

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761040Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

BLA 761040 Multi-disciplinary Review and Evaluation

Application Type	BLA
Application Number(s)	761040
Priority or Standard	Priority
Submit Date(s)	December 20, 2016
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Division/Office	CDER/OHOP/DHP
Review Completion Date	August 15, 2017
Established Name	Inotuzumab Ozogamicin
(Proposed) Trade Name	BESPONSA
Pharmacologic Class	Antibody-Drug Conjugate
Code name	PF-05208773
Applicant	Pfizer
Formulation(s)	Injection
Dosing Regimen	Cycle 1: total dose is 1.8mg/m ² per 3 week cycle given as divided doses on day 1(0.8mg/m ²), Day 8(0.5mg/m ²) and Day 15(0.5mg/m ²). For subsequent cycles, the dose is 1.5mg/m ² per 4 week cycle given as 3 divided doses on day 1(0.5mg/m ²), day 8(0.5mg/m ²) and Day 15(0.5mg/m ²).
Applicant Proposed Indication(s)/Population(s)	Treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia(ALL)
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia(ALL)

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Rachel McMullen, MPH, MHA
Nonclinical Reviewer	Michael L. Manning, Ph.D.
Nonclinical Team Leader	Christopher Sheth, Ph.D.
Office of Clinical Pharmacology Reviewer(s)	Salaheldin S. Hamed, Ph.D.
Office of Clinical Pharmacology Team Leader(s)	Bahru Habtemariam, Pharm.D. and Nitin Mehrotra, Ph.D.
Clinical Reviewer	Tanya Wroblewski M.D.
Clinical Team Leader	Angelo De Claro M.D.
Statistical Reviewer	Qing Xu, Ph.D.
Statistical Team Leader	Yuan Li Shen, Ph.D.
Cross-Disciplinary Team Leader	Angelo De Claro M.D.
Deputy Division Director (DHOT)	Haleh Saber, Ph.D.
Division Director (OCP)	NAM Atiqur Rahman, Ph.D.
Division Director (OB)	Rajeshwari Sridhara, PhD
Division Director (OHOP)	Ann Farrell M.D.
Office Director (or designated signatory authority)	Richard Pazdur, M.D.

Additional Reviewers of Application

OPQ	OBP: Mate Tolnay, PhD Gerald Feldman, PhD Gibbes Johnson, PhD DMA: Pepa (Maria Jose Lopez-Barragan), PhD DS: Natalia Pripuzova, PhD DP: Colleen Thomas, PhD Patricia Hughes., PhD DIA: Wayne Seifert, and Peter Qui ONDP: Charles (Chuck) Jewell and Kasturi Srinivasachar OPQ PM: Andrew Shiber CC Labeling: Vicky Borders Hemphill, PharmD
Microbiology	
OPDP	Rachael Conklin, MS, RN Kathleen Davis, RN
OSI	Anthony Orencia, MD Min Lu, MD
OSE/DEPI	Carolyn McCloskey, MD, MPH

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761040}
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OSE/DMEPA	Hina Mehta, Pharm D Nicole Garrison, Pharm D, BCPS Neil Vora, Pharm D, MBA
OSE/DRISK	Naomi Redd, PharmD, DRISK Mei-Yean Chen, Pharm.D.
DHP DDS	Barry Miller, MS, CRNP
QT-IRT	Hongshan Li, Ph.D. Lars Johannesen, Ph.D. Janell E Chen, MS Mohammad A Rahman, Ph.D. Michael Y Li, MS Christine E Garnett, PhD.
Other	CDRH/OIR/DIHD: Jacqueline Cleary Kelly Oliner

OPQ=Office of Pharmaceutical Quality
 OPDP=Office of Prescription Drug Promotion
 OSI=Office of Scientific Investigations
 OSE= Office of Surveillance and Epidemiology
 DEPI= Division of Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADA	antidrug antibody (ies)
ADC	antibody-drug conjugate
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALL	acute lymphoblastic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BCR-ABL	breakpoint cluster region Abelson
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BSA	body surface area
C	cycle
CBER	Center for Biologics Evaluation and Research
CD22	cluster of differentiation-22
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	complete remission
CRh	complete remission with partial hematological recovery
CRI	complete remission with incomplete hematological recovery
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CT	computerized tomography
CYP	cytochrome P450
DIC	disseminated intravascular coagulation
DHOT	Division of Hematology Oncology Toxicology
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	data monitoring committee

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EAC	endpoint adjudication committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCTD	electronic common technical document
EOT	end of treatment
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FISH	fluorescence in situ hybridization
FLAG	fludarabine, cytarabine, granulocyte-colony stimulating factor
GCP	good clinical practice
G-CSF	granulocyte colony stimulating factor
GGT	gamma-glutamyl transpeptidase
GRMP	good review management practice
GVHD	graft versus host disease
HCV	hepatitis C virus
HEAB	hepatic events adjudication board
HIDAC	high dose cytarabine
HIV	human immunodeficiency virus
Hgb	hemoglobin
HLA	human leukocyte antigen
HR	hazard ratio
Hyper-CVAD	cyclophosphamide, vincristine, doxorubicin, dexamethasone (part A), methotrexate and cytarabine (part B)
IA	interim analysis
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IND	Investigational New Drug
InO	inotuzumab ozogamicin
INR	international normalized ratio
Inv Choice	Investigator's Choice
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
ITT218	intent to treat for initial 218 patients randomized
LDH	lactate dehydrogenase
LFT	liver function tests
LLN	lower limit normal
LVEF	left ventricular ejection fraction
Max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat

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{BESPOLSA; Inotuzumab Ozogamicin}

mITT218	modified intent to treat for initial 218 patients randomized
MLL	mixed lineage leukemia
MRD	minimal residual disease
MTD	maximum tolerated dose
MXN/Ara-c	mitoxantrone and cytarabine
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NHL	non-Hodgkin's lymphoma
NME	new molecular entity
NYHA	New York Heart Association
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PFS	progression free survival
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PO	orally
PP	per protocol
PP218	intent to treat for initial 218 patients in PP population
PPI	patient package insert
PREA	Pediatric Research Equity Act
pRBC	packed red blood cells
PRO	patient reported outcome
PSUR	Periodic Safety Update report
QTc	Qt interval correct for heart rate
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
SOS	sinusoidal obstruction syndrome
TEAE	treatment emergent adverse event
TKI	tyrosine kinase inhibitor
TLS	tumor lysis syndrome
ULN	upper limit normal
VAD/CAD	vincristine, doxorubicin, dexamethasone/cyclophosphamide, vincristine, doxorubicin, dexamethasone

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761040}
{BESPONSA; Inotuzumab Ozogamicin}

VOD	veno-occlusive disease
WBC	white blood cell
WHO	World Health Organization

APPEARS THIS WAY ON ORIGINAL

1 Executive Summary

1.1. Product Introduction

Pfizer (Applicant) submitted BLA 761040 for Inotuzumab Ozogamicin (Besponsa®), also known as PF-05208773, a new biological (monoclonal antibody drug conjugate [ADC]) for the treatment of relapsed or refractory precursor B-cell acute lymphoblastic lymphoma (ALL). Inotuzumab ozogamicin is a CD22 targeted antibody-drug conjugate comprised of a humanized immunoglobulin IgG4 covalently attached via a linker to the small molecule, N-acetyl-gamma-calicheamicin.

The applicant's proposed indication is, "treatment of patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia." For the first cycle, the recommended total dose is 1.8 mg/m² per 3 week cycle given as 3 divided doses on day 1 (0.8 mg/m²), day 8 (0.5 mg/m²) and day 15 (0.5 mg/m²). For subsequent cycles, the recommended total dose is 1.5 mg/m² per 4 week cycle given as 3 divided doses on day 1 (0.5 mg/m²), day 8 (0.5 mg/m²) and day 15 (0.5 mg/m²) for patients who achieve complete response (CR) or complete response with incomplete hematologic recovery (CRI) or 1.8mg/m² given as 3 divided doses (day 1 [0.8 mg/m²], day 8 [0.5 mg/m²],day 15 [0.5 mg/m²]) for patients who do not achieve CR or CRI.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Information submitted by the Applicant provides substantial evidence for the effectiveness of inotuzumab ozogamicin for the treatment of adult patients with relapsed or refractory precursor B-cell ALL. The efficacy of inotuzumab ozogamicin has been established, primarily on the results of a single randomized, phase 3 study in patients greater than or equal to 18 years of age with relapsed or refractory ALL. The endpoints of complete response (CR) and duration of response in the first 218 randomized patients were used to inform the regulatory decision making process. Complete response was achieved by 39/109 (36%) patients (95% CI; 27%, 46%) in the inotuzumab ozogamicin arm versus 19/109 (17%) patients (95% CI: 11%, 26%) in the investigator's choice of chemotherapy arm. The response was durable with estimated median duration of CR of 8 months (95% CI: 5, 10 months) in the inotuzumab ozogamicin arm compared to 5 months (95% CI: 3, 7 months) in the investigator's choice of chemotherapy arm. The conclusion of effectiveness is supported by the achievement of MRD negativity (defined as $< 1 \times 10^{-4}$ of bone marrow nucleated cells by flow cytometry) in patients who achieved CR: 35/39 (90%) in inotuzumab ozogamicin arm compared to 6/19 (32%) in investigator's choice of chemotherapy arm. The results were consistent with the analysis of the full intent-to-treat (ITT) population (N=326) and consistent across the subpopulations tested.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Inotuzumab ozogamicin is a CD22 targeted antibody-drug conjugate comprised of a humanized immunoglobulin IgG4 covalently attached via a linker to the small molecule, N-acetyl-gamma-calicheamicin. The benefit-risk assessment supports full approval of inotuzumab ozogamicin for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

The efficacy of inotuzumab ozogamicin is based on the results of single large, randomized, open-label, controlled phase 3 study that compared inotuzumab ozogamicin, administered in split doses, to investigator's choice of chemotherapy (control arm) in patients greater than or equal to 18 years of age with relapsed or refractory B-cell ALL. In the analysis of the primary endpoint of complete response or complete response with incomplete hematological recovery (CR/CRi) in the first 218 patients enrolled who received inotuzumab ozogamicin, the CR/CRi rate was 81% (95% CI: 72%, 88%) compared with 29% (95% CI: 21%, 39%) for the patients who received a investigator's choice of chemotherapy.

The regulatory basis for recommendation of approval is founded upon the secondary endpoints of CR and duration of response. Complete response was achieved by 36% (39/109) subjects (95% CI; 27%, 46%) in the inotuzumab ozogamicin arm compared with 17% (19/109) subjects (95% CI: 11%, 26%) in the investigator's choice of chemotherapy arm. The response was durable with median duration of complete response of 8 months (95% CI: 5, 10) in the inotuzumab ozogamicin arm compared with a median of 5 months (95% CI: 3, 7) in the investigator's choice of chemotherapy arm.

Additional support for the conclusion of effectiveness is based upon the attainment of MRD $<1 \times 10^{-4}$ as MRD levels less than $<1 \times 10^{-4}$. The conclusion of effectiveness is supported by the finding that 35/39 (89.7%) of the patients in the inotuzumab ozogamicin arm not only had a CR but also had a reduction in minimal residual disease (MRD) to $<1 \times 10^{-4}$ compared with 6/19 (31.6%) in the investigator's choice of chemotherapy arm. In the inotuzumab arm, the patients with CRi appear to be comparable to patients who attained CR with regard to MRD status and durability of response. The CRi responders performed better overall with respect to MRD negativity and duration of response compared with patients who attained CRi in the chemotherapy control arm. In the inotuzumab ozogamicin arm, the rate of attainment of CRh (29%) in the ITT218 population per EAC is comparable to the rate of CR (35.8%) and CRi (45.0%). The magnitude of difference between the attainment of CRh in the inotuzumab arm (29%) compared with the investigator choice arm (5%) is notable, as is the rate of MRD negativity for

the patients with CRh (71.8%) in the inotuzumab ozogamicin arm versus 20% in the investigator choice arm.

Among the initial 218 patients, as per EAC assessment, 32/109 (29%) in the inotuzumab arm achieved complete remission with partial hematologic recovery (CRh; (defined as <5% blasts in the bone marrow, and ANC > 0.50 x 10⁹/L, and platelet counts > 50 x 10⁹/L but not meeting full recovery of peripheral blood counts) versus 6/109 (65%) in the investigator's choice of chemotherapy arm, and 71/109 (65%) in the BESPOLSA arm achieved CR/CRh versus 25/109 (23%) in the investigator's choice of chemotherapy arm .

An improvement in overall survival for the full ITT population (N=326) did not reach statistical significance in the pivotal phase 3 study (B1931022) as it exceeded the prespecified 1-sided p-value boundary of 0.0104. The estimated hazard ratio (primary analysis cutoff date of 8 March 2016) for the primary endpoint of overall survival (OS) in the ITT population was 0.770 (97.5% CI: 0.578, 1.026) with an estimated median OS of 7.7 months (95% CI 6, 9.2) for inotuzumab ozogamicin versus 6.7 months (95% CI 4.9 8.3) in the control arm. In a competing risk analysis, for patients who proceeded to subsequent hematopoietic stem cell transplantation (HSCT), there was an increase in non-relapse mortality in the inotuzumab ozogamicin arm of 38% (29/77) compared with 24% (8/33) in the investigator's choice of chemotherapy arm. Hepatic VOD was the main contributing factor leading to the increase in non-relapse mortality in the inotuzumab ozogamicin arm.

The safety database for inotuzumab ozogamicin consists of 880 patients exposed to inotuzumab ozogamicin with the primary assessment for safety from two studies (B1931022 and B1931010) in patients with relapsed or refractory B- cell ALL. In general, the safety profile for inotuzumab ozogamicin is manageable for myelosuppression, infections, and hemorrhage. Common adverse events (≥20%) included thrombocytopenia, neutropenia infection, anemia, leukopenia, fatigue, hemorrhage, pyrexia, nausea, headache, febrile neutropenia, increased transaminases, abdominal pain, hyperbilirubinemia, and increased gamma-glutamyltransferase. The most frequent serious adverse event in the inotuzumab ozogamicin arm was VOD (13%, 22/164) compared to investigator's choice of chemotherapy arm (<1%, 1/143). Of the 77 patients in the inotuzumab ozogamicin arm who proceeded to subsequent HSCT, 17 patients (22%) developed VOD. The increase in transplant related non-relapse mortality for patients who received inotuzumab ozogamicin and subsequent transplantation (38%, 29/77) compared with the investigator choice arm (24%, 8/32) was primarily due to VOD and complications from VOD (e.g. multi-organ failure). Prior HSCT, the use of HSCT conditioning regimens that contain two alkylating agents and last total bilirubin level ≥ upper limit of normal before follow-up HSCT are associated with an increased risk of VOD in patients who receive inotuzumab ozogamicin. Other risk factors for development of VOD in patients administered inotuzumab ozogamicin include increased age, greater number of treatment cycles, busulfan conditioning regimens, later lines of salvage therapy, and history of liver disease prior to treatment. The safety risks of post-transplantation non-relapse mortality and hepatic VOD warrant a boxed warning in the USPI.

In summary, the current standard of care for the treatment of relapsed or refractory ALL is intensive combination chemotherapy and the results with this approach continue to remain disappointing. Effective new treatments are needed for patients with relapsed or refractory ALL. The conclusion on the substantial evidence of effectiveness is founded on the CR rate of 36% and durable response (median 8 months), which were substantially better than the responses for the control arm of investigator choices of single agent or combination chemotherapy regimens. Moreover, an MRD response was noted in 89.7% of patients who attained a CR compared with only 31.6% in the investigator’s choice of chemotherapy arm. Taken together, the efficacy outcomes (CR, durability, and MRD negativity) in the inotuzumab ozogamicin arm compared with the control arm form a strong basis for a conclusion of effectiveness. Although inotuzumab ozogamicin failed to demonstrate statistical significance for overall survival, subjects in the inotuzumab arm who proceeded to subsequent transplantation had better survival outcome than the control subjects after 18 months. The failure of the attainment of CR to translate into an improvement in overall survival that was statistically significant was due to more early deaths and post-transplantation non-relapse mortality in the inotuzumab ozogamicin arm. Hepatic VOD was the main contributing factor to the non-relapse mortality rate. In general, the safety profile for inotuzumab ozogamicin is manageable for myelosuppression, infections, and hemorrhage. The most significant risks of inotuzumab ozogamicin are VOD and post-transplant non-relapse mortality, which can be adequately understood and managed by hematologists-oncologists who treat patients with acute leukemia. These risks are acceptable for a population with serious and life-threatening condition in the context of the efficacy. Overall, the risk-benefit assessment of inotuzumab ozogamicin is favorable for the treatment of patients with relapsed or refractory precursor B-cell ALL.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Long-term survival is <1 % for patients with relapsed or refractory B-cell ALL (R/R ALL). • Even with allogenic transplantation, survival is only about 35%.	R/R ALL is a fatal disease.
Current Treatment Options	• Remission rates using current available therapy are low (<10%) with single agents and 25-46% with combination chemotherapy.	There is a need for effective agents for the treatment of R/R ALL.
Benefit	• Study 1022 was a phase 3, randomized, open-label trial of inotuzumab ozogamicin versus investigator’s choice of chemotherapy (choice of 3 regimens) in patients with R/R ALL.	Inotuzumab ozogamicin improves complete remission rates in patients with R/R ALL with durable responses compared to standard

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• In the analysis of the primary endpoint of complete response or complete response with incomplete hematological recovery (CR/CRi) in the first 218 patients enrolled who received inotuzumab ozogamicin, the CR/CRi rate was 81% (95% CI: 72%, 88%) compared to 29% (95% CI: 21%, 39%) for the patients who received a investigator’s choice of chemotherapy. • The CR rate in the inotuzumab arm was 36% (95% CI; 27%, 46%) vs 17% (95% CI: 11%-26%) in the investigator’s choice of chemotherapy arm with estimated median duration of complete response of 8 months (95% CI; 5, 10 months) in the inotuzumab ozogamicin arm compared 5 months (95% CI: 3, 7 months) in the investigator’s choice of chemotherapy arm for the ITT218 population. • For patients who achieved CR/CRi in the ITT population (N=326), a reduction in MRD to less than 1×10^{-4} was achieved by 92/120 (78%) subjects (95% CI: 68%, 87%) in the inotuzumab ozogamicin arm versus 19/50 (38%) subjects (95% CI: 24%, 47%) in the investigator’s choice of chemotherapy arm. • An improvement in overall survival for the full ITT population (N=326) did not reach statistical significance in the pivotal phase 3 study (B1931022) as it exceeded the prespecified 1-sided p-value boundary of 0.0104 with the estimated hazard ratio in the ITT population of 0.770 (97.5% CI: 0.578, 1.026) with an estimated median OS of 7.7 months (95% CI 6, 9.2) for inotuzumab ozogamicin versus 6.7 months (95% CI 4.9, 8.3) in the control arm. • In a competing risk analysis for patients who went to HSCT, there were few early deaths in the control arm however subjects in the inotuzumab arm had better survival outcomes than the control subjects after 18 months.	chemotherapy. An improvement in attainment of MRD negativity was demonstrated for patients who received inotuzumab ozogamicin.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Risk</u>	- For patients who proceeded to subsequent hematopoietic stem cell transplantation, the non-relapse mortality rate in patients who received inotuzumab ozogamicin and subsequent HSCT was 38% (29/77) versus 24% (8/32) in the investigator’s choice of chemotherapy arm. - The most frequent SAE is VOD with VOD in 22/164 (13%) of patients who received inotuzumab. For the 77 patients in the inotuzumab ozogamicin arm who proceeded to transplantation 17 (22%) developed VOD. The increase in post-HSCT non-relapse mortality is due to increase in VOD and complications such as multi-organ failure and infections. - Inotuzumab ozogamicin has manageable profile for treatment emergent adverse events of myelosuppression, infections, and hemorrhage. - Common (≥20%) reactions include thrombocytopenia, neutropenia infection, anemia, leukopenia, fatigue, hemorrhage, pyrexia, nausea, headache, febrile neutropenia, transaminase increased, abdominal pain, hyperbilirubinemia, and gamma-glutamyl transferase increased.	Overall safety profile of inotuzumab ozogamicin is manageable for patients with relapsed or refractory ALL, provided adequate warning and precautions for hepatic VOD and post-HSCT non-relapse mortality are described in the USPI. An improvement in overall survival did not reach statistical significance. In a competing risk analysis, there was increased risk in post-HSCT non-relapse mortality for patients who received inotuzumab ozogamicin. VOD was the contributory factor causing increase in non-relapse mortality.
<u>Risk Management</u>	- Inotuzumab ozogamicin can cause serious or life-threatening hepatotoxicity to include VOD. Risks of VOD may be mitigated by identifying risk factors and limiting treatment cycles in patients who proceed to subsequent HSCT for development of VOD. - Inotuzumab ozogamicin can cause an increase in post-transplant non-relapse mortality in patients who proceed to subsequent HSCT. - Hematologists and hematopoietic stem cell transplantation physicians have expertise in the identification and management of the VOD.	To minimize risks, labeling should include a boxed warning that includes increased risk of hepatotoxicity to include VOD and increased post-transplantation non-relapse mortality. Labeling should include risk factors for VOD and recommended number of treatment cycles for patients who proceed to subsequent HSCT.

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R. Angelo de Claro, MD
Cross-Disciplinary Team Leader

2 Therapeutic Context

Analysis of Condition

Acute lymphoblastic leukemia (ALL) is a neoplasm of lymphoblasts committed to the B-cell lineage involving the bone marrow and blood and occasionally presenting with primary involvement in nodal or extranodal sites. According to the National Cancer Institute's SEER database, it is estimated that there were 6590 new cases and 1430 deaths from ALL in the United States in 2016. ALL is most common in children, adolescents and young adults or those ages 15-39 years of age. The median age at diagnosis is 15. The 5-year relative survival has improved from 31% in 1975 to about 71.7% in 2008 (SEER database) although most of the improvements have occurred in younger and pediatric patients. ALL is slightly more common in males compared to females and three times as frequent in whites as in blacks. Hispanics have the highest incidence of any ethnicity.

Relapsed or refractory precursor B-cell ALL is a fatal disorder with median survival in adults of 3-6 months. The use of single agent chemotherapy results in CR in 8% (95% CI, 4-14%). The standard of care is intensive combination chemotherapy. With the use of combination chemotherapy, CR is achieved by 25-36% of patients with R/R ALL and in general is not durable. Older age, short first remission, more than one prior relapse and relapse after hematopoietic stem cell transplantation are associated with a lower CR rate. Long term survival in 7-24% of patients with relapsed disease occurs only with allogeneic HSCT (Fielding AK, Blood 2007). Older adult patients have the worst outcome with 5-year OS of 24% for patients age 40-59 and 17% for patients age 60-69 (Pulte 2014). A reduction in MRD to $<10^{-4}$ is associated with improvement outcome. This level of MRD is reportedly only achieved by about 30% of patients in CR with chemotherapy. There remains a need for additional effective therapies for R/R ALL.

2.2. Analysis of Current Treatment Options

A variety of agents are approved for treatment of ALL in general or during induction treatment, while other agents are approved for maintenance treatment or palliation. Agents with approval relevant to the treatment of relapsed or refractory precursor B cell ALL—both Philadelphia positive (Ph^+) or Philadelphia negative (Ph^-) ALL—are listed in the table below.

Table 1 Approved Agents with Indication(s) Relevant to Treatment of Relapsed or Refractory Precursor B-Cell Acute Lymphoblastic leukemia

Product (s) Name	Excerpted Indication
Asparaginase(E.coli)	Indicated as a component of multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia(ALL)
Asparaginase(Erwinia)	Indicated as a component of multi-agent chemotherapeutic regimen

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Product (s) Name	Excerpted Indication	
	for the treatment of patients with acute lymphoblastic leukemia(ALL)	
Clofarabine	Treatment of pediatric patients 1-21 years old with relapsed or refractory acute lymphoblastic leukemia after at least 2 prior regimens	
Cyclophosphamide	Cyclophosphamide, although effective alone in susceptible malignancies is more frequently used concurrently or sequentially with other antineoplastic drugs. The following malignancies are often susceptible to cyclophosphamide treatment: acute lymphoblastic (stem-cell) leukemia in children.	
Cytarabine	Useful in treatment of acute lymphoblastic leukemia	
Daunorubicin	In combination with other approved anticancer drugs is indicated.... For remission induction in acute lymphocytic leukemia of children and adults.	
Dexamethasone	For palliative management of leukemia's and lymphomas in adults, acute leukemia of childhood	
Doxorubicin	To produce regression in disseminated neoplastic conditions such as acute lymphoblastic leukemia	
Mercaptopurine	For maintenance therapy of acute lymphatic(lymphocytic, lymphoblastic) leukemia as part of a combination regimen	
Methotrexate	Used in maintenance therapy in combination with other chemotherapeutic agents.	
Methylprednisolone	For palliative management of leukemias and lymphomas in adults, acute leukemia of childhood	
Pegasparaginase	Indicated as a component of multi-agent chemotherapeutic regimen for the treatment of patients with ALL and hypersensitivity to native forms of L-asparaginase	
Prednisone	For palliative management of leukemias and lymphomas in adults, acute leukemia of childhood	
Teniposide	In combination with other approved anticancer agents, is indicated for induction therapy in patients with refractory childhood acute lymphoblastic leukemia	
Thioguanine	Indicated for remission induction and remission consolidation treatment of acute nonlymphocytic leukemias. Reliance upon thioguanine alone is seldom justified for initial remission induction.	
Vincristine	Indicated in acute leukemia	
More Recently Approved Agents for ALL		
Product Name	Year	Excerpted Indication
Imatinib	2006	Treatment of adult patients with relapsed or refractory Ph+ Acute lymphoblastic Leukemia
Dasatanib	2006	Treatment of adults with Ph+ acute lymphoblastic leukemia with resistance or intolerance to prior therapy
Liposomal vincristine	2012	Treatment of adult patients with Philadelphia chromosome negative Ph ⁻ acute lymphoblastic leukemia (ALL) in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies.
Ponatinib	2012	Treatment of adult patients with Ph+ ALL for whom no other tyrosine kinase inhibitor therapy is indicated

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Product (s) Name	Excerpted Indication
Blinatumumab	2014 Treatment of patients with Philadelphia negative relapsed or refractory B-cell precursor ALL

In patients with relapsed or refractory ALL, combination chemotherapy regimens with or without hematopoietic stem cell transplantation are the mainstay of therapy. In patients who cannot tolerate chemotherapy regimens, single agent salvage therapy is used with very poor results. In two large reviews of adults treated for relapsed or refractory leukemia, single agents resulted in CR in 10 out of 124 patients (8%, 95% CI, 4%-14%) (O'Brien, Thomas, et al 2008; Kantarjian, Thomas et al 2010). Factors that affect the outcome after combination chemotherapy for relapsed or refractory B-cell ALL include age, duration of first remission, number of prior relapses, and relapse after HSCT. The CR rate can vary from 25 to 46% (Gokbuget, Stanze et al 2012) but responses are often not durable. Long-term survival is <1% for patients treated with chemotherapy alone and improves to ~36% for patients with Ph negative ALL who are able to proceed to HSCT. Approximately 20-30% of adult patients with ALL are Philadelphia chromosome positive. The use of tyrosine kinase inhibitors in combination with front-line chemotherapy has improved the CR rates to 96-100% and 2 year overall survival rates to ~60%. In patients with relapsed Ph+ ALL, the median overall survival is only 6.5 months to 9.1 months (Lilly 2010).

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3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Inotuzumab ozogamicin is a new molecular entity (NME) and is not currently marketed in the U.S.

3.2. Summary of Presubmission/Submission Regulatory Activity

Table 2 Regulatory History

Date	Meeting or Event
Apr 13, 2011	Type C meeting on the discussion of the clinical development plan for inotuzumab ozogamicin and discussion of study design for Phase 3 Study B1931022.
Mar 25, 2013	FDA grants Orphan Drug Designation for inotuzumab ozogamicin for the treatment of precursor B-cell ALL.
Apr 30, 2013	Type C meeting to discuss an alternative registration pathway for inotuzumab ozogamicin for the treatment of relapsed or refractory B-cell ALL.
Apr 24, 2014	Type C meeting to discuss need for a CD22 companion diagnostic for use with inotuzumab ozogamicin for treatment of patients with relapsed or refractory B-cell ALL.
May 19, 2014	Type A meeting to discuss revisions to Phase 3 Study B1931022 due to patient discontinuations on the control arm prior to dosing.
Oct 20, 2014	Type B meeting to discuss the proposal for planned analysis of the primary endpoint in the Phase 3 Study B1921022 (sensitivity analysis for complete remission/complete remission with incomplete hematologic recovery (CR/CRi).
Nov 10, 2014	Type C meeting to seek agreement to the proposed format and content of the original Biologicals License Application(BLA)
May 29, 2015	Type C meeting to discuss data from Phase 3 study B1931022 to see if data can support approval of inotuzumab ozogamicin
Jul 31, 2015	FDA requested that eDMC submit the interim overall survival data from B1931022 directly to the FDA at the time of the BLA submission without unblinding the study team.
Oct 15, 2015	FDA grants Breakthrough Therapy Designation to inotuzumab ozogamicin for treatment of relapsed or refractory B-Cell ALL.
Dec 29, 2015	FDA grants request for rolling submission and review for planned BLA submission for inotuzumab ozogamicin for B-Cell ALL.

The FDA granted Breakthrough Therapy Designation to inotuzumab ozogamicin for the treatment of relapsed or refractory B-cell ALL on October 15, 2015.

The Applicant was granted rolling submission of the BLA on December 29, 2015. Rolling submission components 1, 2, and 3 of the BLA were submitted on January 21, 2016, March 30, 2016, and November 28, 2016, respectively. The content of the fourth and final portion of the BLA was submitted December 20, 2016. The Applicant requested priority review with the submission of the final portion of the BLA, and the FDA granted priority review of the application.

Important Issues with Consideration to Related Drug

- Gemtuzumab ozogamicin (Mylotarg®) is a calicheamicin-conjugated monoclonal antibody that targets CD33 cells on myeloblasts in acute myeloid leukemia (AML). The adverse drug reactions associated with gemtuzumab ozogamicin (hepatic veno-occlusive disease, infusion related reactions, and myelosuppression) were taken into consideration in the evaluation of this application.
- There are no approved agents that target CD22, but there are several monoclonal antibodies that target CD20 and deplete B cells. This class of agents carries warnings in the prescribing information regarding infusion reactions, hepatitis B reactivation, progressive multifocal leukoencephalopathy (PML), tumor lysis syndrome, infections, and cytopenias.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations conducted inspections for Study B1931022 at three clinical sites: Site 1058 (Dana-Farber Cancer Institute), Site 1047 (University of Texas, MD Anderson Cancer Center), and Site 1063 (Stanford Cancer Institute). These sites were selected based on highest accrual, deaths and patients who were randomized but did not receive treatment and/or greatest impact on primary endpoint. The final classification for inspections for Site 1058 and Site 1063 was No Action Indicated (NAI) and for Site 1047 was voluntary action indicated (VAI) due to improperly documented informed consent in one subject.

The Office of Scientific Investigations concluded that the study data appear reliable. An excerpt from the May 25, 2017 clinical inspection summary states: “the study derived from the three clinical sites are considered acceptable in support of the requested indication.”

4.2. Product Quality

Novel excipients: No

Any impurity of concern: No

Refer to CMC Application Technical Lead review for details. The Office of Pharmaceutical Quality, CDER, recommends Approval of STN761040 for Besponsa (inotuzumab ozogamicin) manufactured by Pfizer, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Besponsa is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

Refer also to CMC review regarding CMC-related post-marketing commitments.

4.3. **Clinical Microbiology**

Not applicable. Refer to CMC review for product quality microbiology.

4.4. **Devices and Companion Diagnostic Issues**

Minimal residual disease analyses were performed at least once in patients with prior assessment of CR or CRi in Study B1931022. Bone marrow aspirates, collected at screening and on study were sent to a central ((b) (4)) for assessment of MRD. Bone marrow aspirates were analyzed by a central laboratory using multi-parametric flow cytometry. The antibody combinations were designed to maximize discrimination between normal and abnormal cells of B-cell lineage and similar maturational state and included antibodies detecting CD9, CD10, CD13, CD19, DCD20, CD33, CD34, CD38, CD45, CD58, CD66c, and CD123. MRD-negativity was considered to be achieved if the lowest value of MRD from the first date of CR/CRi to end-of-treatment was 1×10^{-4} blasts/nucleated cell.

The Division of Immunology and Hematology Devices (DIHD) in the Office of In Vitro Diagnostics and Radiological Health (OIR) in the Center for Devices and Radiological Health (CDRH) conducted an assessment of the MRD assay. OIR requested additional information from the Applicant on June 26, 2017, August 9, 2017 and August 10, 2017 regarding details of the assay that were not included in the clinical study report.

Upon review of the additional information provided by the Applicant, CDRH agreed with the Applicant's conclusions from the MRD data to include the following

- Panel for CD markers that the Sponsor is using is appropriate for the detection of MRD in patients with B-cell ALL.
- Hematopathologist reviewing the flow cytometry data were blinded to the patient data.
- In the inotuzumab ozogamicin arm and Investigator's choice of chemotherapy arm, the majority of post-baseline samples that were reported as either MRD-positive or MRD-negative were from samples with > 250K viable WBCx.
- There were more post-treatment samples in the inotuzumab ozogamicin arm (n=382)

compared to the Investigator's choice of chemotherapy arm (n=154) reflecting a longer treatment duration in the inotuzumab ozogamicin arm.

- The percentage of samples that were MRD-positive was consistent across all groups, acknowledging the small sample size in some groups.
- The difference in the rate of MRD-negativity between the inotuzumab ozogamicin arm and the Investigator's choice of chemotherapy arm was consistent across all groups, acknowledging the small sample size in some groups.

An excerpt from the final recommendation from DIHD (taken from CDRH consult review by Douglas Jeffery Ph.D. and Kelly Oliner, Ph.D. on August 11, 2017) states:

We agree with the sponsor's conclusions from the MRD data in the document the sent on August 10, 2017. We think it is important to note that the sponsor has used MRD assay results that are likely at the limit of sensitivity of the assay as part of their secondary endpoint analysis. At this time, we do not have a reason to suspect that the MRD data that we have seen affect the outcome of the secondary endpoint."

For additional details refer to DIHD/OIR/CDRH consult by Doug Jeffery Ph.D. and Kelly Oliner Ph.D.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Reviewer note: Unless explicitly noted otherwise, the concentrations and doses of inotuzumab ozogamicin described in this review are expressed as unconjugated calicheamicin equivalents, as this represents how the concentrations and doses were described in the study reports. For the label, however, the animal doses are reported based on the antibody-drug conjugate (ADC) equivalents, because patients will be receiving the product based on the ADC dose. The ADC equivalent doses have been calculated and presented together with their calicheamicin equivalents under the animal studies reviewed.

Inotuzumab ozogamicin (Besponsa[®], CMC-544) is an ADC consisting of a humanized CD22-directed IgG4 monoclonal antibody (inotuzumab, G544) and a semi-synthetic derivative of the cytotoxic natural product γ -calicheamicin (N-acetyl- γ -calicheamicin dimethylhydrazide or N-Ac- γ -calicheamicin DMH), with a small molecule-to-antibody ratio of approximately 6:1 (see Product Quality review). The Applicant sought to evaluate the binding characteristics of inotuzumab ozogamicin and the antibody constituent G544 by surface plasmon resonance (SPR). Unconjugated G544 and inotuzumab ozogamicin each bound recombinant human CD22 with picomolar affinity ($K_D=120-150$ pM) and conjugation of the calicheamicin payload did not affect the antigen binding characteristics of G544. G544 binding was further assessed by flow cytometry using acute lymphocytic leukemia (ALL) and non-Hodgkin's lymphoma (NHL) cell lines known to express CD22. G544 bound all four cancer cell lines tested, as well as normal B cells from human whole blood. The Applicant evaluated binding of G544 to B cells, granulocytes, monocytes (MONO), and T cells from mice, rats, rabbits, and cynomolgus monkeys; no cross-species reactivity was observed, indicating the utility of toxicology studies will be limited to the assessment of target-independent toxicities associated with conjugated and unconjugated calicheamicin.

Inotuzumab ozogamicin elicited CD22-directed cytotoxicity against cancer cell lines of B cell origin ($IC_{50}=9-430$ pM), while sparing the CD22-negative acute myeloid leukemia (AML) cell line HL-60 ($IC_{50}>2.5$ μ M). The cytotoxicity was calicheamicin-dependent as unconjugated G544 had no effect on the proliferation of any of the cell lines evaluated. ALL cell lines were generally more sensitive to inotuzumab ozogamicin treatment than NHL cell lines, despite ALL cell lines expressing lower amounts of CD22 than NHL cell lines. ALL cell lines were also generally more sensitive to treatment with unconjugated calicheamicin than NHL cell lines, suggesting an intrinsic difference in the susceptibility of NHL and ALL cells to inotuzumab ozogamicin. G544 internalized to the lysosome, and inotuzumab ozogamicin caused a dose-dependent increase in DNA double-strand breaks. The in vivo antitumor activity of inotuzumab ozogamicin was evaluated in xenograft and systemically disseminated ALL mouse models. In both mouse models, treatment with inotuzumab ozogamicin resulted in dose-dependent antitumor activity. Together, the above findings are consistent with notion that the G544 targeting moiety delivers

the cytotoxic calicheamicin payload in a CD22-directed manner causing apoptosis and cell death.

A cardiovascular (CV) safety pharmacology study with inotuzumab ozogamicin in cynomolgus monkeys identified a small and transient effect on arterial blood pressure; the toxicological significance of this finding is unclear. Central nervous system (CNS) and respiratory safety pharmacology studies (both in male rats) with inotuzumab ozogamicin did not identify any toxicologically-significant effects.

The Applicant conducted repeat-dose toxicity studies of up to 6 months duration in rats and cynomolgus monkeys to investigate the chronic toxicity of inotuzumab ozogamicin; the studies were conducted using the intravenous (IV) route, consistent with the intended clinical route of administration. In the 6 month rat study, inotuzumab ozogamicin was administered IV at doses of 1, 3, or 10 µg/kg once weekly. Inotuzumab ozogamicin was associated with decline in body weight and correlating decrease in food consumption at the 10 µg/kg dose level. Adverse effects in the liver (cell foci, angiectasis, adenoma, sinusoidal dilatation, hypertrophy, hyperplasia, karyomegaly, cellular vacuolation, and/or extramedullary hematopoiesis [EMH]) and testes (tubular degeneration) were observed at the ≥1 µg/kg dose levels. In the 4-week rat study, inotuzumab ozogamicin was administered IV at doses of 5, 15, or 50 µg/kg once weekly. Findings in the 4-week study mirrored the findings in the 6-month study; however, there were additional changes in hematology parameters (red blood cells [RBC], hemoglobin [HGB], hematocrit [HCT], lymphocytes [LYM], and reticulocytes [RETI]) and significant increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

In the 6-month cynomolgus monkey study, inotuzumab ozogamicin was administered IV at doses of 0.5, 1.5, or 5 µg/kg once weekly. One premature death at the 5 µg/kg dose level was attributed to test article-related protein-losing glomerulonephritis, while the cause of moribundity in two other early decedents was not determined. Inotuzumab ozogamicin was associated with significant dose-dependent increases in AST and MONO. Adverse effects in the liver (sinusoidal dilatation, hypertrophy, and focal alteration), ovary (atrophy), and/or lymphoid tissues (spleen, mesenteric lymph node, and thymus - all decreased cellularity) were observed at the ≥0.5 µg/kg dose levels. In the 4-week monkey study, inotuzumab ozogamicin was administered IV at doses of 2.5, 8, or 25 µg/kg once weekly. Emesis, fecal changes, and decreased food consumption were observed. Significant increases in ALT and AST were observed without correlating histopathologic evidence of hepatotoxicity. Target organs identified by histopathology included the bone marrow, lymphoid organs, uterus, ovary, and testes.

Taken together, the primary inotuzumab ozogamicin target organs identified by the chronic toxicity studies were the liver, hemolymphopoietic tissues, and the male and female reproductive organs. After a 4-week recovery period, partial to complete resolution of liver findings was observed. The liver findings were also observed in a 9-week monkey study with a non-binding ADC, demonstrating liver toxicity was calicheamicin-related; the liver findings were

consistent with microvascular liver injury and were considered to represent the early stages of veno-occlusive disease that has been reported in clinical trials. The bone marrow and lymphoid findings included changes in hematology parameters (RBC mass, RETI, platelets [PLT], white blood cells [WBC], LYM, and/or MONO) and correlated with decrease in hematopoietic cellularity in the bone marrow and lymphoid depletion in the thymus, spleen, lymph nodes, and/or gut-associated lymphoid tissue (GALT). While the thrombocytopenia was considered secondary to liver-specific endothelial injury, other hematological changes were attributed to target-independent, calicheamicin-related effects. Toxicity profiles for N-Ac- γ -calicheamicin DMH and other calicheamicin derivatives were comparable to the ADC.

When inotuzumab ozogamicin was spiked into rat, monkey, or human plasma and incubated for 96 hours, >90% of the calicheamicin remained associated with protein, indicating that the hydrolytic release of free calicheamicin from inotuzumab ozogamicin in plasma is limited.

In a fertility and early embryonic development study in female rats, daily IV administration (from 2 weeks prior to cohabitation with untreated males until gestation day (GD) 7) of inotuzumab ozogamicin at 0.15, 0.5, or 1.5 $\mu\text{g}/\text{kg}$ resulted in decrease in maternal body weight and body weight gain, and decrease in food consumption at the high dose level. An increase in the proportion of resorptions and decrease in the number of viable embryos and gravid uterine weights at the 1.5 $\mu\text{g}/\text{kg}$ (approximately 0.11 mg/m^2 of the ADC) dose level were observed. The dose of 1.5 $\mu\text{g}/\text{kg}$ results in an exposure in rats that is approximately 2 times the exposure in patients based on the area under the concentration-time curve (AUC) at the maximum recommended human dose.

Embryo-fetal development studies were conducted in rabbits and rats. Inotuzumab ozogamicin (0.1, 0.3, or 1.0 $\mu\text{g}/\text{kg}$) was administered IV to mated female rabbits on GDs 6-19, and a necropsy/cesarean was performed on GD 29. No developmental toxicity was observed at any dose level. The highest dose of 1.0 $\mu\text{g}/\text{kg}$ (approximately 0.15 mg/m^2 of the ADC) results in an exposure in rabbits that is approximately 3 times the exposure in patients based on the AUC at the maximum recommended human dose. In rats, inotuzumab ozogamicin (0.15, 0.5, or 1.5 $\mu\text{g}/\text{kg}$) was administered IV to dams on GDs 6-17, and a necropsy/cesarean was performed on GD 21. Maternal toxicity at the 1.5 $\mu\text{g}/\text{kg}$ (approximately 0.11 mg/m^2 of the ADC) dose level was observed, characterized by decrease in food consumption, body weight, and body weight gain. Fetal toxicity including decreased live fetal weights and reduced fetal skeletal ossification were observed at the 1.5 $\mu\text{g}/\text{kg}$ dose level. Slightly decreased live fetal weights were also observed at the 0.5 $\mu\text{g}/\text{kg}$ dose level (approximately 0.04 mg/m^2 of the ADC). Maternal exposures at the 0.5 and 1.5 $\mu\text{g}/\text{kg}$ dose levels are approximately 0.4 and 2 times the exposure in patients based on the AUC at the maximum recommended human dose. Of note, in a good laboratory practice (GLP) compliant dose range finding embryo-fetal development study of similar design with doses up to 5 $\mu\text{g}/\text{kg}$ (approximately 0.36 mg/m^2 of the ADC), increased resorptions and fetal growth retardation were observed at the 1.5 $\mu\text{g}/\text{kg}$ dose level (approximately 0.11 mg/m^2 of the ADC), and complete litter loss was observed at the 5 $\mu\text{g}/\text{kg}$ dose level. The Applicant did not

conduct pre- and postnatal development studies as these studies are not required to support a marketing application for products intended to treat patients with advanced cancer.

Findings in the rat embryo-fetal development studies support the inclusion of a warning for embryo-fetal toxicity in the Besponsa[®] label. In the acute and chronic general toxicity studies in rats and monkeys both the male (testes, epididymides, seminal vesicles, and/or prostate) and female (uterus and ovary) reproductive tracts were affected by inotuzumab ozogamicin, sometimes irreversibly. These findings support the inclusion of a statement in the label that male and female fertility may be compromised by Besponsa[®].

Inotuzumab ozogamicin was clastogenic in mice at doses ≥ 28 $\mu\text{g}/\text{kg}$ (approximately 1.1 mg/m^2 of the ADC), consistent with the known DNA-reactive activity of the calicheamicin payload. The calicheamicin payload was positive in both the bacterial reverse mutation test and the in vitro micronucleus assay. Due to the genotoxicity, the Besponsa[®] label recommends that females of reproductive potential use effective contraception for ≥ 8 months after the last dose, and males with female partners of reproductive potential use effective contraception for ≥ 5 months after the last dose. No carcinogenicity studies were conducted or required to support a marketing application for the current indication. However, in the 6-month rat study, there was evidence of preneoplastic (oval cell hyperplasia and altered cell foci) and neoplastic (adenomas) changes in the liver at the ≥ 1 $\mu\text{g}/\text{kg}$ dose levels (approximately ≥ 0.07 mg/m^2 of the ADC dose).

The nonclinical pharmacology and toxicology data submitted to this BLA are adequate to support the approval of inotuzumab ozogamicin for the proposed indication.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

A. In vitro studies

The binding characteristics of both inotuzumab ozogamicin and the antibody constituent G544 were evaluated by SPR. Unconjugated G544 bound a human CD22-linked biosensor chip ($K_D=130$ pM) with similar affinity as inotuzumab ozogamicin that was heavily- or lightly-loaded with calicheamicin ($K_D=150$ and 120 pM, respectively), indicating drug loading did not impact the antigen binding of G544. G544 binding was also assessed by flow cytometry using CD22-expressing cancer cell lines; G544 bound all four cancer cell lines tested (Reh, RS4;11, Ramos, and Jeko-1) and normal B cells from human whole blood. Estimated K_D values were not provided. G544 did not bind B cells from mouse, rat, rabbit, or cynomolgus monkey whole blood, or granulocytes, MONO, or T cells from any species evaluated, including humans. The lack of G544 cross-species reactivity indicates the utility of the nonclinical toxicology studies will be limited to the assessment of target-independent toxicities associated with conjugated and unconjugated calicheamicin.

The growth inhibitory effect of inotuzumab ozogamicin was evaluated with an in vitro MTS cell viability assay and by propidium iodide exclusion analyzed by flow cytometry (see Table 3). In the in vitro MTS cell viability assay, inotuzumab ozogamicin inhibited the proliferation of the CD22-positive ALL and NHL cell lines (IC_{50} =13.3-100 pM) but not the CD22-negative control cell line HL-60 (IC_{50} =7500 pM). Furthermore, inotuzumab ozogamicin was 16- to 63-fold more potent than gemtuzumab ozogamicin (non-binding control ADC) and equally to 6-fold more potent than unconjugated calicheamicin in inhibiting the proliferation the ALL and NHL cell lines. When measured by the flow cytometry assay, inotuzumab ozogamicin inhibited the proliferation of the NHL cell lines (IC_{50} =9-430 pM) but not the CD22-negative control cell line HL-60 (IC_{50} =2500 pM). Inotuzumab ozogamicin that was heavily-loaded with calicheamicin was more potent than lightly-loaded inotuzumab ozogamicin (data not shown). Unconjugated G544 had no effect on the in vitro proliferation of any of the B lymphoma cell lines evaluated.

Table 3 The effect of inotuzumab ozogamicin and related molecules on the in vitro proliferation of various cell lines

Cell line	In vitro MTS cell viability assay			Propidium iodide exclusion (flow cytometry)			
	IC_{50}^* (pM)			$IC_{50}^{\#}$ (pM)			
	IO	GO	CalichDMH	IO	GO	CalichDMH	G544 ^S
Reh	13.3 (13, 14)	440 (380, 507)	66.7 (60,73)	ND	ND	ND	ND
RS4;11	46.7 (33, 67)	1060 (820, 1347)	100 (53, 153)	ND	ND	ND	ND
SUP-B15	53.3 (27, 113)	846.7 (620, 1153)	48 (33, 80)	ND	ND	ND	ND
RL	ND	ND	ND	9 (6-12)	500 (400-600)	248 (226-270)	>100,000
Daudi	ND	ND	ND	21	1886	260	>100,000
Raji	ND	ND	ND	430 (300-560)	3450 (2800-4100)	475 (460-490)	>100,000
Ramos	100 (93, 113)	6333 (5133, 7800)	586 (507, 680)	230 (200-260)	ND	850 (700-1000)	>100,000
HL-60	7500	50	500	2500	<200	750	ND

IC_{50} values are presented as pM equivalents of unconjugated calicheamicin; *: mean (95% CI); #: mean (range); ^S: IC_{50} values are presented as ng/mL G544; IO: inotuzumab ozogamicin loaded with 65-87 μ g of calicheamicin per mg of antibody; GO: gemtuzumab ozogamicin; CalichDMH: unconjugated calicheamicin; ND: not determined;

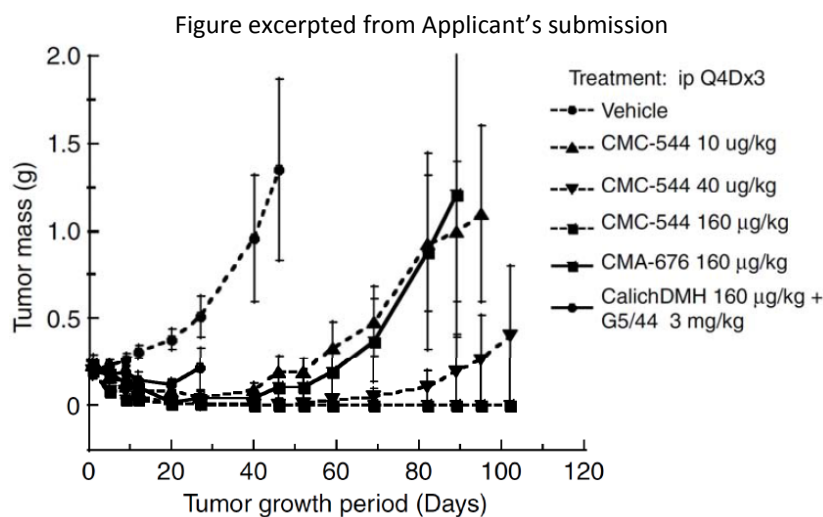
To further characterize inotuzumab ozogamicin at the cellular level the internalization pathway for G544 was evaluated by imaging flow cytometry. The cancer cell lines (Reh, RS4;11, and Ramos) and normal B cells from human whole blood internalized G544 at varying internalization rates (internalization score $t_{1/2}$ =12.0 mins [range 2.8-34.3 mins], cytosol intensity $t_{1/2}$ =20.4 [range 9.3-44.5 mins]); internalization rates did not directly correlate with CD22 expression levels. Normal B cells from human whole blood internalized G544 the fastest (internalization score $t_{1/2}$ =2.8 mins), and internalization rates were very similar between the five donors (standard deviation=0.6 mins). In a parallel experiment in Ramos cells, G544 co-localized with the lysosomal marker LAMP-1, indicating intracellular trafficking of G544 to the lysosomes. The inotuzumab ozogamicin mechanism of action (MOA) was confirmed by assessing DNA damage in ALL cells. Short-term exposure (1 hour) of the ALL cell line Reh to

inotuzumab ozogamicin caused a dose-dependent increase in the number and intensity of 53BP1 staining foci (data not shown), considered a marker of the cellular response to DNA double-strand breaks. The DNA double-strand breaks caused by inotuzumab ozogamicin are consistent with the well-established MOA of the calicheamicin payload.

B. In vivo studies

The antitumor activity of inotuzumab ozogamicin was evaluated in an established subcutaneous ALL xenograft mouse model and a systemically disseminated ALL mouse model. In the subcutaneous ALL xenograft mouse model female athymic nude mice were irradiated (400 rad) prior to subcutaneous injection of 5×10^6 Reh ALL cells into the right flank. Once tumors were palpable mice were treated with vehicle control, inotuzumab ozogamicin, or gemtuzumab ozogamicin (non-binding control ADC) intraperitoneally every 4 days for a total of three doses. Treatment with inotuzumab ozogamicin resulted in initial tumor regression and then a dose-dependent delay in tumor growth (see Figure 1). Tumor regrowth was observed by Days 30 and 60 for mice treated with inotuzumab ozogamicin at the 10 and 40 $\mu\text{g}/\text{kg}$ dose levels, respectively. Mice treated with inotuzumab ozogamicin at the 160 $\mu\text{g}/\text{kg}$ dose level remained tumor-free until the end of the observation period. The antitumor activity of gemtuzumab ozogamicin was much less potent than that of inotuzumab ozogamicin at an equivalent dose. Finally, a mixture of unconjugated G544 and CalichDMH did not inhibit the growth of tumors and was associated with early treatment-related death.

Figure 1 The effect of inotuzumab ozogamicin on the growth of subcutaneous ALL xenografts

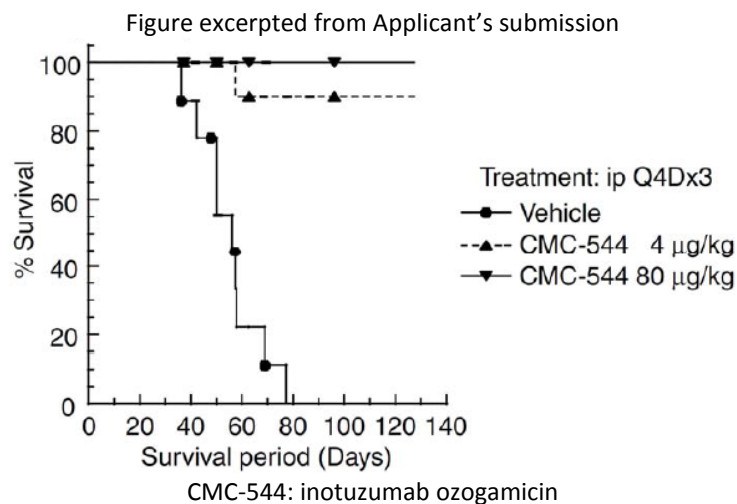


CMC-544: inotuzumab ozogamicin; CMA-676: gemtuzumab ozogamicin; CalichDMH: unconjugated calicheamicin; G5/44: G544;

In the systemically disseminated ALL mouse model male SCID mice were injected with 3×10^6 Reh cells via the tail vein. Following a 9 day dissemination period mice were treated with vehicle control or inotuzumab ozogamicin intraperitoneally every 4 days for a total of three doses. Treatment with inotuzumab ozogamicin at the 4 and 80 $\mu\text{g}/\text{kg}$ dose levels resulted in

90% and 100% survival at the end of the observation period, respectively (see Figure 2). The median survival period of vehicle-treated mice was 55 days, and by Day 77 all mice in this treatment group were euthanized.

