature condition. The data for the primary batches demonstrate that the quality attributes remain in compliance with the proposed commercial stability specification. The proposed shelf life of 18 months at the recommended storage condition of -55 ± 10 °C is accepted for the active substance inotuzumab ozogamicin. In accordance with EU GMP guidelines (6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union), any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and European Medicines Agency (EMA).

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The finished product Besponsa is a lyophilised powder for concentrate for solution for infusion containing 1 mg/vial of inotuzumab ozogamicin. The excipients are: tromethamine (buffer), sucrose (cryoprotectant, bulking agent), polysorbate 80 (surfactant) and sodium chloride (tonicifier). All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. After reconstitution with 4 mL of (sterile) water for injection, the concentration of the finished product is 0.25 mg/mL inotuzumab ozogamicin. The finished product is packaged in a 20 mL amber glass vial. The finished product contains no preservative and is for single use only. No solvent is provided with the product.

An appropriate description of the pharmaceutical development has been submitted.

Inotuzumab ozogamicin is sensitive to light exposure. An amber glass container is utilized for light protection during packaging and storage of the finished product. The commercial lyophilized product primary container is a 20 mL amber vial with a rubber stopper closure and aluminum flip-off seal. The secondary container, which is a carton, additionally limits light exposure.

Besponsa is administered as an IV infusion, which must be completed within 8 hours from start of reconstitution to end of infusion. Upon reconstitution, the Besponsa can be used immediately or refrigerated at 2-8 °C. Following dilution with 0.9% sodium chloride, the Besponsa solution can be infused immediately, held at room temperature, or refrigerated at 2- 8 °C. If stored refrigerated, equilibrate to room temperature for one hour prior to infusion and infuse immediately.

Manufacture of the product and process controls

The manufacturing process of Besponsa 1 mg/vial finished product is as follows. The inotuzumab ozogamicin active substance is supplied as a frozen liquid. The frozen active substance is thawed under controlled conditions, mixed and then filtered into a container. The formulation buffer is then added to the mixed active substance to dilute the protein concentration to 0.25 mg/mL. The formulated finished product is then sterile filtered and aseptically filled into vials. Upon completion of the lyophilization cycle, the vials are stoppered and capped with an overseal. Following the capping operation, the vials are visually inspected and stored at 2-8 °C. The lyophilzation process has been adequately documented, and suitable process controls including CPPs have been set.

Product specification

The specifications for Besponsa at release include tests for the following quality attributes: characteristics, identity, purity, biological activity, product related impurities and safety.

Except for reconstitution time and container closure system, the methods are either compendial or the same as used for control of the active ingredient. Descriptions and validation for the methods for reconstitution time and container closure integrity have been submitted. The specification limits in accordance with clinical experience are acceptable.

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

Batch analysis

The batch analyses data of the finished product lots used for non-clinical, clinical trials, stability and process validation met the specifications at the time of release and additionally, the process validation lots also met the commercial specifications.

Reference materials

Reference standards are described in the active substance section.

Stability of the product

The proposed shelf life of Besponsa (inotuzumab ozogamicin) finished product is 24 months when stored at recommended temperature of 2-8 °C.

Stability information for inotuzumab ozogamicin finished product stored under recommended 2-8 °C conditions has been provided. All primary finished product stability lots were manufactured with the commercial active substance. All test results at the recommended storage conditions met the commercial specifications As more stability data becomes available, the Applicant expects to extend the shelf life based on the suitability of the data.

Adventitious agents

The viral testing of unprocessed bulk is in line with what is expected for material derived from Chinese hamster ovary (CHO) cells and is considered acceptable.

The virus validation studies are acceptable in terms of number of validated steps and model viruses used and effective reduction of A-MuLV, Reo 3 and PPV is indicated by the results. Validation reports are be provided for each study of virus reduction.

The establishment of MCB and WCB have been set up in AHO free conditions..

All materials are sourced and manufactured consistent with the current industry guidelines including those from the EMA, the Therapeutic Goods Administration (TGA), and the World Health Organization (WHO) for minimizing the risk of transmitting transmissible spongiform encephalopathies (TSE), including bovine spongiform encephalopathies (BSE). The risk with TSE is considered negligible.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Four major objections were initially identified during the marketing authorisation application procedure. The first major objection pertained to the description of the manufacturing process for all three parts of the active substance as it was considered not to be sufficiently detailed to assure that future commercial batches will be representative for the validation batches and batches that has been used in clinical trials. During the procedure the applicant has provided the necessary level of detail required. As the QP declaration originally

submitted with the application was based upon audits carried out by Regulatory Authorities, major objection 2 requested a new QP declaration covering all relevant active substance manufacturing sites, independently audited on behalf of the proposed MIAH. A satisfactory QP declaration for the active substance was provided to address the second major objection. The third major objection highlighted that the GMP certificate, issued by in July 2015 by the MHRA, did not cover some Wyeth Pharmaceuticals, Pearl River buildings used in the manufacture of Besponsa; hence; a new inspection was required. A new valid GMP certificate, following an inspection of the buildings used in the manufacture of Besponsa in Wyeth Pharmaceuticals, Pearl River was provided and resolved major objection 3. The fourth major objection was related to the fact that the acceptance criteria applied in the specification of the finished product was set without taking clinical qualification into account and are in many cases considerably less stringent compared to the clinical batches. The applicant clinically justified and/or tightened the acceptance criteria, which was acceptable. Hence all the major abjections were resolved.

2.2.5. Conclusion on chemical, pharmaceutical and biological aspects

The quality of this product, as updated during the procedure, is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends several points for investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

All studies (toxicity, reproductive and developmental, genetic toxicity and tissue cross-reactivity) were conducted in accordance with US FDA Good Laboratory Practice (GLP) regulations. Safety studies were performed in accordance with GLP. The in vitro hERG assay with N-Ac-γ-calicheamicin DMH was not GLP compliant but this did not affect the safety assessment.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro studies

The binding of inotuzumab ozogamicin and unconjugated antibody (G544) to human CD22 was evaluated by surface plasmon resonance (SPR) using human CD22-Fc fusion protein (RPT-44320). Both inotuzumab ozogamicin and unconjugated G544 antibody bound human CD22 with similar affinities by Biacore analysis.

Competitive blocking studies showed that the G544 antibody-binding site on CD22 was localized to the first Ig-like domain of CD22, known as CD22 epitope A/ Ig-like domain 1 of CD22 (Report –RPT-48437).

The cell surface expression of CD20 and CD22 was shown to be lower in Reh and RS4;11 ALL cell lines compared to Ramos B-cell lymphoma cells. The pre-B ALL cell line SUP-B15 did not demonstrate readily-detectable expression of CD-20 or CD22. As expected, B-cell ALL cell lines expressed undetectable or only negligible levels of CD33 (Report 145820).

Specific binding of PE-labeled G544 was detected in normal human B-cells. Binding of G544-PE to B-cells from mouse, rat, rabbit, or cynomolgus monkey was not observed in these experiments. Furthermore, staining was not detected in granulocytes, monocytes, or T-cells in whole blood from any nonclinical species examined (Report 145201).

The internalization and trafficking of G544 was evaluated using imaging flow cytometry (Amnis) after binding to CD22-positive B-ALL (Reh, RS4;11) or the B-cell Lymphoma (Ramos) cell lines. The constant exposure method was used to assess the internalization rate of G544. The internalization score (IS) and membrane and cytosolic intensity for each sample was determined using Amnis IDEAS software. To determine the internalization rate, the IS and cytosolic intensity were plotted versus time and nonlinear regression was used to derive a half-time (t½) when a saturable response with time was observed (Report 115037).

Co-localization of G544 antibody with Lysosymal-associated membrane protein 1 (LAMP-1) was detected in the CD22-positive Ramos, Reh and RS4;11 cell lines (Report 115037).

The effect of inotuzumab ozogamicin on 53BP1 foci formation was tested in CD22-positive Reh ALL cells. Short-term (1 hour) incubation with inotuzumab ozogamicin caused induction of 53BP1 foci formation in the nuclei of most cells, indicative of DNA damage. These data suggest that inotuzumab ozogamicin elicits its anti-tumor activity due to the calicheamicin payload causing DNA damage (Report 145820).

The ability of inotuzumab ozogamicin and unconjugated G544 antibody to induce CDC and to mediate ADCC was evaluated with CD20-positive, CD22-positive Ramos B-lymphoma cells. In contrast to the IgG1 expressing anti-CD20 antibody rituximab, neither the G544 antibody nor the inotuzumab ozogamicin conjugate showed effector functions in the CDC and ADCC assays. This is in line with known lack of CDC and ADCC effector function for IgG4 antibodies (Report RPT-51502).

Cell viability studies using a colorimetric assay were conducted with ALL (Reh, RS4;11, SUP-B15) and lymphoma (Ramos) cell lines. The half maximal inhibitory concentration (IC_{50}) values ranged from 0.33 (Reh cells) to 2.5 ng/ml (Ramos cells). The nonbinding control gemtuzumab ozogamicin was up to 63-fold less cytotoxic against the CD22-positive cell line tested. All CD22-positive cell lines tested displayed increased sensitivity (75 to 564-fold) towards the cytotoxic effect of inotuzumab ozogamicin compared to control CD33-positive HL-60 cells, which do not express CD22 (Report 145820).

In vivo studies

Tolerability was studied in nude and SCID mice after three IP injections of inotuzumab ozogamicin every four days. The maximum non-lethal dose (MND) of inotuzumab ozogamicin in non-tumorbearing nude mice was 9.87 mg/m^2 (Report-44320) and in SCID mice 3.3 mg/m^2 (Report RPT-51502).

A B-ALL Reh SC xenograft model with tumor cells implanted in irradiated, athymic nude mice was utilized to study the antitumor activity of inotuzumab ozogamicin. The study included the antibody drug conjugate

gemtuzumab ozogamicin, where the antibody recognized CD33, another B-cell marker. Compared to vehicle-treated mice, both inotuzumab ozogamicin and gemtuzumab ozogamicin significantly ($p < 0.05$) inhibited tumor growth from day 20 onward. The control compound, gemtuzumab ozogamicin at the dose of 13.71 mg/m^2 was significantly less potent compared to inotuzumab ozogamicin administered at 6.57 mg/m^2. The mixture of G544 antibody (9 mg/m^2) and unconjugated N-Ac-γ-calicheamicin DMH (160 µg/kg) administered IP Q4Dx3 was ineffective in inhibiting the growth of Reh xenografts and was associated with treatment-related deaths of all (6/6) tumor-bearing mice (Report PF-05208773).

The ability of inotuzumab ozogamicin to protect SCID mice against systemically disseminated Reh B-ALL was examined. Mice dosed with vehicle (PBS) developed hind-limb paralysis and all of these vehicle-treated mice died due to the disseminated disease by day 77. Inotuzumab ozogamicin administered at a dose of 3.3 mg/m^2 resulted in 100% survival of treated mice over the 127 day observation period. At a 20-fold lower dose (0.18 mg/m^2), 90% of the mice survived throughout the observation period (Report 190248).

Flow cytometric analysis of bone marrow cells collected from the femur of treated mice showed a 75% reduction in the engraftment of the human CD45-positive leukemic cells in inotuzumab ozogamicin-treated mice (Report 190248).

The antitumor efficacy of single-agent inotuzumab ozogamicin was evaluated in aggressive Ramos and RL models of B-cell lymphoma in nude mice. Ramos is a Burkitt's lymphoma-derived cell line whereas RL was originally derived from a non-Burkitt's follicular lymphoma. The minimum effective dose (MED) of inotuzumab ozogamicin in the Ramos model was 0.42 mg/m^2. Complete tumor regressions were observed at 6.57 mg/m^2 in Ramos tumors which lasted throughout the study observation period. In contrast, the G544 antibody control had little effect on the growth of Ramos B-cell lymphoma. In the RL B-cell lymphoma model, inotuzumab ozogamicin treatment induced dose-dependent regressions of RL xenografts over a 3 week period. The MED of inotuzumab ozogamicin in the RL lymphoma model was shown to be 0.81 mg/m2 Q4Dx3. The route of administration (IV or IP) did not affect the antitumor activity at any of these three dose levels of inotuzumab ozogamicin (Report RPT-44320).

Inotuzumab ozogamicin was shown to be effective in disseminated disease Ramos B-cell lymphoma regardless of whether it was administered on day 3 (early disease) or day 9 (advanced disease). The disseminated B-cell lymphoma studies in both early disease and advanced disease resulted in the best response at 1.65 mg/m^2. The most likely explanation for decreased survival of mice at higher dose levels compared to lower dose levels in this study is that inotuzumab ozogamicin in the high dose group (6.57 mg/m^2) was administered above the tolerated dose levels for SCID mice (Report RPT-51502).

The effects of CHOP chemotherapy on the survival of SCID mice bearing disseminated Ramos B-cell lymphoma was examined. CHOP treatment had only a minor impact on the development of hind-limb paralysis and/or death of SCID mice with disseminated B-cell lymphoma ($p > 0.05$ versus vehicle-treated mice). In contrast, inotuzumab ozogamicin treatment almost completely inhibited ($p < 0.05$ versus vehicle- or CHOP-treated mice) growth of disseminated B-cell lymphoma (Report 172726).

Nude mice implanted with Ramos SC xenografts initially responded to CVP or CHOP therapy and then the tumors relapsed within approximately 10 days for CVP and 40 days for CHOP after the initiation of the chemotherapy. The relapsed Ramos xenografts were poorly responsive to re-treatment with CVP or CHOP but remained responsive and regressed upon treatment with inotuzumab ozogamicin (Report PF-05208773 and Report 172726).

Concurrent administration of CVP and inotuzumab ozogamicin induced regression of established Ramos xenografts and significantly ($p < 0.05$) improved the antitumor activity over chemotherapy or inotuzumab ozogamicin treatment alone (Report 172726).

In contrast to the results in the developing RL tumor model, rituximab had little effect on the growth of small, staged lymphoma tumors, while inotuzumab ozogamicin inhibited growth throughout the 40 day study. G544 antibody treatment was largely ineffective in inhibiting tumor growth (Report RPT-44320).

In the developing B-cell lymphoma model, the combination of rituximab and inotuzumab ozogamicin led to a statistically significant increase in survival over each of the single agents ($p < 0.05$) (Report RPT-51502). In contrast, the combination of inotuzumab ozogamicin and rituximab was not effective against B-cell lymphoma xenografts allowed to grow to small, staged tumors of ≥ 0.3 g (Report RPT-48437). Also in the disseminated Ramos B-cell lymphoma model, the addition of rituximab to inotuzumab ozogamicin did not result in an significant improvement over inotuzumab ozogamicin alone (Report RPT-48437).

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies have been conducted with inotuzumab ozogamicin (see discussion on non-clinical aspects).

Safety pharmacology programme

Inotuzumab ozogamicin was evaluated for potential effects on cardiovascular (CV), respiratory, and central nervous system (CNS) *in vivo*. In addition, an *in vitro* hERG current inhibition assay was conducted with N-Ac-γ-calicheamicin DMH.

The potential for inotuzumab ozogamicin to cause neurofunctional effects was assessed following administration of a single IV dose to male Sprague-Dawley rats. Evaluated parameters included mortality, general and detailed clinical observations, and assessment of CNS function (functional observational battery assessment, measurement of hind limb foot splay, measurement of forelimb and hind limb grip strength, and measurement of rectal temperature). Inotuzumab ozogamicin administered IV as a single dose of 0.78, 2.4, or 8.46 mg/m^2 to male rats had no toxicologically important effects on CNS function (Report RPT-47140)

The potential effect of inotuzumab ozogamicin on pulmonary function was assessed following administration of a single IV dose to male Sprague-Dawley rats. Respiratory function (respiratory rate, tidal volume, and derived minute volume) was evaluated using head out plethysmography and evaluations were conducted prior to dosing and approximately 0.5, 8, and 24 hours after dosing. Inotuzumab ozogamicin administered IV as a single dose of 0.78, 2.4, or 8.46 mg/m^2 to male rats did not produce any biologically or toxicologically relevant effects on respiratory function (Report RPT-47139).

The potential for inotuzumab ozogamicin to cause cardiovascular effects was evaluated following administration of a single IV dose to conscious cynomolgus monkeys. Daily clinical signs were collected and telemetered data consisted of arterial blood pressures (systolic, diastolic, and mean), heart rate, and electrocardiogram (ECG; heart rate, PR, QRS, QT, and QT interval). Heart rate, PR, QRS, and QT were measured and the heart rate corrected QT interval (QTc) was calculated for 3 time points prior to dosing and 3 time points post dosing from ECG recordings for each animal administered vehicle control and 8.16 mg/m^2 (high dose) of inotuzumab ozogamicin. Single IV doses of inotuzumab ozogamicin were associated with mild

increases in mean arterial blood pressure at ≥1.68 mg/m^2. There were no changes in PR, QRS, QT or QTc interval duration at a dose of 8.16 mg/m^2 (Report RPT-47509).

The IC_{50} for the inhibitory effect of N-Ac-γ-calicheamicin DMH on hERG potassium channels was >6.77 µM (10,000 ng/mL) (Report N-acetyl-gamma-calicheamicin-DMHHERG).

Pharmacodynamic drug interactions

No pharmacodynamic drug interactions studies have been conducted with inotuzumab ozogamicin (see discussion on non-clinical aspects).

2.3.3. Pharmacokinetics

Several assays were developed for an integrated characterization of the PK/TK of inotuzumab ozogamicin. Enzyme-linked immunosorbent assays (ELISAs) were used for the quantitation of inotuzumab ozogamicin, total G544 antibody, unconjugated calicheamicin, and ADA in mouse, rat, rabbit, and/or monkey serum. In addition, ELISAs were used for the quantitation of calicheamicin equivalents in rat and dog plasma. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) assays were used for the quantitation of total calicheamicin in rat, rabbit, and/or monkey serum.

Single dose Pharmacokinetics

Single dose pharmacokinetic studies were conducted in non-tumor bearing and tumor bearing mice after IP dosing and in rats and monkeys after IV dosing. The mean PK parameters after a single dose of inotuzumab ozogamicin in mice, rats and monkeys are presented in Table 1,

Table 2 and Table 3 respectively.

Table 1. Mean PK Parameters after a Single IP Dose of Inotuzumab Ozogamicin in Mice

Report	Dose	Analyte	Sex/ n	$t_{½}$ (h)	C_{max} (ng/mL)[a]	AUC_{inf} (ng•h/mL)[a]
RPT-47740 (Non-tumor bearing)	9.6 mg/m^2 [b] 3.2 mg/kg[c] 160 µg/kg[d]	Inotuzumab ozogamicin	F/4[e]	34.2	51200	2900000
		G544 antibody	F/4[e]	54.6	40000	4040000
RPT-47740 (Tumor bearing)	9.6 mg/m^2 [b] 3.2 mg/kg[c] 160 µg/kg[d]	Inotuzumab ozogamicin	F/4[e]	35.0	47800	1860000
		G544 antibody	F/4[e]	64.1	40800	2850000

Notes: Inotuzumab ozogamicin = PF-05208773, CMC-544, or WAY-207294; G544 antibody = Anti-CD22 antibody.
Abbreviations: AcBut = 4-(4′-acetylphenoxy) butanoic acid; AUC_{inf} = Area under the concentration-time curve from time 0 to infinity; CD22 = Cluster of differentiation 22; C_{max} = Maximum observed concentration; DMH = Dimethylhydrazide; F = Female; h = Hour; IP = Intraperitoneal; n = Number of animals; N-Ac = N-acetyl; PK = Pharmacokinetic; $t_{½}$ = Apparent terminal elimination half-life; - = Data not available.

a. Inotuzumab ozogamicin and G544 antibody concentrations reported as $ng_{protein}$/mL.
b. Protein (G544 antibody) dose equivalent; $mg_{protein}$/kg was converted to $mg_{protein}/m^2$ using a conversion factor (k_m) of 3.
c. Protein (G544 antibody) dose equivalent; $mg_{protein}$/kg determined using the loading of calicheamicin onto the CD22 antibody (50 µg of calicheamicin per mg of antibody).
d. N-Ac-γ-calicheamicin DMH AcBut dose equivalent.
e. 4 animals/time point.

Table 2. Mean PK Parameters after a Single IV Dose of Inotuzumab Ozogamicin in Rats

Dose	Analyte	Sex/ n	CL (mL/min/kg)	V_{ss} (L/kg)	$t_{½}$ (h)	C_{5min}[a] (ng/mL)	AUC_{inf}[a] (ng•h/mL)
2.9 mg/m^2 [b] 0.49 mg/kg[c] 35 µg/kg[d]	Inotuzumab ozogamicin	M/3	0.0388	0.185	54.9	7980	209000
		F/3	0.0352	0.128	41.7	8790	232000
	G544 antibody	M/3	0.0195	0.142	84.8	10000	420000
		F/3	0.0192	0.130	78.5	10600	429000
	Unconjugated calicheamicin	M/3	ND	ND	ND	3.10[e]	10.6[e,f]
		F/3	ND	ND	ND	3.76[e]	9.23[e,f]
7.68 mg/m^2 [b] 1.28 mg/kg[c] 100 µg/kg[d]	Inotuzumab ozogamicin	M/3	0.0237	0.099	48.5	37500	903000
		F/3	0.0325	0.110	39.1	40300	655000
	G544 antibody	M/3	0.0178	0.139	90.3	22500	1190000
		F/3	0.0340	0.166	56.2	22000	643000
	Unconjugated calicheamicin	M/3	ND	ND	ND	15.5[e]	257[e,f]
		F/3	ND	ND	ND	16.2[e]	144[e,f]

Notes: Inotuzumab ozogamicin = PF-05208773, CMC-544, or WAY-207294; G544 antibody = Anti-CD22 antibody.
Abbreviations: AcBut = 4-(4′-acetylphenoxy) butanoic acid; AUC_{inf} = Area under the concentration-time curve from time 0 to infinity; CD22 = Cluster of differentiation 22; CL = Systemic plasma clearance; C_{5min} = Concentration observed at 5 minutes postdose; DMH = Dimethylhydrazide; F = Female; IV = Intravenous; M = Male; n = Number of animals; N-Ac = N-acetyl; ND = Not determined; PK = Pharmacokinetic; $t_{½}$ = Apparent elimination half-life; V_{ss} = Apparent volume of distribution at steady-state.

a. Inotuzumab ozogamicin and G544 antibody concentrations reported as $ng_{protein}$/mL. Unconjugated calicheamicin concentrations reported as $ng_{calicheamicin}$/mL.
b. Protein (G544 antibody) dose equivalent; $mg_{protein}$/kg was converted to $mg_{protein}/m^2$ using a conversion factor (k_m) of 6.
c. Protein (G544 antibody) dose equivalent; $mg_{protein}$/kg.
d. N-Ac-γ-calicheamicin DMH AcBut dose equivalent; $\mu g_{calicheamicin}$/kg.
e. Determined from mean concentration-time profiles.
f. AUC_{last} = Area under the concentration-time curve from time 0 to the time of the last measurable concentration.

Table 3. Mean PK Parameters after a Single IV Dose of Inotuzumab Ozogamicin in Monkeys

Dose	Analyte	Sex/ n	CL (mL/min/kg)	V_{ss} (L/kg)	$t_{½}$ (h)	C_{5min} [a] (ng/mL)	AUC_{inf} [a] (ng•h/mL)
4.11 mg/m^2 [b]	Inotuzumab	M/2	ND	ND	ND	18800	260000[e]
0.34 mg/kg[c]	ozogamicin	F/2	ND	ND	ND	16700	246000[e]
25 µg/kg[d]	G544 antibody	M/2	0.0185	0.128	86.9	6160	310000
		F/2	0.0198	0.136	90.9	6120	290000
8.22 mg/m^2 [b]	Inotuzumab	M/2	0.0230[f]	0.0911[f]	64.0[f]	35200	449000[e]
0.68 mg/kg[c]	ozogamicin	F/2	ND	ND	ND	37400	718000[e]
50 µg/kg[d]	G544 antibody	M/2	0.0177	0.137	105	11800	649000
		F/2	0.0143	0.104	102	14500	800000
16.4 mg/m^2 [b]	Inotuzumab	M/2	0.0205	0.0701	60.0	66000	1120000
1.37 mg/kg[c]	ozogamicin	F/2	0.0175	0.0541	51.3	64200	1310000
100 µg/kg[d]	G544 antibody	M/2	0.0183	0.139	103	22400	1320000
		F/2	0.0205	0.125	78.2	22500	1120000

Notes: Inotuzumab ozogamicin = PF-05208773, CMC-544, or WAY-207294; G544 antibody = Anti-CD22 antibody.
Abbreviations: AcBut = 4-(4′-acetylphenoxy) butanoic acid; AUC_{inf} = Area under the concentration-time curve from time 0 to infinity; CD22 = Cluster of differentiation 22; CL = Systemic plasma clearance; C_{5min} = Concentration observed at 5 minutes postdose; DMH = Dimethylhydrazide; F = Female; IV = Intravenous; M = Male; n = Number of animals; N-Ac = N-acetyl; NC = Not calculated; ND = Not determined; PK = Pharmacokinetic; $t_{½}$ = Apparent elimination half-life; V_{ss} = Apparent volume of distribution at steady-state.

a. Inotuzumab ozogamicin and G544 antibody concentrations reported as $ng_{protein}$/mL.
b. Protein (G544 antibody) dose equivalent; $mg_{protein}$/kg was converted to $mg_{protein}/m^2$ using a conversion factor (k_m) of 12.
c. Protein (G544 antibody) dose equivalent; $mg_{protein}$/kg.
d. N-Ac-γ-calicheamicin DMH AcBut dose equivalent; $\mu g_{calicheamicin}$/kg.
e. AUC_{336} = Area under the concentration-time curve from time 0 to 336 hours postdose.
f. n=1.

Repeat dose Toxicokinetics

The mean TK parameters after a repeat dose of inotuzumab ozogamicin are presented in Table 4, Table 5 and Table 6.

Table 4. Mean (±SE) Toxicokinetic Parameters in Male and Female Rats after Repeat-Dose Administration of Inotuzumab Ozogamicin

Study	Protein (G544 antibody) Dose Equivalent		N-Ac-γ-Calicheamicin DMH AcBut Dose Equivalent	Day	Sex[a]	Inotuzumab Ozogamicin[b]		G544 antibody[b]		Total Calicheamicin[b]	
	(mg/m^2/week)	(mg/kg/week)	(µg/kg/week)			C_{5min} (ng/mL)	AUC_{168} (ng·h/mL)	C_{5min} (ng/mL)	AUC_{168} (ng·h/mL)	C_{5min} (ng/mL)	AUC_{168} (ng·h/mL)
4-Week Toxicity[c] (RPT-46910)	4.01[d]	0.68[d]	0[d]	1	M	NA	NA	11900±2170	595000±37100	NA	NA
	0.41	0.07	5	1	M	1780±73	42600±1220	1140±77	50000±2150	-	-
	1.24	0.21	15	1	M	3370±1180	116000±5660	1910±618	117000±4280	-	-
					F	5080±1570	113000±10900	3010±835	142000±5220	-	-
	4.07	0.69	50	1	M	19700±660	461000±19600	10600±1280	483000±32800	-	-
	4.01[d]	0.68[d]	0[d]	22	M	NA	NA	12700±1180	815000±57400	NA	NA
	0.41	0.07	5	22	M	1980±24	50700±1770	1510±75	74400±4470	-	-
	1.24	0.21	15	22	M	4560±1800	182000±7920	3010±1130	200000±9620	-	-
					F	5610±518	160000±6200	4010±377	195000±12300	-	-
	4.07	0.69	50	22	M	17600±2320	619000±26300	12000±2090	654000±59700	-	-
26-Week Toxicity[e] (RPT-65042)	0.073	0.012	1	1	M	252±6	7630±340	262±7	9550±365	21.3±0.7	657±35
	0.218	0.036	3	1	M	806±22	23700±679	838±33	31900±1080	68.1±5.1	2530±79
	0.727	0.121	10	1	M	2760±85	83900±8200	4710±789	142000±19500	266±20	9840±1040
	0.073	0.012	1	169	M	NM	NM	NM	NM	3.90±2.46	NA[f]
	0.218	0.036	3	169	M	325±167	20200±4650	862±436	31000±7070	42.4±12.6	2370±536
	0.727	0.121	10	169	M	2790±187	64000±10600	252±6	109000±18100	258±21	8270±1480

AUC_{168} = Area under the serum concentration-time curve from time 0 to 168 hours postdose; CD22 = Cluster of differentiation 22; C_{5min} = Concentration at 5 minutes postdose; F = Female; M = Male; NA = Not applicable; NM = Not measurable; SE = Standard error; - = Data not available.

a. 3 animals per time point per sex per dose group.

b. Inotuzumab ozogamicin and G544 antibody concentrations reported as $ng_{protein}$/mL. Total calicheamicin concentrations reported as $ng_{calicheamicin}$/mL.

c. 1 dose/week; Loading of calicheamicin onto the CD22 antibody was 73 µg of calicheamicin per mg of antibody; Units of $mg_{protein}$/kg were converted to $mg_{protein}/m^2$ in RPT-46910 using a conversion factor (k_m) of 5.9.

d. Animals dosed with G544 antibody alone; not conjugated to calicheamicin.

e. 1 dose/week; Loading of calicheamicin onto the CD22 antibody was 82.5 µg of calicheamicin per mg of antibody; Units of $mg_{protein}$/kg were converted to $mg_{protein}/m^2$ using a conversion factor (k_m) of 6.

f. AUC reported in RPT-65042 was calculated using only 1 quantifiable time point.

Table 5. Mean (±SD) Toxicokinetic Parameters in Male and Female Monkeys after 4-Week Repeat-Dose Administration of Inotuzumab Ozogamicin

Study	Protein (G544 antibody) Dose Equivalent[a]		N-Ac-γ-Calicheamicin DMH AcBut Dose Equivalent	Day	Sex[b]	Inotuzumab Ozogamicin[c]		G544 antibody[c]	
	(mg/m^2/week)	(mg/kg/week)	(µg/kg/week)			C_{5min} (ng/mL)	AUC_{168} (ng·h/mL)	C_{5min} (ng/mL)	AUC_{168} (ng·h/mL)
4-Week Toxicity[d] (RPT-46909)	4.08[e]	0.34[e]	0[e]	1	M	NA	NA	4040±370	115000±12000
					F	NA	NA	7530±3110	352000±180000
	0.36	0.03	2.5	1	M	1350±110	6240±4580	508±96	14100±1900
					F	1310±90	7970±3770	426±128	11600±700
	1.32	0.11	8	1	M	5440±1740	51500±19200	2020±180	57700±6000
					F	3590±1810	38800±30500	2100±90	54200±14300
	4.20	0.35	25	1	M	15600±3500	314000±44000	6830±730	230000±16000
					F	14100±800	282000±88000	6090±220	213000±40000
	4.08[e]	0.34[e]	0[e]	22	M	NA	NA	4280±130	225000±20000
					F	NA	NA	8810±4050	509000±275000
	0.36	0.03	2.5	22	M	1550±90	33000±30800	576±93	25000±4700
					F	1320±110	20000±9300	497±74	19900±1200
	1.32	0.11	8	22	M	4820±260	145000±31000	2160±30	114000±11000
					F	4340±1040	92800±22300	2290±300	97400±3400
	4.20	0.35	25	22	M	13600±2300	628000±102000	7110±260	416000±17000
					F	13900±2500	576000±104000	6820±850	385000±44000

AUC_{168} = Area under the serum concentration-time curve from time 0 to 168 hours postdose; CD22 = Cluster of differentiation 22; C_{5min} = Concentration at 5 minutes postdose; F = Female; M = Male; NA = Not applicable; NC = Not calculated, n<3; SD = Standard deviation; - = Data not available.

a. Units of $mg_{protein}$/kg were converted to $mg_{protein}/m^2$ using a conversion factor (k_m) of 12.

b. 3 to 5 animals per sex per dose group.

c. Inotuzumab ozogamicin and G544 antibody concentrations reported as $ng_{protein}$/mL.

d. 1 dose/week; Loading of calicheamicin onto the CD22 antibody was 72 µg of calicheamicin per mg of antibody.

e. Animals dosed with G544 antibody alone; not conjugated to calicheamicin.

Table 6. Mean (±SD) Toxicokinetic Parameters in Male and Female Monkeys after 26Week Repeat-Dose Administration of Inotuzumab Ozogamicin

Study	Protein (G544 antibody) Dose Equivalent[a]		N-Ac-γ-Calicheamicin DMH AcBut Dose Equivalent	Day	Sex[b]	Inotuzumab Ozogamicin[c]		G544 antibody[c]		Total Calicheamicin[c]	
	(mg/m^2/week)	(mg/kg/week)	(µg/kg/week)			C_{5min} (ng/mL)	AUC_{168} (ng·h/mL)	C_{5min} (ng/mL)	AUC_{168} (ng·h/mL)	C_{5min} (ng/mL)	AUC_{168} (ng·h/mL)
26-Week Toxicity[d] (6617-260 [RPT-65773])	0.072	0.006	0.5	1	M	123±48	837±360	149±35	1520±471	12.7±1.5	87.8±14.5
					F	156±69	1030±643	142±41	1260±447	15.2±3.2	98.3±27.8
	0.216	0.018	1.5	1	M	424±177	4650±2490	413±50	5800±1870	49.1±10.2	727±356
					F	457±81	6710±2950	429±46	11500±4520	40.8±8.3	890±422
	0.732	0.061	5.0	1	M	2590±989	24200±5530	1530±144	27800±3950	154±24	2670±123
					F	1590±416	22300±4880	1450±175	32800±8830	129±17	2400±589
	0.072	0.006	0.5	169	M	187±32	4430±1910	183±16	6470±2950	18.5±2.0	737±441
					F	181±29	3230±604	183±18	6270±3320	17.2±3.0	667±498
	0.216	0.018	1.5	169	M	614±139	23200±6500	479±60	24400±5870	57.4±11.1	3680±432
					F	504±136	20200±10400	444±69	32200±4590	50.7±4.3	3430±727
	0.732	0.061	5.0	169	M	1770±77	86100±2520	1610±95	100000±4600	203±19	15600±800
					F	1980±NC	95200±NC	1950±NC	126000±NC	193±NC	15600±NC

AUC_{168} = Area under the serum concentration-time curve from time 0 to 168 hours postdose; CD22 = Cluster of differentiation 22; C_{5min} = Concentration at 5 minutes postdose; F = Female; M = Male; NA = Not applicable; NC = Not calculated, n<3; SD = Standard deviation; - = Data not available.

a. Units of $mg_{protein}/kg$ were converted to $mg_{protein}/m^2$ using a conversion factor (k_m) of 12.
b. 4 animals per sex per dose group.
c. Inotuzumab ozogamicin and G544 antibody concentrations reported as $ng_{protein}/mL$. Total calicheamicin concentrations reported as $ng_{calicheamicin}/mL$.
d. 1 dose/week; Loading of calicheamicin onto the CD22 antibody was 82.5 µg of calicheamicin per mg of antibody.

The tissue distribution of [^{3}H]inotuzumab ozogamicin radioequivalents in male Sprague-Dawley rats over the time course of 0.083 to 336 hours postdose was evaluated by tissue dissection/combustion and LSC after a single IV administration (1.88 mg/m^2, 62.8 µCi/kg) of [^{3}H]inotuzumab ozogamicin. Distribution of [3H]inotuzumab ozogamicin radioequivalents into tissues was limited, with tissue-to-plasma AUC_{inf} ratios ≤0.6 for all tissues evaluated. These findings were consistent with the small V_{ss} observed in rats, which was largely limited to plasma volume. The highest tissue-to-plasma ratios were observed in the liver (0.6), blood (0.5), spleen (0.4), lung (0.3), and kidney (0.3). Radioequivalents in brain were <2% of those in plasma, suggesting limited distribution of inotuzumab ozogamicin and metabolites across the blood-brain barrier. The $t_{½}$ values for [^{3}H]inotuzumab ozogamicin-derived radioactivity were similar in both plasma (73.0 hours) and blood (73.4 hours). However, longer retention of [^{3}H]inotuzumab ozogamicin radioequivalents was observed in all other tissues evaluated relative to plasma, with $t_{½}$ values ranging from 87.7 hours in skeletal muscle to 265 hours in the kidney.

The extent of *in vitro* binding of N-Ac-γ-calicheamicin DMH to mouse, rat, rabbit, monkey, and human plasma proteins was determined using equilibrium dialysis at a concentration of 1.8 µM (2660 ng/mL). N-Ac-γ-calicheamicin DMH was highly bound to plasma proteins in all species evaluated. The geometric mean plasma fraction unbound (fu) was 0.000942, 0.00679, 0.0263, 0.0310, and 0.0279 in mouse, rat, rabbit, monkey, and human, respectively.

Blood-to-plasma partitioning was estimated *in vivo* in rats administered a single IV dose of [^{3}H]inotuzumab ozogamicin. In rats, [^{3}H]inotuzumab ozogamicin radioequivalents in blood were lower than in plasma (blood/plasma radioactivity AUC_{inf} ratio of 0.5), indicating that [^{3}H]inotuzumab ozogamicin-derived radioactivity preferentially distributed into plasma relative to red blood cells.

In vitro, N-Ac-γ-calicheamicin DMH demonstrated limited distribution into red blood cells, with blood-to-plasma partition ratios of 0.63, 0.84, and 0.71 in rat, monkey, and human, respectively. Thus,

N-Ac-γ-calicheamicin DMH concentrations measured in plasma are representative of the systemic exposure in the evaluated species.

The primary metabolic pathway for inotuzumab ozogamicin was hydrolysis (deconjugation) at the hydrazone moiety to release N-Ac-γ-calicheamicin DMH. Overall, inotuzumab ozogamicin is anticipated to be cleared from circulation (with concomitant deconjugation) by both target- and non-target-mediated pathways (Gerber et al, 2013; Kraynov et al, 2016). The former pathway involves binding of inotuzumab ozogamicin to antigen on the surface of CD22-expressing cells, followed by internalization via receptor-mediated endocytosis, trafficking from endosomes to lysosomes, and intracellular release (hydrolysis) of N-Ac-γ-calicheamicin DMH in the acidic lysosomal environment. In the latter case, inotuzumab ozogamicin would be cleared by the normal pathways mediating IgG disposition, ie, non-specific uptake via pinocytosis by certain cell types (eg, endothelial cells) in multiple organs, including the liver. Upon internalization, inotuzumab ozogamicin could be recycled to the circulation by the neonatal Fc receptor (FcRn) or translocated to lysosomes, resulting in hydrolytic release of N-Ac-γ-calicheamicin DMH and catabolism of the IgG4 portion of inotuzumab ozogamicin. For released N-Ac-γ-calicheamicin DMH, the primary metabolic pathways was reduction (at the disulfide moiety). Hydrolysis (at the hydrazide moiety), oxidation, and adduction (with pyruvic acid) were minor metabolic pathways.

Metabolic profiling and identification were conducted utilizing plasma, urine, fecal, and bile samples from the mass balance and excretion study in male and female intact and BDC rats after IV administration of a single 0.91 mg/m2 (47.3 µCi/kg) dose of [^{3}H]inotuzumab ozogamicin. The majority of radioactivity was recovered in the feces (approximately 80%). The vast majority of circulating radioactivity (~98%) remained associated with protein, and unconjugated calicheamicin-related radioactivity accounted for only ~2% of total circulating radioactivity. In plasma, the major extractable radiochemical peaks detected were M13, N-Ac-γ-calicheamicin DMH (M17), and M11, accounting for 0.4%, 0.3%, and 0.2% of total plasma radioactivity, respectively, in male rats, and 0.3%, <0.1%, and 0.3% of total plasma radioactivity, respectively, in female rats.

The *in vivo* metabolism of inotuzumab ozogamicin was evaluated in patients with relapsed or refractory NHL administered 3 cycles of IV inotuzumab ozogamicin (1.8 mg/m^2, q4 weeks). Following the third cycle of inotuzumab ozogamicin, serum and urine samples were collected at 1 (immediately before the end of infusion), 3, and 48 hours postdose, pooled, and qualitatively profiled for the presence of metabolites. The only metabolite detected in serum was the expected hydrolytic product of inotuzumab ozogamicin, N-Ac-γ-calicheamicin DMH (M17).

2.3.4. Toxicology

Single dose toxicity

A summary of single-dose toxicity studies performed with inotuzumab ozogamicin is presented in rformed with IV administration.

Table 7. All studies were performed with IV administration.

Table 7. Summary of single-dose toxicity studies performed with Inotuzumab Ozogamicin

Study ID/ GLP	Species/ Sex/Number/Group	Dose (µg/kg)/ Route	Approximate Lethal Dose /Observed max non-lethal dose/NOAEL	Noteworthy findings
RPT-43870 /non-GLP Exploratory	Sprague-Dawley rat/3/sex/ group	0, 10, 35, 50, 100 /Intravenous	ND / 100/ND	≥10: ↓bw,↓WBC, ↓neutrophil, ↓lymphocyte, ↓monocyte,↓glucose, ≥35: ↓thyroxine≥50: ↑RBC, ↑hemoglobin, ↑hematocrit, ↓triglyceride, ↓MCV, ↓MCH 100: ↓Inorganic phosphorous, ↑AST
RPT-46645 / GLP	Sprague-Dawley rat/6/sex/ group	0, 100, 200/ Intravenous	200/100/ND	Mortality: 3♂ and 1♀ at 200 µg/kg died post dose on SD5 due to inotuzumab ozogamicin-related multiple organ toxicity in liver (centrilobular necrosis), spleen (lymphoid atrophy), thymus (lymphoid atrophy), bone marrow hypocellularity), and testes (tubular degeneration). Other findings: 0: anaphylactoid response (swelling of nose, ears, and/or feet) ≥100:↓BW, ↓food consumption, ↓RBC, ↓WBC, ↓thyroxine, liver wt (↑rel wt: oval cell hyperplasia), kidney (↑rel wt: interstitial fibrosis), adrenal gland (↑rel wt),, bone marrow (hypocellularity), GALT (lymphoid atrophy), small testes and testicular tubular degeneration
RPT-46644 / GLP	Cynomolgus monkey/2 /sex/group	0, 25, 50, 100 Intravenous	ND/100/ND	≥25: emesis, fecal alterations,↓platelet, ↓WBC, ↓cholesterol, ↓total protein; ↑fibrinogen, ↑PT, ↑APTT, ↑ALT, ↑AST ≥50:↓RBC, ↑hemoglobin, ↑hematocrit, ↑total bilirubin, ↓glucose 100: ↑AST and ↑total bilirubin (considered toxicologically significant).

Repeat dose toxicity

A summary of repeat-dose toxicity studies performed with inotuzumab ozogamicin is presented in Table 8. Inotuzumab ozogamicin was administered IV (bolus) to animals of both sexes with once-weekly dosing.

Table 8. Summary of repeat-dose toxicity studies performed with inotuzumab ozogamicin

Study ID /GLP/ Duration	Species/Sex/ Number/Group	Dose[a]/ Route	NOAEL/NOEL
RPT-46910 / GLP/ 4 weeks + 4 weeks recovery	Sprague Dawley Rats/15-24/sex/group (5/sex for recovery, ctrl, G544, and 4.07). 18 males/group for TK (except 18/sex for 1.24 group).	0/0/0 0/0.68/4.01 5/0.07/0.41 15/0.21/1.24 50/0.69/4.07 /IV once weekly	**NOAEL:** None
Mortality: 4♂ and 1♀ died during the study. 3♂ died following blood collection (not treatment related), and 1♂ was housed with males during shipping, and was terminated along with pups. Male #178 (50 µg/kg/week) died due to an anaphylactoid reaction resulting from a component of the formulation (dextran 40). No macroscopic evaluation present, but microscopic observations in line with those seen in final necropsy. Clinical signs: >5: Fecal changes dose-dependently. Anaphylactoid responses mostly in G544 high-dose groups on day of dosing. 13 animals received medical treatment due to anaphylaxis plus Benadryl treatment. Body weight, food consumption: >5♂♀: weight gain ↓ dose-dependently. Similar reductions in food consumption			

Study ID /GLP/ Duration	Species/Sex/ Number/Group	Dose[a]/ Route	NOAEL/NOEL
Ophthalmoscopy: No compound related effects Serum chemistry: ≥5:↑ALT (15-135%). At 50 µg/kg (↑134-135%) there was correlation with hepatocellular degeneration. ≥5:↑AP (17-54%), ↓TRIG (16-63%). ≥15♂♀:↑AST (17-70%)↑GLUC (10-26%) 50♂: CHOL↑ (24-44%), ↓T4 (22%). Changes in TRIG, GLUC, and CHOL possibly related to food consumption ↓ Haematology: 50:↓lymphocytes (42-56%), ↓reticulocytes (84-89%), ↓RBC, HGB, HCT (18-35%), ↓WBC (14-45%), NEU (46-53%), ↓PLT (21% only ♀), ↓EOS (32-63%) Organ weights: ♂:↓Thymus, testes, epididymis and prostate dose-dependently. Thymus protein control and LD were slightly ↑. ♀: ↓Thymus dose-dependently including protein control,↓ Ovaries dose-dependently, ↑Uterus (19- 31%) except HD which was↓ (21%). No effects on brain weight (♂♀). Macroscopic findings: ≥5:↓ testes; ≥15:↓epididymides, 5 and 50:↓seminal vesicle, 50: ↓prostate, thymus (also ♀) Histopathology: ***Liver:*** ≥15:↑extramedullary hematopoiesis dose-dependently, hypertrophy. 50: Oval cell hyperplasia, oval cell degeneration, karyomegaly. ***Lymphoid tissue:*** ≥15: mild to average bone marrow atrophy (♀at 50), lymphoid atrophy of thymus, spleenand gut accompanied by single cell necrosis (slight-average) ***Kidneys*:** 50: mild proteinaceous intraluminal tubular casts in renal parenchyma (11/15) ***Male reproductive system:*** ≥5: testicular tubular degeneration dose-dependently (mild to severe). Seminiferous tubules were shrunken and frequently only contained a layer of Sertoli cells. Interstitial cells were absent. Atrophy of mammary tissue. ≥15: epididymal hypospermia dose-dependently. 50: atrophy of the prostate and seminal vesicles. ***Female reproductive system:*** 50: ovarian, uterine, and vaginal atrophy (correlated with decreased ovarian and uterine weights). Mammary gland atrophy (1/15). In the ovaries, fewer secondary and tertiary follicles were present, and primary follicles were degenerating. ***Lung:*** ≥5♂♀:↑alveolar macrophages (amphophilic, foamy) randomly scattered in the pulmonary parenchyma (slight). ***Nervous system:*** ≥15: incidence of axonal degeneration in sciatic nerve. ♀50: concurrent degeneration of axons within the cervical spinal cord. 1♂, 1♀:slight axonal degeneration - trigeminal nerve. Thus, microscopic correlates for macroscopic observations included: testicular tubular degeneration, epididymal hypospermia, atrophy of the seminal vesicles and prostate, thymic lymphoid atrophy and uterine atrophy. Recovery: At recovery necropsy, slight to mild hepatocellular hypertrophy was seen in 5/5 males and 2/5 females given CMC-544 at 50 ug/kg/week. Testicular tubular degeneration and epididymal hypospermia were still present at recovery at marked to severe average severity. Tubular intraluminal proteinaceous casts were still present, randomly distributed in the renal parenchyma. In males given CMC-544 at 50 ug/kg/week, pulmonary alveolar macrophages were still randomly scattered within the parenchyma following a 4-week recovery period. The incidence was 3/5 in males. Microscopic evidence of sciatic nerve axonal degeneration at a greater severity was seen in males and females previously given CMC-544 at 50 ug/kg/week. A similar observation was made in the cervical spinal cord segment examined and trigeminal nerve section. Additionally, axonal degeneration (dorsal and lateral funiculi) was seen in the lumbar spinal cord in both males and females previously given CMC-544 at 50ug/kg/week. [a] In this study, doses of inotuzumab ozogamicin expressed as calicheamicin equivalents on the basis of µg/kg of body weight were 0 (saline), 0 (antibody), 5, 15, or 50 µg/kg, and when expressed as dose equivalents of the G544 antibody on the basis of mg/kg of body weight were 0 (saline), 0.68 (antibody), 0.07, 0.21, or 0.69 mg/kg. Doses in mg/kg of body weight were converted to mg/m^2 of body surface area using a conversion factor of 5.9 for rat.			
RPT-65042/GLP 26 weeks	Sprague Dawley Rats/20/sex/group TK included (9males/group (5 for controls)). 5 males /group for ADA response analysis	0/0/0[e] 1/0.073/0.012 3/0.218/0.036 10/0.727/0.121 /IV once weekly	**NOAEL:** None
Mortality: There were 2 unscheduled deaths (controls) not related to treatment. Clinical signs: No treatment related clinical observations are reported			

Study ID /GLP/ Duration	Species/Sex/ Number/Group	Dose[a]/ Route	NOAEL/NOEL
Body weight: ♂♀:↓dose-dependently in all treated groups (slight to marked (24%)). Adverse at 10 µg/kg/week. Food consumption: ♂♀:↓ dose-dependently in all treated groups (slight to marked (12%)) Ophthalmoscopy: No effects observed. Haematology: 3: ♂↑NEUT(29%); 10: ↓RBC, HGB, HCT (5-13%). ↓RETI (14-55%). ↑ RDW (7%), MCV(2-7%), MCH (3-7%). ↑ NEUT (20-78%), MONO(28-80%) Clinical chemistry,: 3♂♀:↓TRIG(19-38%; 10:♂↑ALT(28-32%), AST(14-17%), AP (14%). ♀↑ AP (21-44%). Correlated to hepatocellular hypertrophy. ♂♀: ↓ALB (9-18%), ↑GLOB(10-19%), ↓TP(3-4%), ↑CHOL (55-95%),) Organ weights: ***Liver:*** Verum: Mean relative to body liver weights ↑(♂12-25%, ♀9-30%). This correlated macroscopically with enlargement of the liver and microscopically with hepatocellular hypertrophy. ***Testes:*** >1: ↓testes dose-dependently, 28-65% ($p<0.05$ in all treated groups). Correlated macroscopically with small testes and microscopically with testicular degeneration. 10: ↓Adrenals, brain, heart, kidneys, ovaries, pituitary, prostate, and thyroid secondary to decreased body weight. Gross pathology: ***Liver:*** >1: Enlarged liver (correlated with increased absolute and relative liver weights and microscopic hepatocellular hypertrophy). Multifocal, dark depressions, affecting single or multiple lobes (correlated microscopically with angiectasis). Focal or multifocal discoloration (correlated microscopically with adenoma or basophilic and eosinophilic foci). ***Testes:*** >1: Small testes and epididymis (correlated microscopically with tubular degeneration in the testes and hypospermia in the epididymides). ***Kidneys:*** >10♂♀: Cortical discoloration and granular surface (correlated microscopically with marked chronic progressive nephropathy. Histopathology: ***Liver:*** >3: Hepatocellular hypertrophy and karyomegaly (slight to moderate) typically associated with single cell apoptosis or degeneration. Karyomegaly consisted of enlargement of the liver cell nuclei with irregular shape and hyperchromatophilia. 10: Increased incidence and severity with lobular architecture effacement. Slight to moderate oval cell hyperplasia. Cholangiofibrosis (1♂ at 10). Angiectasis occurred dose-dependently. Mild fibrosis and hepatocellular vacuolation (slight and multifocal) >1: ♂Increased extramedullary hematopoiesis. ***Testes:*** >1: Testicular tubular degeneration dose-dependently (slight –marked). Dose-dependent (slight to marked) epididymal hypospermia and slight to moderate mammary gland atrophy (♂ not ♀). ***Kidneys:*** >3: Dose-dependent chronic progressive nephropathy (slight to marked) 10: Renal parenchyma entirely affected with prominent eosinophilic tubular casts, degenerative and inflammatory lesions. ***Lungs:***♀10: alveolar macrophages (slight) [e] In this study, doses of inotuzumab ozogamicin expressed as calicheamicin equivalents on the basis of µg/kg of body weight were 0, 1, 3, or 10 µg/kg, and when expressed as dose equivalents of the G544 antibody on the basis of mg/kg of body weight were 0, 0.012, 0.036, or 0.121 mg/kg. Doses in mg/kg of body weight were converted to mg/m^2 of body surface area using a conversion factor of 6 for rat. Inotuzumab ozogamicin in a formulation containing sucrose, polysorbate 80, Tris, and sodium chloride.			
RPT-46909/GLP 4 weeks + 4 week recovery	Cynomolgus monkey 3/sex/group (5/sex/group ctrl, 25) 2/sex/group for recovery TK included	0/0[a]/0[a] 0/0.34/4.08 2.5/0.03/0.36 8/0.11/1.32 25/0.35/4.20/IV once weekly	**NOAEL** None
Mortality: No mortalities. 11 monkeys received medical treatment (of which 8 received additional fruit). The other 3 medical treatments were pre-dosing or not related to test article administration. Clinical signs: All treated: Emesis, fecal alterations (liquid feces, mucoid feces, and/or soft feces), and decreased feces. ↑Incidence and frequency in HD at 25. Body weight: No effects. None of the monkeys lost more than 0.2 kg, and none of the monkeys gained more than 0.4 kg. Food consumption: >2.5: ↓ food consumption, most in animals receiving 25 µg/kg/week.			

Study ID /GLP/ Duration	Species/Sex/ Number/Group	Dose[a]/ Route	NOAEL/NOEL
Ophthalmoscopy: No compound- or vehicle-related ophthalmologic changes reported. Haematology: ≥8: ↓RBC, HGB, and HCT (9-31%). Toxicologically significant at 25 supported by the finding of decreased RETI (33% to 50%).≥8: ↓LYM (46-83%). 25:↓WBC (47-67%).↓PLT (40-93%, marked). Mild-moderate effects on PLT also at 2.5 (1♀) and 8 (3/sex): ↑FBGN (15-79% (slight-mild)) Clinical chemistry: ≥8: ↑GLOB (24-66%, mild-moderate). 25: ↓ALB (15-26%, slight-mild),↓INPH (10-40%), ↓BUN(37-65%), ↓T4(35-45%). ↑AST (108-332%, mild), ↑ALT (151-225%) Urinalysis: 25♀: hyposthenuric urine (spec. grav. <1.008). Organ weights: ≥2.5: ↓Ovary (21-50%), ↓Uterus (33-53%. Uterus weights correlated with atrophy at 25 µg/kg/week, and also related to ovarian effects. Gross pathology: No macroscopic findings at final or recovery necropsies. Male reproductive organs (testes, prostate, epididymides, and seminal vesicles) in most control and CMC-544 (inotuzumab ozogamicin)-treated monkeys at final necropsy and all monkeys at recovery necropsy were small in size due to the immaturity of these monkeys. Histopathology: ***Lymphoid:*** ≥2.5: thymus lymphoid atrophy (slight-marked). ≥8: bone marrow hypocellularity (slight), mandibular lymph node atrophy (slight-severe). ***Ovary:*** ≥8♀***:*** atrophy, slight-marked (absence/reduction of developing follicles). 25:Uterine atrophy (slight-mild). ***Testes:*** Immature in all but one monkey (spermatogenesis effect not possible to evaluate). HD: Sertoli cell changes (2/5). Recovery: 25:Uterus changes recovered completely. Bone marrow hypocellularity, lymphoid atrophy (mandibular and mesenteric lymph nodes, spleen, and thymus), and ovarian atrophy changes remained at recovery. [a] Dosage based on antibody (G544 protein). Calculations are based on theoretical values of 72 µg calicheamicin per mg protein, 1 mg of protein per vial, and a factor of 12 to convert dosages from mg/kg/week to mg/m^2/week			
RPT-65773 / GLP 26 weeks	Cynomolgus monkey 4/sex/group TK included	0/0/0[a] 0.5/0.072/0.006 1.5/0.216/0.018 5.0/0.732/0.061/IV once weekly	**NOAEL** ~~1.5 µg/kg~~ ND **LOAEL** 0.5
Mortality: 5: 3 monkeys (2♀, 1♂) were electively euthanized due to a moribund condition that was considered CMC-544(inotuzumab ozogamicin)-related. **Male I06983:** Was electively euthanized on day 37 at approximately 26 hrs after its last dose on day 36 (received total of 6 doses during study). Moribundity was attributed to a protein-losing glomerulonephritis. Glomerulonephritis with or without systemic vasculitis is uncommon in cynomolgus monkeys. It could have been spontaneous in this monkey; however because of the temporal association with the administration of CMC-544, it was attributed to CMC-544. **Female I06998:** Was electively euthanized on day 87 at approximately 50 hrs after its last dose on day 85 (received total of 13 doses during study). Mortality was attributed to CMC-544; however, the mechanism could not be determined. **Female I06999:** Was electively euthanized on day 142 at approximately 187 hrs after its last dose on day 134 (received total of 20 doses during study). Moribundity was attributed to CMC-544; however, the mechanism could not be determined. Clinical signs: 5 ♂: Swollen areas (periorbital, muzzle) in 3 surviving males from week 22 to termination. 6 animals received medical treatment. Only CMC-544 related treatment was fruit supplement. Body weight: There were no CMC-544-related effects on individual body weight in the animals that survived to scheduled study termination. Ophthalmoscopy: No CMC-544-related findings were noted during ophthalmic examinations. Food consumption: There were no CMC-544-related effects on individual food consumption in the animals that survived to scheduled study termination. Serum chemistry: ≥1.5: ♀↑Globulin (14-39%), ↑AST (63-302%); ≥1.5: ♂↑ AST (76-297%), 5:♂↑ALT (63-302%). 5:♂↑Globulin (9-13%), ↓Albumin (11-21%). Haematology: ≥1.5♂♀: ↓RBC (10-22%), ↓Hemoglobin (8-20%), ↓ Hematocrit (10-20%) , ↓Platelets (11-44%), ↑monocytes (49-214%). ≥5: ↓WBC (36-44%), ↓lymphocytes (-43-53%).			

Study ID /GLP/ Duration	Species/Sex/ Number/Group	Dose[a]/ Route	NOAEL/NOEL
Urinalysis: No effects Organ weights: ↓Testis dose-dependently (5µg/kg: p<0.05), ≥0.5♀: ↓ Brain (♂ only at 5), ≥1.5:↓Ovary, 5♂:↓ Liver/gall bladder Gross pathology: ≥0.5: Discolored and mottled liver (correlates with microscopic observations). 5.0: Small testis (1/3). Histopathology: ***Liver:*** ≥0.5♂♀: Dilatation of sinusoids with hepatocyte atrophy (minimal-moderate). ≥1.5♂♀: hepatocellular hypertrophy (minimal). 5♀(1/5): focus of hepatocellular alteration (focus of approximately a third the average size of a lobule comprised of slightly larger hepatocytes with abundant pale staining cytoplasm and a vesicular nucleus. There was no apparent compression of the adjacent liver parenchyma but few apoptotic cells were present near the edge. ***Thymus*** ↓cellularity dose-dependently, but incidence and severity increased at 5 µg/kg (♂). ***Spleen:*** 5♂: ↓cellularity of germinal centers/marginal zones (minimal-moderate) ***Mesenteric lymph nodes:*** ≥0: ↓cellularity of germinal centers (minimal-slight) ***Ovaries:*** 5: ↑Atrophy of ovaries (slight) [a] In this study, doses of inotuzumab ozogamicin expressed as calicheamicin equivalents on the basis of µg/kg of body weight were 0, 0.5, 1.5, or 5 µg/kg, and when expressed as dose equivalents of the G544 antibody on the basis of mg/kg of body weight were 0, 0.006, 0.018, or 0.061 mg/kg. Doses in mg/kg of body weight were converted to mg/m^2 of body surface area using a conversion factor of 12 for monkey.			

Genotoxicity

A summary of the results of the *in vitro* and *in vivo* GLP genotoxicity studies performed with inotuzumab ozogamicin is presented in Table 9.

Table 9. Summary of *in vitro* and *in vivo* GLP genotoxicity studies performed with inotuzumab ozogamicin

Type of test/study ID/GLP	Test system	Concentrations/ Concentration range/ Metabolising system	Results Positive/negative/equivocal
Bacterial Reverse Mutation Assay RPT-48308 Inotuzumab ozogamicin GLP	*S. typhimurium* TA98, TA100, TA1535, and TA1537. *E coli* WP2 *uvrA* pKM101	Initial assay: All strains ±S9: 0.073-7.3 µg (calicheamicin equivalents)/plate Confirmatory assay: All strains ±S9: 0.073-7.3 µg (calicheamicin equivalents)/plate	Adequate positive and negative controls produced expected effects. Initial assay: no substantial increases in revertant colony counts of any bacterial strain were observed in the presence or absence of S9 activation. Confirmatory assay: In the Confirmatory Mutagenicity Assay, no significant toxicity was evident up to the highest concentration of the test article, 7.3 µg per plate, in the presence and absence of S9 metabolic activation. In both the initial and confirmatory assays, no positive mutagenic response was observed. Therefore, CMC-544 (inotuzumab ozogamicin) for injection, 1.0 mg vial was concluded to be non-mutagenic in this assay. **Negative**
Bone marrow micronucleus study	CD-1 male mice, micronuclei in	First experiment 0, 28, 56, 122.5, 225, 450 µg/kg	Adequate positive and negative controls produced expected effects. A significant dose responsive increase in

RPT-47573 Inotuzumab ozogamicin GLP	bone marrow 4 /group (DRF study)	The Study Director determined that due to the bone marrow cytotoxicity observed in the high dose group (substantial cytotoxicity in the bone marrow at dosages of 225 and 450 ug/kg) and the high proportion of micronucleated PCEs from 0.28 to 122.5 ug/kg in the dose range finding study, that there was no need to complete the definitive study.	the frequency of micronucleated PCEs was observed in the analysis performed on coded slides from animals treated at 0, 28, 56, and 122.5 µg/kg calicheamicin equivalents, based on a trend test analysis ($p = 0.001$). Also, each dose group had a significantly higher proportion of micronucleated PCEs in comparisons with the vehicle control group ($p \leq 0.01$, one-tailed Dunnett's test). CMC-544 (inotuzumab ozogamicin)was positive for inducing micronucleated PCEs in the bone marrow of male mice in this study. **Cytotoxic at concentrations equal to or greater than 225 µg/mL (calicheamicin equivalents). High proportion of mPCEs at 0.28 to 122.5 ug/kg**
Bacterial Reverse Mutation Assay 15GR143 N-Ac-γ-calicheamicin DMH GLP	*S. typhimurium* TA98, TA100, TA1535, and TA1537. *E coli* WP2 *uvrA* pKM101	All strains ±S9: 0.0121-395 µg N-Ac-γ-calicheamicin DMH /plate	Adequate positive and negative controls produced expected effects. N-Ac-γ-calicheamicin DMH was positive for mutagenic activity in the E. coli strain WP2 uvrA pKM101, with and without metabolic activation, and negative for mutagenic activity in the S. typhimurium strains TA98, TA100, TA1535, and TA1537 with and without metabolic activation under the conditions of this assay. **Positive in the *E. coli* strain WP2 uvrA pKM101, with and without metabolic activation.**
In Vitro Micronucleus Assay In TK6 Cells 15GR142 N-Ac-γ-calicheamicin DMH GLP	TK6 cells during short (4-hour) and long (27-hour) incubations with or without an exogenous metabolic activation system	<u>First experiment</u> 0.00223 to 0.395 ng/mL <u>Second experiment</u> 0.00235 to 39.5 ng/mL	Adequate positive and negative controls produced expected effects. Optimal cytotoxicity was not observed with any treatment; therefore, a repeat micronucleus assay was conducted at concentrations ranging from 0.00235 to 39.5 ng/mL. Micronuclei were evaluated in 2000 cells per concentration. Statistically significant increases in the percent of micronucleated cells were observed at 0.198 ng/mL in the 4-hour treatment without metabolic activation, at 0.0417 and 0.0989 ng/mL in the 27-hour treatment without metabolic activation and at 0.395 and 0.618 ng/mL in the 4-hour treatment with metabolic activation. Thus N-Ac-γ-calicheamicin DMH was positive for inducing micronuclei *in vitro* in TK6 cells with and without metabolic activation under the conditions of this test system. **Positive**

Carcinogenicity

No carcinogenicity studies have been conducted with inotuzumab ozogamicin (see discussion on non-clinical aspects).

Reproduction Toxicity

Table 10. Summary of embryo-fetal developmental toxicity studies performed with inotuzumab ozogamicin in Sprague-Dawley rats and in NZW rabbits

Study type/ Study ID/GLP	**Species; Number Female/ group**	**Dose (µg/kg/day) /Route**	**Dosing period**	**NOAEL (µg/kg/day)**
Embryo-foetal developmental toxicity study DRF RPT-67396 GLP	Sprague Dawley rat 10♀/group	0, 0.5, 1.5, 5 IV/once daily	GD6-GD17 Cesarean sections were performed on all rats on GD 21.	Maternal: NA Fetal: NA
Mortality: None. Clinical signs: No remarkable clinical observations Body weight: ≥1.5:↓(18-91% , GD6-17); 5:↓(137% post-dosing period). Food consumption: 5:↓(25%) and ↓47% (post-dosing). Organ weights: ≥1.5:↓Gravid uterine weights (22-98%) Uterine and litter observations: ≥1.5: early resorptions dose-dependently. 5: complete litter loss (early resorptions) in all animals. Placental morphology: No effects Fetal malformations and variations: ≤1.5: No compound-related effects on fetal external development. HD not examined due to complete litter loss.				
Embryo-foetal developmental toxicity study RPT-68342 GLP	Sprague Dawley rat 25♀/group 9♀/group for TK	0, 0.15, 0.5,1.5 IV/once daily	GD6-GD17 Caesarean sections were performed on all rats on GD 21.	Maternal: 0.5 Fetal: 0.15
Mortality: None. Clinical signs: No remarkable clinical observations. Body weight: 1.5:↓(26% GD6-17) No effects post-dosing. Food consumption: 1.5:↓(11%) . No effects post-dosing. Organ weights: 1.5:↓Gravid uterine weights (19%). Correlated to decreased fetal weights. Placental morphology: No effects Uterine and litter observations: 1.5:↑resorptions (1.12 vs 0.44, but due to 15 early resorptions in one dam). Fetal malformations and variations: ≥0.5:↓fetal weights (5-22%); Reduced skeletal ossification dose-dependently (29-70%);1.5: short/thick humerus, misshapen scapula, and/or misshapen ulna (correlated to fetal growth retardation and decrease in skeletal ossification).				
Embryo-foetal developmental toxicity study DRF RPT-70227 GLP	New Zealand White rabbit 8♀/group	0, 0.1, 0.3, 1 or 3 IV/once daily	GD6-GD19 Cesarean sections were performed on all surviving rabbits on GD 29.	Maternal:NA Fetal: NA
Mortality: One doe given 3 µg/kg/day was found dead on GD 15. Antemortem observations were liquid feces containing red pigment and feces adhered to fur. Postmortem examination revealed red discoloration of the external walls of the vagina and colon, liquid feces in the colon, and irregular surface of the spleen. Although a cause of death could not be determined, a relationship to treatment with CMC-544 cannot be ruled out. A doe at 0.3 µg/kg/day was electively euthanized on GD 24 due to apparent trauma that occurred that day.				

Study type/ Study ID/GLP	Species; Number Female/ group	Dose (µg/kg/day) /Route	Dosing period	NOAEL (µg/kg/day)
Clinical signs: No remarkable clinical observations Body weight: ≥0.3:↓(13-39% GD6-19). Partial recovery in post-dosing period. Food consumption: 3:↓(23%) and ↓13% (post-dosing). Organ weights: 3:↓Gravid uterine weights (11%) Uterine and litter observations: 3: ↑early resorptions (2.29 vs 0.57 Ctrl).↑post-implantation loss (23.6 vs 11.6 Ctrl). ↓ viable fetuses (10%) Placental morphology: 3:↑incidence of discolored placentae. Fetal malformations and variations: 3:↓ fetal weight (21%). No remarkable external observations in any fetuses.				
Embryo-foetal developmental toxicity study RPT-72134 GLP	New Zealand White rabbit 20♀/group	0, 0.1, 0.3, 1 IV/once daily	GD6-GD19 Cesarean sections were performed on all surviving rabbits on GD 29.	Maternal:1 Fetal: 1
Mortality: None Clinical signs: An abortion at 0.1 µg/kg/day (female 25) was not considered CMC-544(inotuzumab ozogamicin)-related due to the singular incidence and lack of a dose response. One doe given 1 µg/kg/day (female 76) displayed total early interruption of pregnancy on the day of scheduled euthanasia. Body weight: 1:↓(46% GD12-15 then normalized) Food consumption: 1:↓(7%, and 9% post-dosing) Organ weights: No findings Uterine and litter observations: No findings Placental morphology: No findings Fetal malformations and variations: No CMC-544-related effects on fetal external, visceral or skeletal morphology.				

Toxicokinetic data

Toxicokinetic data from both studies pivotal embryo-fetal development study in rats (RPT-68342) and NZW rabbit (RPT-72134) are presented in Table 12.

Table 11 and Table 12.

Table 11. Toxicokinetic summary for inotuzumab ozogamicin pivotal embryo-fetal development study in rats (RPT-68342)

Dose[a] (µg/kg/day)	C_{5min} (µg/mL)	AUC_{0-24} (µg•hr/mL)	AUC_{0-24}/Dose
0.15	0.0286 ± 0.0011	0.364 ± 0.020	2.43 ± 0.13
0.5	0.145 ± 0.012	1.68 ± 0.13	3.36 ± 0.26[b]
1.5	0.533 ± 0.026	6.90 ± 0.42	4.60 ± 0.28[c]

a. Based on calicheamicin equivalents (82.5 µg calicheamicin/mg protein)
b. Value is significantly different than corresponding values at 0.15 or 1.5 µg/kg/day
c. Value is significantly greater than corresponding values at 0.15 or 0.5 µg/kg/day

Table 12. Toxicokinetic summary for inotuzumab ozogamicin pivotal embryo-fetal development study in NZW rabbit (RPT-72134)

Analyte	Dosage[a] (µg/kg/day)	AUC_{0-24} (ng•hr/mL)	AUC_{0-24}/Dose
CMC-544	0.1	1349 ± 47	13485 ± 470
	0.3	4187 ± 254	13957 ± 848
	1	13264 ± 872	13264 ± 872
Total Calicheamicin	0.1	106 ± 10	1056 ± 103
	0.3	452 ± 25	1505 ± 82[b]
	1	1052 ± 34	1052 ± 34

a. Calicheamicin equivalents (82.5 µg calicheamicin/mg protein)
b. Value significantly different ($p < 0.05$) than corresponding value at 0.1 and 1 µg/kg/day dosage.

Local Tolerance

A separate local tolerance study was not conducted with inotuzumab ozogamicin. Instead, local injection sites were evaluated macroscopically and microscopically in a single-dose toxicity study in rats and in the 4- and 26-week toxicity studies in rats and monkeys. No inotuzumab ozogamicin-related findings were observed at the injection sites in animals in any of these studies.

Other Toxicity Studies

Inotuzumab ozogamicin did not show an *in vitro* potential for inducing haemolysis or methemoglobin formation in rats, monkeys, or humans (Report RPT-46353).

There were no adverse clinical signs or effects on body weight in monkeys administered Inotuzumab ozogamicin with Neumega (rhuIL-11). A combination study with inotuzumab ozogamicin and Numega (rhIL-11) suggested that animals given Neumega following inotuzumab ozogamicin have a slightly more rapid resolution of the (induced) thrombocytopenia (Report RPT-63930).

G544 antibody specifically stained cryosections of the positive control human tonsil (follicular center and mantle lymphocytes, and intra-epithelial [migrating] or submucosal locations). G544 did not stain lymphocytes in the interfollicular areas of human tonsil (putative T-cells) and the negative control IgG4 antibody did not specifically interact with any tonsillar tissues. There was no specific G544 binding observed in any rhesus monkey tissue examined (Report RPT-46813).

G544 antibody specifically stained cryosections of the positive control human tonsil (follicular center and mantle lymphocytes, and intra-epithelial [migrating] or submucosal locations). G544 did not stain lymphocytes in the interfollicular areas of human tonsil (putative T-cells) and the negative control IgG4 antibody did not specifically interact with any tonsillar tissues. G544-stained human lymphocytes were observed in the follicular centers and mantle regions of the lymph node and spleen, and G544 also stained rare to very rare lymphocytes in the interstitium in nonlymphoid tissues such as kidney, liver, and striated

skeletal muscle. G544 did not stain human bone marrow, blood vessels (endothelium), or small intestine from any donor examined. There was no G544-specific staining of any monkey, dog, rabbit, rat, or mouse tissue examined (Report RPT-46814).

Examination of the panel of human test tissues stained with the G544 antibody revealed staining of lymphocytes in lymph node (follicular), spleen (follicular and mantle; red pulp), tonsil (follicular and mantle), GALT, mononuclear cell infiltrates, and blood smears. Staining was localized to the membrane and cytoplasm. In most, but not all cases, staining was present at both concentrations of the G544 antibody (Report RPT-63271).

No studies on immunogenicity have been performed by the applicant. However, immunogenicity of inotuzumab ozogamicin was assessed in 4- and 26-week repeat-dose toxicity studies in rats and monkeys by measuring the levels of anti-drug antibodies (ADA) in satellite animals (rats) or main study animals (monkeys). Two of 20 satellite rats (10%) administered inotuzumab ozogamicin (1 animal given 4.07 mg/m^2/week) or G544 antibody (1 animal) for 4 weeks tested positive for ADA 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 designated for ADA analysis and administered inotuzumab ozogamicin for 26 weeks tested positive for ADA at one or more timepoints after the initiation of dosing (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, ADA was not detected in any animals after administration of inotuzumab ozogamicin or the G544 antibody. Samples from monkeys given 0.216 mg/m^2/week inotuzumab ozogamicin for 26 weeks had detectable drug concentrations at the last time point of sample collection which may have hindered the detection of an ADA response.

PF-06647259, a nonbinding calicheamicin conjugate, induced thrombocytopenia and liver microvascular injury in cynomolgus monkeys. Characterization of liver microscopic findings showed loss of SECs associated with platelet sequestration on Day 3 followed by phenotypic alterations of recovered SECs (CD34 overexpression indicative of sinusoidal capillarization) and parenchymal remodelling consisting mostly of sinusoidal dilation and/or hepatocellular atrophy on Day 63. Evaluation of platelet counts showed acute reversible platelet decreases during the 1st cycle secondary to liver SEC injury and prolonged platelet decreases during subsequent cycles of uncertain exact pathogenesis. Serum HA levels were increased in test article-dosed animals and correlated well with AST and liver microscopic changes, suggesting that HA could be a sensitive mechanism-based diagnostic marker of liver microvascular injury (Report 14GR346).

The toxicity of N-Ac-γ-calicheamicin DMH (released unconjugated calicheamicin) was evaluated in mice, rats and/or dogs after single- or repeat-dose administration. No new important target organ toxicities were observed with N-Ac-γ-calicheamicin DMH administration versus those reported for inotuzumab ozogamicin. Nevertheless, there were differences in the severity and/or incidence of the toxicities between the two derivatives which perhaps can be attributed to differences in ADME properties (Reports MIRACL-24627, MIRACL-26628, MIRACL-26629, MIRACL-26630, MIRACL-26707).

In studies with N-Ac-Epsilon-Calicheamicin in rats, mean heart weights were slightly decreased, and mean thymus weights were slightly increased. The organ weight changes were not associated with any macroscopic or microscopic findings. There were no N-Ac-Epsilon-Calicheamicin-related findings presented in the dog. Thus, it can be concluded that the ε-form of calicheamicin seems to be less toxic than the γ-form (Reports MIRACL-25706 and MIRACL-25707).

2.3.5. Ecotoxicity/environmental risk assessment

Table 13. Summary of main study results

Substance (INN/Invented Name): inotuzumab ozogamicin			
CAS-number (if available): 635715-01-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	See table above conjugated calicheamicin log D at pH 5, 7.4 and 9 are 1.65,2.32 and 1.87	Potential PBT No
PBT-statement :	The compound is not considered as PBT		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	2.4 x 10^{-7}	μg/L	> 0.01 threshold No
Other concerns (e.g. chemical class)	N/A	-	(Y/N)

2.3.6. Discussion on non-clinical aspects

Inotuzumab ozogamicin is an ADC composed of a CD22 directed monoclonal antibody that is covalently linked to N acetyl gamma calicheamicin dimethylhydrazide. Inotuzumab is a humanised immunoglobulin class G subtype 4 (IgG4) antibody that specifically recognises human CD22. The small molecule, N acetyl gamma calicheamicin, is a cytotoxic product. N acetyl gamma calicheamicin is covalently attached to the antibody via an acid-cleavable linker. Nonclinical data suggest that the anticancer activity of BESPONSA is due to the binding of the ADC to CD22 expressing tumour cells, followed by internalisation of the ADC-CD22 complex, and the intracellular release of N acetyl gamma calicheamicin dimethylhydrazide via hydrolytic cleavage of the linker. Activation of N acetyl gamma calicheamicin dimethylhydrazide induces double-stranded DNA breaks, subsequently inducing cell cycle arrest and apoptotic cell death (SmPC section 5.1).

In vivo, inotuzumab ozogamicin exhibited dose-dependent regression of subcutaneous B-cell ALL and lymphoma xenografts. Sustained tumour regression was achieved in inotuzumab ozogamicin treated tumours compared to controls that included G544 antibody, unconjugated N-Ac-γ-calicheamicin DMH, or gemtuzumab ozogamicin. B-cell lymphoma xenografts treated with rituximab or chemotherapy had shorter duration responses, but relapsed tumours regressed upon further treatment with inotuzumab ozogamicin. In a disseminated model of ALL, treatment with inotuzumab ozogamicin effectively suppressed tumour growth in mice, leading to 100% survival and strongly inhibited the engraftment of human CD45-positive leukemic cells in mice with disseminated disease.

Inotuzumab ozogamicin is currently intended as single agent treatment for ALL. Any concomitant medicines (i.e. steroids, anti–infectives etc.) that may be used at the time of treatment were administered during the clinical trials and thus specific non clinical studies are not considered warranted. It is however not anticipated that there will be any interaction with any routine medications that might be taken by ALL patients, as such medication would not be expected to have a significant effect on either CD22 binding or the DNA targeting of inotuzumab ozogamicin. The lack of formal pharmacodynamic interaction studies with common concomitant drugs, with the exception of the combination with chemotherapy above, is accepted.

Hydrolytic release of N-Ac-γ-calicheamicin DMH from inotuzumab ozogamicin in circulation was limited. Plasma protein binding of N-Ac-γ-calicheamicin DMH was high in mouse, rat, rabbit, monkey, and human plasma.

Distribution of inotuzumab ozogamicin into tissues of rats was limited. A metabolism study conducted in the rat showed that most of the plasma radioactivity was associated with protein(s). In rats, N-Ac-γ-calicheamicin DMH was extensively metabolised following release from inotuzumab ozogamicin and the predominant metabolic pathway was reduction (at the disulfide moiety) resulting in formation of N-Ac-ε-calicheamicin (M16) and tetrasaccharide metabolites (M1, M5) via a putative reductive deglycosylation mechanism. In serum from patients administered inotuzumab ozogamicin, the only metabolite detected was N-Ac-γ-calicheamicin DMH. All metabolites detected in patient samples were also observed in rats. *In vitro* studies showed that the metabolism of N-Ac-γ-calicheamicin DMH occurs primarily via non-enzymatic reduction.

Ex vivo, inotuzumab ozogamicin showed bioconjugative transformation in plasma, with the major product identified as an apparent adduct formed via a putative disulfide exchange reaction mechanism between N-Ac-γ-calicheamicin and an unidentified high MW protein. Following IV administration to rats, the major route of excretion of drug-related radioactivity was via faeces, secondary to biliary elimination.

In animals, the primary target organs included the liver, bone marrow and lymphoid organs with associated haematological changes, kidney and nervous system (SmPC section 5.3). Effects in the liver included adenomas, basophilic and eosinophilic foci, angiectasis and sinusoidal dilation, oval cell hyperplasia and cholangiofibrosis, hepatocellular hypertrophy, karyomegaly, hepatocellular vacuolation, fibrosis and increased extramedullary haemopoiesis.

In non-clinical studies, cranial and peripheral sensory neuropathy was target independent and likely a primary cytotoxic effect of calicheamicin on cell bodies in ganglia with subsequent axonal degeneration. Neurotoxicity has been categorized as a potential risk (see Risk Management Plan).

Animal studies demonstrated chronic progressive nephropathy (rats) and glomerulonephritis (1 monkey).. The former is a common spontaneous finding in rats but the latter in monkeys, although low incidence, is unusual and a potential link with the compound cannot be dismissed. Nephrotoxicity has been categorized as a potential risk (see Risk Management Plan).

Other observed changes included male and female reproductive organ effects and preneoplastic and neoplastic liver lesions (SmPC section 5.3). Effects in reproductive organs were tubular degeneration in the testes, hypospermia in the epididymides, atrophy in the male mammary gland, decreased colloid in the seminal vesicles as well as effects on female organs.

Most effects were reversible to partially reversible except for effects in the liver and nervous system. The relevance of the irreversible animal findings to humans is uncertain (SmPC section 5.3).

The observation of inotuzumab ozogamicin-related effects in multiple target organs in 2 non-clinical species is consistent with non-specific cytotoxicity attributable to the lack of tissue-specific binding of inotuzumab ozogamicin in either species, since the antibody component of inotuzumab ozogamicin targets the human CD22 antigen and does not cross-react with the CD22 antigen expressed in either rats or monkeys.

Inotuzumab ozogamicin was clastogenic in vivo in the bone marrow of male mice. This is consistent with the known induction of DNA breaks by calicheamicin and other enediyne antitumour antibiotics. Inotuzumab ozogamicin was not mutagenic in an in vitro bacterial reverse mutation (Ames) assay when tested up to the maximum feasible dose (SmPC section 5.3).

Formal carcinogenicity studies have not been conducted with inotuzumab ozogamicin. In line with current guidance (i.e. ICH S9), the lack of dedicated carcinogenicity bioassays is acceptable.

In toxicity studies, rats developed oval cell hyperplasia, altered hepatocellular foci, and hepatocellular adenomas in the liver at approximately 0.3 times the human clinical exposure based on AUC. In 1 monkey, a focus of hepatocellular alteration was detected at approximately 3.1 times the human clinical exposure based on AUC at the end of the 26 week dosing period. The relevance of these animal findings to humans is uncertain (SmPC section 5.3). The observed liver toxicity is consistent with the mechanism of action of calicheamicin and considered a cytotoxic effect.

Administration of inotuzumab ozogamicin to female rats at the maternally toxic dose (approximately 2.3 times the human clinical exposure based on AUC) prior to mating and during the first week of gestation resulted in embryo-foetal toxicity, including increased resorptions and decreased viable embryos. The maternally toxic dose (approximately 2.3 times the human clinical exposure based on AUC) also resulted in foetal growth retardation, including decreased foetal weights and delayed skeletal ossification. Slight foetal growth retardation in rats also occurred at approximately 0.4 times the human clinical exposure based on AUC (SmPC section 5.3)

Inotuzumab ozogamicin is considered to have the potential to impair reproductive function and fertility in men and women based on nonclinical findings. In repeat dose toxicity studies in rats and monkeys, female reproductive findings included atrophy of ovaries, uterus, vagina, and mammary gland. The no observed adverse effect level (NOAEL) for the effects on female reproductive organs in rats and monkeys was approximately 2.2 and 3.1 times the human clinical exposure based on AUC, respectively. In repeat dose toxicity studies in rats, male reproductive findings included testicular degeneration, associated with hypospermia, and prostatic and seminal vesicle atrophy. The NOAEL was not identified for the effects on male reproductive organs, which were observed at approximately 0.3 times the human clinical exposure based on AUC (SmPC section 5.3).

Women of childbearing potential should avoid becoming pregnant while receiving inotuzumab ozogamicin. Women should be advised to use effective contraception during treatment with inotuzumab ozogamicin and for at least 8 months after the last dose. Men with female partners of childbearing potential should use effective contraception during treatment with inotuzumab ozogamicin and for at least 5 months after the last dose (SmPC, section 4.6).

Inotuzumab ozogamicin must not be used during pregnancy unless the potential benefit to the mother outweighs the potential risks to the foetus. Pregnant women, or patients becoming pregnant while receiving inotuzumab ozogamicin, or treated male patients as partners of pregnant women, must be apprised of the potential hazard to the fetus (SmPC, section 4.6).

There are no data on the presence of inotuzumab ozogamicin or its metabolites in human milk, the effects on the breast-fed child, or the effects on milk production. Because of the potential for adverse reactions in breast-fed children, women must not breast-feed during treatment with inotuzumab ozogamicin and for at least 2 months after the final dose (SmPC, section 4.6).

In a combination toxicity study with Neumega (rhuIL-11) in monkeys, a slightly more rapid resolution of induced thrombocytopenia was seen with Neumega compared to inotuzumab ozogamicin alone.

An *in vitro* blood compatibility study showed no potential for erythrocyte lysis in rats, monkeys or humans.

In tissue cross-reactivity studies, unconjugated antibody did not show specific staining in any of the selected non-human tissues. In the cross-reactivity study in human tissues, inotuzumab ozogamicin reacted with potential CD22-expressing cells in the tissues evaluated. The staining appeared to be consistent with distribution of CD22 reported in the literature.

The PECsurfacewater was calculated to 2.4x10-7, which is below the cation level 0,01. Therefore no further environmental testing is required for inotuzumab ozogamicin. Accordingly, the introduction of inotuzumab ozogamicin is not expected to result in an increased environmental risk.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical documentation submitted for inotuzumab ozogamicin was considered adequate. The relevant information has been included in the SmPC (sections 4.6, 5.1, 5.3).