Figure 2 The effect of inotuzumab ozogamicin on the survival of SCID mice with disseminated ALL



Secondary Pharmacology

No formal studies were conducted.

Safety Pharmacology

A. CNS

In a GLP study, male CD VAF rats (8/group) were administered a single IV dose of inotuzumab ozogamicin (10, 30, or 105.75 µg/kg) or vehicle control (2.78% sucrose, 0.018% polysorbate 80, 0.54% sodium chloride, 0.449% Tris, in sterile water for injection). CNS functional assessments (including sensory, motor, and behavioral endpoints) were evaluated predose and approximately 0.5, 8, and 24 hours after dosing. Inotuzumab ozogamicin had no toxicologically-significant effects on CNS function at the doses evaluated.

B. Respiratory

In a GLP study, male CD VAF rats (8/group) were administered a single IV dose of inotuzumab ozogamicin (10, 30, or 105.75 µg/kg) or vehicle control (2.78% sucrose, 0.018% polysorbate 80, 0.54% sodium chloride, 0.449% Tris, in sterile water for injection). Respiratory functional assessments (including respiratory rate, tidal volume, and minute volume) were evaluated using head out plethysmography. Parameters were assessed predose and approximately 0.5, 8, and 24 hours after dosing. Inotuzumab ozogamicin had no toxicologically-significant effects on respiratory function at the doses evaluated.

C. CV

In a non-GLP study, N-acetyl- γ -calicheamicin-DMH did not inhibit the hERG potassium channel expressed in stably transfected HEK293 cells at concentrations $\leq 6.77 \mu\text{M}$; the IC_{50} was not determined.

In a GLP study, telemetered male and female cynomolgus monkeys (4/sex) were administered a single IV dose of vehicle control (2.78% sucrose, 1.67% dextran-40, 0.018% polysorbate 80, 0.54% sodium chloride, 0.449% Tris, in sterile water for injection); approximately 48 hours later the same monkeys (2/sex/group) were administered a single IV dose of inotuzumab ozogamicin (10 or 50 $\mu\text{g}/\text{kg}$). CV functional assessments (including heart rate, mean arterial blood pressure, diastolic blood pressure, systolic blood pressure, and electrocardiogram) were evaluated by telemetry 24 hours prior to and following dosing with vehicle control and inotuzumab ozogamicin. Telemetry data were collected every 60 seconds or 5 minutes. At the 50 $\mu\text{g}/\text{kg}$ dose level, there was an approximately 10% decrease in mean arterial blood pressure 5:15 to 7:15 hours after dosing. At this same dose level, there was an approximately 6% increase in mean arterial blood pressure 16:15 to 23:30 hours after dosing. The small and transient changes in mean arterial blood pressure at the 50 $\mu\text{g}/\text{kg}$ dose level were considered related to inotuzumab ozogamicin, however the toxicological significance of this finding is unclear. There were no other treatment-related changes on CV function at the doses evaluated.

5.4. **ADME/PK**

Type of Study	Major findings																					
Distribution Protein Binding of PF-06649266 in Mouse, Rat, Rabbit, Monkey and Human Plasma / Study Report 160926	N-Ac- γ -calicheamicin DMH was highly bound to plasma proteins in all species tested. Fraction N-Ac-γ-calicheamicin DMH unbound <table border="1"> <thead> <tr> <th>Plasma source</th> <th>n</th> <th>Geometric mean</th> </tr> </thead> <tbody> <tr> <td>Mouse (CD-1)</td> <td>10</td> <td>0.000942</td> </tr> <tr> <td>Rat (Wistar Han)</td> <td>10</td> <td>0.0145</td> </tr> <tr> <td>Rat (Sprague Dawley)</td> <td>12</td> <td>0.00679</td> </tr> <tr> <td>Rabbit (NZW)</td> <td>12</td> <td>0.0263</td> </tr> <tr> <td>Monkey (cynomolgus)</td> <td>12</td> <td>0.0310</td> </tr> <tr> <td>Human</td> <td>12</td> <td>0.0279</td> </tr> </tbody> </table>	Plasma source	n	Geometric mean	Mouse (CD-1)	10	0.000942	Rat (Wistar Han)	10	0.0145	Rat (Sprague Dawley)	12	0.00679	Rabbit (NZW)	12	0.0263	Monkey (cynomolgus)	12	0.0310	Human	12	0.0279
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Metabolism Characterization of the Ex Vivo Plasma Stability of [^3H]Inotuzumab Ozogamicin (PF-05208773) / Study Report 110807	[^3H]inotuzumab ozogamicin or [^3H]N-Ac- γ -calicheamicin DMH was spiked into plasma or 1% bovine serum albumin and incubated at 37°C for up to 96 hours. Samples were precipitated with acetonitrile followed by liquid scintillation counting or size exclusion HPLC with radiochemical detection. Most [^3H]calicheamicin remained associated with protein (91-92%); some unconjugated [^3H]calicheamicin underwent bioconjugative transformation forming adducts with high molecular weight proteins (7-27%). % Total radioactivity in acetonitrile precipitate after incubation at 37°C <table border="1"> <thead> <tr> <th>Test article</th> <th>Rat plasma</th> <th>Monkey plasma</th> <th>Human plasma</th> <th>1% BSA</th> </tr> </thead> <tbody> <tr> <td>[^3H]IO</td> <td>91.1</td> <td>90.8</td> <td>90.8</td> <td>92.1</td> </tr> <tr> <td>[^3H]N-Ac-γ-calicheamicin DMH</td> <td>6.6</td> <td>22.6</td> <td>10.6</td> <td>26.6</td> </tr> </tbody> </table> BSA: Bovine serum albumin; IO: inotuzumab ozogamicin;	Test article	Rat plasma	Monkey plasma	Human plasma	1% BSA	[^3H]IO	91.1	90.8	90.8	92.1	[^3H]N-Ac- γ -calicheamicin DMH	6.6	22.6	10.6	26.6						
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Excretion Excretion, Metabolism, and Pharmacokinetics of [³ H]Inotuzumab Ozogamicin ([³ H]PF-05208773) in Sprague Dawley Rats Following a Single Intravenous Bolus Dose / Study Report 8296878	The primary route of inotuzumab ozogamicin elimination was fecal. Mean cumulative excretion of [³H]IO-derived radioactivity after 504 hours (% of dose) <table border="1"> <thead> <tr> <th>Urine</th> <th>Feces</th> <th>Cage wash</th> <th>Cage wipe</th> <th>Carcass</th> </tr> </thead> <tbody> <tr> <td colspan="5" style="text-align: center;">Males</td> </tr> <tr> <td>9.09</td> <td>79.5</td> <td>0.146</td> <td>0.151</td> <td>8.54</td> </tr> <tr> <td colspan="5" style="text-align: center;">Females</td> </tr> <tr> <td>8.38</td> <td>80.1</td> <td>0.220</td> <td>0.228</td> <td>7.40</td> </tr> </tbody> </table> Total recovery: 98.4%/97.7% (M/F)	Urine	Feces	Cage wash	Cage wipe	Carcass	Males					9.09	79.5	0.146	0.151	8.54	Females					8.38	80.1	0.220	0.228	7.40																																										
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Miscellaneous PK study Single-Dose Intravenous Toxicity Study in Monkeys / Study Report RPT-46644	There were no observed gender differences; data is shown for males only. Unconjugated calicheamicin concentrations were below the limit of quantitation (<70.4 ng/mL) for all animals at all time points. TK parameters after single dose <table border="1"> <thead> <tr> <th>Dose (µg/kg)</th> <th>Analyte</th> <th>C_{min} (ng/mL)</th> <th>t_{1/2} (h)</th> <th>AUC₀₋₃₃₆ (ng·h/mL)</th> </tr> </thead> <tbody> <tr> <td rowspan="2">25 (LD)</td> <td>IO</td> <td>18800</td> <td>ND</td> <td>260000</td> </tr> <tr> <td>G544</td> <td>6160</td> <td>86.9</td> <td>289000</td> </tr> <tr> <td rowspan="2">50 (MD)</td> <td>IO</td> <td>35200</td> <td>64.0</td> <td>449000</td> </tr> <tr> <td>G544</td> <td>11800</td> <td>104.8</td> <td>588000</td> </tr> <tr> <td rowspan="2">100 (HD)</td> <td>IO</td> <td>66000</td> <td>60.0</td> <td>1086000</td> </tr> <tr> <td>G544</td> <td>22400</td> <td>103.4</td> <td>1191000</td> </tr> </tbody> </table> IO: inotuzumab ozogamicin; G544: anti-CD22 antibody; ND: not determined;	Dose (µg/kg)	Analyte	C _{min} (ng/mL)	t _{1/2} (h)	AUC ₀₋₃₃₆ (ng·h/mL)	25 (LD)	IO	18800	ND	260000	G544	6160	86.9	289000	50 (MD)	IO	35200	64.0	449000	G544	11800	104.8	588000	100 (HD)	IO	66000	60.0	1086000	G544	22400	103.4	1191000																																			
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Twenty-Six Cycle (1 Dose/Week) Intravenous Toxicity Study in Rats / Study Report RPT-65042	t _{1/2} : not estimated Accumulation: MD and HD <1.0; determination of accumulation at the LD was confounded by the presence of anti-drug antibodies (ADAs). Dose proportionality: dose proportional at the MD and HD; determination of dose proportionality at the LD was confounded by the presence of ADAs. TK was analyzed in satellite groups (males only). Concentrations of unconjugated calicheamicin were below the limit of quantitation (<10.5 ng/mL) in most animals at most time points. TK parameters after cycle 1 <table border="1"> <thead> <tr> <th>Dose (µg/kg)</th> <th>Analyte</th> <th>C_{min} (ng/mL)</th> <th>AUC₀₋₁₆₈ (ng·h/mL)</th> <th>R</th> </tr> </thead> <tbody> <tr> <td rowspan="3">1 (LD)</td> <td>Total</td> <td>21.3</td> <td>657</td> <td>NA</td> </tr> <tr> <td>IO</td> <td>252</td> <td>7632</td> <td>NA</td> </tr> <tr> <td>G544</td> <td>262</td> <td>9553</td> <td>NA</td> </tr> <tr> <td rowspan="3">3 (MD)</td> <td>Total</td> <td>68.1</td> <td>2529</td> <td>NA</td> </tr> <tr> <td>IO</td> <td>806</td> <td>23690</td> <td>NA</td> </tr> <tr> <td>G544</td> <td>838</td> <td>31854</td> <td>NA</td> </tr> <tr> <td rowspan="3">10 (HD)</td> <td>Total</td> <td>266</td> <td>9840</td> <td>NA</td> </tr> <tr> <td>IO</td> <td>2763</td> <td>83940</td> <td>NA</td> </tr> <tr> <td>G544</td> <td>4709</td> <td>142146</td> <td>NA</td> </tr> </tbody> </table> TK parameters after cycle 25 <table border="1"> <thead> <tr> <th>Dose (µg/kg)</th> <th>Analyte</th> <th>C_{min} (ng/mL)</th> <th>AUC₀₋₁₆₈ (ng·h/mL)</th> <th>R</th> </tr> </thead> <tbody> <tr> <td rowspan="3">1 (LD)</td> <td>Total</td> <td>3.90</td> <td>11.9</td> <td>0.0181</td> </tr> <tr> <td>IO</td> <td>NM</td> <td>NM</td> <td>ND</td> </tr> <tr> <td>G544</td> <td>NM</td> <td>NM</td> <td>ND</td> </tr> <tr> <td>3 (MD)</td> <td>Total</td> <td>42.4</td> <td>2367</td> <td>0.936</td> </tr> </tbody> </table>	Dose (µg/kg)	Analyte	C _{min} (ng/mL)	AUC ₀₋₁₆₈ (ng·h/mL)	R	1 (LD)	Total	21.3	657	NA	IO	252	7632	NA	G544	262	9553	NA	3 (MD)	Total	68.1	2529	NA	IO	806	23690	NA	G544	838	31854	NA	10 (HD)	Total	266	9840	NA	IO	2763	83940	NA	G544	4709	142146	NA	Dose (µg/kg)	Analyte	C _{min} (ng/mL)	AUC ₀₋₁₆₈ (ng·h/mL)	R	1 (LD)	Total	3.90	11.9	0.0181	IO	NM	NM	ND	G544	NM	NM	ND	3 (MD)	Total	42.4	2367	0.936
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Type of Study	Major findings				
Study in Rats / Study Report RPT-68342	0.15 (LD)	IO	28.6	364*	2.43
	0.5 (MD)	IO	145	1680^	3.36
	1.5 (HD)	IO	533	6900	4.60
	IO: inotuzumab ozogamicin; *: exposure at developmental NOAEL; ^: exposure at maternal NOAEL;				
Intravenous Developmental Toxicity Study in Rabbits / Study Report RPT-72134	TK parameters on Day 15				
	0.1 (LD)	Dose (µg/kg)	Analyte	AUC ₀₋₂₄ (ng·h/mL)	AUC ₀₋₂₄ /Dose (ng·h/mL)
		Total	IO	106	1056
	0.3 (MD)	Total	IO	452	1505
		Total	IO	4187	13957
	1.0 (HD)	Total	IO	1052	1052
		Total	IO	13264*	13264
Total: total calicheamicin; IO: inotuzumab ozogamicin; *: exposure at developmental NOAEL;					

5.5. Toxicology

5.5.1. General Toxicology

Twenty-Six Cycle (1 Dose/Week) Intravenous Toxicity Study in Rats / Study Report RPT-65042

Key study findings:

- Decline in body weight and correlating decrease in food consumption were observed at the 10 µg/kg dose level.
- Adverse effects in the testes and liver were observed at the ≥1 µg/kg dose levels, including hepatocellular adenomas at the 10 µg/kg dose level.

Conducting laboratory and location:

Wyeth European DSM Research Center, Catania, Italy

GLP compliance: Yes

Methods

Dose and frequency of dosing:

Dose level	Dose levels	
	Calicheamicin equivalents (µg/kg)	ADC equivalents (mg/m ²)
Control	0	0
LD	1	0.073
MD	3	0.218
HD	10	0.727

Test article was administered once weekly for 26 weeks

Route of administration:

IV (bolus)

Formulation/vehicle:

5% sucrose, 0.01% polysorbate 80, 20 mM Tris, 50 mM sodium chloride, in sterile water for injection

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761040}
 {BESPOLSA; Inotuzumab Ozogamicin}

Species/strain: Rat/Crl:CD(SD)
 Number/sex/group: Toxicology study: 20/sex/group
 TK study: 5-9/M/group
 ADA study: 5/M/group
 Age: Approximately 7 weeks old
 Satellite groups/ unique design: TK and ADA study/ No
 Deviation from study protocol affecting interpretation of results: No

Observations and results: changes from control

Parameters	Major findings (end of study)																																																																																																	
Mortality	- One vehicle control male (toxicity study) was found dead on Day 94; this death was considered unrelated to test article. - One vehicle control male (TK study) was euthanized on Day 106; this death was considered unrelated to test article.																																																																																																	
Clinical signs	HD: ↓10%/↓12% food consumption (M/F);																																																																																																	
Body weights	HD: ↓18%/↓24% (M/F);																																																																																																	
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Gross pathology	Incidence of macroscopic findings <table border="1"> <thead> <tr> <th rowspan="3"></th> <th colspan="4">Males</th> <th colspan="4">Females</th> </tr> <tr> <th colspan="4">Dose level (µg/kg)</th> <th colspan="4">Dose level (µg/kg)</th> </tr> <tr> <th>0</th> <th>1</th> <th>3</th> <th>10</th> <th>0</th> <th>1</th> <th>3</th> <th>10</th> </tr> </thead> <tbody> <tr> <td>Number examined</td> <td>19</td> <td>20</td> <td>20</td> <td>20</td> <td>20</td> <td>20</td> <td>20</td> <td>20</td> </tr> <tr> <td>Liver</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Enlarged</td> <td>0</td> <td>5</td> <td>8</td> <td>7</td> <td>0</td> <td>0</td> <td>0</td> <td>0</td> </tr> <tr> <td>Depression</td> <td>0</td> <td>3</td> <td>6</td> <td>4</td> <td>0</td> <td>0</td> <td>1</td> <td>7</td> </tr> <tr> <td>Discoloration</td> <td>0</td> <td>1</td> <td>0</td> <td>5</td> <td>0</td> <td>0</td> <td>2</td> <td>1</td> </tr> <tr> <td>Testes</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Small</td> <td>0</td> <td>9</td> <td>12</td> <td>20</td> <td>-</td> <td>-</td> <td>-</td> <td>-</td> </tr> <tr> <td>Epididymides</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>		Males				Females				Dose level (µg/kg)				Dose level (µg/kg)				0	1	3	10	0	1	3	10	Number examined	19	20	20	20	20	20	20	20	Liver									Enlarged	0	5	8	7	0	0	0	0	Depression	0	3	6	4	0	0	1	7	Discoloration	0	1	0	5	0	0	2	1	Testes									Small	0	9	12	20	-	-	-	-	Epididymides								
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	Small	0	6	10	11	-	-	-	-
	Kidneys								
	Cortex discolored	0	0	0	2	0	0	0	1
	Granular surface	0	0	0	3	0	0	0	1
Organ weights	% Mean difference relative to terminal BW vs. concurrent controls								
		Males			Females				
		Dose level (µg/kg)			Dose level (µg/kg)				
		1	3	10	1	3	10		
	Liver								
	Number examined	20	20	20	20	20	20		
	% difference	+12%	+22%	+25%	+9%	+14%	+30%		
	Testes								
	Number examined	20	20	20	-	-	-		
	% difference	-28%	-35%	-58%	-	-	-		
Histopathology Adequate battery: Yes	Summary data are presented here. A full table of group incidences and severities of test article-related microscopic findings is presented in the Appendix. LD: cell foci, angiectasis, cellular vacuolation, and EMH in the liver; tubular degeneration in testes; hypospermia in epididymides; atrophy in male mammary gland; progressive nephropathy in kidneys; MD: cell foci, angiectasis, hypertrophy, karyomegaly, cellular vacuolation, and EMH in the liver; tubular degeneration in testes; hypospermia in epididymides; atrophy in male mammary gland; progressive nephropathy in kidneys; HD: cell foci, angiectasis, adenoma, sinusoidal dilatation, hypertrophy, hyperplasia, karyomegaly, cellular vacuolation, and EMH in the liver; alveolar macrophages in lung; tubular degeneration in testes; hypospermia in epididymides; decreased content in seminal vesicles; atrophy in male mammary gland; progressive nephropathy in kidneys;								
ADA analysis	LD: ADAs detected in 2/5 rats (40% incidence);								

LD: low dose; MD: mid dose; HD: high dose; ↓: reduction in parameters compared to control; ↑: increase in parameters compared to control;

Twenty-Six Cycle (1 Dose/Week) Intravenous Toxicity Study in Monkeys / Study Report RPT-65773

Key study findings:

- Three monkeys at the 5 µg/kg dose level were prematurely sacrificed in moribund condition. Moribundity in one monkey was attributed to test article-related protein-losing glomerulonephritis. The cause of moribundity in the other two early decedents was not determined.
- Target organs were the liver, ovary, and hematolymphopoietic tissues (spleen, mesenteric lymph node, and thymus).

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:

Dose levels		
Dose level	Calicheamicin	ADC equivalents

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761040}
 {BESPOLSA; Inotuzumab Ozogamicin}

	equivalents ($\mu\text{g}/\text{kg}$)	(mg/m^2)
Control	0	0
LD	0.5	0.072
MD	1.5	0.216
HD	5.0	0.732

Test article was administered once weekly for 26 weeks

Route of administration: IV (bolus)
 Formulation/vehicle: 5% sucrose, 0.01% polysorbate 80, 20 mM Tris, 50 mM sodium chloride, in sterile water for injection
 Species/strain: Monkey/cynomolgus
 Number/sex/group: 4/sex/group
 Age: 2 to 5 years old
 Satellite groups/ unique design: No/ No
 Deviation from study protocol affecting interpretation of results: No

Observations and results: changes from control

Parameters	Major findings (end of study)																																																																											
Mortality	- One HD male was euthanized on Day 37; clinical signs included body weight gain (due to fluid accumulation), hypoactivity, and low food consumption. Moribundity was considered test article-related and attributed to protein-losing glomerulonephritis. - One HD female was euthanized on Day 87; clinical signs included body weight loss, emaciation, and low food consumption. Moribundity was considered test article-related however the mechanism was not determined. - One HD female was euthanized on Day 142; clinical signs included body weight loss, emaciation, and low food consumption. Moribundity was considered test article-related however the mechanism was not determined.																																																																											
Clinical signs	Unremarkable																																																																											
Body weights	HD: $\downarrow$ 13%/ $\downarrow$ 11% (M/F);																																																																											
Ophthalmoscopy	Unremarkable																																																																											
Hematology	% Mean differences vs. concurrent controls (Week 26) <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th rowspan="3"></th> <th colspan="3">Males</th> <th colspan="3">Females</th> </tr> <tr> <th colspan="3">Dose level ($\mu\text{g}/\text{kg}$)</th> <th colspan="3">Dose level ($\mu\text{g}/\text{kg}$)</th> </tr> <tr> <th>0.5</th> <th>1.5</th> <th>5</th> <th>0.5</th> <th>1.5</th> <th>5</th> </tr> </thead> <tbody> <tr> <td>RBC</td> <td>-</td> <td>-</td> <td>-22%</td> <td>-</td> <td>-11%</td> <td>-21%</td> </tr> <tr> <td>HGB</td> <td>-</td> <td>-</td> <td>-15%</td> <td>-</td> <td>-12%</td> <td>-20%</td> </tr> <tr> <td>HCT</td> <td>-</td> <td>-</td> <td>-16%</td> <td>-</td> <td>-12%</td> <td>-20%</td> </tr> <tr> <td>RDW</td> <td>-</td> <td>-</td> <td>+8%</td> <td>-</td> <td>-</td> <td>+5%</td> </tr> <tr> <td>PLT</td> <td>-</td> <td>-39%</td> <td>-41%</td> <td>-</td> <td>-28%</td> <td>-37%</td> </tr> <tr> <td>WBC</td> <td>-</td> <td>-</td> <td>-43%</td> <td>-</td> <td>-</td> <td>-39%</td> </tr> <tr> <td>LYM</td> <td>-</td> <td>-</td> <td>-44%</td> <td>-</td> <td>-</td> <td>-48%</td> </tr> <tr> <td>MONO</td> <td>-</td> <td>+108%</td> <td>+71%</td> <td>-</td> <td>+121%</td> <td>+214%</td> </tr> </tbody> </table>		Males			Females			Dose level ($\mu\text{g}/\text{kg}$)			Dose level ($\mu\text{g}/\text{kg}$)			0.5	1.5	5	0.5	1.5	5	RBC	-	-	-22%	-	-11%	-21%	HGB	-	-	-15%	-	-12%	-20%	HCT	-	-	-16%	-	-12%	-20%	RDW	-	-	+8%	-	-	+5%	PLT	-	-39%	-41%	-	-28%	-37%	WBC	-	-	-43%	-	-	-39%	LYM	-	-	-44%	-	-	-48%	MONO	-	+108%	+71%	-	+121%	+214%
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	Dose level (µg/kg)			Dose level (µg/kg)		
	0.5	1.5	5	0.5	1.5	5
ALB	-	-	-11%	-	-	-
GLOB	-	-	+13%	-	+33%	+33%
A:G	-	-	-21%	-	-31%	-31%
AST	-	+139%	+297%	-	+119%	+302%
ALT	-	-	+106%	-	-	-
Urinalysis	Unremarkable					
Gross pathology	Unremarkable					
Organ weights	Unremarkable					
Histopathology Adequate battery: Yes Summary data are presented here. A full table of group incidences and severities of test article-related microscopic findings is presented in the Appendix.	LD: sinusoidal dilatation in the liver; decreased cellularity in the thymus; MD: sinusoidal dilatation, hypertrophy in the liver; decreased cellularity in the spleen and thymus; HD: sinusoidal dilatation, hypertrophy, focal alteration in the liver; decreased cellularity in the spleen and thymus; decreased cellularity in the mesenteric lymph node; atrophy of the ovary.					
ADA analysis	Unremarkable					

LD: low dose; MD: mid dose; HD: high dose. ↓: reduction in parameters compared to control; ↑: increase in parameters compared to control;

General toxicology; additional studies

Four Cycle (1 Dose/Week) Intravenous Toxicity Study in Rats, with 4-Week Recovery / Study Report RPT-46910

CMC-544 was administered IV once weekly at dose levels of 5, 15, or 50 µg/kg (0.41, 1.24, or 4.07 mg/m² of ADC) for 4 weeks (4 doses) to Crl:CD (SD) rats. There were no test article-related deaths, and clinical signs were limited to discolored feces (≥5 µg/kg) and body weight loss (≥15 µg/kg) which correlated with decreased food consumption. Dose-dependent decrease in RBC, HGB, HCT, and LYM was observed; RETI was increased at all dose levels with no dose dependence. Significant increases in ALT (↑135%), AST (↑70%), and alkaline phosphatase (AP) (↑54%) correlated with hepatocellular hypertrophy and degeneration, consistent with test article-related hepatotoxicity. Serious and nonreversible toxicity to the male reproductive tract was observed including severe tubular degeneration in the testes which was associated with epididymal hypospermia. All other findings were partially to fully reversible after a 4 week recovery period.

Four Cycle (1 Dose/Week) Intravenous Toxicity Study in Monkeys, with 4-Week Recovery / Study Report RPT-46909

CMC-544 was administered IV once weekly at dose levels of 2.5, 8, or 25 µg/kg (0.36, 1.32, or 4.20 mg/m² of ADC) for 4 weeks (4 doses) to cynomolgus monkeys. There were no test article-related deaths, and clinical signs were limited to emesis, fecal changes, and decreased food consumption. Dose-dependent decrease in RETI, WBC, and LYM were observed, as was dose-dependent increase in fibrinogen (FBGN). Significant increases in ALT (↑83%) and AST (↑160%) were observed without correlating histopathologic evidence of hepatotoxicity. Target organs

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identified by histopathology included the bone marrow, lymphoid organs, uterus, ovary, and testes; all histologic findings were partially or completely reversible.

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

***Salmonella-E. Coli*/Mammalian Microsome Reverse Mutation Assay / Study Report 15GR143**

Key study findings:

- N-Ac- γ -calicheamicin DMH increased the number of revertant colony counts in WP2 *uvrA* pKM101 at ≥ 3.09 $\mu\text{g}/\text{plate}$ without metabolic activation and at ≥ 12.3 $\mu\text{g}/\text{plate}$ with metabolic activation.

GLP compliance: Yes

Test system: *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537; *Escherichia coli* strain WP2 *uvrA* pKM101; up to 395 $\mu\text{g}/\text{plate}$; +/- S9 activation;

Study is valid: Yes

In Vitro Assays in Mammalian Cells

In Vitro Micronucleus Assay in TK6 Cells / Study Report 15GR142

Key study findings:

- N-Ac- γ -calicheamicin DMH induced micronuclei in TK6 cells at ≥ 0.0417 ng/mL without metabolic activation and at ≥ 0.395 ng/mL with metabolic activation.

GLP compliance: Yes

Test system: TK6 lymphoblastoid cells; up to 0.618 ng/mL; +/- S9 activation;

Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Single Dose Intravenous Bone Marrow Micronucleus Study in Male Mice / Study Report RPT-47573

Key study findings:

- In a dose range finding study, CMC-544 induced dose-dependent micronuclei formation in polychromatic erythrocytes (PCEs) at all dose levels evaluated; a definitive study was not conducted.
- CMC-544 was clastogenic in mice at doses ≥ 28 $\mu\text{g}/\text{kg}$.

GLP compliance: Yes

Test system: CD-1 VAF mice; single IV dose (0, 28, 56, 122.5, 225, or 450 $\mu\text{g}/\text{kg}$); doses ≥ 225 $\mu\text{g}/\text{kg}$ caused bone marrow cytotoxicity;

Study is valid: Yes

Table 4 Summary of findings, mouse bone marrow micronucleus study

Dose level	mPCEs		% PCEs	
	% mPCEs	mPCEs/total PCEs scored	Mean	Difference from vehicle control [#]
0 µg/kg	0.075	6/8000	48.30	NA
28 µg/kg (1.14 mg/m ²) [^]	0.575*	46/8000	48.98	-0.68
56 µg/kg (2.31 mg/m ²) [^]	1.088*	87/8000	46.30	2.00
122.5 µg/kg (5.04 mg/m ²) [^]	1.938*	155/8000	46.05	2.25

[^] ADC equivalents; * p≤0.05; [#] difference in mean from vehicle control; NA: not applicable;

5.5.3. Carcinogenicity

Not conducted per ICH S6, ICH S1, and ICH S9.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Intravenous Fertility Study in Female Rats / Study Report RPT-69733

Key study findings:

- CMC-544 caused maternal toxicity at the 1.5 µg/kg dose level characterized by decrease in body weight, body weight gain, and food consumption.
- An increase in proportion of resorptions and decrease in number of viable embryos were seen at the maternally toxic dose of 1.5 µg/kg; exposure (AUC) at this dose is approximately 2 times the exposure in patients at the maximum recommended human dose.
- The maternal and reproductive performance NOAELs were considered to be 0.5 µg/kg/day.

Conducting laboratory and location: Wyeth European DSM Research Center,
Catania, Italy

GLP compliance: Yes

Methods

Dose and frequency of dosing:

Dose level	Dose levels	
	Calicheamicin equivalents (µg/kg)	ADC equivalents (mg/m ²)
Control	0	0
LD	0.15	0.011
MD	0.5	0.036
HD	1.5	0.109

Test article was administered once daily for

48

Version date: February 1, 2016 for initial rollout (NME/original BLA reviews)

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 {BESPOUSA; Inotuzumab Ozogamicin}

Route of administration: approximately 3-6 weeks
 IV (bolus)
 Formulation/vehicle: 5% sucrose, 0.01% polysorbate 80, 20 mM Tris,
 50 mM sodium chloride, in sterile water for
 injection
 Species/strain: Rat/Crl:CD(SD)
 Number/sex/group: 25/F/group
 Satellite groups: TK: CMC-544 administered once daily for 2
 weeks followed by a 4 week treatment-free
 period (3-6/F/group)
 Study design: Daily administration of CMC-544 to females
 starting 2 weeks prior to cohabitation with
 untreated males until GD 7, followed by
 necropsy/cesarean on GD 12
 Deviation from study protocol affecting interpretation of results: No

Observations and results: changes from control

Parameters	Major findings
Mortality	None
Clinical signs	HD: Food consumption ↓9%
Body weights	HD: BW gain ↓86% (during pre-mating period); BW gain ↓26% (during gestation dosing period);
Necropsy findings	HD: Gravid uterine weights ↓17%; increased proportion of resorptions (0.08 vs 0.03 in control) and slight decrease in number of viable embryos (↓5% vs control);

LD: low dose; MD: mid dose; HD: high dose; ↓: reduction in parameters compared to control;

Embryo-Fetal Development

Intravenous Developmental Toxicity Study in Rats / Study Report RPT-68342

Key study findings:

- CMC-544 caused maternal toxicity at the 1.5 µg/kg dose level characterized by decrease in food consumption, body weight, and body weight gain.
- Fetal toxicity characterized by decreased live fetal weights and reduced fetal skeletal ossification were observed at the maternally toxic dose of 1.5 µg/kg. Slightly decreased live fetal weights were also observed at the 0.5 µg/kg dose level. Maternal exposures at the 0.5 and 1.5 µg/kg dose levels are approximately 0.4 and 2 times the human clinical exposure based on AUC at the recommended human dose.
- The maternal toxicity and developmental toxicity NOAELs were considered to be 0.5 and 0.15 µg/kg/day, respectively.
- In a dose range finding study of similar design [see Study RPT-67396, below], increased resorptions and fetal growth retardation were observed at the 1.5 µg/kg dose level.

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761040}
{BESPOLSA; Inotuzumab Ozogamicin}

Conducting laboratory and location: Wyeth European DSM Research Center,
Catania, Italy

GLP compliance: Yes

Methods

Dose and frequency of dosing:

Dose levels		
Dose level	Calicheamicin equivalents (µg/kg)	ADC equivalents (mg/m ²)
Control	0	0
LD	0.15	0.011
MD	0.5	0.036
HD	1.5	0.109

Test article was administered once daily for 12 days

Route of administration: IV (bolus)

Formulation/vehicle: 5% sucrose, 0.01% polysorbate 80, 20 mM Tris, 50 mM sodium chloride, in sterile water for injection

Species/strain: Rat/Crl:CD(SD)

Number/sex/group: 25/F/group

Satellite groups: TK: CMC-544 administered once daily for 10 days (9/F/group)

Study design: Pregnant rats were administered CMC-544 daily on GDs 6-17, with necropsy/cesarean on GD 21

Deviation from study protocol affecting interpretation of results: No

Observations and results: changes from control

Parameters	Major findings
Mortality	None
Clinical signs	HD: Food consumption ↓11% (during dosing period);
Body weights	HD: BW gain ↓26% (during dosing period); BW gain ↓21% (at necropsy); final BW ↓5%;
Necropsy findings Cesarean section data	HD: Gravid uterine weights ↓19% (related to decreased fetal weights);
Necropsy findings Offspring	MD: Live fetal weights ↓6%; HD: Live fetal weights ↓22%; decreased fetal skeletal ossification ↑112%; increased incidences of short/thick humerus, misshapen scapula, and/or misshapen ulna (related to fetal growth retardation and a decrease in skeletal ossification);

LD: low dose; MD: mid dose; HD: high dose; ↓: reduction in parameters compared to control; ↑: increase in parameters compared to control;

Intravenous Developmental Toxicity Dose Ranging Study in Rats / Study Report RPT-67396

In a GLP-compliant dose range finding study, CMC-544 was administered to pregnant rats IV once daily on GDs 6-17 at dose levels of 0.5, 1.5, or 5 µg/kg (0.036, 0.109, 0.364 mg/m² of ADC), with necropsy/cesarean performed on GD 21. Fetal toxicity characterized by increased resorptions and decreased live fetal weights were observed at the 1.5 µg/kg dose level, while complete litter loss was observed in all animals at the 5 µg/kg dose level. Maternal toxicity including decreased body weight gain and decreased food consumption were observed at the ≥1.5 and 5 µg/kg dose levels, respectively.

Intravenous Developmental Toxicity Study in Rabbits / Study Report RPT-72134

Key study findings:

- CMC-544 caused slight maternal toxicity at the 1.0 µg/kg dose level characterized by transient decrease in food consumption.
- No developmental toxicity was observed at any dose level therefore the developmental NOAEL was 1 µg/kg/day; maternal exposure at this dose level is approximately 3 times the human clinical exposure based on AUC at the recommended human dose.

Conducting laboratory and location: Wyeth European DSM Research Center,
Catania, Italy

GLP compliance: Yes

Methods

Dose and frequency of dosing:

Dose level	Dose levels	
	Calicheamicin equivalents (µg/kg)	ADC equivalents (mg/m ²)
Control	0	0
LD	0.1	0.015
MD	0.3	0.044
HD	1.0	0.145

Test article was administered once daily for 14 days

Route of administration: IV (bolus)
Formulation/vehicle: 5% sucrose, 0.01% polysorbate 80, 20 mM Tris, 50 mM sodium chloride, in sterile water for injection
Species/strain: Rabbit/New Zealand White
Number/sex/group: 20/F/group
Satellite groups: None
Study design: Mated female rabbits were administered CMC-544 daily on GDs 6-19, with necropsy/cesarean on GD 29
Deviation from study protocol affecting interpretation of results: No

Observations and results: changes from control

Parameters	Major findings
Mortality	Unremarkable
Clinical signs	HD: Food consumption ↓16%/↓9% (dosing period/post-dosing period);
Body weights	Unremarkable
Necropsy findings Cesarean section data	Unremarkable
Necropsy findings Offspring	Unremarkable

LD: low dose; MD: mid dose; HD: high dose; ↓: reduction in parameters compared to control;

Prenatal and Postnatal Development

Not conducted per ICH S9.

5.5.5. Other Toxicology Studies

Cross-Reactivity Study with Normal Human Tissues / Study Report RPT-63271

Key study findings:

- G544 stained the membrane and cytoplasm of lymphocytes consistent with the known pattern of CD22 expression.
- Unexpectedly, G544 stained the stromal fibers in the dermis of the skin, breast (mammary gland), and uterus-cervix (external os).

Conducting laboratory and location:

(b) (4)

GLP compliance:

Yes

The cross-reactivity of G544 (unconjugated anti-CD22 IgG4 antibody portion of inotuzumab ozogamicin) antibody was evaluated in a panel of human tissue cryosections at two concentrations (0.5 and 10 µg/mL). G544 stained the membrane and cytoplasm of lymphocytes in lymph node (follicular), spleen (follicular and mantle; red pulp), tonsil (follicular and mantle), GALT, mononuclear cell infiltrates, and blood smears. Unexpectedly, G544 stained the stromal fibers in the dermis of the skin, breast (mammary gland), and uterus-cervix (external os). G544 stained positive and negative control tissues as expected.

9-Week Intravenous Bolus Investigative Toxicity Study of PF-06647259 in Cynomolgus Monkeys / Study Report 14GR346

This study evaluated the target-independent toxicities of antibody-calicheamicin conjugates using a humanized nonbinding IgG1 monoclonal antibody conjugated to calicheamicin via the acid-labile AcBut linker (PF-06647259). Necropsies were conducted 48 hours after the first dose (Day 3) or 21 days after the third dose (Day 63).

Key study findings:

- Decreased PLT counts were observed in all test article-dosed animals, consistent with acute reversible thrombocytopenia; there was no correlating microscopic evidence of decreased PLT production.
- Liver findings included initial loss of VEGFR2 staining in endothelial cells followed by increased CD34 staining, PLT staining in sinusoids, and increased serum levels of AST, hyaluronic acid, and miR-122.
- Thrombocytopenia was considered the result of PLT sequestration secondary to test article-mediated liver-specific endothelial injury, and not the result of direct bone marrow toxicity.

Conducting laboratory and location:

Pfizer Worldwide Research & Development, Groton, CT

GLP compliance: No

Methods

Dose and frequency of dosing: 0 or 20 µg/kg (6 mg/m² ADC equivalents) every 3 weeks for 9 weeks

Route of administration: IV (bolus)

Formulation/vehicle: 8.5% sucrose, 0.02% polysorbate 80, 20 mM Tris, 0.005% disodium EDTA (pH 8.0) diluted in PBS

Species/strain: Monkey/cynomolgus

Number/sex/group: 7 (control) 8 (PF-06647259) males

Age: Approximately 3.5 to 4.5 years old

Satellite groups/ unique design: No/ No

Deviation from study protocol: No

affecting interpretation of results:

Observations and results: changes from control

Parameters	Major findings
Mortality	Unremarkable
Clinical signs	Increased pigmentation (dark) was observed on the body (thorax, inguinal area, hindlimbs, forelimbs) and around the injection site;
Body weights	Unremarkable
Hematology	↓ PLT (pronounced after first cycle, then less pronounced but protracted after subsequent cycles); ↓ LYM and ↓ WBC at various times points; ↑APTT and ↑FIB (occasional);
Clinical chemistry	↑100% AST; ↑49% ALT; ↑365% hyaluronic acid;
microRNA analysis	↑629% miR-122;
Gross pathology	Abnormal dark color and/or wound/scar/crust at injection site;
Organ weights	Unremarkable
Histopathology Adequate battery: Limited* *Day 3 necropsy: kidney, liver, lung, spleen; Day 63 necropsy: liver, spleen;	Day 3 liver findings: loss of VEGFR2 staining in endothelial cells of the midzonal and centrilobular regions; PLT staining in sinusoids in midzonal regions, consistent with PLT sequestration; Day 63 liver findings: increased CD34 expression in sinusoidal

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	endothelial cells; multifocal sinusoidal dilation and/or hepatocyte atrophy (single animal); Day 63 other organ findings: increased cellularity in the sinusoids, decreased lymphoid cellularity in the spleen;

↓: reduction in parameters compared to control; ↑: increase in parameters compared to control;

Appendix:

Table 5 26 week rat study, group incidences and severities of inotuzumab ozogamicin-related microscopic findings

	Males				Females			
	Dose level (µg/kg)				Dose level (µg/kg)			
	0	1	3	10	0	1	3	10
Liver								
Number examined	19	20	20	20	20	20	20	20
B-hepatocellular adenoma	0	0	0	2	0	0	0	1
Basophilic cell foci	0	0	11	12	0	0	0	2
Slight	0	0	8	5	0	0	0	1
Mild	0	0	3	7	0	0	0	1
Eosinophilic cell foci	0	5	14	17	0	0	1	2
Slight	0	5	2	6	0	0	1	0
Mild	0	0	11	10	0	0	0	2
Moderate	0	0	1	1	0	0	0	0
Angiectasis	0	3	6	6	0	0	2	11
Slight	0	1	2	0	0	0	0	4
Mild	0	2	4	4	0	0	2	3
Moderate	0	0	0	2	0	0	0	2
Marked	0	0	0	0	0	0	0	2
Sinusoidal dilatation	0	0	0	0	0	0	0	13
Slight	0	0	0	0	0	0	0	13
Oval cell hyperplasia	0	0	0	20	0	3	1	20
Slight	0	0	0	11	0	3	1	0
Mild	0	0	0	9	0	0	0	12
Moderate	0	0	0	0	0	0	0	8
Cholangiofibrosis	0	0	1	0	0	0	0	0
Mild	0	0	1	0	0	0	0	0
Hepatocellular hypertrophy	0	0	10	20	0	0	1	15
Slight	0	0	10	5	0	0	1	4
Mild	0	0	0	8	0	0	0	7
Moderate	0	0	0	7	0	0	0	4
Karyomegaly	0	0	6	19	0	0	2	13
Slight	0	0	6	8	0	0	1	4
Mild	0	0	0	8	0	0	1	8
Moderate	0	0	0	3	0	0	0	1
Hepatocellular vacuolation	0	3	11	3	0	0	0	0
Slight	0	2	9	0	0	0	0	0
Mild	0	1	2	3	0	0	0	0
Fibrosis	0	0	4	2	0	0	0	0
Slight	0	0	3	2	0	0	0	0
Mild	0	0	1	0	0	0	0	0
Increased EMH	0	5	8	17	9	8	10	20
Slight	0	5	8	16	9	8	10	18
Mild	0	0	0	1	0	0	0	2
Testes								
Number examined	19	20	20	20	-	-	-	-

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	Males				Females			
	Dose level (µg/kg)				Dose level (µg/kg)			
	0	1	3	10	0	1	3	10
Tubular degeneration	0	9	13	20	-	-	-	-
Slight	0	1	0	0	-	-	-	-
Mild	0	0	0	1	-	-	-	-
Moderate	0	2	0	0	-	-	-	-
Marked	0	6	13	19	-	-	-	-
Epididymides								
Number examined	19	20	20	20	-	-	-	-
Hypospermia	0	9	13	20	-	-	-	-
Slight	0	0	0	1	-	-	-	-
Mild	0	1	0	0	-	-	-	-
Marked	0	8	13	19	-	-	-	-
Mammary gland (male)								
Number examined	18	18	7	16	-	-	-	-
Atrophy	0	5	11	12	-	-	-	-
Slight	0	5	1	1	-	-	-	-
Mild	0	0	10	9	-	-	-	-
Moderate	0	0	0	2	-	-	-	-
Seminal vesicles								
Number examined	19	0	20	20	-	-	-	-
Decreased content	0	0	0	5	-	-	-	-
Slight	0	0	0	5	-	-	-	-
Kidneys								
Number examined	19	20	20	20	20	20	20	20
Chronic progressive nephropathy	6	4	10	17	3	3	10	18
Slight	6	4	9	5	3	3	10	11
Mild	0	0	0	2	0	0	0	3
Moderate	0	0	1	4	0	0	0	4
Marked	0	0	0	6	0	0	0	0
Lung								
Number examined	19	0	0	20	20	0	20	20
Alveolar macrophages	2	0	0	4	3	0	5	16
Slight	2	0	0	4	3	0	5	16

Table 6 26 week monkey study, group incidences and severities of inotuzumab ozogamicin-related microscopic findings

	Males				Females			
	Dose level (µg/kg)				Dose level (µg/kg)			
	0	0.5	1.5	5	0	0.5	1.5	5
Number examined	4	4	4	3	4	4	4	2
Liver								
Dilatation, sinusoidal, with hepatocyte atrophy								
Not noted	4	0	0	0	4	1	0	0
Minimal	0	2	0	2	0	3	3	1
Slight	0	2	3	1	0	0	1	1
Moderate	0	0	1	0	0	0	0	0
Hypertrophy, hepatocellular								
Not noted	4	4	3	1	4	4	2	0
Minimal	0	0	1	2	0	0	2	2
Cellular alteration, focal								
Not noted	4	4	4	3	4	4	4	1
Slight	0	0	0	0	0	0	0	1

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	Males				Females			
	Dose level (µg/kg)				Dose level (µg/kg)			
	0	0.5	1.5	5	0	0.5	1.5	5
Spleen								
Decreased cellularity, germinal centers/marginal zone								
Not noted	4	4	4	0	4	4	3	2
Minimal	0	0	0	0	0	0	1	0
Moderate	0	0	0	3	0	0	0	0
Mesenteric lymph node								
Decreased cellularity, germinal centers								
Not noted	4	4	4	0	3	4	4	1
Minimal	0	0	0	1	1	0	0	1
Slight	0	0	0	2	0	0	0	0
Thymus								
Decreased cellularity								
Not noted	3	2	3	0	3	4	1	1
Minimal	1	1	1	2	1	0	3	1
Slight	0	1	0	1	0	0	0	0
Ovary								
Atrophy								
Not noted	-	-	-	-	4	4	4	0
Slight	-	-	-	-	0	0	0	2

Michael L. Manning, Ph.D.
 Primary Reviewer

Christopher Sheth, Ph.D.
 Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

Inotuzumab ozogamicin is an ADC consisting of a humanized monoclonal antibody targeting CD22+ B-cells linked N-acetyl- γ -calicheamicin, which binds to the DNA minor groove and induces DNA double strand breakage and cell death. The proposed indication for inotuzumab ozogamicin is the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

In the phase 3 trial, the CR/CRi rate was 73.2% (95% CI: 65.7-79.8%) in the inotuzumab ozogamicin arm vs. 30.9% (95% CI: 23.9-38.6%) in the control arm (investigator's choice of chemotherapy). Inotuzumab did not show a statistically significant survival advantage; the hazard ratio for overall survival was 0.77 (95% CI: 0.578 - 1.026).

A major focus of this review was the appropriateness of the proposed dose of 1.8 mg/m². This dose was identified as the maximum tolerated dose (MTD) in the dose finding trials. The major safety concern for this drug is VOD. The rate of VOD in patients treated with inotuzumab ozogamicin was 13.4% compared to a rate of 0.1% in patients treated with chemotherapy. In addition, the rate of VOD in patients who proceeded to hematopoietic stem cell transplant (HSCT) was even higher; 22.1% in the inotuzumab arm compared to 3.1% in the control arm. Inotuzumab ozogamicin appears to amplify the VOD properties of the preparatory regimen (chemotherapy + radiation) that is administered prior to HSCT.

Exposure-response relationship for efficacy (CR/CRi) and safety (VOD) were observed at the proposed 1.8 mg/m² dose. The dose escalation study evaluated a narrow range of inotuzumab doses (1.2 mg/m², 1.6 mg/m², and 1.8 mg/m²) and enrolled limited number of patients (N=3) at the lowest dose. Therefore, a dose finding PMR will be issued for the following reasons:

- Dose finding trial was not robust and didn't identify the optimal dose of inotuzumab ozogamicin that balances safety and efficacy.
- Inotuzumab ozogamicin caused very high rate of VOD, including mortalities.
- Prior experience with calicheamicin containing antibody (gemtuzumab ozogamicin) showed very high rate of VOD post approval.

6.1.1. Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in BLA 761040. This BLA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations are summarized below:

Review Issues	Recommendations and Comments
Supportive Evidence of Effectiveness	Evidence of effectiveness was obtained from the pivotal Phase 3 trial B1931022 and the supportive Phase 1/2 trial B1931010. The exposure-response analysis identified a correlation between

	exposure and probability of achieving CR/CRi. The analysis was conducted with data primarily from one dose level and thus needs to be interpreted with caution.
General Dosing Instructions	The recommended dosing for inotuzumab ozogamicin during the first cycle of treatment is 1.8 mg/m ² divided into three weekly doses of 0.8 mg/m ² on Day 1, 0.5 mg/m ² on Day 8, and 0.5 mg/m ² on Day 15 of a 21-day-cycle. In subsequent cycles, three doses of 0.5 mg/m ² are given on Days 1, 8, and 15 of a 28-day-cycle.
Dosing in Patient Subgroups (Intrinsic and Extrinsic Factors)	No dose adjustments are proposed based on intrinsic factors or extrinsic factors.
Labeling	Labeling recommendations are generally adequate.
Bridge between the “to-be-marketed” and clinical trial formulation	The to-be-marketed formulation was used in a subset of patients in the registration trial. Additionally, analytical comparability studies between the to-be-marketed formulation and the clinical trial formulation was established.

6.1.2. Post-Marketing Requirements and Commitments

PMR or PMC	Key Issues to be Addressed	Rationale	Key Considerations for Design Features
PMR	Dose Selection	The proposed inotuzumab ozogamicin dose of 1.8 mg/m² may not be optimal in balancing safety and efficacy. The relatively high rate of VOD adverse events is a significant concern. (b) (4) was not informed by a robust dose finding study, a lower dose may provide a better balance of safety and efficacy.	Conduct a randomized trial of at least 2 dose levels of inotuzumab ozogamicin in patients with relapsed or refractory acute lymphoblastic leukemia who are potential candidates of HSCT and at high risk for developing veno-occlusive disease (VOD). High risk is defined as patients with prior hematopoietic stem cell transplantation (HSCT), ongoing or prior liver disease, older patients (≥ 55 years), or later salvage line (Salvage ≥ 2). Safety parameters will include hepatic VOD, transplant related mortality (non-relapse mortality), and non-transplant related mortality. Descriptive analyses of safety and efficacy

			(including achievement of minimal residual disease [MRD]-negativity) will be conducted for the intent-to-treat population and the per-protocol population that excludes patients who do not proceed to HSCT. The study will include sufficient clinical pharmacokinetic sampling to analyze the exposure-response relationship for efficacy and safety. Submit complete clinical study report and datasets.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Mechanism of Action: inotuzumab ozogamicin consists of a humanized IgG4 monoclonal antibody targeting CD22+ B-cells and N-acetyl- γ -calicheamicin, which induces DNA double-strand breaks resulting in cell cycle arrest and apoptosis.

Absorption: inotuzumab ozogamicin is administered as a 1- hour IV infusion.

Distribution: inotuzumab ozogamicin volume of distribution is approximately 12 liters, based on population PK analysis. Unconjugated calicheamicin is ~97% bound to plasma proteins and exhibits limited partitioning into red blood cells.

Metabolism: N-acetyl- γ -calicheamicin is the only metabolite detected in plasma and is produced non-enzymatically by hydrolytic release. CYP450 enzymes isoforms and UGT enzymes are not involved in the metabolism of calicheamicin.

Elimination: Non-clinical studies suggest that biliary excretion is the primary route of calicheamicin elimination and renal excretion exhibit minor involvement (8-9%).

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended dosing for inotuzumab ozogamicin during the first cycle of treatment is 1.8 mg/m² divided into three weekly doses of 0.8 mg/m² on Day 1, 0.5 mg/m² on Day 8, and 0.5 mg/m² on Day 15. The duration of the first cycle is 21 days and can be extended to 28 days for patients who achieve CR/CRi or to allow for recovery from toxicity.

Subsequent treatment cycles are 28 days. The recommended dosing is 1.5 mg/m² divided into 3 weekly doses of 0.5 mg/m² on Day 1, Day 8, and Day 15 for patients who achieve CR/CRi. The recommended dosing for patients who do not achieve CR/CRi is 1.8 mg/m² divided into 3 weekly doses of 0.8 mg/m² on Day1, 0.5 mg/m² on Day 8, and 0.5 mg/m² on Day 15.

For patients proceeding to hematopoietic stem cell transplant (HSCT), the recommended duration of treatment is 2 cycles. A third cycle should be considered for patients who do not achieve CR/CRi and minimal residual disease (MRD) negativity after 2 cycles.

For patients not proceeding to HSCT (b) (4) up to 6 cycles of treatment may be administered. Patients who do not achieve a CR/ CRi within 3 cycles of treatment should discontinue treatment.

Due to lack of robust dose finding data and very high rate of VOD, a PMR will be issued in order to identify an optimal dose of inotuzumab ozogamicin.

Therapeutic Individualization

No dose adjustments are proposed based on intrinsic or extrinsic factors. Based on population PK analyses, inotuzumab ozogamicin PK was not affected by mild, moderate or severe renal and hepatic impairment. Of note, only one patient had severe hepatic impairment. In addition, age, race, or sex did not influence the PK of inotuzumab ozogamicin. *In vitro* studies suggest that inotuzumab ozogamicin exhibits low potential for drug-drug interactions.

Outstanding Issues

The applicant selected the maximum tolerated dose of 1.8 mg/m² for the pivotal efficacy study. At this dose, the rate of VOD is substantially higher than the control arm, especially in patients proceeding to HSCT. Since the dose escalation study enrolled very few patients at doses lower than 1.8 mg/m², robust dose or exposure-response data were not available to enable optimal dose selection. Based on available data, we cannot determine whether 1.8 mg/m² of inotuzumab ozogamicin sufficiently balances safety and efficacy.