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study No. Study Status	**Title**	**Dosage (n)**	**Total No. Patients Enrolled (Treated with Inotuzumab Ozogamicin)**
Patients with relapsed or refractory ALL who received single-agent inotuzumab ozogamicin			
B1931022 (pivotal Phase 3 study) Ongoing	Open-label, randomized Phase 3 study of inotuzumab ozogamicin compared to a defined Investigator's choice in adults with relapsed or refractory CD22-positive ALL	Arm 1 (n=164 ITT) (164 for safety analyses and 109 initially randomized for efficacy analyses of CR/CRi), inotuzumab ozogamicin: 1.8 mg/m2/21-28-day cycle (0.8 mg/m2 on Day 1 and 0.5 mg/m2 on Days 8 and 15); subsequent reduction to 1.5 mg/m2/28-day cycle (0.5 mg/m2 on Days 1, 8, and 15) for patients achieving remission Arm 2 (n=162 ITT) (143 for safety analyses and 109 initially randomized for efficacy analyses of CR/CRi), Investigator's choice of chemotherapy: FLAG, MXN/Ara-C or HIDAC	326 (164)

Study No. Study Status	Title	Dosage (n)	Total No. Patients Enrolled (Treated with Inotuzumab Ozogamicin)
B1931010 (supportive Phase 1/2 study) Completed	Open-label, Phase 1/2 study of inotuzumab ozogamicin in subjects with relapsed or refractory CD22-positive ALL	Phase 1 (n=37), inotuzumab ozogamicin: 1.2 mg/m2/28-day cycle (n=3), 1.6 mg/m2/28-day cycle (n=12) or 1.8 mg/m2/28-day cycle (n=9) Dose-expansion: 1.8 mg/m2/28-day cycle (n=13) Phase 2 (n=35), inotuzumab ozogamicin: 1.8 mg/m2/28-day cycle (0.8 mg/m2 on Day 1 and 0.5 mg/m2 on Days 8 and 15). Subsequent dose reduction to 1.6 mg/m2/28-day cycle (0.8 mg/m2 on Day 1 and 0.4 mg/m2 on Days 8 and 15) for patients achieving remission (limited to Phase 2 + Dose-expansion; n=48)	72 (72)

2.4.2. Pharmacokinetics

The population PK analysis included pooled PK data from two studies in patients with relapsed or refractory ALL (B1931010 and B1931022) and 9 studies in patients with relapsed or refractory NHL (B1931001, B1931002, B1931003, B1931004, B1931005, B1931006, B1931007, B1931008 and B1931016).

Absorption

Inotuzumab ozogamicin is administered intravenously, therefore absorption is not applicable.

Distribution

In vitro, the binding of the N-acetyl-gamma-calicheamicin dimethylhydrazide to human plasma proteins is approximately 97%. In vitro, N-acetyl-gamma-calicheamicin dimethylhydrazide is a substrate of P glycoprotein (P-gp). In humans, the total volume of distribution of inotuzumab ozogamicin was approximately 12 L (SmPC, section 5.2).

In vitro, N-acetyl-gamma-calicheamicin dimethylhydrazide was primarily metabolised via nonenzymatic reduction. In humans, serum N-acetyl-gamma-calicheamicin dimethylhydrazide levels were typically below the limit of quantitation (50 pg/mL) (SmPC, section 5.2).

Elimination

Inotuzumab ozogamicin pharmacokinetics were well characterised by a 2-compartment model with linear and time-dependent clearance components. In 234 patients with relapsed or refractory ALL, the clearance of inotuzumab ozogamicin at steady state was 0.0333 L/h, and the terminal elimination half life (t½) at the end of Cycle 4 was approximately 12.3 days. Following administration of multiple doses, a 5.3 times accumulation of inotuzumab ozogamicin was observed between Cycles 1 and 4 (SmPC, section 5.2).

Dose proportionality and time dependencies

Dose proportionality

The CL or CL/f of inotuzumab ozogamicin, total calicheamicin, and total antibody following a single dose of inotuzumab ozogamicin ranging from 1.3 to 2.4 mg/m^2 is shown in Table 14. The CL or CL/f was not estimable at the 0.4 and 0.8 mg/m^2 dose levels.

Table 14 Pharmacokinetic parameters following administration of a single dose of 1.3 to 2.4 mg/m^2 of inotuzumab ozogamicin in patients with relapsed or refractory NHL (Studies B1931002 and B1931016)

Dose (mg/m^2)	CL (L/hr) Inotuzumab Ozogamicin	CL/f (L/hr) Total Calicheamicin	CL/f (L/hr) Total Antibody
B1931002			
1.34	. (. [0])	0.563 (. [1])	0.0958 (38[3])
1.8	. (. [0])	1.92 (93[2])	0.101 (37[3])
1.8	0.266 (26 [8])	1.53 (91[17])	0.0946 (65[20])
2.4	. (. [0])	2.34 (46[2])	0.301 (65[2])
B1931016			
1.3	. (. [0])	2.35 (58[3])	0.21 (35[3])
1.8	0.24(40[6])	1.61 (54[6])	0.25 (101[9])

The CL or CL/f of inotuzumab ozogamicin, total calicheamicin and total antibody following multiple doses of 0.8 to 2.4 q3w inotuzumab ozogamicin is shown in Table 15. The CL or CL/f was not estimable at the 0.4 mg/m^2 dose level.

Table 15 Summary statistics of clearance following multiple doses of 0.4 to 2.4 mg/m^2 inotuzumab ozogamicin q3w in patients with relapsed or refractory NHL (B1931002)

Dose (mg/m^2)	Inotuzumab Ozogamicin CL (L/hr)	Total Calicheamicin CL/f (L/hr)	Total Antibody CL/f (L/hr)
0.8 q3w	. (. [0])	. (. [0])	0.0926 (. [1])
1.34 q3w	0.288 (. [1])	0.386 (38 [3])	0.0598 (24 [4])
1.8 q3w	. (. [0])	0.565 (38 [2])	0.0574 (24 [3])
2.4 q3w	0.197 (72 [2])	0.344 (. [1])	0.0547 (46 [2])

Time dependencies

Based on the simulation from population pharmacokinetic analysis, the mean half-life of inotuzumab ozogamicin (estimated from the beta $t_{1/2}$) at steady state was 12.3 days. With the recommended dosing regimen of inotuzumab ozogamicin at a total dose of 1.8 mg/m^2 per cycle (Day 1: 0.8 mg/m^2, Days 8 and 15: 0.5 mg/m^2), the geometric mean ratio (90% CI) for accumulation in patients with ALL was 5.30 (5.12, 5.47).

Table 16.Summary of AUC Ratios (Multiple/Single Dose) for Inotuzumab Ozogamicin in Patients With Relapsed or Refractory Acute Lymphoblastic Leukemia

Geometric Mean Ratios (90% CI)		
$AUC_{cycle4}/AUC_{cycle1}$	AUC_{tau} on C4D1/ AUC_{tau} on C1D1	AUC_{tau} on C4D1/ AUC_{inf} on C1D1
5.30 (5.12, 5.47)	7.32 (7.11, 7.54)	5.90 (5.67, 6.15)

CI=confidence interval; Std Dev=standard deviation; AUC_{inf}=area under the concentration-time curve from 0 to infinity; AUC_{cycle1}=area under the concentration-time curve during first cycle; AUC_{cycle4}=area under the concentration-time curve during fourth cycle; AUC_{tau}=area under the concentration-time curve within a dosing interval; C1D1=Cycle 1 Day 1; C4D1=Cycle 4 Day 1.

Special populations

The effect of renal function on the inotuzumab CL was evaluated using baseline creatinine clearance (BCCL) in a population pharmacokinetic analysis.

Table 17 Inotuzumab Ozogamicin Clearance and Baseline Creatinine Clearance by Renal Function

Severity (BCCL)	N	BCCL (mL/min)		Clearance (L/h)[a]	
		Median (Range)	Mean ± Std Dev	Median (Range)	Mean ± Std Dev
Acute Lymphoblastic Leukemia					
Normal (≥90)	184	134 (90.0-368)	147 ± 48.9	0.0394 (0.0151-1.91)	0.104± 0.206
Mild (60-89)	32	79.2 (63.0-89.7)	78.9 ± 7.74	0.0403 (0.0143-0.208)	0.0587 ± 0.0506
Moderate (30-59)	17	49.7 (36.3-59.3)	49.6 ± 7.51	0.0308 (0.0145-0.951)	0.117 ± 0.224
Severe (15-29)	1	29.4 (NA)	29.4 ± NA	0.0273 (NA)	0.0273 ± NA
Overall	**234**	**122 (29.4-368)**	**130 ± 54.7**	**0.0394 (0.0143-1.91)**	**0.098 ± 0.193**
Non-Hodgkin Lymphoma					
Normal (≥90)	218	114 (90.5-264)	120 ± 28.6	0.132 (0.0284-1.76)	0.160 ± 0.162
Mild (60-89)	205	74.6 (60.1-89.9)	74.9 ± 8.37	0.104 (0.0455-0.711)	0.130 ± 0.0953
Moderate (30-59)	105	48.6 (32.3-59.7)	47.8 ± 7.36	0.0954 (0.0414-1.90)	0.126 ± 0.183
Severe (15-29)	3	23.7 (18.2-24.3)	22.1 ± 3.38	0.0825 (0.0487-0.0827)	0.0713 ± 0.0196
Overall	**531**	**81.8 (18.2-264)**	**87.9 ± 34.8**	**0.111 (0.0284-1.90)**	**0.141 ± 0.145**
Acute Lymphoblastic Leukemia Plus Non-Hodgkin Lymphoma (Adjusted Clearance)[b]					
Normal (≥90)	402	120 (90.0-368)	133 ± 41.4	0.0405 (0.00836-1.91)	0.0943 ± 0.178
Mild (60-89)	237	74.9 (60.1-89.9)	75.4 ± 8.39	0.0353 (0.0134-0.618)	0.0804 ± 0.0984
Moderate (30-59)	122	48.9 (32.3-59.7)	48.1 ± 7.38	0.0329 (0.0122-2.00)	0.114 ± 0.259
Severe (15-29)	4	24.0 (18.2-29.4)	23.9 ± 4.59	0.0751 (0.0218-0.149)	0.0801 ± 0.0651
Overall	**765**	**93.1 (18.2-368)**	**101 ± 46.2**	**0.0394 (0.00836-2.00)**	**0.0930 ± 0.174**

NA=not applicable; N=number of patients; Std Dev=standard deviation; ALL=acute lymphoblastic leukaemia; NHL=non-Hodgkin lymphoma; BCCL=baseline creatinine clearance; CL1=linear clearance; CL2=clearance associated with time-dependent clearance; kdes=decay coefficient associated with time-dependent clearance.
a. Total clearance (CL) calculated as CL=CL1+CLt, where CLt=CL2•e (-kdes•Time). CL was obtained at the last time point of the last cycle for each patient.
b. In order to summarize the ALL and NHL patients together, the total clearance (CL) was adjusted for NHL patients to include the covariate effects from ALL patients.

The impact of hepatic function on inotuzumab ozogamicin CL was evaluated using the hepatic function defined by National Cancer Institute Organ Dysfunction Working Group (NCI ODWG) (normal [A], mild [B1], mild [B2], moderate [C], and severe [D]) as a categorical covariate and baseline laboratory values of BALT, BAST, and BBIL as continuous covariates in a population pharmacokinetic analysis.

Table 18. Inotuzumab Ozogamicin Clearance by Hepatic Impairment

NCI ODWG Criteria for Hepatic Impairment	Severity	N	Clearance (L/h)[a]	
			Median (Range)	Mean ± Std Dev
Acute Lymphoblastic Leukemia				
A	Normal	167	0.0363 (0.0143-1.91)	0.0893 ± 0.187
B1	Mild	58	0.0520 (0.0151-1.48)	0.131 ± 0.222
B2	Mild	8	0.0382 (0.0233-0.152)	0.0501 ± 0.0424
C	Moderate	1	0.0238 (NA)	0.0238 ± NA
D	Severe	0	NA	NA
	Overall	**234**	**0.0394 (0.0143-1.91)**	**0.098 ± 0.193**
Non-Hodgkin Lymphoma				
A	Normal	444	0.109 (0.0284-1.90)	0.138 ± 0.140
B1	Mild	75	0.129 (0.0487-1.27)	0.166 ± 0.182
B2	Mild	9	0.0926 (0.0694-0.136)	0.0943 ± 0.0224
C	Moderate	2	0.117 (0.0769-0.157)	0.117 ± 0.0568
D	Severe	1	0.155 (NA)	0.155 ± NA
	Overall	**531**	**0.111 (0.0284-1.90)**	**0.141 ± 0.145**
Acute Lymphoblastic Leukemia Plus Non-Hodgkin Lymphoma (Adjusted Clearance)[b]				
A	Normal	611	0.0373 (0.00836-2.00)	0.0873± 0.173
B1	Mild	133	0.0514 (0.0151-1.48)	0.126 ± 0.189
B2	Mild	17	0.0307 (0.0204-0.166)	0.0456 ± 0.0437
C	Moderate	3	0.0238 (0.0227-0.0463)	0.0309 ± 0.0133
D	Severe	1	0.222 (NA)	0.222 ± NA
	Overall	**765**	**0.0394 (0.00836-2.00)**	**0.0930 ± 0.174**

NA=not applicable; N=number of patients; Std Dev=standard deviation; ALL=acute lymphoblastic leukaemia; NHL=non-Hodgkin lymphoma; NCI ODWG=National Cancer Institute Organ Dysfunction Working Group; CL1=linear clearance; CL2=clearance associated with time-dependent clearance; kdes=decay coefficient associated with time-dependent clearance.
a. Total clearance (CL) calculated as CL=CL1+CLt, where CLt=CL2•e (-kdes•Time). CL was obtained at the last time point of the last cycle for each patient.
b. In order to summarize the ALL and NHL patients together, the total clearance (CL) was adjusted for NHL patients to include the covariate effects from the ALL patients.

In the population PK analysis 458 patients were males and 307 females. Since gender was highly correlated with baseline body surface area (BBSA), it was not tested in the GAM or SCM. The incorporation of BBSA as covariate in the final model corrected any previous trends with respect to gender.

In the population PK analysis 534 patients were Caucasian, 20 were Black, 155 were Asian (including 101 Japanese), 53 'Other' and 3 unknown. In the graphical plots, Asian patients tended to have lower CL1, CL2 and V1 relative to non-Asian patients (Caucasians, Blacks and Other grouped together). During the GAM analysis, the effect of Asian ethnicity (Asian [including Japanese] versus non-Asian) on PK parameters CL1, CL2, V1 and k_{des} was not significant (based on AIC criteria) and hence, was not further tested for statistical significance in the SCM.

Although Asian ethnicity was not tested in the SCM analysis, the ETAs on the PK parameters were corrected for Asian ethnicity due the effect of BBSA on CL1, CL2 and V1 in the final model and the correlation between Asian ethnicity and BBSA. BBSA in Asians tended to be lower compared to non-Asians, approximately 12% difference in the medians. The BBSA medians (ranges) for Asians (including Japanese) and non-Asians were 1.66 m^2 (1.13-2.08 m^2) and 1.90 m^2 (1.27-2.81 m^2), respectively.

The PK trials in elderly population are presented in Table 19.

Table 19. PK trials in elderly population

PK Trials	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Acute Lymphoblastic Leukaemia: Study B1931022 + Study B1931010	32/234	9/234	0/234
Non-Hodgkin's Lymphoma: Studies B1931001, B1931002, B1931003, B1931004, B1931005, B1931006, B1931007, B1931008, and B19310016	182/531	88/531	3/531
Acute Lymphoblastic Leukaemia + Non-Hodgkin's Lymphoma: Studies B1931001, B1931002, B1931003, B1931004, B1931005, B1931006, B1931007, B1931008, B1931010, B19310016, and B1931022	214/765	97/765	3/765

The median BBSA in the population PK analysis was 1.84 m^2 with 10th and 90th percentile BSAs of 1.55 m^2 and 2.21 m^2, respectively.

Increasing BBSA was correlated with an increase in CL1, CL2 and V1. In order to evaluate the magnitude of the effect of BBSA on inotuzumab ozogamicin PK, CL1, CL2 and V1 were calculated at extreme values of BBSA (10th and 90th percentile in the analysis population) and compared with the typical values at a median baseline BBSA of 1.84 m^2. The magnitudes of the effects of BBSA were as follows:

- Relative to the CL1 typical value of 0.113 L/h for a BBSA of 1.84 m^2, CL1 decreased by 23.4% for a BBSA of 1.55 m2 and increased by 32.8 % for a BBSA of 2.21 m^2.
- Relative to the CL2 typical value of 0.368 L/h for a BBSA of 1.84 m^2, CL2 decreased by 24.8% for a BBSA of 1.55 m2 and increased by 35.3% for a BBSA of 2.21 m^2.
- Relative to the V1 typical value of 6.70 L for a BBSA of 1.84 m^2, V1 decreased by 22.7% for a BBSA of 1.55 m2 and increased by 28.8% for a BBSA of 2.21 m^2.

Pharmacokinetic interaction studies

In vitro

The potential for inotuzumab ozogamicin to reversibly inhibit the catalytic activity of 8 CYP enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5) was investigated in human liver microsomes (HLM). Inotuzumab ozogamicin showedlittle or no inhibition for the CYP enzyme activities tested, with IC50 >10 µM (highest concentration tested) and an estimated inhibition constant (Ki) of >5 µM.

Assessment of DDI potential with inotuzumab ozogamicin for reversible CYP inhibition, based on the IC50 values of >10 µM determined from in vitro studies and the mean steady-state (total) Cmax of 308 ng/mL (00192µM) following multiple dose administration of 1.8 mg/m^2 of inotuzumab ozogamicin to humans, indicated a low potential for inotuzumab ozogamicin to inhibit the activities of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 (R1 value of <1.1, and Cmax/Ki <0.02).

Inotuzumab ozogamicin was also examined for time-dependent inhibition effects with several CYP enzyme activities in pooled HLM. Inotuzumab ozogamicin showed little or no change in time-dependent inhibitory potency for CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 activities.

Inotuzumab ozogamicin did not cause induction of CYP1A2, CYP2B6, or CYP3A4 mRNA expression and/or enzyme activity in any of the 3 hepatocyte lots evaluated at concentrations ranging from 0.003 to 0.32 µM of inotuzumab ozogamicin (highest concentration evaluated).

N-Ac-γ-calicheamicin DMH was a substrate for the P-gp efflux transporter, but not the BCRP efflux transporter. In MDCK type II cells expressing P-gp, the mean basolateral-to-apical permeability (B-A) to apical-to-basolateral permeability (A-B) efflux ratio for N-Ac-γ-calicheamicin DMH was approximately 5 and efflux was inhibited by the P-gp inhibitor PSC 833. The efflux ratio for the positive control P-gp substrate, quinidine, was 12. In MDCK cells expressing BCRP, the mean B-A to A-B efflux ratio for N-Ac-γ-calicheamicin DMH was 1.2, whereas the efflux ratios for the positive control BCRP substrates, topotecan and pitavastatin, were 23 and 26, respectively.

Uptake of rosuvastatin (1 µM), a known substrate for hepatic uptake transporters OATP1B1 and OATP1B3, was used as a positive control to confirm active uptake. The rate of hepatic uptake of N-Ac-γ-calicheamicin DMH was not inhibited by rifamycin SV. In contrast, the rate of hepatic uptake of rosuvastatin (positive control) was fully inhibited by rifamycin SV (97% inhibition). These results indicate that in vitro, N-Ac-γ-calicheamicin DMH enters human hepatocytes by passive diffusion and that the hepatic uptake transporters OATP1B1 and OATP1B3 are unlikely to be a major contributing factor in facilitating the entry of N-Ac-γ-calicheamicin DMH into hepatocytes.

N-Ac-γ-calicheamicin DMH showed little or no reversible inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6 with IC50 values >10 µM (highest concentration tested) and an estimated inhibition constant (Ki) of >5 µM. However, N-Ac-γ-calicheamicin DMH did show reversible inhibition of CYP3A4/5, with IC50 values of 5.5, 0.42 and 0.40 µM for testosterone 6β-hydroxylation, midazolam 1'-hydroxylation and nifedipine oxidation, respectively.

Assessment of DDI potential with N-Ac-γ-calicheamicin DMH for reversible CYP inhibition, based on the IC50 values determined from *in vitro* studies and the mean steady-state (total) Cmax of ≤0.050 ng/mL (≤0.000034 µM) or unbound Cmax of ≤9.5 x 10-7 µM following multiple dose administration of 1.8 mg/m^2 of inotuzumab ozogamicin (administered as 0.8, 0.5, and 0.5 mg/m^2 on Days 1, 8 and 15 of a 21-28 day cycle) to humans, indicated a low potential for N-Ac-β-calicheamicin DMH to reversibly inhibit the activities of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4/5 at clinically relevant concentrations (R1 value of <1.1, and unbound Cmax/Ki <0.02).

N-Ac-γ-calicheamicin DMH showed little or no change in time-dependent inhibitory potency for CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP2D6 activities. However, N-Ac-γ-calicheamicin DMH did show time-dependent inhibitory activity of CYP2C8 and CYP3A4/5 activity (as measured by testosterone 6β-hydroxylation and midazolam 1'-hydroxylation). N-Ac-γ-calicheamicin DMH showed very weak time-dependent inhibition of CYP2C8, with the concentration at half the maximal rate of enzyme inactivation (KI) of >30 µM; thus, definitive in vitro inactivation kinetic parameters could not be estimated. For CYP3A4/5, the KI and maximal rate of enzyme inactivation (kinact) parameters were 0.077 µM and 0.00368 min^{-1} for midazolam and 0.237 µM and 0.00434 min^{-1} for testosterone, respectively.

Assessment of DDI potential with N-Ac-γ-calicheamicin DMH for time-dependent CYP3A4/5 inhibition, based on the inactivation parameters determined *in vitro*, a CYP3A4/5 k_{deg} value of 0.00032 min^{-1} (Fahmi et al, 2008 and Obach et al, 2007), and the mean steady-state (total) Cmax of ≤0.050 ng/mL (≤0.000034 µM),

indicated a low potential for N-Ac-γ-calicheamicin DMH to inhibit CYP3A4/5 in a time-dependent manner at clinically relevant concentrations (R2 values of <1.1).

N-Ac-γ-calicheamicin DMH did not cause induction of CYP1A2, CYP2B6 or CYP3A4 mRNA expression and/or enzyme activity in any of the 3 hepatocyte lots evaluated at up to 0.3 µM of N-Ac-γ-calicheamicin DMH (highest concentration evaluated).

In humans, the mean steady-state total N-Ac-γ-calicheamicin DMH Cmax after multiple dose administration of 1.8 mg/m^2 inotuzumab ozogamicin was ≤0.050 ng/mL (≤0.000034 µM) (Study B1931022). Since N-Ac-γ-calicheamicin DMH did not show an induction effect on the evaluated CYP enzymes at up to 0.3 µM, which was >50x the Cmax, the potential for N-Ac-γ-calicheamicin DMH to induce CYP1A2, CYP2B6 or CYP3A4 activities is considered to be low at clinically relevant concentrations.

In the presence or absence of 2% BSA, N-Ac-γ-calicheamicin DMH showed little or no reversible inhibition of UGT1A4, UGT1A6, UGT1A9 and UGT2B7 catalyzed activities (IC50 >10 µM). However, N-Ac-γ-calicheamicin DMH inhibited UGT1A1 activity with IC50 values of 0.61 and 1.4 µM, in the absence or presence of 2% BSA, respectively. The unbound IC50 value could not be determined due to instability of N-Ac-γ-calicheamicin DMH in the 5 hour in vitro HLM-BSA binding assay.

Assessments based on the comparison of the IC50 (total) and N-Ac-γ-calicheamicin DMH Cmax values (≤3.4 x 10^{-5} and ≤9.5 x 10^{-7} µM for total and unbound, respectively) following multiple dose administration of 1.8 mg/m^2 of inotuzumab ozogamicin (administered as 0.8, 0.5 and 0.5 mg/m^2 on Days 1, 8, and 15 of a 21-28 day cycle) to humans indicate a low likelihood of DDI involving N-Ac-γ-calicheamicin DMH and the evaluated UGT enzymes (R1 value of <1.1, and total or unbound Cmax to Ki values <0.02).

N-Ac-γ-calicheamicin DMH showed little or no inhibition of the bidirectional transport of digoxin (P-gp substrate) or pitavastatin (BCRP substrate). The efflux ratio of digoxin in the absence and presence of N-Ac-γ-calicheamicin DMH (0.3 µM) was 39.1 and 48.2, respectively, indicating no decrease in digoxin efflux ratio at the highest concentration of N-Ac-γ-calicheamicin DMH evaluated. The efflux ratio of pitavastatin in the absence and presence of N-Ac-γ-calicheamicin DMH (0.3 µM) was 9.52 and 7.99, respectively, indicating a 16% decrease in pitavastatin efflux ratio at the highest concentration of N-Ac-γ-calicheamicin DMH evaluated. The IC50 of N-Ac-γ-calicheamicin DMH-mediated inhibition of P-gp and BCRP was estimated to be >0.3 µM, and the Ki was estimated to be >0.15 µM.

N-Ac-γ-calicheamicin DMH demonstrated concentration-dependent inhibition of BSEP, with a maximal inhibition of 35% at 1.0 µM (the highest concentration evaluated). No concentration-dependent inhibition of MRP2 at concentrations up to 1 µM was observed. The estimated IC_{50} values for N-Ac-γ-calicheamicin DMH-mediated inhibiton of BSEP and MRP2 were >1.0 µM, with estimated Ki values of >1.0 µM (Ki ~ IC_{50}, as the assay substrate concentration <<K_m) and >0.5 µM (calculated Ki = IC_{50}/2), respectively.

N-Ac-γ-calicheamicin DMH, over the concentrations evaluated (0.0002 to 1.0 µM), did not inhibit MATE1 or MATE2K, while the positive control inhibitor (cimetidine) inhibited the activity for these transporters by >97%. The IC_{50} of N-Ac-γ-calicheamicin DMH-mediated transporter inhibition was estimated to be >1.0 µM (Ki >1.0 µM, as the assay substrate concentration <<K_m [Michealis constant]).

N-Ac-γ-calicheamicin DMH inhibited the OATP1B1- OATP1B3 and OCT1-mediated transport of the respective probe substrate, in a concentration-dependent manner. Inhibition of OATP1B1 and OATP1B3 at the highest concentration of N-Ac-γ-calicheamicin DMH evaluated (0.1 µM) was 30% and 16%, respectively, while rifamycin SV (100 µM, positive control inhibitor) inhibited the transport of pravastatin and rosuvastatin by 98% and 57%, respectively. The IC50 of N-Ac-γ-calicheamicin DMH-mediated inhibition of OATP1B1 and

OATP1B3 was estimated to be >0.1 µM, and the Ki was estimated to be >0.05 µM. N-Ac-γ-calicheamicin DMH inhibited the OCT1-mediated transport of the respective probe substrate, with a corresponding IC_{50} and K_i of 0.530 µM (Ki ~ IC_{50}, as the assay substrate concentration <<K_m). Results indicate a low potential for an interaction between N-Ac-γ-calicheamicin DMH and these transporters at clinically relevant concentrations as the ratio of total C_{max}/IC_{50} was <0.1, and 50 × the unbound C_{max} (4.7×10^{-5} µM) did not exceed the estimated Ki values.

N-Ac-γ-calicheamicin DMH, over the concentrations evaluated (0.002 to 0.5 µM for OAT1 and at a concentration range of 0.0004 to 0.1 µM for OAT3 and OCT2, did not inhibit OAT1, OAT3 or OCT2), while the positive control inhibitors (probenecid for OAT1 and OAT3 and verapamil for OCT2) inhibited the activity for these transporters by >95%. The IC50 of N-Ac-γ-calicheamicin DMH-mediated transporter inhibition was estimated to be >0.5 µM (Ki >0.25 µM) for OAT1 and >0.1 µM (Ki >0.05 µM) for OAT3 and OCT2.

In vivo

No formal pharmacokinetic drug-drug interaction studies have been conducted with inotuzumab ozogamicin.

The effects of concomitant medications on inotuzumab ozogamicin PK were tested in the population pharmacokinetic analysis. There were varying numbers of patients taking P-glycoprotein (PGP) inhibitors (18.2%), granulocyte colony-stimulating factors (GCSF, 23.9%), hydroxyurea (HYDR, 1.70%), inotuzumab ozogamicin given with concomitant treatment for first 2 cycles (COMB, 57.8%), prior radiotherapy (RADIO, 25.0%), inotuzumab ozogamicin administered with rituximab (RITX, 50.22%), and salvage therapy (SALV, Salvage 1 = 54.7%, Salvage 2 = 32.9%, and Salvage 3+ = 11.5%). For HYDR, patients were all from the ALL studies and, for RITX, patients were all from the NHL studies. For SALV, patients were from the ALL studies, as this was not applicable/ collected in the NHL studies; and patients that were Salvage 3 were all from Study B1931010.

The effects of PGP, GCSF, HYDR, COMB, RADIO and SALV were tested on parameters CL1 and CL2, and only SALV on kdes. The GAM results showed no significant effects (based on AIC criteria) of PGP, GCSF, COMB and RADIO on CL1 and CL2; however SALV was significant on kdes, and HYDR and RITX were significant on CL1. After testing the covariates in the SCM, RITX was retained as the only significant covariate on CL1. Hence, covariates PGP, GCSF, HYDR, COMB, RADIO and SALV were concluded to not affect the PK of inotuzumab ozogamicin. In the final model, the effect of RITX (patients that were not administered rituximab with inotuzumab ozogaminicin) was estimated to increase CL1 by 15.5% (95%CI: 4.64%-26.4%)

Pharmacokinetics using human biomaterials

Immunogenicity

The immunogenicity evaluation was performed as per the CHMP Guideline on Immunogenicity assessment of Biotechnology-derived therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 and Draft EMEA/CHMP/BMWP/42832/2005 Rev1) using screening, confirmatory and neutralization assays. Determination of titres was also incorporated. There was no positive control (PC) against the whole molecule but the approach taken is reasonable. It was shown that the assay detects antibodies against inotuzumab ozogamicin in 2 ways – by use of anti-G544 (PC1) which gave a positive signal in the assay and by spiking high and low concentrations of PC1 with the whole molecule which resulted in ~ 95% and 78% inhibition. For establishing drug interference, PC1 at high and low concentrations was incubated with different

concentrations of the whole molecule and binding assessed. The drug concentrations in the assay were higher than those that would be encountered in clinical samples.

To determine assay sensitivity, affinity purified antibody was used and the sensitivity in mass calculated. For all other evaluations within the validation exercise, non-purified rabbit polyclonal serum at a certain dilution was used.

No anti-drug antibodies (ADAs) were detected in Study B1931010.

In study B1931022 ADAs were detected in 7 of 155 (4.5%) of patients tested. Four of these patients had low titre pre-existing antibodies that became undetectable during the study. In five patients, the antibodies appeared to be specific for the calicheamicin portion of inotuzumab ozogamicin. One patient had anti-G544 antibodies of low specificity with borderline competition results. One patient with ADAs at the EOT had a mixed response to calicheamicin and G544 of low specificity with borderline results in the confirmation assay. Neutralizing antibodies were not detected in any of the 6 patients.

Using post-hoc clearance (CL) in the ALL studies derived from the population -PK analysis, CL of inotuzumab ozogamicin appeared to be comparable between patients who tested positive and negative for ADAs.

2.4.3. Pharmacodynamics

Mechanism of action

No clinical pharmacodynamic studies were submitted.

Primary and Secondary pharmacology

Percentage CD22 positivity

The antibody component of inotuzumab ozogamicin, G544, specifically recognises human CD22. Prior to enrolment in the ALL studies, patients were screened for CD22 positivity on the blast cell surface. Testing was conducted at local laboratories followed by analysis of samples from subjects who tested CD22-positive locally at central laboratories [Genoptix, Carlsbad, CA, US (Study B1931022) or University of Washington, Seattle, WA, US (Study B1931010)]. Eligibility was based on local laboratory analysis for both studies. In Study B1931022 patients who were CD22-negative by local laboratory testing and subsequently determined to be CD22-positive by the central laboratory could be considered for eligibility.CD22 measurement was primarily by fluorescence activated cell sorting (FACS) with immunohistochemistry analysis in patients with inadequate bone marrow aspirate or insufficient circulating blasts for FACS. Leukaemic cells were defined as CD22 positive if the level of fluorescence associated with binding of the CD22 monoclonal antibody [mouse anti-human monoclonal antibody clone RFB-4] was greater than the threshold value typically set based on the fluorescent intensity of leukemic cells stained with an isotype-matched control antibody. The validation report and addendums regarding peripheral blood specimens and inter-laboratory qualification were provided.

Initially samples were considered to be positive if $\geqslant$20% of leukaemic blasts expressed surface CD22. The cut-off value was subsequently changed to >0% blasts (Protocol Amendment 2, StudyB1931022) based on

the finding that some subjects that failed screening in the Phase 1/2 study B1931010 tested CD22 negative locally (⩾20% cut-off) but were CD22-positive based on Central laboratory testing.

To assess concordance between local and central testing, patients were divided into groups (≥90%, ≥70- <90%, >0 -<70%, 0%)) based on the % of CD22+ leukaemic blasts in their baseline specimen. Similar results were seen for both ALL studies. By central testing (Study B1931022) most patients had over 90% CD22 + leukaemic blasts at baseline. There was good concordance (~99.6%) for evaluable subjects (252/253) between central and local testing for CD22-positivity > 0%. However, concordance was poor (~37%) between Central and Local laboratories with regards to the level of positivity (≥90%, ≥70 - <90%, 90%, >0 - <70%, 0%)). In general, a higher percentage of blasts were CD22-positive when measured by central versus local laboratory testing, suggesting that the central laboratory test was more sensitive.

There was reasonable concordance (87.7%) between bone marrow and peripheral blood by Central laboratory for assessment of the % blasts that were CD22 + at baseline based on 57 evaluable patients.

Overall, in Studies B1931022 and B1931010, 415 patients (333 patients in Study B1931022 and 82 patients in Study B1931010) were evaluable by CD22 testing at a central laboratory at baseline (including 342 enrolled patients and 73 patients who screen-failed) and, of these, 1/415 (0.2%) patients was CD22-negative (i.e. CD22 positivity=0%) by central laboratory testing.

Overall, of enrolled patients in Studies B1931022 and B1931010, 367 patients (305 patients in Study B1931022 and 62 patients in Study B1931010) were evaluable for CD22 testing at a local laboratory at baseline. Of these 367 patients, only one (who subsequently exhibited 86% CD22 positivity by central laboratory test) had CD22-negative B-cell ALL by local lab testing (ie, CD22 positivity=0%), consistent with CD22 positivity being an inclusion criterion for these studies. It is not possible to determine the true proportion of locally tested patients who were CD22-negative, since local laboratory CD22 test results were not formally captured for patients who failed screening and not all those who were screened negative locally were sent for central review.The applicant analysed reduction in CD22 % blast positivity with each cycle of treatment by central laboratory. Over half of the patients were missing or not evaluable by the end of Cycle 1 in the Phase 3 study, partly reflecting limited sampling time-points in this study; the Phase 1/2 study had less missing information. From Baseline through to Cycle 2, where there are results for a reasonable number of patients, CD22+ leukaemic blasts as a proportion of the total number of blasts declined more in the inotuzumab ozogamicin groups.

Table 20 CD22-Positive Leukemic Blasts (Per Central Laboratory) in Subjects Randomized to Study who had an Evaluable Sample for CD22 Analysis at Baseline and Over Time

CD22+ Leukaemic Blasts (%)[a]	Study B1931022		Study B1931010
	Inotuzumab Ozogamicin	Control[b]	Inotuzumab Ozogamicin[c]
	Patients, n (%)[d]	Patients, n (%)[d]	Patients, n (%)[d]
Baseline[e]	**(n=164)**	**(n=162)**	**(n=48[c])**
≥90	107 (65.2)	93 (57.4)	37 (77.1)
≥70-<90	30 (18.3)	18 (11.1)	6 (12.5)
>0-<70	5 (3.0)	18 (11.1)	4 (8.3)
0	0	0	0
Not evaluable	3 (1.8)	6 (3.7)	--
Missing	19 (11.6)	27 (16.7)	1 (2.1)
Cycle 1	**(n=164)**	**(n=143)**	**(n=48)**
≥90	27 (16.5)	40 (28.0)	17 (35.4)
≥70-<90	12 (7.3)	7 (4.9)	6 (12.5)
>0-<70	22 (13.4)	11 (7.7)	10 (20.8)
0	0	0	10 (20.8)

Not evaluable Missing	64 (39.0) 39 (23.8)	25 (17.5) 60 (42.0)	-- 5 (10.4)
Cycle 2	**(n=127)**	**(n=27)**	**(n=38)**
≥90 ≥70-<90 >0-<70 0 Not evaluable Missing	6 (4.7) 5 (3.9) 6 (4.7) 0 73 (57.5) 37 (29.1)	3 (11.1) 0 0 0 7 (25.9) 17 (63.0)	4 (10.5) 2 (5.3) 5 (13.2) 20 (52.6) -- 7 (18.4)

Note: A large number of patients had missing results since local laboratory results were provided but sufficient sample was lacking for central laboratory assessment. Non-evaluable was not resolved from missing category for Study B1931010.
a CD22+ leukaemic blasts (%) is calculated based on the number of leukaemic blasts with CD22 greater than negative control values relative to all leukaemic blasts in the specimen.
b Control is a defined chemotherapy regimen
c Includes patients who received a total starting dose of 1.8 mg/m^2/cycle inotuzumab ozogamicin with a protocol-specified reduction in dose upon achievement of response to treatment
d Number of patients in the indicated CD22+ leukaemic blasts (%) category relative to all patients treated in the indicated arm at the corresponding time-point. Screening and Baseline percentages are based on all patients randomized.
e Baseline is based on the latest CD22 assessment from the central laboratory on or prior to Cycle 1 Day 1

Similar proportions of patients who achieved CR/CRi also achieved MRD negativity (60.0 – 83.1%) in the inotuzumab ozogamicin arm regardless of the baseline percentage leukaemic blasts that were CD -22 positive. The CR/CRi rate in the inotuzumab ozogamicin arm was 77.6% for patients who had ⩾90% CD22-positive leukaemic blasts at baseline and 66.7% for those with ⩾70% to <90%. Only 5 patients had <70% CD22-positive leukaemic blasts at baseline per Central laboratory of whom 3 achieved CR/CRi.

Based on the PK E-R modelling analysis of the efficacy of inotuzumab ozogamicin in patients with relapsed or refractory B-ALL (PMAR-EQDD-B193a-DP4- 205 Supplement), the percentage of leukaemic blasts that were CD22-positive was a significant predictor of CR/CRi and achieving MRD-negativity. By the end of the second cycle (Cycle 3 Day 1), patients with ALL had a median predicted probability of 82% (95% CI: 67-91) of achieving CR/CRi when the percentage of leukaemic blasts that were CD22-positive at baseline was ⩾70%.

In Study B1931022, based on both univariate and multivariate stepwise Cox regression analysis, baseline ≥90% CD22 positivity was associated with a lower risk of death than <90% CD22 positivity when CD22 positivity was analysed as a categorical variable. For patients with <90% leukaemic blasts CD22-positive at baseline, there was no statistically significant difference in OS between the inotuzumab ozogamicin arm and the control arm. CD22 positivity per central laboratory was not significantly associated with risk of death when assessed as a continuous variable in this analysis (p=0.09).

In Study B1931022, there were signs of improved PFS with inotuzumab ozogamicin independent of CD22 positivity, whereas DoR improvement for inotuzumab ozogamicin over control was apparent only in patients with CD22 positivity ≥90%.

Although evaluable subject numbers were low, in Study 1931022 and Study 1931010, recurrent disease was not generally attributable to outgrowth of CD22-negative clones, although there were signs of potential outgrowth of clones with relatively low CD22 expression.

Gene expression

The relationship between clinical outcome and expression of genes involved in DNA damage response, apoptosis and B-cell antigen expression was examined. No relationship was apparent between baseline CD22 mRNA levels in peripheral blood and efficacy outcomes. In Study B1931010, CD22 mRNA levels in peripheral blood decreased by Day 15 relative to baseline (median 97% decrease). By Day 15 CD22 mRNA levels in patients who subsequently achieved CR/CRi and MRD negativity were significantly lower than in patients who

did not subsequently achieve CR/CRi. Post-baseline changes in CD22 mRNA levels were not assessed in Study B1930122.

QTc prolongation

QTc prolongation was evaluated in three exposure- response models. The first, involving only 8 NHL patients, suggested an effect of inotuzumab ozogamicin on QT interval with a calculated average QTcF increase of 6.32 milliseconds (msec) (90% CI: 1.85 – 10.8) at the mean inotuzumab ozogamicin Cmax (569 ng/mL).

The second model was developed from 80 NHL subjects; the average QTcS increase was calculated to be 4.66 msec (90% CI: 2.60-6.71) at the median total calicheamicin Cmax (61 ng/mL). Treatment cycle was suggested to be an additional covariate; after four treatment cycles, the expected increase in QTcS interval was 7.83 msec (90% CI: 4.83-10.8) at the median total calicheamicin Cmax.

The final population PK-QTc model involved patients 250 treated with single-agent inotuzumab ozogamicin for relapsed/ refractory B-cell ALL (Study B1931022 and Study B1931010) or relapsed/ refractory NHL (Study B1931007). The final model is considered the most relevant for the ALL indication, as the others involved the 4-weekly NHL dosing regimen with a higher Cmax. Simulated QTcF showed that the median QTcF increased by 2.53 msec from baseline (97.5^{th} percentile: 4.92 msec) at the average maximum serum concentration (C_{max}) estimated for patients with relapsed or refractory ALL (371 ng/mL) and by 3.87 msec (97.5^{th} percentile: 7.54 msec) at a 1.5 times higher average C_{max} (569 ng/mL).

2.4.4. Discussion on clinical pharmacology

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

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

In vitro, N-acetyl-gamma-calicheamicin DMH was primarily metabolised via nonenzymatic reduction. In humans, serum N-acetyl-gamma-calicheamicin DMH levels were typically below the limit of quantitation (50 pg/mL).

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

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

No formal pharmacokinetic studies of inotuzumab ozogamicin have been conducted in patients with hepatic impairment. Based on a population pharmacokinetic analysis in 765 patients, the clearance of inotuzumab ozogamicin in patients with hepatic impairment defined by National Cancer Institute Organ Dysfunction

Working Group (NCI ODWG) category B1 (total bilirubin ⩽ ULN and AST > ULN; n=133) or B2 (total bilirubin > 1.0 1.5 × ULN and AST any level; n=17) was similar to patients with normal hepatic function (total bilirubin/AST ⩽ ULN; n=611) (see section 4.2). In 3 patients with hepatic impairment defined by NCI ODWG category C (total bilirubin > 1.5 3 × ULN and AST any level) and 1 patient with hepatic impairment defined by NCI ODWG category D (total bilirubin > 3 × ULN and AST any level), inotuzumab ozogamicin clearance did not appear to be reduced (SmPC, section 5.2).

No formal pharmacokinetic studies of inotuzumab ozogamicin have been conducted in patients with renal impairment. Based on population pharmacokinetic analysis in 765 patients, the clearance of inotuzumab ozogamicin in patients with mild renal impairment (CLcr 60 89 mL/min; n=237), moderate renal impairment (CLcr 30 59 mL/min; n=122), or severe renal impairment (CLcr 15 29 mL/min; n=4) was similar to patients with normal renal function (CLcr ⩾ 90 mL/min; n=402). Inotuzumab ozogamicin has not been studied in patients with end stage renal disease (SmPC, section 5.2).

Based on a population pharmacokinetic analysis in 765 patients, body surface area was found to significantly affect inotuzumab ozogamicin disposition. The dose of inotuzumab ozogamicin is administered based on body surface area (SmPC, section 5.2 and 4.2.).

Based on in vitro data, coadministration of inotuzumab ozogamicin with inhibitors or inducers of cytochrome P450 (CYP) or uridine diphosphate glucuronosyltransferase (UGT) drug metabolising enzymes are unlikely to alter exposure to N-acetyl-gamma-calicheamicin DMH. In addition, inotuzumab ozogamicin and N-acetyl gamma-calicheamicin DMH are unlikely to alter the exposure of substrates of CYP enzymes, and N-acetyl gamma-calicheamicin DMH is unlikely to alter the exposure of substrates of UGT enzymes or major drug transporters (SmPC, section 4.5).

The extent of partitioning of N-Ac-γ-calicheamicin DMH into red blood cells was determined in vitro in rat, monkey, and human whole blood at a concentration of 1.0 µM (1480 ng/mL). The blood to plasma concentration ratios of N-Ac-γ-calicheamicin DMH were 0.63, 0.84, and 0.71 in rat, monkey, and human, respectively. These data indicated limited distribution of N-Ac-γ-calicheamicin DMH into red blood cells of rats, monkeys, and humans.

The various local tests used in the two ALL clinical studies to screen for CD22 at baseline were not as sensitive as the single central laboratory test. Most patients in the ITT population of Study B1930122 were ⩾90% positive per central analysis, making analysis in the other small samples of lower CD22 positivity more difficult to interpret. CR/CRi rates showed a statistically significant advantage over control in both those ⩾90% CD22 positivity per central analysis and those ⩾70-<90%. A positive trend was seen in the small group < 70%. OS was statistically significantly improved in the inotuzumab group compared to control only in patients with ⩾90% CD22 positivity per central analysis (and ⩾70% CD22 positivity by local analysis based on ⩾70- <90% and ⩾90% CD22 positivity groups. The confidence intervals were so wide in the lower groups that conclusions could not be drawn. Study B1931022 was not designed to prospectively evaluate the benefit of inotuzumab ozogamicin compared to the control within or between subgroups of patients defined by CD22 positivity cut-offs.

Efficacy and safety of Besponsa has not been evaluated in CD22 negative ALL patients and it is expected that the presence of the target is essential for the drug to exert an anti-tumour effect therefore CD22-positive status is specified in the indication. There is no clear difference in outcome amongst patients with different levels of CD22 positivity so there is no need to specify a minimum level of CD22 expression.

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

expression was assessed using immunohistochemistry in patients with an inadequate bone marrow aspirate and insufficient circulating blasts (SmPC section 5.1).

In the clinical study, the sensitivity of some local tests was lower than the central laboratory test. Therefore only validated tests with demonstrated high sensitivity should be used (SmPC section 5.1).

Based on a pharmacokinetic exposure-response analysis in 250 patients with relapsed or refractory ALL or other haematological malignancies who received 1.8 mg/m2/cycle inotuzumab ozogamicin administered as 3 divided doses on Days 1 (0.8 mg/m2), 8 (0.5 mg/m2), and 15 (0.5 mg/m2) of a 21 to 28 day cycle or 1.8 mg/m2/cycle administered once every 4 weeks, respectively, the median QTcF increased by 2.53 milliseconds (msec) from baseline (97.5th percentile: 4.92 msec) at the average Cmax estimated for patients with relapsed or refractory ALL (371 ng/mL) and by 3.87 msec from baseline (97.5th percentile: 7.54 msec) at a 1.5 times higher average Cmax (569 ng/mL) (SmPC, section 5.2).

Modelling analysis suggested that QTcF prolongation was not likely in ALL patients at the mean Cmax of inotuzumab ozogamicin seen in the ALL studies (see discussion on clinical safety).

The immunogenic potential of inotuzumab ozogamicin is considered to be low. No conclusions can be drawn regarding the impact of ADAs on efficacy/safety endpoints due to the limited number of patients involved (See discussion on clinical efficacy and clinical safety).

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetics of inotuzumab ozogamicin in patients with ALL has been described using a population PK model supplemented by PK data obtained from patients with NHL. The pharmacokinetics of inotuzumab ozogamicin and related covariates have been reasonably well described and reflected in the SmPC. The CHMP recommended that the results from a study evaluating the extent of partitioning of inotuzumab ozogamicin (PF-05208773) into red blood cells in vitro in rat, monkey, and human whole blood should be submitted by the applicant post-authorisation.

2.4.6. Clinical efficacy

2.4.6.1. Dose response study

Study B1931010 (referred to as Study 1010)

This was a single-arm, multi-center, open-label, Phase 1/2 clinical study evaluating single-agent inotuzumab ozogamicin in patients with CD22 positive relapsed or refractory B-cell ALL. The study was conducted at 8 centers in the US between 26 August 2011 and 25 August 2014. The data cut-off date for the CSR was 30 January 2015 and a supplemental CSR was provided with the final results after the last patient last visit (15 January 2016).

The study was divided into:

Phase 1

Dose – escalation: Assessed the safety, tolerability and preliminary efficacy at increasing dose levels of inotuzumab ozogamicin to select the RP2D. Evidence of clinical activity was determined by the preliminary

satisfactory response rate after receiving the first dose of study drug, defined as any response other than progressive disease (i.e. CR/CRi/PR/resistant disease)

Dose –expansion cohort: Further evaluated safety and efficacy at the RP2D schedule.

Phase 2: Evaluated the efficacy of inotuzumab ozogamicin, as measured by the haematologic remission rate (CR/CRi by investigator assessment) in patients in second or later salvage setting. Secondary objectives included evaluation of overall safety, duration of remission, MRD-negativity (per central laboratory), PFS, OS and PK. PD and pharmacogenomics effects were explored.

Important inclusion criteria: relapsed/ refractory ALL with ≥20% blasts CD22 positive by local laboratory assessment. For Phase 2, patients had to be due to receive ≥Salvage 2 therapy and, if Ph^+ ALL, had to have failed treatment with at least 1 tyrosine kinase inhibitor (TKI).

Important exclusion criteria: allogeneic HSCT ≤4 months before randomization or a history of VOD/SOS.

Results

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

Phase 1 dose escalation: 24 patients were treated with inotuzumab ozogamicin by IV infusion in 2 or 3 divided doses over a 28 day cycle for a maximum of 6 cycles.

Table 21: Summary of Safety Outcomes in Phase 1 dose-finding portion used to determine recommended Phase 2 Dose of Inotuzumab Ozogamicin (Study B1931010)(N=24)

Dosing Regimen	No. of Patients	No. of Patients With Cycle 1 DLTs	DLTs
1.2 mg/m^2/cycle (0.8 mg/m^2 Day 1, 0.4 Day 15)	3	0	
1.6 mg/m^2/cycle (0.8 mg/m^2 Day 1, 0.4 Day 8 & 15)	12	0	
1.8 mg/m^2/cycle (0.8 mg/m^2 Day 1, 0.5 Day 8 & 15)	9	1	Lipase increased (1)

The DLT (elevated lipase) occurred on Day 2 in a patient with pre-existing abdominal pain after the standard initial dose of 0.8 mg/m^2. There was 1 event of Grade 3 increased alanine aminotransferase (ALT) in each of the 1.6 and 1.8 mg/m^2 dose level cohorts. In the 1.8 mg/m^2/cycle cohort, AEs leading to dose delay were common (78%), mainly thrombocytopenia, neutropenia and elevated liver function tests.

CR/CRi rate and preliminary satisfactory response rate were reported:

Table 22: Study B1931010: Phase 1 Satisfactory response rate and CR/CRi rate (N=24)

Dose (mg/m^2/cycle)	Satisfactory response rate	CR/CRi rate
1.2	100%	66.7% (2/3 patients [95% CI: 9.4, 99.2])
1.6	91.7%	75.0% (9/12 patients [95% CI: 42.8, 94.5])
1.8	88.9%	88.9% (8/9 patients [95% CI: 51.8, 99.7])

At the 1.8 mg/m^2/cycle dose level, all responding patients achieved MRD-negativity

Phase 1 dose expansion: 13 patients received inotuzumab ozogamicin at a starting dose of 1.8 mg/m^2/cycle, with subsequent dose reduction to 1.6 mg/m^2/cycle for patients achieving CR/CRi. The decision to dose-reduce was based on observed dose delays for patients treated at the 1.8 mg/m^2/cycle dose level and increased inotuzumab ozogamicin exposure with subsequent doses.

Given the importance of inducing remission quickly, the RP2D was determined to be 1.8 mg/m^2/cycle for up to 6 cycles with a dose reduction to 1.6 mg/m^2/cycle after achieving a CR or CRi (0.8 mg/m^2 day 1 and 0.4 mg/m^2 on days 8 and 15).

Phase 2: 35 patients were treated at the RP2D of inotuzumab ozogamicin.

Table 23: Study B1931010: CR/CRi (per Investigator's Assessment; ITT Population) (N=72)

	Phase 1 Expansion (n=13) 1.8 mg/m^2	**Phase 2 (n=35) 1.8 mg/m^2**	**Total (N=72) All Doses**
CR/CRi, n (%) (95% CI)	6 (46.2) 19.2-74.9	24 (68.6) 50.7-83.2	49 (68.1) 56.0-78.6
CR	2 (15.4)	10 (28.6)	23 (31.9)
CRi	4 (30.8)	14 (40.0)	26 (36.1)
Median time to CR/CRi, weeks (range)	3.9 (3.0-12.1)	3.6 (2.1-13.0)	3.9 (2.1-13.0)

Table 24: Study B1931010: Secondary Efficacy Endpoints (ITT Population) (N=72)

	Phase 2 (n=35) 1.8 mg/m^2	**Total (N=72) All Doses**
Median DoR, months (95% CI)	3.8 (2. 2-5.8)	4.6 (3.8-6.6)
Median PFS, months (95% CI)	3.7 (2.6-4.7)	3.9 (3.0-5.4)
Post-treatment HSCT rate; n (%)[a]	8 (22.9)	24[a] (33.3)
MRD-negativity[b] in patients who achieved a CR/CRi	18/24 (75.0)	41/49 (83.7)
Number of deaths, n (%)	30 (85.7)	55 (76.4)
Number of censored patients, n (%)	5 (14.3)	17 (23.6)
Median OS, months (95% CI)	6.4 (4.5-7.9)	7.4 (5.7-9.2)

a	Out of 24 patients who proceeded to HSCT, 1 patient had a partial response and 1 patient achieved remission only after subsequent anti-cancer therapy and then proceeded to HSCT. 22 (30.6%) patients who achieved a CR/CRi during study therapy proceeded to HSCT.
b	MRD negativity defined as <1x10^{-4} blasts/mononucleated cells by flow cytometry based on centralized laboratory analysis

Study B1931010 completed in 15 January 2016 (last subject last visit), 72 patients had discontinued the study; 16 (22.2%) completed 2-year study follow-up, 55 (76.4%) had died and 1 (1.4%) discontinued due to 'other' reasons. Overall, 59/72 (81.9%) patients had PFS events. The median PFS was the same as originally reported. The estimated median OS was the same as originally reported overall and in the Phase 2 portion of the study. The overall probability of survival at Month 24 was 22.8% (95% CI: 13.9-33.1%) and, in the Phase 2 portion, was 12.1% (95% CI: 3.9 -25.5%).

Duration of remission and overall survival were slightly shorter in the Phase 2 portion of the study compared to the total population. Phase 2 had a marginally greater proportion of adverse prognostic factors compared to the full population, Salvage ≥2 (91.4% vs. 76.4%), complex cytogenetics (31.4% vs. 20.8%) and prior allogenic HSCT (42.9% vs. 31.9%).

Results from study B1931010 supported further investigation of inotuzumab ozogamicin in CD22 positive relapsed/ refractory ALL in the Phase 3 setting.

The study was designed to determine the recommended Phase 2 dose (RP2D) of inotuzumab ozogamicin based on both safety and efficacy parameters. Inotuzumab ozogamicin was administered on a weekly or biweekly schedule with a cumulative dose per 28-day cycle of 1.2, 1.6, and 1.8 mg/m^2/cycle. One patient (out of 9 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; thus, the DLT did not occur due to a higher dose received. There were no discernible differences between the 1.6- and 1.8-mg/m^2 dose groups for gr≥3 hepatic AEs during Cycle 1, with only 1 event of gr3 ALT increased in each group.

Responses (CR/CRi) were observed across all dose levels. Acknowledging small sample sizes, an exploratory analysis suggested a potential correlation between dose and MRD negativity. The 1.8-mg/m^2/cycle dose level had the highest CR/CRi rate of 89% (8/9 patients achieved CR/CRi), and all responding patients achieved MRD negativity.

Adverse Events (AEs) associated with dose delays were reported for 78% of patients in the 1.8-mg/m^2/cycle cohort. Although a MTD was not formally established, it was concluded that the starting dose/cycle should be 1.8 mg/m^2/cycle based on the importance of inducing a remission quickly. Due to the rate of AEs requiring dose delays at this dose level, which limits dose intensity, higher dose levels were not examined, and a dose reduction was recommended for subsequent cycles after achievement of remission. PK results from prior NHL studies showing increasing exposure to inotuzumab ozogamicin with later cycles of therapy supported a dose reduction in subsequent cycles after achievement of remission.

Therefore, the RP2D was determined to be 1.8 mg/m^2/cycle (divided as 0.8 mg/m^2 on Day 1 and 0.5 mg/m^2 on Days 8 and 15 of a 28-day cycle), followed by a dose reduction to 1.6 mg/m^2/cycle (0.8 mg/m^2 on Day 1 and 0.4 mg/m^2 on Days 8 and 15 of a 28-day cycle) once patients achieved CR or CRi. The dosing regimen used in study 1022 and recommended for therapeutic use is presented in Table 25.

Table 25. Dosing Regimen Used in Study 1022 and Recommended for Therapeutic Use

Dosing Regimen for Cycle 1			
	Day 1	**Day 8**	**Day 15**
All patients:			
Dose (mg/m^2)	0.8	0.5	0.5
Cycle length	21 days*		
Dosing Regimen for Subsequent Cycles Depending on Response to Treatment			
Patients who achieve CR or CRi			
Dose (mg/m^2)	0.5	0.5	0.5
Cycle length	28 days		
Patients who do not achieve CR or CRi			
Dose (mg/m^2)	0.8	0.5	0.5
Cycle length	28 days		

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

2.4.6.2. Main study

B1931022 (1022 Study)

Methods

This was an open-label, randomized phase 3 study of inotuzumab ozogamicin compared to a defined investigator's choice in adult patients with relapsed or refractory CD22-positive acute lymphoblastic leukaemia (ALL).

Study Participants

CD22 immuno-phenotyping was performed at screening on bone marrow aspirate (or peripheral blood) by local laboratories. If CD22 was negative by local laboratory, the central laboratory result for CD22 immunophenotyping was considered for eligibility. Karyotyping was performed locally and cytogenetics (FISH) was performed by the central laboratory.

Important inclusion criteria:

- Relapsed or refractory CD22-positive ALL due to receive Salvage 1 or 2 therapy provided either arm of randomized study therapy offered a reasonable treatment option
- Salvage 1 patients with late relapse had to be deemed poor candidates for re-induction with initial therapy
- Ph^+ ALL patients had to have failed treatment with at least 1 second or third generation TKI and standard multi-agent induction chemotherapy
- *Important exclusion criteria:*
- Allogeneic HSCT or other anti-CD22 immunotherapy $\leq$4 months before randomization, chemotherapy within 2 weeks of randomization except that given to reduce the circulating lymphoblast count or palliation (steroids, hydroxyurea or vincristine) or for ALL maintenance (mercaptopurine, methotrexate, vincristine, thioguanine and/or TKIs)
- History of hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) or chronic liver disease
- Continued immunosuppression therapy for treatment of GvHD at enrolment; Grade ≥ 2 acute GvHD or extensive chronic GvHD at randomization
- Peripheral absolute lymphoblast count $\geqslant$10,000 /uL (hydroxyurea and/or steroids/vincristine permitted within 2 weeks of randomisation to reduce WBC count)

Main exclusion criteria

- Isolated extramedullary relapse (testicular or CNS)
- Burkitt's or mixed phenotype acute leukaemia
- Active CNS leukaemia, defined by unequivocal morphologic evidence of lymphoblasts in the cerebrospinal fluid; use of CNS directed local treatment for active disease within the prior 28 days;

symptomatic CNS leukaemia (cranial nerve palsies or other significant neurologic dysfunction) within 28 days

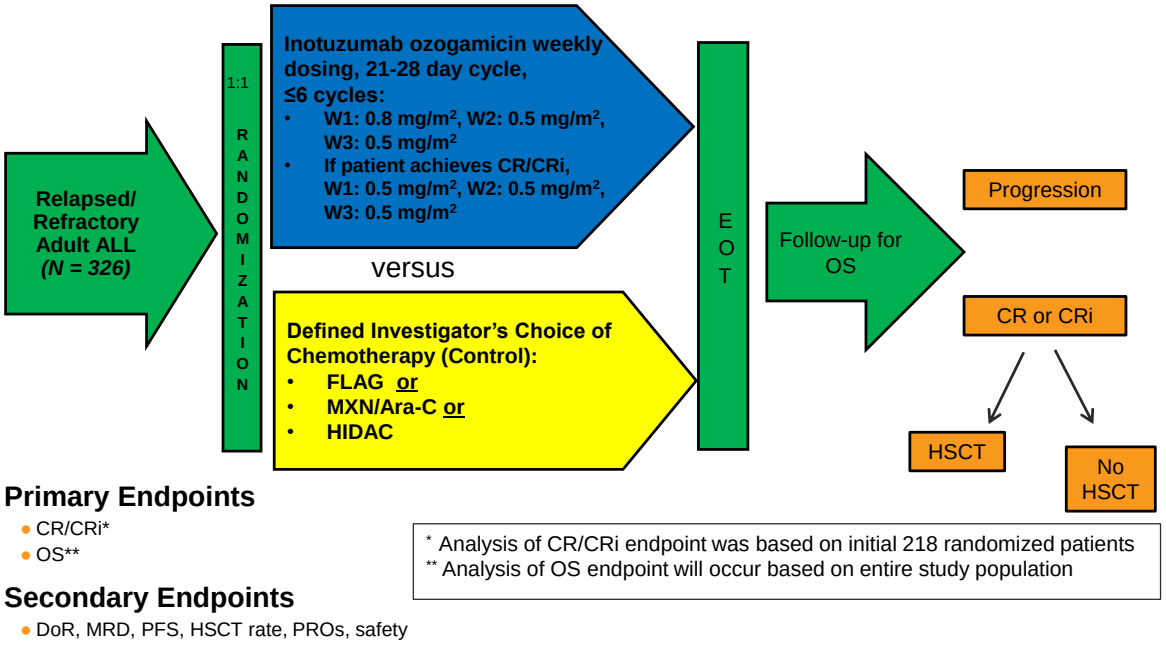
- Monoclonal antibodies within 6 weeks of randomization (rituximab within 2 weeks), allogeneic HSCT or other anti-CD22 immunotherapy ≤4 months before randomization, chemotherapy within 2 weeks of randomization except that given to reduce the circulating lymphoblast count or palliation (steroids, hydroxyurea or vincristine) or for ALL maintenance (mercaptopurine, methotrexate, vincristine, thioguanine and/or TKIs)
- History of hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS)
- Continued immunosuppression therapy for treatment of GvHD at enrolment; at randomization, patients must not have Grade ≥ 2 acute GvHD or extensive chronic GvHD
- To reduce the risk of cardiac arrhythmias the following were excluded - QTcF >470 msec [based on the average of 3 consecutive ECGs]; history of clinically significant ventricular arrhythmia, unexplained syncope or chronic bradycardic states; uncontrolled electrolyte disorders

Treatments

An overview of regimen and follow up for each treatment group is shown in

Figure 1.

Figure 1 Study scheme (Study B1931022)



Inotuzumab ozogamicin was administered by intravenous infusion at a dose of 1.8 mg/m^2/cycle (0.8 mg/m^2 on Day 1 and 0.5 mg/m^2 on Days 8 and 15 of a 21-day cycle). For patients who achieved CR/CRi the duration of Cycle 1 could be extended up to 28 days. For patients achieving CR/ CRi, the recommended subsequent inotuzumab ozogamicin dose was 1.5mg/m^2/cycle (0.5 mg/m^2 on Days 1, 8 and 15 of a 28-day

cycle). Patients not achieving CR/CRi continued with the dose of 1.8 mg/m^2/cycle, split and administered on Day 1, 8 and 15 of a 28 day cycle. Treatment with inotuzumab ozogamicin was continued until disease progression or unacceptable toxicity up to a maximum of 6 cycles.

Dose delays

Dose delays within a cycle were required for non-haematologic toxicity. A minimum of 6 days was to be maintained between doses. Dose delay >7 days resulted in omission of the next dose within the cycle. If the beginning of the next cycle was delayed by more than 28 days due to treatment -related toxicity, study treatment was permanently discontinued unless otherwise agreed by Sponsor and investigator. Following an interruption of ≥14 days due to treatment-related toxicity patients were to resume with a single 25% dose reduction for the subsequent cycle (e.g. from 0.5 to 0.375 mg/m^2) once adequate recovery was achieved. If further dose modification was indicated, the number of doses within the cycle was to be reduced to 2. Following dose reduction for a drug-related toxicity, the dose was not to be re-escalated.

Dosing with inotuzumab was to be permanently discontinued for any patient with possible, probable or confirmed VOD/SOS or other severe liver toxicity.

Prior to the start of each cycle patients in both arms had to have:

- No evidence of progressive extramedullary disease (EMD) and a decrease in blast percentage or stable disease on the peripheral blood count and bone marrow evaluation
- Recovery to Grade 1 or baseline non-haematologic treatment-related toxicity
- Serum bilirubin ≤1.5 x ULN (≤2 x ULN if elevated due to tumour) and AST, ALT ≤2.5 x ULN
- Serum creatinine ≤2 x ULN or estimated creatinine clearance ≥40 mL/min
- Recovery of ANC and platelets
    - For patients with pre-treatment ANC ≥1 x 10^9/L: ANC ≥1 x 10^9/L;
    - For patients with pre-treatment platelets ≥50 x 10^9/L: platelets ≥50 x 10^9/L;
    - For patients with baseline ANC <1 x 10^9/L and/or platelets <50 x 10^9/L: ANC and platelets must recover at least to baseline values obtained for the prior cycle, or ANC ≥1 x 10^9/L and platelets ≥50 x 10^9/L, or the most recent bone marrow must demonstrate stable or improved disease, and the ANC and platelets are believed to be low due to disease, not test article
- QTcF ≤470 msec (average ozogamicin of 3 ECGs); Day 1 of Cycles 1, 2 and 4 only

To reduce the risk of hepatotoxicity, it was recommended to limit treatment with inotuzumab ozogamicin to 2 cycles or the fewest number required to achieve a CR/ CRi (if not achieved after 2 cycles) in patients who were proceeding to allogeneic HSCT. A gap of 5-6 weeks from the last dose of inotuzumab ozogamicin to HSCT was advocated.

Dose reductions

Following an interruption of ≥14 days due to treatment-related toxicity patients were to resume with a single 25% dose reduction for the subsequent cycle (e.g. from 0.5 to 0.375 mg/m^2) once adequate recovery was achieved (Protocol Amendment 3 dated 28 March 2014). If further dose modification was indicated, the number of doses within the cycle was to be reduced to 2 for subsequent cycles. Dose reduction of inotuzumab ozogamicin by 25% was also recommended for patients with CRi, whose platelet counts had not

recovered to those values obtained prior to the start of the previous cycle. Once a patient had a dose reduction for a drug-related toxicity, the dose was not to be re-escalated. Patients who were unable to tolerate a 25% dose reduction followed by a decrease in the number of doses per cycle to 2 doses were withdrawn from treatment.

For patients who were proceeding to allogeneic HSCT, it was recommended that treatment with inotuzumab ozogamicin be limited to 2 cycles of induction or the fewest number required to achieve a CR or CRi (if not achieved after 2 cycles) in order to potentially reduce the risk of hepatotoxicity, including VOD/SOS, after HSCT. To balance the risk of relapse against the potential risk of toxicity associated with an early alloSCT, a gap of 5-6 weeks after the last dose of inotuzumab ozogamicin was considered reasonable.

Patients had to be weighed within 72 hours prior to every cycle Day 1 and the inotuzumab dose recalculated if the weight changed by >10%. If the dose administered was 10% greater or lower than the one prescribed, it was reported as a dosing medication error.

Defined Investigator's choice of chemotherapy

Patients randomized to the control arm therefore receive 1 of 3 predefined control chemotherapy regimens:

FLAG - fludarabine/ cytarabine/ granulocyte-colony stimulating factor for up to 4 cycles (4 weeks per cycle)

MXN/Ara-C - methotrexate/ cytarabine for up to 4 cycles (15 to 20 days per cycle) or

HIDAC- high dose cytarabine every 12 hours for up to 12 doses (a second cycle was allowed after haematological recovery)

The dose of defined Investigator's choice of chemotherapy was reduced when necessary to manage treatment-related adverse drug reactions. Dose reductions or omissions were to be based on institutional guidelines or standard of care.

Study drug(s) could be discontinued in any cycle due to initiation of new anti-cancer therapy (i.e. conditioning for HSCT), disease progression, patient refusal or unacceptable toxicity. Patients with a suitable donor who achieved a response could undergo *stem-cell transplantation* at the discretion of the investigator.

Other therapy during study

Hydroxyurea was permitted for temporary control of elevated white blood cell counts in patients with aggressive disease both prior to and during the first 5 days of study treatment (both arms, first cycle only). Concurrent therapy for CNS prophylaxis/treatment (e.g. intrathecal methotrexate) was strongly encouraged. Growth factors such as granulocyte-colony stimulating factor (G-CSF), including pegfilgrastim, and granulocyte-macrophage-colony stimulating factor (GM-CSF), and corticosteroids were allowed if clinically indicated.

Other anti-cancer treatments were prohibited during active treatment but allowed post end-of-treatment (EOT) visit. Craniospinal radiation (CSXRT) was prohibited during study treatment. Medications known to predispose to Torsades de Pointes were prohibited; if considered medically necessary to treat a life-threatening condition, the Sponsor had to be notified immediately, and additional ECGs may be required prior to re-dosing with study drug.

Objectives

The two primary objectives included the comparison of haematological remission and the comparison of overall survival (OS) in patients with relapsed/refractory B-cell ALL randomized to receive inotuzumab ozogamicin (Arm A) versus patients randomized to receive active comparator (Arm B).

Secondary objectives included comparison of the rate of HSCT and the rate of VOD following HSCT between inotuzumab ozogamicin and the active comparator arm and to determine the population pharmacokinetic parameters of inotuzumab ozogamicin and confirm sources of exposure variability.

Exploratory objectives included determination of the relationship between inotuzumab ozogamicin exposure and efficacy, inotuzumab ozogamicin plasma concentration and QTcF interval the effect of exposure on circulating micro RNA.

Outcomes/endpoints

The two primary endpoints were haematological remission (CR/CRi) per blinded external independent endpoint adjudication committee (EAC) and OS.

CR was defined as a disappearance of leukaemia as indicated by <5% marrow blasts and the absence of peripheral blood leukaemic blasts, with recovery of hematopoiesis defined by ANC ≥1000/µL and platelets ≥100,000/µL. CRi was defined as CR except with ANC <1000/µL and/or platelet counts <100,000/µL. C1 extramedullary disease (EMD) status was required and assessed using the same technique as at baseline. Response was determined in a step-wise manner by the EAC according the EAC Charter: pathologists reviewed the slides and, if the patient had <5% blasts in the bone marrow, haematologists reviewed the radiology reports and then, if applicable, blood counts to determine CR vs. CRi.

Overall Survival (OS) was defined as the time from randomization to date of death due to any cause. Patients without an OS event, including those who withdrew from study refusing further follow-up, were censored at the last known alive date.

Secondary efficacy endpoints included:

- CR/CRi per Investigator's assessment
- MRD-negativity – lowest value of MRD minimal residual disease from first date of CR/CRi (CR complete remission ; CRi complete remission with partial haematological recovery rate) to EOT <1 x 10^{-4} blasts/nucleated cells by flow cytometry per central laboratory analysis (Genoptix, Carlsbad, CA, USA)
- DoR - Duration of Remission , defined as the time from date of first remission (CR/CRi) to progression or death
- Hematopoietic Stem Cell Transplant (HSCT) Rate
- PFS - time from date of randomization to earliest date of any of the following - progressive disease (including investigator determined clinical progression, relapse from CR/CRi, treatment discontinuation due to global health deterioration); death from any cause; starting new induction therapy or post-therapy HSCT without achieving CR/CRi
- PROs: Patient Reported Outcomes Health-related quality of life and health status as measured by the European Organization for Research and Treatment of Cancer questionnaire (EORTC QLQ-C30,

Version 3.0) and the EuroQol-5 Dimension (EQ-5D) questionnaire were collected at baseline (Cycle 1, Day 1), Day 1 of each subsequent cycle and at the end of treatment. They were completed prior to any tests or discussion of progress with healthcare personnel.

Disease assessment involved bone marrow evaluation and information from laboratory, clinical and radiological assessment performed at Day 16 to 28 of Cycles 1, 2, and 3, then every 1 to 2 cycles and at the EOT visit and whenever clinically indicated. For patients who had not progressed at EOT, disease was assessed every 12 weeks for up to 1 year from randomization and every 24 weeks between Year 1 and 2, until relapse. All patients were followed for survival every 3 months following discontinuation of study treatment for up to 5 years or 2 years after randomization of the last patient, whichever occurred first. Patients who underwent HSCT were followed for disease progression and survival. Potential VOD/SOS cases, irrespective of grade, causality or treatment arm were reported for up to 2 years from randomization.

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

Sample size

For the CR/CRi endpoint, 218 patients gave at least 88.5% power to detect a difference of response probabilities between 61% in the inotuzumab vs. 37% in the control arm for one-sided alpha=0.0125 for each analysis.

The study was also designed to detect a clinically meaningful difference in OS (hazard ratio 0.67 corresponding to medians 4.30 months on comparator arm and 6.45 months on investigational arm) with 80% power for one-sided alpha=0.0125. Assuming accrual of 2 patients per month for the first 6 months and 9.33 patients per month thereafter, approximately 3 months of follow-up after the last patient is accrued, 20% dropout within 15 days, 25% dropout total on the control arm and 5% dropout total on the InO arm, then a total sample size of 325 patients was required.

It was planned to randomize at least 218 patients, unless stopped earlier by the eDMC, over approximately 29 months for the CR/CRi endpoint. An additional 107 patients (325 patients total) were to be randomized for determination of OS in approximately 12 more months. If accrual was not complete one year after the second interim analysis, the study could be stopped short of the planned 325 patients. The original sample size was increased from 292 patients (see Protocol Amendment 3).The number of patients randomized who were due to receive Salvage 2 was capped at a third of the entire trial population and the number of patients with Philadelphia chromosome positive disease was capped at approximately 20% of the entire trial population.

Randomisation

Patients were randomized in a 1:1 ratio to the investigational treatment of single-agent inotuzumab ozogamicin or defined Investigator's choice of chemotherapy (FLAG, MXN/Ara-C or HIDAC). Once chosen, patients randomized to the comparator arm (Arm B) may not switch to an alternative investigator's choice therapy.

Randomization was stratified by 3 prognostic factors: duration of first remission (<12 vs ≥12 months), line of salvage (Salvage 1 vs 2) and patient age at randomization (<55 vs ≥ 55 years).

Blinding (masking)

This was an open label study.

Statistical methods

There was no control of type I error across secondary endpoints, which were tested at 1-sided 0.025 (2-sided 0.05).

Two interim analyses of OS were planned and reviewed by an independent external Data Monitoring Committee (e-DMC).

The first interim analysis was planned to assess futility only and the trial could not be stopped for efficacy at the first interim analysis. Assuming the interim analysis occurred at exactly 62 events, the trial could be stopped for futility if the p-value was greater than 0.61 (corresponding to hazard ratio of >1.07).

The second interim analysis was planned to assess futility and efficacy when at least 60% of the target OS events were observed and was to be considered the final OS analysis if the pre-specified efficacy boundary was crossed. Assuming the interim analysis occurred at exactly 149 events, the trial could be stopped for futility if the p-value was greater than 0.17 (corresponding to hazard ratio of >0.86) or for efficacy if the p-value was less than 0.003 (corresponding to hazard ratio of <0.64).

The second interim analysis of OS was conducted based on a data cutoff date of 19 January 2015 when 163 OS events had occurred in 326 randomized patients. The e-DMC reviewed the results on 11 March 2015 and recommended the study to continue as planned.

Adjusting for the interim analysis the final analysis for OS was conducted using 1-sided p=0.0104 as the cut-off (equivalent to 2-sided p=0.0208).

Haematological remission

The final analysis of CR/CRi was planned for after the first 218 patients had been followed for at least 3 months post-randomization. Patients who did not achieve CR/CRi, including patients who did not receive study treatment, were considered as non-responders. CR/CRi rates were compared between the inotuzumab ozogamicin arm and the control arm using the Chi-square test or Fisher's exact test (if any cell size was under 5) at 1-sided α =0.0125 significance level. For each treatment arm, the CR/CRi rate along with the 95% confidence interval (CI) around the rate was computed. The estimate of the difference in CR/CRi rate between the 2 treatment arms and its 97.5% CI was computed.

Sensitivity analyses were conducted to investigate the robustness of the primary analysis, CR/CRi per EAC assessment, including analysis of the following populations: mITT218, PP218 and ITT218 assuming all untreated patients are responders. Logistic regression multiple imputation analyses (missing at random [MAR] and missing not at random [MNAR]) and a weighted Chi-square test were conducted. The latter applied weights on each patient in the mITT218 population based on their probability of early drop-out, aiming to mitigate the impact on the response analysis resulting from the early dropouts without treatment in the defined Investigator's choice of chemotherapy arm (B) compared with no early dropout in the inotuzumab arm (A). All patients in the Arm B of mITT218 population were given equal weight of 1; while for

Arm A lower weights were given to patients whose baseline characteristics predisposed them to higher probability of early dropout had they been randomized to the control arm.

The potential correlation between CR/CRi and intrinsic and extrinsic baseline factors were evaluated in mITT218 Population using logistic regression to include the treatment arm and the following covariates: age, race (white, other), gender, disease characteristics (blasts %), ECOG performance scores (0/1, >1), baseline HRQoL (standardized global health/QoL score), duration of first remission (<1 year, ⩾1 year), salvage treatment (Salvage 1, 2), response to most recent prior regimen (CR, other), cytogenetics (normal, other) and absolute circulating blasts.

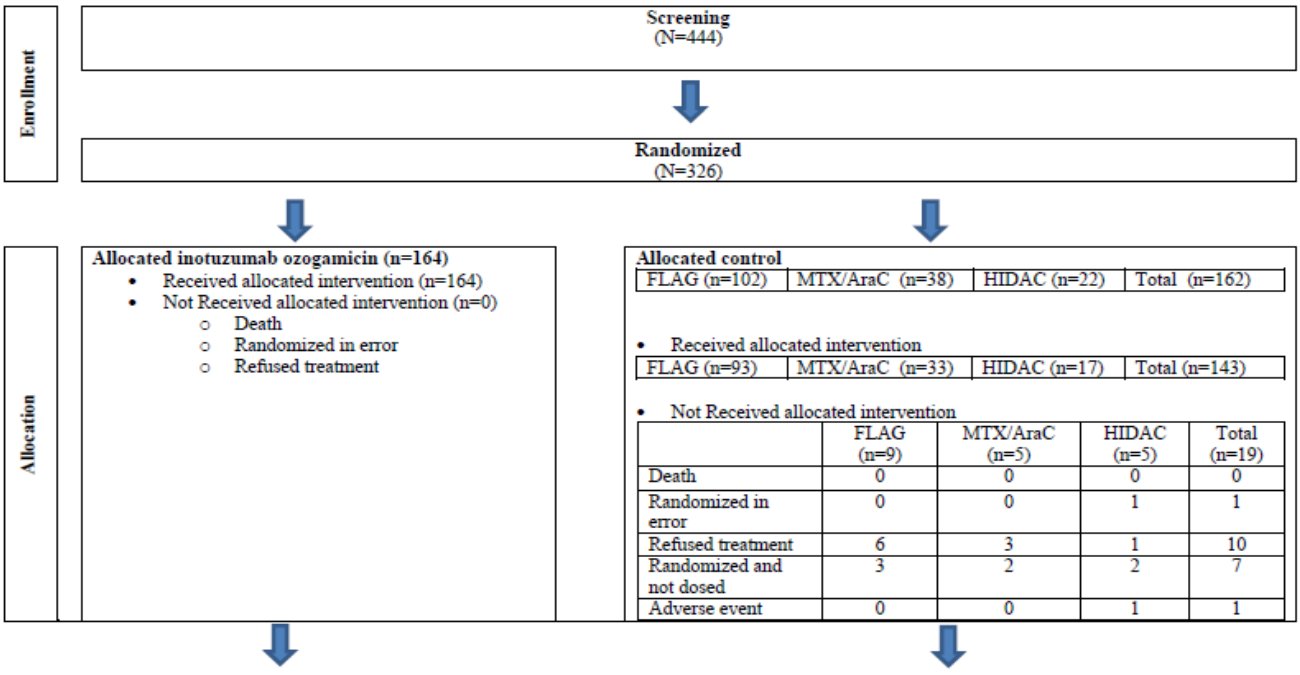
An additional set of sensitivity analyses were conducted using Cochran-Mantel-Haenszel (CMH) test stratified by stratification factors at randomization. This was performed for both CR/CRi per EAC and CR/CRi per Investigator's assessment.

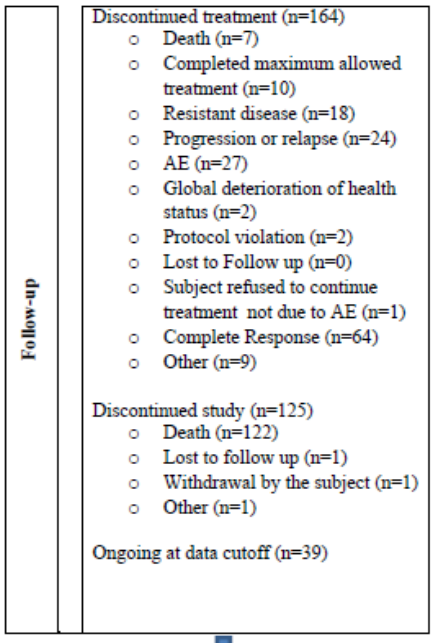
Overall survival

Final OS analysis was planned for when approximately 248 required events were observed in 326 randomized patients. OS was analysed based on the log-rank test and the hazard ratio and corresponding 97.5% 2-sided confidence interval using stratified Cox proportional hazard regression presented. The median OS was estimated using the Kaplan-Meier method and reported with 2 sided 97.5% confidence intervals for each arm.

Results

Participant flow: Treated patients (ITT=) (Study B1931022)

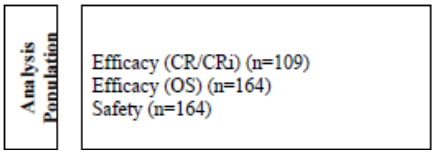




Discontinued treatment	FLAG (n=93)	MTX/AraC (n=33)	HIDAC (n=17)	Total (n=143)
Death	4	1	1	6
Completed maximum allowed treatment	0	0	1	1
Resistant disease	46	7	9	62
Progression or relapse	12	7	1	20
AE	3	5	2	10
Global deterioration of health status	1	1	2	4
Protocol violation	0	0	0	0
Lost to Follow up	0	0	0	0
Subject refused treatment not due to AE	6	2	1	9
Complete response	12	9	0	21
Other	9	1	0	10

Discontinued study	FLAG (n=91)	MTX/AraC (n=35)	HIDAC (n=21)	Total (n=147)
Death	85	27	17	129
Lost to follow up	0	1	0	1
Withdrawal by the subject	5	7	4	16
Other	1	0	0	1

Ongoing at data cutoff	FLAG	MTX/AraC	HIDAC	Total
	11	3	1	15



	FLAG	MTX/AraC	HIDAC	Total
Efficacy (CR/CRi)	69	25	15	109
Efficacy (OS)	102	38	22	162
Safety	93	33	17	143

Recruitment

A total of 444 patients were screened at centres across Europe, America, Asia and Australia. Of these, 326 were randomized (N=164 to inotuzumab ozogamicin and N=162 to the control chemotherapy arm i.e. the ITT population). The first subject first visit was 2 August 2012 and the last patient was randomized on 4 January 2015.

Conduct of the study

Table 26 Summary of Protocol Amendments for the Study B1931022

Document	Version Date	Summary of Changes
Amendment 3	28 March 2014	• Inotuzumab ozogamicin clinical background was updated. • The total sample size is increased due to higher number of patients withdrawing from treatment before start of therapy and loss of follow-up data in ARM B. • To reflect the ALL adult population, randomization of patients with Philadelphia chromosome positive ALL that have failed TKI based therapies has been capped to approximately 20% of the entire trial population. • Recommendations to reduce the risk of VOD for patients proceeding to SCT were further clarified and include avoidance of hepatotoxic myeloablative regimens for subsequent SCT and limiting the number of cycles of inotuzumab ozogamicin treatment in patients proceeding to SCT. • Central CD22 results will be considered for eligibility in the setting of local negative results because some samples found to be negative with local testing have subsequently been determined to be positive by the central laboratory. • Medications used as prophylaxis for hepatotoxicities or for the treatment of VOD are required to be reported for up to 2 years from randomization. • Clarifications and revisions are made throughout the protocol.

Amendment 2	24 Jun 2013	• Removed TTP as a secondary endpoint. • Dose of inotuzumab ozogamicin will be reduced to 0.5 mg/m^2 at Day 1 of cycle 2 and beyond in patients achieving either CR or CRi. • Approximately 190 sites required for study completion. • Made a correction on the power for testing CR/CRi. It is changed from 88% to 89%. • Immunohistochemistry allowed for the determination of CD22 expression at screening in patients with inadequate BM aspirate and no circulating blasts. • An additional marrow sample will be collected for analysis of leukemic blast phenotype/genotype by other test methods. • Timing of disease assessment changed. • Updated information on other inotuzumab ozogamicin ALL studies. • Revised and clarified some inclusion/exclusion criteria (inclusion # 1, 2, 4, 7, 10 and exclusion #2, 4, 5, 7 and 26). • Updated study drug administration tables. • Modified dose reduction schema allowed for drug related toxicities in Arm A. • Updated section on destruction of partially used or empty drug vials.

		• Provided clarification regarding disease assessment. • Updated SAE reporting section. • More details on the sample size calculation are added. • Clarifications and typographical corrections throughout the protocol.
Amendment 1	09 Apr 2012	• Inclusion criteria #1, 3 and exclusion criteria #3, 17 and 18 were added or modified. • The assessment of bone marrow biopsies is only required for patients with inadequate hematologic recovery. • Patient follow up time for survival is now extended. Requirement for effective contraception extended to 90 days post therapy. Redundant/unnecessary laboratory tests were removed. Administrative corrections and clarifications done throughout the protocol.
Original protocol	26 Jan 2012	N/A
This amendment incorporates all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.		

The important protocol deviations are reported in Table 27.

Table 27 : Summary of Potentially Important Protocol Deviations - ITT Population (Study B1931022) as of 08 March 2016 data cut-off date

Protocol Deviation Coded Term	Inotuzumab Ozogamicin (N=164) n (%)	Defined Investigator's Choice of Chemotherapy (N=164) n (%)
Concomitant medications		
Took prohibited med during treatment	21 (13.1)	27 (17.0)
ICD issues		
ICD not dated by patient/site	4 (2.5)	7 (4.4)
Signed ICD not in site file/lost	1 (0.6)	1 (0.6)
Study procedure prior to consent	3 (1.9)	5 (3.1)
Inclusion/exclusion criteria		
Specify in comments	19 (11.9)	24 (15.1)
Patient didn't have study condition	2 (1.3)	5 (3.1)
Patient on excluded medication(s)	0	1 (0.6)
Study drug		
Dosing noncompliance	39 (24.4)	31 (19.5)
Specify in comments	26 (16.3)	34 (21.4)
Patient took incorrect dose	14 (8.8)	3 (1.9)

Defined Investigator's choice of chemotherapy (control arm) was 1 of the defined chemotherapy regimens (FLAG, MXN/Ara-C, or HIDAC).
Percentage was calculated based on the number of patients.
Abbreviations: FLAG=fludarabine + cytarabine + G-CSF; G-CSF=granulocyte-colony stimulating factor; HIDAC=high-dose cytarabine; ICD=informed consent form; ITT=intent-to-treat; MXN/Ara-C=cytarabine and mitoxantrone; n=number of patients that met the criteria; N=number of patients.