Prior experience with gemtuzumab ozogamicin demonstrated that the rate of VOD decreased substantially with dose reduction. Therefore, the applicant will be asked to conduct a post-marketing dose finding study to assess the safety and efficacy of lower inotuzumab ozogamicin doses.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

PHARMACOLOGY	
Structure	Inotuzumab ozogamicin is a CD22-targeted antibody-drug conjugate. The antibody is a humanized immunoglobulin type G, which specifically recognizes human CD22. The small molecule, N-acetyl- γ -calicheamicin

	dimethyl hydrazide (DMH), is a deoxyribonucleic acid (DNA) minor groove binding cytotoxic natural product that induces double strand DNA breaks. N-acetyl- γ -calicheamicin DMH is covalently attached to the antibody via a linker.
Mechanism of Action	The anticancer activity of inotuzumab ozogamicin is due to the binding of the ADC to CD22 expressing cells, followed by internalization of the ADC-CD22 complex, and the release of N-acetyl- γ -calicheamicin DMH via hydrolytic cleavage in the acidic environment in lysosomes. Binding of N-acetyl- γ -calicheamicin DMH to DNA leads to DNA strand breakage, subsequently inducing cell cycle arrest and apoptosis.
QT Prolongation	In the pivotal phase 3 study, increase in QTcF of ≥ 60 msec from baseline were measured in 4/162 (3%) patients in the inotuzumab arm compared to 3/124 (2%) patients in the investigator's choice arm. Increases in QTcF of > 500 msec were not observed in the inotuzumab arm. Central tendency analysis of the QTcF interval changes from baseline showed that the highest mean (upper bound of the 2-sided 90% CI) for QTcF was 15.3 (21.1) msec, which was observed at cycle 4/Day 1/1 hour in the BESPONSA arm.
GENERAL INFORMATION	
Bioanalysis	<u>ALL Patients (Study B1931010 and B1931022)</u> Plasma concentrations of inotuzumab ozogamicin and unconjugated calicheamicin were measured using a validated high performance liquid chromatography tandem mass spectrometry assay (HPLC/MS-MS). <u>NHL Patients (9 Studies)</u> ELISA methods were used to measure the serum PK concentrations of inotuzumab ozogamicin, total calicheamicin, unconjugated calicheamicin, and total antibody. <u>Immunogenicity</u> In patients with relapsed or refractory ALL, ECL and cell-based assays were used to detect ADA and nAb to inotuzumab ozogamicin in human serum.
Dose Proportionality	Single doses ranging from 0.4, 0.8, 1.34, 1.8, and 2.4 mg/m ² were studied in patients with NHL. The C _{MAX} of inotuzumab ozogamicin appeared to increase in a less-than-proportional manner with increasing dose (logarithmic slope =0.58); however, the 90% confidence interval included zero. Similar trend was observed for total calicheamicin C _{MAX} . The AUC _{INF} of total calicheamicin increased in a more-than-dose proportional manner with increasing dose (logarithmic slope = 1.32); however, the 90% confidence interval included zero.
Accumulation	At the proposed dosing regimen, the accumulation ratio (total AUC at Cycle 4 versus total AUC at Cycle 1) in patients with relapsed or refractory ALL was

	estimated to be 5.30. The unconjugated calicheamicin concentrations in serum at pre-dose and end of infusion were below the limit of quantitation for most of the samples.
Variability	Pharmacokinetic data obtained from the pivotal study show that inotuzumab ozogamicin exhibits high variability. The %CV for C_{MAX} and C_{trough} ranged 44% to 139% and 42% to 301%, respectively. Based on the population PK modeling estimates, the variability for cumulative AUC ranged from 53% to 79%.
Immunogenicity	In clinical studies of inotuzumab ozogamicin in patients with relapsed or refractory ALL, 7/236 (3%) patients tested positive for anti-inotuzumab ozogamicin antibodies. In patients testing positive for anti-drug antibodies (ADA), neutralizing antibodies (nAbs) were not detected. The CL of inotuzumab ozogamicin appeared to be comparable between patients who tested positive or negative for ADAs.
DISTRIBUTION	
Volume of Distribution	Based on population PK analysis, the total volume of distribution was approximately 12 L.
Plasma Protein Binding	Unconjugated calicheamicin was highly bound to plasma proteins (97.2%).
Blood-to-Plasma & Tissue-to-plasma ratio	In preclinical studies, inotuzumab ozogamicin exhibited limited distribution into tissues, with tissue-to-plasma ratio < 0.6. Additionally, limited distribution to red blood cells was observed in rats. The blood-to-plasma ratio was approximately 0.5.
ELIMINATION	
Mean Terminal Half-Life	The mean terminal half-life of inotuzumab ozogamicin after Cycle 1 Day 1 dose was 144 hours (6 days) and 329 hours (13.7 days) by the end of Cycle 4. Inotuzumab ozogamicin clearance is influenced by the interaction with CD22-positive B-cells and binding with neonatal Fc receptor (FcRN). The observed increase in half-life is attributed to the depletion of the target CD22-positive B-cells
METABOLISM	
Primary Metabolic Pathways	In the serum of patients who were treated with inotuzumab ozogamicin, the only metabolite detected was N-acetyl-γ-calicheamicin DMH. The hydrolytic release of N-acetyl-γ-calicheamicin from the ADC in plasma is limited and the metabolism of N-acetyl-γ-calicheamicin DMH occurs primarily via non-enzymatic reduction.
Transporter Substrate	Bidirectional permeability assays in MDCK cells demonstrated that unconjugated calicheamicin is substrate for the P-gp efflux transporter but

	not BCRP. <i>In vitro</i> studies in hepatocytes demonstrated that unconjugated calicheamicin was not a substrate of the hepatic uptake transporters OATP1B1 or OATP1B3.
DDI Potential	<u>CYP450 Inhibition</u> <i>In vitro</i> studies demonstrated that calicheamicin inhibited CYP450 isozymes (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4) with IC₅₀ values ranging from 0.42 to >10 mM, which are orders of magnitude higher than clinical concentrations. Inotuzumab ozogamicin IC₅₀ for CYP450 isozymes inhibition could not be determined (IC₅₀ was higher than the highest concentration tested). There was no time-dependent inhibition of CYP450 enzymes when incubated with inotuzumab ozogamicin or unconjugated calicheamicin <u>CYP450 Induction</u> Inotuzumab ozogamicin and unconjugated calicheamicin did not induce mRNA expression or enzymatic activities of CYP1A2, CYP2B6, or CYP3A4 in hepatocytes <i>in vitro</i>. <u>UGT Inhibition</u> Unconjugated calicheamicin inhibited the activities of UGT1A4, UGT1A6, UGT1A9, and UGT2B7 <i>in vitro</i> with IC₅₀ values >10 μM. The IC₅₀ of UGT1A1 <i>in vitro</i> inhibition was 0.61 μM, which is orders of magnitude higher than the expected C_{MAX} at steady state (0.000034 μM). <u>Transporter Inhibition</u> Unconjugated calicheamicin exhibited no inhibition of P-gp or BCRP <i>in vitro</i>. Similarly, there was no inhibition of the renal uptake transporters OAT1, OAT3, and OCT2 <i>in vitro</i>. There was minimal inhibition of the hepatic uptake transporters OATP1B1 and OATP1B3 (30% and 16% inhibition) <i>in vitro</i> at 0.1 mM concentration, which is orders of magnitude higher than the expected C_{MAX}.
EXCRETION	
Primary Excretion Pathway	In preclinical species, feces, via biliary elimination, is the main route of excretion following IV doses of inotuzumab ozogamicin. Urinary excretion accounting for approximately 9% of the dose. No mass-balance studies were conducted in human subjects.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes, the clinical pharmacology data provide supportive evidence of effectiveness. The applicant submitted results of two key studies to support the proposed BLA (**Table 7**). The first study was a phase 1/2 dose escalation and expansion trial. The second study was a pivotal phase 3 study

designed to evaluate safety and efficacy of inotuzumab ozogamicin compared to available treatment. Results of the dose selection and the pivotal studies are detailed below.

Table 7: Clinical Trials supporting inotuzumab ozogamicin approval

Trial (N)	Description	Study Design	Primary Endpoint(s)	PK Population (N)
B1931010 (N=72)	Phase 1 dose escalation/expansion and Phase 2	Single-arm, open-label, escalating doses, salvage ≥ 2 , Ph ⁻ and Ph ⁺	CR/CRi	72
B1931022 (N=326)	Pivotal Phase 3 trial	Randomized (1:1), open-label, salvage 1 and 2, Ph ⁻ and Ph ⁺	CR/CRi & OS	133

The pivotal study B1931022 was an open-label, randomized, multi-center, global study of inotuzumab ozogamicin compared to control treatment (physician's choice) in adult subjects with relapsed or refractory CD22+ B-cell ALL in Salvage 1 or 2. The primary endpoints were CR/CRi and overall survival. The supportive study B1931010 was a single-arm, multi-center, open-label dose escalation and dose expansion trial in subjects with relapsed or refractory CD22+ ALL.

Dosing Regimen Selection

Dosing Frequency

To support the proposed fractionated dosing, the applicant submitted a literature report comparing the fractionated (weekly dosing) vs. single monthly dosing regimens in patients with relapsed or refractory B-cell ALL (PMID: 23633004). The study compared a single dose 1.8 mg/m² and a fractionated dose of intozumab ozogamicin administered on days 1 (0.8 mg/m²), 8 (0.5 mg/m²), and 15 (0.5 mg/m²) of a 21- to 28-day treatment cycle. The length of the first cycle depended on the recovery of blast counts as well as bone marrow status.

The overall remission rate was 57% and 59% in the monthly and fractionated dosing regimens, respectively. The incidence of adverse events—drug-related fevers, elevated serum bilirubin, and elevated transaminases—were less common with the divided dosing regimen. Monthly dosing was associated with higher rates of liver function abnormalities, occasional VOD after allogenic SCT, and transient febrile and hypotensive episodes (**Table 8**). The study determined that fractionated dosing was a safer alternative to the monthly dosing.

Table 8: Frequency of Grade 3-4 adverse events following singly monthly and fractionated dosing

Grade 3-4 Adverse Event	Monthly (Single) Dose N = 49	Fractionated Dosing n = 41
Drug-Related Fever, d 1-2	9	6

Drug-Related Hypotension, d 1-2	1	0
Raised Bilirubin Concentration	2	0
Raised Aminotransferase Concentration	1	2
Raised Lipase or Amylase Concentration	1	0
Mucositis	1	0
VOD in Patients with Allogenic Stem Cell Transplant	5/22	1/14

Dose Selection (Study B1931010)

The applicant implemented fractionated inotuzumab ozoagamicin dosing in study B1931010, which was a combined phase 1 dose escalation/ expansion and phase 2 study. In the dose escalation phase, study subjects were treated with escalating doses of 1.2 mg/m², 1.6 mg/m², or 1.8 mg/m² to determine the safety, tolerability, preliminary efficacy, and recommended Phase 2 dose of single-agent inotuzumab ozogamicin (Table 9). The study was divided in the 3 parts: dose escalation, dose expansion, and phase 2.

Table 9: Study B1931010 dose escalation and expansion scheme

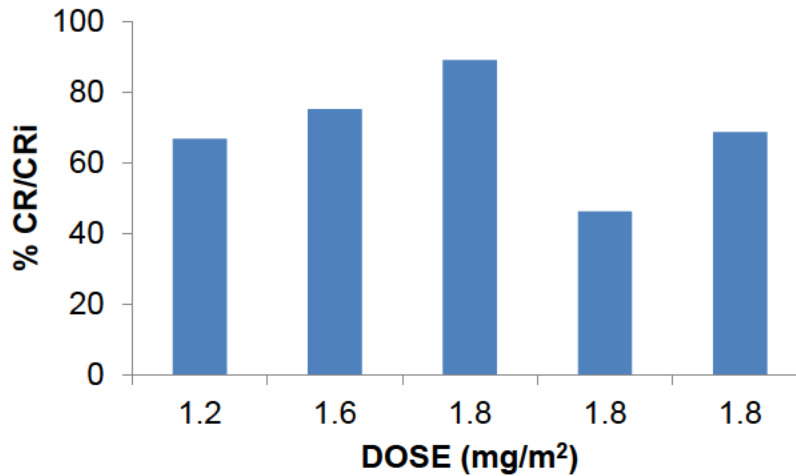
Study Phase	N	Schedule			Dose/Cycle (mg/m ²)
		D1	D8	D15	
1: Dose Escalation	3	0.8		0.4	1.2
	12	0.8	0.4	0.4	1.6
	9	0.8	0.5	0.5	1.8
1: Expansion	13	0.8	0.5	0.5	1.8
2	35	0.8	0.5	0.5	1.8

In the dose escalation part of the study, the rate of CR/CRi was 89% at the 1.8 mg/m² dose level compared to 66.7% at the 1.2 mg/m² dose. Additionally, the duration of remission was substantially longer and the median time to remission was shorter at 1.8 mg/m² (Figure 3).

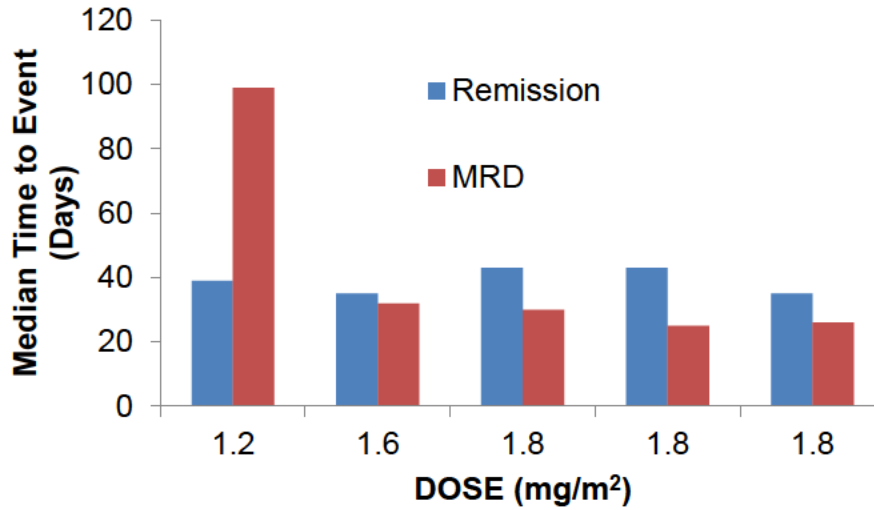
Analysis of the safety data from the dose escalation part did not identify a correlation between dose and the rate of grade 3+ adverse events or the rate of treatment discontinuation. However, 4 cases of VOD occurred in patients receiving the 1.8 mg/m² dose. Based on the safety and efficacy data, the 1.8 mg/m² dose was selected for the dose expansion and Phase 2 parts of the study.

Data from the dose expansion and phase 2 parts, however, suggest that the efficacy of 1.8 mg/m² may not be substantially higher than that of 1.2 mg/m² (Figure 3). The rate of CR/CRi, median time to MRD, and duration of remission in the expansion and phase 2 portions were similar to values achieved at the lower doses in the dose escalation portion. As such, the dose escalation part of the study did not provide complete information regarding the safety and efficacy properties of inotuzumab ozoagamicin at various dose levels.

(A) USA; Inotuzumab Ozogamicin



(B)



(C)

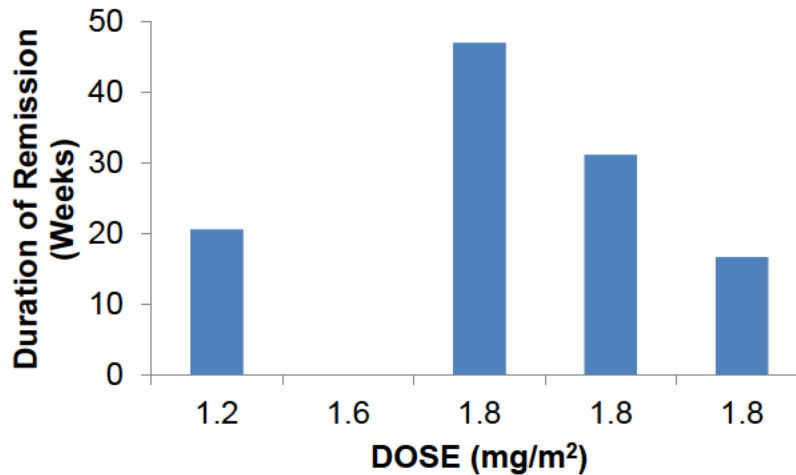


Figure 3: Efficacy results of the dose escalation (1.2 mg/m², 1.6 mg/m², and 1.8 mg/m² in the dose escalation, dose expansion (1.8 mg/m²), and phase 2 (1.8 mg/m²). (A) Rate of CR/CRi. (B)

Median time to remission or MRD negativity. (C) Duration of remission.

Body Surface Area Normalized Dosing

Population PK analysis identified a statistically significant relationship between body surface area and inotuzumab ozogamicin clearance and volume of distribution (see section 13.4.2), thus supporting BSA based dosing. Clearance estimates increased by approximately 36% for BSA of 2.21 m² (90th percentile) and decreased by 24% at BSA of 1.56 m² (10th percentile), relative to the typical value at 1.84 m². Similarly, volume of distribution estimates increased by 28.8% for BSA of 2.21 m² and decreased by 21.6% at BSA of 1.56 m², relative to the typical value at 1.84 m².

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The data and information are insufficient to determine whether the proposed dose of inotuzumab ozogamicin is appropriate. As detailed above, the 1.8 mg/m² dose was selected for the pivotal trial evaluation based efficacy data from the phase 1/2 trial. The pivotal trial B1931022 was an open-label, randomized, multi-center, global study of inotuzumab ozogamicin compared to control treatment (physician's choice) in adult subjects with relapsed or refractory CD22+ B-cell ALL in Salvage 1 or 2. The primary endpoints were CR/CRi and overall survival. The CR/CRi rate was 73.2% (95% CI: 65.7-79.8%) in the inotuzumab ozogamicin arm and 30.9% (95% CI: 23.9-38.6%) in the control arm. The stratified hazard ratio for overall survival was 0.77 (95% CI: 0.578 - 1.026) and the unstratified hazard ratio was 0.748 (95% CI: 0.563 – 0.993).

Exposure-efficacy relationship

Exposure-response analyses for safety and efficacy were conducted using data collected from the Phase 3 trial at a dose of 1.8 mg/m² (n = 164) and the supportive phase 1/2 trial at doses of 1.2 mg/m² (n=2), 1.6 mg/m² (n=12), and 1.8 mg/m² (n =57). Based the data are primarily obtained from a single dose level trial, the exposure-response information presented herein should be interpreted with caution. Detailed exposure-response data sources and analyses are described in section 13.4.1).

Exposure-response analysis for efficacy identified a positive correlation between the cumulative AUC in the first cycle (cAUCP1) and average concentration (C_{AVG}), defined as the cumulative AUC during treatment normalized by the time duration, and the probability of achieving CR/CRi (**Figure 4** and **Figure 5**).

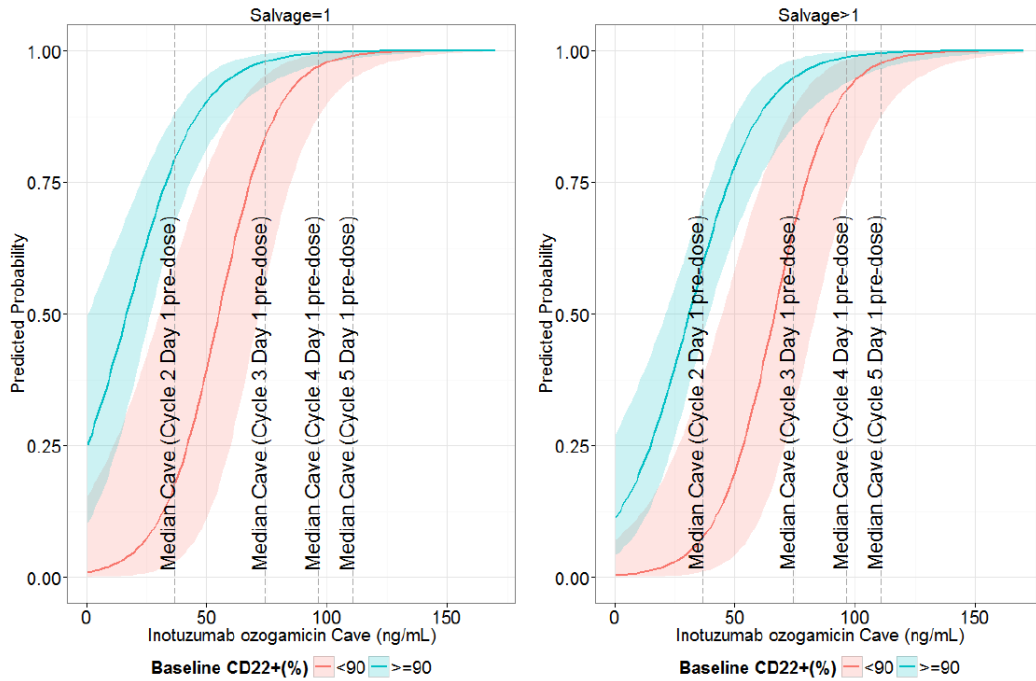


Figure 4: Predicted probability of CR/CRi response with Inotuzumab Ozogamicin treatment for C_{AVG} when stratified by prior salvage therapy or percent CD22-positivity. *Source: report PMAR-EQDD-B193a-DP4-205 applicant's exposure-response analysis.*

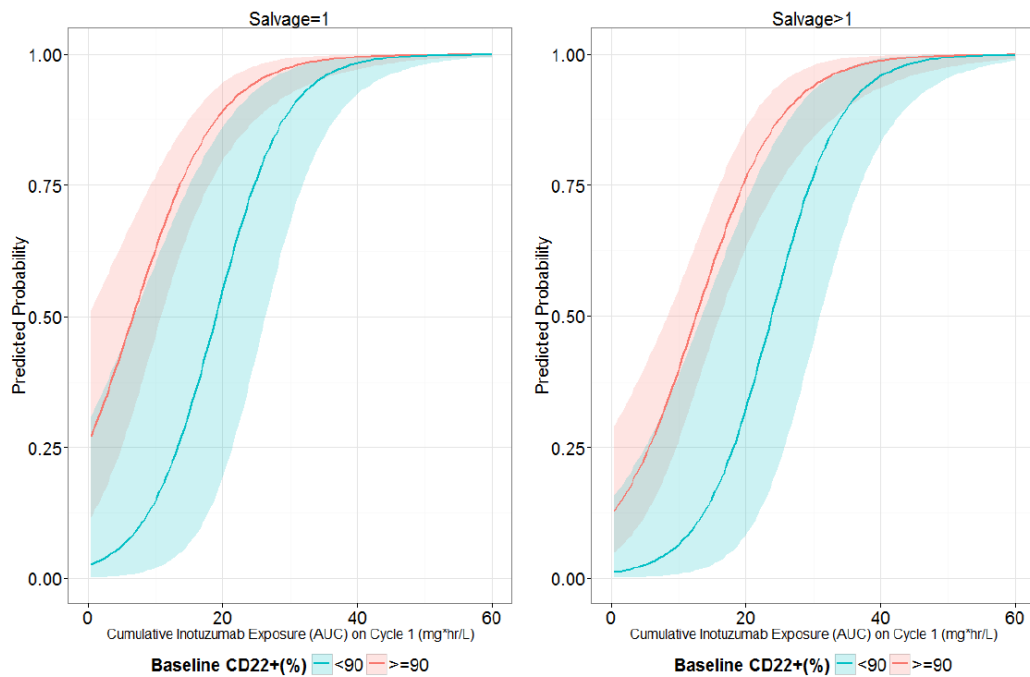


Figure 5: Predicted probability of CR/CRi response with Inotuzumab Ozogamicin treatment for $cAUC_{P1}$ when stratified by prior salvage therapy or percent CD22-positivity. *Source: report PMAR-EQDD-B193a-DP4-205 applicant's exposure-response analysis.*

The probability of achieving CR/CRi was also influenced by the number of prior salvage therapies (1 vs >1) and percentage of CD22-positivity. The probability of achieving CR/CRi was higher in patients with only one prior salvage therapy and >90% CD22+ leukemic blasts at baseline. Based on the goodness-of-fit criteria and the evaluation of model diagnostics, C_{AVG} was the better predictor of probability of CR/CRi compared to $cAUCP1$.

Exposure-Safety Relationship

The rates of grade 3+ adverse events and the most common adverse events (thrombocytopenia, neutropenia, anemia, leukopenia, and febrile neutropenia) were either similar or more favorable in the inotuzumab arm compared to the control arm. However, the rate of VOD was higher in the inotuzumab arm (13.4%) compared to the control arm (0.1%). In the subset of patients who proceeded to HSCT, the rate of VOD was substantially higher in the inotuzumab arm (22.1%) compared to the control arm (3.1%).

Exposure-response analysis for safety did not identify a relationship between inotuzumab exposure and grade 3+ ALT, grade 3+ AST, grade 3+ bilirubin, or hepatic events (defined by a pre-specified cluster term). However, there was a statistically significant relationship between the $AUCP1$ and HEAB-assessed VOD/ sinusoidal obstruction syndrome (SOS) (**Figure 6**). Post-treatment HSCT therapy was also found to be a statistically significant predictor of VOD. For more details refer to the Appendices.

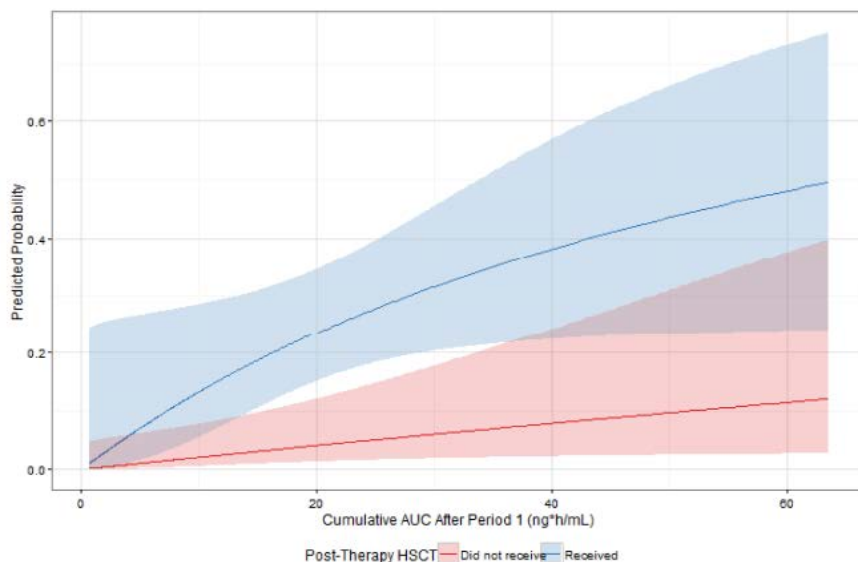


Figure 6: Predicted probability of HEAB-assessed VOD/SOS as a function of cumulative AUC after the first cycle of treatment ($cAUCP1$). Source: report PMAR-EQDD-B193a-DP4-205 applicant's exposure-response analysis.

Collectively, data from the pivotal efficacy study support the clinical benefit of inotuzumab ozogamicin in B-cell precursor ALL at the proposed dose of 1.8 mg/m^2 . However, due to the very high rate of VOD and the corresponding post-HSCT non-relapse mortality (see Clinical Review), the dose of inotuzumab ozogamicin needs to be further optimized. The applicant will be asked to conduct a post-marketing dose finding study. Prior clinical experience with the

similar ADC gemtuzumab ozogamicin—a CD33 mAb linked to calicheamicin—in patients with AML demonstrated that the rates of VOD increased from 1% at the time of approval to 10% at the time of withdrawal (15% in patients who progressed to SCT). Compiled data from the FDA mandated Prospective Observational Registry, FDA Adverse Events Reporting Systems, The Research on Adverse Drug Events and Reports (RADAR), and Southern Network on Adverse Reactions (SONAR) databases demonstrated that the rate of VOD decreased from 15% at the approved 9 mg/m² dose to 3% at doses ≤ 6 mg/m² (PMID:27030962). (b) (4)

previously labeled dose of gemtuzumab ozogamicin (9 mg/m²) and the proposed dose of inotuzumab ozogamicin (1.8 mg/m²). Therefore, the gemtuzumab ozogamicin experience suggests a lower dose of inotuzumab ozogamicin may lead to lower rates of VOD, which will be explored in the agency proposed PMR study.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No, an alternative dosing regimen and management strategy is not required based on age, sex and race. Refer to section “13. **Error! Reference source not found.** Population PK Analysis” for a detailed discussion.

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Renal Impairment

No dose adjustment is required for patients with renal impairment. The effect of renal function on inotuzumab ozogamicin clearance was evaluated using baseline creatinine clearance (BCCL) in patients with normal renal function (n=377), mild (n= 234), moderate (n=121), and severe impairment (n=4). Renal impairment did not influence CL of inotuzumab ozogamicin (**Figure 7**). Additionally, calicheamicin exhibited minimal clearance in the urine in preclinical species and is not likely to be excreted in the urine based on *in vitro* studies.

The rate of thrombocytopenia, neutropenia, VOD, and ALT adverse events was similar among patients with normal, mild, or moderate renal impairment in the phase 3 trial (**Figure 8**). Similarly, the rate of discontinuation due to adverse events was not correlated with normal (13%), mild (18%), and moderate (0%) renal impairment.

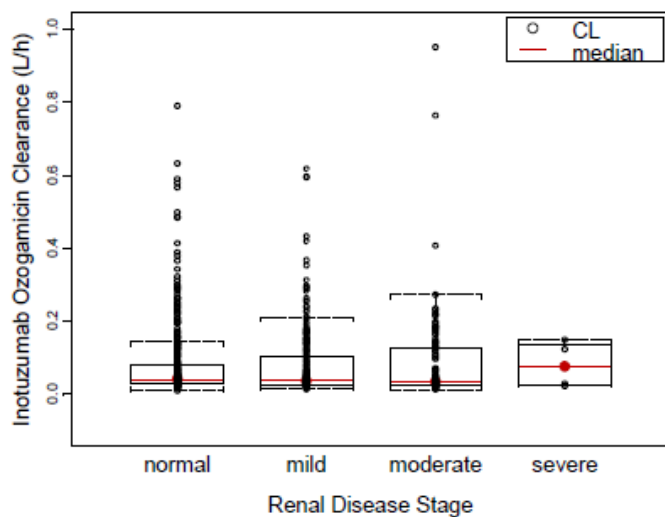


Figure 7: Renal impairment stage does not impact inotuzumab ozogamicin clearance. *Source:* report PMAR-EQDD-B193a-DP4-202 applicant’s population PK analysis.

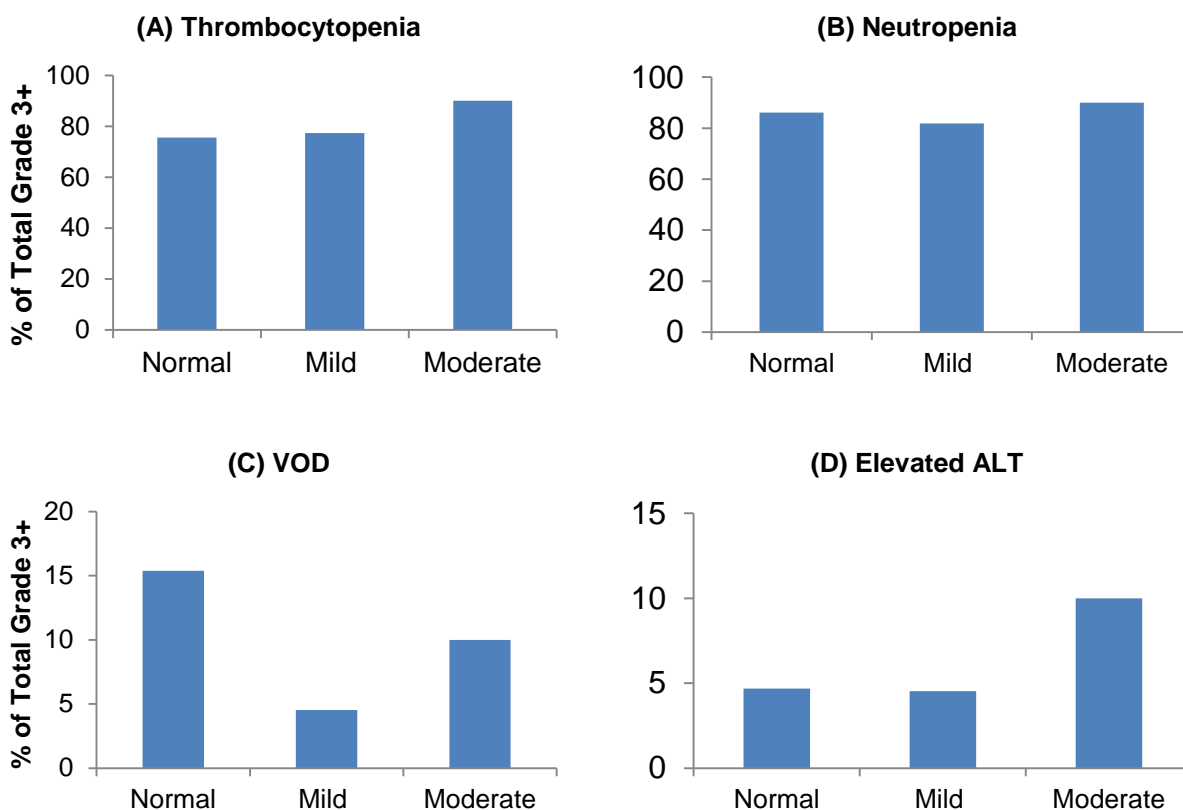


Figure 8: Frequency of grade 3+ thrombocytopenia (A), neutropenia (B), VOD (C), or elevated ALT (D) in patients with normal, mild, or moderate renal impairment

Hepatic Impairment

No dose adjustment is required for patients with hepatic impairment. The impact of hepatic impairment on the clearance of inotuzumab ozogamicin was evaluated using the hepatic function defined by the NCI ODWG (normal [A], mild [B1], mild [B2], moderate [C], and severe [D]) as categorical covariate and baseline laboratory values of BALT, BAST, and BBIL as continuous covariates in the population PK model (section 13.4.2). Hepatic impairment stage classifications and distributions of patients included in the population PK analysis are summarized in **Table 10**.

Table 10: Classification and distribution of patients among with hepatic impairment

N	NCI ODWG	BIL	AST
611	Normal (A)	≤ ULN	≤ ULN
133	Mild (B1)	≤ ULN	> ULN
17	Mild (B2)	> 1.0 – 1.5	Any level
3	Moderate (C)	> 1.5 – 3	Any level
1	Severe (D)	> 3	Any level

Hepatic impairment was not a significant covariate on the CL of inotuzumab ozogamicin; CL was similar in patients with different hepatic impairment stages (**Figure 9**).

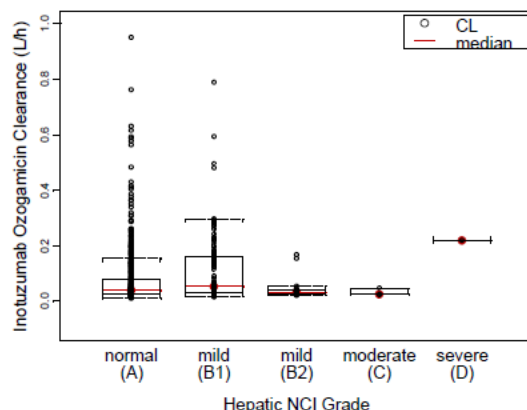


Figure 9: Hepatic impairment does not impact inotuzumab ozogamicin clearance. *Source: report PMAR-EQDD-B193a-DP4-202 applicant’s population PK analysis.*

The rate of thrombocytopenia, neutropenia, VOD, and ALT adverse events was not correlated with the hepatic impairment status (**Figure 10**). Additionally, the rate of treatment discontinuation due to adverse events was similar between patients with normal (13/121) and mild hepatic impairment (7/41) in the phase 3 trial. Only a single patient had severe hepatic impairment, which precluded safety analysis in this population.

Due to the hepatotoxicity observed with inotuzumab ozogamicin, liver function tests are closely monitored in patients, especially patients with liver disease, as per the product label. Dose interruption is recommended for patients with total bilirubin > 1.5 x ULN and AST/ALT > 2.5 x ULN prior to each dose unless due to Gilbert’s syndrome or hemolysis. The recommendation is based on the adverse event profile of inotuzumab ozogamicin and because

there are no safety data for patients with total bilirubin $>1.5 \times \text{ULN}$ and AST/ALT $> 2.5 \times \text{ULN}$, which was one of the exclusion criteria in the pivotal efficacy trial.

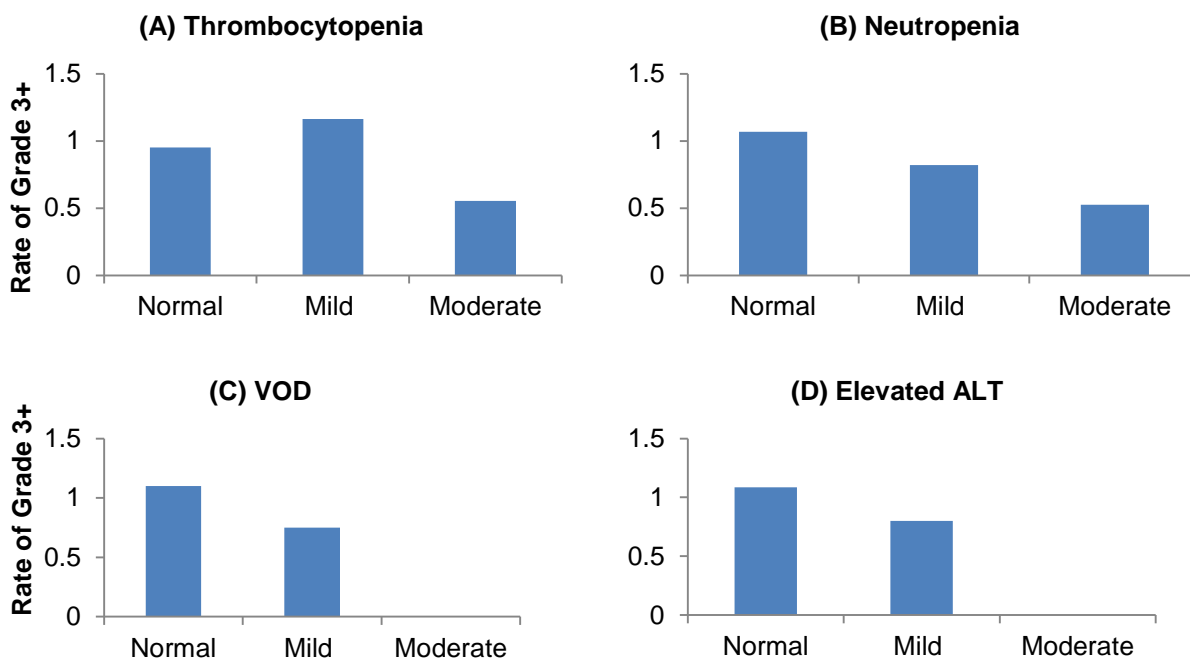


Figure 10: Frequency of grade 3+ thrombocytopenia (A), neutropenia (B), VOD (C), or elevated ALT (D) in patients with normal, mild, or moderate hepatic impairment.

The proposed lack of dose adjustment for patients with hepatic impairment is acceptable given the close monitoring of liver tests in all patients and proposed dose interruptions for patients with elevated AST/ALT and bilirubin. Additionally, a dedicated trial of inotuzumab, with such a hepatotoxic profile, in patients with moderate and severe hepatic impairment is unethical.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

There are no clinically relevant drug-drug interactions anticipated based on the *in vitro* screening.

N-acetyl- γ -calicheamicin is metabolized via non-enzymatic reduction, with no CYP450 isozymes or UGT enzymes involvement. Additionally, *in vitro* studies demonstrated that inotuzumab ozogamicin and unconjugated N-acetyl- γ -calicheamicin inhibit CYP450 isozymes and UGT enzymes at concentrations that are orders of magnitude higher than the anticipated clinical C_{MAX} . Similarly, unconjugated calicheamicin demonstrated low potential to inhibit P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, and OCT2 *in vitro*.

The population PK modeling (see section 13.4.2) did not identify statistically significant covariates affecting inotuzumab ozogamicin clearance due to interaction with other drugs. The investigated drugs are summarized in **Table 11**. According to the population PK model, treatment with rituximab decreased the clearance of inotuzumab ozogamicin in patients with

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NHL by 16% (95% CI: 5.47%-26.5%). Conclusions from the population PK analyses should be interpreted with caution and are only considered supportive. The administration of concomitant medications relative to that of inotuzumab was not included in the model. Concomitant medications were included as a dichotomous variable.

Table 11: Drugs included in the population PK assessment of DDI

Class	Number of Patients (%)	Drugs
Reducing Agents	12 (1.65%)	Hydroxyurea
G-CSF	166 (22.6%)	Filgrastim or lenograstim
Pgp Inhibitors	125 (17%)	Amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporin, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir, ritonavir, quercetin, quinidine, ranolazine, ticagrelor, and verapamil

Salaheldin S. Hamed, Ph.D.
Clinical Pharmacology V
Primary Reviewer

Bahru Habtemariam, Pharm.D.
Clinical Pharmacology V
Team Leader

7 Statistical and Clinical and Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Studies

The Applicant submitted clinical study reports from 11 clinical trials that administered inotuzumab ozogamicin (Table 7). Two studies were of inotuzumab ozogamicin in patients with relapsed or refractory B-Cell ALL. Nine additional studies of inotuzumab ozogamicin alone or in combination with rituximab with or without chemotherapy in patients with Non-Hodgkin Lymphoma were also included in this submission. Raw datasets for clinical review were submitted for the 11 studies.

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Table 12: Listing of Clinical Trials Relevant to this BLA

Trial Identity	Trial Design(Primary Endpoint)	Regimen/schedule/ route	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
<i>Pivotal Study</i>						
B1931022 (Study 1022)	Phase 3, randomized, open-label study of Inotuzumab Ozogamicin compared to a defined investigator's choice (Primary Endpoints: CR/CRi and OS)	Inotuzumab: 1.8mg/m ² 21-28 days cycle 1(0.8mg/m ² on Day 1 and 0.5mg/m ² on Days 8 and Day 15), subsequent reduction to 1.5mg/m ² /28-day cycle 2(0.5mg/m ² on Days 1,8,15) for patients achieving remission	Until PD or relapse or unacceptable toxicity	326 (164 in inotuzumab arm)	Relapsed and Refractory Acute Precursor B-cell Lymphoblastic Leukemia	108 sites and 18 countries
<i>Study to Support Efficacy and Safety</i>						
B1931010 (Study 1010)	Phase 1/ 2, open-label study (Safety and RP2D and efficacy/CR/CRi)	Phase 1: dose finding(1.2-1.8mg/m ² Phase 2: 1.8mg/m ² 21-28 days cycle(0.8mg/m ² on Day 1 and 0.5mg/m ² on Days 8 and Day	Until PD or relapse or unacceptable toxicity	72(48 treated at recommended dose)	Relapsed and Refractory Acute B-Cell Precursor Lymphoblastic Leukemia	8 Sites from North America (USA)

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Trial Identity	Trial Design(Primary Endpoint)	Regimen/ schedule/ route	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
15						
<i>Studies to Support Safety In Patients with Non-Hodgkin Lymphoma(NHL) who received single-agent inotuzumab ozogamicin</i>						
B1931002	Phase 1, open-label, single arm(Safety)	Part 1 3 week cycle 0.4mg/m ² , 0.8mg/m ² , 1.34mg/m ² , 1.8mg/m ² and 2.4mg/m ² Part 2: 1.8mg/m ²	Until PD or relapse or unacceptable toxicity	79	Relapsed or refractory NHL	17 sites and 7 countries
B1931016	Phase 1, open label, single arm(Safety)	1.3mg/m ² /4 week cycle or 1.8mg/m ² /4 week cycle	Until PD or relapse or unacceptable toxicity	13	Relapsed or refractory NHL	3 sites and one country (Japan)
B1931007	Phase 2 open label single arm(ORR)	1.8mg/m ²	Until PD or relapse or unacceptable toxicity	81	Relapsed or refractory indolent NHL	27 and 9 countries
<i>Studies to Support Safety in Patients with NHL who received inotuzumab ozogamicin with rituximab</i>						
B1931005	Phase 1 open label, single arm(Safety)	Rituximab 375mg/m ² Inotuzumab 1.8mg/m ² on Day 2	Until PD or relapse or unacceptable toxicity	10	Relapsed or refractory NHL	4 sites and 1 country (Japan)
B1931004	Phase 1/2 , open-label, single arm(Safety/ORR)	Rituximab 375mg/m ² Inotuzumab on Day 2:	Until PD or relapse or unacceptable toxicity	119	Relapsed or refractory NHL	28 sites and 12 countries

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Trial Identity	Trial Design(Primary Endpoint)	Regimen/ schedule/ route	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		0.8mg/m ² , 1.3mg/m ² and 1.8mg/m ²				
B1931001	Phase 2, open-label, single arm (safety and ORR)	Rituximab 1.8mg/m ² Inotuzumab: 1.8mg/m ²	Until PD or relapse or unacceptable toxicity	63	Relapsed or refractory CD22-positive diffuse large B-cell lymphoma	22 sites and 6 countries
B1931006 (Study 1006)	Phase 3, open-label study of inotuzumab ozogamicin in combination with rituximab compared to defined Investigator's choice of therapy(PFS)	Arm 1: Rituximab 375mg/m ² On day 1 of 4 week cycle Arm 2: R-CVP or R-FND	Until PD or relapse or unacceptable toxicity	29	Relapsed or refractory follicular B-Cell NHL	20 sites and 9 countries
B1931008 (Study 1008)	Phase 3, open-label, randomized study of inotuzumab ozogamicin in combination with rituximab compared to defined Investigator's choice of therapy(OS)	Arm 1: Rituximab 375mg/m ² on day and inotuzumab 1.8mg/m ² on Day 2 of 4 week cycle Arm 2: Rituximab plus bendamustine or gemcitabine	Until PD or relapse or unacceptable toxicity	338	Relapsed or refractory aggressive NHL not candidates for high dose chemotherapy	113 sites and 24 countries
<i>Study to support safety In patients with NHL who received inotuzumab ozogamicin in combination with rituximab plus chemotherapy</i>						

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Trial Identity	Trial Design(Primary Endpoint)	Regimen/schedule/ route	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
B1931003	Phase 1, open-label study of R-CVP or R-GDP(safety)	Arm 1: Inotuzumab 0.8mg and 1/3mg/m ² + R-CVP in 3 week cycle Arm 2: inotuzumab 0.8mg/m ² +R-GDP in 3 week cycle	Until PD or relapse or unacceptable toxicity	103	Relapsed or refractory NHL	17 sites and 9 countries

Source: FDA synopses of individual studies provided by the Applicant in Module 2.7.6

7.1.2. Review Strategy

The FDA clinical and statistical review consisted of one primary clinical reviewer and one primary statistical reviewer.

The key materials used for the review of efficacy and safety include the following:

- BLA 761040
- Relevant published literature
- Relevant information in the public domain

The review of efficacy was primarily based on analysis of Study 1022 and supported as follows:

- Efficacy data from Study 1010 was used to support the analysis of dose selection
- Summarized efficacy data from study 1010
- Efficacy data from Study 1006 and Study 1008 were used to include lack of efficacy in patients with NHL.

The primary review of safety was based on the pivotal trial (Study 1022) and the supportive efficacy and safety study (1010). Due to differences in dosing regimens, different diseases and patient populations, only the NHL studies that used single-agent inotuzumab ozogamicin were reviewed for supportive safety analysis. These studies include B1931002, B1931007 and B1931016. Refer to table 7 for further details.

- Individual study data from Study 1022
- Review and assessment of Applicant analyses of Study 1022 efficacy and safety in the Clinical Study Report
- Review of datasets submitted as SAS transport files
- Review of minutes of key meetings conducted during inotuzumab ozogamicin clinical development
- Pooled safety data from Study 1010 and Study 1022 to support the analysis of the proposed patient population and proposed dose.
- Pooled safety data from single agent inotuzumab ozogamicin studies to look for potential safety signals.

All major efficacy and safety analyses were reproduced or audited. Summaries of data and statistical analyses by the reviewer were performed using SAS version 9.4 and JMP 12.0(SAS institute, Cary, NC). MedDRA Adverse Events Diagnostic 1.3(MAED)(FDA, Silver Spring, MD) was used to look for safety signals.

Data and Analysis Quality

The applicant submitted this BLA including the data to the FDA CDER Electronic Document Room (EDR). The data in this submission are in electronic Common Technical Document (eCTD)

format, in accordance FDA guidance on electronic submission. The data sets were well documented and included definition files. The clinical study reports and datasets are located at the following location:

[\\CDSESUB1\EVSPROD\BLA761040\761040.ENX](#)

Upon further clarifications from the applicant's per FDA's information requests (IRs), the reviewers were able to:

- Reproduce the applicant's analysis and analysis results
- Evaluate documentation of data quality control/assurance procedures
- Conduct FDA sensitivity analyses

7.2. Review of Relevant Individual Trials Used to Support Efficacy

Study B1931022: 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 Leukemia (ALL)

Trial Design

B1931022 (also referred to as Study 1022) was a multicenter, global, open-label, 2-arm randomized (1:1) phase 3 study, designed to compare the efficacy of inotuzumab ozogamicin (Arm A, investigational arm) versus defined Investigator's choice of chemotherapy (Arm B, control arm), in adult patients with relapsed or refractory CD22-positive B-cell ALL due to receive either Salvage 1 or 2 treatment. Defined Investigator's choice of chemotherapy (control arm therapy) was included either fludarabine + cytarabine + granulocyte-colony stimulating factor (G-CSF) (FLAG), mitoxantrone + cytarabine (MXN/Ara-C), or high-dose cytarabine (HIDAC).

Patients in Arm A were treated with inotuzumab ozogamicin at a starting dose of 1.8 mg/m² (according to BSA) per cycle with a divided-dose regimen using 3 weekly administrations. Patients received 0.8 mg/m²/cycle on Week 1 (Day1), following by 0.5mg/m² on Week 2 (Day8) and Week 3 (Day 15) of a 21-day cycle administered as an intravenous (IV) infusion over 60 minutes. For patients who achieved a CR or CRi, or to allow recovery from toxicity, the length of Cycle 1 could be extended up to 28 days (i.e., 1 week treatment-free interval starting on Day 21). For patients who achieved CR or CRi, the Week 1 dose was reduced to 0.5mg/m² (for a total dose of 1.5mg/m²/cycle)for Cycles 2 through 6 (maximum number of cycles permitted). For Cycle 2 through 6, the cycle length was 28 days for all patients (regardless of remission status).

Reviewer Comment: Control Group (Comparator Group):

In the salvage setting of ALL, a variety of regimens are used ranging from single agents to

combination therapies. Patients with Ph+ ALL are treated with combinations including tyrosine kinase inhibitors. In this protocol, it is expected that most patients will have been treated with intensive combination chemotherapy and that physicians will select therapies based on patient's condition, prior therapies and standard practice. The comparator arm includes a defined list of 3 induction chemotherapy regimens commonly used in relapsed and refractory ALL.

Diagnostic Criteria

The patient population consists of patients with relapsed or refractory CD22-positive ALL (>5% marrow blasts) assessed by morphology due to receive either salvage 1 or salvage 2 and for which either arm of the randomized study therapy offers a reasonable option. Patients with Ph+ ALL must have failed at least 1 second or third generation tyrosine kinase inhibitor and standard multi-agent chemotherapy.

Reviewer Comment:

CD22 is expressed in over 90% of lymphoblasts in patients with ALL. Standard diagnostic evaluation of patients with relapsed or refractory ALL includes flow cytometry or immunohistochemistry both of which include analysis of CD22. Given the routine testing of CD markers in the diagnostic evaluation of patients with ALL and the high prevalence of CD22 positivity in lymphoblasts this reviewer recommends no restriction on CD22+ testing.

Patients were stratified at randomization based on the following baseline characteristics:

- Duration of first remission (<12 months or ≥12 months);
- Salvage treatment that the patient was to receive on study (Salvage 1 or 2);
 - Salvage 1 was defined as therapy given in response to morphological relapse after initial treatment or resistant disease (no CR or CRi) after initial treatment;
 - Salvage 2 was defined as therapy given in response to morphological relapse after Salvage 1 therapy or resistant disease (no CR or CRi) after Salvage 1;
- Patient age at randomization (<55 or ≥55 years).

Patients were allowed to receive study treatment for up to 6 cycles of inotuzumab ozogamicin and for up to 4 cycles of the Investigator's choice of FLAG or MXN/Ara-C, and up to 2 cycles of HIDAC; these regimens are all considered to be standard of care. Study drug(s) could be discontinued at any time due to initiation of new anti-cancer therapy (ie, conditioning for HSCT), disease progression, patient refusal, or unacceptable toxicity, whichever occurred first. Patients who achieved a response to treatment and who had a suitable donor could proceed to allogeneic HSCT at the discretion of the Investigator and were followed for disease progression and survival. Patients whose treatment was stopped early due to toxicity or other reasons were followed for safety, disease progression and survival. Use of anti-cancer treatments, other than those allowed by the protocol, were prohibited during the active treatment phase. After discontinuation of study treatment, subsequent anti-cancer therapy was per Investigator's discretion.

Following discontinuation of study treatment, patients were followed for:

- Disease progression for up to 2 years from randomization, unless the patient progressed during treatment;
- Potential onset of VOD/SOS, irrespective of grade, causality or treatment arm for up to 2 years from randomization ;
- Survival for up to 5 years or 2 year from randomization of the last patient, whichever occurred first.

The study was planned to be conducted in approximately 190 sites over a period of approximately 4 years.

Primary Efficacy Endpoint

The study has two primary endpoints which include hematologic remission (CR+CRi) assessed by the Endpoint Adjudication Committee (EAC) and OS.

Hematologic remission (CR/CRi) assessed by EAC

CR was defined as disappearance of leukemia as indicated by <5% marrow blasts and the absence of peripheral blood leukemic blasts, with recovery of hematopoiesis defined by absolute neutrophil count (ANC) $\geq 1000/\mu\text{L}$, platelets $\geq 100,000/\mu\text{L}$, and resolution of any extramedullary disease.

CRi was defined as CR except with absolute neutrophil count (ANC) $< 1000/\mu\text{L}$ and/or platelets $< 100,000/\mu\text{L}$.

In addition to assessment by the EAC, remission was also assessed by investigators.

Overall survival

OS was defined as the time from randomization to death due to any cause. For patients last known to be alive, OS was censored at date of last contact.

Reviewer's Comments

As stated in the protocol CR/CRi was referred to as the primary endpoint and OS was referred to as a key secondary endpoint. In SAP v3.0, it was clarified that OS was 1 of the 2 primary endpoints.

Secondary Efficacy Endpoints

Secondary endpoints include the following

- Progression-free survival (PFS): defined as time from date of randomization to earliest date of the following events:
 - Death
 - Progressive disease
 - Objective progression
 - Relapse from CR/CRi
 - Treatment discontinuation due to global deterioration of health status
 - Starting new induction therapy or post-therapy SCT without achieving CR/CRi.

Observations for subjects without a PFS event at time of analysis were planned to be censored at the last valid disease assessment. In addition, observation for subjects with documentation of an event after an unacceptably long 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 would be censored at the time of the previous assessment (date of randomization if no post-baseline assessment). Post-study treatment follow-up disease assessments would be included. In addition duration of remission and minimal residual disease status were also captured.

- Duration of remission (DoR)
DoR is defined as time from date of first response in responders (CR/CRi by investigator assessment) to date of PFS event (see definition of PFS endpoint above). Responders without PFS event were censored at the last valid disease assessment including follow-up disease assessment. Note: DoR is defined as duration of response in the protocol, but is changed to duration of remission in this SAP.
- Minimal residual disease (MRD) levels (positive, negative) and cytogenetics in patients achieving a CR/CRi (investigators assessed and centrally reviewed).