Within the inotuzumab ozogamicin arm, medication errors per protocol definition (administered dose 10% higher or lower than the prescribed dose) were reported for 15 patients. No single doses of inotuzumab >0.8 mg/m^2 or total doses of >1.8 mg/m^2 in a 21 day period were administered. Dose delays for AEs (mostly hepatic and haematological) were not implemented for 20 patients in the inotuzumab ozogamicin arm. Re-dosing in the setting of elevated liver enzymes was reported for 10 patients. Among these, two patients were dosed with an elevated bilirubin. Both patients proceeded to HSCT and developed Grade 3 and Grade 4 VOD, respectively.

Ten patients with protocol deviations regarding eligibility criteria were excluded from the PP Population; 9 did not meet the first eligibility criterion (<20% CD22 blast positivity per local laboratory assessment, due Salvage 3 therapy, <5% blasts in the BM). One patient in the inotuzumab ozogamicin arm was not eligible per the Sponsor's assessment due to multi-agent chemotherapy (EPOCH) administered after a second relapse while awaiting study enrolment. This therapy was considered a salvage induction regimen by the Sponsor (Salvage 3) but maintenance by the Investigator. One patient was not withdrawn from the study at the end of Cycle 1 following progressive disease, but continued inotuzumab ozogamicin treatment until the end of Cycle 3.

Baseline data

For the ITT Population, the majority of patients were male (193/326 [59.2%]) and White (232/326 [71.2%]). The median age was 47.0 years (range 18 to 79 years). A higher percentage of patients were aged 65 years

or over in the inotuzumab ozogamicin arm than in the control arm (18.3% vs 13.6%). The median weight was 74.0 kg (range 40.0 to 192.0 kg).

In the safety population, a total of 29 (17.7%) patients in the inotuzumab ozogamicin arm and 26 (18.2%) patients in the control arm had a pre-study HSCT.

Demographic and Baseline Characteristics are summarized in Table 28.

Table 28 Key Demographic and Baseline Characteristics (ITT [as of 8 March 2016 data cut-off date] and ITT218 Populations) Study B1931022

Characteristic	Inotuzumab Ozogamicin		Defined Investigator's Choice of Chemotherapy[a]	
	ITT (N=164)	ITT218 (N=109)	ITT (N=162)	ITT218 (N=109)
Age (years)				
Median (range)	46.5 (18-78)	47.0 (18-78)	47.5 (18-79)	47.0 (18-79)
Central CD22 [n, (%)]				
≥90	107 (65.2)	74 (67.9)	93 (57.4)	63 (57.8)
≥70- <90	30 (18.3)	21 (19.3)	18 (11.1)	12 (11.0)
<70	5 (3.0)	3 (2.8)	18 (11.1)	12 (11.0)
Missing	22 (13.4)	11 (10.1)	33 (20.4)	22 (20.2)
Salvage status (CRF data) [n (%)]				
1	111 (67.7)	73 (67.0)	104 (64.2)	69 (63.3)
2	51 (31.1)	35 (32.1)	57 (35.2)	39 (35.8)
Other[b]	2 (1.2)	1 (0.9)	1 (0.6)	1 (0.9)
Karyotype (local lab)				
Normal	46 (28.0)	27 (24.8)	42 (25.9)	23 (21.1)
Abnormal	98 (59.8)	66 (60.6)	98 (60.5)	70 (64.2)
Unknown/Missing	20 (12.2)	16 (14.7)	22 (13.6)	16 (14.7)
Chromosomal Abnormalities [n(%)]				
Ph^{+c}	22 (13.4)	14 (12.8)	28 (17.3)	18 (16.5)
Ph^{+}(local laboratory)	12 (7.3)	9 (8.3)	19 (11.7)	10 (9.2)
Ph^{+} (medical history only)	5 (3.0)	2 (1.8)	6 (3.7)	5 (4.6)
t (4,11)	6 (3.7)	3 (2.8)	7 (4.3)	6 (5.5)
Response to prior regimen #1 (first induction regimen)				
Complete response (CR1)	136 (82.9)	93 (85.3)	129 (79.6)	90 (82.6)
Partial response	12 (7.3)	7 (6.4)	6 (3.7)	3 (2.8)
Resistant disease	15 (9.1)	7 (6.4)	20 (12.3)	10 (9.2)
Progressive disease	1 (0.6)	2 (1.8)	5 (3.1)	5 (4.6)
Unknown	0	0	2 (1.2)	1 (0.9)
Duration of CR1 (months)				
Median (range)	11.4 (0.5, 118.6)		9.3 (0.5, 194.2)	
Response to prior regimen #2 (only includes subjects with >1 prior treatment)				
Complete response	31 (56.4)	15 (42.9)	29 (50.0)	19 (46.3)
Other[d]	24 (43.6)	19 (54.3)	29 (50.0)	22 (53.7)

Characteristic	Inotuzumab Ozogamicin		Defined Investigator's Choice of Chemotherapy[a]	
	ITT (N=164)	ITT218 (N=109)	ITT (N=162)	ITT218 (N=109)
Unknown[d]	0	1 (2.9)	0	0
Peripheral blast count by local laboratory (/μL)[e]				
N	163	108	159	108
Median	107.6	175.4	30.0	39.3
Min, Max	0.0, 42660.0	0.0, 42660	0.0, 43331.4	0.0, 31500
Peripheral blast count (/μL) by local laboratory n (%)				
0	71 (43.3)	42 (38.5)	74 (45.7)	48 (44.0)
>0 - 1,000	37 (22.6)	32 (29.4)	44 (27.2)	35 (32.1)
>1,000 - 5,000	33 (20.1)	22 (20.2)	23 (14.2)	12 (11.0)
>5,000 - 10,000	16 (9.8)	8 (7.3)	9 (5.6)	7 (6.4)
>10,000	6 (3.7)	4 (3.7)	9 (5.6)	6 (5.5)

a One of the defined chemotherapy regimens (FLAG, MXN/Ara-C or HIDAC).
b Includes Salvage 3, up or missing
c Ph^+ status by central laboratory FISH analysis (BCR ABL ≥7%) or local laboratory results or medical history (if both central FISH and local results missing). Normal, t(4;11) and Other collected from local cytogenetic analysis.
d Percentages calculated using the number of patients who received prior regimen #2 as the denominator.
e Peripheral blast count = (peripheral blasts x 0.01) x (WBC x 1000)

Other baseline characteristics of ITT population, including primary diagnoses and duration, are reported in Table 29.

Table 29: Summary of Primary Diagnoses and Durations - ITT Population Study B1931022 (as of 8 March 2016 data cut-off date)

Primary Diagnosis	Inotuzumab Ozogamicin (N=164)	Defined Investigator's Choice of Chemotherapy (N=162)	Total (N=326)
B-cell ALL			
Number of patients	153 (93.3)	156 (96.3)	309 (94.8)
Duration since initial histopathological diagnosis (months)[a]			
n	153	156	309
Mean	20.4	18.6	19.5
SD	23.12	17.86	20.62
Median	12.5	13.0	12.9
Minimum, maximum	1.08, 195.11	1.05, 113.01	1.05, 195.11
B-cell lymphoblastic lymphoma			
Number of patients	11 (6.7)	6 (3.7)	17 (5.2)
Duration since initial histopathological diagnosis (months)[a]			
n	11	6	17
Mean	19.6	41.5	27.3
SD	16.78	76.65	46.13
Median	10.5	12.9	12.2
Minimum, maximum	1.45, 45.80	4.07, 197.67	1.45, 197.67

Defined Investigator's choice of chemotherapy (control arm) was 1 of the defined chemotherapy regimens (FLAG, MXN/Ara-C, or HIDAC).
Abbreviations: ALL=acute lymphoblastic leukemia; FLAG=fludarabine + cytarabine + G-CSF; G-CSF=granulocyte-colony stimulating factor; HIDAC=high-dose cytarabine; ITT=intent-to-treat; MXN/Ara-C=mitoxantrone + cytarabine; n=number of patients that met the criteria; N=number of patients; SD=standard deviation.

a. Durations were counted from date of first diagnosis to collection date of current histopathological diagnosis. If collection date of initial histopathological diagnosis was missing then duration was counted to date of first dose.

Prior and Concomitant Treatments

Table 30: Study B1931022: Prior TKI treatment in Ph+ ALL Patients[a] in Study B1931022 (as of 08 March 2016 data cut-off date)

	B1931022 Ph+ ALL Patients[a]			
	Inotuzumab ozogamicin (N=22)		Investigator's choice of chemotherapy (N=28) [a]	
TKI	**n**	**%**	**N**	**%**
Prior TKI:	19	86.4	26	92.9
Dasatinib	18	81.8	24	85.7
Imatinib	10	45.5	14	50
Ponatinib	4	18.2	7	25
Nilotinib	4	18.2	6	21.4
Bosutinib	1	4.5	0	0
Prior 2nd or 3rd generation TKI [b]	19	86.4	25 [b]	89.3 [b]
No prior TKI [b]	3	13.6	2 [b]	7.1 [b]
Number of prior TKI-containing regimens				
0	3	13.6	2 [b]	7.1 [b]
1	13	59.1	15	53.6
2	6	27.3	11	39.3
Best Response to first prior TKI-containing regimen				
CR	16	72.7	25	89.3
PR	1	4.5	0	0
RD/SD	2	9.1	1	3.6
No prior TKI	3	13.6	2 [b]	7.1 [b]
Duration of Response to first prior TKI-containing regimen				
<12 months	11	50.0	16	57.1
>=12 months	6	27.3	9	32.1
No response	2	9.1	1	3.6
No prior TKI	3	13.6	2 [b]	7.1 [b]
Best Response to most recent prior TKI-containing regimen				
CR	15	68.2	21	75.0
PR	0	0	2	7.1
RD/SD	4	18.2	3	10.7
No prior TKI	3	13.6	2 [b]	7.1 [b]

a Ph+ status per local laboratory cytogenetics, central laboratory cytogenetics, or reported medical history. In the control arm, includes 1 Ph- ALL patient who was incorrectly identified as having Ph+ ALL b In the inotuzumab ozogamicin arm, 3 Ph+ ALL patients did not have prior TKI reported. In the control arm, 1 Ph+ ALL patient did not have prior TKI reported and (a) 1 Ph- ALL patient was incorrectly identified as having Ph+ ALL and was included as a patient who did not receive prior TKI, and (b) 1 Ph+ ALL patient did not have prior treatment with a 2nd- or 3rd-generation TKI reported at the time of table generation (only prior treatment with imatinib was reported; prior treatment with dasatinib was later reported).

Table 31: Summary of Steroids and Other Anti-Cancer Drugs Given within 2 Weeks from Randomization to End of Cycle 1 Day 5 - Safety Population Study B1931022 (as of 8 March 2016 Data Cutoff Date)

Preferred Term	Inotuzumab Ozogamicin (N=164) n (%)	Defined Investigator's Choice of Chemotherapy (N=143) n (%)
Number of patients with any drug treatment	154 (93.9)	95 (66.4)
Betamethasone	2 (1.2)	1 (0.7)
Celestamine/00252801	4 (2.4)	0
Dexamethasone	46 (28.0)	54 (37.8)
Fludrocortisone	1 (0.6)	0
Hydrocortisone	46 (28.0)	8 (5.6)
Hydroxycarbamide[a]	20 (12.2)	15 (10.5)
Mercaptopurine	1 (0.6)	2 (1.4)
Methotrexate	0	1 (0.7)
Methylprednisolone	67 (40.9)	22 (15.4)
Prednisolone	17 (10.4)	6 (4.2)
Prednisone	23 (14.0)	11 (7.7)
Vinblastine	1 (0.6)	0
Vincristine	9 (5.5)	4 (2.8)
Vindesine	2 (1.2)	0

Defined Investigator's choice of chemotherapy (control arm) was 1 of the defined chemotherapy regimens (FLAG, MXN/Ara-C, or HIDAC).
WHO-Drug (June 2014) coding dictionary applied.
Abbreviations: FLAG=fludarabine + cytarabine + G-CSF; G-CSF=granulocyte-colony stimulating factor; HIDAC=high-dose cytarabine; MXN/Ara-C=cytarabine and mitoxantrone; n=number of patients that met the criteria; N=number of patients; WHO=World Health Organization.
a. Also known as hydroxyurea.

a. Also known as hydroxyurea.

Steroids were also allowed to be used as CNS prophylaxis (intrathecal chemotherapy), pre- medication prior to study drug administration (1 day), to treat hypersensitivity reactions (1 day) and as anti-emetics (up to 8 days/cycle).

Table 32 shows the summary of steroids administered after randomization within the safety population of Study B1931022.

Table 32: Summary of Steroids Administered After Randomization – Safety Population Study B1931022 (as of 8 March 2016 Data Cutoff Date)

Steroid Administered	Inotuzumab Ozogamicin (N=164) n (%)	Defined Investigator's Choice of Chemotherapy (N=143) n (%)
Number of patients with any steroid	157 (95.7)	100 (69.9)
Betamethasone	3 (1.8)	2 (1.4)
Budesonide	1 (0.6)	0
Celestamine/00252801	4 (2.4)	0
Dexamethasone	50 (30.5)	57 (39.9)
Hydrocortisone	57 (34.8)	25 (17.5)
Methylprednisolone	75 (45.7)	26 (18.2)
Prednisolone	20 (12.2)	5 (3.5)
Prednisone	21 (12.8)	9 (6.3)
Triamcinolone[a]	1 (0.6)	0

Defined Investigator's choice of chemotherapy (control arm) was 1 of the defined chemotherapy regimens (FLAG, MXN/Ara-C, or HIDAC).
WHO-Drug (June 2014) coding dictionary applied.
Abbreviations: FLAG=fludarabine + cytarabine + G-CSF; G-CSF=granulocyte-colony stimulating factor; HIDAC=high-dose cytarabine; MXN/Ara-C=mitoxantrone + cytarabine; n=number of patients meeting pre-specified criteria; N=number of patients; WHO=World Health Organization.
a. Triamcinolone was applied topically to 1 Patient for Worsening of osteoarthritis, right wrist (intra-articular).

Table 33: Summary of Medical History for Pre-Specified Hepatic Medical Conditions – ITT Population Study B1931022 (as of 8 March 2016 Data Cutoff Date)

Medical Condition[a]	Inotuzumab Ozogamicin (N=164)					Defined Investigator's Choice of Chemotherapy (N=162)				
	Yes	No	Unknown	Not Assessed	Missing	Yes	No	Unknown	Not Assessed	Missing
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Hepatic steatosis	12 (7.3)	151 (92.1)	1 (0.6)	0	0	7 (4.3)	150 (92.6)	3 (1.9)	0	2 (1.2)
Neoplasm NOS	11 (6.7)	151 (92.1)	2 (1.2)	0	0	11 (6.8)	147 (90.7)	2 (1.2)	0	2 (1.2)
Gallbladder disorder	10 (6.1)	152 (92.7)	2 (1.2)	0	0	7 (4.3)	151 (93.2)	3 (1.9)	0	1 (0.6)
Cholelithiasis	8 (4.9)	154 (93.9)	2 (1.2)	0	0	6 (3.7)	151 (93.2)	4 (2.5)	0	1 (0.6)
Ascites	2 (1.2)	160 (97.6)	2 (1.2)	0	0	1 (0.6)	157 (96.9)	2 (1.2)	0	2 (1.2)
VOD[b]	1 (0.6)	163 (99.4)	0	0	0	1 (0.6)	159 (98.1)	0	0	2 (1.2)
Nodular hepatic disease	0	162 (98.8)	2 (1.2)	0	0	0	157 (96.9)	3 (1.9)	0	2 (1.2)

Defined Investigator's choice of chemotherapy (control arm) was 1 of the defined chemotherapy regimens (FLAG, MXN/Ara-C, or HIDAC). MedDRA (v18.1) coding dictionary applied.
Individual patients may have had >1 condition. Table reported the medical condition as collected in the case report form (pre-specified fields) not the coded preferred terms.

a. Medical condition included: Hepatic steatosis, Neoplasm NOS (coded to neoplasm), Gallbladder disorder, Ascites, Cholelithiasis, Venoocclusive disease, and Nodular hepatic disease (coded to hepatic neoplasm).
b. One patient in the control arm was noted to have a medical history for the pre-specified hepatic medical condition of VOD/SOS by mistake, as the patient had superior limb thrombophlebitis

Numbers analysed

ITT: included all randomized patients, with study drug assignment designated according to initial randomization.

ITT218: a subset of the ITT population that included the initial 218 randomized patients. This was the primary population for the final analysis of CR/CRi, DoR and MRD as pre-specified in the SAP.

mITT: all randomized patients who started treatment, with study drug assignment designated according to initial randomization.

mITT218: a subset of both the mITT and ITT218 populations that included patients among the initial 218 patients randomized who started treatment, with study drug assignment designated according to initial randomization. This population was used for the sensitivity analysis of CR/CRi.

PP: patients who met all of the following criteria: randomized and received at least one dose of study drug; no major protocol violations and had an adequate baseline disease assessment.

PP218: a subset of the PP population, included patients among the initial 218 patients randomized who met the criteria for PP population. The PP218 population was used for the sensitivity analysis of CR/CRi.

Safety: all randomized patients who receive at least 1 dose of study drug, with treatment assignments designated according to actual study treatment received.

Outcomes and estimation

Primary endpoints

Haematological Remission (CR/CRi per EAC)

Table 34: Summary of CR/CRi (per EAC Assessment) (ITT218, mITT218 and PP218 Populations) (data cut-off 2 October 2014) - Study B1931022

Analysis Population	Inotuzumab Ozogamicin n/N (%) [95% CI]	Defined Investigator's Choice of Chemotherapy n/N (%) [95% CI]	CR/CRi Rate Difference % [97.5% CI]	Chi-Square Test 1-sided p-value
ITT218				
CR/CRi (Primary)	88/109 (80.7) [72.1, 87.7]	32/109 (29.4) [21.0, 38.8]	51.4 [38.4, 64.3]	<0.0001
CR	39 (35.8) [26.8, 45.5]	19 (17.4) [10.8, 25.9]	18.3 (5.2, 31.5)	0.0011
CRi	49 (45.0) [35.4, 54.8]	13 (11.9) [6.5, 19.5]	33.0 [20.3, 45.8]	<0.0001
CR or CRi not met No post-baseline samples ⩾5% blasts by central laboratory <5% blasts by central laboratory[a]	21 (19.3) 11 (10.1) 9 (8.3) 1 (0.9)	77 (70.6) 36 (33.0) 36 (33.0) 5 (4.6)		
mITT218				
CR/CRi	88/109 (80.7) [72.1, 87.7]	32/96 (33.3) [24.0, 43.7]	47.4 [33.7,61.1]	<0.0001
PP218				
CR/CRi	87/106 (82.1) [73.4, 88.8]	31/90 (34.4) [24.7, 45.2]	47.6 [33.6,61.6]	<0.0001

a. Patients with <5% bone marrow blasts by central lab, but did not meet criteria for CR or CRi due to the presence of peripheral blasts, EMD, or missing assessments.

For the individual therapies in the defined Investigator's choice of chemotherapy arm, the CR/CRi rates per EAC assessment were as follows (October 2014 data cutoff):

- FLAG (n=69) - 27.5% (95% CI: 17.5, 39.6)
- MXN/Ara-C (n=25) - 44.0% (95% CI: 24.4, 65.1)
- HIDAC (n=15) - 13.3% (95% CI: 1.7, 40.5)

Table 35: CR/CRi, CR and CRi Rates (per Investigator) – Updated Analysis of ITT218 Population (data cut-off date 8 March 2016) - Study B1931022

	Inotuzumab Ozogamicin (N=109)	Defined Investigator's Choice of Chemotherapy (N=109)	Rate Difference	P-value[a]
CR, n (%)	39 (35.8)	18 (16.5)		
CRi, n (%)	45 (41.3)	14 (12.8)		
CR/CRi rate, n (%)	84 (77.1)	32 (29.4)	47.7	<0.0001
95% CI for rate and 97.5% CI for rate difference	(68.0, 84.6)	(21.0, 38.8)	(34.4, 61.0)	
CR rate, n (%)	39 (35.8)	18 (16.5)	19.3	0.0006
95% CI for rate and 97.5% CI for rate difference	(26.8, 45.5)	(10.1, 24.8)	(6.2, 32.3)	
CRi rate, n (%)	45 (41.3)	14 (12.8)	28.4	<0.0001
95% CI for rate and 97.5% CI for rate difference	(31.9, 51.1)	(7.2, 20.6)	(15.7, 41.2)	

Source: Table 14.2.1.1.1

Table 36: CR/CRi, CR and CRi Rates (per Investigator) –ITT population (data cut-off 8 March 2016) - Study B1931022

	Inotuzumab Ozogamicin (N=164)	Defined Investigator's Choice of Chemotherapy (N=162)	Rate Difference	P-value[a]
Complete remission (CR), n (%)	55 (33.5)	26 (16.0)		
Complete remission with incomplete hematologic recovery (CRi)	65 (39.6)	24 (14.8)		
CR/CRi rate, n (%)	120 (73.2)	50 (30.9)	42.3	<0.0001
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, n (%)	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, n (%)	65 (39.6)	24 (14.8)	24.8	<0.0001
95% CI for rate and 97.5% CI for rate difference	(32.1, 47.6)	(9.7, 21.2)	(14.2, 35.4)	

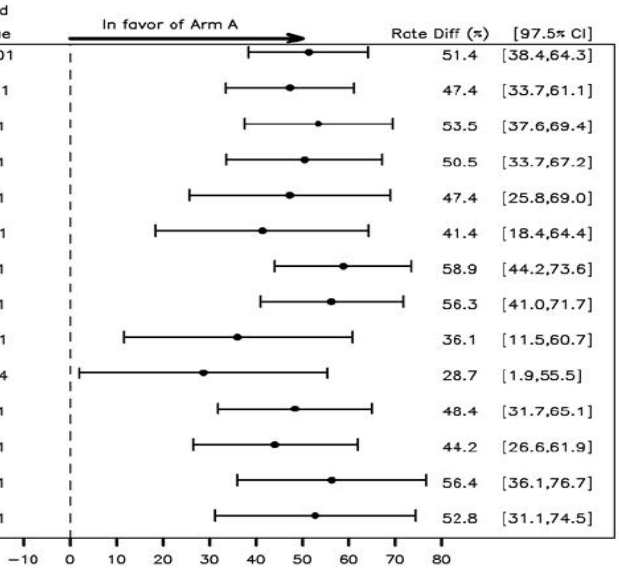
Source: Table 14.2.1.1.1.1

In the mITT326 population, the CR/CRi rate per investigator was 73.2% (95% CI: 65.7-79.8) in the inotuzumab ozogamicin arm compared with 35% (95% CI: 27.2-43.4) in the control arm. The rate difference was 38.2% (97.5% CI: 26.4-50.0) (1-sided p<0.0001 [Chi-square test]).

Subgroup analyses by the stratification factors are shown in Figure 2.

Figure 2: Forest Plot of CR/CRi Results (Per EAC) by Stratification Factors at Randomization - ITT218 and mITT218 Populations Study B1931022 (2 October 2014 data cut-off)

Analysis	Population	Sample size (CR/CRi) Arm A	Arm B	CR/CRi Rate (%) Arm A	Arm B	1-sided p-value	Rate Diff (%)	[97.5% CI]
All patients	ITT218	109(88)	109(32)	80.7	29.4	<.0001	51.4	[38.4,64.3]
All patients	mITT218	109(88)	96(32)	80.7	33.3	<.0001	47.4	[33.7,61.1]
DFR < 12 mo	ITT218	71(55)	71(17)	77.5	23.9	<.0001	53.5	[37.6,69.4]
DFR < 12 mo	mITT218	71(55)	63(17)	77.5	27.0	<.0001	50.5	[33.7,67.2]
DFR >=12 mo	ITT218	38(33)	38(15)	86.8	39.5	<.0001	47.4	[25.8,69.0]
DFR >=12 mo	mITT218	38(33)	33(15)	86.8	45.5	0.0001	41.4	[18.4,64.4]
Salvage 1	ITT218	73(64)	73(21)	87.7	28.8	<.0001	58.9	[44.2,73.6]
Salvage 1	mITT218	73(64)	67(21)	87.7	31.3	<.0001	56.3	[41.0,71.7]
Salvage 2	ITT218	36(24)	36(11)	66.7	30.6	0.0011	36.1	[11.5,60.7]
Salvage 2	mITT218	36(24)	29(11)	66.7	37.9	0.0104	28.7	[1.9,55.5]
Age < 55	ITT218	66(53)	69(22)	80.3	31.9	<.0001	48.4	[31.7,65.1]
Age < 55	mITT218	66(53)	61(22)	80.3	36.1	<.0001	44.2	[26.6,61.9]
Age >= 55	ITT218	43(35)	40(10)	81.4	25.0	<.0001	56.4	[36.1,76.7]
Age >= 55	mITT218	43(35)	35(10)	81.4	28.6	<.0001	52.8	[31.1,74.5]



In the ITT218 Population, in the inotuzumab ozogamicin arm compared to the control arm the CR/CRi rate was 82.4% versus 36.5% and 81.0% versus 16.7% for patients who had ⩾90% or ⩾70% to <90% CD22-positive leukaemic blasts at baseline, respectively. In the control arm the CR/CRi rate was 33.3% for patients who had <70% CD22-positive leukaemic blasts at baseline. In the inotuzumab ozogamicin arm, only 3 patients had <70% CD22-positive leukaemic blasts at baseline so comparison for CR/CRi was not conducted.

In the ITT218 population, 13 patients who were randomized to the defined Investigator's choice of chemotherapy arm refused to be treated. A sensitivity analysis was conducted to investigate the potential impact of these drop-outs on the analysis of CR/CRi by assuming that all untreated patients are responders. Assuming that the 13 patients that refused treatment in the control arm were responders, was highly

conservative and remained statistically significantly in favour of inotuzumab ozogamicin (CR/CRi 80.7% vs. 41.3%; rate difference 39.4% (97.5% CI 31.9, 51.1%, p<0.0001).

Results in the mITT218 population (where the untreated patients were excluded) were consistent with those from the ITT128. The CR rate (per EAC) was 35.8% (95% CI: 26.8, 45.5) in the inotuzumab ozogamicin arm compared with 19.8% (95% CI: 12.4, 29.2) in the control arm. The rate difference was 16.0% (97.5% CI: 2.2, 29.7) and was statistically significant (1-sided p=0.0056 [Chi-square test]). The CRi rate (per EAC) was 45.0% (95% CI: 35.4, 54.8) in the inotuzumab ozogamicin arm compared with 13.5% (95% CI: 7.4, 22.0) in the control arm. The rate difference was 31.4% (97.5% CI: 18.2, 44.7) and was statistically significant (1-sided p<0.0001 [Chi-square test]).

In the PP population, the CR rate (per EAC) was 35.8% (95% CI: 26.8, 45.7) in the inotuzumab ozogamicin arm compared with 20.0% (95% CI: 12.3, 29.8) in the control arm. The rate difference was 15.8% (97.5% CI: 1.8, 29.9) and was statistically significant (1-sided p=0.0072). The CRi rate (per EAC) was 46.2% (95% CI: 36.5, 56.2) in the inotuzumab ozogamicin arm compared with 14.4% (95% CI: 7.9, 23.4) in the control arm. The rate difference was 31.8% (97.5% CI: 18.1, 45.4) and was statistically significant (1-sided p<0.0001).

Table 37: Concordance of EAC and Investigator Assessed Remission (CR/CRi) – mITT218 or ITT218 populations - Study B1931022 (2 October 2014 data cut-off)

	Investigator's Assessment			
	Inotuzumab Ozogamicin		Defined Investigator's Choice of Chemotherapy	
	Yes	No	Yes	No
EAC Assessment	n (%)	n (%)	n (%)	n (%)
CR/CRi ITT218, N	109		109	
Yes	84 (77.1)	4 (3.7)	27 (24.8)	5 (4.6)
No	1 (0.9)	20 (18.3)	4 (3.7)	73 (67.0)
p-value (McNemar's test)[a]	**0.3750**		**1.0000**	
CR/CRi mITT218, N	109		96	
Yes	84 (77.1)	4 (3.7)	27 (28.1)	5 (5.2)
No	1 (0.9)	20 (18.3)	4 (4.2)	60 (62.5)
p-value (McNemar's test) [a]	**0.3750**		**1.0000**	

a. Two-sided p-value was used from the paired Chi-square test.

Using the logistic regression model to control for the baseline covariates, the effect of ozogamicin versus control) on CR/CRi (per EAC) was statistically significant, with a 2-results are included in

Table 38.

Table 38: Logistic Regression on Effect of Treatment and Baseline Covariates on CR/CRi (per EAC) – mITT218 Population - Study B1931022 (2 October 2014 data cut-off)

	Estimate	SE	95% CI	p-value[a]
Treatment	2.3	0.50	1.4, 3.3	<0.0001
Age	-0.0	0.01	0.0, 0.0	0.1088
Race	-0.3	0.50	-1.3, 0.7	0.5516
Gender	0.2	0.50	-0.7, 1.2	0.6330
ECOG scores	0.5	0.87	-1.2, 2.2	0.5563
Baseline HRQoL	0.0	0.01	0.0, 0.0	0.2205
BM blasts	-0.0	0.01	0.0, 0.0	0.5951
Absolute circulating blasts	-0.0	0.00	0.0, 0.0	0.1075
Duration of first remission	-0.1	0.50	-1.0, 0.9	0.9185
Salvage treatment	0.9	0.63	-0.3, 2.1	0.1490
Response to most recent prior regimen	-1.1	0.62	-2.3, 0.2	0.0883
Cytogenetics	0.3	0.60	-0.9, 1.5	0.5908

mITT218=included patients among the first 218 randomized who started treatment, with study drug assignment designated according to initial randomization

a. Two-sided p-value calculated

Table 39: Effect of Treatment on CR/CRi (per EAC) Adjusting for Stratification Factors (Logistic Regression) – mITT218 Population- Study B1931022 (2 October 2014 data cut-off)

Comparison	Estimate	Odds Ratio	SE	95% CI	p-value[a]
Treatment	2.5	12.030	0.42	5.301, 27.304	<0.0001
Age	-0.4	0.688	0.41	0.309, 1.532	0.3594
Salvage treatment	0.3	1.369	0.44	0.572, 3.274	0.4802
Duration of first remission	0.3	1.343	0.40	0.610, 2.957	0.4639

a. Two-sided p-value calculated

In the ITT218 population, 152/218 (69.7%) patients had relapsed and 65/218 (29.8%) patients refractory B-cell ALL. In the ITT population, 232/326 (71.2%) patients had relapsed and 93/326 (28.5%) patients refractory B-cell ALL.

Table 40: Subgroup Analysis of CR/CRi in Inotuzumab Ozogamicin Arm According to Disease Status at Study Entry (ITT218 and ITT Populations) - Study B1931022

Patient Population	Disease Status at Study Entry	CR/CRi Rate		Rate Difference % (97.5% CI)
		Inotuzumab Ozogamicin n/N (%)	Defined Investigator's Choice of Chemotherapy n/N (%)	
ITT218[a]	Relapsed	66/78 (84.6)	27/74 (36.5)	48.1 (32.6-63.7)
	Refractory	21/30 (70.0)	5/35 (14.3)	55.7 (32.7-78.7)
	Unknown	1/1 (100.0)	-	-
ITT[b]	Relapsed	93/121 (76.9)	36/111 (32.4)	44.4 (31.3-57.6)
	Refractory	27/43 (62.8)	14/50 (28.0)	34.8 (13.0-56.6)
	Unknown	-	0/1 (0.0)	-
CR=complete remission; CRF=case report form; CRi=complete remission with incomplete haematologic ITT=intent-to-treat; ITT218=intent-to-treat in initial 218 patients '-': no patient in this category				
[a] ITT218=based on 2 October 2014 data cutoff date; assessments per endpoint adjudication committee				
[b]ITT=based on 8 March 2016 data cutoff date; assessments per Investigator.				

The median duration of treatment was 8.3 weeks in the inotuzumab ozogamicin arm and 0.9 weeks in the control arm, respectively, based on the 2 October 2014 data cut-off date, and 8.9 weeks in the inotuzumab ozogamicin arm and 0.9 weeks in the control arm based on the 8 March 2016 data cut-off date. The median number of cycles administered in the inotuzumab ozogamicin arm was 3 compared to 1 in the control arm Cumulatively, Cycles 1, 2, or 3 were the last cycles initiated by 119/164 (72.6%) patients and Cycles 4, 5, or 6 were the last cycles initiated by 45/164 (27.4%) patients. In the inotuzumab ozogamicin arm, 70.8%, 25.8% and 3.3% of patients who achieved CR/CRi first achieved remission (CR or CRi) in Cycles 1, 2, and 3, respectively. No responding patient first achieved remission (CR or CRi) after Cycle 3.

Table 41: Summary of CR/CRi by Cycle (ITT Population) (cut-off date 8 March 2016) - Study B1931022

Cycle in which remission first achieved	Inotuzumab ozogamicin n (% of total CR/CRi)	Investigator's choice of chemotherapy n (% of total CR/CRi)
1	85/120 (70.8%)	44/50 (88.0%)
2	31/120 (25.8%)	4/50 (8.0%)
3	4/120 (3.3%)	0
4-6	0	0
Other[a]	0	2/50 (4.0%)
[a]Remission first achieved after 42 days of last dose and before new anti-cancer therapy.		

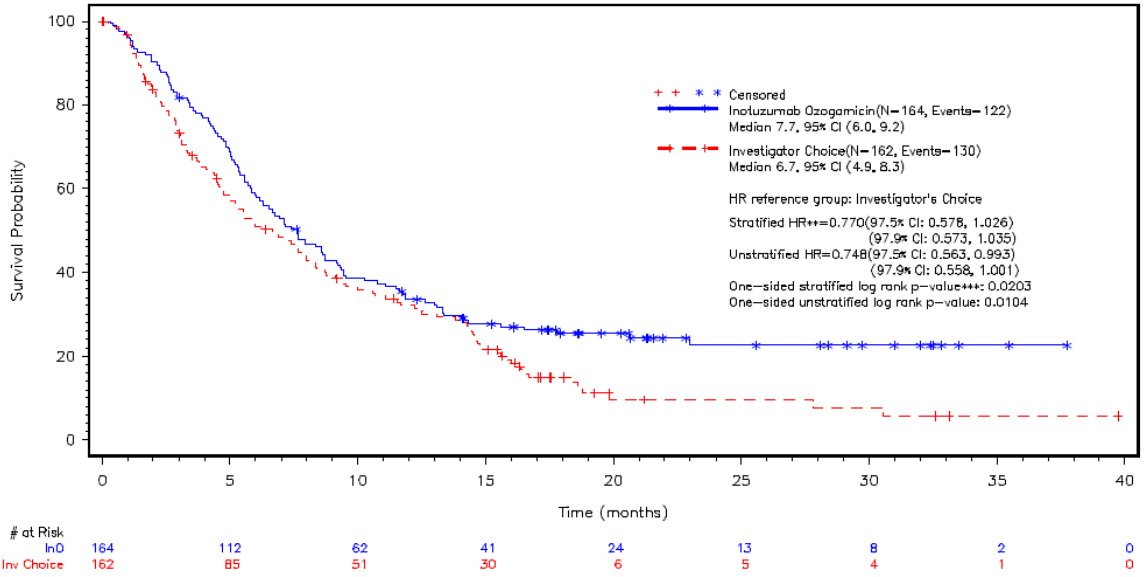
Overall Survival (OS) – ITT(N=326) population

As of 8 March 2016 the data cut-off date, a total of 252 deaths (77.3% of 326 patients) were observed, with 122 deaths (74.4% of 164 patients) in the inotuzumab ozogamicin arm and 130 deaths (80.2% of 162 patients) in the Investigator' s chemotherapy of choice arm.

Table 42: Overall Survival in the ITT population Study B1931022 (08 March 2016 Data Cut-off Date)

	Inotuzumab Ozogamicin (N=164)	Defined Investigator's Choice of Chemotherapy (N=162)
Number of deaths, n (%)	122 (74.4)	130 (80.2)
Number censored, n (%)	42 (25.6)	32 (19.8)
Survival probability at Month 24[a] (95% CI)	22.6 (15.8, 30.0)	9.6 (4.8, 16.3)
Kaplan–Meier estimates of time to event (months)[a]		
50% quartile (95% CI)	7.7 (6.0, 9.2)	6.7 (4.9, 8.3)
Cox proportional hazards model		
Stratified HR (97.5% CI)[b]	0.770 (0.578, 1.026)	
1-sided p-value[c]	0.0203	
Unstratified HR (97.5% CI)	0.748 (0.563, 0.993)	
1-sided p-value	0.0104	

Figure 3: Kaplan Meier Plot of Overall Survival (ITT Population) Study B1931022 (08 March 2016 Data Cut-off Date)



**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.
***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.

Table 43: Overall Survival in the mITT population Study B1931022 (8 March 2016 Data Cut-off Date)

	Inotuzumab Ozogamicin (N=164)	Defined Investigator's Choice of Chemotherapy (N=143)
Number of deaths, n (%)	122 (74.4)	121 (84.6)
Number censored, n (%)	42 (25.6)	22 (15.4)
Survival probability at Month 24[a] (95% CI)	22.6 (15.8, 30.0)	9.1 (4.3, 16.2)
Kaplan–Meier estimates of time to event (months)[a]		
50% quartile (95% CI)	7.7 (6.0, 9.2)	6.7 (5.0, 8.4)
Cox proportional hazards model		
Stratified HR (97.5% CI)[b]	0.767 (0.572, 1.029)	
1-sided p[c]	0.0209	
Unstratified HR (97.5% CI)	0.750 (0.562, 1.002)	
1-sided p-value	0.0125	

Table 44: Study B1931022: Summary of Overall Survival Based on 4 January 2017 LSLV Date - ITT and mITT Populations

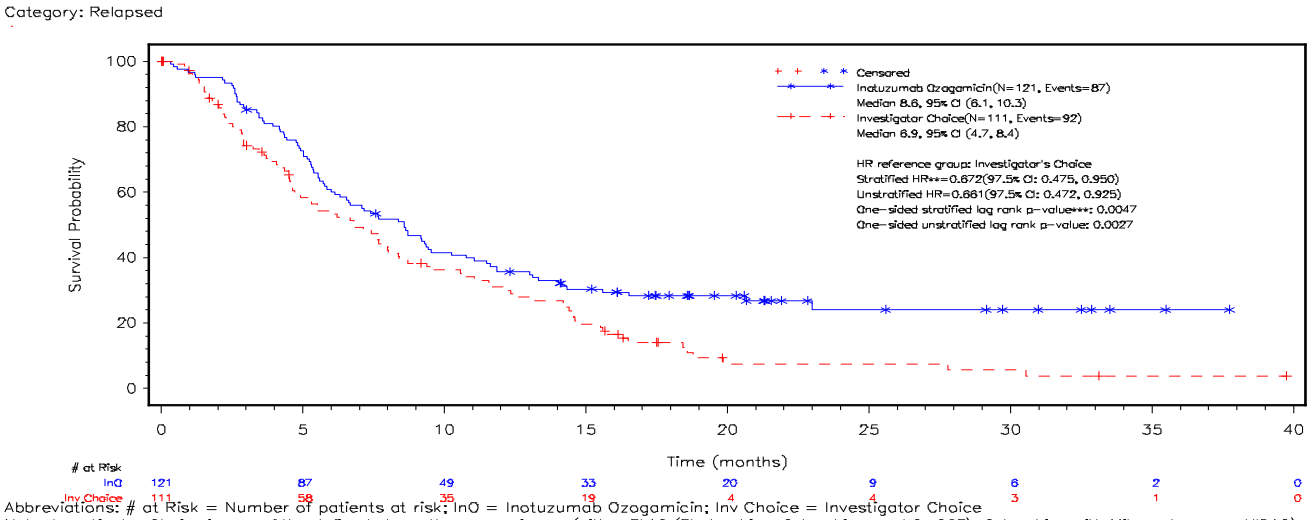
OS	Summary		04 January 2017 LSLV Date (Updated Analysis)	
			Inotuzumab Ozogamicin	Investigator's Choice of Chemotherapy
ITT Population	Events/N (%)		131/164 (79.9)	136/162 (84.0)
	Median in mo [95% CI]		7.7 [6.0, 9.2]	6.2 [4.7, 8.3]
	OS rate (%) at 24mo [95% CI]		22.8 [16.7, 29.6]	10.0 [5.7, 15.5]
	Stratified Analysis	HR [97.5% CI]	0.751 [0.568, 0.993]	
		p-value (1-sided)	0.0105	
	Unstratified Analysis	HR [97.5% CI]	0.741 [0.562, 0.977]	
		p-value (1-sided)	0.0073	
mITT Population	Events (%)		131/164 (79.9)	126/143 (88.1)
	Median in mo [95% CI]		7.7 [6.0, 9.2]	6.7 [5.0, 8.4]
	OS rate (%) at 24mo [95% CI]		22.8 [16.7, 29.6]	9.9 [5.6,15.7]
	Stratified Analysis	HR [97.5% CI]	0.750 [0.564, 0.997]	
		p-value (1-sided)	0.0115	
	Unstratified Analysis	HR [97.5% CI]	0.745 [0.562, 0.987]	
		p-value (1-sided)	0.0092	

When excluding patients who withdrew from the study and refused further follow-up, the HR was 0.748 (97.5% CI: 0.561-0.998) with 1-sided p-value = 0.0117 based on the stratified analysis. The median OS was

7.7 months (95% CI: 6.0-9.2) in the inotuzumab ozogamicin arm and 6.0 months (95% CI: 4.6-8.0) in the control arm (08 March 2016 Data Cut-off Date)..

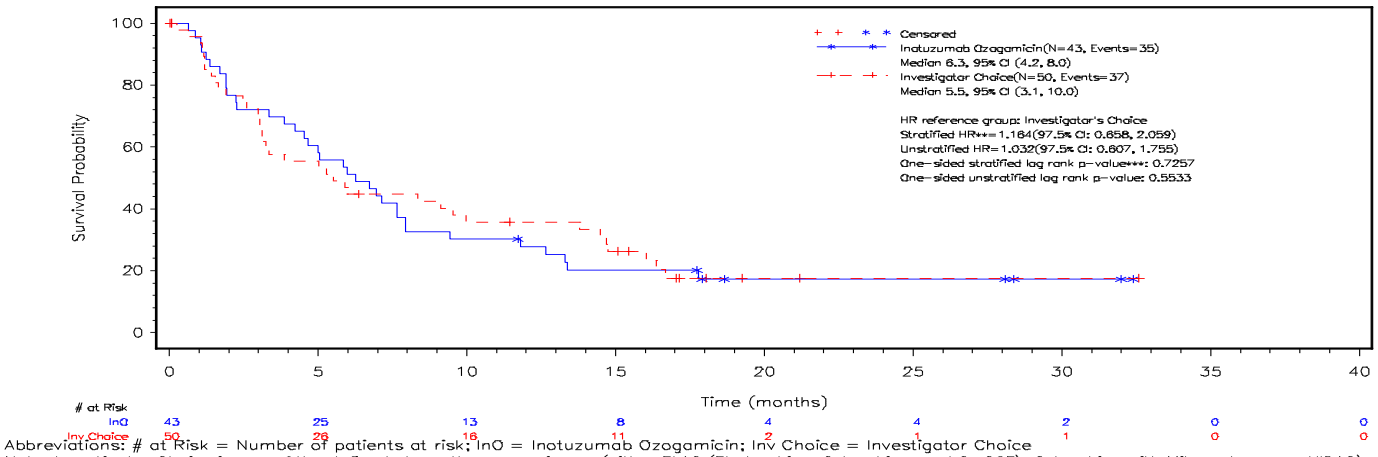
In the ITT population, the estimated unstratified HR for OS was 0.661 (97.5% CI: 0.472, 0.925; unstratified 1-sided p=0.0027) in patients with relapsed B-cell ALL and 1.032 (97.5% CI: 0.607, 1.755; unstratified 1-sided p=0.5533) in patients with refractory B-cell ALL (8 March 2016 Data Cut-off Date).

Figure 4 : Kaplan-Meier Plot of Overall Survival in Patients who had Relapsed B-cell ALL at Study Entry – ITT Population- Study B1930122 (08 March 2016 Data Cut-off Date)



Abbreviations: # at Risk = Number of patients at risk; InO = Inotuzumab Ozogamicin; Inv Choice = Investigator Choice
Note: Investigator Choice is one of the defined chemotherapy regimens (either FLAG (Fludarabine, Cytarabine, and G-CSF), Cytarabine with Mitoxantrone, or HIDAC).
**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 per IVRS.
***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 per IVRS.
Patients who achieved Complete Response after to most recent induction regimen prior to randomization into the study are considered Relapsed patients while Patients who achieved Partial response, Stable disease, Resistant disease and Progressive disease are considered Refractory patients.

Figure 5: Kaplan-Meier Plot of Overall Survival in Patients who had Refractory B-cell ALL at Study Entry – ITT Population - Study B1930122 (8 March 2016 Data Cut-off Date)



Abbreviations: # at Risk = Number of patients at risk; InO = Inotuzumab Ozogamicin; Inv Choice = Investigator Choice
Note: Investigator Choice is one of the defined chemotherapy regimens (either FLAG (Fludarabine, Cytarabine, and G-CSF), Cytarabine with Mitoxantrone, or HIDAC).
**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 per IVRS.
***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 per IVRS.
Patients who achieved Complete Response after to most recent induction regimen prior to randomization into the study are considered Relapsed patients while Patients who achieved Partial response, Stable disease, Resistant disease and Progressive disease are considered Refractory patients.

An exploratory post-hoc analysis based on the RMST method and 08 March 2016 data cutoff date was conducted. A truncation time (τ) of 37.7 months was chosen as the minimum of the maximum OS time in the 2 arms of the study. The restricted mean OS time was 13.9 months (standard error [SE]: 1.1) in the inotuzumab ozogamicin arm and 9.9 months (SE: 0.85) in the Investigator' s choice of chemotherapy arm which resulted in a difference in restricted mean OS time between arms of 3.9 months with a 1-sided p-value of 0.0023 (data not shown).

Secondary endpoints

MRD Negativity

Table 45: Summary of MRD Status by Cycle in Patients Who Achieved CR/CRi (per EAC) (ITT218 Population) (cut-off date of 2 October 2014) - Study B1931022

	Inotuzumab ozogamicin N=88	**Investigator's choice of chemotherapy N=32**
Number of Subjects with Total MRD Negativity n (%)	69 (78.4)	9 (28.1)
Number of Subjects with Total MRD Positivity n (%)	16 (18.2)	22 (68.8)
Number of Subjects with MRD status unknown n (%)	3 (3.4)	1 (3.1)
Number of Subjects with MRD status in Cycle 1:		
First Negative (95% CI)	31 (35.2) (25.3, 46.1)	7 (21.9) (9.3, 40.0)
First Positive	14 (15.9)	21 (65.6)
Number of Subjects with MRD status in Cycle 2:		
Negative in previous cycles	31 (35.2)	7 (21.9)
First Negative (95% CI)	29 (33.0) (23.3, 43.8)	0 (0.0, 10.9)
First Positive	1 (1.1)	1 (3.1)
Number of Subjects with MRD status in Cycle 3:		
Negative in previous cycles	60 (68.2)	7 (21.9)
First Negative (95% CI)	8 (9.1) (4.0, 17.1)	0 (0, 10.9)
First Positive	1 (1.1)	0
Number of Subjects with MRD status in Cycle 4:		
Negative in previous cycles	68 (77.3)	7 (21.9)
First Negative (95% CI)	1 (1.1) (0.0, 6.2)	0 (0.0, 10.9)
First Positive	0	0

Among patients in the ITT population who achieved CR/CRi per investigator (8 March 2016 data cutoff date), 92/120 (76.7%) patients achieved MRD-negativity in the inotuzumab ozogamicin arm compared with 19/50 (38.0%) patients who achieved MRD negativity in the control arm (1-sided p<0.0001).

Table 46 Summary of MRD-Negativity Rates in Patients with CR/CRi, CR or CRi (Per EAC) - ITT218 Population- Study B1931022 (2 October 2014 data cutoff date)

Response	MRD-Negativity[a] n/N (%, [95% CI])		
	Inotuzumab Ozogamicin	Defined Investigator's Choice of Chemotherapy	1-sided p-value[b]
CR/CRi	69/88 (78.4, [68.4, 86.5])	9/32 (28.1, [13.7, 46.7])	<0.0001
CR	35/39 (89.7, [75.8, 97.1])	6/19 (31.6, [12.6, 56.6])	<0.0001
CRi	34/49 (69.4, [54.6, 81.7])	3/13 (23.1, [5.0, 53.8])	0.0034

Source Table 14.2.1.5.2

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

Negative if minimum MRD (that is the minimum MRD % from post-baseline to EOT + 7 days MRD test) was <0.01%.

a. One-sided p-value for MRD-negative based on the test conducted on the MRD negative rates between the 2 treatment arms.

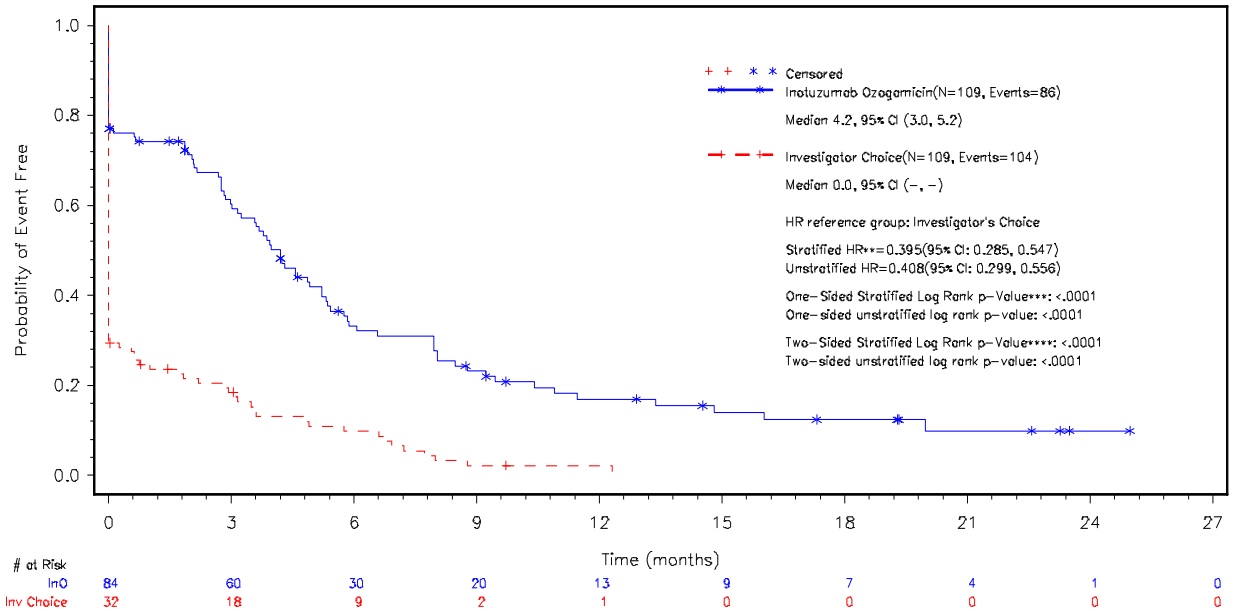
b. One-sided p-value based on Chi-square test or Fisher's exact test (if any cell count was <5).

Duration of remission (DoR)

In the ITT218 population (8 March 2016 data cutoff), the median duration of remission in patients who achieved CR/CRi was longer in the inotuzumab ozogamicin group (84 patients) than the chemotherapy control (32 patients [5.4months (95% CI 4.2, 8.0months) vs. 3.5months (95% CI 2.9, 6.6months)] .

The median DoR in the ITT218 population (i.e. initial 218 patients randomized) was 4.2 months (95% CI: 3.0-5.2) in the inotuzumab ozogamicin arm and 0.0 months (95% CI: NA-NA) in the control arm. The observed HR was 0.395 (95% CI: 0.285-0.547) with 1-sided p<0.0001 based on the stratified analysis using the stratification factors at randomization. The median DoR in the ITT population (08 March 2016 data cutoff date for the analysis with patients without remission being given a duration of zero and considered an event) was 3.7 months (95% CI: 2.8-4.3) in the inotuzumab ozogamicin arm and 0.0 months (95% CI: NA-NA) in the control arm. The observed HR was 0.468 (95% CI: 0.363-0.603) with 1-sided p<0.0001 based on the stratified analysis using the stratification factors at randomization.

Table 47 : Kaplan–Meier Plot of Duration of Remission per Investigator Assessment (Patients without Achieving CR/CRi Reaching an Event with Duration of Zero) – ITT218 Population (8 March 2016 data cutoff date)



Abbreviations: # at Risk = Number of patients at risk; InO = Inotuzumab Ozogamicin; Inv Choice = Investigator Choice
Note: Investigator Choice is one of the defined chemotherapy regimens (either FLAG (Fludarabine, Cytarabine, and G-CSF), Cytarabine with Mitoxantrone, or HIDAC).
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.
**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.
***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.
****From Two 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.
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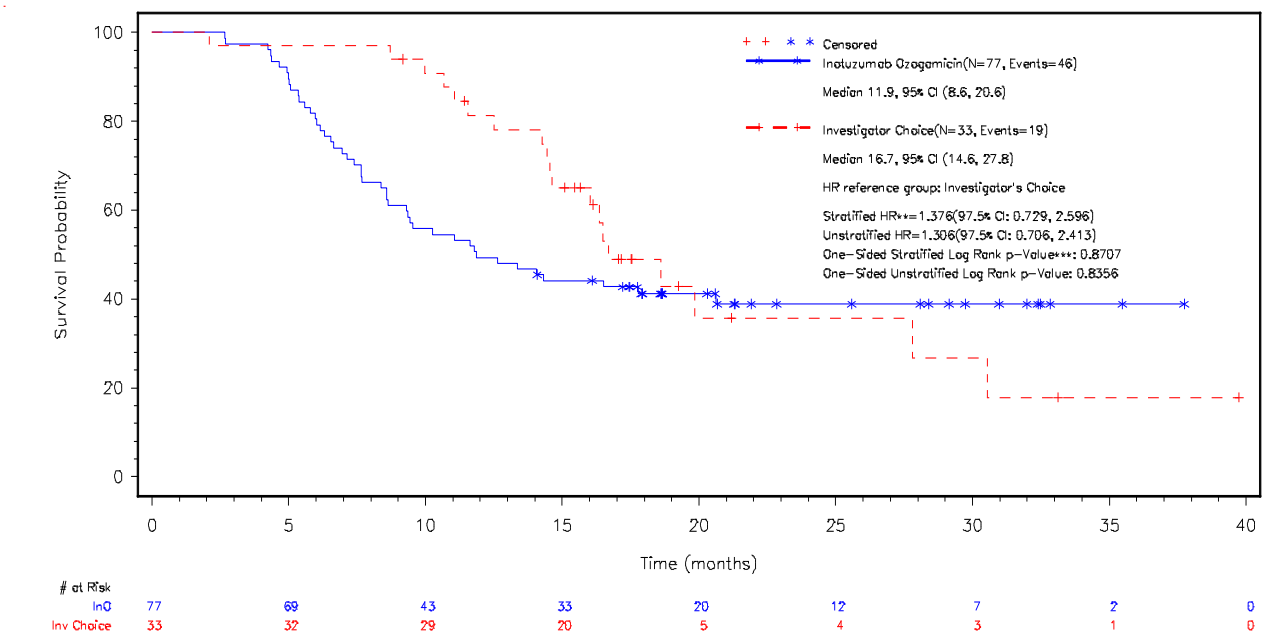
Haematopoietic stem cell transplant (HSCT)

Table 48 : Overall Survival in Patients who underwent a follow-up HSCT (8 March 2016 data cutoff date)

	Inotuzumab Ozogamicin (N=164)	**Defined Investigator's Choice of Chemotherapy (N=162)**
Follow-up HSCT: Yes		
N	77	33
Number of deaths, n (%)	46 (59.7)	19 (57.6)
Number censored, n (%)	31 (40.3)	14 (42.4)
Survival probability at Month 24[a] (95% CI)	38.9 (27.6, 50.0)	35.7 (16.3, 55.8)
Kaplan–Meier estimates of time to event (months)[a]		
50% quartile (95% CI)	11.9 (8.6, 20.6)	16.7 (14.6, 27.8)
Cox proportional hazards model		
Stratified HR (97.5% CI)[b]	1.376 (0.729, 2.596)	
1-sided p-value[c]	0.8707	
Unstratified HR (97.5% CI)	1.306 (0.706, 2.413)	
1-sided p-value	0.8356	

Table 49 : Study B1930122: Kaplan-Meier Plots of Overall Survival in Patients who received a Follow-Up HSCT – ITT Population (8 March 2016 data cutoff date)

Follow-up SCT: Yes



Abbreviations: # at Risk = Number of patients at risk; InO = Inotuzumab Ozogamicin; Inv Choice = Investigator Choice
Note: Investigator Choice is one of the defined chemotherapy regimens (either FLAG (Fludarabine, Cytarabine, and G-CSF), Cytarabine with Mitoxantrone, or HIDAC).
**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.
***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.

PFIZER CONFIDENTIAL Source:Table 530.180 Data Extraction: 12APR2016 Cutoff Date:08MAR2016 File Generation: 120CT2016:16:25

Among responders, 92/120 (76.7%) patients in the inotuzumab ozogamicin arm and 36/50 (72%) patients in the control arm were still in remission by the end of treatment assessment (08 March 2016 data cutoff date). Of these, 65/92 (70.6%) patients in the inotuzumab ozogamicin arm and 16/36 (44.4%) patients in the control arm received HSCT after study therapy. More patients in the inotuzumab ozogamicin than in the control arm proceeded to HSCT after study therapy i.e. without another intervening induction therapy and regardless of CR/CRi status. In the ITT population, 71/164 (43.3%) patients in the inotuzumab ozogamicin arm and 18/162 (11.1%) patients in the control arm proceeded to HSCT after study treatment (p<0.0001). In the Besponsa arm, 6/77 (7.8%) and, in the control arm, 15/33 (45.5%) patients were transplanted after a new induction.

The time from HSCT to recurrence or death was analyzed in two patient populations: firstly, patients who received follow-up HSCT before the start of new induction therapy (PTPFS1) and, secondly, all patients who received follow-up HSCT regardless of the start of new induction therapy (PTPFS2).

Table 50: Summary of Post-Transplant Progression-Free Survival 1 (PTPFS1) in Patients who Underwent Follow-up HSCT ITT Population (8 March 2016 data cutoff date)

	Inotuzumab Ozogamicin (N=71)	Defined Investigator's Choice of Chemotherapy (N=18)
Total patients with events[a], n (%)	34 (47.9)	6 (33.3)
Death	22 (64.7)	1 (16.7)
Recurrence	12 (35.3)	5 (83.3)
Number (%) of censored patients	37 (52.1)	12 (66.7)
Median PTPFS1 (months)[b]		
50th percentile (95% CI)	5.7 (3.7, 12.4)	7.4 (0.5, -)
Cox proportional hazards model		
Stratified HR (97.5% CI) [c]	1.185 (0.383, 3.669)	
Unstratified HR (97.5% CI)	1.115 (0.411, 3.027)	
One-sided stratified log-rank p[d]	0.6319	
One-sided unstratified log-rank p	0.5969	

Table 51 : **Summary of Post-Transplant Progression-Free Survival 2 (PTPFS2) in Patients who Underwent Follow-up HSCT Regardless of the Start of New Induction Therapy - ITT Population (8 March 2016 data cutoff date)**

	Inotuzumab Ozogamicin (N=77)	Defined Investigator's Choice of Chemotherapy (N=33)
Total patients with events[a], n (%)	35 (45.5)	8 (24.2)
Death	23 (65.7)	3 (37.5)
Recurrence	12 (34.3)	5 (62.5)
Number (%) of censored patients	42 (54.5)	25 (75.8)
Median PTPFS2 (months)[b]		
50th percentile (95% CI)	5.7 (3.7, 12.2)	6.9 (1.0, -)
Cox proportional hazards model		
Stratified HR (97.5% CI) [c]	0.945 (0.354, 2.523)	
Unstratified HR (97.5% CI)	0.947 (0.391, 2.292)	
One-sided stratified log-rank p[d]	0.4488	
One-sided unstratified log-rank p	0.4451	

Figure 6: Kaplan-Meier Plots of overall survival censored for Transplant-Related Deaths –ITT326 population (8 March 2016 data cutoff date)

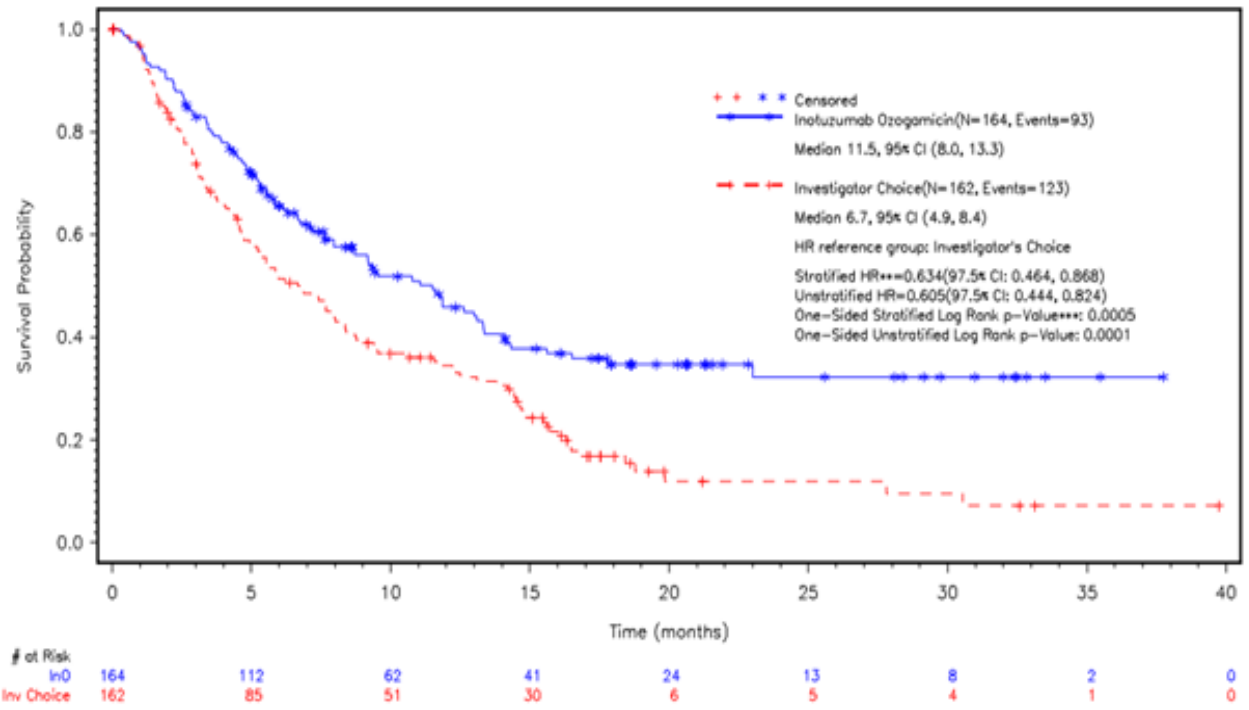


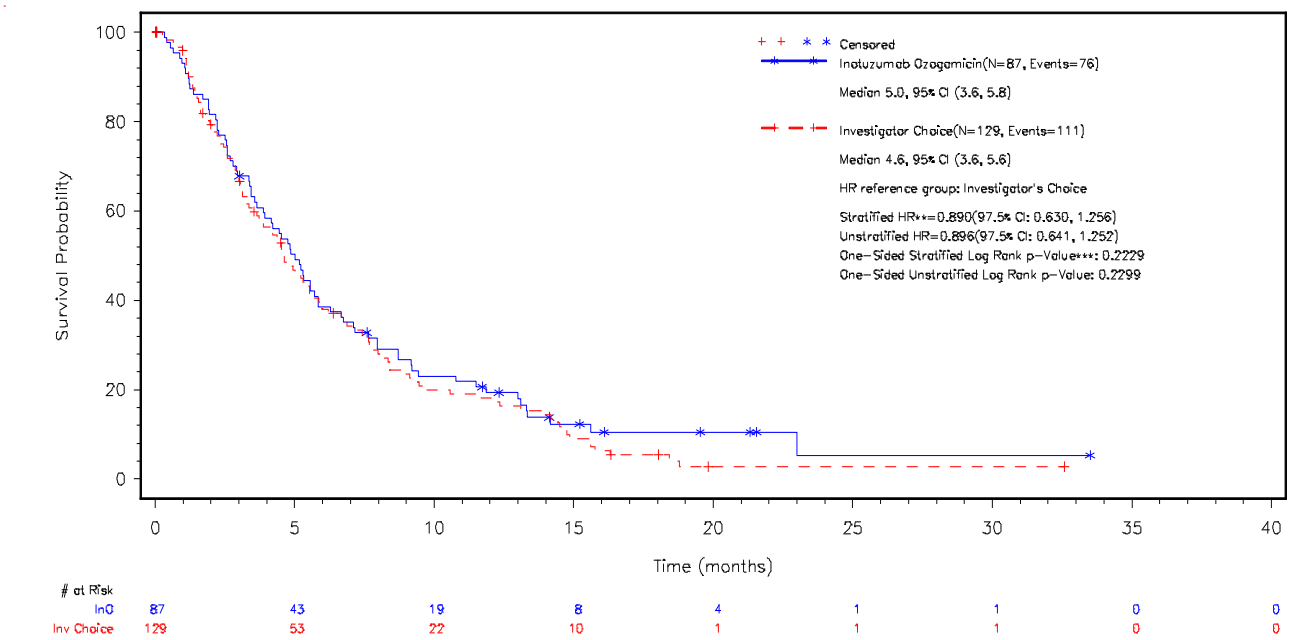
Table 52: OS in patients who did not undergo follow-up HSCT (8 March 2016 data cutoff date)

	Inotuzumab Ozogamicin (N=164)	**Defined Investigator's Choice of Chemotherapy (N=162)**
Follow-up HSCT: No		
N	87	129
Number of deaths, n (%)	76 (87.4)	111 (86.0)
Number censored, n (%)	11 (12.6)	18 (14.0)
Survival probability at Month 24a (95% CI)	5.3 (0.7, 17.4)	2.7 (0.6, 7.8)
Kaplan–Meier estimates of time to event (months)a		
50% quartile (95% CI)	5.0 (3.6, 5.8)	4.6 (3.6, 5.6)
Cox proportional hazards model		
Stratified HR (97.5% CI)b	0.890 (0.630, 1.256)	
1-sided p-valuec	0.2229	
Unstratified HR (97.5% CI)	0.896 (0.641, 1.252)	
1-sided p-value	0.2299	

a. Calculated using Kaplan–Meier method.
b. Stratification factors per IVRS were duration of first remission (<12 months or ≥12 months); salvage treatment (Salvage 1 or 2); patient age at randomization (<55 years or ≥55 years).
c. From 1-sided stratified log-rank test. Stratification factors as for b.

Figure 7: Study B1930122: Kaplan-Meier Plots of Overall Survival in Patients who did Not Receive a Follow-Up HSCT – ITT Population (8 March 2016 data cutoff date)

Follow-up SCT: No



Abbreviations: # at Risk = Number of patients at risk; InO = Inotuzumab Ozogamicin; Inv Choice = Investigator Choice
Note: Investigator Choice is one of the defined chemotherapy regimens (either FLAG (Fludarabine, Cytarabine, and G-CSF), Cytarabine with Mitoxantrone, or HIDAC).
**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.
***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.

PFIZER CONFIDENTIAL Source:Table 530.180 Data Extraction: 12APR2016 Cutoff Date:08MAR2016 File Generation: 12OCT2016:16:25

Fifty-one patients who received Besponsa achieved CR/CRi not followed by transplant (08 March 2016 data cutoff date). Of these, 18 received 1-3 cycles and 33 patients, 4 to 6 cycles. The latter group (N=33) had longer DOR and OS than the former. 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; median OS of 8.0 and 5.3 months, respectively).

Table 53: 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 cutoff date)

	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

Progression Free Survival

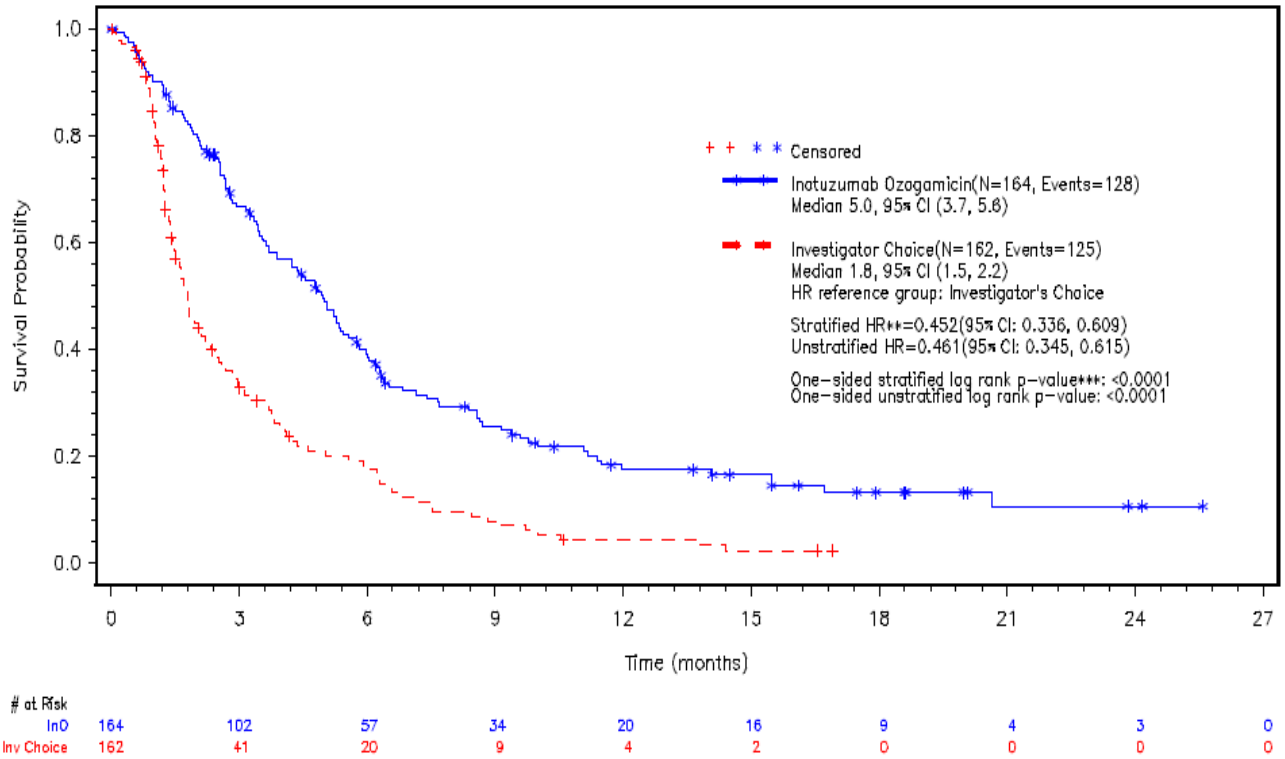
As of the 8 March 2016 data cut-off date, a total of 253 PFS events (77.6%) were observed in the ITT population, with 128 (78.0%) in the inotuzumab ozogamicin arm and 125 (77.2%) in the Investigator's chemotherapy of choice arm.

Table 54: PFS (ITT Population; Stratified and Unstratified Analysis) Study B1931022 Data cut-off date: 8 March 2016

Summary		**Inotuzumab Ozogamicin** (N=164)	**Investigator's Choice of Chemotherapy** (N=162)
Events (%)		128 (78.0)	125 (77.2)
Median (mo) [95% CI]		5.0 [3.7, 5.6]	1.8 [1.5, 2.2]
Stratified Analysis[a]	HR [97.5% CI] p-value (1-sided)	0.452 [0.349, 0.586] <0.0001	
Unstratified Analysis	HR [97.5% CI] p-value (1-sided)	0.461 [0.345, 0.615] <0.0001	

a Based on stratifications factors at randomization

Figure 8: Kaplan Meier Plot of Progression-free Survival (ITT Population) Study B1931022 (08 March 2016 data cut-off date)



**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.
***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.

In the analysis of PFS where switch of therapy is not considered an event (8 March 2016 data cutoff date), a standard definition of PFS was used. In the ITT Population, the estimated HR (inotuzumab ozogamicin versus the control arm) was in line with the reported results of the PFS that was pre-defined in the protocol [HR =0.535 (97.5% CI: 0.376-0.761; 1-sided p <0.0001) based on the stratified analysis]. The median PFS was 5.6 months (95% CI: 4.9-6.3) in the inotuzumab ozogamicin arm versus 3.6 months (95% CI: 2.3-4.1) in the control arm.

Table 55: Study B1931022: Summary of Early and Late PFS events (ITT population 8 March 2016 data cutoff date)

	Early events (<4 months)		Late events (≥4 months)	
	Besponsa (n=78)	Control (n=132)	Besponsa (n=86)	Control (n=30)
Total patients with PFS events	68 (87.2%)	99 (75%)	60 (69.8%)	26 (86.7%)
Death	18 (26.5)	23 (23.2)	27 (45.0)	7 (26.9)
PD	31 (45.6)	26 (26.3)	31 (51.7)	19 (73.1)
New therapy/ HSCT without CR/CRi	19 (27.9)	50 (50.5)	2 (3.3)	0
Patients censored	10 (12.8%)	33 (25%)	26 (30.2%)	4 (13.3%)
Median PFS (mo)	2.3 (1.8-2.7)	1.4 (1.3-1.6)	8.6 (6.4-10)	6.8 (5.9-8.8)

Ancillary analyses

Patient reported outcomes

EORTC QLQ-C30:

For patient-reported outcomes, most functioning and symptoms scores were in favour of BESPONSA compared to Investigator's choice of chemotherapy. For patient-reported outcomes measured using the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30), BESPONSA resulted in significantly better estimated mean postbaseline scores (BESPONSA and Investigator's choice of chemotherapy, respectively) in role functioning (64.7 versus 53.4; p=0.0065), physical functioning (75.0 versus 68.1; p=0.0139), social functioning (68.1 versus 59.8; p=0.0336), and appetite loss (17.6 versus 26.3; p=0.0193) compared to Investigator's choice of chemotherapy. Although not reaching statistical significance, BESPONSA resulted in better estimated mean postbaseline scores (BESPONSA and Investigator's choice of chemotherapy, respectively) in global health status/Quality of Life (QoL) (62.1 versus 57.8; p=0.1572), cognitive functioning (85.3 versus 82.5; p=0.1904), dyspnoea (14.7 versus 19.4; p=0.1281), diarrhoea (5.9 versus 8.9; p=0.1534), fatigue (35.0 versus 39.4; p=0.1789), nausea and vomiting (8.7 versus 10.4; p=0.4578), financial difficulties (29.5 versus 32.0; p=0.4915), insomnia (25.4 versus 27.1; p=0.6207), and pain (21.3 versus 22.0; p=0.8428). Although not reaching statistical significance, BESPONSA resulted in worse estimated mean post-baseline scores (BESPONSA and Investigator's choice of chemotherapy, respectively) in emotional functioning (77.4 versus 79.6; p=0.3307) and constipation (12.1 versus 10.7; p=0.6249) (SmPC section 5.1).

EQ-5D Index and EQ-VAS:

For patient-reported outcomes measured using the EuroQoL 5 Dimension (EQ-5D) questionnaire, although not reaching statistical significance, BESPONSA resulted in better estimated mean postbaseline scores (BESPONSA and Investigator's choice of chemotherapy, respectively) for the EQ-5D index (0.80 versus 0.76; p=0.1710) and the EQ visual analogue scale (EQ-VAS) (67.1 versus 62.5; p=0.1172) (SmPC section 5.1).

Table 56. Patient-Reported Outcomes Based on EORTC QLQ-C30, EQ-5D Index, and EQ-VAS – Between Treatment Comparisons ITT Population Study B1931022

Overall Comparison	Inotuzumab Ozogamicin (N=164)		Defined Investigator's Choice of Chemotherapy (N=162)		Inotuzumab Ozogamicin – Defined Investigator's Choice of Chemotherapy		
	Estimated Mean	95% CI	Estimated Mean	95% CI	Estimated Mean	95% CI	P-value
EORTC QLQ-C30							
Physical functioning	75.0	(72.1, 77.8)	68.1	(63.4, 72.7)	6.9	(1.4, 12.3)	0.0139
Role functioning	64.7	(60.8, 68.7)	53.4	(46.3, 60.4)	11.4	(3.2, 19.5)	0.0065
Emotional functioning	77.4	(75.0, 79.7)	79.6	(75.7, 83.6)	-2.3	(-6.9, 2.3)	0.3307
Cognitive functioning	85.3	(83.1, 87.4)	82.5	(78.9, 86.1)	2.8	(-1.4, 7.0)	0.1904
Social functioning	68.1	(64.3, 72.0)	59.8	(53.1, 66.5)	8.4	(0.7, 16.1)	0.0336
Global health status/QoL	62.1	(59.1, 65.1)	57.8	(52.6, 63.0)	4.3	(-1.7, 10.3)	0.1572
Dyspnoea	14.7	(11.8, 17.7)	19.4	(14.1, 24.8)	-4.7	(-10.8, 1.4)	0.1281
Insomnia	25.4	(21.9, 28.8)	27.1	(21.1, 33.1)	-1.7	(-8.7, 5.2)	0.6207
Appetite loss	17.6	(14.1, 21.1)	26.3	(19.9, 32.7)	-8.7	(-16.0, -1.4)	0.0193
Constipation	12.1	(9.2, 15.0)	10.7	(5.6, 15.7)	1.4	(-4.4, 7.3)	0.6249
Diarrhoea	5.9	(3.9, 7.8)	8.9	(5.2, 12.6)	-3.0	(-7.2, 1.1)	0.1534
Financial difficulties	29.5	(25.9, 33.0)	32.0	(25.7, 38.2)	-2.5	(-9.7, 4.7)	0.4915
Fatigue	35.0	(31.7, 38.3)	39.4	(33.9, 44.9)	-4.4	(-10.8, 2.0)	0.1789
Nausea and vomiting	8.7	(6.6, 10.8)	10.4	(6.6, 14.2)	-1.6	(-6.0, 2.7)	0.4578
Pain	21.3	(18.0, 24.6)	22.0	(16.2, 27.7)	-0.7	(-7.3, 6.0)	0.8428
EQ-5D Index	0.80	(0.77, 0.82)	0.76	(0.73, 0.80)	0.03	(-0.01, 0.07)	0.1710
EQ-VAS	67.1	(64.0, 70.2)	62.5	(57.6, 67.4)	4.6	(-1.2, 10.4)	0.1172

Source: Table 14.2.5.2.2, Table 14.2.6.2.2, Table 14.2.6.3.2
Defined Investigator's choice of chemotherapy (control arm) was 1 of the defined chemotherapy regimens (FLAG, MXN/Ara-C, or HIDAC).
Least squares means were estimated from longitudinal mixed-effects models with random intercepts and slopes with treatment, time, treatment-by-time interaction, and baseline as covariates. The average postbaseline scores for each PRO domain were computed at approximately Week 9 (data available upon request).
EQ-5D analysis based on longitudinal mixed effects model with random intercepts and slopes with treatment, time, treatment-by-time interaction, and baseline as covariates. US weight was used for the calculation of EQ-5D Index. The average postbaseline scores for each PRO domain were computed at approximately Week 9. The overall treatment comparisons were estimated at approximately Week 9.
8 inotuzumab ozogamicin and 10 defined Investigator's choice of chemotherapy patients' Cycle 1 Day 1 data were collected postdose for EORTC QLQ-C30; 8 inotuzumab ozogamicin and 9 defined Investigator's choice of chemotherapy patients' Cycle 1 Day 1 data were collected postdose for EQ-5D Index and EQ-VAS.
Abbreviations: CI=confidence interval; EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-VAS=EuroQoL visual analogue scale; EQ-5D=EuroQoL 5 Dimension questionnaire; FLAG=fludarabine + cytarabine + G-CSF; G-CSF=granulocyte-colony stimulating factor; HIDAC=high-dose cytarabine; ITT=intent-to-treat, MXN/Ara-C=mitoxantrone + cytarabine; N=number of patients; PRO=patient-reported outcomes; QoL=quality of life; US=United States.

Overall missing data were slightly above 20% with substantial imbalance between the 2 treatment arms in terms of missing data, with 35% missing in the control arm compared with 15% in the inotuzumab ozogamicin. MNAR is assumed, due to the likely poorer health status of the control arm patients.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Title: An open-label, randomized phase 3 study of inotuzumab ozogamicincompared to a defined investigator's choice in adult patients with relapsed or refractoryCD22-positive acute lymphoblastic leukaemia (ALL)		
Study identifier	B1931022	
Design	Multicentre, global, open-label study in adults with relapsed/ refractory Philadelphia chromosome negative or Philadelphia chromosome positive B cell ALL due to receive Salvage 1 or 2 therapy. CD22 immuno-phenotyping performed at screening.	
	Duration of main phase:	Up to 6 cycles of inotuzumab ozogamicin, follow up for 5 years or 2 years from randomization of the last patient

	Duration of Run-in phase: Duration of Extension phase:		not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Inotuzumab ozogamicin Number randomized =164		1.8mg/m^2/cycle (0.8mg/m2 Day 1, 0.5mg/m2 Days 8 + 15, q21-28). Dose reduce to 1.5mg/m2/cycle (0.5mg/m2 days 1, 8 and 15, q28) if haematological remission. Maximum 6 cycles. (ITT218 = 109)
	Investigators choice from 3 specified chemotherapy regimens Number randomized = 162		FLAG - fludarabine/ cytarabine/ granulocyte-colony stimulating factor for up to 4 cycles (4 weeks per cycle) (ITT 218 = 69)
			MXN/Ara-C - methotrexate/ cytarabine for up to 4 cycles (15 to 20 days per cycle) (ITT 218 = 25)
			HIDAC- high dose cytarabine every 12 hours for up to 12 doses (a second cycle was allowed after haematological recovery)(ITT 218 = 15)
Endpoints and definitions	Co-Primary endpoint	Haematological remission (CR/ CRi) per blinded EAC assessment	CR= <5% marrow blasts and absence of peripheral leukaemic blasts with recovery of haematopoeisis CRi= as CR except ANC<1000/µL +/or platelets <100,000/µL
	Co-Primary endpoint	Overall survival	Time from randomization to date of death due to any cause (pre specified 1-sided p-value boundary 0.0104)
	Secondary	Minimal residual disease (MRD) negativity	Lowest value of MRD from first date of CR/CRi to EOT <1 x 10^{-4} blasts/nucleated cells by flow cytometry per central laboratory analysis
	Secondary	HSCT rate	Patients progressing to HSCT post treatment
	Secondary	Progression-free survival	Time from randomization to progressive disease/ relapse/ death/ new induction therapy or HSCT without achieving CR/CRi
Database lock	Final analysis of CR/CRi = 2 October 2014 (initial CSR) Final analysis of OS= 8 March 2016		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (ITT218 for CR/CRi)		
Descriptive statistics and estimate variability	Treatment group	Inotuzumab ozogamicin	Investigator's choice of chemotherapy
	Number of subjects	ITT = 164 ITT 218=109	ITT=162 ITT 218 = 109
	CR/CRi per EAC %	80.7%	29.4%
	95% CI	72.1, 87.7	21.0, 38.8
	OS months	7.7	6.7

	95% CI	6.0, 9.2	4.9, 8.3
	MRD negativity in patients with CR/CRi (%)	69/88 (78.4%)	9/32 (28.1%)
	95% CI	68.4, 86.5	13.7, 46.7
	HSCT rate (%)	77/164 (47%)	33/162 (20.4%)
	PFS months 95% CI	5.0 3.7, 5.6	1.8 1.5, 2.2
Effect estimate per comparison	Co- Primary endpoint: CR/CRi per EAC	Comparison groups	Inotuzumab ozogamicin vs. Investigators choice chemotherapy (ITT 218)
		CR/CRi rate difference	51.4%
		95% CI	38.4, 64.3
		P-value (2-sided)	<0.0001
	Co-Primary endpoint: OS	Comparison groups	Inotuzumab ozogamicin vs. Investigators choice chemotherapy (ITT)
		HR stratified analysis	0.770
		95% CI	0.599, 0.990
		P-value (2-sided)	0.0407
	Secondary endpoint: MRD negativity in patients with CR/CRi	Comparison groups	Inotuzumab ozogamicin vs. Investigators choice chemotherapy (ITT218)
		P-value (2-sided) by chi-squared test	<0.0001
	Secondary endpoint: PFS	Comparison groups	Inotuzumab vs. Investigators choice chemotherapy PFS (ITT)
		Stratified HR	0.452
		95% CI	0.349, 0.586
		P value (2 sided)	<0.0001

Analysis performed across trials (pooled analyses and meta-analysis)

Clinical studies in special populations

No clinical studies have been conducted in special populations. Subjects excluded from the Phase 3 clinical trial included those with isolated testicular/ CNS relapse due to presumed lack of penetration of the blood-brain and blood-testes barrier, Burkitts or mixed phenotype ALL and active CNS leukaemia.

Patients were recruited to the inotuzumab arm up to 78 years of age (median 47 years). A total of 23 patients aged ≥65 years received inotuzumab ozogamicin in study 1022. The results of

Complete remission estimation in patients by age <65 years and ⩾65 years in the Phase 3 study are summarized in Table 57.