Key Inclusion Criteria (summarized)

- Relapsed or refractory CD22-positive ALL($\geq 5\%$ marrow blasts, assessed by morphology) due to receive either salvage 1 or salvage 2 therapy and for which either arm of randomized study therapy offers a reasonable option.
- Ph+ ALL patients must have failed treatment with at least 1 second or third generation tyrosine kinase inhibitor and standard multi-agent induction chemotherapy.
- Patients in salvage 1 with late relapsed should be deemed poor candidates for re-induction with initial therapy.
- Patients with lymphoblastic lymphoma and bone marrow involvement $\geq 5\%$ lymphoblasts by morphological assessment.
- Age ≥ 18 years
- Eastern Cooperative Oncology Group(ECOG) PS of 0-2.
- Adequate liver function including total serum bilirubin ≤ 1.5 x upper limit of normal (ULN) unless the patient has Gilbert syndrome and AST and ALT ≤ 2.5 x ULN. If organ function abnormalities are considered due to tumor, total serum bilirubin must be ≤ 2 x ULN and AST/ALT ≤ 2.5 x ULN.
- Serum creatinine ≤ 1.5 x ULN or any serum creatinine level associated with a measured or calculated creatinine clearance of ≥ 40 ml/min.
- Male or female patients of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception throughout the study and for a minimum of 90 days after the last dose of assigned treatment.

Key Exclusion Criteria

- Isolated extramedullary relapse

- Burkitt's or mixed phenotype acute leukemia based on the WHO 2008 criteria.
- Active central nervous system(CNS) leukemia, use of CNS-directed local treatment for active disease within 28 days prior, symptomatic CNS leukemia within 28 days. Prophylactic intrathecal medication is not a reason for exclusion.
- Prior chemotherapy within 2 weeks before randomization with the following exceptions:
 - To reduce circulating lymphoblast count or palliation.
 - For ALL maintenance: mercaptopurine, methotrexate, vincristine, thioguanine and /or tyrosine kinase inhibitors.
- Patients must have recovered from acute non-hematological toxicity(to $\leq$ Grade 1) of all previous therapy prior to enrollment.
- Prior monoclonal antibodies within 6 weeks of randomization with the exception of rituximab which must be discontinued at least 2 weeks prior to randomization.
- Prior allogeneic hematopoietic stem cell transplant (HSCT) or other anti-CD22 immunotherapy $\leq$ 4 months before randomization.
- Known systemic vasculitides, primary or secondary immunodeficiency.
- Current or chronic hepatitis B or C infection or known seropositivity for human immunodeficiency virus (HIV).
- Cardiac function as measured by left ventricular ejection fraction(LVEF) that is less than 45% or the presence of New York Heart Association stage III or IV congestive heart failure.
- QTcF $>$ 470msec(based on average of 3 consecutive ECGs).
- Myocardial infarction within $\leq$ 6 months before randomization.
- History of clinically significant ventricular arrhythmia or unexplained syncope.
- Uncontrolled electrolyte disorders that can compound the effects of a QTc prolonging drug.
- History of chronic liver disease or history of hepatic VOD.
- Pregnant females, breastfeeding females, males and females of childbearing potential not using highly effective contraceptive techniques or not agreeing to continue highly effective contraception for a minimum of 90 days after the last dose of investigational product.

Dose Modification and Delays

Patients in inotuzumab ozogamicin and control arm must meet the following criteria prior to the start of each cycle or else all study therapy will be delayed:

- No evidence of progressive disease(PD)
- Decrease in blast percentage or stable disease
- Recovery to grade 1 or baseline non-hematologic test article-related toxicity
- Serum bilirubin $\leq$ 1.5 x ULN(or if elevated due to tumor, bilirubin $\leq$ 2 x ULN and AST, ALT $\leq$ 2.5 x ULN irrespective of the causality(prior to each dose of inotuzumab ozogamicin).
- Serum creatinine $\leq$ 2 x ULN or estimated creatinine clearance $\geq$ 40 mL/min as calculated using the method standard for the institution (prior to each dose of inotuzumab ozogamicin).

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- For patients with pre-treatment ANC $\geq 1 \times 10^9/L$: ANC $\geq 1 \times 10^9/L$
- For patients with pre-treatment platelets $\geq 50 \times 10^9/L$; platelets $\geq 50 \times 10^9/L$ and platelets must recover at least to baseline values obtained for the prior cycle, or ANC $> 1 \times 10^9/L$ and platelets $> 50 \times 10^9/L$ 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.
- QTcF ≤ 470 msec(average 3 ECGs)

Inotuzumab ozogamicin dosing should be permanently discontinued for any patients with possible, probable or confirmed VOD or other severe liver toxicity. For inotuzumab ozogamicin, dose delays ≥ 7 days, will result in omission of the next dose within the cycle; the patient remains eligible to receive the subsequent planned dose assuming all dosing criteria are met. If a dose within a cycle is delayed, the next dose will be delayed. A minimum of 6 days should be maintained between doses. If the beginning of the next cycle is delayed by more than 28 days of the current cycle, then the day when treatment is restarted will be considered Day 1 of the next cycle. If the beginning of the next cycle is delayed by more than 28 days due to test article-related toxicity/ies study treatment will be permanently discontinued unless otherwise agreed by sponsor and investigator.

Dose Reductions

In the inotuzumab ozogamicin arm, patients experiencing a treatment interruption due to test article-related toxicity ≥ 14 days will resume dosing with a single 25% reduction in inotuzumab ozogamicin for the subsequent cycle ($0.5\text{mg}/\text{m}^2$ to $0.375\text{mg}/\text{m}^2$) once adequate recovery is achieved. If further dose modification is indicated after a 25% dose reduction, the number of doses within the cycle should be reduced to two for subsequent cycles. Dose reductions of inotuzumab ozogamicin by 25% are recommended for patients with CRi, whose platelet counts have not recovered to those values obtained prior to the start of previous cycle.

Dose reductions or omissions of drug for Arm B (investigator choice arm) should be based on institutional guidelines or standard of care.

Concomitant Medications

The use of hydroxyurea is permitted for temporary control of WBC elevations in patients with aggressive disease both prior and during the first 5 days of study treatment. Reduction of peripheral blast counts to at least 10,000/uL is required for randomization and may improve the initial PK profile of inotuzumab ozogamicin. Concurrent therapy for CNS prophylaxis treatment is strongly encouraged. Growth factors such as granulocyte-colony stimulating factor(G-CSF), including pegfilgrastim and GM-CSF may be used as supportive care with each cycle if clinically indicated after the last dose of study drug or chemotherapy in accordance with local guidelines and medical practice.

Prohibited concomitant medications: craniospinal radiation (CSXRT) is prohibited during study treatment. Medications known to predispose to Torsade's de Pointes are prohibited throughout the treatment period of study.

Administrative Structure

The study also used an external Hepatic Events Adjudication Board which reviewed safety data with respect to hepatic events. The HEAB was a blinded external expert advisory group composed by a chair and 2 other board members (all board certified hepatologists with expertise in VOD/SOS and drug induced liver injury (DILI) established to adjudicate hepatobiliary events occurring in Study 1022 as detailed in the HEAB Charter.

Definition of VOD on protocol

VOD was defined in Study 1022 as the occurrence of 2 out of the following clinical criteria: total serum bilirubin level >2.0mg/dL, an increase in liver size from baseline or development of right upper quadrant pain of live origin, sudden weight gain >2.5% due to fluid accumulation in the weeks following infusion of study drug or chemotherapy, or HSCT conditioning/preparative regimen or development of ascites not present at baseline following such exposures, and the absence of other explanations for these signs and symptoms. In addition, VOD was also defined as development of bilirubin elevation, weight gain or hepatomegaly plus histologic abnormalities on liver biopsy demonstrating hepatocyte necrosis in zone 3 of the liver acinus, sinusoidal fibrosis and centrilobular hemorrhage with or without fibrosis of the terminal hepatic venules.

Statistical Analysis Plan

Sample Size and Power

The sample size was calculated to assess the difference between the 2 treatment arms in hematologic remission (CR/CRi) and OS separately by splitting 1-sided alpha of 0.025 evenly between the 2 primary endpoints.

Based on a review of the literature, the expected CR/CRi rate in the control arm (first and second salvage setting) was approximately 37% assuming that up to one third of patients may receive Salvage 2. Remission rates in the Salvage 1 setting have typically been reported between 30% and 50% with remission rates in the Salvage 2 setting being typically much lower at around 16% to 18%. With 218 patients, the study had at least 88.5% power to detect a difference of response probabilities between 61% in inotuzumab ozogamicin arm versus 37% in the control arm for 1-sided alpha=0.0125 for the analysis based on the intent to treat population (ITT). In order to maintain design properties, the original sample size was increased in protocol Amendment 3 (dated 28 March 2014) due to a higher than expected number of early discontinuations after randomization in the control arm prior to dosing, and also due to a higher number of patients lost to survival follow-up for those randomized to the control arm.

The study was also designed to detect a difference in OS (hazard ratio [HR] 0.67 corresponding to 50% improvement in OS, i.e., this translated to an improvement in the median survival from 4.30 months on defined Investigator's choice of chemotherapy to 6.45 months on inotuzumab ozogamicin) with 80% power for 1-sided $\alpha=0.0125$. Assuming accrual of 2 patients per month for the first 6 months and 9.33 patients per month thereafter, 20% dropout within 15 days and 25% dropout total in the defined Investigator's choice of chemotherapy arm, and 5% dropout total in the inotuzumab ozogamicin arm, a total sample size of 325 patients was required. It was planned that accrual would continue to a target sample size for OS of 325 patients unless the External Data Monitoring Committee eDMC stopped accrual earlier and that the final analysis for OS would be performed after 248 OS events, if accrual of 325 patients was achieved.

For the OS endpoint, the study used a group sequential design with 2 interim analyses with the opportunity to stop the study for futility at the first interim analysis. At the second interim analysis, the study could have been stopped for futility or efficacy. If the second interim analysis occurred at exactly 149 events, the study could be stopped for futility if the p-value (p) was greater than 0.17 or for efficacy if $p < 0.003$.

Analysis Population

Intent-to Treat (ITT) Population: The ITT population included all subjects who are randomized into the study and it was primary population for efficacy evaluation.

Modified Intent-to-Treat (mITT) Population: included all randomized patients who started study treatment.

Per Protocol Population (PP): The PP included patients who met all of the following criteria: randomized and received at least 1 dose of study drug; no major protocol violations and had an adequate baseline disease assessment.

Safety Population: included all randomized subjects who receive at least 1 dose of treatment (either inotuzumab ozogamicin or investigator's choice). This patient population excluded only subjects who never received any treatment or were not randomized.

Missing Data

If any pattern of missing data was identified, the analysis plan stated that additional efforts such as sensitivity analysis will be made to ensure the analysis is not unduly affected by the missing data. For time to event variables, missing data are handled by censoring observations. All subjects would be followed for PFS until a PFS event has occurred or until the data cutoff. Sensitivity analyses may be performed to assess the robustness of the result of the primary analysis of PFS. Patients without post-baseline tumor assessment, including patients who did not receive any treatment, are counted as non-responders (did not achieve CR or CRi) for the

primary analysis. Sensitivity analyses for CR/CRi will be done to address missing response information in patients who discontinue the study prior to treatment

Statistical Methodologies

The 2 primary endpoints (CR/CRi and OS) were tested separately by splitting alpha evenly between them.

Final analysis of hematologic remission (CR/CRi), DoR, and MRD were to be performed after the first 218 randomized patients had been followed for at least 3 months after randomization.

The primary endpoint of OS was planned to be analyzed at 2 interim analyses and final analysis. The 2 planned interim analyses were conducted when approximately 25% and at least 60% of the required OS events were reached (for futility [first interim analyses], and efficacy and futility [second interim analyses]). The final analysis for OS is planned to occur after approximately 248 (100%) of OS events have been reported. The interim OS analysis results are not included in this CSR.

Primary Analysis of CR/CRi

The primary analysis of CR/CRi was based on the ITT218 Population which included the first 218 randomized patients. Patients were analyzed in the randomized treatment arms regardless of the actual treatment given. Patients who did not achieve CR/CRi, including patients who did not receive study treatment, were considered as non-responders.

Assuming delta (Δ) was the true difference in the probability of CR/CRi between the 2 treatment arms (inotuzumab ozogamicin arm versus control arm), the hypotheses were $H_0: \Delta \leq 0$ versus $H_a: \Delta > 0$. 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 $\alpha=0.0125$ significance level. For each treatment arm, the CR/CRi rate along with the 95% CI around the rate was computed. The estimate of Δ and its 97.5% CI was computed. CIs of CR/CRi rates for the 2 treatment arms were computed using the F-distribution method. CIs of Δ was computed using normal approximation.

Sensitivity analysis for CR/CRi

Sensitivity analyses were planned to investigate the robustness of the primary analysis. The sensitivity analyses described below were performed based on CR/CRi per EAC. In addition, investigator's assessment performed based on CR/CRi was also analyzed. Sensitivity analyses were based on the mITT218 and the PP218 population.

Analysis assuming untreated patients as responders:

An ITT218 sensitivity analysis was conducted assuming all untreated patients were successes (achieved CR or CRi). This approach produced an overestimate of the probability of remission with the most extreme assumption, and would lead to bias favoring the treatment arm with more untreated patients and against the arm with fewer or no untreated patients. Assuming

the probability of not receiving treatment on the control arm was 0.2 and that dropout and remission were independent, the null remission probability was 0.5 on the control arm instead of 0.37 and power was reduced from 88.5% to <30%

Logistic Regression Multiple Imputation (Missing at Random):

This sensitivity analysis was based on the first 218 randomized patients (ITT218), in which responses were imputed for untreated patients. Patients who started treatment and did not have a response assessment were assumed non-responders. This analysis was based on the assumption of missing at random (MAR), i.e., given observed data, the missing mechanism for response does not depend on the unobserved data, and the missing value mechanism for response can be expressed solely in terms of observations. Logistic regression was used to model the association between remission and observed baseline factors.

This was a less biased approach compared to assigning either all success or all failure to patients who discontinued from the study after randomization but never receiving study treatment.

Imputation was performed according to treatment arm. Therefore, only the control arm had imputed responses since all patients randomized to the inotuzumab ozogamicin arm received randomized treatment. The method was appropriate under the MAR assumption (but not missing completely at random [MCAR] because imputation was not needed if MCAR).

A logistic regression model was fitted using treated patients.

The probability of remission in the control arm was estimated by the mean of the estimates from the imputed complete datasets. The CI was calculated based on the estimate and the binomial distribution. Estimates of probability of remission between the inotuzumab ozogamicin and control arms were compared using a Chi-square test. For each imputed complete dataset, the Chi-square statistic was calculated based on the imputed responses (control arm) and observed data from the inotuzumab ozogamicin arm. These Chi-square statistics were combined to calculate the p-value for comparing the treatment arms.

Primary Analysis of OS

The primary analysis of OS was based on the ITT population. Patients who did not have OS event were censored at the date they were last known to be alive.

The null hypothesis for the primary efficacy comparison is that the distribution of OS between the 2 treatment groups is the same. The corresponding alternative hypothesis is that the distribution of OS between the 2 treatment groups is different and in favor of the inotuzumab ozogamicin arm.

The OS of patients randomized to the inotuzumab ozogamicin arm was compared with that of the control arm using the stratified log-rank test at a 1-sided 0.0125 significance level. The

hazard ratio and corresponding 97.5% 2-sided CI using stratified Cox proportional hazard regression (same stratification factors as for randomization) is presented. The median OS was estimated using the Kaplan-Meier method and is reported with 2-sided 95% CIs for each arm using the method described by Bookmeyer and Crowley. In addition, KM estimate of the survival functions was computed and plotted for each treatment arm.

Sensitivity Analysis of OS

Sensitivity analyses of OS were to include the following:

- mITT analysis, excluding patients who did not receive study treatment;
- PP analysis based on the PP population;
- Censored at HSCT date: Sensitivity analyses were conducted by censoring OS at the time when a patient received first post-treatment HSCT
- Censored at Subsequent Therapies: Sensitivity analyses were conducted by censoring OS at the time when a patient received a specific or all subsequent therapies (e.g., censored for blinatumomab, censored for inotuzumab ozogamicin for control arm, or censored for follow-up induction therapies)

FDA's Exploratory Post-Hoc Analysis of OS

Competing Risk Analyses

The usual technique for time-to-event analysis applied in the presence of competing risks may give biased or uninterpretable results. The estimation of the probability of the event using the cumulative incidence function is needed (Gray, The Annals of Statistics, 1988). Analyses for OS modeling either cause-specific hazard or subdistribution hazard of death due to relapse or progression were conducted for the ITT population, the patients in the ITT with follow-up HSCT, and for the patients in the ITT who achieved CR/CRi per Investigator's assessment, respectively. In these analyses, death due to relapsed or progression was the primary event of interest, while death due to cause other than relapse or progression was considered to be competing risk.

Time dependent covariate Cox model

One of the strengths of the Cox model is its ability to encompass covariates that changes over time. The practical reason that time-dependent covariates work is based on the underlying way in which the Cox model works: at each event time the program compares the current covariate values of the subject who had the event to the current values of all others who were at risk at that time. The model has a theoretical foundation in martingale theory.

Analysis of Secondary Efficacy Endpoints

Minimal Residual Disease (MRD)

MRD-negativity was assessed in patients in the ITT Population who achieved CR/CRi per EAC assessment by the central laboratory(flow cytometry), as well as in all patients in the ITT Population. The MRD-negativity rate was compared between the 2 treatment arms. Subgroup analysis of MRD by type of hematologic remission (CR and CRi) was also conducted, respectively.

Duration of Remission (DoR) and Duration of Complete Remission (DoCR)

All the comparisons for DoR and DoCR specified in this section were conducted between the 2 arms using the 1-sided stratified log-rank test respectively. The HR and corresponding 95% 2-sided CI using stratified Cox PH regression were presented. The median DoRs were estimated using the KM method and were reported with 2-sided 95% CIs for each arm using the method described by Brookmeyer and Crowley. In addition, KM estimates of the survival function were computed and plotted for each treatment arm

DoR and DoCR were analyzed in patients in the ITT218 Population who achieved CR/CRi per Investigator's assessment. The DoR and DoCR were compared between the 2 arms using the 1-sided stratified log-rank test respectively. The HR and corresponding 95% 2-sided CI using stratified Cox proportional hazard regression (same stratification factors as for randomization) were presented. The median DoRs were estimated using the Kaplan-Meier method and were reported with 2-sided 95% CIs for each arm using the method described by Brookmeyer and Crowley (1982). In addition, Kaplan-Meier estimate of the survival functions were computed and plotted for each treatment arm.

Reviewer's Comments:

Comparison of Duration of response are not valid, since having a response is a treatment related outcome, formal statistical comparisons of duration of response will not be interpretable.

Progression-Free Survival (PFS)

As planned in the protocol, PFS of the inotuzumab ozogamicin arm was to be compared with that of the defined Investigator's choice of chemotherapy using a stratified log-rank test in the ITT population. The median PFS of both treatment arms was estimated using the KM method. A stratified Cox proportional hazards regression model was also used to estimate the relative hazards of PFS events for patients in the inotuzumab ozogamicin arm versus the Investigator's choice of chemotherapy arm. The hazard ratio and corresponding 97.5% CI were calculated.

Protocol Amendments

Table 13 Protocol Amendments

Document	Date	Summary of Major Protocol Changes in Amendments
Original Protocol	Jan 26, 2012	Original protocol submitted
Amendment 1	April 9, 2012	• Inclusion criteria modified • Assessment of bone marrow biopsies only required for patients with inadequate hematologic recovery • Patient follow-up time for survival is extended • Requirement for effective contraception extend to

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Document	Date	Summary of Major Protocol Changes in Amendments
Original Protocol	Jan 26, 2012	Original protocol submitted 90 days post therapy
Amendment 2	June 24, 2013	- Removed time to progression(TTP) as secondary endpoint - Dose of inotuzumab ozogamicin will be reduced to 0.5mg/m² at Day 1 of cycle 2 and beyond in patients with CR or CRi. - Approximately 190 sites required for study completion. Change in correction for power of study for CR/CRi from 88% to 89%. - Immunohistochemistry allowed for CD22 determination expression at screening for patients with inadequate BM aspirate and no circulating blasts - Timing of disease assessment changed, additional marrow sample will be collected for analysis of leukemic blast phenotype/genotype
Amendment 3	March 28, 2014	- Total sample size increased due to high numbers of patients withdrawing from treatment before start of therapy and loss of follow-up on 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 population - Recommendations to reduce the risk of VOD for patients proceeding to HSCT were clarified and include avoidance of hepatotoxic myeloablative regimens for subsequent SCT and limiting the number of cycles of inotuzumab ozogamicin in treatment of patient proceeding to SCT - Central CD22 results will be considered for eligibility in the setting of local negative results because some samples found negative with local testing have subsequently been determined to be positive by central laboratory testing - Medications used as prophylaxis for hepatotoxicity or treatment for VOD are required to be reported for up to 2 years from randomization

Substantial Statistical Analysis Plan (SAP) amendments are summarized in the table below:

Table 14 Revision History

Date	Version #	Description of Revision (S)
27 April 2012	1	Original version
30 May 2014	2	The following changes were made with this SAP amendment • Sample size increase • Cap Ph+ patient at approximately 20% • Addition of an analysis population-Modified ITT (mITT) • Endpoint TTP removed • Addition of details for per-protocol population definition • Addition of details for PFS, DoR and PRO data analyses • Clarification for subgroup analysis • Correction of typos
15 December 2014	3	The following changes were made with this SAP amendment: • Provided clarification that CR/CRi and OS are two (multiple) primary endpoints. Note: this is not a change of design or analysis. • Added sensitivity analyses for primary endpoints CR/CRi and OS • Added additional subgroup analyses for efficacy and safety endpoints

7.2.2. Study Results

Compliance with Good Clinical Practices

The Applicant provided attestation that the study was conducted in accordance with legal and regulatory requirements as well as general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Patients (Council for International Organization of Medical Sciences 2002), Guidelines for GCP (ICH 1996) and the Declaration of Helsinki World Medical Association 1996 and 2008). In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirement and laws.

Financial Disclosure

A summary of financial disclosures for Study 1022 is provided in the appendix. Certification of financial interests and arrangements of the clinical investigators was submitted in the BLA. Pfizer provided a summary of steps taken to minimize the potential for bias in Study 1022.

Patient Disposition

As specified in the protocol, the final analysis for CR/CRi was to be performed after the first 218 patients had been followed for at least 3 months after randomization. Since the 218th patients were randomized to the study on 26 June 2014, the data cutoff date was selected to be 02 October 2014.

A summary of patients disposition is presented in the table below. Of the 279 patients randomized into the study as of the data cutoff, a total of 259 (92.8%) (98.6% patients in the inotuzumab ozogamicin arm and 87.0% patients in the control arm). A total 3 (2.1%) patients in the inotuzumab ozogamicin arm and 1 (0.7%) patients in the control arm had completed the treatment. A total of 127 (45.5%) patients (50.4% patients in the inotuzumab ozogamicin arm and 40.6% patients in the control arm) were ongoing (either still in treatment or on follow-up for disease progression or survival). AEs were reported for 137/141 (97.2%) patients in the inotuzumab ozogamicin arm and 119/138 (86.2%) patients in the control arm. Of note, considering the ITT population, 20 patients (2 in the inotuzumab ozogamicin arm and 18 in the control arm) were randomized but not treated at the time of the data cutoff. In the safety population, 13 patients randomized to the control arm were randomized but not dosed and were excluded from the safety population.

Of the first 218 patients randomized, 205 (94.0%) patients (100% patients in the inotuzumab ozogamicin arm and 88.1% patients in the control arm) had received study therapy. A total of 3 (2.8%) patients in the inotuzumab ozogamicin arm and 1 (0.9%) patient in the control arm had completed the maximum doses of treatment allowed by the protocol.

Table 15 Summary of Patient Evaluation Groups

Number of patients (%)	Inotuzumab	Investigator's Choice of Chemotherapy	Total
Randomized	141	138	279
Treated	139 (98.6)	120 (87.0)	259 (92.8)
Completed treatment	3 (2.1)	1 (0.7)	4 (1.4)
Discontinued study	68 (48.2)	64 (46.4)	132 (47.3)
Ongoing at date of cutoff	71 (50.4)	56 (40.6)	127 (45.5)
Analyzed for safety			
Adverse events	137 (97.2)	119 (86.2)	256 (91.8)
Laboratory data	139 (98.6)	120 (87.0)	259 (92.8)
First 218 randomized patients			
Randomized	109	109	218
Treated (mITT 218)	109 (100.0)	96 (88.1)	205 (94.0)
Completed study	3 (2.8)	1 (0.9)	4 (1.8)
Discontinued study	63 (57.8)	62 (56.9)	125 (57.3)
Ongoing at date of cutoff	46 (42.2)	34 (31.2)	80 (36.7)

Number of patients (%)	Inotuzumab	Investigator's Choice of Chemotherapy	Total
Analyzed safety			
Adverse events	109 (100.0)	96 (88.1)	205 (94.0)
Laboratory data	109 (100.0)	96 (88.1)	205 (94.0)

The table below summarizes permanent discontinuations from the study for the ITT Population as of the data cutoff date of 02 October 2014. In the ITT Population, 68/141 patients in the inotuzumab ozogamicin arm and 79/138 patients in the control arm discontinued from the study. The most common reason for discontinuation from the study was patient died (47.5% in inotuzumab ozogamicin arm, 40.6% patients in control arm).

Table 16 Summary of Discontinuation from Study -ITT

	Inotuzumab N=141	Investigator's Choice N=138
Discontinued from study	68	79
Patient died	67 (47.5)	56 (40.6)
Patient refused further	1 (0.7)	23 (16.7)

Table below shows summary of patients distribution by region using ITT population. The majority of patients were randomized from North America (136/279 patients, 48.7%) and the EU (114/279 patients, 40.9%); the remainder were accrued from Asia (9.7%) and Australia (0.7%).

Table 17 Summary of Patient Distribution by Region (ITT)

Region n(%)	Inotuzumab N=141	Investigator's Choice N=138	Total N=279
USA	68 (48.2)	67 (48.6)	135 (48.4)
Canada	0	1 (0.7)	1 (0.4)
European Union	55 (39.0)	59 (42.8)	114 (40.9)
Asia	16 (11.3)	11 (8.0)	27 (9.7)
Other	2 (1.4)	0	2 (0.7)

Summary of the analysis population for the first 218 randomized patients is given in the table below. In the mITT 218 population, a total of 13 (6.0%) were excluded who were randomized but not dosed patients in the control arm. In the PP218 population, a total of 22 (10.1%) patients were excluded and the reasons for exclusion included randomized but not dosed

Table 18 Analysis Population –First 218 Randomized Patients

	Inotuzumab	Investigator's Choice	Total

ITT218 population	109 (100.0)	109 (100.0)	218 (100.0)
mITT218 population	109 (100.0)	96 (88.1)	205 (94.0)
PP 218 population	106 (97.2)	90 (82.6)	196 (89.9)

As specified in the protocol, the final analysis for OS was to be performed after at least 248 OS events, if accrual of 325 patients was achieved. The study completed its enrollment on 04 January 2015 with 326 randomized. A total of 252 OS events were reported in the CRF by 08 March 2016. Therefore, 08 March 2016 was selected as the database cutoff date for results summarized in this submission.

A summary of patient disposition is presented in table below. The ITT population included all 326 patients randomized in the study. In the ITT Population, a total of 307 (94.2%) patients had received study therapy. A total of 10 (6.1%) patients in inotuzumab ozogamicin arm and 1 (0.6%) patients in the control arm had completed maximum number of cycles and doses of treatment allowed by the protocol. A total of 23.8% (39/164) patients in the inotuzumab ozogamicin arm and 9.3% (15/162) patients in the control arm were ongoing (either in follow-up for disease progression or survival). All 164 (100%) patients in the inotuzumab ozogamicin arm and 143/162 (88.3%) patients in the control arm were analyzed for safety. Of note, 19 patients in the ITT population (0 in the inotuzumab ozogamicin arm and 19 in the control) were randomized but never treated. These patients were excluded from the safety population.

Table 19 Summary of Patient Evaluation Groups-ITT Population

Number (%) of patients	Inotuzumab Ozogamicin	Defined Investigator's Choice of Chemotherapy	Total
All patients	164	162	326
Randomized (as of the database cutoff 08 March 2016)	164	162	326
Treated	164 (100.0)	143 (88.3)	307 (94.2)
Completed treatment ^a	10 (6.1)	1 (0.6)	11 (3.4)
Completed study ^b	0	0	0
Discontinued study ^c	125 (76.2)	128 (79.0)	253 (77.6)
Ongoing at date of cutoff ^d	39 (23.8)	15 (9.3)	54 (16.6)
Analyzed for safety ^e	164	143	307
Adverse events ^f	163 (99.4)	143 (88.3)	306 (93.9)
Laboratory data	164 (100.0)	143 (88.3)	307 (94.2)

Data Source: Applicant's CSR Table 12

The table below summarizes permanent discontinuations from the study for the ITT Population. In the ITT Population, 76.2% (125/146) patients in the inotuzumab ozogamicin arm and 90.7% (147/162) patients in the control arm permanently discontinued from the study. The most common reason for discontinuation from the study was patient died (74.4% patients in inotuzumab ozogamicin arm and 79.6% patients in control arm). One (0.6%) patient refused further follow-up in the inotuzumab ozogamicin arm, while 16 (9.9%) patients refused further follow-up in the control arm.

Table 20 Summary of Permanent Discontinuations from Study-ITT Population

	Inotuzumab N=164	Investigator's Choice N=162
Discontinued from study	125 (76.2)	147 (90.7)
Reason for discontinuation		
completed	0	0
Patient died	122 (74.4)	129 (79.6)
Lost to follow-up	1 (0.6)	1 (0.6)
Study terminated by Sponsor	0	0
Patient refused further follow-up	1 (0.6)	16 (9.9)
Other	1 (0.6)	1 (0.6)

Reviewer's Comment

Based on protocol, the definition of completed treatment was patients who completed the maximum number cycles and doses of treatment per protocol. Patients were allowed to receive study treatment for up to 6 cycles of inotuzumab ozogamicin and for up to 4 cycles of the Investigator's choice of chemotherapy, or 2 cycles of 12 doses of HIDAC. The definition of completed the study was patients who completed survival follow-up for 5 years from randomization of last patient.

Protocol Violations/Deviations

The table below summarizes potentially important protocol deviations by deviation coded term for the study.

Table 21 Summary Potentially Important Protocol Deviations

Protocol Deviation Coded Term	Inotuzumab N=143	Investigator's Choice N=141
Concomitant medications		
Took prohibited medication during treatment	7 (4.9)	10 (7.1)
ICF issues		
ICF not dated by patient/site	4 (2.8)	7 (5.0)
Study procedure prior to consent	2 (1.4)	5 (3.5)
Inclusion/exclusion criteria		
Specify in comments	14 (9.8)	23 (16.3)
Patient did not have study condition	0	3 (2.1)
Patient on excluded medication (s)	0	1 (0.7)
Study Drug		
Dosing non-compliance	34 (23.8)	31 (22.0)
Specify in comments	22 (1.54)	31 (22.0)
Patient took incorrect dose	12 (8.4)	3 (2.1)

There were 10 patients with protocol violations regarding eligibility criteria that could potentially compromise the efficacy outcome and the Applicant excluded them from the PP population. Four patients were in the inotuzumab ozogamicin arm and 6 were in the control arm.

Reviewer Comment: Based upon review of these protocol deviations, the reviewer agrees with the assessment by the Sponsor that these 10 patients with protocol deviations relating to eligibility criteria should be excluded from the per protocol population.

None of the major protocol violations would likely bias the study in favor of the inotuzumab ozogamicin arm; all patients were included in the FDA's analysis of efficacy endpoints. Additional efficacy analysis of CR/CRi and OS based on the PP protocol were similar to the findings in the ITT population. The inclusion of the 10 patients does not bias the study in favor of inotuzumab ozogamicin.

Demographic Characteristics

A summary of demographic characteristics for the ITT218 Population is presented in the table below. Demographic characteristics were generally similar across treatment arms. Overall, the majority of patients were male and white (71.1%) patients. The mean age was 46.0 years (range 18 to 79 years). Notably, a numerically higher percentage of patients were aged 65 years or over in the inotuzumab ozogamicin arm compared with the control arm (21.1% versus 12.8%).

Table 22 Summary of Demographic Characteristics ITT 218 Population

Demographic Characteristic	Inotuzumab N=109	Investigator's Choice N=109
Gender		
Male	61	73
Female	48	36
Age		
<55 years	66 (60.6)	69 (63.3)
≥55 years	43 (39.4)	40 (36.7)
≥65 years	23 (21.1)	14 (12.8)
Race		
White	76 (69.7)	79 (72.5)
Black	1 (0.9)	2 (1.8)
Asian	17 (15.6)	17 (15.6)
Other	15 (13.8)	11 (10.1)
BMI		
N	109 (100.0)	108 (99.1)
Mean (SD)	26.23 (6.06)	26.34 (6.15)
Median	25.7	25.1
Range	17.0-46.6	15.6-51.5

Demographic Characteristic	Inotuzumab N=109	Investigator's Choice N=109
Body surface area		
N	109 (100.0)	108 (99.1)
Mean (SD)	1.86 (0.28)	1.88 (0.26)
Median	1.8	1.9
Range	1.3-2.5	1.3-2.7

A summary of demographic characteristics for the OS Population is presented in the table below. Demographic characteristics were generally similar across treatment arms. Overall, the majority of patients were male (59.2% patients) and white (71.2%) patients. The median age was 47.0 years (range 18 to 79 years). The median weight was 74.0 kg (range 40.0 to 192.0 kg), the median BMI was 25.5 kg/m² (range 13.8 to 51.5 Kg/m²), and the median BSA was 1.9 m² (range 1.3 to 2.8 m²).

Table 23 Summary of Demographic Characteristics –ITT Population

Demographic Characteristic	Inotuzumab N=164	Investigator's Choice N=162
Gender		
Male	91 (55.5)	102 (63.0)
Female	73 (44.5)	60 (37.0)
Age		
<55 years	104 (63.4)	103 (63.6)
≥55 years	60 (36.6)	59 (36.4)
Race		
White	112 (68.3)	120 (74.1)
Black	4 (2.4)	3 (1.9)
Asian	31 (18.9)	24 (14.8)
Other	17 (10.4)	15 (9.3)
BMI		
N	164 (100.0)	161 (99.4)
Mean (SD)	25.91 (5.64)	26.92 (6.08)
Median	25.4	25.6
Range	17.0-46.6	13.8-51.5
Body surface area		
N	164 (100.0)	161 (99.4)
Mean (SD)	1.85 (0.273)	1.90 (0.263)
Median	1.8	1.9
Range	1.3-2.5	1.3-2.8

Other Baseline Characteristics

A summary of primary diagnoses and duration since initial diagnosis for the ITT population is presented in the table below. The total number of patients with a primary diagnosis of B-cell ALL

was 309 and was evenly distributed per arm (93.3% vs 96.3%). The median duration since initial histopathological diagnosis between treatment arms was matched similar (12.5 months in the inotuzumab ozogamicin arm vs 13.0 months in the control arm).

The total number of patients with B-cell lymphoblastic lymphoma was 17 (11 patients in the inotuzumab ozogamicin arm and 6 patients in the control arm). The median duration since initial histopathological diagnosis was 10.5 months in the inotuzumab ozogamicin arm vs. 12.9 months in the control arm.

Table 24 Summary of Primary Diagnoses and Duration-ITT Population

Primary Diagnosis	Inotuzumab N=164	Investigator's Choice N=162
B-cell ALL		
N	153	156
Duration (months)		
Mean	20.4	18.6
SD	23.12	17.86
Median	12.5	13.0
Min, max	1.1, 195.1	1.1, 113.0
B-cell lymphoblastic lymphoma		
N	11	6
Duration (months)		
Mean	19.6	41.5
SD	16.78	76.65
Median	10.5	12.9
Min, Max	1.5, 45.8	4.1, 197.7

The table below summarizes other baseline characteristics for the ITT 218 Population. Baseline characteristics including duration of first remission (<12 month and ≥ 12 months), salvage treatment status (per CRF), Ph+ (assessed by local laboratory, medical history and FISH central laboratory results), and t(4;11) translocation were generally balanced across treatment arms.

Table 25 Summary of Other Baseline Characteristics-ITT218 Population

Baseline Characteristic	Inotuzumab N=109	Investigator's Choice N=109
Ph+	14 (12.8)	18 (16.5)
t (4;11)	3 (2.8)	6 (5.5)
other	49 (45.0)	46 (42.2)
Salvage status (CRF data)		
Salvage 1	73 (67.0)	69 (63.3)
Salvage 2	35 (32.1)	39 (35.8)
Other	1 (0.9)	1 (0.9)

Baseline Characteristic	Inotuzumab N=109	Investigator's Choice N=109
Duration of first remission		
<12 months	62 (56.9)	71 (65.1)
≥12 months	47 (43.1)	38 (34.9)
Priory radiation for primary diagnosis		
Yes	23 (21.1)	24 (22.0)
No	86 (78.9)	85 (78.0)
Induction therapy regimens		
1	75 (68.8)	69 (63.3)
2	33 (30.3)	39 (35.8)
3	1 (0.9)	1 (0.9)
ECOG performance status		
0	43 (39.4)	45 (41.3)
1	50 (45.9)	53 (48.6)
2	15 (13.8)	10 (9.2)
Missing	1 (0.9)	1 (0.9)
Local CD22		
≥90	33 (30.3)	31 (28.4)
≥70-<90	22 (20.2)	22 (20.2)
<70	48 (44.0)	43 (39.4)
Missing	6 (5.5)	13 (11.9)
Central CD22		
≥90	74 (67.9)	63 (57.8)
≥70-<90	21 (19.3)	12 (11.0)
<70	3 (2.8)	12 (11.0)
Missing	11 (10.1)	22 (20.2)
White blood cells median range	3.5 (0.0, 47.4)	3.8 (0.1, 51.0)
Number of patients with peripheral blasts count>0 by local laboratory	66 (60.6)	60 (55.0)
Missing	1 (0.9)	1 (0.9)

CD22 immunophenotyping was performed on peripheral blood or BM aspirates. CD22 expression was assessed at local study sites for eligibility and at central laboratory. The central laboratory results demonstrated a higher percentage of patients with CD22 expression (≥90%) when compared with the local results for the ITT population.

Reviewer Comment: CD22 is expressed in over >90% of lymphoblasts in patients with ALL (Shah 2015). Testing for CD markers including CD19, CD20, and CD22 is routine in the diagnostic evaluation of patients with ALL. Given the high expression of CD22 in lymphoblasts and that CD22 expression is routinely tested for in the diagnosis of ALL, no restrictions on CD22 expression is required in the UPSI.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Each dose of study drug and control drug was administered intravenously by study personnel. All study participants received concomitant medications. The most commonly used concomitant medications were antidepressants and anti-anxiety agents, pain medications, and antimicrobials used for infection prophylaxis and treatment. There was more use of antibiotics in the investigator choice arm than the inotuzumab ozogamicin arm.

Table 26 Concomitant Medications given to > 20% of patients with a difference > 10% between treatment arms (safety population)

Concomitant Medications	Inotuzumab N=164 n(%)	Investigator's Choice N=143 n(%)
Infections		
Cefepime	41(25)	57(40)
Meropenem	41(25)	63(44)
Metronidazole	17(10)	30(21)
Piperacillin/tazobactam	35(21)	66(46)
Posaconazole	13(8)	33(23)
Vancomycin	50(31)	91(64)
Voriconazole	25(15)	48(34)
Antihistamines		
Diphenhydramine	81(49)	48(34)
Anxiolytics		
Lorazepam	47(29)	59(41)
Nausea Prophylaxis		
Ondansetron	76(46)	105(73)
Prochlorperazine	23(14)	40(28)
Pain		
Morphine	3(22)	50(35)
Hydromorphone	21(13)	35(24)
Liver damage prophylaxis		
Ursodexycolic acid	77(47)	41(29)
CNS prophylaxis		
Methotrexate	42(26)	20(14)
Edema		
Furosemide	48(29)	73(51)
VOD/SOS prophylaxis or treatment		
defibrotide	13(8)	0(0)

Source: FDA Analysis ADCM dataset

The use of corticosteroids and other anticancer drugs were allowed to be given within 2 weeks from randomization to the end of Cycle 1 day 5. These agents were allowed to reduce the

number of circulating blasts to < 10,000/uL. Some medications were used as maintenance therapy prior to relapse. During the course of the study, corticosteroids were allowed for CNS prophylaxis (intrathecal chemotherapy), as premedication for up to 1 day, to treat hypersensitivity reactions for up to 1 day and as anti-emetics for up to 8 days/cycle as supportive care. Within the safety population, 94% of patients in the inotuzumab ozogamicin arm and 95(66%) of patients in the control arm receive systemic corticosteroids or other anticancer medications during this time period. Hydroxyurea was administered to 20 patients (12%) in the inotuzumab ozogamicin arm and 15(11%) in the control arm within 2 weeks from randomization to end of Cycle 1 day 5.

Corticosteroids for premedication, rash or conjunctivitis or CNS prophylaxis used in the inotuzumab arm and control arm respectively: Dexamethasone (38% vs 61%), hydrocortisone (39% vs 24%), methylprednisolone (46% vs 22%). During the study period, more patients in the inotuzumab ozogamicin arm (87.8%) versus 57.5% received systemic steroid treatment.

Hematopoietic growth factor use was used less frequently in the inotuzumab arm compared to the investigator choice arm (67/164, 41%) versus 117/142(82%), respectively.

Reviewer Comment: There are likely two reasons for discrepancy between corticosteroid use in the inotuzumab ozogamicin arm compared to the investigator choice arm. The first is that corticosteroids were required as a protocol-specified premedication prior to each dose of inotuzumab ozogamicin. Second, the study duration of therapy for the inotuzumab ozogamicin arm was longer compared to the control arm (median of 3 cycles versus 1 cycle).

Drug Exposure

Table below shows the summary of the duration of administered treatment in the inotuzumab ozogamicin and control arms using the Safety Population.

Table 27 Summary of Drug Exposure-Safety Population

	Inotuzumab N=164	Investigator's Control N=143
Median weeks on treatment range (range)	8.9 (0.1, 26.4)	0.9 (0.1, 15.6)
Median # cycles started per patient (range)	3.00 (1.00, 6.00)	1.00 (1.00, 4.00)

Reviewer's Comments:

The distributions of treatment duration are imbalanced between inotuzumab ozogamicin arm and control arm. The median duration of treatment was 8.9 weeks for patients who received inotuzumab ozogamicin and 0.9 weeks for patients who received control arm therapy.

Efficacy Results – Primary Endpoint CR/CRi

Table 23 below shows summary of primary analyses results for CR/CRi (per EAC) in the ITT218 based on data cutoff of 02 October 2014. The CR/CRi rate per EAC was 80.7% with 95% CI of (72.1, 87.7) in the inotuzumab ozogamicin arm compared with 29.4% with 95% CI of (21.0, 38.8) in the control arm. The rate difference was 51.4% with 97.5% CI of (38.4, 64.3) and was statistically significant (1-sided p<0.0001 using Chi-square test). The CR rate was 35.8% in the inotuzumab ozogamicin arm, and 17.4% in the control arm; the rate difference was 18.3% (97.5% CI: 5.2, 31.5). The CRi rate was 45.0% in the inotuzumab ozogamicin arm, and 11.9% in the control arm; the rate difference was 33.0% with 97.5% CI of (20.3, 45.8).

Table 28 Summary of Primary Efficacy Endpoint of CR/CRi-ITT218 Population

	CR/CRi		CR		CRi	
	Inotuzumab N=109	Control N=109	Inotuzumab N=109	Control N=109	Inotuzumab N=109	Control N=109
n (%) (95% CI)	88 (80.7) (72.1, 87.7)	32 (29.4) (21.0, 38.8)	39 (35.8) (26.8, 45.5)	19 (17.4) (10.8, 25.9)	49 (45.0) (35.4, 54.8)	13 (11.9) (6.5, 19.5)
Rate% Difference (97.5% CI)	51.4 (38.4, 64.3)		18.3 (5.2, 31.5)		33.0 (20.3, 45.8)	
1-sided p	<0.0001		0.0011 (nominal p)		<0.0001(nominal p)	

Table below shows sensitivity analyses results for the primary efficacy endpoint of CR/CRi rate. The results demonstrated that the Inotuzumab ozogamicin significant improvement in the primary efficacy endpoint CR/CRi compared with the control arm. The conclusions from these sensitivity analyses were consistent with those from the primary analysis of CR/CRi.

Table 29 Sensitivity Analyses Results for the Primary Efficacy Endpoint

Assessment	Analysis Population	Inotuzumab Ozogamicin (95% CI)	Investigator's Choice (95% CI)	CR/CRi Rate Difference (97.5% CI)	P-value by Chi-Square
EAC	mITT218	88/109 (80.7) (72.1, 87.7)	32/96 (33.3) (24.0, 43.7)	47.4 (33.7, 61.1)	<0.0001
	PP	82.1% (73.4, 88.8)	34.4% (24.7, 45.2)	47.6 (33.6, 61.6)	<0.0001
Investigator	ITT 218	85/109 (78.0) (69.0, 85.4)	31/109 (28.4) (20.2, 37.9)	49.5 (36.4, 62.7)	<0.0001
	mITT218	85/109 (78.0) (69.0, 85.4)	31/96 (32.3) (23.1, 42.6)	45.7 (31.8, 59.6)	<0.0001
Untreated patients as responders		80.7% (72.1, 87.7)	41.3% (31.9, 51.1)	39.4% (25.9, 53.0)	<0.0001
Logistic regressing with MAR		80.7%	35.8%		<0.0001

A summary of concordance between EAC and Investigator assessment CR/CRi in the ITT218 Population is presented in the table below. There were a total of 14/218 patients (5/109 patients in the inotuzumab ozogamicin arm and 9/109 patients in the control arm) with discordant assessment of CR/CRi between the EAC and Investigator. There were no statistically significant differences between EAC and Investigator assessment in either treatment arm.

Table 30 Concordance of EAC and Investigator-Assessed Remission (CR/CRi) –ITT 218 Population

EAC Assessment	Inotuzumab Ozogamicin N=109 Investigators' assessment		Investigator Choice N=109 Investigators' assessment	
	Yes	No	Yes	No
CR/CRi				
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)
Nominal P-value (McMemar's test)	0.375		1.0000	

CR/CRi Subgroup Analyses

A summary of subgroup analyses by gender, race, region, and other baseline characteristics for the CR/CRi is presented in the Table below. The results demonstrated the Inotuzumab ozogamicin improvement in the primary efficacy endpoint CR/CRi compared with those from the control arm by gender, race, region, and other baseline characteristics. In general, the rate difference appears to be consistent across the subgroups. However, the interpretation should be taken with caution due to the some small sample size in some subgroups.

Table 31 Subgroup Analyses for CR/CRi by Gender, Race, Region, and Other Baseline Characteristics-ITT218 Population

	Inotuzumab Ozogamicin N=109	Investigator's Choice N=109	Rate Difference (97.5% CI)
Male, n	61	73	52.1
Rate	45 (75.4)	17 (23.3)	(35.5, 68.7)
Female, n	48	36	42.4
Rate	39 (81.3)	14(38.9)	(20.2, 64.5)
White, n	76	79	52.5
Rate	62 (81.6)	23 (29.1)	(37.3, 67.6)
Black, n	1	2	-50.0
Rate	0	1 (50.0)	(-100.0, 29.2)
Asian, n	17	17	64.7
Rate	14 (82.4)	3 (17.6)	(35.4, 94.0)

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	Inotuzumab Ozogamicin N=109	Investigator's Choice N=109	Rate Difference (97.5% CI)
Other, n	15	11	23.6
Rate	9 (60.0)	4 (36.4)	(-19.5, 66.8)
Asia, n	14	7	57.1
Rate	12 (85.7)	2 (28.6)	(13.5, 100.0)
North America, n	48	52	47.9
Rate	35 (72.9)	13 (25.0)	(28.2, 67.6)
EU, n	45	47	50.3
Rate	37 (82.2)	15 (31.9)	(30.4, 70.2)
Others, n	2	3	16.7
Rate	1 (50.0)	1 (33.3)	(-83.3, 100.0)
CD22 <70, n	3	12	33.3
Rate	2 (66.7)	4 (33.3)	(-34.9, 100.0)
CD22 ≥70-<90, n	21	12	59.5
Rate	16 (76.2)	2 (16.7)	(27.7, 91.4)
CD22 ≥90, n	74	63	44.8
Rate	59 (79.7)	22 (34.9)	(27.8, 61.9)

A summary of subgroup analyses by stratification factors for the CR/CRi is presented in the Table below. The results demonstrated the Inotuzumab ozogamicin improvement in the primary efficacy endpoint CR/CRi compared with the control arm by the stratification factors. In general, the rate difference appears to be consistent across the stratification factors. However, the interpretation should be taken with caution due to the some small sample size in some subgroups.

Table 32 Subgroup Analyses by Stratification Factors for CR/CRi-ITT218 Population

	Inotuzumab Ozogamicin N=109	Investigator's Choice N=109	Rate Difference (97.5% CI)
Duration of First Remission			
<12 month, n	71	71	53.5
Rate	55 (77.5)	17 (23.9)	(37.6, 69.4)
(95% CI)	(66.0, 86.5)	(14.6, 35.5)	
≥12 month, n	38	38	47.4
Rate	33 (86.8)	15 (39.5)	(25.8, 69.0)
(95% CI)	(71.9, 95.6)	(24.0, 56.6)	
Salvage 1, n	73	73	58.9
Rate	64 (87.7)	21 (28.8)	(44.2, 73.6)
(95% CI)	(77.9, 94.2)	(18.8, 40.6)	
Salvage 2, n	36	36	36.1

	Inotuzumab Ozogamicin N=109	Investigator's Choice N=109	Rate Difference (97.5% CI)
Rate (95% CI)	24 (66.7) (49.0, 81.4)	11 (30.6) (16.3, 48.1)	(11.5, 60.7)
<55 year, n	66	69	48.4
Rate (95% CI)	53 (80.3) (68.7, 89.1)	22 (31.9) (21.2, 44.2)	(31.7, 65.1)
≥55 year, n	43	40	56.4
Rate (95% CI)	35 (81.4) (66.6, 91.6)	10 (25.0) (12.7, 41.2)	(36.1, 76.7)

Efficacy Results – Primary Endpoint OS

The first IA of OS was conducted based on data cutoff date of 21 April 2014, after 70 OS events had occurred in 174 randomized patients. The eDMC reviewed the results on 16 June 2014, and recommended the study continue as planned. The second IA of OS was conducted based on data cutoff date of 19 January 2015, when 163 OS events had occurred. The eDMC reviewed the results on 11 March 2015, and recommended the study continue as planned. The efficacy boundary at the final OS analysis was determined based on the timing of 2 IAs in conjunction with the actual number of event at the time of final OS analysis. Since the percentages of deaths were different from the planned percentage at the interim analyses, the actual p-value to reject the null hypothesis (i.e., stop for efficacy at the second interim analysis and the p-values to stop for futility at both interim analyses were based on the alpha (efficacy) and beta (futility) spending functions and the fraction of information. Table below shows the actual stopping boundaries at the interim and final analyses (p-value are 1-sided).

Table 33 Actual Stopping Boundaries for OS at Interim Analyses and Final Analysis

Analysis	Actual number of events observed	Cumulative alpha spent	Cumulative beta spent	Efficacy boundary Z (p-value)	Futility boundary Z (p-value)
First IA	70 (28.2)	0	0.035	3.455 (0.00028)	-0.121 (0.5482)
Second IA	163 (65.7)	0.004	0.097	2.637 (0.0042)	1.187 (0.1176)
FA	252 (101.6)	0.0125	0.202	2.312 (0.0104)	2.312 (0.0104)

The primary analysis for OS in the ITT Population is presented in the table below. The estimate HR (inotuzumab ozogamicin vs the control arm) was 0.77 (97.5% CI: 0.58-1.03); 1-sided p=0.02)

based on pre-specified primary stratified analysis. The result failed to demonstrate the inotuzumab ozogamicin significant improvement in OS endpoint compared with control arm. The estimated HR was 0.75 (97.5% CI 0.56-0.99; 1-sided p=0.01) based on the unstratified analysis. The estimated median OS was 7.7 months (95% CI: 6.0-9.2) in the inotuzumab ozogamicin arm compared with 6.7 months (95% CI: 4.9-8.3) in the control arm.

Table 34 Analysis Results Overall Survival –ITT Population

	Inotuzumab Ozogamicin N=164	Investigator’s Choice N=162
Number of deaths	122 (74.4)	130 (80.2)
Number of censored	42 (25.6)	32 (19.8)
Median survival time (95% CI)	7.7 (6.0, 9.2)	6.7 (4.9, 8.3)
Stratified HR (97.5% CI)	0.77 (0.58, 1.03) p=0.02 (stratified log-rank test)	
Unstratified HR (97.5% CI)	0.75 (0.56, 0.99) p=0.01 (unstratified log-rank test)	

Table 30 below shows the FDA’s sensitivity analyses using the Cox PH model for OS. The sensitivity analyses in the table below include OS censored on the date of HSCT, OS censored for subsequent therapies, using mITT Population and PP Population.

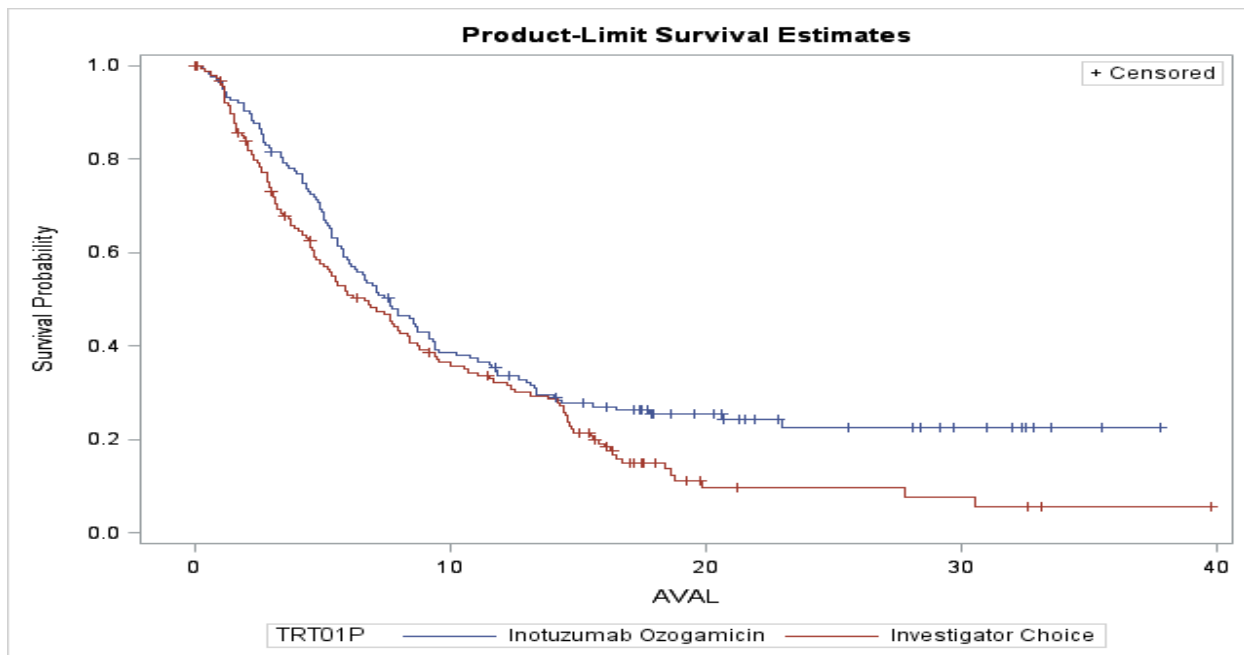
- For the OS censored at HSCT date, the HR was 0.74 with 97.5% CI interval of (0.521, 1.038).
- For the OS censored for subsequent therapies, the HR was 0.74 with 97.5% CI interval of (0.548, 1.000).
- In the mITT Population, the HR was 0.77 with 97.5% CI interval of (0.572, 1.029).
- In the PP Population, the HR was 0.78 with 97.5% CI interval of (0.572, 1.044).

Table 35 Sensitivity Analyses for OS

	HR (97.5% CI)	Nominal p-value using log-rank test
Censored at HSCT date	0.735 (0.521-1.038)	0.0221 (1-sided)
Censored for subsequent therapies	0.74 (0.548-1.000)	0.012 (1-sided)
mITT Population	0.77 (0.572, 1.029)	0.0209 (1-sided)
PP Population	0.775 (0.572, 1.044)	0.0269 (1-sided)

Figure 3 below shows the Kaplan-Meier Plot for overall survival using ITT population.

Figure 11 Kaplan-Meier Plot of Overall Survival –ITT Population



Reviewer's Comments:

A central assumption of Cox regression is that covariate effects on the hazard rate, namely hazard ratio, are constant over time. Violations of the proportional hazard assumption may cause bias in the estimated coefficients as well as incorrect inference regarding significance of effects. If the assumption of proportional hazards holds, the graphs of the survival function should look parallel, in the sense that they should have basically the same shape, should not cross and the curves should not be close in earlier period and then diverge slowly through follow up time. However, Kaplan-Meier estimates of the survival function plotted for OS using ITT population crossed at around 13 months, indicating a violation of the assumption of proportional hazard. The non-proportionality in hazard rates was also examined by plotting the Schoenfeld residuals, as shown in the figure below. Significant deviation from zero in the slope of the Schoenfeld residuals indicates a violation of the proportional hazard assumption. Further examinations of potential confoundings that led to the non-PH are presented in the following sections.

Figure 12 Schoenfeld Residuals

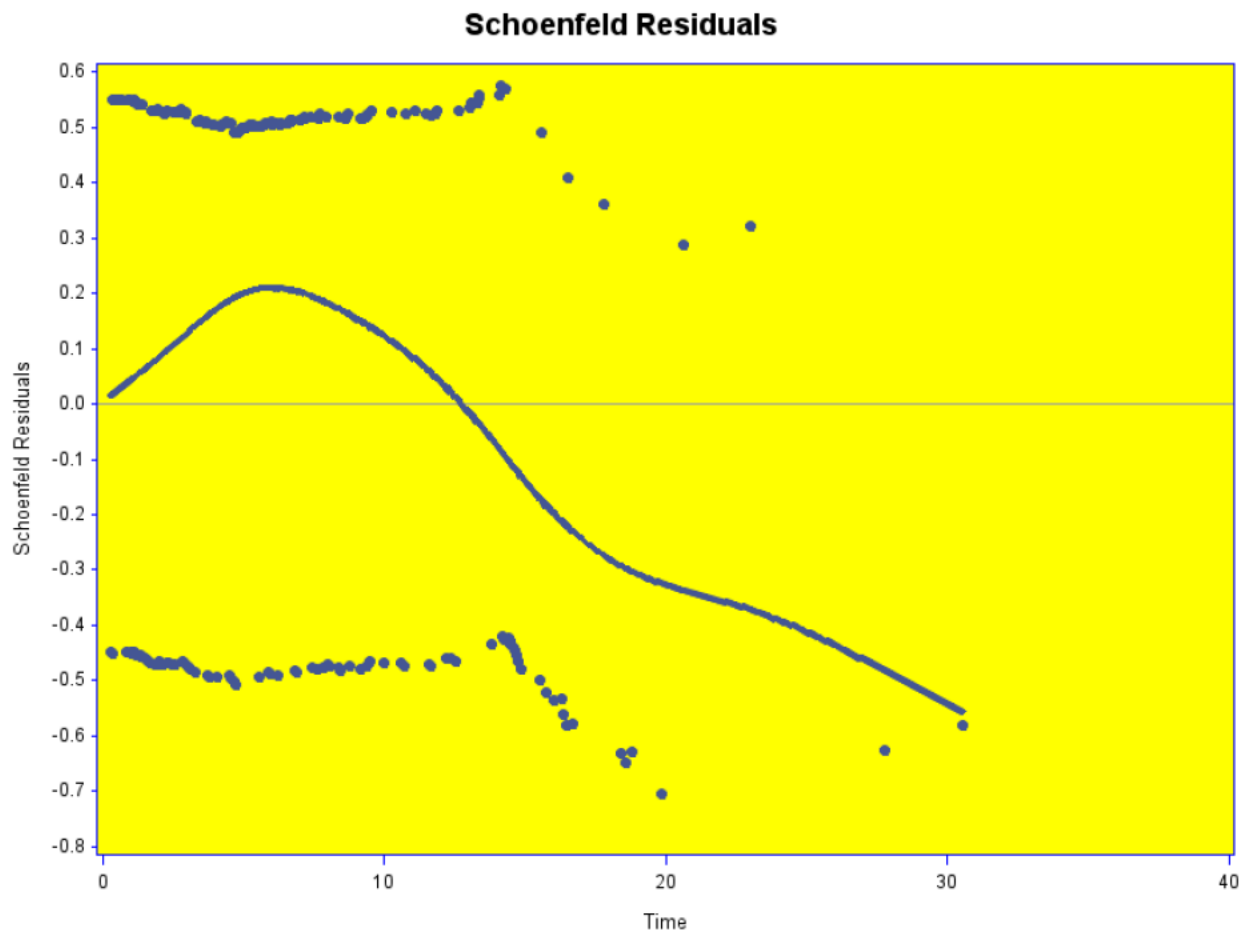


Table 31 below shows the summary of censoring distributions between two treatment arms. One possible reason that caused the non-proportionality may be the unbalanced censoring distribution between the two treatment groups. There were more early censored observations in the control arm compared with those from Inotuzumab ozogamicin arm.

Table 36 Distribution of Censoring –ITT Population

Time (Month)	Inotuzumab Ozogamicin N=164	Investigator's Choice N=162
5	1 (0.6)	13 (8.0)
10	2 (1.2)	15 (9.3)
15	6 (3.7)	16 (9.9)
20	20 (12.2)	28 (17.3)
25	29 (17.7)	29 (17.7)
30	34 (20.7)	29 (17.9)
35	40 (24.4)	31 (19.1)
40	42 (25.6)	32 (19.8)

Table 32 shows the distributions of the stem cell transplantation and subsequent therapies. The stem cell transplantation and subsequent therapies distributions are also imbalanced.

Table 37 Distribution of Stem Cell Transplantation and Subsequent Therapies

	Inotuzumab Ozogamicin N=164	Investigator's Choice N=162
With SCT between first dose date to start of post induction therapy	71 (43.3%) (35.6%, 51.2%)	18 (11.1%) (6.7%, 17.0%)
≥ 1 follow-up re-induction regimen	49 (29.9%)	84 (51.95)
Blinatumomab	9 (5.5%)	20 (12.3%)
Tyrosine kinase inhibitor	4 (2.4%)	16 (9.9%)
CAR-T	1 (0.6%)	2 (1.2%)
Inotuzumab ozogamicin	0	7 (4.3%)

Reviewer's Comments:

Overall survival (OS) is considered to be an important safety endpoint in oncology studies. In the study under discussion, it was observed that the OS result was confounded by imbalance in patients receiving hematopoietic stem cell transplant (HSCT), as well as imbalance in subsequent therapies, transplant related mortality, duration of overall survival follow-up, and censoring. 43.3% of patients in the Inotuzumab ozogamicin treated arm and 11% in the control received HSCT during the course of the treatment. Of note is that the decision to undergo treatment may have depended on the availability of donors, and investigators decisions which may have depended on the treatment responses after induction treatment and/or MRD prior to HSCT. FDA performed the following exploratory analysis to assess the impact of the confounding effect on OS due to the stem cell transplant:

- *Cox model with time dependent covariate (HSCT) with stratified covariates:*
 - *The hazard ratio for the treatment effect was 0.81 with 95% CI of (0.64-1.05)*
 - *The hazard ratio for the time dependent covariate of HSCT was 0.50 with 95% CI of (0.35-0.70)*
- *Cox model including interaction HSCT by treatment:*
 - *The hazard ratio for treatment effect was 0.72 with 95% CI of (0.55-1.01)*
 - *The hazard ratio for the time dependent covariate of HSCT was 0.34 with 95% CI of (0.20, 0.57)*

- *Nominal p-value for the treatment by HSCT interaction was 0.04*

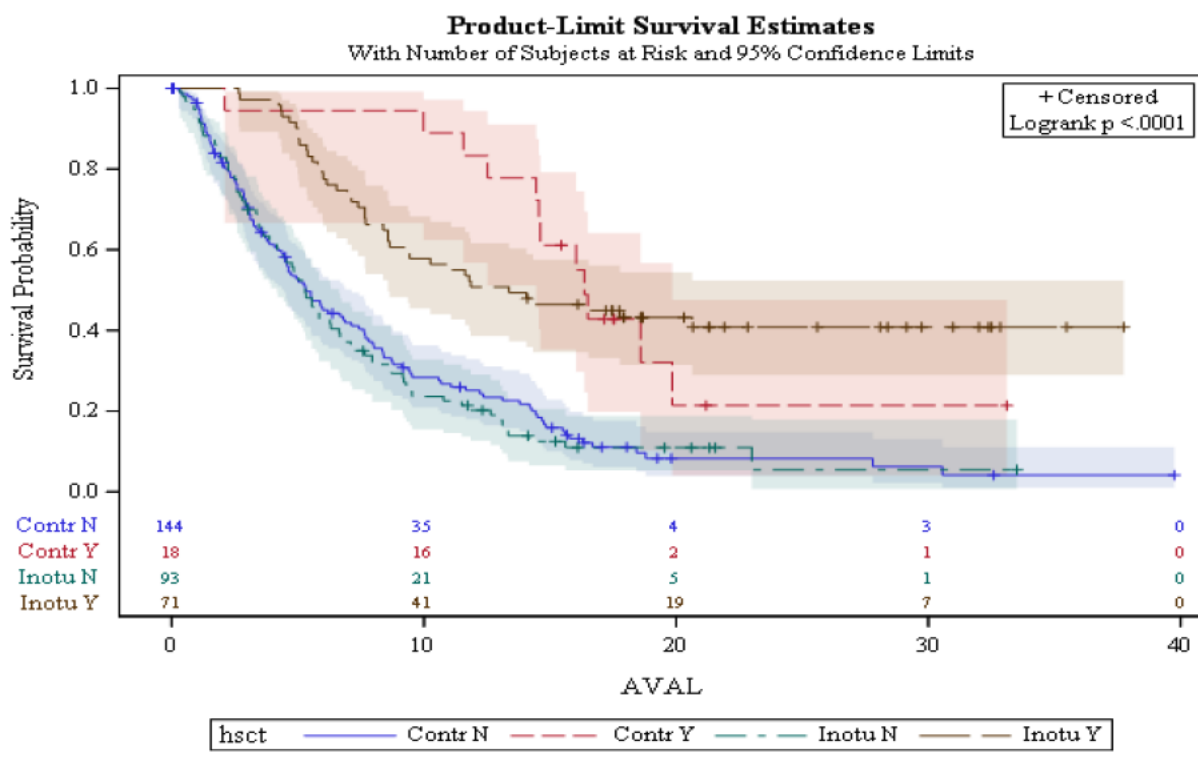
The figure below shows FDA's exploratory analyses for the association between HSCT and OS (post HSCT). The plot demonstrates that:

- *The OS results confounded by HSCT*
- *No difference seen between treatments in subjects not receiving HSCT*
- *For those subjects receiving HSCT, there are fewer early deaths in the control arm, but the inotuzumab subjects have a better survival outcome than the control subjects after 18 months.*

If HSCT effect is considered in the analysis, we cannot make conclusion about the effect of treatment regarding OS; it is not clear whether the effect on OS is due to the treatment or due to the HSCT.

Clinical Reviewer Comment: Some of these salvage therapies are associated with improved response rate, PFS or OS. The greater use of salvage therapies in the control arm after disease progression or relapse may confound the interpretation of OS. Patients in the Inotuzumab Ozogamicin arm were more likely to proceed directly to a post-study HSCT. There was more post-HSCT related toxicity and mortality including non-relapse mortality in the inotuzumab ozogamicin arm (VOD and infectious complications) compared to the control arm. Analysis of OS shows that the patient who benefit the most from inotuzumab ozogamicin were those patients in achieved CR/Cri and MRD negativity and underwent a follow-up HSCT.

Figure 13 Analysis of Association between HSCT and OS



*AVAL=time, Contr N=patient in the control arm without receiving HSCT; Contr Y=patient in the control arm received HSCT; Inotu N=patient in the inotuzumab arm without receiving HSCT; Inotu Y=patient in the inotuzumab arm received HSCT

Table below shows the FDA’s exploratory analysis using competing risk analysis which allows separating events by different causes. Death due to relapse or progression, or disease related death, is the event that we are interested, and death due to other cause as competing risk. Using competing risk model, the HR was 0.585 with 97.5% CI of (0.43, 0.79)

Table 38 Summary of Analysis of Competing Risk for OS

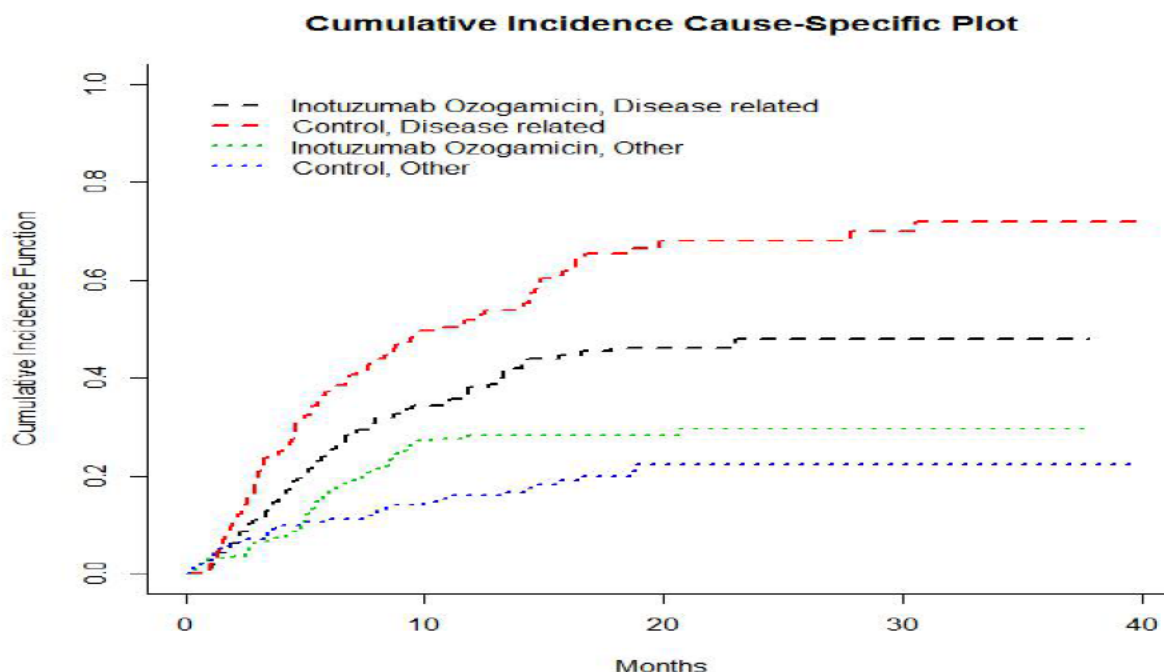
	Inotuzumab	Investigator’s Choice
Disease related	75 (45.7%)	99 (61.1%)
Other cause	47 (28.7%)	31 (19.1%)
HR (97.5% CI)	0.585 (0.43, 0.79)	

The figure below shows FDA’s analysis of cumulative incidence rate, cause-specific plot by using the competing risk model. The curve on the top demonstrated worst outcome while the curve in the bottom demonstrates better outcome. The plot demonstrates:

- There are more disease related death compared with death due to other cause (competing risk)

- Among patients with disease related death, the Inotuzumab ozogamicin group has a lower event rate compared with control group. In other words, patients have better survival outcome with disease related death in the inotuzumab ozogamicin group.
- Among patients with death due to other cause, the results are reversed. Control arm has better outcome compared with patients in inotuzumab ozogamicin.

Figure 14 Cumulative Incidence Cause-Specific Plot for OS



Subgroup Analyses for OS

Table 34 below shows summary of subgroup analyses by gender, region, and other baseline characteristics for the primary efficacy endpoint OS.

Table 39 Subgroup Analyses by Gender, Region, and Other Baseline Characteristics for OS-ITT Population

	Inotuzumab ozogamicin N=164	Investigator's Choice N=162	HR (97.5% CI)
Gender			
Male, n	91	102	0.665
Event	59	83	(0.46, 0.96)
Median in months	8.6	5.3	
Female, n	73	60	0.905
Event	53	47	(0.58, 1.42)

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	Inotuzumab ozogamicin N=164	Investigator's Choice N=162	HR (97.5% CI)
Median in months	6.7	8.7	
North America, n	75	79	0.77
Event	54	66	(0.51, 1.16)
Median in months	7.7	6.4	
Asia, n	26	17	1.23
Event	23	12	(0.54, 2.82)
Median in months	6.5	5.3	
EU, n	61	66	0.61
Event	44	52	(0.38, 0.97)
Median in months	8.4	6.9	
Other, n	2	0	
Event	1		
Median in mon			
BMA blasts <50%, n	53	48	0.69
Event	37	42	(0.41, 1.15)
Median in months	7.4	9.1	
BMA blasts ≥50%, n	109	113	1.12
Event	84	87	(0.70, 1.79)
Median in months	7.7	5.5	
Ph+, n	22	28	0.99
Event	18	22	(0.48, 2.02)
Median in months	8.7	7.7	
Ph-, n	142	134	0.71
Event	104	108	(0.52, 0.97)
Median in months	7.4	5.9	
Complex, n	27	22	0.61
Event	22	18	(0.30, 1.25)
Median in months	7.2	3.9	
Normal with metaphases ≥20, n	35	34	0.64
Event	24	28	(0.34, 1.19)
Median in mon	8.6	8.9	
Pre-study transplant Yes, n	29	31	1.36
Event	24	20	(0.69, 2.69)
Median in months, n	8.4	13.1	
Pre-study transplant No, n	135	131	0.66
Event	98	110	(0.48, 0.90)
Median in months	7.2	5.5	

Reviewer's comments:

When patients BMA blasts $\geq 50\%$, or patients received pre-study transplant, the hazard ratios are great than 1 in favor of control arm. However, the interpretation of those results is difficult since the estimate of the treatment difference for each subgroup almost certainly has lower precision because of smaller sample sizes unless the precision of subgroup estimate has been considered properly in planning the sample size or the variability of the response is sufficiently small in the subgroup. Consequently, the statistical power for detecting the same magnitude of the treatment effect may be insufficient in those subgroup analyses. Therefore, we recommend that those subgroup analysis interpretations are only exploratory and suggestive, and the results are yet to be confirmed by prospective studies of the subgroups.

Table 35 below shows summary of subgroup analyses by stratification factors for the primary efficacy endpoint OS.

Table 40 Subgroup Analyses for OS by Stratification Factors-ITT Population

	Inotuzumab N=164	Investigator's Choice N=162	HR (97.5% CI)
Duration of First Remission			
<12 month, n	109	107	0.83
Event	89	89	(0.60, 1.17))
Median in months	6.6	5.3	
≥ 12 month, n	55	55	0.59
Event	33	41	(0.34, 1.00)
Median months	11.1	9.4	
Salvage 1, n	108	107	0.65
Event	75	87	(0.46, 0.93)
Median in months	8.6	7.1	0.97
Salvage 2, n	56	55	(0.60, 1.56)
Event	47	43	
Median in months	6.2	5.2	
<55 year, n	104	103	0.68
Event	70	79	(0.47, 0.98)
Median in months	8.6	8.0	
≥ 55 year, n	60	59	0.90
Event	52	51	(0.58, 1.41)
Median in months	5.6	5.3	

Reviewer's Comments:

The analysis of OS across the stratification variables of duration of first remission, age, and salvage was consistent with the primary analysis of OS on the ITT population. The hazard ratios

from the analysis of stratification variables are all less than 1 in favor of inotuzumab ozogamicin arm.

Efficacy Results – Secondary and other relevant endpoints

PFS Analysis Results

A summary of PFS analysis in the ITT population based on cutoff date of 08 March 2016 summarized in the table blow. A total of 128 (78.0%) PFS events were observed in the inotuzumab ozogamicin arm and 125 (77.2%) PFS events were observed in the control arm. The estimated median PFS was 5.0 months with 95% CI of (3.7, 5.6) in the inotuzumab ozogamicin arm and 1.8 months with 95% CI of (1.5, 2.2) in the control arm. The estimated HR was 0.45 with 97.5% CI of (0.34-0.61) based on stratified analysis Cox PH model.

Table 41 Summary of PFS Analysis Results-ITT Population

	Inotuzumab N=164	Investigator’s Choice N=162
Event	128 (78.0)	125 (77.2)
Censored patients	36 (22.0)	37 (22.8)
Median PFS (month) (95% CI)	5.0 (3.7, 5.6)	1.8 (1.5, 2.2)
HR (97.5% CI)	0.45 (0.34, 0.61)	

DoR

Table 42 summarizes the DoR and time to remission for patients who achieved CR/CRi in the ITT218 Population, based on database cutoff date of 08 March 2016. In total, 84 (77.1%) patients achieved CR/CRi in the inotuzumab ozogamicin arm compared with 32 (29.4%) patients in the control arm. The estimated median DoR was 5.4 months with 95% CI of (4.2-8.0) in the inotuzumab ozogamicin arm and 3.5 months with 95% CI of (2.9, 6.6) for patients in the control arm. For patients who achieved CR/CRi, the estimated median time from randomization to remission was 0.72 months (range 0.5 to 1.8 months) for patients in the inotuzumab ozogamicin arm and 0.92 months (range 0.7 to 2.6 months) for patients in the control arm.

Table 42 Summary of Analysis of DoR

	Inotuzumab N=109	Investigator’s Choice N=109
Patients with a remission (CR/CRi)	84 (77.1)	32 (29.4)
Median DoR (95% CI)	5.4 (4.2, 8.0)	3.5 (2.9, 6.6)
Median time to remission (Range)	0.72 (0.5-1.8)	0.92 (0.7, 2.6)

MRD Negativity

Table 43 below summarizes the MRD negativity analysis (based on central laboratory) in patients achieving CR/CRi in the ITT Population. In patients achieving a CR/CRi in the ITT Population, a greater proportion of patients in the inotuzumab ozogamicin arm achieved MRD negativity compared with the control arm. Among patients who achieved CR/CRi, 76.7% achieved MRD negativity in the inotuzumab ozogamicin arm and 38.0% achieved MRD negativity in the control arm for a rate difference of 38.7%.

Table 43 Summary of Analysis of MRD Negativity

	Inotuzumab N=164	Investigator's Choice N=162	nominal p-value from Chi-square test
# of patients with CR/CRi	120	50	<0.0001
MRD Negative (95% CI)	92 (76.7) (68.1, 83.9)	19 (38.0) (24.7, 52.8)	

PRO Analyses Results

Patients completed self-administered questionnaires predose at baseline (Cycle 1 Day 1), Day 1 of each subsequent cycle, and at the EOT.

EORTC QLQ-C30

For questionnaires where patients completed at least 1 question, the overall completion rate was 85.3% for the inotuzumab ozogamicin arm and 65.3% for the control arm. For questionnaires where patients completed all questions, the overall completion rate was 81.6% for the inotuzumab ozogamicin arm and 62.0% for the control arm. The least square means were estimated from longitudinal mixed-effects model.

Table 44 Summary of Completers Analyses Results for PRO Endpoint-ITT Population

Mean (95% CI)	Mean Inotuzumab Ozogamicin N=164	Mean Investigator's Choice N=162	Mean difference
EORTC QLQ-C30 Physical functioning	75.0 (72.1, 77.8)	68.1 (63.4, 72.7)	6.9 (1.4, 12.3)
Role functioning	64.7 (60.8, 68.7)	53.4 (46.3, 60.4)	11.4 (3.2, 19.5)
Emotional functioning	77.4 (75.0, 79.7)	79.6 (75.7, 83.6)	-2.3 (-6.9, 2.3)
Cognitive functioning	85.3 (83.1, 87.4)	82.5 (78.9, 86.1)	2.8 (-1.4, 7.0)
Social functioning	68.1 (64.3, 72.0)	59.8 (53.1, 66.5)	8.4 (0.7, 16.1)
Global health status	62.1 (59.1, 65.1)	57.8 (52.6, 63.0)	4.3 (-1.7, 10.3)
Dyspnea	14.7 (11.8, 17.7)	19.4 (14.1, 24.8)	-4.7 (-10.8, 1.4)

Mean (95% CI)	Mean Inotuzumab Ozogamicin N=164	Mean Investigator's Choice N=162	Mean difference
Insomnia	25.4 (21.9, 28.8)	27.1 (21.1, 33.1)	-1.7 (-8.7, 5.2)
Appetite loss	17.6 (14.1, 21.1)	26.3 (19.9, 32.7)	-8.7 (-16.0, -1.4)
Constipation	12.1 (9.2, 15.0)	10.7 (5.6, 15.7)	1.4 (-4.4, 7.3)
Diarrhea	5.9 (3.9, 7.8)	8.9 (5.2, 12.6)	-3.0 (-7.2, 1.1)
Financial difficulties	29.5 (25.9, 33.0)	32.0 (25.7, 38.2)	-2.5 (-9.7, 4.7)
Fatigue	35.0 (31.7, 38.3)	39.4 (33.9, 44.9)	-4.4 (-10.8, 2.0)
Nausea and vomiting	8.7 (6.6, 10.8)	10.4 (6.6, 14.2)	-1.6 (-6.0, 2.7)
Pain	21.3 (18.0, 24.6)	22.0 (16.2, 27.7)	-0.7 (-7.3, 6.0)
EQ-5D Index	0.80 (0.77, 0.82)	0.76 (0.73, 0.80)	0.03 (-0.01, 0.07)
EQ-VAS	67.1 (64.0, 70.2)	62.5 (57.6, 67.4)	4.6 (-1.2, 10.4)

Reviewer's Comments:

The PRO analysis results were generally in favor of patients in the inotuzumab ozogamicin arm compared to those in the control arm. However, the distribution of questionnaires is imbalanced between the two arms. For questionnaires of EQRTC QLQ-C30 where patients completed at least 1 question, the overall completion rate was 85.3% for the inotuzumab ozogamicin arm and 65.3% from the control arm. In addition, in the control arm the number of patients remaining on treatment decreased markedly by Cycle 2 (16.7%), with only 3.1% patients and 0.6% patients remaining by Cycle 3 and Cycle 4, respectively. Due to the imbalanced distribution of missing data between the two arms, the results should be interpreted with caution.

Additional Analyses Conducted on the Individual Trial

The FDA requested the Applicant to conduct additional analyses to better describe the treatment effect of inotuzumab on the following parameters: red cell transfusions, platelet transfusions, incidence and time to transfusion independence, support, length of hospitalization from time of randomization, and intubation/ventilatory support in the intensive care unit. The results were reviewed by the clinical reviewer.

Transfusions

Transfusion independence was defined as patients who did not receive transfusions within the last 4 weeks prior to the end of treatment. Data was only collected by Applicant until the end of the treatment date.

Table 45 Summary of Red Blood Cell and Platelet Transfusions and Transfusion independence

	Inotuzumab Ozogamicin N=164	Investigator's Choice N=143 n(%)

	n(%)	
Number of Subjects with Transfusions n(%)	122(74)	142(99)
Platelets	106(65)	139(97)
Days of platelet transfusions		
Total	1090	1278
Median	7	7
Range	(1,51)	(1,30)
PRBC's	103(63)	138(97)
Days of PRBC transfusions		
Total	468	816
Median	3	5
Range	(1,28)	(1,20)
Number of patients with transfusion independence(within last 4 weeks to EOT)	90(55)	16(11)
Platelet independence	98(60)	26(18)
RBC independence	117(71)	19(13)
Platelet and RBC independence	90(55)	16(11)

Source: Summarized data from Applicants Table 5.3.5.1

*only transfusion on or after first dose date and within 42 days of last dose are summarized.

*transfusion is packed RBC, other-irradiated leukocyte-poor RBC, other-erythrocyte autotransfusion or other-leukocyte depleted RBC.

Hospitalizations

A summary of length of hospitalization from time of randomization is displayed in the table below.

Table 46 Study 1022: Summary of Hospitalizations

	Inotuzumab Ozogamicin N=164 n(%)	Investigator's Choice N=143 n(%)
Hospitalization in all Cycles	136(83)	135(94)
Total days during Treatment	136	29
Median	16.5	28
(Range)	(2,174)	(3,81)
Hospitalization in Cycle 1		
Total days in Cycle 1	124	135
Median	12	26
(Range)	(1,56)	(1,55)

Source: summarized from Applicants submission, M5.3.5.1

Additional exploratory analyses were requested by the FDA given the difference in magnitude between the CR/CRi, MRD, and the overall survival results. FDA requested additional analyses

pertaining to post transplant mortality and transplant related mortality. Additional datasets requested included analyses of survival (overall survival, Day 100 and day + 180) in patients who underwent hematopoietic stem cell transplantation (HSCT) from the time of HSCT. Refer to the efficacy reviewer for the further discussion and analysis of the post transplantation survival and transplant related mortality. Refer to the safety review for discussion of baseline disease characteristics and transplant characteristics that impacted survival after transplantation.

Additional MRD Analyses

MRD negativity was defined by flow cytometry as leukemic cells comprising $< 1 \times 10^{-4}$ (<0.01%) of bone marrow nucleated cells. MRD results were also analyzed based on overall survival and by subjects who attained a CR or CR/CRi. Figure 7 displays the survival curves for the inotuzumab arm based on response and MRD negativity as assessed by the EAC.

Figure 15: Overall Survival for Inotuzumab Ozogamicin Arm for CR or CRi and MRD

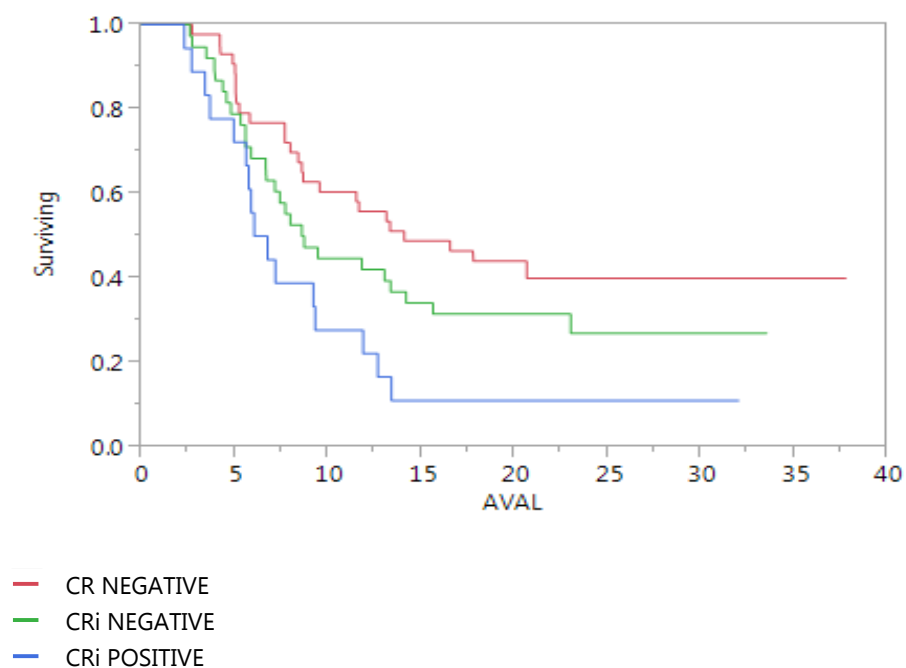


Table 47 Summary of OS(Number Failed and Censored)

Group	Number Failed	Number Censored
CR MRD negative	25	19
CRi MRD negative	27	11
CRi MRD Positive	16	2

Source: FDA Analysis of TTE dataset

An FDA exploratory analysis of the overall survival based on response as assessed by EAC and MRD negativity was performed for the inotuzumab ozogamicin arm. The CR MRD positive arm was not included in survival curves due to the small number of subjects. The depth of response for patients who attained a CRi with MRD negativity provides support for the inclusion of patients who attained a CRi in supportive conclusion of the rate of MRD negativity in patients who attained either a CR or CRi in the inotuzumab ozogamicin arm. The numbers in the control arm were too small to conduct any meaningful analysis.

Reviewer Comment: Patients who attained a CR and MRD negativity had longer overall survival compared to patients who failed to attain MRD negativity (for the inotuzumab ozogamicin arm). Patients who also attained CRi and MRD negativity also demonstrated longer survival.

Analysis of CRh

Additional analysis of the number of patients who attained CRh was performed for the ITT218 population (EAC) and the full ITT population (n=326) base on investigator assessment was performed by the clinical reviewer. The following tables describe the rate of CR, CRi, and CRh for the inotuzumab ozogamicin arm compared to the investigator choice arm for the ITT218 and full ITT population.

- CRh is defined as ANC>500/microliter and platelet count>50,000/microliter with < 5% blasts in the bone marrow.
- CRi is defined as < 5 blasts in the bone marrow and the absence of peripheral blood leukemic blasts, partial recovery of peripheral blood counts(platelets < 100 x 10⁹/L and ANC<1 x 10⁹/L).
- CR is defined as < 5% blasts in the bone marrow and absence of peripheral blood leukemic blasts, full recovery of peripheral blood counts(platelets ≥ 100 x 10⁹/L and ANC ≥ 1 x 10⁹/L and resolution of any extramedullary disease.

Table 48: Rates of CR, CRi and CRh in the ITT 218 population for Study 1022(EAC)

	CR		CRi		CRh	
	Inotuzumab N=109	Inv Choice N=109	Inotuzumab N=109	Inv Choice N=109	Inotuzumab N=109	Inv Choice N=109
n(%) [95%CI]	39(35.8) [26.8,45.5]	19(17.4) [10.8,25.9]	49(45.0) [35.4,54.8]	13(11.9) [6.5,19.5]	32(29) [23.2, 40.7]	6(5) [1.5,10.4]
MRD- negativity n(%)	35/39(89.7)	6/19(31.6)	34/49(69.4)	3/13(32.1)	23/32(71.8)	1/5(20)

Table 49 Rates of CR, CRi and CRh in the ITT(n=326) population per INV assessment for Study 1022.

	CR		CRi		CRh	
	Inotuzumab N=164	Inv Choice N=163	Inotuzumab N=164	Inv Choice N=163	Inotuzumab N=164	Inv Choice N=163
n(%)	55(34)	26(16)	65(39.6)	24(14.8)	38(23.2)	13(7.9)

The rate of MRD negativity in the patients who attained CRh in the inotuzumab ozogamicin arm was 26/38(68.4) and was 4/13(30.7) in the investigator choice arm.

Reviewer Comment: In the inotuzumab ozogamicin arm, the rate of attainment of CRh(29%) in the ITT218 population per EAC is comparable to the rate of CR(35.8%) and CRi(45.0%). The magnitude of difference between the attainment of CRh in the inotuzumab arm (29%) compared with the investigator choice arm (5%) is notable as is the rate of MRD negativity for the CRh(71.8%) versus 20% (inotuzumab vs investigator choice arm).

Updated OS Analysis Results Based on the 04 January 2017 Last Subject Last Visit (LSLV)

On April 2017, the sponsor submitted updated OS data based the 04 January 2017 last subject last visit (LSLV) to the Agency. The sponsor proposes to include updated OS results in the labeling. The table below includes the reviewer’s analysis results based on the 04 January 2017 last subject last visit. Between the primary analysis (08 March 2016 cutoff date) and updated analysis (04 January 2017 LSLV date), an additional 15 deaths were observed.

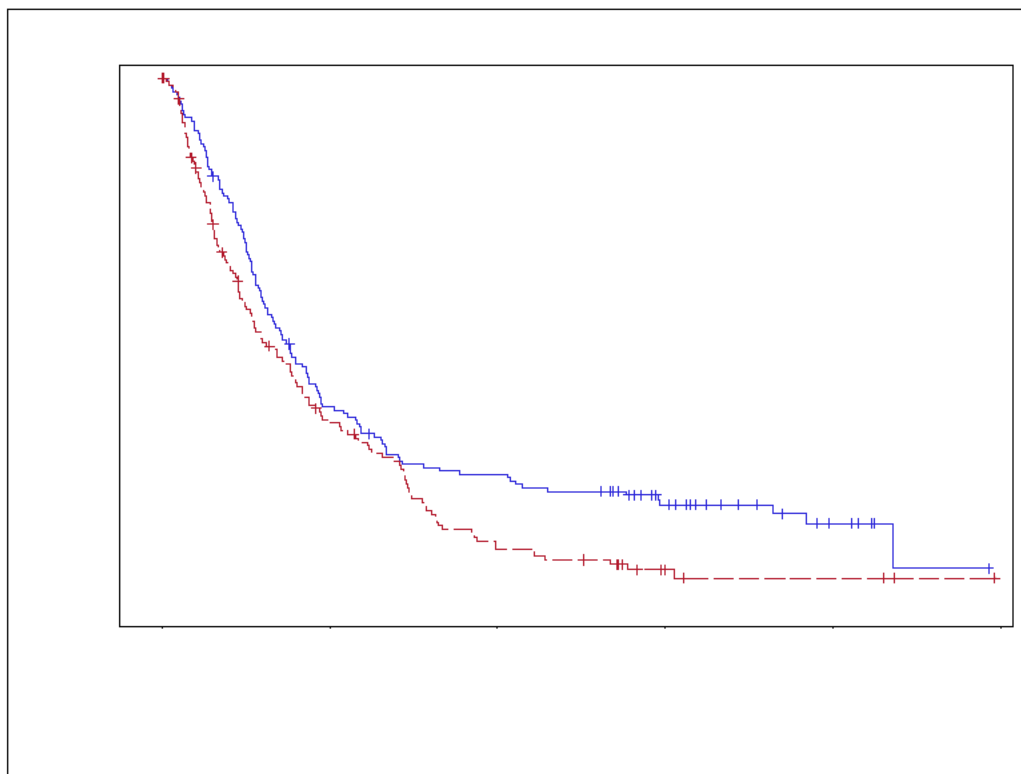
Table 50 Analysis Results for Overall Survival-ITT Population

Analysis Results for Overall Survival-ITT Population	Inotuzumab Ozogamicin	Investigator’s Choice
Number of deaths	131/164 (79.9%)	136/162 (84.0%)
Median survival time (95% CI)	7.51 (6.0, 9.2)	6.7 (4.7, 8.3)
Stratified HR (97.5% CI)	0.751 (0.568, 0.993) p=0.0105 (stratified log-rank test)	
Unstratified HR (97.5% CI)	0.741 (0.562, 0.977) p=0.0073 (unstratified log-rank test)	

Reviewer’s Comments: The estimated HR (inotuzumab ozogamicin vs. control) based on the updated OS data was 0.75 (97.5% CI: 0.57-0.99) ; 1-sided p=0.0105) based on the stratified analysis. There is a minor numerical difference between the primary analysis (08 March 2016 cutoff date) and updated analysis (04 January 2017 LSLV date), but the difference did not alter the conclusion that the result failed to demonstrate significant improvement in OS endpoint in the inotuzumab ozogamicin arm compared with control arm. The estimated median OS was 7.5 months (95% CI: 6.0-9.2) in the inotuzumab ozogamicin arm compared with 6.7 months (95% CI: 4.7-8.3) in the control arm.

Figure below shows the Kaplan-Meier Plot for the overall survival using ITT population based on updated OS data. The Kaplan-Meier plot also indicates that the difference in survival between the 2 treatment arms varied during the study. The survival probability at 24 months was 22.8% (95% CI: 16.7-29.6) in the inotuzumab arm compared to 10.0% (95% CI: 5.7-15.5) in the control arm.

Figure 16 Kaplan-Meier Plot for Overall Survival-ITT Population



Study B1931010 (Study 1010)

Study Design

The principal evidence for the clinical efficacy and safety of inotuzumab ozogamicin is derived from 2 studies of patients with relapsed or refractory B-cell ALL: pivotal phase 3 Study B1931022 and supportive phase 1/2 single-arm Study B1931010. In this section, the study design and efficacy analysis results for the supportive Study B1931010 are briefly summarized.

The Study B1931010 was an open-label, single-arm, multicenter, phase 1/2 study of single agent inotuzumab ozogamicin in adult patients with relapsed or refractory CD22- positive ALL. The objective of the phase 1 dose escalation portion of the study was to identify and characterize the RP2D. The phase 2 single-arm 2-stage portion of the study further evaluated

the efficacy, safety, and tolerability profile of inotuzumab ozogamicin in adult patients with relapsed or refractory CD22-positive ALL to second or later salvage therapy.

Treatment with inotuzumab ozogamicin was continued until disease progression, patient refusal, unacceptable toxicity, or up to a maximum of 6 cycles, whichever occurred first. Patients received 2 to 3 weekly doses of inotuzumab ozogamicin over a 28-day cycle for a maximum of 6 cycles. Up to 6 dose levels and schedules of administration were planned. If changes were required to the proposed doses, schedules, and PK time points based on emerging data, the protocol was amended accordingly during the study. Approximately 30 to 70 patients were expected to be enrolled.

In the phase 1 dose-finding portion of the study of the study, the exact sample size was not pre-specified in advance since it was an outcome-adaptive Bayesian procedure, but a maximum of 36 patients were to be enrolled. In the phase 1 dose-expansion portion of the study, an additional 12 patients were enrolled to further assess the safety, tolerability, and efficacy of the RP2D.

In the phase 2 portion of the study, approximately 35 patients were to be enrolled. In this portion of the study, the dose of inotuzumab ozogamicin was based on the RP2D and schedule determined in the phase 1 portion of the study. A 2-stage design was used, with 12 patients expected to be treated in the first stage and 23 patients treated in the second stage. For enrollment to proceed to the second stage, at least 2 patients had to achieve a complete response (CR/CRi) in the first stage. At the end of the study, at least 12 complete responses (CR/CRi) in 35 treated patients were required in order to recommend further studies of this dose and schedule in the patient population.

Efficacy Results-Phase 2

In the phase 2 study population, the CR/CRi rate was 68.6% (95% CI: 50.7-83.2). The median time to CR/CRi for the 24 patients who achieved CR/CRi was 25.5 days (range: 15 to 91 days). Of the 24 patients who achieved CR or CRi, 18/24 (75%) patients also achieved MRD-negativity and the median time to MRD-negativity was 25.5 days (range: 21-80 days). The median DoR1 (duration of remission [CR/CRi]) was 16.6 weeks (95% CI: 9.4, 25.1) (i.e., 3.8 months [95% CI: 2.2-5.8]). The median PFS was 16.0 weeks (95% CI: 11.3-20.6) (i.e., 3.7 months [95% CI: 2.6-4.7]). The median OS was 27.9 weeks (95% CI: 19.6-34.3) (i.e. 6.4 months [95% CI: 4.5-7.9]). In this late stage salvage setting population, 8/35 (22.9%) patients underwent HSCT after study therapy or subsequent induction therapy.

Reviewer's Comments:

(b) (4) (b) (4) *this study is a single arm early phase study intended to evaluate activity of the treatment, the analysis results should be considered as exploratory.* (b) (4)

(b) (4) *Also time to event endpoints such as PFS and OS are not interpretable in a single arm study.*

7.2.3. Study 1931008 (Study 1008)

Study 1008 is an open-label, randomized, Phase 3 Study of Inotuzumab Ozogamicin administered in combination with Rituximab Compared to Defined Investigator's Choice Therapy in Subjects with Relapsed or Refractory CD22+ Aggressive NHL who are not candidates for Intensive High-Dose Chemotherapy.

The primary endpoint of Study 1008 was overall survival. The planned sample size was 377 subjects and the study enrolled 322 subjects. At the first interim analysis the median overall survival was (b) (4) months in the Inotuzumab Ozogamicin plus rituximab arm compared to (b) (4) months in the control arm. (b) (4) The study was stopped for futility since p-value (b) (4).

7.2.4. Study 1931006(Study 1006)

Study 1006 is an open-label, randomized, Phase 3 Study of Inotuzumab Ozogamicin Administered in Combination with Rituximab Compared to a Defined Investigator's Choice Therapy in Subjects with Relapsed or Refractory CD22 Positive Follicular B Cell NHL.

The primary endpoint was progression free survival but only enrolled 29 of planned 978 subjects. The study was terminated early as it was unlikely that the study would ever meet estimated enrollment.

Reviewer Comment: There is no efficacy data for the use of inotuzumab ozogamicin in patients with Non-Hodgkin Lymphoma. Inclusion of lack of efficacy in subjects with NHL in the USPI is recommended.

7.3. Integrated Review of Effectiveness

7.3.1. Assessment of Efficacy Across Trials

Primary Endpoints

There were two primary efficacy endpoints (CR/CRi and OS) in Study 1022. The study had at least 88.5% power to detect a difference of response probabilities between the inotuzumab ozogamicin arm versus the control arm. In the inotuzumab ozogamicin arm, the primary efficacy endpoint of CR/CRi was attained in 81% subjects(95% CI: 72%,88%) vs 29% subjects(95% CI: 21%,39%) in the control arm for a rate difference of 51% with 1-sided p< 0.0001 based on the primary analysis of the initial 218 randomized patients. This improvement was consistent when evaluating the ITT population (all 326 patients) for CR/CRi [73% (95% CI: 66%, 80% in inotuzumab ozogamicin arm vs 31% (24-39)] in the control arm, rate difference 42% with 1-sided p< 0.0001. For the primary analysis of overall survival in the ITT population the estimated hazard ratio for overall survival was 0.77(97.5% CI 0.58, 1.03) with one- sided p-

0.0203 for the inotuzumab ozogamicin arm compared to the control arm in Study 1022. This difference did not reach statistical significance as it exceeded the prespecified 1-sided p-value boundary of 0.0104. The number of patients who underwent follow-on HSCT was 77/164(47%) in the inotuzumab arm compared to 19/33(58%) in the control arm. The overall post study therapy HSCT mortality was 60% (46/164) in the inotuzumab arm and 58% (19/162) in the control arm and the post study therapy HSCT non-relapse mortality was 38%(29/77) in the inotuzumab ozogamicin arm versus 24%(8/33) in the control arm.

The efficacy results from Study 1010 are comparable to study 1022 noting that subjects in Study 1010 were more heavily pretreated with 78% in Salvage 2 or greater. In study 1010, the CR/CRi rate was 68% (95% CI 56, 78.6) for all 72 patients.

Secondary and Other Endpoints

In the pivotal study, improvement was consistent for all secondary endpoints. In particular rates of MRD negativity in patients who achieved CR/CRi were higher in the inotuzumab ozogamicin arm compared to the chemotherapy arm based on the ITT population [77%(95% CI: 74%,88%)] vs [38%(95% CI:26%,43%)] for a rate difference of 50% with 1-sided $p < 0.0001$). The rate of MRD negativity in patients in patients who received inotuzumab ozogamicin and who achieved a CR was 90% (95% CI: 76%- 97%) compared with the investigator's choice of chemotherapy arm of 32% (95% CI: 13%- 57%) in the ITT218 population. The subjects who attained CR/CRi and MRD negativity and with subsequent HSCT, the estimated median overall survival was 17.8 months vs patients with CR/CRi and MRD positivity and subsequent HSCT with an estimated median overall survival of 11.9 months. It is unclear if this longer survival is due to MRD status or treatment effect of inotuzumab.

In the ITT 218 population, 45%(49/109)patients attained a CRi(EAC assessment) and of these patients 34/49(69.4%) attained MRD negativity. In the investigator choice of chemotherapy arm, 11.9%(13/109) achieved a CRi with only 3/13(23%) attaining MRD negativity. In the inotuzumab arm, the median duration of response for patients who attained a CRi was 4.6 months(95% CI 3.7,5.7) compared to investigator choice arm of median duration of response of 2.9 months with 95% CI(0.6, 5.7). In the ITT population,(investigator assessment), there were 65/164(39.6%) patients with CRi compared with 24/162(14.8%) patients with CRi in the control arm.

Based on the data from this randomized study, the CRi responders performed better overall with respect to MRD response and duration of response compared to the chemotherapy control arm. In patients with relapsed ALL in CR2, MRD may be a more powerful predictor of outcome than CRp or CRi with regard to relapse free survival and patients with MRD positivity are likely to have higher risk of relapse (Saygin 2017). HSCT in CR2 also appears to independent prognostic predictor for OS and RFS (Saygin 2017). The depth and magnitude of response for patients who attained a CRi with MRD negativity provides additional support for the inclusion of the composite CR(CR and CRi).

Subpopulations

The improvement in CR/CRi was consistent across all prespecified stratification subgroups (duration of first remission, line of salvage and age at randomization).

7.3.2. Integrated Assessment of Effectiveness

The efficacy of inotuzumab ozogamicin in relapsed or refractory ALL has been established, primarily on the results of a single randomized, phase III study in patients greater than or equal to 18 years of age with relapsed or refractory ALL in which patients (ITT218 population) who received inotuzumab ozogamicin had better complete response and complete responses with incomplete hematological recovery (CR/CRi) 81% (95% CI: 72%, 88%) compared to the patients who received a defined investigator's choice of chemotherapy (29%, 95% CI: 21, 39%). The responses were consistent in analysis of the full ITT population and essentially consistent across the subpopulations tested.

The secondary endpoints of CR and duration of response were used to inform the regulatory decision making process. CR was achieved by 39/109 (36%) subjects (95% CI: 27%, 46%) in the inotuzumab ozogamicin arm vs 19/109 (17%) subjects (95% CI: 11%, 26%) in the investigator's choice of chemotherapy arm. The response was durable with estimated median duration of complete response of 8 months (95% CI: 5, 10 months) in the inotuzumab ozogamicin arm compared to 5 months (95% CI: 3, 7 months) in the investigator's choice of chemotherapy arm.

Subjects on Study 1022 were tested for MRD using flow cytometry and MRD levels less than $<1 \times 10^{-4}$ are expected to be reasonably likely to predict clinical benefit in the intended population. In patients who received inotuzumab ozogamicin and attained a CR, a reduction in MRD to less than 10^{-4} was achieved by 90% (95% CI: 76%, 97%) compared to the investigator's choice of chemotherapy arm of 32% (95% CI: 13%, 57%) in the ITT218 population. For patients who achieved CR/CRi in the ITT population (n=326), a reduction in MRD to less than 10^{-4} was achieved by 92/120 (78%) subjects (95% CI: 68%, 87%) in the inotuzumab ozogamicin arm versus 19/50 (38%) subjects (95% CI: 24%, 47%) in the investigator's choice of chemotherapy arm. An FDA exploratory analysis of the overall survival based on response as assessed by EAC and MRD negativity was performed. The depth of response for patients who attained either a CR or CRi with MRD negativity provides additional support for the inclusion of the MRD negativity rate for patients who attained a CRi. Based on the data Study 1022, the CRi responders performed better overall with respect to MRD response and duration of response compared to the patients in the chemotherapy control arm who attained a CRi. In the inotuzumab arm, the patients with CRi appear to be comparable to patients who attained CR with regard to MRD negativity and durability of response.

In the inotuzumab ozogamicin arm, the rate of attainment of CRh (29%) in the ITT218 population per EAC is comparable to the rate of CR (35.8%) and CRi (45.0%). The magnitude of difference between the attainment of CRh in the inotuzumab arm (29%) compared to the investigator choice arm (5%) is notable as is the rate of MRD negativity for the CRh (71.8%)

versus 20%(inotuzumab vs investigator choice arm). The patients with CRh appear to be comparable to patients who attained a CR with regard to response and MRD negativity.

An improvement in the second primary endpoint of overall survival did not reach statistical significance as it exceeded the prespecified 1-sided p-value boundary of 0.0104 in the pivotal phase 3 study (B1931022). The estimated hazard ratio for the primary endpoint of OS in the ITT population was 0.770 (97.5% CI: 0.578, 1.026) with an estimated median OS of 7.7 months (95% CI 6, 9.2) for inotuzumab ozogamicin versus 6.7 months (95% CI 4.9 8.3) in the control arm with one- sided p-0.0203. For subjects who received HSCT, there were fewer early deaths in the control arm however subjects in the inotuzumab arm have better survival outcome than the control subjects after 18 months (p-value for treatment effect by HSCT interaction <0.05). In the competing risk analysis when death was attributed to disease only, there are fewer cumulative deaths over time in the inotuzumab arm than the control arm. When considering deaths attributed to causes other than disease, the reverse was true, there were more cumulative deaths over time in the inotuzumab arm compared to the control arm (non-relapse mortality in inotuzumab arm of 38%(29/77) versus 24%(8/33) in the control arm).

The higher non-relapse mortality in the inotuzumab ozogamicin arm is due primarily to the occurrence of hepatic VOD and resulting complications in patients who proceeded to subsequent HSCT after inotuzumab ozogamicin. The increased risk of post-HSCT non-relapse mortality in patients with relapsed or refractory ALL who receive inotuzumab ozogamicin and proceed to subsequent HSCT warrants a boxed warning in the product label.

In summary, the current standard of care for the treatment of relapsed or refractory ALL is intensive combination chemotherapy. The CR rate of 36% with a durable response (median 8 months) are better than the responses for the control arm of defined investigator choices of single agent or combination chemotherapy regimens. Moreover, an MRD response was noted in 78% of patients who attained a CR/CRi compared to only 38% in the chemotherapy arm. Although inotuzumab ozogamicin failed to reach statistical significance for overall survival, subjects in the inotuzumab arm had better survival outcome than the control subjects after 18 months. In the inotuzumab arm, for patients who proceeded to transplantation, the early deaths and worse non-relapse mortality were due to VOD. Taken together, the efficacy outcomes (CR, durability, and MRD) in the inotuzumab ozogamicin arm form a strong basis for a conclusion of effectiveness provided that the safety risks (VOD, increase in non-relapse mortality) are adequately described in the labeling information.

Given the prevalence of CD22 expression on lymphoblasts in patients with ALL and the routine testing for CD22 expression in patients with ALL, no restriction on CD22 + expression is recommended. The pivotal study included patients with Philadelphia chromosome positive ALL(Ph+ ALL) and there appears to be no difference in response for patients with Ph+ ALL versus those with Philadelphia chromosome negative ALL and thus the indication includes all patients with relapsed or refractory precursor B-cell ALL. Data from studies 1006 and 1008 in subjects with NHL demonstrates no evidence for efficacy and the prescribing information

should include statement regarding the lack of efficacy for inotuzumab ozogamicin in patients with NHL.