Table 57: Summary of Complete Remission (CR + CRi) by Age (<65 by CRF, >=65 by CRF) Study B1931022

	Age <65		Age ≥ 65	
	Inotuzumab n= 86	Chemotherapy n=95	Inotuzumab n=23	Chemotherapy n=14
CR/CRi rate (%) 95% CI	68 (79.1) 69.0, 87.1	29 (30.5) 21.5, 40.8	20 (87.0) 66.4, 97.2	3 (21.4) 4.7, 50.8
Rate difference 97.5% CI P-value (1-sided)	48.5 34.1, 63.0 <0.0001		65.5 36.3, 94.7 <0.0001	
CR rate (%) 95% CI	29 (33.7) 23.9, 44.7	16 (16.8) 9.9, 25.9	10 (43.5) 23.2, 65.5	3 (21.4) 4.7, 50.8
Rate difference 97.5% CI P-value (1-sided)	16.9 2.6, 31.2 0.0043		22.0 -11.7, 55.8 0.1571	
CR/CRi rate (%) 95% CI	39 (45.3) 34.6, 56.5	13 (13.7) 7.5, 22.3	10 (43.5) 23.2, 65.5	0 0.0, 23.2
Rate difference 97.5% CI P-value (1-sided)	31.7 17.3, 46.1 <0.001		43.5 20.3, 66.6 0.0033	

95% CI for CR/CRi rate, CR rate and CRi rate were calculated using exact method, 97.5% CI for the rate difference was calculated using approximation method assuming Normal distribution

Supportive study

Study B1931010

Study B1931010 was a single-arm, multi-center, open-label, Phase 1/2 clinical study evaluating single-agent inotuzumab ozogamicin in patients with relapsed or refractory B-cell ALL.

Eligible patients were male or female, 18 years or older, with relapsed or refractory CD22-positive ALL (≥20% blasts were CD22 positive by local assessment). For the Phase 2 part of the study, the patients must have been due to receive ≥Salvage 2 therapy. Patients with Ph+ ALL were to have failed treatment with at least 1 TKI. Patients were to have adequate organ function and an ECOG performance status of 0 to 3. Patients were excluded from the study if they had isolated extramedullary relapse or active CNS leukaemia. In addition, patients who received chemotherapy within 2 weeks before their first dose of study treatment, monoclonal antibodies within 6 weeks of treatment, or allogeneic HSCT or other anti-CD22 immunotherapy ≤4 months before randomization, or had evidence or history of VOD/SOS were excluded.

Of 93 screened patients, 72 patients were assigned to study drug and treated with BESPONSA. The median age was 45 years (range 20-79); 76.4% were Salvage status ⩾ 2; 31.9% had received a prior HSCT and 22.2% were Ph+. The most common reasons for treatment discontinuation were: disease progression/relapse (30 [41.7%)], resistant disease (4 [5.6%]); HSCT (18 [25.0%]), and adverse events (13 [18.1%]) (SmPC section 5.1).

In the Phase 1 portion of the study, 37 patients received BESPONSA at a total dose of 1.2 mg/m^2 (n=3), 1.6 mg/m^2 (n=12), or 1.8 mg/m^2 (n=22). The recommended BESPONSA dose was determined to be 1.8

mg/m^2/cycle administered at a dose of 0.8 mg/m^2 on Day 1 and 0.5 mg/m^2 on Days 8 and 15 of a 28 day cycle with a dose reduction upon achieving CR/Cri (SmPC section 5.1).

In the Phase 2 portion of the study, patients had to have received at least 2 prior treatment regimens for ALL and patients with Ph+ B cell ALL had to have failed treatment with at least 1 TKI. Of the 9 patients with Ph+ B-cell ALL, 1 patient had received 1 previous TKI and 1 patient had received no prior TKIs (SmPC section 5.1).

Results

Table 58: Efficacy results in patients ≥ 18 years of age with relapsed or refractory B-cell precursor ALL who received 2 or more prior treatment regimens for ALL (Study B1931010)

	BESPONSA (N=35)
CR/CRi; n (%) [95% CI]	24 (68.6%) [50.7%-83.2%]
CR; n (%) [95% CI]	10 (28.6%) [14.6%-46.3%]
CRi[b]; n (%) [95% CI]	14 (40.0%) [23.9%-57.9%]
Median DoR; months [95% CI]	2.2 [1.0 to 3.8]
MRD negativity for patients achieving CR/CRi; rate[d] (%) [95% CI]	18/24 (75%) [53.3%-90.2%]
Median PFS[e]; months [95% CI]	3.7 [2.6 to 4.7]
Median OS; months [95% CI]	6.4 [4.5 to 7.9]
Abbreviations: ALL=acute lymphoblastic leukaemia; ANC=absolute neutrophil counts; CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete haematological recovery; DoR=duration of remission; HSCT=haematopoietic stem cell transplant; MRD=minimal residual disease; N/n=number of patients; OS=overall survival; PFS=progression-free survival.	

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

2.4.7. Discussion on clinical efficacy

Design and conduct of clinical studies

The pivotal trial was an open label Phase 3 Study (B1931022) that randomised patients with CD-922 positive relapsed/ refractory B-cell ALL to inotuzumab ozogamicin or investigator's choice of chemotherapy from one of 3 pre-defined regimens (FLAG, MN/Ara-C or HIDAC). The choice of the control arm after randomisation may potentially result in bias; however in the view of the clear difference between the 2 arms it can be considered that this uncertainty has no impact on the demonstration of efficacy.

There was no standard of care for Ph- relapsed/ refractory B cell ALL at the time that the trial was initiated, so the control arm is acceptable, although Blincyto has since been authorised in the EU. The proportion of patients with Ph+ disease was capped at 20% of the full trial population. Ph+ patients also had to have failed

treatment with at least 1 second or third generation TKI and standard multi-agent induction chemotherapy. Of 49 patients Ph+ ALL, 4 did not receive a prior TKI and 28 received only 1 prior TKI. This was in line with the protocol but the ESMO guidelines recommend that Ph+ patients with persistent MRD or progressive disease switch to another TKI while screening for TKI resistance mutations and adapt the TKI choice according to the resistance profile.

To reduce the risk of hepatotoxicity, inotuzumab ozogamicin was limited to 2 cycles, or the smallest number necessary to achieve CR/CRi, in patients who were continuing to allogeneic HSCT. Patients with a history of VOD or HSCT in the previous 4 months were excluded.

The two co-primary endpoints (haematological remission and OS) are appropriate. As this is an open-label trial the primary analysis of CR/CRi was based upon the assessment of the blinded external Endpoint Adjudication Committee (EAC). This was conducted, as pre-specified in the first 218 randomised patients, the ITT218 population. More patients allocated to the control arm (13 in the ITT218 population) withdrew before receiving treatment. Therefore, the mITT218, where these untreated patients are excluded, is important to ensure that any apparent efficacy is not due to these early withdrawals.

To control multiplicity the alpha was split equally between the two primary endpoints, both of which were tested at the 1-sided 0.0125 level. Therefore, technically, the study is positive if either primary endpoint is positive. As it is required that both primary endpoints are positive, each could have been tested at the full 5% level (1-sided 0.025). Two interim analyses were planned and reviewed by an independent external Data Monitoring Committee (e-DMC). The second interim analysis assessed efficacy so adjustment was required and the final analysis for OS was conducted using 1-sided p=0.0104 as the cut-off (equivalent to 2-sided p=0.0208). As it is required that both primary endpoints are positive, after adjusting for the interim analysis, testing at 1-sided p=0.0229 could be allowed while still controlling the type I error at conventional levels.

Protocol deviations mainly involved the inclusion/ exclusion criteria and drug dosing. These should not have an impact on the interpretation of the efficacy results.

Efficacy data and additional analyses

There was a statistically significant improvement in the first primary endpoint, the rate of haematological remission with inotuzumab ozogamicin compared to control. In the ITT218 population, the CR/CRi rate (per EAC assessment) was 80.7% in the inotuzumab ozogamicin arm and 29.4% in the defined Investigator's choice of chemotherapy arm (rate difference = 51.4% [97.5% CI: 38.4, 64.3%], Chi-square test 1-sided p-value<0.0001). The results in the mITT 218 population (excluded untreated patients), PP218 population and per investigator assessment were similar to and supported the primary analysis. A statistically significant improvement with inotuzumab ozogamicin was maintained when CR and CRi were analysed separately and in the sensitivity analysis where the patients that withdrew prior to treatment in the chemotherapy arm were designated as responders.

The improvement in CR/CRi rate per EAC was consistent across the pre-specified stratification subgroups (duration of first remission, line of salvage and age at randomization). Using the logistic regression model to control for the baseline covariates, the effect of treatment (inotuzumab ozogamicin versus control) on CR/CRi (per EAC) was statistically significant in the mITT218 population (2-sided p<0.0001). Apart from treatment, response to most recent prior regimen (estimate -1.1; 2-sided p=0.0883) was the baseline covariate associated with the greatest predictive value for CR/CRi (per EAC) outcome in the mITT218 population.

Refractory ALL has a worse prognosis than relapsed disease; the statistically significant improvement in CR/ CRi rates for inotuzumab ozogamicin over control was maintained in the refractory population (70.0% vs. 14.3%; rate difference 55.7% (97.5% CI 32.7-78.7%).

Results of subgroup analysis of CR/CRi were consistent with the primary analysis;a numerical benefit was seen in those who were Ph+ and with prior HSCT. Only patients with t(4,11) translocation did not show a benefit with inotuzumab ozogamicin but this involved very small numbers (3 vs. 6 patients) and is known to carry a poor prognosis.

For the second primary endpoint OS there was not a statistically significant improvement in median OS for inotuzumab ozogamicin compared to the chosen chemotherapy regimens (7.7 vs. 6.7 months) according to the pre-specified cut-off level of 1-sided $p<0.0104$ (adjusted for the interim analysis) [stratified HR 0.770 (97.5% CI 0.578, 1.026), p=0.0203]. However, the planned testing strategy is over-conservative. If both primary endpoints are tested at 1-sided $p<0.025$, the OS result could be considered to be positive while still controlling the type I error at conventional levels (required 1-sided $p<0.0229$ after adjusting for the interim analysis). Additional weighted comparisons were conducted using different weight functions. The Fleming-Harrington, which places more weight on late observations, was found to be most appropriate, given the distribution of the observed OS data, with late separation of the survival curves; this resulted in statistical significance (1 sided p =0.0101). The mITT analysis of OS, confirmed the statistically significant OS result when using the 1-sided p-value boundary of 0.0229 (HR of 0.767 [97.5% CI: 0.572-1.029] and 1-sided p=0.0209. The OS rate at 2- years favoured inotuzumab ozogamicin.

Overall survival showed an improvement in the inotuzumab ozogamicin arm compared with the control arm with respect to all stratification factors per IVRS examined (duration of first remission [<12 months or $\geqslant$12 months], salvage status [Salvage 1 or 2] and age at randomization [<55 years or $\geqslant$55 years]). In general, patients with more favourable prognostic factors had a better survival outcome. Using Cox regression modelling, in the univariate analyses, baseline characteristics associated with lower risk of death in the inotuzumab ozogamicin arm (2-sided $p<0.05$) were younger age (<55 years), Salvage 1, duration of first remission $\geqslant$12 months and baseline leukaemic blast CD22 positivity per central laboratory $\geqslant$90%.

Inotuzumab ozogamicin allowed more patients to proceed directly to HSCT. Overall, 77/164 (47.0%) patients in the inotuzumab ozogamicin arm and 33/162 (20.4%) patients in the Investigator's choice of chemotherapy arm had a follow-up HSCT. This included 71 and 18 patients in the inotuzumab ozogamicin and control arm, respectively, who proceeded directly to HSCT and 6 and 15 patients respectively who were transplanted after a new induction. The OS improvement for inotuzumab ozogamicin over control was seen in patients who underwent HSCT, although there was an excess of early deaths post-transplant (pre 100 days) in the inotuzumab ozogamicin arm, a late survival benefit was evident. It was not possible to draw conclusions regarding the subgroup that proceeded directly to HSCT without further induction therapy due to the small number of patients in the control arm.

Some of the documentation relating to HSCT was poor so answers had to be surmised or extrapolated rather than obtained directly. This included the reason that an individual in CR/CRi did not proceed to HSCT and the number of transplant-related deaths. Possible reasons why relatively more of the patients in remission underwent HSCT in the experimental arm (70.6% vs. 44.4%) included more ongoing Grade $\geqslant$3 TEAEs (66% vs. 50%) and Grade $\geqslant$3 infections (20% vs. 5.8%) and a shorter duration of remission (3.6 months [95% CI: 2.9-5.2]) vs. 5.3 months [95% CI: 4.2-7.0]) in the control arm. In a retrospective analysis of OS, deaths after follow-up HSCT not due to documented relapse were considered as transplant-related deaths and censored. In this population the improvement with inotuzumab was more marked. The median OS

censored for transplant-related deaths was 11.5 months (95% CI: 8.0-13.3) in the inotuzumab ozogamicin arm and 6.7 months (95% CI: 4.9-8.4) in the control arm [estimated HR = 0.634 (97.5% CI: 0.464-0.868), 1-sided p-value = 0.0005 based on the stratified analysis]. Therefore, although there is a benefit in OS in the full population, this is small due to the increased early transplant related mortality.

More patients in the control arm received follow up induction therapy (51.9% vs. 29.9%), although the proportions receiving any follow-up systemic therapy were similar in both arms (66.0% vs. 71.3%). Sensitivity analyses of OS censored at the time when a patient received a specific post-study therapy (blinatumomab, inotuzumab ozogamicin, any induction ALL therapy or HSCT) were consistent with an OS benefit for inotuzumab ozogamicin over control.

Duration of remission in those who achieved CR/CRi was longer with inotuzumab ozogamicin. DoR results were consistent in the analyses of the ITT218 and ITT populations that included all patients, with patients without remission being given a duration of zero.

Median PFS was clinically and statistically significantly longer in the inotuzumab ozogamicin than the control arm [5.0 months (95% CI 3.7, 5.6) vs. 1.8 months (1.5, 2.2), stratified HR 0.452 (97.5% CI 0.336, 0.609) 1-sided p value <0.0001]. The curves separated early, before 3 months. In the standard definition of PFS, where switch of therapy was not considered an event, the median PFS was 5.6 months and 3.6 months in the inotuzumab ozogamicin and the control arm, respectively. It is possible that switch of therapy, which was more frequent in the control arm, explains the longer median PFS according to the standard censoring.

The median number of cycles of inotuzumab ozogamicin was 3. In the inotuzumab ozogamicin arm (ITT, N= 326, population), 70.8%, 25.8% and 3.3% of patients who achieved CR/CRi first achieved remission (CR or CRi) in Cycles 1, 2, and 3, respectively. No responding patient first achieved remission (CR or CRi) after Cycle 3. For patients who achieved CR/CRi but 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; median OS of 8.0 and 5.3 months, respectively). Therefore, it is appropriate that patients who do not achieve CR/CRi stop after 2 (or a maximum of 3 cycles); patients who achieve CR/CRi but do not continue to HSCT could receive a maximum of 6 cycles of inotuzumab ozogamicin.

For patient-reported outcomes, most functioning and symptoms scores were in favour of inotuzumab ozogamicin compared to Investigator's choice of chemotherapy. For patient-reported outcomes measured using the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30), inotuzumab ozogamicin resulted in significantly better estimated mean postbaseline scores (inotuzumab ozogamicin and Investigator's choice of chemotherapy, respectively) in role functioning (64.7 versus 53.4; p=0.0065), physical functioning (75.0 versus 68.1; p=0.0139), social functioning (68.1 versus 59.8; p=0.0336), and appetite loss (17.6 versus 26.3; p=0.0193) compared to Investigator's choice of chemotherapy. Although not reaching statistical significance, inotuzumab ozogamicin resulted in better estimated mean postbaseline scores (inotuzumab ozogamicin and Investigator's choice of chemotherapy, respectively) in global health status/Quality of Life (QoL) (62.1 versus 57.8; p=0.1572), cognitive functioning (85.3 versus 82.5; p=0.1904), dyspnoea (14.7 versus 19.4; p=0.1281), diarrhoea (5.9 versus 8.9; p=0.1534), fatigue (35.0 versus 39.4; p=0.1789), nausea and vomiting (8.7 versus 10.4; p=0.4578), financial difficulties (29.5 versus 32.0; p=0.4915), insomnia (25.4 versus 27.1; p=0.6207), and pain (21.3 versus 22.0; p=0.8428). Although not reaching statistical significance, inotuzumab ozogamicin resulted in worse estimated mean post-baseline scores (inotuzumab ozogamicin and Investigator's choice of

chemotherapy, respectively) in emotional functioning (77.4 versus 79.6; p=0.3307) and constipation (12.1 versus 10.7; p=0.6249) (SmPC section 5.1).

For patient-reported outcomes measured using the EuroQoL 5 Dimension (EQ-5D) questionnaire, although not reaching statistical significance, inotuzumab ozogamicin resulted in better estimated mean postbaseline scores (BESPONSA and Investigator's choice of chemotherapy, respectively) for the EQ-5D index (0.80 versus 0.76; p=0.1710) and the EQ visual analogue scale (EQ-VAS) (67.1 versus 62.5; p=0.1172) (SmPC section 5.1).

2.4.8. Conclusions on clinical efficacy

Data from pivotal study B1931022 showed a clinically significant response rate of haematological remission (CR/CRi) in adults with relapsed or refractory acute lymphoblastic leukaemia compared to investigators choice of chemotherapy. These results are further supported by a 1 month improvement in median OS compared to control and the high rates of negative MRD responses observed.

The clinical efficacy data available are adequate to support the efficacy of inotuzumab ozogamicin adults with relapsed or refractory CD22-positive B cell precursor ALL. Adult patients with Philadelphia chromosome positive (Ph^+) relapsed or refractory ALL should have previously failed treatment with at least one tyrosine kinase inhibitor (TKI).

2.5. Clinical safety

Patient exposure

As of 08 March 2016 cut-off (updated analysis), a total of 1207 patients were treated in Pfizer-sponsored studies (Phases 1 to 3), including 880 patients who received at least 1 dose of inotuzumab ozogamicin. Of these 880 patients, 236 with relapsed or refractory ALL and 173 with NHL were exposed to single agent inotuzumab ozogamicin; 212 ALL patients (164 in Study 1022 and 48 in Study 1010) received inotuzumab ozogamicin at the recommended starting dose of 1.8mg/m^2; An updated analysis of safety from the Phase 3 study was included in the sCSR, with an additional 25 patients in the inotuzumab arm (N=164, 8 March 2016 cut-off). The information below is from the initial MAA unless otherwise specified.

Table 59 Study 1022 (Updated Analysis, 08 March 2016 Data Cutoff), Study 1010 (Initial MAA), and the Pooled ALL Population (Initial MAA)- Treatment Summary (Safety Populations)

	Study 1022					Study 1010 (Phase 2 + Dose Expansion Cohort)	Pooled ALL Population
	Inotuzumab Ozogamicin	Control				Inotuzumab Ozogamicin	Inotuzumab Ozogamicin
		FLAG	MXN/Ara-C	HIDAC	Total		
	(N = 164)	(n = 93)	(n = 33)	(n = 17)	(N = 143)	(n = 48)	(N = 187)
Duration of treatment (weeks):							
Median	8.9	0.9	1.1	1.0	0.9	10.1	8.9
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 patients with dose reduction [a]:							
	21 (12.8)	3 (3.2)	2(6.1)	0	5(3.5)	3 (6.3)	29 (15.5)
Number (%) of patients with dose delay [a]:							
	73 (44.5)	10 (10.8)	2 (6.1)	2(11.8)	14 (9.8)	19 (39.6)	87 (46.5)
Number of cycles started per patient [b]:							
Mean (cycles)	2.8	1.3	1.1	1.2	1.2	2.9	2.7
Median (range)	3 (1, 6)	1 (1, 4)	1 (1, 2)	1 (1, 2)	1 (1, 4)	3 (1, 6)	3 (1, 6)

Abbreviations: FLAG=fludarabine+cytarabine+granulocyte-colony stimulating factor; HIDAC=high-dose cytarabine; MXN/Ara-C=mitoxantrone+cytarabine

a. The pooled data contains additional Study 1010 reductions. Study 1010 relied on sites indicating a dose reduction in the CRF. In Study 1022, sites needed to indicate dose reductions in the CRF, but in instances where this was not indicated, a ≥ 10% reduction based on actual dose levels were counted as dose reductions. The pooled data used the Study 1022 approach applied to both studies.

b. Only 4 cycles of FLAG and MXN/Ara-C, and 2 cycles of HIDAC were allowed per protocol.

In study b1931022 (updated analysis, 08 March 2016 data cutoff), the median total dose of inotuzumab ozogamicin was 4.215mg/m^2 (range 0.78 to 9.59 mg/m^2); the median dose intensity was 1.575mg/m^2/cycle (range 0.77 to 2.06 mg/m2/cycle) based on the proposed cycle lengths.

Adverse events

All AEs were coded according to MedDRA Version 17.1 with severity grade defined by the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0. Treatment emergent AEs (TEAEs) were defined as all causality AEs that began on or after C1D1 but within 42 days of the last dose of study drug and included all treatment-related AEs after C1D1 as well as VOD/SOS within 2 years of randomization.

Table 60 Study 1022 (Updated Analysis [08 March 2016 data cutoff]),, Study 1010 (Initial MAA), and the Pooled ALL Population (Initial MAA) - Number (%) of Patients with AEs in (Safety Populations)

	Study 1022		Study 1010 (All Doses)-	Pooled ALL Population
	Inotuzumab Ozogamicin N = 164	Control N = 143	Inotuzumab Ozogamicin N = 72	Inotuzumab Ozogamicin N = 187
Number of AEs[a]	2022	2104	701	2146
Number of TRAEs[a]	764	978	285	796
Patients with AEs	163 (99.4)	143 (100.0)	72 (100.0)	184 (98.4)
Patients with TRAEs	144 (87.8)	130 (90.9)	61 (84.7)	161 (86.1)
Patients with SAEs	84 (51.2)	71 (49.7)	51 (70.8)	103 (55.1)
Patients with treatment-related SAEs	51 (31.1)	42 (29.4)	23 (31.9)	53 (28.3)
Patients with Grade 3 or 4 AEs	147 (89.6)	137 (95.8)	57 (79.2)	164 (87.7)
Patients with Grade 3 or 4 TRAEs	114 (69.5)	113 (79.0)	39 (54.2)	124 (66.3)
Patients with Grade 5 AEs	26 (15.9)	16 (11.2)	9 (12.5)	24 (12.8)
Patients with Grade 5 TRAEs	9 (5.5)	3 (2.1)	2 (2.8)	5 (2.7)
Patients discontinued due to AEs	30 (18.3)*	12 (8.4)	12 (16.7)	32 (17.1)
Patients discontinued due to TRAEs	15 (9.1)	7 (4.9)	9 (12.5)	17 (9.1)
Patients with dose reduced due to AEs	5 (3.0)	3 (2.1)	7 (9.7)	6 (3.2)
Patients with dose reduced due to TRAEs	4 (2.4)	1 (0.7)	7 (9.7)	6 (3.2)
Patients with temporary discontinuation due to AEs	72 (43.9)	17 (11.9)	37 (51.4)	84 (44.9)
Patients with temporary discontinuation due to TRAEs	51 (31.1)	12 (8.4)	29 (40.3)	59 (31.6)

Note: Except for the number of AEs, patients were counted only once per treatment in each row.
Abbreviations: AE=treatment-emergent adverse event; TRAE=treatment-related AE.
a. For each patient, multiple reported AEs with the same MedDRA preferred term are counted only once.
* does not include 1 additional patient with non-treatment emergent AE leading to discontinuation.

In study b1931022 (updated analysis, 08 March 2016 data cutoff), AEs associated with permanent discontinuations, temporary discontinuations/dose delays and dose reductions were more frequent in the inotuzumab ozogamicin arm; however, the median duration of treatment was longer in the inotuzumab ozogamicin (8.9weeks, 3 cycles) than in the control arm (0.9 weeks, 1 cycle).

TEAEs associated with treatment delay were reported for 43.9% (72/164) patients in the inotuzumab ozogamicin arm and 11.9% (17/143)of patients in the control. In the inotuzumab ozogamicin arm these TEAEs included neutropenia (17.1%), thrombocytopenia ((9.8%)), febrile neutropenia (4.9%), hyperbilirubinemia (4.3%) increased AST (4.3%%), increased GGT (4.3%), and increased ALT (3.0%).

TEAEs that led to dose reductions were reported in 5 patients (3.0%) in the inotuzumab ozogamicin arm and 3 (2.1%) in the control arm. In the updated analysis (08 March 2016), a total of 7 (4.3%) time to dose reduction (TTDR) events were observed for Besponsa and 5 (3.5%) in the control arm. The median TTDR was not reached. The KM curve suggests that the time to dose reduction was generally longer for patients in the experimental arm compared to control. In the safety population, the stratified HR for the TTDR was 0.183 (97.5% CI: 0.035-0.955). The ascribed reasons for dose reduction were provided (neutropenia and sepsis, VOD/SOS, thrombocytopenia and hemorrhage, elevated liver enzymes).

Table 61 : Study 1022 (Updated Analysis, 08 March 2016 data cutoff), Study 1010 (Initial MAA), and Pooled ALL Population (Initial MAA)– All-Causality AEs Summarized by Maximum Severity Grade (Decreasing Frequency ≥10% Based on All-Grade AEs in Study 1022 Inotuzumab Ozogamicin Arm) (Safety Populations)

	---------- Study 1022 ----------				Study 1010 (As-treated Population)		Pooled ALL Population	
	Inotuzumab ozogamicin N=164		Control N=143		Inotuzumab ozogamicin N=72		Inotuzumab Ozogamicin N = 187	
Preferred Term	All Grades n (%)	Grades 3-5 n (%)	All Grades n (%)	Grades 3-5 n (%)	All Grades n (%)	Grades 3-5 n (%)	All Grades n (%)	Grades 3-5 n (%)
Any AEs	163 (99.4)	149 (90.9)	143 (100.0)	137 (95.8)	72 (100.0)	58 (80.6)	184 (98.4)	166 (88.8)
Thrombocytopenia	81 (49.4)	67 (40.9)	87 (60.8)	85 (59.4)	26 (36.1)	24 (33.3)	78 (41.7)	67 (35.8)
Neutropenia	80 (48.8)	77 (47.0)	66 (46.2)	63 (44.1)	15 (20.8)	15 (20.8)	75 (40.1)	72 (38.5)
Anaemia	55 (33.5)	37 (22.6)	79 (55.2)	63 (44.1)	11 (15.3)	9 (12.5)	49 (26.2)	32 (17.1)
Nausea	53 (32.3)	3 (1.8)	68 (47.6)	0	25 (34.7)	1 (1.4)	60 (32.1)	4 (2.1)
Pyrexia	52 (31.7)	5 (3.0)	60 (42.0)	8 (5.6)	17 (23.6)	0	52 (27.8)	5 (2.7)
Leukopenia	47 (28.7)	44 (26.8)	54 (37.8)	53 (37.1)	2 (2.8)	2 (2.8)	39 (20.9)	36 (19.3)
Headache	45 (27.4)	4 (2.4)	38 (26.6)	1 (0.7)	13 (18.1)	3 (4.2)	48 (25.7)	4 (2.1)
Febrile neutropenia	44 (26.8)	44 (26.8)	77 (53.8)	77 (53.8)	22 (30.6)	19 (26.4)	55 (29.4)	48 (25.7)
Fatigue	42 (25.6)	4 (2.4)	24 (16.8)	3 (2.1)	13 (18.1)	0	37 (19.8)	4 (2.1)
AST increased	37 (22.6)	7 (4.3)	16 (11.2)	5 (3.5)	19 (26.4)	2 (2.8)	39 (20.9)	9 (4.8)
GGT increased	35 (21.3)	18 (11.0)	12 (8.4)	7 (4.9)	10 (13.9)	1 (1.4)	34 (18.2)	2 (1.1)
Hyperbilirubinaemia	35 (21.3)	10 (6.1)	24 (16.8)	9 (6.3)	10 (13.9)	1 (1.4)	27 (14.4)	12 (6.4)
Lymphopenia	31 (18.9)	27 (16.5)	35 (24.5)	35 (24.5)	1 (1.4)	0	25 (13.4)	22 (11.8)
Diarrhoea	30 (18.3)	1 (0.6)	55 (38.5)	1 (0.7)	12 (16.7)	1 (1.4)	34 (18.2)	2 (1.1)
Constipation	28 (17.1)	0	34 (23.8)	0	17 (23.6)	1 (1.4)	34 (18.2)	1 (0.5)
Vomiting	26 (15.9)	2 (1.2)	35 (24.5)	0	20 (27.8)	2 (2.8)	37 (19.8)	2 (1.1)
ALT increased	25 (15.2)	6 (3.7)	18 (12.6)	7 (4.9)	9 (12.5)	2 (2.8)	26 (13.9)	4 (2.1)
Hypokalaemia	25 (15.2)	11 (6.7)	33 (23.1)	13 (9.1)	7 (9.7)	3 (4.2)	29 (15.5)	12 (6.4)
Epistaxis	24 (14.6)	2 (1.2)	12 (8.4)	2 (1.4)	11 (15.3)	0	30 (16.0)	1 (0.5)
Insomnia	24 (14.6)	0	22 (15.4)	0	3 (4.2)	0	23 (12.3)	0
Blood ALP increased	22 (13.4)	3 (1.8)	10 (7.0)	0	12 (16.7)	2 (2.8)	24 (12.8)	3 (1.6)
Cough	22 (13.4)	0	23 (16.1)	1 (0.7)	11 (15.3)	0	24 (12.8)	0
VOD[a]	22 (13.4)	18 (11.0)	1 (0.7)	1 (0.7)	4 (5.6)	3 (4.2)	19 (10.2)	16 (8.6)
Abdominal pain	21 (12.8)	3 (1.8)	27 (18.9)	2 (1.4)	4 (5.6)	1 (1.4)	21 (11.2)	4 (2.1)
Decreased appetite	19 (11.6)	2 (1.2)	18 (12.6)	3 (2.1)	9 (12.5)	1 (1.4)	17 (9.1)	3 (1.6)
Back pain	18 (11.0)	5 (3.0)	10 (7.0)	1 (0.7)	5 (6.9)	1 (1.4)	16 (8.6)	5 (2.7)
Chills	18 (11.0)	0	17 (11.9)	0	7 (9.7)	0	19 (10.2)	0

a. All VOD events within 2 years of randomization date regardless of causal attribution to study therapy are included.

The TEAEs that increased in frequency by ≥5% from the 02 October 2014 to 08 March 2016 data cutoff dates included hyperbilirubinaemia (all grades: 15.1% vs 21.3%, respectively; Grade ≥3: 3.6% vs 6.1%, respectively) and pyrexia (all grades: 26.6% vs 31.7%, respectively; Grade ≥3: 3.6% vs 3.0%, respectively). Some of the increases in hyperbilirubinaemia were due to late reporting of this AE and some were due to new events. In the control arm, the frequency of hyperbilirubinaemia also increased in frequency by ≥5% (10.0% vs 16.8%, respectively) for similar reasons.

In study b1931022 (updated analysis, 08 March 2016), the most common (⩾5%) Grades ⩾3 all-causality TEAEs the inotuzumab ozogamicin arm in Study B1931022 included neutropenia (47.0 %), thrombocytopenia (40.9%), leukopenia (26.8%), febrile neutropenia (26.8%), anaemia (22.6%), lymphopenia (16.5%), VOD (11.0%), increased GGT (11.0%), hypokalaemia (6.7%) and decreased WBC count (6.1%). During Cycle 1,

Grade 3 AEs were reported for 28.7% (47/164) of patients in the inotuzumab ozogamicin arm and 16.8% (24/143) of patients in the control arm, while Grade 4 AEs were reported for 45.7% (75/164)of patients in the inotuzumab ozogamicin arm and 68.5% (98/143) of patients in the control arm.

Table 62: Studies 1022 (updated Analysis, 08 March 2016 data cutoff)a and 1010 (Initial MAA)and Pooled ALL Studies (Initial MAA) - Summary of Treatment-Related AEs Summarized by Maximum Severity Grade (All Grades; Frequency ≥5% Based on All Grades in the Study 1022 Inotuzumab Ozogamicin Arm) - Safety Population

	Study 1022				Study 1010 (All Doses)		Pooled ALL Population	
	Inotuzumab ozogamicin N=164		Control N=143		Inotuzumab ozogamicin N=72		Inotuzumab ozogamicin N=187	
Preferred Term	**All Grades n (%)**	**Grades 3-5 n (%)**	**All Grades n (%)**	**Grades 3-5 n (%)**	**All Grades n (%)**	**Grades 3-5 n (%)**	**All Grades n (%)**	**Grades 3-5 n (%)**
Any AEs	144 (87.8)	115 (70.1)	130 (90.9)	113 (79.0)	61 (84.7)	39 (54.2)	161 (86.1)	124 (66.3)
Neutropenia	63 (38.4)	60 (36.6)	57 (39.9)	54 (37.8)	14 (19.4)	14 (19.4)	57 (30.5)	54 (28.9)
Thrombocytopenia	55 (33.5)	40 (24.4)	71 (49.7)	70 (49.0)	24 (33.3)	22 (30.6)	54 (28.9)	42 (22.5)
Anaemia	33 (20.1)	20 (12.2)	60 (42.0)	50 (35.0)	8 (11.1)	6 (8.3)	31 (16.6)	20 (10.7)
Leukopenia	31 (18.9)	29 (17.7)	37 (25.9)	36 (25.2)	1 (1.4)	1 (1.4)	23 (12.3)	21 (11.2)
Febrile neutropenia	23 (14.0)	23 (14.0)	65 (45.5)	64 (44.8)	11 (15.3)	9 (12.5)	33 (17.6)	29 (15.5)
Nausea	26 (15.9)	0	50 (35.0)	0	15 (20.8)	0	32 (17.1)	0
GGT increased	21 (12.8)	8 (4.9)	2 (1.4)	2 (1.4)	9 (12.5)	1 (1.4)	19 (10.2)	6 (3.2)
Lymphopenia	21 (12.8)	19 (11.6)	23 (16.1)	23 (16.1)	1 (1.4)	0	16 (8.6)	15 (8.0)
Pyrexia	23 (14.0)	3 (1.8)	34 (23.8)	4 (2.8)	8 (11.1)	0	22 (11.8)	2 (1.1)
AST increased	17 (10.4)	1 (0.6)	8 (5.6)	1 (0.7)	19 (26.4)	2 (2.8)	24 (12.8)	3 (1.6)
Fatigue	23 (14.0)	2 (1.2)	15 (10.5)	1 (0.7)	11 (15.3)	0	18 (9.6)	2 (1.1)
Headache	13 (7.9)	2 (1.2)	13 (9.1)	0	4 (5.6)	0	16 (8.6)	1 (0.5)
VOD[a]	20 (12.2)	16 (9.8)	0	0	4 (5.6)	3 (4.2)	17 (9.1)	14 (7.5)
ALT increased	14 (8.5)	2 (1.2)	8 (5.6)	1 (0.7)	8 (11.1)	2 (2.8)	16 (8.6)	1 (0.5)
Hyperbilirubinaemia	16 (9.8)	6 (3.7)	12 (8.4)	4 (2.8)	7 (9.7)	0	16 (8.6)	4 (2.1)
Lipase increased	10 (6.1)	4 (2.4)	0	0	1 (1.4)	1 (1.4)	10 (5.3)	4 (2.1)
Vomiting	11 (6.7)	1 (0.6)	25 (17.5)	0	12 (16.7)	1 (1.4)	18 (9.6)	0
WBC count decreased	9 (5.5)	9 (5.5)	7 (4.9)	7 (4.9)	4 (5.6)	3 (4.2)	12 (6.4)	12 (6.4)
Blood ALP increased	10 (6.1)	0	5 (3.5)	0	10 (13.9)	1 (1.4)	14 (7.5)	1 (0.5)
Diarrhoea	10 (6.1)	0	31 (21.7)	1 (0.7)	3 (4.2)	0	10 (5.3)	0

Decreased appetite	11 (6.7)	2 (1.2)	12 (8.4)	2 (1.4)	4 (5.6)	0	6 (3.2)	2 (1.1)
a All VOD events within 2 years of randomization date regardless of causal attribution to study therapy are included.								

AEs of Special Interest

Hepatotoxicity, including venoocclusive liver disease/sinusoidal obstruction syndrome (VOD/SOS)

In the pivotal clinical study (N=164), VOD/SOS was reported in 22 (13%) patients including 5 (3%) patients during study therapy or in follow-up without an intervening HSCT. Among the 77 patients who proceeded to a subsequent HSCT (6 of whom received additional salvage therapy after treatment with BESPONSA before proceeding to HSCT), VOD/SOS was reported in 17 (22%) patients. Five of the 17 VOD/SOS events that occurred post-HSCT were fatal.

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

Among patients who proceeded to HSCT after BESPONSA treatment, VOD/SOS was reported in 5/11 (46%) patients who received an HSCT both prior to and after BESPONSA treatment and 12/66 (18%) patients who only received an HSCT after BESPONSA treatment.

Regarding other risk factors, VOD/ SOS was reported in 6/11 (55%) patients who received a HSCT conditioning regimen containing 2 alkylating agents and 8/52 (15%) patients who received a HSCT conditioning regimen containing 1 alkylating agent, 7/17 (41%) patients who were $\geqslant$ 55 years old and 10/60 (17%) patients who were < 55 years old, and 7/12 (58%) patients with a serum bilirubin $\geqslant$ ULN prior to HSCT and in 10/65 (15%) patients with a serum bilirubin < ULN prior to HSCT.

In the pivotal study (N=164), hyperbilirubinaemia and increased transaminases were reported in 35 (21%) and 43 (26%) patients, respectively. Grade $\geqslant$ 3 hyperbilirubinaemia and increased transaminases were reported in 9 (6%) and 11 (7%) patients, respectively. The median time to onset of hyperbilirubinaemia and increased transaminases was 73 days and 29 days, respectively (SmPC, section 4.8).

Infections

In the pivotal study (N=164), infections, including serious infections, some of which were life threatening or fatal, were reported in 79 (48%) patients. The frequencies of specific infections were: sepsis and bacteraemia (16%), lower respiratory tract infection (12%), upper respiratory tract infection (12%), fungal infection (9%), viral infection (8%), gastrointestinal infection (4%), skin infection (4%), and bacterial infection (1%). Fatal infections, including pneumonia, neutropenic sepsis, sepsis, septic shock, and pseudomonal sepsis, were reported in 8 (5%) patients (SmPC, section 4.8).

Bleeding /Haemorrhage

In the pivotal clinical study (N=164), bleeding/haemorrhagic events, mostly mild in severity, were reported in 54/ (33%) patients. The frequencies of specific bleeding/haemorrhagic events were: epistaxis (15%), upper gastrointestinal haemorrhage (5%), lower gastrointestinal haemorrhage (4%), and central nervous system (CNS) haemorrhage (1%). Grade 3/4 bleeding/haemorrhagic events were reported in 8/164 (5%) patients. One Grade 5 bleeding/haemorrhagic event (intra abdominal haemorrhage) was reported (SmPC, section 4.8).

Myelosuppression/cytopenias

In the pivotal study (N=164), thrombocytopenia and neutropenia were reported in 83 (51%) and 81 (49%) patients, respectively. Grade 3 thrombocytopenia and neutropenia were reported in 23 (14%) and 33 (20%) patients, respectively. Grade 4 thrombocytopenia and neutropenia were reported in 46 (28%) and 45 (27%) patients, respectively. Febrile neutropenia, which may be life-threatening, was reported in 43 (26%) patients (SmPC, section 4.8).

Infusion related reactions

In the pivotal study (N=164), infusion related reactions were reported in 17 (10%) patients. All events were Grade $\leqslant$ 2 in severity. Infusion related reactions generally occurred in Cycle 1 and shortly after the end of the inotuzumab ozogamicin infusion and resolved spontaneously or with medical management (SmPC, section 4.8).

Tumour lysis syndrome (TLS)

In the pivotal study (N=164), TLS, which may be life-threatening or fatal, was reported in 4/164 (2%) patients. Grade 3/4 TLS was reported in 3 (2%) patients. TLS occurred shortly after the end of the inotuzumab ozogamicin infusion and resolved with medical management (SmPC, section 4.8).

QT interval prolongation

In the pivotal study (N=164), increases in QT interval corrected for heart rate using the Fridericia formula (QTcF) $\geqslant$ 60 msec from baseline were measured in 4/162 (3%) patients. No patients had QTcF values > 500 msec. Grade 2 QT prolongation was reported in 2/164 (1%) patients. No Grade $\geqslant$ 3 QT prolongation or events of Torsades de Pointes were reported (SmPC, section 4.8).

Increased amylase and lipase

In the pivotal study (N=164), increases in amylase and lipase were reported in 8 (5%) and 15 (9%) patients, respectively. Increases in Grade ⩾ 3 amylase and lipase were reported in 3 (2%) and 7 (4%) patients, respectively (SmPC, section 4.8).

Immunogenicity

In clinical studies of BESPONSA in patients with relapsed or refractory ALL, 7/236 (3%) patients tested positive for anti-inotuzumab ozogamicin antibodies. No patients tested positive for neutralising anti inotuzumab ozogamicin antibodies. In patients who tested positive for anti inotuzumab ozogamicin antibodies, no effect on clearance of BESPONSA was detected based on population pharmacokinetic analysis. The number of patients was too small to assess the impact of anti inotuzumab ozogamicin antibodies on efficacy and safety (SmPC, section 4.8).

Neurotoxicity

An updated review of neurotoxicity was provided (cut-off 8 March 2016). In Study B1931022, neurotoxicity AEs were reported in 17 (10.4%) and 10 (7%) patients in the inotuzumab ozogamicin arm and control arm. The median time to onset was 39 days for the patients in the inotuzumab ozogamicin and 11.5 days for patients in the Investigator's choice of chemotherapy arm. The only AE reported with frequency ≥2% in the inotuzumab ozogamicin arm compared with the control arm was peripheral neuropathy (6 [3.7%] vs 2 [1.4%] patients). One patient in the inotuzumab ozogamicin arm (0.6%) and 2 patients in the investigator's choice arm (1.4%) reported Grade ≥3 neurotoxicity AEs. No patient in either treatment arm had Grade 4 or 5 neurotoxicity AEs.

Nephrotoxicity

In Study B1931022, nephrotoxicity AEs were reported in equal proportions of patients receiving inotuzumab ozogamicin and control (5%). The most frequently reported AE in the inotuzumab ozogamicin arm was acute renal failure (4 patients). Increased creatinine was recorded with similar frequency in the inotuzumab ozogamicin (8.6%) and control arm (11.4 %). All were Grade 1 and 2 events.

Interstitial lung disease

One patient in the inotuzumab ozogamicin arm in Study B1931022 was reported to have Grade 1 bronchiolitis obliterans and pneumonitis 8 days prior to death due to disease progression.

Pancreatitis

In study B1931022, pancreatitis AEs were reported in 18/164(11%) patients treated with inotuzumab ozogamicin compared to 3(2.1%) patients receiving control therapy. AEs in the inotuzumab ozogamicin arm were increased lipase (15 [9.1%], including 4 Grade 3 and 3 Grade 4 events), increased amylase (8 [4.9%], including 3 Grade 3 and no Grade 4 events), Grade 1 pancreatic pseudocyst and Grade 1 pancreatitis necrotising in the same patient (1 [0.6%]) and Grade 3 pancreatitis (1 [0.6%]). Grade 1 increased amylase

and Grade 2 pancreatitis were reported in 1 patient each in the control arm. There were no permanent treatment discontinuations or Grade 5 pancreatitis AEs.