7.4. Review of Safety

Safety Review Approach

The clinical reviewer confirmed the Applicant's safety analyses from the 2 studies in patients with relapsed or refractory B-Cell ALL: the pivotal study B1931022 and supportive Study B1931010. The clinical reviewer also reviewed the safety analysis performed by the Applicant from 9 studies in patients with relapsed or refractory non-Hodgkin lymphoma (NHL) treated with inotuzumab ozogamicin as a single agent, in combination with rituximab, or in combination with rituximab plus chemotherapy. The analyses were conducted primarily using MedDRA Adverse event Diagnosis Service (MAED) and JMP statistical programs.

A key safety issue with inotuzumab ozogamicin identified *a priori* is hepatic veno-occlusive (VOD) disease or sinusoidal obstructive syndrome (SOS). There is a known safety issue with the use of a related drug (Mylotarg) and the risk for development of hepatic VOD. Particular attention was given to hepatotoxicity and in particular hepatic VOD/SOS during this review.

7.4.2. Review of the Safety Database

Overall Exposure

A total of 880 patients have received at least one dose of inotuzumab ozogamicin in applicant sponsor studies. This safety review focuses on the comparison of the 164 patients who received inotuzumab ozogamicin compared to the investigator choice (N=143) in Study 1022. In addition, the pooled R/R ALL population consists of the 164 patients from Study 1022 and 48 patients who received the proposed dose (of inotuzumab ozogamicin from study 1010. The following table describes the various safety populations.

Table 51 Description of Safety Database

Safety Populations	Number of patients treated with inotuzumab ozogamicin n
<i>Studies in R/R ALL</i>	
Study 1022*	164
Study 1010	72
Propose Dose	48
Dose finding portion of study	32
<i>POOLED ALLR/R at proposed dose*</i>	212

Safety Populations	Number of patients treated with inotuzumab ozogamicin n
Studies in NHL	
Pooled Single agent inotuzumab in B-cell NHL Study 1002 Study 1016 Study 1007	173
Pooled Inotuzumab Ozogamicin +rituximab in B-Cell NHL Study 1005 Study 1004 Study 1001 Study 1006 Study 1009	368
Inotuzumab Ozogamicin + rituximab + chemotherapy in B-Cell NHL Study 1003	103
Total NHL	644
Total exposed to Inotuzumab in Applicant clinical trials	880
Investigator Initiated research studies¹	307
Compassionate Use Patients¹	N~211

Source: FDA Summary of Applicants Datasets and SCS Module 2

*Primary source of safety analysis

¹no datasets to review, summary of adverse events provided by Applicant

A summary of exposure to inotuzumab ozogamicin in Study 1022 by weeks and cycles is provided in Tables 51 and 52. In Study 1022, the median total dose for inotuzumab was 4.2mg/m² (range 0.8, 9.6mg/m²). The median dose in the inotuzumab ozogamicin arm was 1.8mg/m² for Cycle 1. The median dose in Cycle 2, 3, 4 and 5 was 1.5mg/m² and was 1.4mg/m² for Cycle 6. After Cycle 1, 71% of patients responded to treatment (achieved remission in cycle 1). The median actual dose intensity (mg/m²/cycle) in the inotuzumab ozogamicin arm was 1.57(range 0.77, 2.06) with a median relative dose intensity of 100.684(range 57.14, 118.17). The median total dose of inotuzumab ozogamicin was 4.215mg/m² (range 0.78, 9.59mg/m²) with median dose intensity of 1.575mg/m²/cycle (range 0.77 to 2.06mg/m²/cycle).

In Study 1022, the majority of subjects (43 subjects, 26%) received inotuzumab for 8-< 12 weeks and 117 subjects (82%) received investigator choice chemotherapy for 0 to < 4 weeks (control arm). The median duration of treatment was 8.9 weeks for patients who received inotuzumab ozogamicin and 0.9 weeks for patients in the control arm. The majority of patients in the inotuzumab arm (127 subjects, 77%) started more than 1 cycle with only 10 patients (6%) completing all 6 cycles. The median number of cycles was 3 in the inotuzumab arm and 1 in the control arm.

Table 52 Treatment Duration in Safety Population for Study 1022(in weeks)

	Inotuzumab Ozogamicin N=164 n(%)	Investigator's Choice(Control Arm)			Total Control Arm N=143 n(%)
		FLAG N=93 n(%)	MXN/Ara-C N=33 n(%)	HIDAC N=17 n(%)	
Duration of treatment(weeks) Median(range)	8.9 (0.1, 26.4)	0.9 (0.4, 15.6)	1.1 (0.4, 8.6)	1.0 (0.6, 9.7)	0.9 (0.1, 15.6)
Duration by weeks n(%)					
0 to < 4	40(24.4)	72(77.4)	31(93.9)	14(82.4)	117(81.8)
4 to <8	35(21.3)	15(16.1)	1(3.0)	1(5.9)	17(11.9)
8 to <12	43(26.2)	2(2.2)	1(3.0)	2(11.8)	5(3.5)
12 to <16	16(9.8)	4(4.3)	0(0)	0(0)	4(2.8)
16 to <20	12(7.3)	0(0)	0(0)	0(0)	0(0)
20 to <24	13(7.9)	0(0)	0(0)	0(0)	0(0)
>24	5(3.0)	0(0)	0(0)	0(0)	0(0)

Source: FDA Analysis ADEX dataset

Table 53 Treatment Duration in Safety Population for Study 1022(by cycles)

	Inotuzumab Ozogamicin N=164 n(%)	Investigator's Choice(Control Arm)			Total Control Arm N=143 n(%)
		FLAG* N=93 n(%)	MXN/Ara-C* N=33 n(%)	HIDAC* N=17 n(%)	
Number of patients starting a cycle, n(%)					
Any Cycle	164(100)	93(100)	33(100)	17(100)	143(100)
1 Cycle	37(22.6)	72(77.6)	31(93.9)	13(76.5)	116(81.1)
2 cycles	40(24.4)	16(17.2)	2(6.1)	4(23.5)	22(15.4)
3 cycles	42(25.6)	4(4.3)	0(0)	0(0)	4(2.8)
4 cycles	19(11.6)	1(1.1)	0(0)	0(0)	1(0.7)
>5 cycles	26(15.9)	0(0)	0(0)	0(0)	0(0)
Median number of cycles per patient Range	3 (1.0, 6.0)	1.0 (1.0, 4.0)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	1.0 (1.0, 4.0)

Source: FDA Analysis ADeX

*Only 4 cycles of FLAG and MXN/Ara-C and only 2 cycles of HIDAC allowed per protocol.

Study 1010

In the phase 2 dose expansion cohort (n=48), the median duration of treatment was 10 weeks and median number of cycles was 3. For the entire population at all dose ranges, the median duration of treatment was 9 weeks (range 0.1, 41.1).

Table 54 Duration of Exposure in Study 1022 and Pooled ALL populations

	Study 1022		Study 1010	Pooled ALL at proposed dose N=212	NHL Studies Single Agent N=173
	Inotuzumab Ozogamicin N=164	Investigator's Choice N=143	Phase 2 Dose expansion cohort N=48		
Duration of treatment(weeks) Range	8.9 (0.1, 26.4)	0.9 (0.1,15.6)	10.1 (0.1, 41.1)	9.1 (0.1, 41.1)	7.6 (0.1, 37.6)
Number of cycles range	3 (1,6)	1.2 (1,4)	3 (1,6)	2.8 3(1,6)	2 N/A

Source: FDA Analysis ADEX dataset

Relevant characteristics of the safety population:

Demographic information for patients enrolled in Study 1022 as well as the R/R pooled ALL safety population is summarized in Table 54. The demographics of the pooled safety R/R database are very similar to the efficacy populations in Study 1022.

Table 55 Demographics of Safety Populations

	Study 1022		Pooled R/R	Single Agent
	Inotuzumab Ozogamicin N=164 n(%)	Investigator Choice N=162* n(%)	ALL Population N=212 n(%)	Inotuzumab NHL N=173 n(%)
Age(years)				
Median (range)	46.5 (18,78)	47.5 (18,79)	46 (18,79)	61 (26,84)
Sex				
Male	91(56)	102(63)	125(59)	98(57)
female	73(45)	60(37)	87(41)	75
Race				
White	112(68)	120(74)	147(69)	124(72)
Black	4(2)	3(2)	5(2)	5(3)
Asian	31(19)	24(15)	36(17)	41(24)
Other	17(10)	15(9)	21(10)	3(2)
Prior HSCT	29(18)	26(18)	47	N/A

	Study 1022		Pooled R/R	Single Agent
	Inotuzumab Ozogamicin N=164 n(%)	Investigator Choice N=162* n(%)	ALL Population N=212 n(%)	Inotuzumab NHL N=173 n(%)
Salvage Status, n(%)				
1	111(68)	104(64.2)	120	N/A
2	51(31)	57(35.2)	108	N/A
3 and beyond	2(1)	1(0.6)	21	N/A

Source: FDA Analysis ADSL datasets

*Includes 19 patients who were randomized but never treated as of 8 March 2016.

Adequacy of the safety database:

The size of the safety database is adequate to provide a reasonable estimate of adverse reactions that may be observed with inotuzumab ozogamicin and the duration of treatment is adequate to allow assessments of adverse reactions over time. Study 1022 and the pooled R/R populations are representative of typical patients with R/R ALL that participate on clinical trials. However, non-white and Hispanic patients are under-represented compared to the overall ALL population in the United States.

7.4.3. Adequacy of Applicant’s Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

This submission was of adequate quality for clinical review. Overall, the submission was well-organized with appropriate analyses and detailed reports and summaries. There are no concerns regarding the integrity of the submission.

A data fitness assessment was performed in collaboration with the Office of Computational Science (OCS). The data fitness review included assessments of data fitness for Study B1931022 and Study B1931010 including but not limited to: availability of appropriate variables, variables populated by expected data points, appropriate use of standard terminology, data well described by metadata. There were no major issues regarding data integrity identified during the course of the review.

Categorization of Adverse Events

Adverse events (AE) were reported down to the verbatim term. The adverse events were coded using MedDRA version 18.1 coding dictionary and V 3.0 Common Terminology Criteria Adverse (CTCAE) events. For Study 1010, MedDRA version 17.1 coding dictionary and V 3.0 CTCAE criteria were applied. The safety data cut-off date for Study 1022 is March 8, 2016. For Study 1010, the safety data cut-off is January 30, 2015. For the pooled R/R ALL studies, March 8, 2016 safety cut-off date was used for study 1022 and for Study 1010 the safety data cut-off date was

January 15, 2016. The FDA compared the verbatim adverse event term with the MedDRA preferred term for all adverse events reported in Study 1022 and did not identify any irregularities.

The definition of treatment-emergent adverse events for the all studies (Study 1022 and Study 101) includes all causality AEs that began on or after Cycle 1 Day 1 but within 42 days of the last dose, any treatment-related AEs that began on or any time after C1D1, and any VOD event that began within 2 years after the randomization date regardless of attribution to study therapy. For the NHL studies, all causality AEs that began on or after C1D1 but within 56 days after the last dose and VOD event that began at any time on or after C1D1 regardless of casual attribution to study therapy. The treatment emergent adverse event definition for the adverse drug reaction for the proposed labeling is defined as: all causality AEs that commenced on after C1D1 within 42 days after the last dose but prior to new anti-cancer treatment (including (b) (4) HSCT).

Reviewer Comment: The Applicant applied a different definition for ADRs to identify events considered by the Applicant to be at least partially related to single-agent inotuzumab ozogamicin excluding the effect of subsequent anti-cancer therapy. This reviewer agrees that this approach likely captures adverse events at least partially related to single-agent inotuzumab ozogamicin however all events of VOD should be included in this analysis.

Routine Clinical Tests

Clinical laboratory assessments were performed as specified in each individual protocol with routine blood tests performed at least every 4 weeks. In study 1022, laboratory abnormalities were to be reported as AEs if meeting any of the following criteria:

- Accompanied by clinical symptoms
- Results in medical intervention
- Results in change of study treatment(e.g., dosage administration, treatment interruption or treatment discontinuation)
- Clinically significant in the investigator's judgement.

The safety assessment methods and time points described in the protocols seem adequate for the population, disease and indication being investigated.

7.4.4. Safety Results

Deaths

Deaths were assessed by the Applicant for all deaths on study to include the follow-up period, deaths within 42 days after last dose, and Grade 5 TEAEs. The following table provides a summary of death categorizations.

Table 56 Summary of Deaths in Study 1022 and Pooled R/R ALL Population

	Study 1022		R/R Pooled N=212 n(%)
	Inotuzumab Ozogamicin N=164 n(%)	Investigator Choice N=143 n(%)	
All Deaths	122(74)	121(85)	162(76)
On or within 42 days after last dose	32(20)	19(13)	42(20)
Grade 5 TEAEs	26(16)	16(11)	33(16)
Number of patients who went to transplant	77(47)	33(20)	88(42)
Death after transplantation(all mortality)	46/77(60)	19/33(57)	53/88(60)

Source: FDA Analysis of TEAE and ADSL datasets

In the single agent NHL studies, there were a total of 60/173(35%) deaths and 9/173(5%) grade 5 SAEs reported.

All Deaths in the Safety Population Study 1022

All reported deaths for the safety population for Study 1022 are detailed below. There were 122(84%) deaths in the inotuzumab arm versus 121(85%) in the control arm. More patients in the control arm (66%) died of progressive disease under the study compared to the inotuzumab arm (46%).

Table 57 Study 1022: Deaths

	Inotuzumab Ozogamicin N=164 n(%)	Investigator's Choice N=143 n(%)
All Deaths	122(74)	121(85)
Disease under study(progressive disease)	75(46)	95(66)
Study Treatment Toxicity	8(5)	2(1)
Unknown	3(2)	7(5)
Other Causes	46(28)	23(16)
Infection	20(12)	11(8)
ALL Treatment toxicity(non-study drugs)	4(2)	2(1)
Hemorrhage	5(3)	1(<1)
GVHD	4(2)	1(<1)
Cardiac Disorders	3(2)	2(1)
Respiratory Disorders	3(2)	1(<1)
General Disorders	3(2)	1(<1)
Others	3(2)	4(3)
ALL relapse	1(<1)	0(0)

Source: FDA Analysis TEAE datasets

Deaths after Cycle 1 Day 1 and within 42 Days after the Last Dose

Deaths that occurred after Cycle 1 day 1 and within 42 days after the last dose are shown in the Table 57. The clinical reviewer reviewed narratives for the patients with disease under study (progressive disease). FDA considered the cause of death to be the primary malignancy when supported by worsening disease in the marrow or peripheral blood by blast count, imaging report or description of other objective evidence. The majority of deaths were due to primary malignancy.

Table 58 Deaths On or Within 42 Days after the Last Dose

Deaths	Inotuzumab Ozogamicin N=164 n(%)	Investigator's Choice N=143 n(%)
Total Deaths	32(20)	19(13)
Disease Under Study(progressive disease)*	22(13)	11(8)
Study Treatment Toxicity	2(1)	2(1)
Other causes	11(7)	9(6)
Infection	7(4)	6(4)
Hemorrhage	3(2)	1(<1)
Ischemic Colitis	1(<1)	0(0)
DIC or TLS	0(0)	1(<1)
Multi-organ failure	0(0)	1(<1)

Source: FDA Analysis TEAE datasets

*includes patients with ongoing infection and liver toxicity or CNS hemorrhage.

The FDA reviewed narratives for subjects with primary cause of death as progressive disease with ongoing liver and infectious toxicities at time of death. There were 2 patients with progressive ALL with ongoing hepatotoxic events, 3 patients with progressive ALL in setting of hemorrhagic events, and 6 patients with progressive disease in setting of progressive ALL.

The remainder of the deaths due disease under study did not have any other mechanisms of death reported.

The FDA reviewed individual patient narratives for the subjects with deaths due to other reasons (13 subjects) than progressive disease for the inotuzumab ozogamicin arm. In patients with ALL, it can be difficult to determine the root cause of death in a course of treatment due to high incidence of baseline comorbid conditions many of which can be caused by the underlying disease.

Table 59 Root Cause of Death (COD)

Arm	Subject	FDA ROOT	Investigator COD

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761040}
 {BESPOLNSA; Inotuzumab Ozogamicin}

		COD	
Inotuzumab Ozogamicin	100501001	Infection	Infection: Neutropenic Sepsis
	10091002	Infection	Infection: Multi-lobar pneumonia
	10191001	Infection	Infection: Sepsis
	11071004	Cardiac	Cardiac death secondary to hemorrhage
	11301001	Infection	Infection: lactic acidosis due to ischemic bowel
	11681001	Infection	Infection: bronchopneumonia
	11781001	Infection	Ischemic colitis
	12451003	Hemorrhage	Hemorrhage: GI bleed
	10171001	Hemorrhage	Hemorrhage: grade 5 CNS hemorrhage
	10291001	Infection	Infection: sepsis in setting of disease progression
	10601001	Infection	Infection: pneumonia
	12121002	Cardiac	Acute respiratory distress syndrome leading to cardiac death
	12151002	Infection	Pneumonia

Source: FDA Analysis

GRADE 5 TEAEs

For the assessments of deaths, the Applicant reviewed all causality Grade 5 TEAEs that occurred on therapy or within 42 days after the end of study treatment as well as all VOD/SOS during study treatment and follow-up period for up to 2 years after randomization. In Study 1022, the applicant identified 26/164(16%) grade 5 TEAEs in the inotuzumab arm and 16/142(11%) in the control arm.

Table 60 Grade 5 TEAEs in Study 1022 and Pooled ALL R/R Population

	Study 1022		Pooled All N=212 n(%)
	Inotuzumab Ozogamicin N=164 n(%)	Investigator Choice N=143 n(%)	
Any Grade 5 TEAEs	26(16)	16(11)	33(16)
General Disorders and administration site conditions	9(6)	7(5)	13(6)
Disease Progression	8(5)	5(4)	12(6)
Multi-organ failure	1(<1)	2(1)	1(<1)
Infections and Infestations	8(5)	7(5)	10(5)
Pneumonia	3(2)	0(0)	4(2)
Sepsis	2(1)	2(1)	2(<1)
Neutropenic Sepsis	1(<1)	0(0)	1(<1)

	Study 1022		Pooled All N=212 n(%)
	Inotuzumab Ozogamicin N=164 n(%)	Investigator Choice N=143 n(%)	
Pseudomonas sepsis	1(<1)	0(0)	1(<1)
Septic Shock	1(<1)	1(<1)	1(<1)
Hepatobiliary Disorders	5(3)	0(0)	6(3)
VOD	5(3)	0(0)	6(3)
Gastrointestinal Disorders	4(2)	0(0)	4(2)
Ischemic colitis	1(<1)	0(0)	1(<1)
Gastrointestinal hemorrhage	1(<1)	0(0)	1(<1)
Intestinal ischemia	1(<1)	0(0)	1(<1)
Intra-abdominal hemorrhage	1(<1)	0(0)	1(<1)
Cardiac Disorders	1(<1)	0(0)	1(<1)
Respiratory, Thoracic and Mediastinal Disorders	1(<1)	3(2)	1(<1)
Vascular Disorders	1(<1)	0(0)	1(<1)
Nervous System Disorders	0(0)	1(<1)	0(0)

Source: FDA Analysis TEAE dataset

The grade 5 VOD events occurred after study treatment and subsequent HSCT. The subject who died of multi-organ failure died 133 days after the last dose of inotuzumab ozogamicin but had ongoing grade 4 VOD/SOS at time of death which occurred after HSCT. The following narratives describe the 5 patients who died due to VOD/SOS.

Subject 10081002: Patient is a 46 year-old male who received 4 cycles of inotuzumab ozogamicin and developed grade 2 hyperbilirubinemia and attained a MRD negative CRi after Cycle 1. He proceeded to HSCT (mMUD, CY/TBI conditioning regimen) and developed CMV infection, multi-organ failure and Grade 4 VOD 16 days after HSCT. No defibrotide was used. Fatal VOD occurred Day + 46 post HSCT and 91 days after last study dose. HEAB assessed second liver event as VOD/SOS.

Subject 10141007: Patient is a 29 year-old female who received 3 cycles of inotuzumab ozogamicin and achieved CRi after Cycle 1. She had pre-study HSCT(MUD: Cy/TBI) then relapsed prior to enrollment and went on to receive 3 cycles of inotuzumab ozogamicin. She subsequently underwent a second HSCT (mMUD, CY/BU/CLO) and developed grade 4 VOD 38 days post-HSCT. Fatal VOD occurred 94 days after HSCT. HEAB assessed event as definite VOD.

Subject 11511010: Patient is a 23 year-old male who received 3 cycles of inotuzumab ozogamicin and proceeded to HSCT(MUD, BU/FLU/thiotepa/TBI conditioning therapy) and developed fungal pneumonia and Grade 2 VOD 6 days after HSCT. The patient did achieve CRi after Cycle 1. HEAB assessed as possible severe VOD.

Subject 12111001: The patient is a 65 year-old male who received 2 cycles of inotuzumab ozogamicin and achieved a CRi. He proceeded to HSCT (RIC: flu/MEL) and developed grade 4 VOD 2 months post-HSCT. He received defibrotide for treatment of VOD. Fatal VOD occurred 89 days after HSCT and patient died VOD per investigator. HEAB assessment was that liver biopsy was more consistent with intrahepatic cholestatic disease. HEAB assessed as no evidence of VOD in material reviewed.

Subject 12721004: The patient is a 42 year-old female who received 2 cycles of inotuzumab ozogamicin and attain a CRi. The patient had prior history of 2 previous HSCT. The patient underwent a third MUD and died 21 days after HSCT. Per report, patient developed Grade 3 VOD (treated with defibrotide) as well as disseminated mucormycosis. HEAB assessed as VOD. VOD was noted in autopsy as well as disseminated mucormycosis.

Reviewer Comment: In the inotuzumab arm, there were 12 deaths between Cycle 1 Day 1 and 42 days after the last dose of study that were not reported as grade 5 AEs. All of these deaths occurred more than 28 days after the last dose of study drug and did not require reporting as AEs per the protocol. Of these 12 deaths, 6 were due to disease under the study and 6 were due to: CNS hemorrhage and disease progression, sepsis and pulmonary infection in setting of disease progression, pseudomonas sepsis, multi-organ failure and disease under the study, pneumonia and disease under the study, cerebral hemorrhage and disease under the study and disease progression and cellulitis.

In the control arm there were 3 deaths between Day 1 and Day 42 after last dose of study drug that were not reported as Grade 5 AEs. All 3 deaths were due to disease under the study occurring beyond 28 days after last dose of study drug.

Deaths within 30 days of Cycle 1 Day 1(safety population) in Study 1022

There were 9/164(6%) deaths in the inotuzumab arm compared to 8/143(6%) in the control arm that occurred within 30 days of Cycle 1 in Study 1022. Death due to disease under study occurred in 4 patients (2%) in the inotuzumab arm and 3 patients(2%) in the control arm. The other causes for death in the inotuzumab included hemorrhage from GI bleed (1 subject) and infectious etiologies (4 subjects). In the control arm, the other causes of death included multi-organ failure, infections, disseminated intravascular coagulopathy and tumor lysis syndrome.

Additional Studies

In the NHL studies, grade 5 SAEs were reported in 45/644(7%) in all the inotuzumab treated patients in the NHL studies. In the pooled single agent NHL studies 9/173(5%) had a grade 5 TEAE.

Post-transplant Mortality

In study 1022, 77/164(47%) patients in the inotuzumab arm underwent follow-up HSCT and of these patients, 46/77(60%) developed post-transplant mortality. In the control arm 33/162

patients (20%) went on to follow-up HSCT and of these 19/33(57%) had post-transplant mortality.

Post-transplant non-relapse mortality was adjusted for competing risks with competing risk defined as death due to relapse from CR/CRi. The number of patients with post-transplant non-relapse mortality was 29(38%) patients in the inotuzumab arm compared to 8(24%) in the control arm. A summary of post-transplant survival for patients with follow-up HSCT in the ITT population is displayed in the following table for Study 1022. For additional details, refer to the statistical efficacy results for Study 1022.

Table 61 Post-transplant mortality in Study 1022 and in the Pooled R/R ALL population

	Inotuzumab Ozogamicin N=164 n(%)	Control Arm (investigator's Choice) N=162 n(%)	Pooled ALL N=212 n(%)
Number of patients who underwent follow-up transplant	77(47%)	33(20%)	88(42%)
Post-transplant mortality	46(60%)	19(58%)	53(60%)
Post-HSCT Non-relapse mortality	29(38%)	8(24%)	N/A

Source: FDA Analysis

Additional details regarding post-transplant mortality based on conditioning regimen and type of donor for Study 1022 is described in the Table 61.

Table 62 Summary of Post-Transplant Mortality and Non-relapse mortality by type of Conditioning Therapy for Patients who proceeded directly to HSCT.

	Inotuzumab Ozogamicin n(%)	Investigator's Choice n(%)
Post-transplant Mortality/Conditioning Regimen		
Myeloablative	48	13
Death after myeloablative transplant	27/48(56%)	9/13(69%)
Reduced Intensity	23	4
Death after RIC	14/23(61%)	2/4 (50%)
Non-Relapse Mortality/Conditioning Regimen		
Myeloablative	48	13
Non-relapse mortality*	19/48(40%)	5/13(39%)
Reduced Intensity	23	4
Non-Relapse Mortality	10/23(44%)	0

	Inotuzumab Ozogamicin n(%)	Investigator's Choice n(%)
Post-transplant mortality/Type of Donor		
Matched donors	21	11
Death after MUD	13/21(62%)	7/11(64%)
Alternative Donor	56	18
Death after alternative donor	33/56(59%)	9/18(50%)
Non-relapse Mortality/Type of donor		
Matched Related	21	11
Post-transplant NRM mortality	12/21(57%)	4/11(36%)
Alternative Donor	56	18
Post-transplant NRM	18/56(32%)	4/18(22%)

Source: FDA Analysis

*non-relapse mortality defined as patients who died due to reasons other than disease under study

Table 63 Causes of Death for Post-Transplant Survival for Patients with Follow-up HSCT

	Inotuzumab Ozogamicin N=77 n(%)	Investigators Choice N=33 n(%)
Number of deaths	46(60)	19(58)
Disease Under Study(disease progression)	16(35)	11(58)
Study Treatment toxicity	6(13)	0(0)
-inotuzumab ozogamicin	1(2)	0(0)
-VOD/SOS	5(11)	0(0)
Other	26(57)	8(42)
-Infection	8(17)	3(16)
-ALL treatment toxicity(non-study drugs)	4(9)	2(11)
-Cardiac disorders	3(7)	0(0)
-GVHD	3(7)	1(5)
-General Disorders(multi-organ failure)	3(7)	0(0)
-Respiratory Disorders/Failures	3(7)	1(5)
-Other	2(4)	0(0)

Source: FDA Analysis TEAE dataset

Study 1010

There were a total of 54 deaths (54/72, 75%). Of these 54 deaths, 33 were disease under study due to disease progression (46%) and none were assessed as study drug toxicity. Within the active treatment phase of the study there were 12 deaths (17%) with 8 due to disease

progression. There were 42 deaths after active treatment phase with 25 deaths due to disease progression. One patient had VOD and died. There were 24 patients who proceeded to HSCT after inotuzumab ozogamicin treatment and 16(67%) were alive on Day + 100 and 7 patients (29%) died prior to Day + 100. There were 7 patients who died prior to day + 100 and of these, 6 died due to sepsis/septic shock and VOD in 1 patient and one patient with unknown cause of death.

In the Pooled ALL studies, 88 patients (42%) of 212 underwent follow-up HSCT and of these patients 53(60%) had post-transplant death and 35(40%) had non-relapse mortality.

Narratives for all patients who died on Study 1022

The Applicant provided at the request of the Agency efficacy narratives for all patients who died in the inotuzumab ozogamicin arm and the control arm in Study B1930122 with a March 8, 2016 data cut-off date. The purpose of the efficacy narrative summaries and analysis was to provide further understanding of how the treatment effect of inotuzumab ozogamicin impacts CR/CRi but does not translate into similar magnitude of effect on overall survival for patients who received inotuzumab ozogamicin.

Overall, there a total of 252 deaths in Study 1022 with 122 in the inotuzumab arm and 130 in the control arm. The most common cause of death for patients who achieved CR/CRi to study therapy for both treatment arms was progressive disease [inotuzumab ozogamicin arm 47/81(58%) and control arm 31/40(78%)]. The other causes of death amount the 121 patients who achieved CR/CRi after study therapy includes sepsis, GVHD, pneumonia, HSCT complications, study drug toxicity, respiratory failure, acute respiratory distress syndrome, and multi-organ failure.

In the patients who died, VOD was reported in 21/122(17%) of patients in the inotuzumab arm compared to 2/130(2%) in the control arm. Six of the 122(5%) in the inotuzumab ozogamicin arm had hepatic disease as cause of death compared to 2/130(2%) in the control arm and 20/122(16%) of patients in the inotuzumab ozogamicin arm had complications of hepatic disease at the time death compared to 7/130(5%) in the control arm.

Deaths due to infections occurred in 28/122(23%) of patients in the inotuzumab ozogamicin arm compared to 18/130(14%) of patients in the control arm. These events may have occurred during study therapy or after follow-up therapy. Of the 68 patients that proceeded to HSCT after study therapy, infection as reported a cause of death in 12/48(25%) in the inotuzumab arm and 3/20(15%) in the control arm. When looking at cause of death and mechanism of death plus major infectious complications, 58/122(48%) of deaths were associated with infections in the inotuzumab arm compared to 48/130(37%) in the control arm.

Deaths due to hemorrhage as primary cause of death but mechanism of death plus major hemorrhagic complications at time of death 18/122(15%) of deaths in the inotuzumab arm were due this compared to 5/130(4%) in the control arm.

GVHD was reported as cause of death in 7/122(6%) in the inotuzumab arm compared to 2/30(2%) in the control arm.

Overall, most patients died in this study due to relapsed or progressive disease with 87/122(71%) of patients in the inotuzumab ozogamicin arm dying due to progressive disease and 109/130(84%) in the control arm.

Among the patients who achieved CR/CRi who proceeded to transplantation, 16/41(39%) in the inotuzumab arm and 3/15(20%) in the control arm were in remission at the time of death. The substantial toxicity for patients who proceeded to follow-up HSCT was ongoing or fatal hepatic VOD often in setting of infectious complications.

Patients in the control arm received more subsequent salvage therapy for ALL after failure to respond to treatment or after relapsing. Patients in the inotuzumab arm were more likely to proceed to HSCT whereas patients in the control arm were more likely to proceed to new induction/salvage therapy. Among the patients who died, 45% in the inotuzumab arm and 69% of patients in the control arm received at least 1 salvage therapy. Salvage therapies included blinatumomab, inotuzumab, tyrosine kinase inhibitors, CAR-T cell therapy.

Reviewer comment: For patients in the inotuzumab ozogamicin, outside of disease progression, VOD and infectious complications were the most common causes of death with infectious complications occurring in patients who did and did not proceed to transplantation. In patients who proceeded to subsequent post-study transplantation, VOD or multi-organ failure in setting of VOD was cause of death. Often there were ongoing infectious complications occurring at the same time as VOD or MOF. A boxed warning for increased frequency of VOD and complications of VOD to include multi-organ failure should be included in the USPI.

Serious Adverse Events

An SAE occurring within 42 days of the last dose of inotuzumab ozogamicin was reported for 120 subjects in the pooled R/R ALL population, including 84 subjects in the inotuzumab ozogamicin arm in Study 1022. The distribution of SAEs by SOC is shown in Table 63.

Table 64 All Causality Serious Adverse Events in ≥ 2% of Patients

System Organ Class Preferred Term,	Inotuzumab Ozogamicin N=164 n(%)	Control Arm N=143 n(%)	Pooled R/R ALL N=212 n(%)
Patients with SAEs	84(51)	71(50)	120(57)
Infections and Infestations	39(24)	39(27)	47(22)
Pneumonia	10(6)	0(0)	15(7)

System Organ Class Preferred Term,	Inotuzumab Ozogamicin N=164 n(%)	Control Arm N=143 n(%)	Pooled R/R ALL N=212 n(%)
Sepsis	4(2)	10(7)	4(2)
Neutropenic Sepsis	3(2)	4(3)	3(1)
Bacteremia	3(2)	1(<1)	3(1)
Septic Shock	3(2)	3(2)	3(1)
C. Diff Colitis	2(1)	1(<1)	2(<1)
Hepatobiliary disorders	23(14)	4(3)	29(14)
VOD	22(13)	1(<1)	26(12)
Hyperbilirubinemia	0(0)	3(2)	1(<1)
Blood and lymphatic System disorder	21(13)	29(20)	38(18)
Febrile Neutropenia	19(12)	27(19)	32(15)
Neutropenia	2(1)	0(0)	5(2)
Thrombocytopenia	1(<1)	1(<1)	4(2)
Pancytopenia	0(0)	2(1)	0(0)
General disorders and Administration Site Conditions	19(12)	11(8)	24(11)
Disease progression	8(5)	5(4)	12(6)
Pyrexia	5(3)	3(2)	6(3)
Gastrointestinal Disorder	17(10)	6(4)	25(12)
Abdominal Pain	3(2)	1(<1)	15(12)
Cardiac Disorders	7(4)	1(<1)	7(3)
Metabolism and Nutrition Disorders	5(3)	0(0)	10(5)
Musculoskeletal and connective disorders	5(3)	0(0)	8(4)
Nervous System Disorders	4(2)	3(2)	5(2)
Respiratory , Thoracic and Mediastinal disorders	4(2)	8(6)	7(3)
Injury poisoning and procedural complications	2(1)	3(2)	4(2)
Vascular Disorders	1(<1)	5(4)	2(<1)

Source: FDA Analysis

There were 51 patients(31%) in the inotuzumab arm in Study 1022 that developed an SAE considered at least possibly related to inotuzumab ozogamicin compared to 42(29%) in the control arm. The most common treatment related SAE (> 5%) in the inotuzumab ozogamicin arm was VOD/SOS in 20 patients (12%), febrile neutropenia in 13 patients (8%). In the control arm, the most common treatment related SAEs were febrile neutropenia in 24 patients(17%), neutropenic sepsis and sepsis with 4 patients each(3% each).

Reviewer Comment: Overall there was a similar number of SAEs between the inotuzumab ozogamicin arm and the investigator choice arm in Study 1022. There were more SAEs in the

SOC of hepatobiliary disorders for the inotuzumab ozogamicin compared to the investigator's choice arm with VOD/SOS being source of the difference. There were more SAEs within the blood and lymphatic system SOC in the investigator choice arm compared to inotuzumab arm. The pattern of SAEs observed in the inotuzumab ozogamicin arm is consistent with safety signal for hepatotoxicity associated with this drug.

Dropouts and/or Discontinuations Due to Adverse Effect

The following table provides a summary of discontinuations, dose reductions and dose delays due to treatment-emergent adverse events in Study 1022 and in the pooled R/R ALL population.

Table 65 Summary of Discontinuations, Dose reductions and Dose Delays due to Treatment-Emergent Adverse Events in Study 1022 and Pooled R/R ALL Population

	Study 1022		Pooled R/R ALL N=212 n(%)
	Inotuzumab Ozogamicin N=164 n(%)	Investigator Choice N=143 n(%)	
Discontinuation to any AE	30(18)	12(8)	38(18)
Dose Reductions due to AE	5(3)	3(2)	7(3)
Dose/Treatment delay due to AE	72(44)	17(12)	94(44)

Source: FDA Analysis of TEAE dataset

Study 1022

More patients in the inotuzumab ozogamicin arm experienced treatment emergent adverse events that led to permanent treatment discontinuation compared to the Investigator Choice arm. The most common TEAEs associated with treatment discontinuation in the inotuzumab arm were pneumonia (3%), thrombocytopenia (2%), elevated AST, GGT increased(1%), VOD/SOS (1%). There was one patient in the inotuzumab arm who permanently discontinued study drug that occurred 42 days after the start of study treatment due to grade 2 hyperbilirubinemia.

Dose Delays and Dose Reductions

In Study 1022, there were 72/164(44%) treatment delays in the inotuzumab arm ($\geq 5\%$ of patients) compared to 17/143(12%) in the control arm. In the inotuzumab arm, the most common TEAEs by preferred term leading to treatment delays were neutropenia (17%), thrombocytopenia (10%), febrile neutropenia (5%), hyperbilirubinemia (4%), AST increase(4%), GGT increase(4%), ALT increase(3%). In the control arm, there were no single associated treatment emergent adverse events that lead to treatment delays in $\geq 5\%$ of patients.

In Study 1022, very few patients in either treatment arm required dose reductions due to adverse events. In the inotuzumab arm, 5/164 (3%) of patients required dose reductions and 3/143(<1%) of patients in the control arm required dose reductions. The most common reason for

dose was reductions was neutropenia (1.2%) in the inotuzumab arm and infection (<1%) in the control arm.

Reviewer Comment: One possible explanation for the difference in AEs associated with treatment delays is the number of cycles received by patients in the inotuzumab ozogamicin arm compared to the control arm. More patients in the control arm only received 1 cycle of treatment compared to the inotuzumab ozogamicin arm. Another difference in AEs leading to treatment delays is the dosing differences of the arms. Inotuzumab ozogamicin was given on weekly schedule compared to 5-7 days during one cycle and thus more likely to have dose delays with weekly schedule.

Significant Adverse Events

Significant adverse events were evaluated based on relevance of whether events represent an important identified or potential risk for the product based on observed adverse events and study from the nonclinical animal models. The Applicant identified TEAEs called Tier-1 TEAES as pre-specified events of special interested. The Tier-1 events include VOD, neutropenia, thrombocytopenia, pneumonia and infusion related reactions. The following table displays the Tier-1 TEAEs by SOC and preferred term.

Table 66 Tier-1 TEAEs in Study 1022

SOC Preferred term	Inotuzumab Ozogamicin N=164 n(%)	Investigator Choice N=143 n(%)
Blood and Lymphatic System disorders		
Neutropenia	80(49)	66(46)
Thrombocytopenia	81(49)	87(61)
Hepatobiliary disorders		
VOD	22(13)	1(<1)
Infections and Infestations		
Pneumonia	13(8)	12(8)
Injury, poisoning and procedural complications		
Infusion-related reactions	3(2)	0(0)

Source: FDA Analysis of TEAE dataset

The Applicant also identified adverse events of special interest by cluster terms. The following table describes the adverse events of special interest for Study 1022 and the combined R/R ALL population. For the pooled ALL studies (1022 and 1010), grouped terms are defined as any reported preferred terms retrieved by using MedDRA Version 18.1 SMQs.

Table 67 Adverse Events of Special Interest by Individual Study 1022 and POOLED R/R ALL.

Patients with AEs	Study 1022	POOLED R/R ALL

	Inotuzumab ozogamicin		Investigators Choice		N=212	
	All Grades n(%)	Grade ≥3 n(%)	All Grades n(%)	Grade ≥3 n(%)	All grades n(%)	Grade ≥3 n(%)
Hepatotoxicity	83(5)	48(29)	49(34)	21(15)	108(51)	57(27)
Myelosuppression/ Cytopenia	136(83)	133(81)	128(90)	126(88)	169(80)	165(78)
Infections	80(49)	47(29)	110(77)	79(55)	99(47)	59(28)
Hemorrhage	55(34)	10(6)	42(29)	8(6)	72(34)	11(5)
Infusion related Reactions	53(32)	1(<1)	63(44)	7(5)	67(32)	3(1)
Inflammatory Gastrointestinal Event	28(17)	5(3)	41(29)	6(4)	34(16)	7(3)
Pancreatitis	18(11)	8(5)	3(2)	1(<1)	21(10)	11(5)
Neurotoxicity	17(10)	1(<1)	10(7)	2(1)	22(10)	2(<1)
Nephrotoxicity	8(5)	2(1)	8(6)	1(<1)	9(4)	2(<1)
QT prolongation	5(3)	1(<1)	3(2)	0(0)	2(<1)	0(0)
Tumor Lysis Syndrome	4(2)	3(2)	3(2)	1(<1)	5(2)	4(2)

Source: FDA Analysis of TEAE dataset.

There were 8 fatal infections in the inotuzumab ozogamicin arm and seven fatal infections in the investigator choice arm. The most common hemorrhagic event was epistaxis for patients in the inotuzumab ozogamicin arm. The most common infusion related reaction in the inotuzumab arm was pyrexia in 13% of subjects.

In the pooled single-agent NHL studies, the most frequently reported infusion related reactions were rash, pyrexia, and chills. There were single reports of cytokine release syndrome, drug hypersensitivity, hypersensitivity and infusion related reaction.

Table 68 Adverse Events of Special Interest in Pooled Single Agent NHL Studies and Pooled R/R All

	Pooled Single Agent NHL Studies N=173		Pooled ALL N=212	
	All grades n(%)	Grade ≥3 n(%)	All grades n(%)	Grade ≥3 n(%)
Hepatotoxicity	106(61)	26(15)	108(51)	57(27)
Myelosuppression/Cytopenia	157(91)	122(71)	169(80)	165(78)
Infections	83(48)	10(6)	99(47)	59(28)
Hemorrhage	49(28)	5(3)	72(34)	11(5)

	Pooled Single Agent NHL Studies N=173		Pooled ALL N=212	
	All grades n(%)	Grade ≥3 n(%)	All grades n(%)	Grade ≥3 n(%)
Infusion Related Reactions	56(32)	0(0)	67(32)	3(1)

Source: FDA Analysis of TEAE dataset

Treatment Emergent Adverse Events and Adverse Reactions

Common TEAEs were assessed through 42 days after the last dose of inotuzumab ozogamicin. All VOD/SOS events within 2 years after randomization date regardless of attribution to study therapy are included. The number of subjects with TEAEs is shown in table by SOC in decreasing order of incidence for Study 1022 and in the pooled R/R ALL group.

Table 69 TEAE on or within 42 Days of Follow-up for Study 1022 and POOLED R/R ALL Populations by System Organ Class

System Organ Class	Study 1022		Pooled R/R ALL N=212 n(%)
	N=164 n(%)	N=143 n(%)	
Blood and Lymphatic System	135(82)	126(88)	167(79)
Gastrointestinal Disorders	118(72)	113(79)	148(70)
General Disorders and Administration Site Conditions	108(66)	112(78)	134(63)
Investigations	87(53)	62(43)	109(51)
Infections and Infestations	80(49)	110(77)	99(47)
Nervous System Disorders	74(45)	66(46)	91(43)
Metabolism and Nutrition disorders	65(40)	71(50)	83(39)
Respiratory, Thoracic and mediastinal disorders	61(37)	67(47)	80(37)
Hepatobiliary Disorders	54(33)	26(18)	69(33)
Musculoskeletal and connective tissue disorders	54(33)	48(34)	71(33)
Skin and Subcutaneous tissue disorders	54(33)	61(43)	67(32)
Psychiatric disorders	37(23)	42(29)	46(22)
Injury, poison and procedural complications	36(22)	20(14)	44(21)
Cardiac disorders	25(15)	29(20)	30(14)
Vascular disorders	25(15)	40(28)	35(17)
Renal and Urinary disorders	16(10)	19(13)	21(10)
Eye disorders	15(9)	25(18)	21(10)
Neoplasms benign, malignant and unspecified	9(5)	0(0)	12(6)
Ear and Labyrinth disorders	6(4)	0(0)	7(3)
Reproductive system and breast disorders	4(2)	5(4)	7(3)

Source: FDA Analysis TEAE dataset

TEAEs were reported in 163 patients (99%) of subjects in the Inotuzumab Arm, and 143 (100%) in the investigator choice arm. Grade $\geq$ 3 TEAEs were reported in 91% of subjects in the inotuzumab ozogamicin arm and 95% subjects in the investigator choice arm. A TEAE was reported in 211 subjects in the R/R ALL Pooled Population. The number of subjects with common($\geq$ 10% TEAE) are shown in table by preferred term in decreasing order of incidence in the Study treatment group in Study 1022.

Table 70 TEAES within 42 days of follow up by Preferred Term by Maximum Severity Grade For Study 1022 and Pooled R/R Population (Frequency $\geq$ 10% in the Inotuzumab Ozogamicin Arm) with Frequency $\geq$ 10%

Preferred Term	Study 1022				Pooled R/R	
	Inotuzumab Ozogamicin N=164		Investigator's Choice N=143		ALL N=212 n(%)	
	All Grades n(%)	Grade $\geq$ 3 n(%)	All Grades n(%)	Grade $\geq$ 3 n(%)	All Grades n(%)	Grade $\geq$ 3 n(%)

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Preferred Term	Study 1022				Pooled R/R	
	Inotuzumab Ozogamicin N=164		Investigator's Choice N=143		ALL N=212 n(%)	
	All Grades n(%)	Grade ≥3 n(%)	All Grades n(%)	Grade ≥3 n(%)	All Grades n(%)	Grade ≥3 n(%)
Thrombocytopenia	81(49)	67(41)	87(61)	85(59)	104(49)	89(42)
Neutropenia	80(49)	77(47)	66(46)	63(44)	91(43)	88(42)
Anemia	55(34)	37(23)	79(55)	63(44)	70(33)	50(24)
Nausea	53(32)	3(2)	68(48)	0(0)	69(33)	4(2)
Pyrexia	52(32)	5(3)	60(42)	8(6)	67(32)	5(2)
Leukopenia	47(29)	44(27)	54(38)	53(37)	55(26)	52(25)
Headache	45(27)	4(2)	38(27)	1(<1)	54(26)	6(3)
Febrile Neutropenia	44(27)	44(27)	77(54)	77(54)	62(29)	60(28)
Fatigue	42(26)	4(%)	24(17)	3(2)	48(23)	4(20)
AST Increased	37(23)	7(4)	16(11)	5(4)	48(23)	9(4)
GGT Increased	35(21)	18(11)	12(8)	7(5)	38(18)	18(9)
Hyperbilirubinemia	35(21)	10(6)	24(17)	9(6)	46(22)	12(6)
Lymphopenia	31(19)	27(17)	35(25)	35(25)	32(15)	27(13)
Diarrhea	30(18)	1(<1)	55(39)	1(<1)	39(18)	2(1)
Constipation	28(17)	0(0)	34(24)	0(0)	39(18)	1(<1)
Vomiting	26(16)	2(1)	35(25)	0(0)	39(18)	3(1)
ALT increased	25(15)	6(4)	18(13)	7(5)	32(15)	6(3)
Hypokalemia	25(15)	11(7)	33(23)	13(9)	31(15)	13(6)
Epistaxis	24(15)	2(1)	12(8)	2(1)	33(16)	2(1)
Insomnia	24(15)	0(0)	22(15)	0(0)	26(12)	0(0)
Alk Phos Increased	22(13)	3(2)	10(7)	0(0)	30(14)	4(2)
Cough	22(13)	0(0)	23(16)	1(<1)	31(15)	0(0)
VOD	22(13)	18(11)	1(<1)	1(<1)	26(12)	21(10)
Abdominal Pain	21(13)	3(2)	27(19)	2(1)	23(11)	4(2)
Decreased Appetite	19(12)	2(1)	18(13)	3(2)	23(11)	3(1)
Back pain	18(11)	5(3)	10(7)	1(<1)	22(10)	6(3)

Source: FDA Analysis TEAE dataset

The most frequently reported TEAEs in the inotuzumab ozogamicin arm were thrombocytopenia and neutropenia (49% and 29%, respectively) compared to the control arm (61% and 46%). The other frequently reported (≥20%) TEAEs in the inotuzumab arm were anemia (34%), nausea (32%), pyrexia (32%), leukopenia (29%), headache (27%), febrile neutropenia (27%), fatigue (26%), AST increase (23%), GGT increase and hyperbilirubinemia(23% each). In the control arm the most common TEAEs were anemia (55%), febrile neutropenia (54%), nausea (48%), pyrexia (42%), diarrhea (39%), constipation (24%) and hypokalemia (23%).

The most frequently reported Grade 3 or 4 events in the inotuzumab ozogamicin arm were neutropenia and thrombocytopenia (47% and 41%) vs the control arm(44% vs 59%). The other grade 3 and 4 TEAEs reported in $\geq 5\%$ of patients in the inotuzumab ozogamicin were febrile neutropenia and leukopenia(27% each), anemia(23%), lymphopenia(17%), GGT increased(11%), VOD(8%), hypokalemia(7%) and hyperbilirubinemia and WBC count decreased(6% each).

Reviewer Comment: Most of the common TEAEs were lower in the inotuzumab ozogamicin arm compared to the investigator choice arm. The TEAEs that were reported with a frequency of $\geq 10\%$ and $> 10\%$ absolute difference in the inotuzumab ozogamicin arm were AST increase(23% vs 11%), GGT increase(21% vs 8%), and VOD(13% vs $< 1\%$). These findings are consistent with the increased risk of hepatotoxicity with the use of inotuzumab ozogamicin.

TEAEs with a frequency of $\geq 10\%$ that were reported less often in the inotuzumab ozogamicin compared to the investigator arm($> 10\%$ absolute difference) include thrombocytopenia(49% vs 61%), anemia(24% vs 55%), febrile neutropenia(27% vs 54%), nausea(32% versus 48%), pyrexia(32% vs 42%), diarrhea(18% vs 39%), rash(9% vs 19%) and mucosal inflammation(4% vs 14%).

In Study 1022, the median number of cycles in the inotuzumab arm was 3 and the median number of cycles in the investigator arm was 1. The TEAE reported in $\geq 5\%$ of subjects in either treatment by preferred term for Cycle 1 only are in shown in Table 70.

Table 71 TEAEs in Cycle 1 Only Reported in $\geq 5\%$ Patients in the Inotuzumab Ozogamicin arm.

Preferred Term	Inotuzumab Ozogamicin N=164 n(%)	Investigator Choice N=143 n(%)
Any AEs	156(95)	143(100)
Thrombocytopenia	72(44)	84(59)
Neutropenia	67(41)	65(46)
Anemia	47(29)	77(54)
Leukopenia	44(27)	53(37)
Nausea	42(26)	64(45)
Pyrexia	38(23)	58(41)
Febrile Neutropenia	37(23)	74(52)
Headache	35(21)	35(24)
Fatigue	33(20)	24(17)
Lymphopenia	30(18)	32(22)
GGT increased	20(12)	12(8)
Vomiting	20(12)	33(23)
Alanine aminotransferase increased	19(12)	17(12)

Preferred Term	Inotuzumab Ozogamicin N=164 n(%)	Investigator Choice N=143 n(%)
Aspartate aminotransferase increased	19(12)	14(10)
Diarrhea	19(12)	50(35)
Constipation	18(11)	33(23)
Epistaxis	19(11)	12(8)
Hypokalemia	18(11)	32(22)
Chills	14(9)	16(11)
Abdominal Pain	13(8)	21(15)
Blood Alkaline Phosphatase increased	13(8)	10(7)
Hyperbilirubinemia	13(8)	22(15)
Insomnia	13(8)	22(15)
Decreased appetite	12(7)	16(11)
Pain	12(7)	7(5)
Asthenia	11(7)	13(9)
Cough	11(7)	21(15)
Hypotension	11(7)	20(14)
Dizziness	10(6)	15(11)

Source: FDA Analysis TEAE datasets

In the Infections and Infestations SOC, there were 44/164(27%) of patients with TEAEs in the inotuzumab ozogamicin arm compared to 102/143(72%) in the control arm. There were 6/164(4%) patients with pneumonia and 10/143(7%) in the investigator's choice arm. There were also more TEAEs of bacteremia, sepsis and fungal pneumonia reported in the control arm compared to the inotuzumab ozogamicin arm with bacteremia(9% vs 2%), sepsis(7% vs 2%) and fungal pneumonia(6% vs < 1%) in the control arm and inotuzumab arm, respectively.

Reviewer Comment: A similar number of patients reported TEAEs during cycle 1. There were no TEAEs that occurred more commonly in the inotuzumab arm compared to the control arm. The frequency of hyperbilirubinemia was greater in the investigator choice arm during Cycle 1(8% in inotuzumab arm compared to 15% in the control arm). There were no reported events of VOD during Cycle in either arm. There were more infectious TEAEs in the investigator choice arm compared to the inotuzumab ozogamicin arm during Cycle 1.

Adverse Drug Reactions (ADRs)

ADRs were identified by the Applicant based on whether they were reasonably associated with inotuzumab ozogamicin treatment. Preferred terms that were considered to have similar meaning were grouped together (e.g. neutropenia includes PT of neutropenia and neutrophil count decreased). All causality AEs for ADRs were defined as those that stated on or after cycle 1 but within 42 days after the last dose but prior to new anti-cancer treatment. VOD that occurred after follow-up HSCT is not included in the ADR table. This reviewer was able to verify

the ADR for Study 1022.

Table 72 Adverse Drug Reactions by Treatment Arm, SOC and Severity for Study 1022

SOC Preferred Term	Inotuzumab Ozogamicin N=164		Investigator's Choice N=143	
	All grades n(%)	Grade≥3 n(%)	All grades n(%)	Grade ≥3 n(%)
Infection and Infestations¹				
infections	79(48)	46(28)	109(76)	77(54)
Blood and Lymphatic System Disorders				
Thrombocytopenia ²	83(51)	69(42)	87(61)	85(59)
Neutropenia ³	81(49)	78(48)	65(46)	62(43)
Anemia ⁴	59(36)	40(24)	84(59)	67(47)
Leukopenia ⁵	57 (35)	54(33)	61(43)	60(42)
Febrile Neutropenia	43(26)	43(26)	76(53)	76(53)
Lymphopenia ⁶	30(18)	27(16)	37(26)	36(25)
Pancytopenia ⁷	4(2)	2(1)	10(7)	7(5)
Metabolism and Nutrition Disorders				
Decreased appetite	19(12)	2(1)	18(3)	3(2)
Hypokalemia	25(15)	11(7)	36(25)	15(11)
Hyperuricemia	7(4)	3(2)	2(1)	0
Tumor lysis syndrome	4(2)	3(2)	3(2)	2(1)
Nervous System Disorder				
Headache ⁹	46(28)	3(2)	39 (27)	1(1)
Vascular disorder				
Hemorrhage ¹⁰	54(33)	9(6)	41(29)	8(6)
Gastrointestinal Disorders				
Nausea	51(31)	3(2)	66(46)	0(0)
Abdominal pain ¹¹	37(23)	5(3)	33(23)	1(1)
Diarrhea	28(17)	1(1)	54(38)	1(1)
Constipation	27(17)	0(0)	34(24)	0(0)
Vomiting	25(15)	2(1)	35(25)	0(0)
Stomatitis ¹²	21(13)	3(2)	37(26)	4(3)
Abdominal I distention	10(6)	0(0)	2(1)	0(0)
Ascites	6(4)	3(2)	0(0)	0(0)
Hepatobiliary Disorders				
Hyperbilirubinemia	35(21)	9(6)	24(17)	9(6)
VOD ¹³	5(3)	3(2)	0(0)	0(0)
General disorders and administration site conditions				
Fatigue ¹⁴	57(35)	8(5)	36(25)	5(4)

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SOC Preferred Term	Inotuzumab Ozogamicin N=164		Investigator's Choice N=143	
	All grades n(%)	Grade≥3 n(%)	All grades n(%)	Grade ≥3 n(%)
Pyrexia	52(32)	5(3)	60(42)	8(6)
Edema ¹⁵	17(10)	2(1)	19(13)	0(0)
Chills	18(11)	0(0)	16(11)	0(0)
Investigations				
Transaminase increased ¹⁶	46(26)	11(7)	18(13)	7(5)
GGT increased	35(21)	17(10)	11(8)	6(4)
Blood ALP increased	22(13)	3(2)	10(7)	0(0)
Lipase increased	15(9)	7(4)	1(<1)	1(1)
Amylase increased	8(5)	3(2)	1(<1)	0(0)
ECG QT prolonged	2(1)	0(0)	1(<1)	0(0)
Injury, poisoning, and procedural complications				
Infusion related reactions ¹⁷	3(2)	0(0)	2(1)	0(0)

- 1- Infection includes any reported preferred terms using MedDRA Version 18.1 SOC
- 2- Thrombocytopenia- platelet count decreased and thrombocytopenia
- 3- Neutropenia- neutropenia and neutrophil count decreased
- 4- Anemia- anemia and hemoglobin decreased
- 5- Leukopenia- leukopenia, monocytopenia and white blood cell count decreased
- 6- Lymphopenia- B-lymphocyte count decreased, lymphocyte count decreased and lymphopenia
- 7- Pancytopenia- bone marrow failure, febrile bone marrow aplasia, pancytopenia
- 8- Hypokalemia
- 9- Headache- headache, migraine and sinus headache
- 10- I hemorrhage- hemorrhage terms excluding lab terms but includes MedDRA Version 18.1 Standard MedDRA query(narrow) for Hemorrhage terms(refer to appendix)
- 11- Abdominal pain: abdominal pain, abdominal pain upper, abdominal pain lower, abdominal tenderness, esophageal pain and hepatic pain
- 12- Stomatitis- aphthous ulcer, mucosal inflammation, mouth ulceration, oral pain, oropharyngeal pain and stomatitis
- 13- VOD
- 14- Fatigue- asthenia and fatigue
- 15- Edema- peripheral edema, peripheral swelling
- 16- Transaminases- aspartate aminotransferase increased, alanine aminotransferase increased, hepatocellular injury and hypertransaminemia
- 17- Infusion related reaction: infusion related reaction and hypersensitivity
- 18- includes blood potassium decreased

The most common (≥ 20% ADRs) in the inotuzumab ozogamicin arm were thrombocytopenia, neutropenia, infection, anemia, leukopenia, fatigue, hemorrhage, pyrexia, nausea, headache, febrile neutropenia, transaminase increased, abdominal pain, GGT increased and hyperbilirubinemia.

Reviewer Comment: The Applicant is proposing to use the ADR with incidence ≥10% in

inotuzumab ozogamicin arm in the USPI to describe the adverse event profile. The grouping of the MedDRA PTs is acceptable as it provides a more accurate description of adverse events. The most common ADRs are similar to the most common TEAEs described in the prior sections above. The use of the ADR in the USPI is reasonable as it accurately describes the adverse events.

Laboratory Findings

The applicant included an analysis of laboratory parameters based on the ADLB dataset and included median changes from baseline per cycle and at the end of the study as well as shifts from lower to high grades of these abnormalities. The FDA was able to independently reproduce the analysis and the results were consistent with those of the applicant.

Clinical Chemistry

The majority of chemistry laboratory parameters were Grade ≤ 2 in severity for both treatment arms. The following table displays the chemistry laboratory abnormalities in the safety population for Study 1022.

Table 73 Clinical Laboratory Abnormalities in Study 1022

Laboratory Abnormality Study Arm	N	Total n(%)	Grade 3 n(%)	Grade 4 n(%)
Hyperglycemia				
Inotuzumab	161	130(81)	20(12)	1(<1)
Investigator Choice	139	108(78)	9(7)	1(<1)
AST Increase				
Inotuzumab Ozogamicin	162	119(74)	8(5)	1(<1)
Investigator Choice	137	53(39)	5(4)	3(2)
GGT Increase				
Inotuzumab Ozogamicin	158	109(69)	26(17)	1(<1)
Investigator Choice	118	79(67)	19(16)	1(<1)
ALP Increase				
Inotuzumab Ozogamicin	163	94(58)	2(1)	0(0)
Investigator Choice	136	72(53)	4(3)	0(0)
Hypoalbuminemia				
Inotuzumab Ozogamicin	161	83(52)	6(4)	0(0)
Investigator Choice	138	107(76)	7(5)	0(0)
ALT Increase				
Inotuzumab Ozogamicin	163	81(50)	8(5)	0(0)
Investigator Choice	140	66(47)	8(6)	0(0)
Hypokalemia				
Inotuzumab Ozogamicin	163	72(44)	13(8)	1(<1)
Investigator Choice	141	74(53)	18(13)	2(1)

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Laboratory Abnormality Study Arm	N	Total n(%)	Grade 3 n(%)	Grade 4 n(%)
Blood bilirubin Increase				
Inotuzumab Ozogamicin	163	59(36)	8(5)	1(<1)
IC Investigator Choice	141	51(36)	7(5)	2(1)
Hyponatremia				
Inotuzumab Ozogamicin	163	55(34)	8(5)	0(0)
Investigator Choice	141	57(40)	11(8)	0(0)
Hypophosphatemia				
Inotuzumab Ozogamicin	160	53(33)	14(9)	1(<1)
Investigator Choice	135	40(30)	16(12)	4(3)
Hypomagnesemia				
Inotuzumab Ozogamicin	160	47(29)	0(0)	0(0)
Investigator Choice	136	54(40)	1(<1)	0(0)
Lipase increase				
Inotuzumab Ozogamicin	148	44(30)	15(10)	2(1)
Investigator Choice	102	19(18)	2(2)	0(0)
Hypocalcemia				
Inotuzumab Ozogamicin	162	39(24)	1(<1)	1(<1)
Investigator Choice	140	52(37)	2(1)	3(2)
Hyperuricemia				
Inotuzumab Ozogamicin	161	28(17)	0(0)	5(3)
Investigator Choice	127	14(11)	0(0)	1(<1)
Hypoglycemia				
Inotuzumab Ozogamicin	161	24(15)	0(0)	1(<1)
Investigator Choice	139	4(3)	0(0)	0(0)
Serum amylase increased				
Inotuzumab Ozogamicin	157	21(13)	4(3)	0(0)
Investigator Choice	114	12(11)	1(<1)	0(0)
Hypernatremia				
Inotuzumab Ozogamicin	163	18(11)	1(<1)	0(0)
Investigator Choice	141	10(7)	1(<1)	0(0)

Source: FDA Analysis ADLB dataset

In the pooled ALL studies (N=211), the frequency of clinical chemistry abnormalities were similar to that in Study 1022 for the inotuzumab ozogamicin arm. Most laboratory abnormalities were grade 1 to grade 2 in severity. The liver-related abnormalities that were most observed included Grade 3 blood bilirubin 11/211(5%), AST increase, 10/210(5%), ALP increase, 3/208(1%) and ALT increase, 8/211(4%). Grade 4 blood bilirubin was seen in 1/211(<1%) patients and 1/210(<1%).

Hematology Laboratory

The frequencies of hematology laboratory abnormalities were evaluated during all cycles for both arms in Study 1022.

Table 74 Clinical Hematology Laboratory Abnormalities in Study 1022

	N	Total n(%)	Grade 1 n(%)	Grade 2 n(%)	Grade 3 n(%)	Grade 4 n(%)
Platelet Count Decreased						
Inotuzumab Ozogamicin	163	159(98)	14(9)	20(12)	24(15)	101(62)
Investigator Choice	143	143(100)	1(<1)	1(<1)	6(4)	135(94)
Leukocytes decreased						
Inotuzumab Ozogamicin	163	154(95)	8(5)	13(8)	44(27)	89(55)
Investigator Choice	143	141(99)	0(0)	1(<1)	0(0)	140(98)
Hemoglobin decreased						
Inotuzumab Ozogamicin	163	153(94)	26(16)	60(37)	50(31)	17(10)
Investigator Choice	143	143(100)	2(1)	40(28)	84(59)	17(12)
Neutrophil Count decreased						
Inotuzumab Ozogamicin	163	152(93)	6(4)	6(4)	37(23)	103(62)
Investigator Choice	134	123(92)	3(2)	5(4)	16(12)	99(74)
Lymphopenia						
Inotuzumab Ozogamicin	163	151(93)	8(5)	27(17)	71(44)	45(28)
Investigator Choice	131	127(96)	0(0)	9(7)	25(19)	93(71)
Activated PTT						
Inotuzumab Ozogamicin	132	56(42)	43(33)	6(5)	7(5)	0(0)
Investigator Choice	81	29(36)	23(28)	3(4)	3(4)	0(0)
PT time Increased						
Inotuzumab Ozogamicin	119	31(26)	29(24)	2(2)	0(0)	0(0)
Investigator Choice	74	29(39)	27(27)	1(1)	1(1)	0(0)

At baseline, the frequency of grade 3 neutrophil count decrease was similar between the inotuzumab ozogamicin arm and the investigator choice arm (16% and 14%) and grade 3 platelet counts decrease (23% and 25%). During treatment, the maximum grade 3 hematology laboratory tests in the intozumab ozogamicin arm compared to the control arm included: neutrophil count decreased (23% vs 12%), platelet count decreased (15% vs 4%), leukocyte decreased (27% vs 0%), respectively.

The frequency of grade 4 neutrophil count decrease and platelet count decrease were similar in the inotuzumab(20% and 16%) and control arm(20% and 22%), respectively. During treatment, there were more grade 4 hematology test abnormalities in the investigator choice arm: neutrophil count decrease in inotuzumab ozogamicin arm versus investigator choice arm(63% vs 74%), platelet count(62% vs 94%) in the inotuzumab ozogamicin arm versus investigator

choice arm and leukocyte decreased (55% vs 98%) for inotuzumab ozogamicin versus investigator choice arm.

In Study 1022, the median platelet count in the intozumab arm was 54000/mm³ to a median nadir of 22,000/mm³ at Cycle 1(n=162) and improved to 47,000/mm³ (n=126) at Cycle 2 and by cycle 3 had returned to above baseline values (65,500/mm³, n=88). In the control arm the baseline median platelet count was 54,000/mm³ to median nadir of 10,000/mm³ (n=141) at Cycle 1 and after Cycle 2(120,000/mm³).

Table 75 Median Platelet Count During Treatment (C1- C3)

Timepoint	Inotuzumab Ozogamicin	Investigator Choice
Baseline platelet count	N=164	N=143
Median(range)	54(3,219)	54(4,285)
C1D15	N=153	N=131
Median(range)	31(2,317)	17(2,60)
C2D1	N=126	N=23
Median(range)	72(4,327)	242(30,501)
C2D15	N=115	N=23
Median(range)	68(3,272)	20(7,46)
C3D1	N=87	N=21
Median(range)	81(3,307)	221(105,350)

Reviewer Comment: Recovery of platelet counts is slower after treatment with inotuzumab ozogamicin compared to the chemotherapy arm and platelet count may not recover to baseline count prior to the next dose. However the frequency grade 4 hematology laboratory abnormalities are higher in the investigator choice arm compared to the inotuzumab arm. There was also higher platelet transfusion rate in the investigator choice arm. Although there is delayed platelet count recovery with inotuzumab ozogamicin it does not appear to translate into increased transfusion requirements or hemorrghic adverse events.

A similar finding of delayed platelet recovery is noted with similar antibody conjugate, Mylotarg, so possible explanation is the small molecue calichieamicin.

Liver-Related Laboratory Test Abnormalities

An evaluation of laboratory test abnormalities for ALT, AST and blood alkaline phosphatase and blood bilirubin across all treatment cycles in Study 1022 was performed. The table below displays labs greater than upper limit of normal. The count, percent of subjects and event count where the post-baseline lab results are greater than equal to 2x, 3x, 5x, 10x and 20x the upper limit of normal are described. This analysis uses the lab test short name variable (LBTESTCD), the numeric results in standard units and the reference rage upper limit-STD units, the sponsor-derived baseline flag and study days from the laboratory test dataset.

Table 76 Liver Test Abnormalities in Study 1022

Liver Lab Test	Inotuzumab Ozogamicin N=164			Investigator's Choice N=143		
	Event Count	Subject Count	% of subjects	Event Count	Subject Count	% of subjects
ALT > ULN						
2X ULN	134	41	25	79	37	26
3X ULN	57	22	13	35	21	15
5xULN	12	9	6	16	10	7
10xULN	3	2	1	4	2	1
20X ULN	0	0	0	1	1	<1
AST > ULN						
2X ULN	209	54	33	67	32	22
3X ULN	89	30	18	32	21	15
5xULN	18	10	6	14	10	7
10xULN	4	3	2	6	4	3
20X ULN	1	1	<1	5	3	2
TB > ULN						
1.5 x ULN	146	45	27	113	29	20
2X ULN	71	26	16	85	18	13
3X ULN	29	13	8	63	12	8
ALP> ULN						
2X ULN	172	45	27	62	23	16
3X ULN	60	18	11	19	8	6
5xULN	16	4	2	8	6	4
10xULN	1	1	<1	0	0	0
20X ULN	0	0	0	0	0	0

Source: FDA Analysis

Note: all scores are post-baseline. Subject scores may be counted more than once in that they will be counted in all conditions (i.e. 2x, 3x, 5x...) that apply.

Hy's Law

The Sponsor performed an analysis for Hy's Law cases and used a standard definition of Hy's Law case was applied. In Study 1022, all potential Hy's law cases as well as all cases of elevated bilirubin greater than 2mg/dL (independent of other laboratory abnormalities) were assessed by the HEAB to identify possible drug induced liver injury. In the inotuzumab ozogamicin arm, 13 cases were reported to be DILI by the HEAB (5 probable, 8 possible). None of these cases were considered to represent possible Hy's law cases except in one patient. In this patient both AST

and ALT values were elevated prior to dosing, elevation of bilirubin and AST were concomitant and the case did not meet Hy's law criteria since alkaline phosphate was also elevated. The definition of DILI by the HEAB did not require that the laboratory criteria for Hy's law be met but only that the live-related abnormalities observed were thought to be secondary to drug based on their clinical judgment.

In Study 1022, the Sponsor identified two patients in the inotuzumab ozogamicin arm and 4 patients in the control arm with concomitant elevations of ALT or AST (AST/ALT > 3 x ULN and total bilirubin > 2 ULN) while on treatment. AP was elevated in 4 of 6 of these cases. None of these cases met the criteria for true Hy's law since liver dysfunction was attributed to overwhelming infection and/or alkaline phosphate elevation.

The Applicant, based on the analysis described above, did not identify any confirmed Hy's Law cases in study 1022 or 1010. In the single agent NHL studies, there were no confirmed Hy's law cases. In the combination NHL studies, in particular, Study 1003[escalating doses of inotuzumab ozogamicin in combination with rituximab plus chemotherapy(rituximab, cyclophosphamide, vincristine, and prednisone or rituximab, gemcitabine and/or cisplatin and dexamethasone)], there were 2 Hy's law cases confirmed as probable or definite. Additionally, the HEAB from Study 1022 reviewed these cases and confirmed Hy's law. The Applicant provided brief narratives and the FDA reviewer reviewed the cases and agreed with the Applicant's findings.

FDA Analysis of Hy's Law

The FDA reviewer performed analysis of potential Hy's law cases and identified 16 possible Hy's law cases based on AST or ALT > 3, TB > 1.5 x ULN. The following table shows the results of the analysis.

This analysis lists count, percent of subjects and event counts that meet the criteria for a possible Hy's Law case by examining post-baseline lab results for various combinations of ALT, AST, total bilirubin and ALP findings. This analysis uses all laboratory data. This analysis looks at the combinations of lab results in two ways: 1) any visit during the study and 2) any point in the study.

Table 77 Combinations for Possible Hy's Law Cases: At any time during the Study 1022

Liver Lab Test at Same Visit	Inotuzumab Ozogamicin N=164		Investigator's Choice N=143	
	Subject Count	% Subjects	Subject Count	% Subject
ALT or AST > 3 ULN, TB > 1.5 ULN and ALP Normal	14	9	10	7
ALT or AST >3 ULN, TB>2 ULN and ALP Normal	8	5	7	5
AST or AST>5 ULN, TB>3 ULN and ALP normal	2	1	4	3
ALT or AST > 3 ULN, TB > 1.5 ULN and ALP > Normal	15	9	7	5

Liver Lab Test at Same Visit	Inotuzumab Ozogamicin N=164		Investigator's Choice N=143	
	Subject Count	% Subjects	Subject Count	% Subject
ALT or AST >3 ULN, TB>2 ULN and ALP> Normal	9	5	4	3
AST or AST>5 ULN, TB>3 ULN and ALP> normal	3	2	3	2
Total Subjects	16	10	12	8
ALT or AST > 3 ULN, TB > 1.5 ULN	16	10	12	8
ALT or AST >3 ULN, TB>2 ULN	9	5	8	6
AST or AST>5 ULN, TB>3 ULN	3	2	5	4
Total Subjects	16	10	12	8

Source: FDA Analysis

Reviewer Comment: Medical Histories were reviewed by the clinical reviewer for combinations of possible Hy's Law cases in patients at any time during the study. The 16 possible cases of Hy's law cases had reasonable alternative explanations or did not meet the criteria for Hy's law.

Vital Signs

The applicant provided a record of the vital signs and a description of the changes in vital signs during treatment with inotuzumab ozogamicin. The Applicant concluded based on their review of vital signs concluded that no safety signal was identified. Table 77 summarizes the results of the Applicant's analysis.

Table 78 Summary of Vital Signs in Study 1022

Blood Pressure in mm Hg Median(range)	N	Inotuzumab Ozogamicin Arm	N	Investigator Choice
Baseline median SBP	164	120(90,180)	143	120(83,162)
Median SBP C1 D1	160	124(84,183)	104	120(85,167)
Median SBP C2D1	127	118(87,174)	23	115(90,156)
Median SPB EOT	132	122(51,180)	102	120(82,155)
Baseline median DBP	164	74(46,102)	143	72 (50,93)
Median DBP C1D1	160	73(40,102)	103	69(48,94)
Median DBO C2D1	127	70(47,100)	23	66(50,82)
Median DBP EOT	132	74(40,112)	102	72(52,120)
Median baseline Heart Rate(BPM)	164	76(40,131)	143	79(53,111)
Median heart Rate C1D1	160	72(42,118)	103	77(47,109)
Median Heart rate C2D1	127	74(50,133)	23	73(62,105)
Median Heart Rate EOT	132	78(55,138)	102	86(47,132)

Source: Summarized from M. 5.3.5.2 Clinical Study report

Using the preferred term of hypertension in the inotuzumab arm, there were 9 patients (6%) who had hypertension with 2(1%) grade 3 events. In the control arm, there were 9(6%) adverse events of hypertension with 2(1%) grade 3 events. There were no grade ≥ 4 events of hypertension in either arm. In the inotuzumab ozogamicin arm, there were 12(7%) adverse events of hypotension and 1(<1%) grade 3 event. In the investigator choice arm there were 24(17%) adverse events of hypotension with 3(2%) grade 3 and 3(2%) grade 4 events.

Electrocardiograms (ECGs)

ECGs were performed at baseline, throughout treatment and at the end of study visit. TEAEs related to ECG changes were reviewed along with all cardiac adverse events. No patients in the inotuzumab ozogamicin arm had QTcF ≥ 500 msec. One patient in the control arm had QTcF ≥ 500 msec.

Increases from baseline occurred in the inotuzumab ozogamicin arm (89%) compared to the control arm (73%) with 4/162(3%) of patients in the inotuzumab arm and 3/124(2%) in the investigator choice arm having a maximum QTcF increase from baseline ≥ 60 msec. None of these of patients had any reported ventricular cardiac event associated with QTc prolongation. No patients in the inotuzumab arm displayed any maximum CTCAE toxicity grade 3 or 4 events related to QTcF.

In study 1022, adverse events due to QT prolongation are defined as a group of all reported preferred terms by using the MedDRA Version 18.1 SMQ Torsade's de pointes/QT prolongation or reports of cardiac fibrillation, seizure, loss of consciousness, sudden cardiac death, sudden death, syncope, ventricular arrhythmia, ventricular fibrillation, ventricular flutter and ventricular tachyarrhythmia. There were 5(3%) QTc prolongation adverse events in patients who received inotuzumab ozogamicin compared to 3(2%) in the investigator control arm. There were no grade 4 or 5 events. In the inotuzumab ozogamicin arm, there were 3(2%) ECG QT prolongation events, 1(< 1%) syncope event and 1(<1%) ventricular tachycardia event. The event of syncope and ventricular tachycardia were not associated with QT interval prolongation. There was one case of fatal cardiac arrest that occurred which was secondary to post-operative intra-abdominal bleeding and no QTc prolongation was reported.

QT

The FDA Interdisciplinary Review Team (IRT) for QT studies reviewed the thorough QT study. This included the study report for Study 1022 and the electronic datasets. The following summary findings were taken from the IRT review, "Inotuzumab ozogamicin is an antibody-drug conjugate and QTc prolongation is generally not expected for large molecules like inotuzumab ozogamicin, however, prolongation of the QTc interval was observed in multiple clinical studies (Table 1). The observed QTc prolongation does not appear to be due to direct inhibition of the hERG potassium current based on the preclinical data, and the mechanism for the observed QTc prolongation is currently unknown".

Refer to the interdisciplinary review team consult review for additional details.

Immunogenicity

In Study 1022, in the inotuzumab ozogamicin arm, 7/164(4%) patients developed a positive ADA response. Neutralizing antibodies were not detected in any of the tested samples from the patients. Five of the 7 patients who had a positive ADA response had adverse events. Two patients had positive ADA response after treatment with inotuzumab ozogamicin included one patient who developed chills and pyrexia (Grade 1) and anemia (grade 3) and a second patient who developed pyrexia (grade 2). Three patients had positive ADA response prior to treatment with inotuzumab ozogamicin and adverse events included hyperhidrosis and dyspnea (grade 1), intermittent pyrexia, anemia (grade 3) and maculopapular rash (grade 3), hot flush(grade 1) and headaches. There was 1(<1%) AEs of hypersensitivity in the inotuzumab arm (N=164) and 1/143(<1%) in the investigator choice arm.

Reviewer Comment: The incidence of hypersensitivity reactions was very small.

7.4.5. Analysis of Submission-Specific Safety Issues

Hepatotoxicity including VOD/SOS

Hepatotoxicity is an important identified risk for patients who receive inotuzumab ozogamicin. The following table summarizes all hepatotoxicity TEAEs by preferred term occurring in at least 1 patient in the inotuzumab ozogamicin arm in Study 1022. Hepatotoxicity AEs were reported more frequently in the inotuzumab ozogamicin arm in Study 1022 compared to the investigator choice arm (51% versus 34%).

Table 79 Hepatotoxicity in Study 1022, Pooled ALL Studies and Single Agent NHL Studies

Preferred Term	Study 1022				Pooled ALL Studies N=212		Single Agent NHL Studies N=173	
	Inotuzumab ozogamicin N=164		Investigator's Choice N=143		All Grades n(%)	Grade ≥ 3 n(%)	All Grades n(%)	Grade ≥3 n(%)
	All grades n(%)	Grades ≥ 3 n(%)	All grades n(%)	Grades ≥3 n(%)				
Any adverse event	83(51)	48(29)	49(34)	21(15)	108(51)	57(27)	106(61)	26(15)

Preferred Term	Study 1022				Pooled ALL Studies N=212		Single Agent NHL Studies N=173	
	Inotuzumab ozogamicin N=164		Investigator's Choice N=143		All Grades n(%)	Grade ≥ 3 n(%)	All Grades n(%)	Grade ≥ 3 n(%)
	All grades n(%)	Grades ≥ 3 n(%)	All grades n(%)	Grades ≥ 3 n(%)				
AST increased	37(23)	7(4)	16(11)	5(4)	48(23)	9(4)	79(46)	2(1)
GGT increased	35(21)	18(11)	12(8)	7(5)	38(18)	18(9)	30(17)	9(5)
Hyperbilirubinemia	35(21)	10(6)	24(17)	9(6)	46(22)	12(6)	20(12)	2(1)
ALT increased	25(15)	6(4)	18(13)	7(5)	32(15)	6(3)	41(24)	3(2)
ALP increased	22(13)	3(2)	10(7)	0(0)	30(14)	4(2)	58(34)	3(2)
VOD	22(13)	18(11)	1(<1)	1(<1)	26(12)	21(10)	1(<1)	1(<1)
Hypoalbuminemia	10(6)	2(1)	7(5)	2(1)	17(8)	2(1)	14(8)	0(0)
Ascites	8(5)	3(2)	0(0)	0(0)	12(6)	4(2)	7(4)	3(2)
Hepatomegaly	3(2)	0(0)	0(0)	0(0)	3(1)	0(0)	1(<1)	0(0)
Cholestasis	2(1)	1(<1)	0(0)	0(0)	2(<1)	1(<1)	0(0)	0(0)

Source: FDA Analysis TEAE dataset

The AEs of liver related laboratory abnormalities were more frequently reported as grade 1 or 2 events. VOD was reported as Grade 3, 4 or 5 events and was the primary event that was different in terms of frequency and severity between the two treatment arms in Study 1022.

Hepatotoxicity SAEs were reported in 24(15%) versus 4(3%) of patients in the inotuzumab ozogamicin arm versus the control arm, respectively. In the inotuzumab ozogamicin arm, 1 event each of ascites and hepatic vein thrombosis and 13 events of grade 3 or 4 VOD occurred. Five patients had grade 5 events of VOD (all after follow-up HSCT). No grade 5 hepatotoxicity event occurred on or after the study without intervening HSCT.

Reviewer Comment: There most frequently reported hepatotoxicity adverse events in the inotuzumab ozogamicin arm (≥ 5%) compared to the control arm were AST increased (23% vs 11%), GGT increased (21% vs 8%), hyperbilirubinemia (21% vs 17%), ALT increase (15% vs 13%), Blood ALP (13% vs 7%) and VOD (13% vs <1%). The most frequently (≥ 5%) reported ≥ Grade 3 hepatotoxicity adverse events in the inotuzumab arm was GGT increase(11%) and VOD (11%) Hepatotoxicity to include VOD is an important identified risk associated with the use of inotuzumab ozogamicin. Recommend box warning on the USPI for hepatotoxicity and VOD.

Intrinsic and Extrinsic Factors related to hepatotoxicity were explored further. The Applicant conducted a univariate analysis of the association of CTCAE Grade 3-5 hepatotoxicity adverse events and baseline characteristics. This reviewer conducted an independent univariate analysis and this analysis is displayed in the table below.

Table 80 Univariate Analysis of the Association of CTCAE Grade 3-5 Hepatotoxicity Adverse Events and Baseline Characteristics

Univariate Analysis	Odds Ratio	95% CI	P-value
Age(≥ 55, < 55)	1.198	0.6, 2.4	0.608
Gender(F,M)	0.752	0.38, 1.49	0.415
Prior HSCT(yes, no)	2.772	1.2, 6.3	0.015
Salvage status(2 or more, 1)	2.289	1.13, 4.66	0.022
Prior History of Liver disease/hepatitis (yes/no)	5.817	2.77, 12.2	<0.0001
Prior asparaginase	0.773	0.39,1.55	0.468
Hepatic impairment by NIH working group(mild, moderate, severe, normal)	2.184	1.05, 4.55	0.037
Bone marrow blasts (≥ 50%, < 50%)	0.738	0.36, 1.5	0.400
Peripheral Blasts (> 1000/uL < 1000/uL)	0.409	0.19, 0.90	0.027
Baseline ECOG PS 2, 0/1	2.000	0.78, 5.12	0.148
Treatment Duration (Continuous)	1.192	0.79, 1.54	0.566

Source: FDA Analysis

In the univariate analysis there was an association(2 sided p-value < 0.05) between prior HSCT, salvage therapy status, prior history of liver disease/hepatitis, hepatic impairment at baseline, and peripheral blast count with grade ≥ 3 hepatotoxicity.

Reviewer Comment: Based upon the univariate analysis there is an association between prior HSCT, salvage status, prior history of liver disease/hepatitis and hepatic impairment at baseline as well as peripheral blast count with increased risk of grade ≥ 3 hepatotoxicity.

VOD

Hepatic VOD is a serious and life threatening complication of HSCT. In Studies 1022 and 1010, all cases of VOD for up to 2 years after randomization regardless of causality, severity or treatment arm were reported by the investigators. All cases of VOD were reported as SAEs.

Hepatotoxicity to include VOD has been reported for antibody-drug conjugates which contain calicheamicin to include inotuzumab ozogamicin. Across all of the Applicant's sponsored studies there were 34/880(4%) of hepatic VOD after treatment with inotuzumab ozogamicin. The frequency of VOD across the various studies is displayed in the table below.

Table 81 Frequency of VOD/SOS across entire development program for Inotuzumab Ozogamicin

	Study 1022		Study 1010 N=72	Pooled R/R N=212	Single agent NHL studies Pooled N=173	Combination NHL Studies Pooled N=372	Total exposed to inotuzumab N=880
	Inotuzumab Ozogamicin N=164	Control Arm N=143					
VOD	22(13%)	1(<1%)	4(6%)	26(12%)	1(<1%)	6(2%)	34(4%)

Source: FDA Analysis

In Study 1022, of the 22 cases of VOD reported by Investigators in the inotuzumab ozogamicin arm 5/164(3%) occurred on or after study without an intervening HSCT. The rate was lower in patients who did not have pre-study HSCT compared to those who had pre-study HSCT (2.2% vs 6.9%, respectively). A total of 17/77(22%) of VOD occurred after follow-up HSCT. The VOD (occurring post-HSCT) was lower in patients who did not have pre-study HSCT compared with those who had at least 1 prior pre-study HSCT (18% versus 45%), respectively).

In Study 1010, there were 4 patients (6%) who developed VOD and none of these patients received a pre-study HSCT. All 4 of these cases occurred in the Phase 2 Dose expansion cohort (N=48). In the Investigator Initiated Studies, there were a total of 15 VOD events and in the compassionate use of inotuzumab there were a total of 4 VOD events reported.

Reviewer Comment: The majority of VOD cases occurred after follow-up HSCT. Monitoring of patients closely for signs and symptoms of VOD/SOS is paramount. Monitoring should include assessments of liver tests and if development of abnormal liver tests, more frequent monitoring.

There were 3 cases of VOD that occurred in patients on Study 1022 after the March 8, 2016 database lock. The Applicant did not include these 3 cases in any summary of clinical safety tables or listings. Two cases were in the inotuzumab ozogamicin arm and one case was in the control arm.

Deaths due to VOD

In study 1022 there were five patients who were reported to have grade 5 events of VOD. All 5 of these fatal (grade 5 AE) cases occurred after follow-up HSCT. For the 17 patients who developed VOD after HSCT, there were also 6 VOD events ongoing at the time of death due to other causes (ARDS and multi-organ failure, ischemic cardiac disease and myocardial infarction).

Reviewer Comment: VOD with multi-organ failure has mortality rate in excess of 80%. Out of these 17 patients a total of 11 patients died. Five of the deaths were considered grade 5 AEs however 4 patients had MOF as cause of death with ongoing VOD at time of death. It is likely

that cause of death was really attributable to VOD leading to multi-organ failure.

Study 1010:

There was one death reported to have grade 5 hepatotoxicity due to VOD

Timing of VOD: VOD occurring before post-study HSCT or no HSCT occurred

In Study 1022, there were 5/164(3%) patients in the inotuzumab ozogamicin arm who developed VOD during the study treatment or during the follow-up. Four of these events occurred on study and one occurred on day 57 post study. No patient in the investigator choice arm developed VOD within 42 days after the last dose of inotuzumab.

In study 1010, VOD (on or after study without follow-up HSCT) occurred in 2/72(3%) of patients. Overall of the 236 patients in the ALL studies (1022 and 1010) VOD was reported in 7(3%) of patients who received inotuzumab ozogamicin without intervening HSCT.

Timing of VOD: VOD occurring post-study HSCT

In Study 1022, 17/77(22%) of the patients who proceeded to HSCT after study therapy developed VOD/SOS. Five of these patients had a pre-study HSCT. Five of these 17 VOD cases had fatal outcomes, six events resolved and 6 VOD events were ongoing at time of death due to other causes. In the control arm 1/32(3%) who proceeded to HSCT, developed VOD after HSCT.

In Study 1010, VOD after follow-up HSCT was reported in 2/24 patient (8%). One of these patients died from VOD. Overall in studies 1022 and 1010, there were 101 patients with follow-up HSCT and 19 patients (19%) who received inotuzumab developed VOD after HSCT. In the NHL studies, 4 were patients proceeded to transplantation. In the single agent NHL studies, no VOD occurred HSCT and in the combination studies with rituximab or chemotherapy, 3 patients reported to have VOD after conditioning regimen and or autologous or allogeneic HSCT.

Table 82 Frequency of VOD in relation to HSCT (pre or post study HSCT)

Study Arm	VOD on or after study without subsequent HSCT			VOD occurring post follow-up HSCT			VOD Total		
	All	No pre study HSCT	Pre study HSCT	All patients	No Pre stud HSCT	Pre study HSCT	All patients	No pre study HSCT	Pre study HSCT
Study 1022 Number of subject	164	135	29	77	66	11	164	135	29
Inotuzumab	5(3%)	3(2%)	2(7%)	17(22%)	12(18%)	5(46%)	22(13)	15(11%)	7(24%)

	VOD on or after study without subsequent HSCT			VOD occurring post follow-up HSCT			VOD Total		
Control	0 (0%)	0 (0%)	0 (0%)	1/32 (3%)	1/26 (4%)	0 (0%)	1/143 (<1%)	1/117 (<1%)	0 (0%)
Study 1010	2/72 (3%)	2/49 (4%)	0/23 (0%)	2/24 (8%)	2/20 (10%)	0/4 (0%)	4/72 (6%)	4/49 (8%)	0 (0%)

Source: FDA Analysis

Time to Onset of VOD

The following table describes the time to VOD Onset in patients who did not have follow-up HSCT and those patients who did receive follow-up HSCT for Study 1022.

Table 83 Time to Onset of VOD

Parameter	Inotuzumab Ozogamicin N=164
Patients with VOD without post-HSCT, n(%)	5(3)
Time to VOD after 1 st IO dose(days), median, range	30(14,238)
Time to VOD after last dose of IO(days), Median, (range)	16(14,57)
Number of patients with follow up HSCT	77
Patients with VOD after HSCT, n(%)	17(22)
Time from last dose of InO to VOD onset Median(range)	60 (25,144)
Time to VOD after HSCT(days) Median,(range)	15(3,57)

Source: FDA Analysis

InO- inotuzumab ozogamicin

Reviewer Comment: The longest duration between the last dose of inotuzumab ozogamicin and onset of VOD event was 57 days. All patients should be monitored for development of VOD for a minimum of 2 months after the last dose of inotuzumab and longer if patient goes on to subsequent HSCT. For patients who proceed to HSCT, the maximum duration of inotuzumab treatment is 3 cycles.

Risk Factors for VOD (baseline and post-baseline factors)

The following table further describes the potential risk factors that may be associated with developing VOD after HSCT in patients who received inotuzumab versus those who did not develop VOD. The number of patients with each characteristic is used to calculate other

percentages.

Table 84 Baseline and Post-Baseline Factors on Post-HSCT VOD

	Study 1022	
	IO Number VOD/ N HSCT	Control N VOD/ N HSCT
VOD post HSCT	17/77(22%)	1/32(3%)
Preparative Regimen		
Busulfan containing regimen		
Yes	6/13(46%)	0/9(0%)
no	11/64(17%)	1/23(4%)
Alkylator containing regimen		
Dual	6/11(55%)	0/7(0%)
Single	8/52(15%)	1/18(6%)
TBI		
>12gy	0/10(0%)	0/5(0%)
8-<12Gy	5/34(15%)	1/13(8%)
<8 Gy	3/15(20%)	0/3(0%)
Myeloablative Regimen		
Yes	10/51(20%)	1/21(5%)
No	7/26(27%)	0/9(0%)
Donor Type for HSCT(post-study)		
Matched related	3/21(14%)	0/11(0%)
Alternative donor	14/56(25%)	1/18(6%)
HSCT prior to study therapy		
Yes	5/11(46%)	0/6(0%)
>1 Prior HSCT	1/1(100%)	0/0(0%)
NO	12/66(18%)	1/26(4%)
Salvage Status		
1	10/56(18%)	1/24(4%)
2	7/20(35%)	0/8(0%)
Age		
≥55	7/17(4%)	0/6(0%)
<55	10/60(16%)	1/26(4%)
Prior history of liver disease		
Yes	7/20(35%)	0/6(0%)
no	10/57(52%)	1/26(<1%)
Grade >/equal to 3 hepatotoxicity cluster term		
Yes	14/20(70%)	1/5(2%)
no	3/57(5%)	0/27(0%)

	Study 1022	
	IO Number VOD/ N HSCT	Control N VOD/ N HSCT
Last Bilirubin Prior to First HSCT(post inotuzumab)		
<ULN	10/65(15%)	1/31(3%)
≥ULN	7/12	0/1
AST, ALT or bilirubin elevation(baseline)		
Yes	10/36(28%)	1/12(8%)
No	7/41(17%)	0/20(0%)

Source: FDA Analysis

The Applicant performed a univariate and multivariate analysis to explore the association between developing VOD post-HSCT. The Applicant's univariate analysis were verified by this reviewer and displayed in the table below. Of note, during the review of the safety information the Applicant submitted 120 day safety follow-up information which included a total of 79 patients who received follow-up HSCT. The following analysis includes all 79 patients who received post study transplantation.

Table 85 Univariate Analysis for Risk Factors for VOD Study 1022

Univariate Analysis N=79	Odds Ratio	P-value
Last bilirubin prior to follow-up HSCT*(≥ ULN or < ULN)	7.13	0.003
Number of Study Treatment Cycles	1.56	0.048
Dual alkylators(dual or single)	6.6	0.009
Busulfan Containing Regimens(yes or No)	3.87	0.035
Prior SCT(Yes or No)	3.53	0.064
Age(≥ 55 or < 55)	3.24	0.048
Prior history of liver disease(yes or no)	2.95	0.057
Salvage Status(2 or more, 1)	2.3	0.148
Treatment Duration*(last dose of InO to first date of conditioning regimen)	1.006	0.478
Type of SCT(Myeloablative vs non-myeloablative)	0.767	0.632
AST or ALT or bilirubin elevation(baseline), yes or no	1.54	0.401
Duration(time from last dose to first date of conditioning)	1.00	0.478
Last AST or ALT prior to follow-up HSCT(≥ ULN or < ULN)	0.909	0.894

Source: FDA Analysis

*Last bilirubin prior to stem cell infusion (patient already received preparatory regimen).

The univariate analysis suggests that last bilirubin prior to follow-up HSCT(≥ ULN), dual alkylators, Busulfan containing regimens, prior SCT, age >55, prior history of liver disease and

number of study treatment cycles are all risk factors for the development of VOD.

Reviewer Comment: This reviewer recommends box warning for VOD on the USPI for inotuzumab ozogamicin. In addition, section 5 of the USPI, should include the risk factors that are associated with increased risk for development of VOD. Providing the treating physician with the risk factors that increase the likelihood of developing VOD in patients who proceed to transplantation may help to impact the decision as to whether to treat a patient with inotuzumab ozogamicin.

The benefit/risk of administering inotuzumab ozogamicin who have prior history of VOD or ongoing liver disease needs to be carefully weighed in treatment decision. In addition, patients who are older, later lines of salvage or had prior HSCT and prior history of liver disease additional caution should be undertaken. Patients who undergo HSCT should avoid conditioning regimens that contain 2 alkylators and patients who receive inotuzumab who are proceeding to subsequent transplantation should limit number of cycles to 2 of inotuzumab ozogamicin.

The duration of treatment variable(interval from last dose to first date of conditioning regimen) in the univariate analysis did not appear to be as strong of risk factor for development of VOD. Prior experience with gemtuzumab ozogamicin suggested that the interval between last dose of gemtuzumab ozogamicin and start of HSCT should be 4-6 weeks. It is not known what the optimal interval is between last dose of inotuzumab and start of preparatory regimen for HSCT. No definitive recommendations can be made about time interval in the USPI, can just include the interval time and range.

VOD Prophylaxis and Treatment

The treatment of suspected cases of VOD included standard supportive care. Ursodeoxycholic acid and defibrotide were used per Investigator's discretion. Ursodeoxycholic acid use was reported in 78/164(48%) and 41/143(29%) of patients in the inotuzumab ozogamicin and investigator choice arm, respectively.

Table 86 Ursodeoxycholic acid Treatment and Prophylaxis During Study 1022

	Inotuzumab Ozogamicin N=164	Investigator Choice N=143
Number patients who received ursodeoxycholic acid	78/164(48%)	41/143(29%)
Number of patients who received ursodeoxycholic acid during study therapy(C1D1 to last dose Date + 28)	47/164(29%)	16(11%)
Number of patients who did not receive ursodeoxycholic acid during study therapy(C1 to last dose date+ 28)	117/164(71%)	127/143(89%)
Number of patients who received ursodeoxycholic acid at time of HSCT(day of transplant)	52/77(68%)	10/32(31%)
Number of patients who did not receive ursodeoxycholic acid	25/77(33%)	22/32(70%)

	Inotuzumab Ozogamicin N=164	Investigator Choice N=143
at time of HSCT(day of transplant)		
Number of patients who developed VOD during study therapy or during follow-up Prior to or without HSCT		
Received Ursodeoxycholic acid during Study Therapy	2/47(4%)	0(0%)
Did not receive Ursodeoxycholic acid during study therapy	3/117(3%)	0(0%)
Number of patients who VOD during Study therapy or during follow-up prior to or without HSCT		
Received ursodeoxycholic acid at time of transplant	16/52(31%)	0(0%)
Did not receive ursodeoxycholic acid at time of transplant	1/25(4%)	1(5%)

Source: Summarization from Applicant's data CSR, Table 16.2.7.5.2

Reviewer Comment: More patients in the inotuzumab ozogamicin arm received ursodeoxycholic acid(48% vs 29%) than in the control arm. More patients in the inotuzumab ozogamicin received ursodeoxycholic acid at the time of transplantation (68% vs 31%). No relationship can be determined between prophylactic use ursodeoxycholic acid and the development of VOD.

Out of the 22 patients reported by investigators with VOD in the inotuzumab arm and 1 patients in the control arm, 11/22(50%) received treatment with defibrotide. Ten of the 17 patients who developed VOD after post-study HSCT were treated with defibrotide. Out of these ten patients, 3 recovered, VOD was ongoing in 4 patients at time of death due to other causes and 3 patients died. For the 7 patients that did not receive defibrotide, 3 recovered, 2 did not recover and 2 events were fatal.

Table 87 Defibrotide Use in Study 1022

Characteristic	Inotuzumab Ozogamicin N=164
Initiation of Defibrotide*	
Same day as VOD onset	5(3)
1-3 days after VOD onset	4(2)
4-7 days after VOD onset	0
8-10 days after VOD onset	1(<1)
>10 days after VOD onset	1(<1)
Duration of defibrotide during study therapy(screening to last dose date + 28 days or start of conditioning), days	
Median(range)	9(9,9)
Duration of defibrotide post HSCT(days)	
Median, range	17(4,45)

Total who received Defibrotide treatment and outcome	11
VOD During Study(N=5)	1/5(20%)
Died	4/5(80%)
Recovered	1/5(20%)
VOD POST HSCT(N=17)	10/17(59%)
Died	14(82%)
Recovered	3/17(18%)

Source: Summarization of Applicant's table 16.2.7.5.2, CSR module 5.3.5.1

*only initial start and not subsequent initiations

*some patients received intermittent treatment with defibrotide ,in these patients durations for each treatment were added to give total duration of treatment for patients without defibrotide stop date during study therapy, the date of death, last dose date + 28 days, start date of condition prior to HSCT or the data cutoff date was considered defibrotide stop date

For patients without defibrotide stop date post HSCT, the date of death or the data cutoff date was considered defibrotide stop date.

Adjudication of Hepatic Events

All investigators were required to submit severe hepatotoxicity forms (SHTF) for potential hepatic events to the HEAB. Based on the database cut-off date of March 8, 2016, 64 cases from 54 patients were adjudicated from the inotuzumab arm and 25 cases (25 patients) from the control arm. The HEAB adjudicated 24 events from Study 1022 as considered possible, probable or definite VOD/SOS of which 23 were from the inotuzumab arm and confirmed 1 event of grade 3 VOD in the control arm.

Table 88 HEAB Adjudication of Events in Study 1022

	Inotuzumab Ozogamicin				Investigator Choice	
	N=164				N=143	
	n(%)				n(%)	
Number of patients with events adjudicated by HEAB	54(33%)				25(18%)	
Number of events adjudicated	64				25	
Number of Patients with Events Adjudicated as Hepatic by HEAB	53(32%)				24(17%)	
Number of Classifications adjudicated as hepatic	84				34	
VOD	Mild	Moderate	Severe	Total	Severe	Total
VOD Total	2(1%)	10(6%)	11(7%)	23(14%)	1(<1%)	1(<1%)
VOD Definite	0(0%)	2(1%)	5(3%)	7(4%)	0(0%)	0(0%)
VOD Probable	0(0%)	4(2%)	5(3%)	9(6%)	1(<1%)	1(<1%)
VOD/SOS Possible	2(1%)	4(2%)	1(<1%)	7(4%)	0(0%)	0(0%)

Source: FDA Summary of Applicants table 16.2.7.5.4. CSR M 5.3.5.1

The investigators in Study 1022, identified 22 total VOD events and the HEAB assessed 19/22 as possible, probably or definite VOD. The remaining 3 were assessed by the HEAB as intrahepatic cholestasis and 2 due to fatal sepsis and not VOD. There were 4 additional events assessed as at least possible VOD by the HEAB but not by investigators.

Reviewer Comment: Most of the hepatic cases adjudicated by the HEAB as VOD were moderate or severe. The mortality of VOD with multi-organ failure is over 80%. Mitigation strategies and appropriate patient selection will be important clinical considerations in choosing whether to treat a patient with inotuzumab ozogamicin who may subsequently undergo follow-up HSCT.

Of the 4 events assessed as least possible VOD by the HEAB, one event was in a patient during study therapy. For patient 10961001, the investigator reported hyperbilirubinemia due to extrahepatic biliary obstruction and recurrent necrotizing pancreatitis while HEAB decision was extrahepatic c biliary obstruction and possible(moderate VOD).

The other three cases adjudicated by HEAB as possible VOD occurred after HSCT: patient 12721001: reported grade 2 ascites by the Investigator, but considered to be possible VOD by the HEAB, patient 12721003 reported grade 2 ascites by the investigator but considered to be possible VOD by the HEAB and patient 11671102 was reported as multi-organ dysfunction due to HHV6 infection by the investigator but was considered to represent probable VOD/SOS by the HEAB.

Reviewer Comment: Of the 22 events assessed by Investigators in Study 1022 as VOD, the HEAB assessed 19/22 as possible (4 patients), probable (8 patients) or definite (7 patients) with VOD. The remaining 3 cases were assessed as not consistent with VOD per the HEAB. The HEAB assessed 4 additional events as possible VOD (one event during study therapy and 3 after follow-up HSCT). Overall, the investigator assessment of 22 cases of VOD and overall the HEAB assessment of VOD of 23 cases of VOD are comparable. The difference in HEAB assessments and investigator does not have impact on assessment of frequency of VOD.

The most significant risk of inotuzumab ozogamicin is VOD. Mild or moderate VOD usually has self-limiting course and this study was not designed to adequately capture the severity of the VOD. When VOD occurs with multi-organ failure the mortality rate is over 80%(Coppell et al). The clinical criteria used to defined the severity of disease are based upon the clinical course and can only be applied retrospectively and in a study by McDonald et. al(1993) Day + 100 survival was 91% with mild VOD and 77% with moderate disease.

Infusion reactions

Infusion reactions were recorded on a separate case report form specifically designed to capture these events. The Applicant used a cluster term (infusion related reaction) and included any reported preferred terms used for Cluster Terms for Analysis of Safety Version 2.1.

Overall, throughout Study 1022, there were 53(32%) TEAEs in the infusion-related reaction cluster term in the inotuzumab ozogamicin arm and 63(44%) in the investigator choice arm. There was one patient in the inotuzumab ozogamicin arm with a grade 3 infusion-related adverse event of pyrexia and rash maculopapular. In the control arm 7 patients (5%) had ≥ Grade 3 infusion-related reaction adverse events.

Table 89 Infusion Related Reactions in Study 1022

Preferred Term	Inotuzumab Ozogamicin N=164		Investigator's Choice N=143	
	All grades n(%)	Grade ≥ 3 n(%)	All Grades n(%)	Grade ≥ 3 n(%)
Any AE	53(32)	1(<1)	63(44)	7(5)
Pyrexia	21(13)	1(<1)	26(25)	5(4)
Chills	8(5)	0(0)	8(6)	0(0)
Rash	8(5)	0(0)	12(8)	0(0)
Hypotension	7(4)	0(0)	8(6)	1(<1)
Dizziness	4(2)	0(0)	5(4)	0(0)
Hyperhidrosis	4(2)	0(0)	0(0)	0(0)
Hot Flush	3(2)	0(0)	0(0)	0(0)
Infusion related reaction	3(2)	0(0)	0(0)	0(0)
Rash Maculopapular	3(2)	1(<1)	2(1)	0(0)
Dyspnea	2(1)	0(0)	6(4)	1(<1)
Wheezing	2(1)	0(0)	1(<1)	0(0)
Catheter Site rash	1(<1)	0(0)	1(<1)	0(0)
Dermatitis	1(<1)	0(0)	0(0)	0(0)
Eczema	1(<1)	0(0)	0(0)	0(0)
Hypersensitivity	1(<1)	0(0)	1(<1)	0(0)
Rash erythematous	1(<1)	0(0)	2(1)	0(0)
Rash pruritus	1(<1)	0(0)	0(0)	0(0)
Tachycardia	0(0)	0(0)	3(2)	0(0)
Toxic Skin eruption	0(0)	0(0)	2(1)	0(0)
Allergic transfusion Reaction	0(0)	0(0)	1(<1)	0(0)
Eye swelling	0(0)	0(0)	1(<1)	0(0)
Face edema	0(0)	0(0)	1(<1)	0(0)
Pharyngeal edema	0(0)	0(0)	1(<1)	0(0)
urticaria	0(0)	0(0)	1(<1)	0(0)

Source: FDA Analysis TEAE dataset

FDA analysis of infusion reactions included all adverse events that occurred during Cycle 1 to include events that occurred on Cycle 1(Day 1 and 2), Cycle 1(Days 7- 9) or Cycle 1(Days 14-16).

Infusion Related Reactions (Cluster term) during Cycle 1

Overall there were 44 patients with infusion related reactions (per the cluster term) in the inotuzumab arm during Cycle 1. Thirty-two patients had infusion related reaction occurring on Day 1 or day 2, eleven patients on day 7-9 and 8 patients on days 14, 15, 16 or 17. Some patients had infusion related reactions on multiple days of infusion regimen.

During Cycle 1, there were a total of 28 patients with grade 1 adverse events during all of cycle 1 however eight of these patients had treatment given. There were a total of 18 patients with grade 2 adverse events during cycle 2. There were 12 patients with infusion related reactions in Cycle 2 and eight patients with infusion related reactions in Cycle 3 or 4.

The Applicant also identified AEs considered related to infusion reactions recorded by the investigator on a separate CRF specifically designed to capture only these events. The Applicant stated and FDA confirmed that there 17 patients considered to have TEAEs related to an infusion reaction in the inotuzumab arm. Sixteen of these events occurred during Cycle 1. None of the events were grade 3 or higher. In the control arm, 23 patients were considered to have AEs related to an infusion reaction. There were no grade 4 or 5 events reported.

Reviewer Comment: The incidence of infusion related reactions occurred most often during the first cycle with most occurring on day 1 or day 2 of the infusion. The infusion related reactions were manageable and did not prevent subsequent dosing following administration of standard precautions. Premedication with a corticosteroid, antipyretic and antihistamine are recommended prior to dosing and patients should be monitored closely during and for at least 1 hour after end of infusion for potential onset of infusion-related reactions

Myelosuppression/Cytopenias

Overall in Study 1022, there were 136 (83%) treatment emergent adverse events of myelosuppression/cytopenias in the inotuzumab ozogamicin arm compared to 128/142(90%) in the investigator choice arm per the cluster term analysis. The following table provides the preferred term and all grades and grades ≥ 3 for the safety population in study 1022 for both the inotuzumab ozogamicin and the control arms.

Table 90 Cluster Term Myelosuppression/Cytopenias TEAEs by Preferred Term, in ≥ 2 patients in the Inotuzumab Arm in Study 1022

Preferred Term	Inotuzumab Ozogamicin N=164		Investigator Choice N=142	
	All grades n(%)	Grade ≥ 3 n(%)	All grades n(%)	Grade ≥ 3 n(%)
Any AE	136(83)	133(81)	128(90)	126(88)
Thrombocytopenia	81(49)	67(41)	87(61)	85(59)
Neutropenia	80(49)	77(47)	66(46)	63(44)
Anemia	55(34)	37(23)	79(55)	63(44)

Preferred Term	Inotuzumab Ozogamicin N=164		Investigator Choice N=142	
	All grades n(%)	Grade≥3 n(%)	All grades n(%)	Grade ≥ 3 n(%)
Leukopenia	47(29)	44(27)	54(38)	53(37)
Febrile neutropenia	44(27)	44(27)	77(54)	77(54)
Lymphopenia	31(19)	27(17)	35(25)	35(25)
WBC count decreased	10(6)	10(6)	9(6)	9(6)
Hemoglobin decreased	5(3)	4(2)	7(5)	6(4)
Neutropenic sepsis	5(3)	5 (3)	6(4)	1(<1)
Lymphocyte count decreased	4(2)	1(<1)	2(1)	4(3)
Pancytopenia	2(1)	2(1)	6(4)	3(2)
Bone marrow failure	1(<1)	0(0)	3(2)	1(<1)
Platelet count decreased	2(1)	2(1)	2(1)	0(0)
B-lymphocyte count decreased	2(1)	1(<1)	0(0)	0(0)
Febrile bone marrow aplasia	1(<1)	0(0)	1(<1)	1(<1)
Hematocrit decreased	1(<1)	0(0)	1(<1)	1(<1)
Neutrophil count decreased	1(<1)	1(<1)	1(<1)	0(0)
Eosinopenia	1(<1)	0(0)	0(0)	0(0)
Eosinophilia count decreased	1(<1)	0(0)	0(0)	0(0)
Erythropenia	0(0)	0(0)	1(<1)	0(0)
Monocyte count decreased	0(0)	0(0)	1(<1)	0(0)
Monocytopenia	1(<1)	1(<1)	0(0)	0(0)
Neutropenic infection	1(<1)	1(<1)	0(0)	0(0)

Source: FDA Analysis TEAE dataset

The frequency of myelosuppression and cytopenias were similar between the 2 arms, inotuzumab ozogamicin (136/164, 83%) and the investigator choice arm (128/143, 90%) in Study 1022. Grade ≥ 3 myelosuppression/cytopenias AEs were reported for 133/164(81%) versus 126/143(88%) of patients in the control arm.