Inflammatory GI events

In study B1931022, inflammatory GI AEs were reported in 24 (14.6 %) patients receiving inotuzumab ozogamicin and 40 (28.0%) patients receiving control therapy. These included Grade 2 gastritis, Grade 3 colitis (typhlitis) and Grade 5 ischaemic colitis in the inotuzumab ozogamicin arm and Grade 2 gastritis and Grade 3 colitis and enteritis in the control arm.

Serious adverse event/deaths/other significant events

Serious adverse event

In study b1931022 (updated analysis, 08 March 2016 data cutoff), the overall frequency of SAEs was higher for all cycles than Cycles ≤2 (51.2% vs 37.2%, respectively); 23 additional patients had SAEs beyond Cycle 2 (23 of 87 [26.4%] patients who received >2 cycles). In general, the frequencies of individual SAEs were similar for all cycles and for Cycles ≤2. The only individual SAE with a >5% increase in frequency between Cycles ≤2 and all cycles was VOD (5.5% and 13.4%, respectively). The frequencies of SAEs were higher in the SOCs 'Hepatobiliary Disorders' and 'Infections and Infestations', for all cycles compared to Cycles ≤2 (14.0% vs 6.1%, and 23.8% vs 17.7%, respectively); the most common SAEs in these SOCs were VOD and pneumonia, respectively.

Table 63: Study B1931022: Summary of All-Causality SAEs in >1 Patient in Inotuzumab Ozogamicin Arm, Summarized by SOC and Preferred Term (All Cycles and Cycle ≤ 2) –Updated analysis 08 March 2016 Cutoff Date - Safety Population

System Organ Class **Preferred Term**	**Inotuzumab ozogamicin N=164 n (%)**	
	All Cycles	**Cycle ≤2**
Any SAEs	**84 (51.2)**	**61 (37.2)**
Blood and lymphatic system disorders	**21 (12.8)**	**17 (10.4)**
Febrile neutropenia	19 (11.6)	16 (9.8)
Neutropenia	2 (1.2)	1 (0.6)
Cardiac disorders	**7 (4.3)**	**5 (3.0)**
Left ventricular dysfunction	2 (1.2)	2 (1.2)
Gastrointestinal disorders	**17 (10.4)**	**9 (5.5)**
Abdominal pain	3 (1.8)	1 (0.6)
Nausea	2 (1.2)	1 (0.6)
Stomatitis	2 (1.2)	2 (1.2)
General disorders and administration site conditions	**19 (11.6)**	**14 (8.5)**
Disease progression	8 (4.9)	6 (3.7)
Pyrexia	5 (3.0)	3 (1.8)
Asthenia	3 (1.8)	2 (1.2)
Multi-organ failure	2 (1.2)	1 (0.6)
Hepatobiliary disorders	**23 (14.0)**	**10 (6.1)**
Venoocclusive disease	22 (13.4)	9 (5.5)
Infections and infestations	**39 (23.8)**	**29 (17.7)**
Pneumonia	10 (6.1)	4 (2.4)
Sepsis	4 (2.4)	4 (2.4)
Bacteremia	4 (2.4)	3 (1.8)
Neutropaenic sepsis	3 (1.8)	3 (1.8)
Septic shock	3 (1.8)	1 (0.6)
Clostridium difficile colitis	2 (1.2)	2 (1.2)
Escherichia bacteraemia	2 (1.2)	1 (0.6)
Influenza	2 (1.2)	0

System Organ Class Preferred Term	Inotuzumab ozogamicin N=164 n (%)	
Staphylococcal sepsis	2 (1.2)	2 (1.2)
Metabolism and nutrition disorders	**5 (3.0)**	**3 (1.8)**
Hyperglycaemia	2 (1.2)	1 (0.6)
Tumour lysis syndrome	2 (1.2)	2 (1.2)
Musculoskeletal and connective tissue disorders	**5 (3.0)**	**3 (1.8)**
Back pain	2 (1.2)	0
Nervous system disorders	**4 (2.4)**	**2 (1.2)**
Headache	2 (1.2)	1 (0.6)
Renal and urinary disorders	**3 (1.8)**	**1 (0.6)**
Acute kidney injury	2 (1.2)	0
Respiratory, thoracic and mediastinal disorders	**4 (2.4)**	**1 (0.6)**
Respiratory failure	2 (1.2)	1 (0.6)
Abbreviations: N=number of patients; n=number of patients meeting pre-specified criteria; SAE=serious adverse event; SOC=System organ class.		

Deaths

In study B1931022 (updated analysis,data cut-off 08 March 2016), all –causality Grade 5 TEAEs were reported for 26/164 (15.9%) patients in the inotuzumab ozogamicin arm and 16/143 (11.2%) of patients in the control arm, mostly grouped in the 'Infections and infestations' SOC (4.9% in both arms). The most frequently reported Grade 5 SAE was disease progression (4.9 vs. 3.5%).

There were 9 deaths in the inotuzumab ozogamicin arm (n=164) within 30 days of Cycle 1 day 1 and 32 deaths within 42 days after the last dose, mostly due to ALL and infection. In the control arm (n=143), the figures were 8 and 19, respectively, with the majority also due to ALL, followed by infection.

Grade 5 TEAEs considered related to study drug were reported for 9 (5.5%) patients in the inotuzumab ozogamicin arm; these were VOD/SOS (5 patients post follow-up HSCT), intestinal ischaemia/ septic shock (post Cycle 5, Day 8), acute respiratory distress (post Cycle 3, Day 15), pneumonia (post cycle 5, Day 1) and mult-organ failure (post Cycle 5 D8 and HSCT, with ongoing SOS). Grade 5 TEAEs considered treatment related were reported in 3 patients (2.1%) in the control arm; these were intracranial haemorrhage, multi-organ failure and lung infection/ respiratory failure.

In study B1931010, 9 patients (12.5%) had Grade 5 TEAEs, including 5 patients with disease progression. Two SAEs were considered treatment related - septic shock during inotuzumab ozogamicin therapy and VOD post follow-up HSCT.

In IIR studies (as of 01 September 2015 data cutoff), Grade 5 SAEs were reported for 26/231 (11.3%) patients, most commonly VOD (n=5), neutropenia (n=4), pneumonia (n=3) and multi-organ failure and disease progression (n=2 each).

In compassionate use studies (as of 01 September 2015 data cutoff), 16 from an approximate total of 79 patients (~20.3%) had SAEs with fatal outcomes reported in the USA and Europe, most commonly disease progression and pneumonia. Grade 5 treatment-related SAEs were reported for 4 patients; graft-versus-host disease (GVHD) of the GI tract and abnormal hepatic function; hepatocellular injury and cholestasis; hepatorenal syndrome and hepatic failure.

Other significant events

Venoocclusive disease (VOD)/ sinusoidal obstruction syndrome (SOS)

The applicant established processes to help ensure that all VOD/SOS events were captured in Study B19301022. Investigators had to complete a Severe Hepatotoxicity Form for all specified hepatotoxicity AEs (not just SAEs) until the EOT visit and for additional AEs of note (liver failure; liver transplantation; cirrhosis; new ascites; new oesophageal varices; new hepatic encephalopathy; suspected SOS, nodular regenerative hyperplasia, focal nodular hyperplasia or Budd-Chiari Syndrome) until 2 years from randomisation. These forms were reviewed by an independent external Hepatic Events Adjudication Board (HEAB) that provided advice to the e-DMC.

Overall in study B1930122 (updated analysis, 8 March 2016 data cutoff), VOD was reported more frequently in the inotuzumab ozogamicin (22/164 [13.4%]) than control arm (1/143 [0.7%], post follow-up HSCT). Among all 164 patients treated, VOD/SOS was reported in 5/164 (3%) patients during study therapy or in follow-up without an intervening HSCT. Among the 77 patients who proceeded to a subsequent HSCT, VOD/SOS was reported in 17/77 (22.1%) patients. Of these 17 cases, there were 5 deaths due to VOD (all post-follow-up HSCT) in the inotuzumab ozogamicin arm, with 2 of the fatal events occurring after a second or third unrelated donor HSCT, respectively. The median time to onset of VOD after HSCT was 15 days (range 3-57).

In the IIR studies (as of 1 September 2015 data cutoff), VOD (total) included 12 events; there were 3 VOD events reported in CU patients.

Table 64 Frequency of VOD Occurring during Treatment with Inotuzumab Ozogamicin or Post-HSCT: Studies B1931022 and B1931010 (Data cut-off October 2014, updated March 2016)

VOD (without intervening HSCT)[a]			**VOD (post follow-up HSCT)**			**VOD (TOTAL)**		
All n (%)	**Patients with:**		**All n (%)**	**Patients with:**		**All n (%)**	**Patients with:**	
	No Pre Study HSCT n (%)	**Pre-Study HSCT n (%)**		**No Pre Study HSCT n (%)**	**Pre-Study HSCT n (%)**		**No Pre Study HSCT n (%)**	**Pre-Study HSCT n (%)**
B1931022 October 2014 (N=139)								
5[b]/139 (3.6)	3/115 (2.6)	2/24 (8.3)	10/48 (20.8)	7/41 (17.1)	3/7 (42.9)	15/139 (10.8)	10/115 (8.7)	5/24 (20.8)
B1931022 March 2016 (N=164)								
5/164 (3.0)			17/77 (22.1)			22/164 (13.4)		
B1931010								
2/72 (2.8)	2/49 (4.1)	0/23	2/24 (8.3)[c]	2/20 (10.0)	0/4	4/72 (5.6)	4/49 (8.0)	0

a. VOD occurred during treatment with inotuzumab ozogamicin or in follow-up (prior to any new anticancer treatment) and, in patients who proceeded to HSCT, prior to intervening conditioning therapy and HSCT.
b. Includes 1 patient with VOD that occurred at day 57 with no intervening HSCT
c. Both patients died: One fatal VOD event in a Salvage 3 patient post 2 cycles of inotuzumab ozogamicin. One patient (Salvage 4 post 6 cycles of inotuzumab ozogamicin) with VOD ongoing at the time of death due to pneumonia.

Study B1931022 (Updated Analyses, 8 March 2016)

Conditioning regimen for HSCT: Use of dual alkylator conditioning regimens was significantly associated with post-HSCT VOD/SOS. VOD/SOS was reported in 8/52 (15.4 %) patients and 6/11 (54.5%) patients who received single- and dual-alkylator conditioning regimens, respectively. Fatal VOD/SOS was reported in 2/52 (3.8%) patients and 2/11 (18.2%) patients who received single- and dual-alkylator conditioning regimens, respectively. VOD/SOS was reported in 4/5 (80%) patients who received busulfan in combination with thiotepa as the HSCT conditioning regimen.

Age: Age ≥55 was also significantly associated with a higher incidence of VOD/SOS. Among patients who proceeded to HSCT in the inotuzumab ozogamicin arm, VOD/SOS was reported in 10/60 (16.7%) patients and 7/17 (41.2%) patients who were <55 years and ≥55 years, respectively, and 14/71 (19.7%) patients and 3/6 (50%) patients who were <65 years and ≥65 years, respectively.

Other factors that may be associated with an increased risk:

Prior HSCT: Two of the 5 patients who experienced VOD/SOS during treatment with inotuzumab ozogamicin or in follow-up but without an intervening HSCT had undergone HSCT before inotuzumab ozogamicin treatment. Patients treated with more than 1 allogeneic HSCT are at increased risk. The median time from the first dose of inotuzumab ozogamicin to development of VOD was 30.0 days (range 14 – 238). One event resolved and 4 VOD events were ongoing at the time of death due to other causes (progressive leukaemia, pneumonia, neutropaenic sepsis, pseudomonal bacteraemia).

Prior history of liver disease and/or hepatitis: VOD/SOS was reported in 10/57 (17.5%) patients without and 7/20 (35%) patients with a prior history of liver disease who proceeded to HSCT.

Pre-HSCT laboratory analysis: The rates of VOD/SOS in patients who proceeded directly to HSCT were:

- Platelet count <100 x 10^9/L vs. ≥100 x 10^9/L: 10/37 (27%) vs. 5/34 (14.7%)
- ALT/AST > 1.5 x ULN vs. ≤ 1.5 x ULN: 2/12 (16.7%) vs. 13/59 (22%)
- Serum total bilirubin ≥ULN vs. <ULN: 6/11 (54.5%) vs. 9/60 (15%)

Use of ursodeoxycholic acid and defibrotide

The study was not designed to assess the effectiveness of ursodeoxycholic acid and defibrotide. Ursodeoxycholic acid was used prophylactically to reduce the frequency and severity of hepatic toxicity in 77 (47.0%) patients in the inotuzumab ozogamicin arm; 15/ 17 patients with VOD/SOS post-HSCT received ursodeoxycholic acid prior to HSCT.

Defibrotide was used to treat VOD/SOS in 13 (7.9%) patients in the inotuzumab ozogamicin arm in study B1931022. Of the inotuzumab ozogamicin-treated patients with Grade 3/4 SOS, 3 who were treated with defibrotide recovered as opposed to none who were not treated with defibrotide.

Study B1931022 Laboratory findings (Updated Analysis, 8 March 2016 data cutoff)

Expected changes in haematological laboratory parameters were recorded with decreased leucocytes, neutrophils, lymphocytes and platelets. Grade 3 haematology laboratory test abnormalities were more frequent in the inotuzumab ozogamicin arm and Grade 4 abnormalities in the control arm.

Liver-related laboratory test abnormalities were very common but more frequently observed in the inotuzumab ozogamicin than the control arm, including increased AST (73.5% vs 38.7%), ALT (49.7% vs 47.1%), ALP (57.7% vs 52.9%), GGT (69.0% vs 66.9%) and bilirubin (36.2% vs 36.2%). There were 3 Grade 4 abnormalities in each treatment arm, involving increased AST, bilirubin and GGT.

Pancreatic-related laboratory test abnormalities were more frequently observed with inotuzumab ozogamicin, including Grade 3 and 4 AEs: increased lipase (29.7% vs 18.6%, Grade 3: 10.1% vs 2.0%, Grade 4: 1.4%

vs 0%), increased amylase (13.4% vs 10.5%, Grade 3: 2.5% vs 0.9%); there were no Grade 4 abnormalities. Hyperglycemia (mostly Grade 1 or 2) was observed in 80.7% of inotuzumab ozogamicin patients and 77.7% of control patients. Grade 3 and 4 elevations were reported in 12.4% and 0.6% of patients treated with inotuzumab ozogamicin and 6.5% and 0.7% of patients treated with control, respectively. These were not fasting samples and concomitant corticosteroids could contribute.

ECGs

In Study B1931022, increases in QTcF of ⩾ 60 msec from baseline were measured in 4/162 (3%) patients in the inotuzumab ozogamicin arm and 3/124 (2%) in the Investigator' s choice of chemotherapy arm. Increases in QTcF of > 500 msec were observed in none of the patients in the inotuzumab ozogamicin arm and 1/124 (1%) patients in the Investigator's choice of chemotherapy arm (see section 4.8). Mean (90% CI) maximum QTcF changes from baseline were 16.5 msec (14.3 18.7) in the inotuzumab ozogamicin arm and 10.8 msec (8.0 13.6) in the Investigator's choice of chemotherapy arm. Central tendency analysis of the QTcF interval changes from baseline showed that the highest upper bound of the 2 sided 90% CI for QTcF was 21.1 msec (observed at Cycle 4/Day 1/1 hour) in the inotuzumab ozogamicin arm and 21.2 msec (observed at Cycle 2/Day 1/1 hour) in the Investigator's choice of chemotherapy arm (SmPC section 5.2).

Safety in special populations

Table 65 : Study 1022 (Updated Analysis, 08 March 2016 data cutoff)- Summary of Adverse Events (All-Causality and Treatment-Related), Serious Adverse Events, and Permanent Discontinuations Due to Adverse Events by Age Group (<55, ≥55, and <65, ≥65 years)

Number (%) of Patients	Inotuzumab ozogamicin N=164		Control N=143	
Age Group	<55 years (N=104)	≥55 years (N=60)	<55 years (N=91)	≥55 years (N=52)
Patients with AEs	103 (99.0)	60 (100.0)	91 (100.)	52 (100.0)
Grade 3 or 4 AEs	75 (72.1)	48 (80.0)	75 (82.4)	46 (88.5)
Grade 5 AEs	15 (14.4)	11 (18.3)	12 (13.2)	4 (7.7)
SAEs	44 (42.3)	40 (66.7)	44 (48.4)	27 (51.9)
Patients with TRAEs	90 (86.5)	54 (90.0)	85 (93.4)	45 (86.5)
Grade 3 or 4 TRAEs	64 (61.5)	42 (70.0)	68 (74.7)	42 (80.8)
Grade 5 TRAEs	6 (5.8)	3 (5.0)	3 (3.3)	0
TR SAEs	26 (25.0)	25 (41.7)	26 (28.6)	16 (30.8)
D/C due to AEs	20 (19.2)	10 (16.7)	6 (6.6)	6 (11.5)
D/C due to TRAEs	9 (8.7)	6 (10.0)	4 (4.4)	3 (5.8)

Number (%) of Patients	Inotuzumab ozogamicin N=164		Control N=143	
Age Group	<65 years (N=134)	≥65 years (N=30)	<65 years (N=127)	≥65 years (N=16)
Patients with AEs	133 (99.3)	30 (100.0)	127 (100.0)	16 (100.0)
Grade 3 or 4 AEs	100 (74.6)	23 (76.7)	106 (83.5)	15 (93.8)
Grade 5 AEs	19 (14.2)	7 (23.3)	16 (12.6)	0
SAEs	64 (47.8)	20 (66.7)	63 (49.6)	8 (50.0)
Patients with TRAEs	116 (86.6)	28 (93.3)	117 (92.1)	13 (81.3)
Grade 3 or 4 TRAEs	85 (63.4)	21 (70.0)	97 (76.4)	13 (81.3)
Grade 5 TRAEs	7 (5.2)	2 (6.7)	3 (2.4)	0
TR SAEs	38 (28.4)	13 (43.3)	36 (28.3)	6 (37.5)
D/C due to AEs	27 (20.1)	3 (10.0)	10 (7.9)	2 (12.5)
D/C due to TRAEs	12 (9.0)	3 (10.0)	5 (3.9)	2 (12.5)

Immunological events

In Study B1931022 (updated analysis, 08 March 2016 data cutoff),, infusion-related reaction AEs (including only events that occurred from start of infusion to within 1 calendar day of end of infusion) were reported in 53 (32.3 %) patients receiving inotuzumab ozogamicin and 63 (44.1%) patients receiving control therapy; the most frequent reaction was pyrexia (21 [12.8%]vs 36 [25.2%]patients, respectively). Patients treated with inotuzumab ozogamicin were usually pre-medicated with corticosteroid and/or acetaminophen and an antihistamine. Patients received subsequent infusions of inotuzumab ozogamicin without incident.

Safety related to drug-drug interactions and other interactions

No safety concerns related to drug – drug interactions with inotuzumab ozogamicin have been identified.

Discontinuation due to AES

In study B1931022 (updated anaylsis, 08 March 2016 data cutoff),, AEs were associated with treatment discontinuation in 18.9% (31/164) patients (including TEAEs associated with treatment discontinuation in 18.3% (30/164) patients and 1 patient with non-treatment emergent AE associated with treatment discontinuation) in patients treated with inotuzumab ozogamicin, most commonly pneumonia (n= 5) and thrombocytopenia (n=3), increased AST, increased GGT hyperbilirubinemia, sepsis and VOD/SOS (n=2 each). SAEs leading to permanent discontinuation were experienced by 11.0% of patients in the inotuzumab ozogamicin arm versus 7.0% patients in the control arm, most commonly pneumonia (n=5 [3.0%]) VOD/SOS and sepsis (n=2 [1.2%] each) in the inotuzumab ozogamicin arm and febrile neutropenia (n=3 [2.1%]) in the control arm.

In the updated analysis (March 2016), 43 patients (31 (18.9%) in the inotuzumab ozogamicin arm and 12 (8.4%) patients in the control arm) discontinued treatment due to TEAEs. The median time to discontinuation due to AE was 5.7 months (95% CI 5.3, 6.8) in the inotuzumab ozogamicin arm, and not estimable for the control arm. In the safety population, the stratified HR for the time to discontinuation was 0.679 (97.5% CI: 0.291-1.586).

Post marketing experience

N/A.

2.5.1. Discussion on clinical safety

As expected in the relapsed/ refractory ALL population, in Study B1931022 (08 March 2016 data cutoff), most patients (99.4%) experienced AEs, with 87.8% patients experiencing AEs considered related to inotuzumab ozogamicin. The most common events (all causality and those considered treatment-related) were cytopenias, fatigue, pyrexia, abnormal liver function tests and abdominal events (nausea, diarrhoea, vomiting and constipation). Only 3.0% patients were dose reduced due to TEAEs; most patients (43.9%) were managed by dose interruption with only 18.3% requiring permanent treatment discontinuation.

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

In patients who received Besponsa, the most common (⩾ 2%) serious adverse reactions were infection (23%), febrile neutropenia (11%), haemorrhage (5%), abdominal pain (3%), pyrexia (3%), VOD/SOS (2%), and fatigue (2%).SAEs were experienced by 48.2% patients treated with inotuzumab ozogamicin; 25.2% patients suffered SAEs that were considered to be treatment related.

A total of 26 (15.9%) deaths occurred during treatment in the inotuzumab ozogamicin arm and 16 (11.2%) in the control arm, mostly due to infection and disease progression.

Hepatotoxicity was due to the cytotoxic agent (conjugated/ unconjugated) and was target-independent. Increased AST/ ALT and histopathological changes were seen in non-clinical studies in rats and monkeys, including microvascular liver injury in monkeys, considered to represent early venoocclusive liver disease. Severe, life-threatening and sometimes fatal VOD was seen in clinical studies with inotuzumab ozogamicin and with the related ADC gemtuzumab ozogamicin.

VOD is contributed to early transplant related mortality and meant that the median gain in OS was only 1 month. The creation by the Sponsor of the 'Severe Hepatotoxicity Form' and external 'Hepatic Events Adjudication Board' (HEAB) means that we can have reasonable confidence that the hepatotoxic adverse events have been adequately captured and assessed. Factors predisposing to an increased risk of SOS have been identified. These include the use of dual alkylating agents in the HSCT conditioning regimen and age ⩾55 years. Other factors may be influential, including a bilirubin ⩾ ULN pre HSCT and HSCT prior to inotuzumab ozogamicin. Information on these risks is included in the SmPC (see SmPC section 4.4 and 4.8). No evaluation of risk can be undertaken in patients who have experienced prior confirmed severe or ongoing venoocclusive liver disease/sinusoidal obstruction syndrome and in patients with serious ongoing hepatic disease (e.g., cirrhosis, nodular regenerative hyperplasia, active hepatitis), as these patients have not been

treated with inotuzumab ozogamicin. It can only be surmised that their risk of VOD is unacceptably high and that these populations should be contraindicated (SmPC section 4.3). Grade ≥3 and/or serious hepatotoxicity, including all VOD/SOS have been categorized as an identified risk (see Risk Management Plan).

In Study B1931022, myelosuppression/ cytopenia was reported in 82.9% of patients with Grade ⩾3 AEs were reported in 81.1% of patients treated with inotuzumab ozogamicin. Potential consequences of myelosuppression/cytopenia include infection and bleeding. Serious infections, some of which were life-threatening or fatal, were frequently reported with inotuzumab ozogamicin therapy. Myelosuppression/cytopenia has been categorized as an identified risk (see Risk Management Plan).

In addition to cytopenias and hepatobiliary abnormalities, the most common laboratory test abnormalities with inotuzumab ozogamicin were (lipase and amylase) and hyperglycaemia. These blood tests should be measured during treatment which is reflected in the SmPC (sections 4.4 and 4.8).

In Study B1931022, infections were reported in 48.8%, including Grade 3 in 19.5%, Grade 4 in 4.3% and Grade 5 in 4.9% of patients treated with inotuzumab ozogamicin. Haemorrhage was seen in 33.5%, including Grade 3 in 3.7%, Grade 4 in 1.2% and Grade 5 in 1.2% of patients treated with inotuzumab ozogamicin.

The incidence of alveolar macrophages was low in the preclinical studies (higher incidence in females only) and considered non-adverse. Still, they may be treatment-related given that the highest tissue-to-plasma ratios (although low themselves) were observed in the liver (0.6), blood (0.5), spleen (0.4), lung (0.3) and kidney (0.3). Interstitial lung disease has been categorized as a potential risk (see Risk Management Plan).

Only 1 patient in study B1931022 was reported to have bronchiolitis obliterans and pneumonitis (Grade 1) prior to death due to disease progression. However, a few more events were reported in the NHL studies - Grade 1 pneumonitis (n=2), Grade 2 lung infiltration (n=1) and Grade 4 alveolitis (n=1). This patient progressed to multi-organ failure and death despite broad-spectrum antibiotics and haemodynamic support. Autopsy lung findings revealed "diffuse toxic alveolitis".

Pulmonary events were reported with the related product gemtuzumab ozogamicin, possibly as sequelae of infusion reactions and patients with WBC ⩾30000µ/L.

There was 1 Grade 5 event of ischaemic colitis in the pooled ALL studies and none in the NHL studies. Patients with refractory leukaemia, particularly those receiving anti-leukaemic therapy, are susceptible to GI inflammation due to direct injury to the mucosal lining from chemotherapy-induced apoptosis as well as neutropenia. Ischaemic colitis is more likely to occur in older patients, especially those with comorbidities such as ischaemic cardiac disease.

Pancreatic-related AEs were reported in 9.4% % of pooled ALL patients (updated analysis including 212 patients who received 1.8 mg/m2 inotuzumab ozogamicin in studies b1931022 [n=164] and b1931010 [n=48]), including 4 Grade 4 events, mainly increased amylase and lipase. There were single clinical events of pancreatitis, acute pancreatitis and necrotizing pancreatitis. There were no Grade 5 pancreatic AEs or permanent treatment discontinuations. Pancreatitis has been categorized as a potential risk (see Risk Management Plan).

Based on nonclinical data, inotuzumab ozogamicin is clastogenic and, consistent with induction of DNA breaks, calicheamicin is genotoxic and clastogenic. In rats, preneoplastic lesions were observed in the liver after 4 weeks of dosing and neoplastic lesions were observed in the liver after 26 weeks of dosing. An altered hepatocellular focus was seen in 1 monkey. In ALL Study B1931010, a heavily pretreated Salvage >5

patient, was diagnosed with acute myeloid leukaemia (AML) after 3 cycles of inotuzumab ozogamicin treatment. Per Investigator, causal attribution to inotuzumab ozogamicin could not be excluded. Second primary malignancy has been categorized as a potential risk (see Risk Management Plan).

Inotuzumab ozogamicin was associated with toxicity in embryo-foetal nonclinical studies. No pregnancies were reported in female patients or in the partners of male patients during the clinical ALL studies. Inotuzumab ozogamicin is genotoxic and can cause foetal harm when administered to a pregnant woman. Reproductive and developmental toxicity (post exposure during pregnancy and while breast feeding) has been categorized as a potential risk (see Risk Management Plan).

A formal thorough QT study of inotuzumab ozogamicin has not been conducted but evaluation the QTcF interval was an exploratory endpoint in study B1931022. Increases in QTcF were observed and this is adequately reflected in the SmPC (sections 4.4., 4.8, 5.2).

Hispanic and Black patients have been underrepresented in clinical studies of inotuzumab ozogamicin. Therefore, it is not known whether the adverse event (AE) profile in those (and other) racial and/or ethnic groups is different from that seen in White and Asian patients. Use in Hispanic and Black patients has been classified as missing information. This has been adequately reflected in the Risk Management Plan.

Use in patients with moderate or severe hepatic impairment and use in patients with severe renal impairment have been classified as missing information (see Risk Management Plan).

In Study B1931022, out of 7 patients with positive ADAs, there were 2 patients with positive ADAs after treatment with inotuzumab ozogamicin (without positive ADA response prior to treatment) and AEs thought attributable to immunogenic response: 1 patient, with positive ADAs at Cycle 1 Day 1, Cycle 2 Day 1 and EOT, exhibited Grade 2 pyrexia on Days 1 to 4. 1 patient, with a positive ADA at EOT, exhibited Grade 1 chills and pyrexia on Days 1 to 2 and anaemia (Grade 3) on Days 3-5. Chills pyrexia and anaemia were observed in at least 5% of patients in the study.

Besponsa has moderate influence on the ability to drive and use machines. Patients may experience fatigue during treatment with Besponsa. Therefore, caution is recommended when driving or operating machines (SmPC, section 4.7).

In clinical studies in patients with relapsed or refractory ALL, the maximum single and multiple doses of inotuzumab ozogamicin were 0.8 mg/m^2 and 1.8 mg/m^2, respectively, per cycle, given as 3 divided doses on Days 1 (0.8 mg/m^2), 8 (0.5 mg/m^2), and 15 (0.5 mg/m^2). Overdoses may result in adverse reactions that are consistent with the reactions observed at the recommended therapeutic dose. In the event of an overdose, the infusion should be temporarily interrupted and patients should be monitored for liver and haematological toxicities. Re-initiation of Besponsa at the correct therapeutic dose should be considered when all toxicities have resolved (SmPC, section 4.9).

From the safety database all the adverse reactions reported in pivotal phase III study B1931022 have been included in the Summary of Product Characteristics.

2.5.2. Conclusions on the clinical safety

The safety profile of inotuzumab ozogamicin is considered acceptable for use in the treatment of adult patients with for the treatment of adults with relapsed or refractory CD22-positive B cell precursor ALL. Many

of the AEs were expected in the relapsed/ refractory ALL population and were managed with dose interruption or discontinuation of inotuzumab ozogamicin.

2.6. Risk Management Plan

Safety concerns

Table 66: Summary of the Safety Concerns

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

Pharmacovigilance plan

N/A

Risk minimisation measures

Table 67: Summary of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risks		
Grade ≥3 and/or serious hepatotoxicity, including all VOD/SOS	SmPC Section 4.2 (Posology and method of administration) SmPC Section 4.3 (Contraindications) SmPC Section 4.4 (Special warnings and precautions for use) SmPC Section 4.8 (Undesirable effects) SmPC Package Leaflet	None
Myelosuppression/ cytopenia	SmPC Section 4.2 (Posology and method of administration) SmPC Section 4.4 (Special warnings and precautions for use) SmPC Section 4.8 (Undesirable effects) SmPC Package Leaflet	None
Important Potential Risks		

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Interstitial lung disease	None	None
Inflammatory gastrointestinal events	None	None
Pancreatitis	None	None
Second primary malignancy	None	None
Reproductive and developmental toxicity (post exposure during pregnancy and while breast feeding)	SmPC Section 4.6 (Fertility, pregnancy, and lactation) SmPC Section 5.3 (Preclinical safety data) SmPC Package Leaflet	None
Neurotoxicity	None	None
Nephrotoxicity	None	None
Missing Information		
Use in patients with moderate or severe hepatic Impairment	SmPC Section 4.2 (Posology and method of administration) SmPC Section 5.2 (Pharmacokinetic properties) SmPC Package Leaflet	None
Use in patients with severe renal impairment	SmPC Section 4.2 (Posology and method of administration) SmPC Section 5.2 (Pharmacokinetic properties)	None
Use in Hispanic and Black patients	SmPC Section 5.2 (Pharmacokinetic properties)	None
SmPC=Summary of Product Characteristics; SOS=sinusoidal obstruction syndrome; VOD=venoocclusive disease		

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.3 (sign off 08/04/2017) is acceptable.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8. New Active Substance

The applicant declared that inotuzumab ozogamicin has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers inotuzumab ozogamicin to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, BESPONSA (inotuzumab ozogamicin) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The target indication applied for by the Applicant is for the treatment of adult patients with relapsed or refractory B-cell precursor ALL. Patients were screened at baseline for CD22 positivity on the blast cell surface (CD22 >0%) by local laboratory test and were Philadelphia chromosome negative (Ph-) or positive (Ph+); the latter had to have been treated with at least one prior tyrosine kinase inhibitor.

3.1.2. Available therapies and unmet medical need

Modern multi-agent combination chemotherapy regimens in adults with ALL result in complete response rates of 80-90%. However, most patients in complete remission will relapse, with just 30-50% having a disease-free survival of 3 years or more. There is no single standard treatment for relapsed or refractory Ph- ALL. Common re-induction regimens include: 1) therapies based on a backbone of vincristine, corticosteroids, and anthracyclines; 2) 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 plus cytarabine (MXN/Ara-C) or 4) clofarabine or methotrexate based regimens. After early relapse, standard chemotherapy for relapsed/ refractory ALL shows complete remission rates of 31-44% in the first salvage therapy and 18-25% in the second salvage therapy. Obtaining a complete remission is a prerequisite for allogeneic stem cell transplantation, considered the only curative option. Only 5-30% of adults proceed to HSCT.

Blincyto (blinatumomab), a bispecific anti-CD3/CD19 monoclonal antibody, received conditional approval in the EU in 2015 based on early data for treatment of the relapsed/ refractory Ph- B-cell ALL population.

Tyrosine kinase inhibitors (imatinib, dasatinib and ponatinib) are the mainstay of treatment in the R/R Ph+ population. Dasatinib (Sprycel) was approved in 2006 for the treatment of adult patients with resistance or intolerance to prior therapy. Ponatinib (Iclusig) was approved in 2013 for the treatment of adult patients with Ph+ ALL who are resistant to/ intolerant of dasatinib.

Despite these recent advances there remains a significant need for additional effective therapies with an acceptable safety profile that generate durable remissions and improve long-term survival for adult patients with relapsed/ refractory B cell ALL.

3.1.3. Main clinical studies

The main evidence of efficacy submitted is an open-label, randomized phase 3 study comparing inotuzumab ozogamicin (n=164) versus a defined investigator's choice (n=162) in adult patients with relapsed or refractory CD22-positive acute lymphoblastic leukaemia (ALL).

3.2. Favourable effects

In Study B1931022, inotuzumab ozogamicin induced haematological remission (CR/CRi) in 80.7% of treated patients. The improvement in CR/CRi rate compared to the defined Investigator's choice chemotherapy was seen in all populations (ITT218, mITT218, PP218) and across the 3 pre-defined stratification subgroups (duration of first remission, line of salvage and age at randomization). Results of subgroup analysis of CR/CRi rate were consistent with the primary analysis, including a benefit in those who were Ph+ and who underwent prior HSCT. The higher CR/CRi rates for inotuzumab ozogamicin over control were seen in both the relapsed and refractory populations. CR/CRi rate appeared consistent in patients with $\geqslant$70% of leukaemic blasts CD22 positive at baseline by central laboratory analysis.

MRD negativity was superior in the experimental arm (78%), compared to the control arm (28%).

The median time from randomization to remission was 3 weeks for Besponsa and 4 weeks for the composite control. In the inotuzumab ozogamicin arm (ITT 326 population), 70.8% and 25.8% of patients who achieved CR/CRi first achieved remission (CR or CRi) in Cycles 1 and 2, respectively.

The median DOR was in favour of the experiment arm: in the ITT218 population (08 March 2016 data cutoff), the median duration of remission in patients who achieved CR/CRi was longer in the inotuzumab ozogamicin group (84 patients) than the chemotherapy control (32 patients [5.4 months (95% CI 4.2, 8.0 months) vs. 3.5 months (95% CI 2.9, 6.6 months). The median DoR in all patients (ITT population , updated analysis, 08 March 2016, with patients without remission being given a duration of zero) was 3.7months (2.8 to 4.3) in the inotuzumab ozogamicin arm and 0.0 months in the control arm, with a stratified HR (95%CI) of 0.468 (0.363-0.603), 2-sided p<0.0001.

An improvement in median PFS was evident [5.0 months (95% CI 3.7, 5.6) in the inotuzumab ozogamicin arm vs. 1.8 months (95% CI 1.5, 2.2) in the control arm, stratified HR 0.452 (97.5% CI 0.336, 0.609) 1-sided p value <0.0001], as most patients progressed early on chemotherapy. In the standard definition of PFS, where switch of therapy was not considered an event, the median PFS was 5.6 months and 3.6 months in the inotuzumab ozogamicin and the control arm, respectively.

Median OS in the ITT population based on the stratified log rank test was increased by 1 month with inotuzumab ozogamicin compared to chemotherapy (7.7 months [95% CI 6.0, 9.2] vs. 6.7 months [95% CI 4.9, 8.3]. This improvement was not statistically significant according to the pre-specified analysis but the planned testing strategy was over-conservative and the result could be considered positive while controlling the type I error at conventional levels. The primary OS result (HR = 0.77, 1 sided p=0.0203) was statistically significant at the accepted p-value threshold of 0.0229. The OS analyses in the mITT and PP populations were consistent with the results for the full ITT population. Overall survival showed an improvement in the inotuzumab ozogamicin arm compared with the control arm with respect to all stratification factors per IVRS examined (duration of first remission [<12 months or ⩾12 months], salvage status [Salvage 1 or 2] and age at randomization [<55 years or ⩾55 years]). In general, patients with more favourable prognostic factors had a better survival outcome. Using Cox regression modeling, in the univariate analyses, baseline characteristics associated with lower risk of death in the inotuzumab ozogamicin arm (2-sided p<0.05) were younger age (<55 years), Salvage 1, duration of first remission ⩾12 months and baseline leukaemic blast CD22 positivity per central laboratory ⩾90%.

Inotuzumab ozogamicin allowed more patients to proceed directly to HSCT than control (71 vs. 18 patients) in the ITT (N=326) population.

The updated OS (cut-off date 4 January 2017) was consistent with the primary OS analysis.

3.3. Uncertainties and limitations about favourable effects

Certain questions cannot be answered with additional certainty due to the trial planning/ documentation or the small number of patients involved. It is not clear how the responses in the control arm compare with historical data as such comparisons were difficult in the context of the scientific evolution. A methodological weakness of the choice of the control arm that occurred after randomisation may potentially result in bias represent uncertainties, however in the view of the clear difference between the 2 arms it can be considered that this uncertainty has no impact on the demonstration of efficacy.

Unfavourable effects

Most patients treated with inotuzumab ozogamicin experienced adverse events. Adverse effects such as cytopenias, febrile neutropenia, infection, tumour lysis syndrome and haemorrhage did not occur with any greater frequency or severity than would be anticipated in a population with relapsed/ refractory ALL receiving a cytotoxic agent. Cytopenias were responsible for the greatest number of TEAEs, Grade ⩾3 TEAEs and dose reductions due to AEs. Approximately half of patients (51.2%) treated with inotuzumab ozogamicin experienced SAEs and about 31% had 'treatment related' SAEs, particularly febrile neutropenia and venoocclusive disease. Development of anti-drug antibodies was uncommon and infusion-related reactions were mostly mild-moderate and managed with standard pre- medication. Most of the important AEs are due to the cytotoxic agent, calicheamicin, rather than the full ADC and are not related to binding to CD22 on the cell surface.

Grade ⩾3 hepatotoxicity and VOD were important events seen with higher frequency in the inotuzumab ozogamicin than the control arm.

3.4. Uncertainties and limitations about unfavourable effects

The number of ALL patients in the pooled safety population is relatively small but adequate for a MAA in an orphan indication. Given the restricted population size, there is uncertainty regarding the significance of unfavourable events seen in the non-clinical setting, particularly neurotoxicity but also nephrotoxicity. Other events have been observed with low frequency clinically including interstitial lung disease and pancreatitis. All these safety concerns are being followed as important potential risks in the RMP.

3.5. Effects Table

Table 68. Effects Table for Inotuzumab ozogamicin in the treatment of adult patients with relapsed/ refractory B-cell precursor ALL (data cut-off: 2 October 2014 , 08 March 2016 for Safety Data, [OS 4 January 2017]).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Haematological remission	CR/CRi by EAC in ITT218 population	%	80.7	29.4	Strong evidence, no uncertainty, clinical relevance moderate	Study B1931022 CSR and sCSR
OS	Time from randomization to death	months	7.7	6.2	Benefit greater at later time points	
MRD negativity	lowest value of MRD from first date of CR/CRi	%	78.4	28.1	Strong evidence, no uncertainty, clinical relevance moderate	
HSCT rate	Directly post inotuzumab ozogamicin	%	43.3	11.1	Benefit reduced due to VOD, major clinical relevance	
PFS	Time from randomization to progressive disease/relapse/ death/new induction therapy or HSCT without achieving CR/CRi	months	5.0	1.8	PFS2 unknown	
Unfavourable Effects (08 March 2016 data cutoff)						
SAEs (Treatment related)	Incidence	%	51.2 (31.1)	49.7 (29.4)		Study B1931022 sCSR
Grade 5 SAEs	Incidence	%	15.9	11.2	Moderately strong evidence for slight increase	
Neutropenia	Incidence of Grade ≥3	%	47.0	44.1	Evidence strong	
Thrombocytopenia	Incidence of Grade ⩾3	%	40.9	59.4		
Febrile neutropenia	Incidence of Grade ⩾3	%	26.8	53.8		
Hepatotoxicity	Incidence of Grade ⩾3	%	29.3	14.7		
VOD/SOS	Incidence of Grade ⩾3	%	11.0	0.7		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Infection	Incidence of Grade ⩾3	%	28.7	55.2		
Haemorrhage	Incidence of Grade ⩾3	%	6.1	5.6		
Pancreatitis	Incidence of Grade ⩾3	%	0.6	0		
Neurotoxicity	Incidence of Grade ⩾3	%	0.6	1.4	Strong pre-clinical data; clinical uncertainty due to confounding medical factors e.g. diabetes	

Abbreviations: CR: complete remission, CRi: complete remission with partial haematological recovery rate, CSR: clinical study report, sCSR: supplementary clinical study report, HSCT: Hematopoietic Stem Cell Transplant Rate, PFS: progression free survival, OS: overall survival, SAE: serious adverse event, SOS: sinusoidal obstruction syndrome, VOD: Venoocclusive liver disease (single PT) or veno(-)occlusive disease

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

Inotuzumab ozogamicin demonstrated strong proof of superiority over investigators' choice of chemotherapy in the induction of haematological remission in adults with relapsed/ refractor B-cell ALL. This benefit was seen across all relevant subgroups and in the Ph+ subpopulation (around 20% of the full trial population). The high response rate was accompanied by deep molecular responses (high level of MRD negativity). Combined with a longer duration of remission and toxicity that was generally manageable, it allowed more patients to reach transplantation. Although there was a higher frequency of early deaths post HSCT in the inotuzumab ozogamicin arm, a late survival benefit was evident. Median overall survival was increased by 1 month in the full trial population with inotuzumab ozogamicin compared to control chemotherapy.

Overall, the nature of most of the reported AEs were expected in the relapsed/ refractory ALL population and were managed with dose interruption or discontinuation of inotuzumab ozogamicin. The main adverse event reported a higher frequency with inotuzumab ozogamicin was hepatotoxicity, including severe, life-threatening, and sometimes fatal venoocclusive liver disease/sinusoidal obstruction syndrome (VOD/SOS).

3.6.2. Balance of benefits and risks

The efficacy of inotuzumab ozogamicin in the target population is considered clinically relevant and, despite the risk of VOD/SOS, the benefits are considered to outweigh the combined risks.

3.6.3. Additional considerations on the benefit-risk balance

Not applicable

3.7. Conclusions

The overall B/R of BESPONSA as monotherapy for the treatment of adults with relapsed or refractory CD22-positive B cell precursor acute lymphoblastic leukaemia (ALL) - is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Besponsa is not similar to Blincyto, Evoltra, Sprycel, Xaluprine Atriance and Iclusig within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Besponsa is favourable in 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).

The CHMP therefore recommends the granting of the marketing subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that inotuzumab ozogamicin is considered to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

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