Compared to the inotuzumab arm, there were higher incidences of thrombocytopenia (investigator choice arm versus inotuzumab arm): (61% vs 49%), anemia (55% versus 34%) and febrile neutropenia (54% versus 27%) in the investigator arm compared to the inotuzumab arm.

Reviewer Comment: Inotuzumab Ozogamicin can cause myelosuppression and cytopenias and thus potential risk for infections. Routine monitoring of blood counts prior to each dose of inotuzumab, monitoring and use of prophylactic antibiotics for patients should be used at the discretion of providers.

Complications of myelosuppression include infections and hemorrhagic events. Overall for the infections cluster term, there were fewer infections in patients in the inotuzumab ozogamicin arm compared to the control arm (49% versus 77%, respectively). The following table describes

the infections (cluster term) for treatment emergent adverse events by preferred term in Study 1022.

Table 91 Infections TEAEs by Preferred Term in the Inotuzumab Ozogamicin Arm in Study 1022

Preferred term	Inotuzumab Ozogamicin N=164		Investigator Choice N=143	
	All grades n(%)	Grade ≥ 3 n(%)	All grades n(%)	Grade ≥ 3 n(%)
Any AE	80(49)	47(29)	110(77)	79(55)
Pneumonia	13(8)	10(6)	12(8)	6(4)
Bacteremia	7(4)	6(4)	14(10)	10(7)
Urinary Tract Infection	7(4)	3(2)	1(<1)	1(<1)
Oral candidiasis	6(4)	0(0)	2(1)	1(<1)
Neutropenic Sepsis	5(3)	5(3)	6(4)	6(4)
Sepsis	5(3)	5(3)	12(8)	12(8)
Upper respiratory tract infection	5(3)	0(0)	4(3)	1(<1)
Bronchitis	4(2)	1(<1)	1(<1)	1(<1)
Cellulitis	4(2)	1(<1)	7(5)	4(3)
Sinusitis	4(2)	0(0)	8(6)	3(2)
Staphylococcal bacteremia	4(2)	4(2)	3(2)	3(2)
Clostridium difficile colitis	3(2)	2(1)	5(4)	3(2)
Conjunctivitis	3(2)	0(0)	4(3)	0(0)
Influenza	3(2)	2(1)	1(<1)	0(0)
Pharyngitis	3(2)	1(<1)	1(<1)	0(0)
Septic shock	3(2)	3(2)	3(2)	3(2)
Staphylococcal Sepsis	3(2)	3(2)	2(1)	2(1)
Candida infection	2(1)	1(<1)	4(3)	1(<1)
Device related infection	2(1)	1(<1)	3(2)	1(<1)
Escherichia bacteremia	2(1)	2(1)	6(4)	4(3)
Fungemia	2(1)	1(<1)	1(<1)	0(0)
Fungal infection	2(1)	1(<1)	0(0)	0(0)
Herpes simplex	2(1)	0(0)	2(1)	0(0)
Herpes zoster	2(1)	2(1)	0(0)	0(0)
Nasopharyngitis	2(1)	0(0)	1(<1)	0(0)
rhinitis	2(1)	0(0)	0(0)	0(0)

Source: FDA Analysis TEAE dataset

Overall infections were reported in 49% (80/164) of patients receiving inotuzumab ozogamicin and in 77% (110/143) of patients in the investigator arm. Grade > 3 infections were reported in 29% (47/164) of patients in the inotuzumab ozogamicin arm and 55% (79/143) patents in the

investigator choice arm. The most common infections in the inotuzumab arm were pneumonia, sepsis and bacteremia related events.

Reviewer Comment: There were more infectious adverse events in the investigator choice arm even though treatment duration was longer in the inotuzumab ozogamicin arm. The pattern of infections(pneumonia, sepsis and bacteremia) are not unexpected for this heavily pretreated population.

Complications associated with hemorrhage occurred in 55/164 (34%) of patients in the inotuzumab arm and 42/164 (29%) patients in the investigator choice arm. The most common preferred terms in the inotuzumab arm leading to hemorrhage (cluster term) included epistaxis (24/164, 15%), GI Bleed (grouped term)(13/164, 8%) contusion(10/164,6%). In the investigator choice arm, the most common causes for hemorrhage included epistaxis 12/143(8%), petechiae (5/143, 4%) and mouth hemorrhage (5/143,5%).

During the inotuzumab therapy, 6 patients had grade 3 events(2 epistaxis and 1 each of hematuria, GI hemorrhage, gastritis hemorrhage and upper GI hemorrhage) 2 patients had Grade 4 event(intracranial hemorrhage and mesenteric hemorrhage) and 2 patients had three Grade 5 events(GI hemorrhage, intra-abdominal hemorrhage and shock hemorrhage). There were 2 grade 5 hemorrhagic events in the inotuzumab ozogamicin arm and 1 grade 5 event in the control arm.

The grouped term for GI bleed from the cluster terms includes: rectal hemorrhage, Gastrointestinal hemorrhage, hematochezia, gastritis hemorrhagic, hematemesis, intra-abdominal hemorrhage, mesenteric hemorrhage, upper gastrointestinal hemorrhage, hemoptysis and melena.

Reviewer Comment: Epistaxis was the most frequently reported hemorrhage AE in the inotuzumab ozogamicin arm. The two events of fatal (grade 5) hemorrhagic events occurred in setting of disease progression.

Tumor lysis syndrome (TLS)

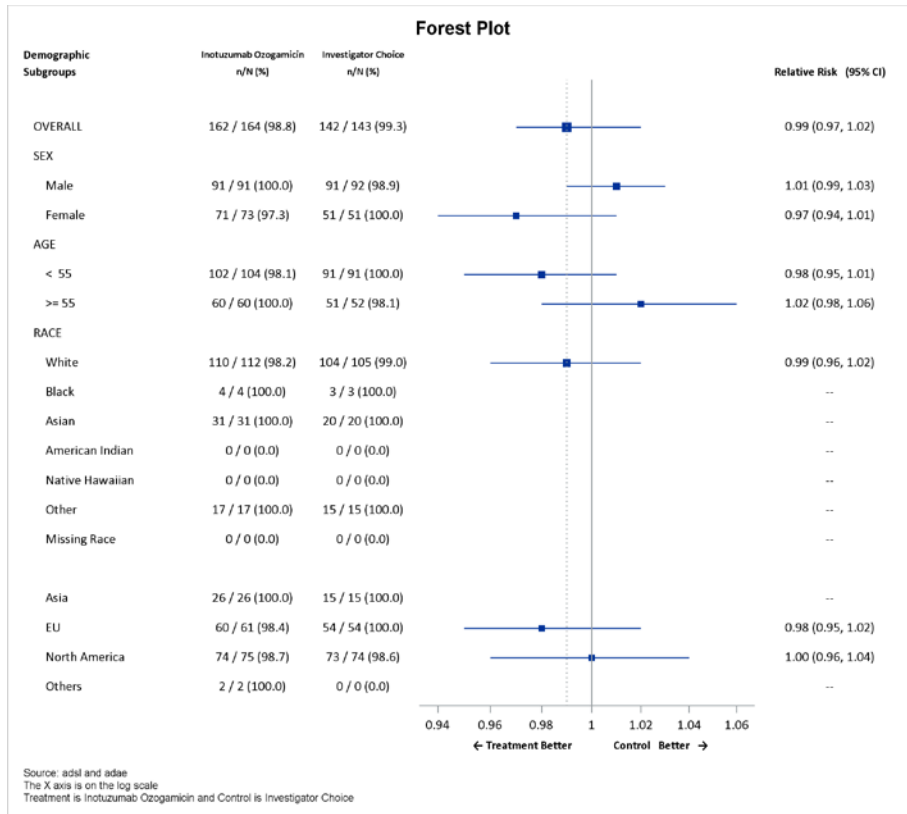
The incidence of tumor lysis in Study 1022 was low with 4 patients (2%) in the inotuzumab arm and 3 patients (2%) patients in the control arm having tumor lysis. Two grade 3 events and one grade 4 event occurred in the inotuzumab ozogamicin arm.

Reviewer Comment: The incidence of TLS was low. Monitor patients for TLS per standard medical practice.

7.4.6. Safety Analyses by Demographic Subgroups

The individual trials are not adequately powered to reach conclusion regarding the safety among the demographic subgroups (sex, race and age). The following figure depicts the relative risk for patients with TEAEs by sex, age and race.

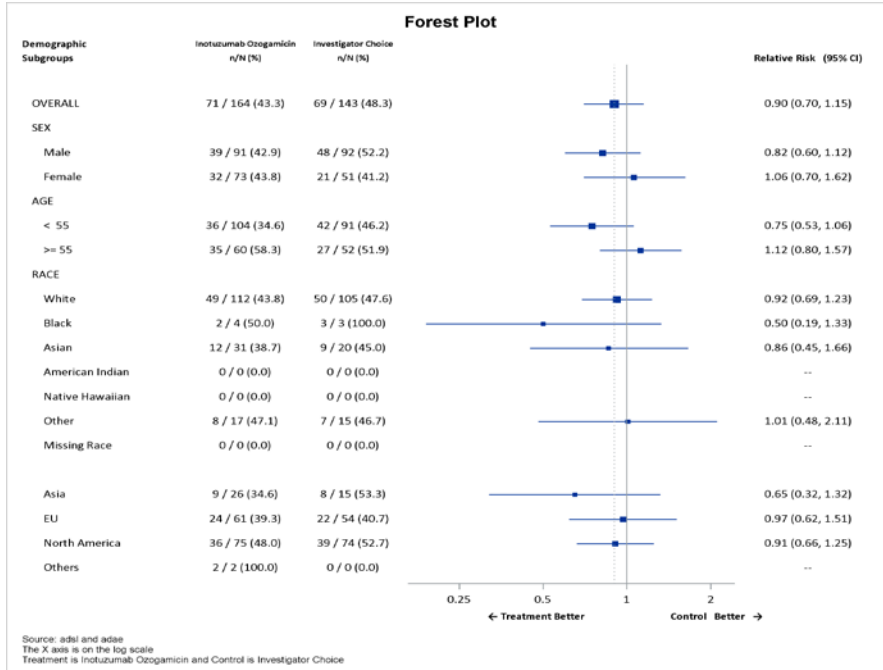
Figure 17 Relative Risk of TEAEs by Demographic Subgroup for Study 1022



The following diagram depicts the relative risk for patients with SAEs by sex, age and race.

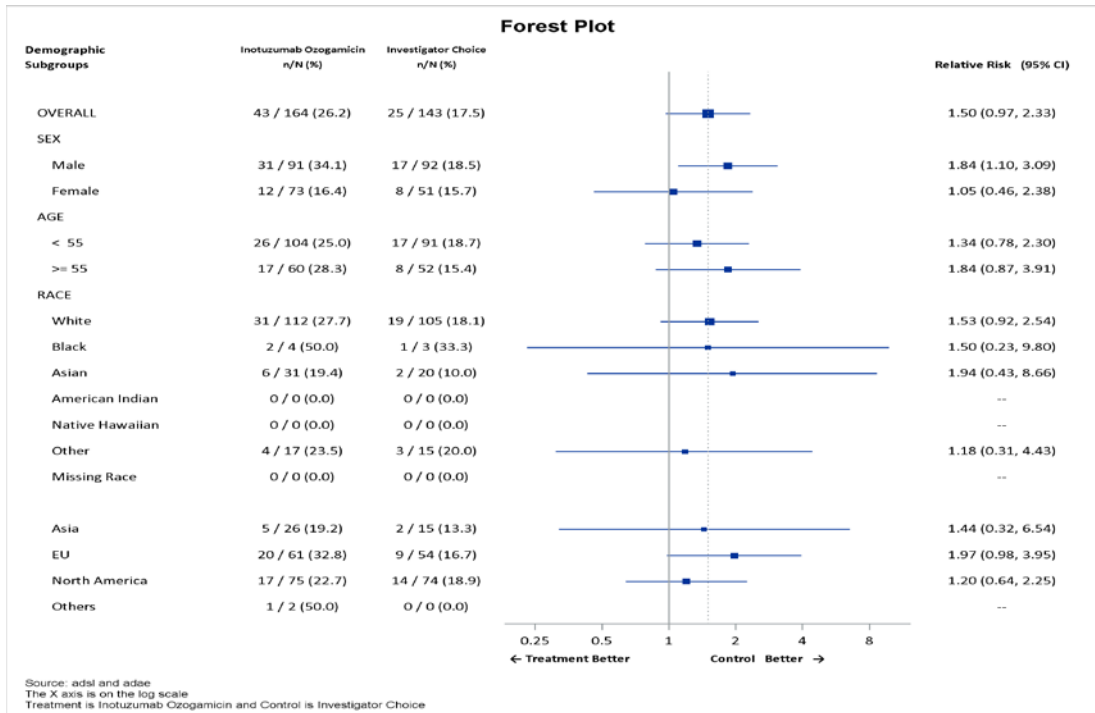
Figure 18 Relative Risk by SAEs by Demographic Subgroup for Study 1022

NDA/BLA Multi-disciplinary Review and Evaluation {BLA 761040}
 {BESPONSA; Inotuzumab Ozogamicin}



The following diagram depicts the relative risk for patients with hepatotoxicity adverse events by demographic subgroups of sex, age and race.

Figure 19 Relative Risk for Patients with Hepatotoxicity in Study 1022



7.4.7. **Specific Safety Studies/Clinical Trials**

No studies or trials were conducted to evaluate a specific safety concern.

7.4.8. **Additional Safety Explorations**

Human Carcinogenicity or Tumor Development

Neoplasms (identified using the Neoplasms, Benign, Malignant and Unspecified SOC) were rare on Study 1022. There were three patients in the inotuzumab ozogamicin arm (2%) who developed neoplasms. Two were related to underlying malignancy (leukemia cutis and chloroma) and the other case was benign.

Pediatrics and Assessment of Effects on Growth

Study 1022 and Study 1010 excluded patients who were less than 18 years of age. The safety of inotuzumab ozogamicin in pediatric patients has not been established.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There was no experience of overdose reported in the clinical studies of inotuzumab ozogamicin in patients with relapsed or refractory ALL. In the NHL study 1004(inotuzumab ozogamicin plus rituximab) one patient with NHL accidentally received inotuzumab ozogamicin at a dose of 2.4mg/m² rather than 1.8mg/m² during cycle 1. The reported AE for this patient included Grade 3 thrombocytopenia and grade 1 AEs (vomiting, diarrhea, hypokalemia, cough, oral herpes, and muscle spasms).

Patients do not self-administer inotuzumab ozogamicin and access to the drug is restricted to healthcare professionals and prescribed by specialists in Hematology and Oncology. There is no evidence observed that inotuzumab ozogamicin produces physical or psychological dependence in patient with hematologic malignancies.

7.4.9. **Safety in the Postmarket Setting**

Safety Concerns Identified Through Postmarket Experience

Inotuzumab ozogamicin is not marketed in any country. There are no post-market safety data.

Expectations on Safety in the Postmarket Setting

7.4.10. **Integrated Assessment of Safety**

A total of 880(73%) patients have received at least 1 dose of inotuzumab ozogamicin and for the purpose of this integrated assessment of safety only the ALL studies with single-agent

inotuzumab ozogamicin (Studies 1022 and Study 1010) are discussed in further detail.

In study 1022, 164 patients received inotuzumab and 143 patients received Investigator's choice of chemotherapy (control arm). The 164 patients received inotuzumab ozogamicin at the proposed dose. Data from the 164 inotuzumab ozogamicin treated patients in Study 1022 were pooled with data from 48/72 patients from Study 1010 given similar dosing regimens (POOLED ALL studies, n=212).

In Study 1022, the median duration of treatment in the inotuzumab ozogamicin arm was 8.9 weeks (median 3 cycles) and 0.9 weeks (median 1 cycle) for patients who received the control therapy. In study 1010, the median duration of treatment was 10.1 weeks (median 3 cycles). In the pooled single agent ALL studies, the median duration of treatment with inotuzumab ozogamicin was 9.1 weeks (median 3 cycles).

Common TEAEs (all reported AEs for up to 42 days after the last dose of study drug as well as all VOD/SOS during study treatment and follow-up period for up to 2 years).

- The most common($\geq 20\%$) all causality TEAEs for inotuzumab ozogamicin versus control therapy were thrombocytopenia(49% vs 61%), neutropenia(49% vs 46%), anemia(34% vs 55%), nausea(32% vs 48%), pyrexia(32% vs 42%), leukopenia(29% vs 38%), headache(27% vs 27%), febrile neutropenia(27% vs 54%), fatigue(26% vs 17%), AST increase(23% vs 11%), GGT increase(21% vs 8%) and hyperbilirubinemia(21% vs 17%).
- TEAEs with frequency $\geq 10\%$ in the inotuzumab ozogamicin arm compared to the control arm($\geq 5\%$ absolute difference) were fatigue(26% vs 17%), AST increase(23% vs 11%), GGT increase(21% vs 8%), epistaxis(26% vs 8%), blood ALP increase 13% vs 7%), and VOD(13% vs 0.7%).
- In the pooled ALL studies, the most commonly reported AEs were thrombocytopenia (49%) and neutropenia (43%), which are similar to AEs in the inotuzumab ozogamicin arm in Study 1022.

Grade 3 AEs

- In Study 1022, the most common ($\geq 10\%$) Grade 3 TEAEs for inotuzumab ozogamicin versus control therapy were neutropenia(47% vs 44%), thrombocytopenia(41% vs 59%), febrile neutropenia (27% vs 54%), leukopenia(27% vs 37%), anemia(23% vs 44%), lymphopenia(17% vs 25%), GGT increase(11% vs 5%) and VOD(11% vs 0.7%).
- In the POOLED ALL studies, the most frequently reported grade ≥ 3 AEs were thrombocytopenia (42%) and neutropenia (42%) and VOD(10%). The other $\geq$ Grade 3 were similar to the inotuzumab ozogamicin arm in study 1022.

SAEs

- The most common ($\geq 2\%$) serious adverse events for inotuzumab ozogamicin vs control therapy were VOD(13% vs $<1\%$), febrile neutropenia(12% vs 19%), pneumonia(6% vs 0%), pyrexia(3% vs 2%), and sepsis(2% vs 7%).
- In the pooled ALL studies, the most frequently reported SAEs ($\geq 5\%$) were febrile

neutropenia(15%), VOD(12%), pneumonia(7%) and disease progression(6%).

Permanent Treatment Discontinuations/Treatment Delays

- In Study 1022, TEAES associated with permanent treatment discontinuations for the inotuzumab ozogamicin arm was 18% compared to 8% in the control arm with pneumonia (3%) and thrombocytopenia (2%) as the most common for the inotuzumab ozogamicin arm.
- In Study 1022, AEs associated with treatment delays were reported in 44% of patients in the inotuzumab arm compared to 12% in the control arm. The most frequently reported AE ($\geq 5\%$) associated with treatment delay in the inotuzumab ozogamicin arm was neutropenia (17%) and thrombocytopenia(10%). In the control arm there were no AE reported with frequency $\geq 5\%$ associated with treatment delays.
- In the pooled ALL studies of single agent inotuzumab ozogamicin, the types of AEs associated with permanent discontinuations, treatment delays and dose reductions were similar to those reported in the inotuzumab ozogamicin treated patients in Study 1022.

Deaths

- In study 1022, grade 5 SAEs were reported in 26/164(16%) of patients in the inotuzumab arm and 16/143(11%) patients in the control arm. The most frequently reported causes of death in the inotuzumab ozogamicin arm versus the control arm were adverse events in the SOC of General Disorders and Administration Site conditions (6% vs 5%- disease progression most frequent) and infections and infestations(5% in both arms of study). Six of the 26 deaths in the inotuzumab ozogamicin arm occurred after subsequent HSCT (5 patients due to VOD and one due to multi-organ failure in setting of VOD).
- In the pooled ALL studies, Grade 5 SAEs were reported in 33(16% of patients).
- All deaths reported in the safety population includes all deaths whether during study or in follow-up period. There were 122(74%) deaths in the inotuzumab arm versus 121 deaths (85%) in the control arm. Disease under study (progressive disease during study) occurred in 75(46%) of patients in the inotuzumab ozogamicin arm compared to 95(66%) in the control arm.
- In the Inotuzumab ozogamicin arm 77/164(47%) patients proceeded to follow-up transplantation and 33/143(20%) of patients in the control arm proceeded to transplantation.
- Post-transplantation mortality was 46/77(60%) in the inotuzumab arm and 19/33(58%) in the control arm.
- Non-relapsed mortality included death as due to other reasons other than disease under study and included patients who had relapsed or disease progression but subsequently died from causes other than disease under study. The number of patients with post-transplant non-relapse mortality was 29/77(38%) in the inotuzumab arm and 8/33(24%) in the control arm. In the inotuzumab ozogamicin arm more patients died due to reasons other than disease under study (infection and VOD)
 - There were 5 fatal VOD cases after subsequent transplantation in the inotuzumab ozogamicin arm and 6 cases of VOD ongoing at the time of death

(death due to other mechanism) after HSCT.

Hepatotoxicity

- Treatment emergent adverse hepatotoxicity events were reported in 51% of patients in the inotuzumab ozogamicin arm and 34% in the control arm (respectively). The most frequently reported hepatotoxicity TEAE in the inotuzumab arm compared to the control arm were AST increase (23% vs 11%), GGT increase (21% vs 8%), hyperbilirubinemia (21% vs 17%) and ALT increase (15% vs 13%).

VOD

- Twenty-two patients(22/164, 13%) in the inotuzumab ozogamicin arm had VOD during or following treatment or following HSCT after completion of treatment and in the control arm VOD was reported in 1/143(<1%) of patients . Five patients had fatal VOD that occurred post-HSCT.
- Of the 22 VOD events in the inotuzumab ozogamicin arm, 5/164(3%) occurred during study therapy or in follow-up without intervening HSCT and 17 occurred in 77 patients (22%) after a subsequent HSCT. Five of the 22 VOD events were fatal (all post-HSCT), 7 patients recovered from VOD (1 without intervening HSCT and 6 post-HSCT) and VOD was ongoing at the time of death for 10 patients.
- Univariate analysis of risk factors for VOD indicated that use of last bilirubin prior to follow-up HSCT ($\geq$ ULN), dual alkylators, Busulfan containing regimens, prior SCT, age $\geq$ 55, history of liver disease and number of study treatment cycles.
- In Study 1010, the VOD total was reported in 4/72 patients(6%) and in the pooled ALL studies VOD total was reported in 26/212(12%) of patients . In the ALL studies 1022 and 1010, there were 101 patients who went to HSCT after inotuzumab ozogamicin and VOD was reported in 19/101(19%) of patients. In the single agent NHL studies VOD was reported in 1/173 patients (< 1%).
- The HEAB adjudicated 19/22 cases in the inotuzumab arm as possible/probable or definite VOD/SOS. In addition, the HEAB adjudicated 4 additional cases as possible/probable or definite VOD for a total of 23 cases of VOD adjudicated by the HEAB compared to 22 cases by Investigators.

In summary, the safety profile for inotuzumab ozogamicin is manageable for myelosuppression, infections and hemorrhage. Common adverse events ($\geq$ 20%) included thrombocytopenia, neutropenia infection, anemia, leukopenia, fatigue, hemorrhage, pyrexia, nausea, headache, febrile neutropenia, transaminase increased, abdominal pain, hyperbilirubinemia and gamma-glutamyltransferase increased. There was less febrile neutropenia and severe infections in the inotuzumab ozogamicin arm compared to the defined investigator choice of chemotherapy however there were more hepatic adverse events (51%) to include VOD in the inotuzumab ozogamicin arm. The most frequent serious adverse event in the inotuzumab ozogamicin arm was VOD(14%) with VOD occurring more frequently in patients who proceeded to subsequent HSCT(18/79,23%). Prior HSCT, the use of HSCT conditioning regimens that contains 2 alkylating agents, and last total bilirubin level $\geq$ upper limit of normal before follow-up HSCT are associated with an increased risk of VOD after HSCT. Other risk factors include increased age, greater number of treatment cycles, busulfan containing regimens, later lines of salvage

therapy and history of liver disease prior to treatment. The high frequency of VOD hepatotoxicity to include VOD warrants a box warning. Mitigation strategies for VOD to include careful consideration for patient selection based on risk factors, limiting number of treatment cycles, close monitoring of patients for VOD described in the prescribing information.

120 Day Safety Update

The Applicant submitted 120 day safety update on February 24, 2017. There were now a total of 79 patients who proceeded to subsequent transplant in the inotuzumab ozogamicin compared to 77. VOD was reported in 14/164(14%) rather than 13 patients. Among the 79 patients who proceeded to subsequent HSCT, VOD was reported in 18/79(23%) compared to 17/77(22%). Five of the 18 VOD events that occurred post-HSCT were fatal. VOD was reported in 13/68(19%) of patients who only received a HSCT after inotuzumab ozogamicin; an increase of one patient (was previously 12/66, 18%).

The Applicant conducted a univariate analysis based on the 79 patients who proceeded to subsequent HSCT. This reviewer confirmed the results of the univariate analysis for the 79 patients (refer to section 7.5.1). For patients who proceed to subsequent HSCT, the use of conditioning regimens that have 2 alkylating agents, last total bilirubin > upper limit of normal (ULN) before follow-up HSCT are associated with significant risk in VOD after HSCT.

SUMMARY AND CONCLUSIONS

7.5. Statistical Issues

In Study B1931022, Inotuzumab ozogamicin demonstrated a statistically significant improvement in the ORR primary endpoint compared to the defined physician's choice of treatment. This improvement was consistent across all pre-specified stratification subgroups. However, the study failed to demonstrate a statistically significant improvement in OS based on the pre-specified criteria in the protocol.

In addition, we observed the following statistical issues:

- Log rank test is most powerful under the assumption of proportional hazard. However, the OS results show that the hazards in the two treatment arms were not proportional. Violation of proportional hazard does not necessarily make the log rank test invalid, but may make the estimated treatment effect difficult to interpret. Log rank test and median of survival may not be the optimal statistics to estimate the treatment effect.
- There exists imbalance in the censoring distributions between the two arms for the primary efficacy endpoint, i.e. OS, analysis. The reasons for the imbalance are unknown.
- The distribution of drug exposure between the inotuzumab ozogamicin arm and the control arm is imbalanced.

- The distribution of anti-cancer therapies between the intozumab ozogamicin arm and the control arm is imbalanced.
- There were more patients in the intozumab ozogamicin arm who received HSCT (43% in intozumab ozogamicin vs. 11% in control)
- The OS result was confounded by HSCT. The interaction between HSCT and treatment in the Cox model is nominally significant (nominal $p < 0.05$).
 - There was no difference seen between the two treatments in subjects who did not receive HSCT
 - For those subjects receiving HSCT, there were fewer early deaths in the control arm, but the intozumab ozogamicin subjects have a better survival outcome than the control subjects after 18 months.

In our exploratory competing risk analysis, when we consider death attributed only to disease, there are fewer cumulative deaths over time in the intozumab ozogamicin arm than the control arm. However, when we consider death attributed to causes other than disease, the trend was reversed.

7.6. Conclusions and Recommendations

Inotuzumab Ozogamicin is a CD22 targeted antibody-drug conjugate comprised of a humanized immunoglobulin IgG4 covalently attached via a linker to the small molecule, N-acetyl-gamma-calicheamicin. The majority of patients (>90%) with B-cell acute lymphoblastic leukemia express CD22 on the surface of malignant B-lymphocyte blast cells. The benefit-risk assessment supports standard approval of inotuzumab ozogamicin for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

The efficacy of inotuzumab ozogamicin is primarily based on the results of single large randomized, open-label controlled phase 3 study that compared inotuzumab ozogamicin, administered in split doses to defined investigator's choice of chemotherapy (control arm) in patients greater than or equal to 18 years of age with relapsed or refractory B-cell ALL. The primary endpoint of CR/CRi in the first 218 patients randomized who received inotuzumab was 81% (95% CI: 72%, 88%) compared to the patients who received a defined investigator's choice of chemotherapy 29% (95% CI: 21%, 39%).

The secondary endpoints of CR and duration of response were used to inform the regulatory decision making process. CR was achieved by 39 (36%) subjects (95% CI; 27%, 46%) in the inotuzumab ozogamicin arm versus 19 (17%) subjects (95% CI: 11%, 26%) in the investigator's choice of chemotherapy arm. The response was durable with estimated median duration of complete response of 8 months (95% CI: 5, 10 months) in the inotuzumab ozogamicin arm

compared to 5 months (95% CI: 3, 7 months) in the investigator's choice of chemotherapy arm. This CR rate for single agent inotuzumab in the intended population is clearly higher than reported for any other single chemotherapeutic agents in the literature. Additional support for the conclusion of effectiveness is based on the attainment of MRD levels less than $<1 \times 10^{-4}$ as MRD levels less than $<1 \times 10^{-4}$ are expected to be reasonably likely to predict clinical benefit in the intended population. The conclusion of effectiveness is strengthened by the finding that 35/39(89.7%) of the patients in the inotuzumab ozogamicin arm not only had a CR but also had a reduction in minimal residual disease (MRD) to $< 1 \times 10^{-4}$ compared to 6/19(31.6%) in the investigator's choice of chemotherapy arm. The responses were consistent in analysis of the full intent-to-treat (ITT) population and consistent across the subpopulations tested. Additional support for the conclusion of effectiveness is strengthened by the finding that 78% (95% CI: 68%, 87%) of the patients in the inotuzumab ozogamicin arm not only had a CR/CRi but a reduction in minimal residual disease (MRD) to $< 1 \times 10^{-4}$ compared to 38% (95% CI: 24%, 47%) in the investigator's choice of chemotherapy arm in the ITT(N=326) population.

In the inotuzumab arm, the patients with CRi appear to be comparable to patients who attained CR with regard to MRD status and durability of response. The CRi responders performed better overall with respect to MRD negativity and duration of response compared to patients who attained CRi in the chemotherapy control arm. In the inotuzumab ozogamicin arm, the rate of attainment of CRh(29%) in the ITT218 population per EAC is comparable to the rate of CR(35.8%) and CRi(45.0%). The magnitude of difference between the attainment of CRh in the inotuzumab arm (29%) compared to the investigator choice arm(5%) is notable as is the rate of MRD negativity for the patients with CRh(71.8%) in the inotuzumab ozogamicin arm versus 20% in the investigator choice arm.

An improvement in overall survival for the full ITT population (N=326) did not reach statistical significance in the pivotal phase 3 study (B1931022) as it exceeded the prespecified 1-sided p-value boundary of 0.0104 in the pivotal phase 3 study(B1931022). The estimated hazard ratio for the primary endpoint of overall survival (OS) in the ITT population was 0.770(97.5% CI: 0.578, 1.026) with an estimated median OS of 7.7 months (95% CI 6, 9.2) for inotuzumab ozogamicin versus 6.7 months (95% CI 4.9 8.3) in the control arm. In the competing risk analysis when death was attributed to disease only, there are fewer cumulative deaths over time in the inotuzumab arm than the control arm. When considering deaths attributed to causes other than disease, the reverse was true, there were more cumulative deaths over time in the inotuzumab arm compared to the control arm (non-relapse mortality in inotuzumab arm of 38%(29/77) versus 24%(8/33) in the control arm). Hepatic VOD was the main contributing factor leading to the increase in non-relapse mortality in the inotuzumab ozogamicin arm. The increase risk of non-relapse mortality in patients with relapsed or refractory ALL who receive inotuzumab ozogamicin and proceed to subsequent HSCT supports a boxed warning in the product label.

The safety database for inotuzumab ozogamicin consists of 880 patients exposed to

inotuzumab ozogamicin with the primary assessment for safety from 2 studies (B1931022 and B1931010) in patients with relapsed or refractory ALL. In general, the safety profile for inotuzumab ozogamicin is manageable for myelosuppression, infections and hemorrhage. Common adverse events ($\geq 20\%$) included thrombocytopenia, neutropenia infection, anemia, leukopenia, fatigue, hemorrhage, pyrexia, nausea, headache, febrile neutropenia, increased transaminases, abdominal pain, hyperbilirubinemia and increased gamma-glutamyltransferase. There was less febrile neutropenia and severe infections in the inotuzumab ozogamicin arm compared to the defined investigator choice of chemotherapy however there were more hepatic adverse events (51%) to include VOD in the inotuzumab ozogamicin arm.

The most frequent serious adverse event in the inotuzumab ozogamicin arm was VOD(14%) with VOD occurring more frequently in patients who proceeded to subsequent HSCT(17/77,22%). The risk factors, prior HSCT, the use of HSCT conditioning regimens that contains 2 alkylating agents, and last total bilirubin level $\geq$ upper limit of normal before follow-up HSCT, are associated with an increased risk of hepatic VOD after HSCT. Other risk factors include increased age, greater number of treatment cycles, busulfan containing regimens, later lines of salvage therapy and history of liver disease prior to treatment. The major safety risk of VOD and post-transplantation non-relapse mortality warrant a boxed warning in the USPI. Mitigation strategies for VOD to be described in the prescribing information include careful consideration for patient selection for administration of inotuzumab ozogamicin based on risk factors, limiting number of treatment cycles, and close monitoring of patients for development of VOD.

In summary, the current standard of care for the treatment of relapsed or refractory ALL is intensive combination chemotherapy and the results with this approach continue to remain disappointing. Effective new treatments are needed for patients with relapsed or refractory ALL. The conclusion on the substantial evidence of effectiveness is founded on the CR rate of 36% and durable response(median 8 months) which were substantially better than the responses for the control arm of defined investigator choices of single agent or combination chemotherapy regimens. Moreover, an MRD response was noted in 89.7% of patients who attained a CR compared to only 31.6% in the defined investigator choice chemotherapy arm. Taken together, the efficacy outcomes (CR, durability and MRD negativity) in the inotuzumab ozogamicin arm compared to the control arm form a strong basis for a conclusion of effectiveness for inotuzumab ozogamicin. Although inotuzumab ozogamicin failed to demonstrative statistical significance for overall survival, patients in the inotuzumab arm who proceeded to subsequent transplantation had better survival outcomes than patients in the control arm after 18 months. The failure of the attainment of CR to translate into an improvement in overall survival that was statistically significant was potentially due to more early deaths and post-transplantation non-relapse mortality in the inotuzumab ozogamicin arm. Hepatic VOD was the main contributing factor to the non-relapse mortality rate. In general, the safety profile for inotuzumab ozogamicin is manageable for myelosuppression, infections and hemorrhage. The most significant risks of inotuzumab ozogamicin are VOD and post-transplant non-relapse mortality which can be adequately understood and managed by hematologists-

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oncologists who treat patients with acute leukemia, and are acceptable for a population with serious and life-threatening condition in the context of the efficacy. Overall, the risk-benefit assessment of inotuzumab ozogamicin is favorable for the treatment of patients with relapsed or refractory precursor B-cell ALL. I recommend full approval of inotuzumab ozogamicin for adult patients with relapsed or refractory B-cell ALL.

Qing Xu, Ph.D
Primary Statistical Reviewer

Yuan Li Shen, Dr.P.H.
Statistical Team Leader

Tanya Wroblewski, MD
Primary Clinical Reviewer

R. Angelo de Claro, MD
Clinical Team Leader

8 Advisory Committee Meeting and Other External Consultations

This Application was not presented to the Oncologic Drug Advisory Committee or any other external consultants.

APPEARS THIS WAY ON ORIGINAL

9 Pediatrics

Patients less than 18 years of age were excluded from Applicant sponsored clinical studies of inotuzumab ozogamicin. The safety of inotuzumab ozogamicin in pediatric patients has not been studied.

APPEARS THIS WAY ON ORIGINAL

10 Labeling Recommendations

10.1 Prescribing Information

The following are recommended major changes to the inotuzumab ozogamicin prescribing information proposed by the reviewer based on this review:

- **HIGHLIGHTS:** Add box warning describing increased non-relapse mortality in patients who proceed to HSCT after inotuzumab ozogamicin and increase risk of hepatic veno-occlusive disease and hepatotoxicity.
- **2 DOSAGE AND ADMINISTRATION:** [REDACTED] (b) (4)
- **5 WARNINGS AND PRECAUTIONS:** Include paragraphs on post-transplant non-relapse mortality and VOD.
- **6 ADVERSE REACTIONS:** Add paragraph describing incidence and risk factors for VOD
- **14 CLINICAL STUDIES:** [REDACTED] (b) (4)

10.2 Patient Labeling

This subsection is not applicable as inotuzumab ozogamicin is administered intravenously to patients in a hospital under supervision.

11 Risk Evaluation and Mitigation Strategies (REMS)

There are no additional risk management strategies beyond recommended labeling. Therefore the subsequent sections are not applicable for this review and have been omitted. Review of the Application and of the findings from the review teams, the Division of Risk Management in the Office of Surveillance and Epidemiology agree that a REMS is not needed to ensure the benefits of (b) (4) exceed its risk.

APPEARS THIS WAY ON ORIGINAL

12 Postmarketing Requirements and Commitments

One clinical trial to evaluate [REDACTED] ^{(b) (4)} efficacy of at least two dose levels of Besponsa in patients at high risk for developing veno-occlusive disease, will be required under FDAAA. One clinical study to characterize toxicity of Besponsa in patients after hematopoietic stem cell transplantation using transplant registry data will be required under FDAAA.

APPEARS THIS WAY ON ORIGINAL

13 Appendices

13.1. References

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13.2. Financial Disclosure

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The Applicant submitted financial disclosure information including bias statements for studies B1931022, B1931010, B1931016, B1931001, B1931002, B1931003, B1931004, B1931005, B1931006, B1931007, B1931008. Form FDA 3454 was submitted that none of the financial interests or arrangements described in 21 CFR Part 54 exists is provided for 2791 of the 2856 clinical investigators. The Applicant identified 1 clinical investigator who was a full-time or part-time employee of the sponsor of the covered study. Due diligence was required for 37 of the 2856 clinical investigators. Twenty-eight of the 2856 clinical investigators listed in the study report had financial information to disclose. All investigator initiated research grants associated with clinical investigators are paid directly to the Institution rather than to the individual clinical investigator.

Covered Clinical Study (Name and/or Number):

Covered Clinical Study (Name and/or Number): B1931022

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>900</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>7</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: <u>7</u> Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X ☐	No ☐ (Request information from Applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>3</u>		
Is an attachment provided with the reason:	Yes X ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): B1931010

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>111</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>4</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: <u>4</u> Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>1</u>		
Is an attachment provided with the reason:	Yes x1 ☐	No ☐ (Request explanation from Applicant)

13.3. Nonclinical Pharmacology/Toxicology

No additional nonclinical data reviewed.

13.4. OCP Appendices (Technical documents supporting OCP recommendations)

13.4.1. Exposure Response

The applicant conducted exposure-response analysis for efficacy and safety for inotuzumab ozogamicin using data obtained from the two efficacy studies conducted in patients with ALL: Study B1931010 and Study B1931022 (**Table 92**). The exposure-response relationships discussed in this BLA are based on a primarily single dose pharmacokinetics. As such, conclusions based on these analyses should be interpreted with caution. The pharmacokinetic data and sampling times from the two clinical studies are summarized in **Table 93**. The PK exposure parameters investigated were observed maximum concentration in plasma (C_{MAX}), cumulative AUC in treatment cycle 1 ($cAUC_{P1}$), cumulative AUC ($cAUC$), and average concentration defined as the cumulative AUC divided by its duration (C_{AVG}).

The pharmacokinetic exposure parameters ($cAUC_{P1}$, $cAUC$, and C_{AVG}) were calculated from the final population PK model (including covariate effects) using individual empirical Bayes estimates (see 13.4.2). Exposure-response analysis was not conducted for unconjugated calicheamicin because it was below the limit of quantitation in ~ 98% of the samples.

Table 92: Design of Studies B1931010 and B1931022 used in the exposure-response analyses

Study (Phase)	Description	Treatment Dosing/Duration	Number of Patients
B1931022 (Phase 3)	Open label, randomized, Phase 3, compared to control in patients with relapsed or refractory ALL	Arm A: Inotuzumab ozogamicin 1.8 mg/m ² /21-28 day cycle (0.8, 0.5, and 0.5 mg/m ² on Days 1, 8 and 15) Arm B: control (FLAG, MXN/Ara-C, or HIDAC (21-28 day cycle)	Inotuzumab ozogamicin (Arm A) = 164 randomized and treated control (Arm B) = 162 randomized and 143 treated
B1931010 (Phase 1/2)	Open label, single arm, Phase 1/2, dose finding with expansion cohort in patients with relapsed or refractory ALL	Phase 1 dose finding: -1.2 mg/m ² /28 day cycle (0.8 and 0.4 mg/m ² on Days 1 and 15, n=3) -1.6 mg/m ² /28 day cycle (0.8, 0.4, and -0.4 mg/m ² on Days 1, 8 and 15, n=12) -1.8 mg/m ² /28 day cycle (0.8, 0.5, and -0.5 mg/m ² on Days 1, 8 and 15, n=9) Phase 1 dose expansion: -1.8 mg/m ² /28 day cycle (0.8, 0.5, and -0.5 mg/m ² on Days 1, 8 and 15, n=13) Phase 2: -1.8 mg/m ² /28 day cycle (0.8, 0.5, and -0.5 mg/m ² on Days 1, 8 and 15, n=35)	72

Table 93: Timing of serum sample collection for pharmacokinetic analyses and disease assessment

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Study	Visit	PK Sampling (hours post first dose per cycle)	Disease Assessment (days post first dose per cycle)
B1931022 (Arm A)	Screening		During clinic visit
	Cycle 1	0 (pre-dose), 1, 2, 4, 72, 192, 193, 198, 360, 361	Day 16-21
	Cycle 2	0 (pre-dose), 1, 2, 192, 194	Day 21-28
	Cycle 3		Day 21-28
	Cycle 4	0 (pre-dose), 1, 192	
Study	Visit	PK Sampling (hours post first dose per cycle)	Disease Assessment (days post first dose per cycle)
	End of Tx		During clinic visit
B1931010	Screening		During clinic visit
	Cycle 1	0 (pre-dose), 1, 3, 360, 361, 363	Day 21 (+7 Days)
	Cycle 2	0 (pre-dose), 1, 3, 360, 361, 363	Day 21 (+7 Days)
	Cycle 4	0 (pre-dose), 1	Day 21 (+7 Days)
	End of Tx		During clinic visit

The models developed for exposure-response analysis consisted of two components: a full covariate model which described the influence of all identified fixed effects (see **Table 94**) on response and a final covariate model which describes the influence all significant fixed effects

Table 94: List of covariates tested in the population PK model

Predictors	Description
Inotuzumab Ozogamicin Exposure	C_{AVG} , $CAUC$, C_{MAX} reached at the time of declared event and $cAUC_{P1}$
Demographic Characteristics	Race, age, gender, and BSA
Baseline Patient Disease Status	ECOG, salvage, prior HSCT
Safety Laboratory Information at Baseline	Albumin, ALT, alkaline phosphatase, bilirubin, baseline creatinine clearance
Concomitant treatment	P-glycoprotein, and growth factor stimulatory treatments
Disease-Related Laboratory Values	Baseline cytogenetics, total blast counts in the peripheral blood at baseline, % of blast in the bone marrow and percentage of blasts that were CD22-positive in bone marrow or peripheral blood

Exposure-Efficacy Relationship

CR/CRi

A binomial logistic regression model was fit to the data to predict the probability of CR/CRi with each of PK exposure parameters run individually along with the remaining covariates in **Table 94** as the full covariate model. The covariates that were not statistically significant were removed from the model to yield the final model. The parameters C_{AVG} (**Table 95**) and $cAUC_{P1}$ (**Table 96**) were found to be statistically significant predictors of response along with salvage number and percentage of CD22-positivity (at a significance value of 0.05). There were no

statistically significant differences among categories 1 and 2 of the ordered salvage variable, so the information was converted into dichotomous salvage variable taking values 0 (Salvage =1) or 1 (Salvage >1).

Table 95: Final exposure-response analysis with C_{AVG}

Coefficient	Estimate	95% CI ^a	z value	Probability> z
Intercept	-6.36	[-10.67, -2.60]	-3.13	$1.8 \cdot 10^{-3}$
C_{ave} (ng/mL)	0.06	[0.04, 0.09]	5.00	$5.6 \cdot 10^{-7}$
CD22+ (%) ^b	0.06	[0.02, 0.10]	3.01	$2.6 \cdot 10^{-3}$
Salvage >1	-0.96	[-1.83, -0.14]	-2.25	0.024
Odds Ratio				
Intercept	$1.7 \cdot 10^{-3}$	$[2.3 \cdot 10^{-5}, 7.4 \cdot 10^{-2}]$	NA	NA
C_{ave} (ng/mL)	1.07	[1.04, 1.10]	NA	NA
CD22+ (%)	1.06	[1.02, 1.10]	NA	NA
Salvage >1	0.38	[0.16, 0.87]	NA	NA
Null-residual deviance ^c	49.7	NA	NA	NA
(df)	(3)			
χ^2	-70.41	NA	NA	NA
1-p-value	$9.28 \cdot 10^{-11}$	NA	NA	NA
AIC	148.82	NA	NA	NA

Table 96: Final exposure-response analysis with cAUCP1

Coefficient	Estimate	95% CI ^a	z value	Probability> z
Intercept	-4.96	[-9.07, 1.32]	-2.51	0.012
cAUCP1 (mg•hr/L)	0.15	[0.10, 0.21]	5.05	$4.5 \cdot 10^{-7}$
CD22-positive (%) ^b	0.04	$[7.8 \cdot 10^{-3}, 0.08]$	2.89	0.022
Salvage >1	-0.94	[-1.80, 0.11]	-2.19	0.028
Odds Ratio				
Intercept	$7.0 \cdot 10^{-3}$	$[1.2 \cdot 10^{-4}, 0.27]$	NA	NA
cAUCP1 (mg•hr/L)	1.16	[1.10, 1.24]	NA	NA
CD22-positive (%)	1.04	[1.01, 1.09]	NA	NA
Salvage >1	0.39	[0.17, 0.89]	NA	NA
Null-residual deviance ^c	51.96	NA	NA	NA
(df)	(3)			
χ^2	-69.28	NA	NA	NA
1-p-value	$3.06 \cdot 10^{-11}$	NA	NA	NA
AIC	146.56	NA	NA	NA

Using the obtained logistic regression parameters, the predicted probabilities were calculated and stratified by the significant predictors (PK parameter, CD22+ B-cells, and salvage). C_{AVG} (**Figure 20**) and cAUCP1 (**Figure 21**) were found to correlate with the probability of achieving CR/CRi.

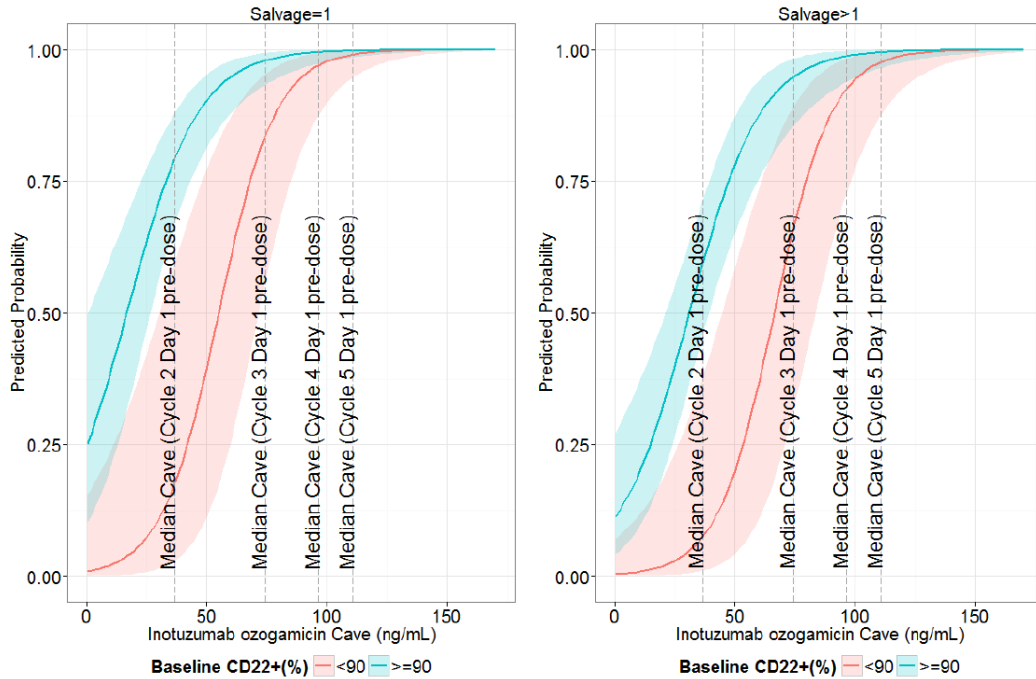


Figure 20: Predicted probability of CR/CRi response with Inotuzumab Ozogamicin treatment for C_{AVG} when stratified by prior salvage therapy or percent CD22-positivity. Source: report PMAR-EQDD-B193a-DP4-205 applicant’s exposure-response analysis.

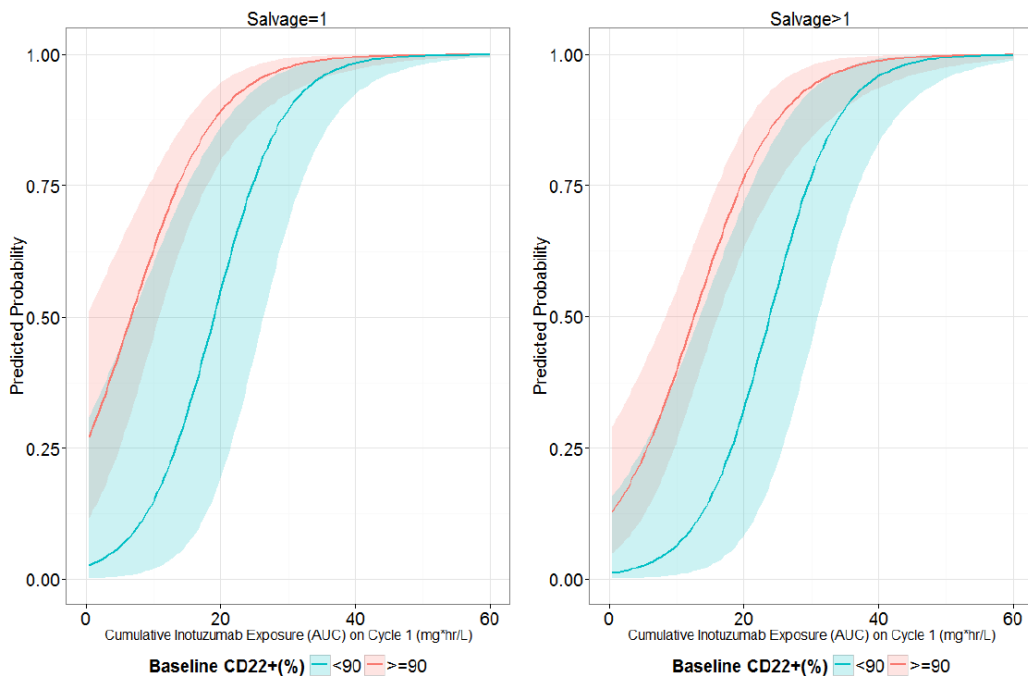


Figure 21: Predicted probability of CR/CRi response with Inotuzumab Ozogamicin treatment for $cAUC_{P1}$ when stratified by prior salvage therapy or percent CD22-positivity. Source: report PMAR-EQDD-B193a-DP4-205 applicant’s exposure-response analysis.

Overall Survival (OS)

The potential relationship between inotuzumab ozogamicin exposure and OS was performed for the ALL patient population with and without censoring for post-study HSCT. The effect of CR/CRi and MRD as prognostic factors was included in the covariate analysis (stepwise selection).

Cumulative AUC was derived from the empirical Bayes estimates obtained from the population PK model and C_{AVG} (cAUC divided by the time of its duration) was chosen as the exposure metric because it represented overall exposure during the entire period of treatment.

Stepwise covariate analysis of the variables listed in (**Table 97**) demonstrated that C_{AVG} was a statistically significant predictor of survival affecting the base hazard. Other factors that significantly improved the survival function fit were age at baseline and BLDH.

Table 97: Covariates tested as potential predictors of overall survival

Predictors	Description
Arm	Inotuzumab ozogamicin/Investigator’s choice
Inotuzumab ozogamicin exposure metrics ^a	C_{avg} , C_{max} , cAUC, and dose
Demographic characteristics	Race, age, and body weight
Baseline patient disease status	ECOG, salvage, HSCT prior to initiate Study therapy, post-study therapy HSCT ^b , and DFR
Disease-related laboratory values at baseline	Baseline cytogenetics, % of blasts in peripheral blood, % of blast in bone marrow, % of blasts that were CD22-positive in bone marrow or peripheral blood
Other laboratory information at baseline	Albumin, alkaline phosphatase, alanine aminotransferase, lactate dehydrogenase, neutrophils, platelet count, hemoglobin

The final model of parameters estimates (**Table 98**) and effect of covariates on the survival function are summarized as follows:

$$\begin{aligned}
 S(t) &= e^{-(covbase \cdot \lambda \cdot t)^{covshape} \cdot \alpha} \\
 covbase &= covAGE \cdot covCAVG \cdot covHSCT \cdot covBLDH \\
 covAGE &= \left(\frac{AGE}{46}\right)^{0.5531} \\
 covCAVG &= \left(\frac{CAVG}{68.59}\right)^{-0.4373} \\
 covHSCT &= (1 - 0.5199) \\
 covBLDH &= e^{0.2909 \cdot (\log(BLDH) - 5.91)}
 \end{aligned}$$

Table 98: Final model parameter estimates for inotuzumab ozogamicin exposure and overall survival without censoring for post-study HSCT

Parameter	Value	RSE (%)	95% CI
$\theta_{\text{Base hazard}}$	0.0032	8.99	(0.003 - 0.004)
$\theta_{\text{Shape of hazard}}$	1.2396	5.79	(1.099 - 1.380)
$\theta_{\text{AGE on base (years)}}$	0.5531	34.71	(0.177 - 0.929)
$\theta_{\text{CAVG on base (ng/mL)}}$	-0.4373	-16.97	(-0.583 - -0.292)
$\theta_{\text{HSCT (+) on base}}$	-0.5199	-15.77	(-0.681 - -0.359)
$\theta_{\text{LBDH on base}}$	0.2909	26.12	(0.142 - 0.440)
OFV	2346.8874	-	-

Progression Free Survival (PFS)

Similar to the overall survival E-R analysis, C_{AVG} along with the remaining covariates was investigated for its effect on PFS in with and without post-study HSCT censoring. C_{AVG} appeared as a statistically significant predictor of PFS affecting the base hazard. Other factors that significantly improved the survival function fit were BMAR and BLDH. The final model of parameters estimates (**Table 99**) and effect of covariates on the survival function are summarized as follows:

$$\begin{aligned}
 S(t) &= e^{-(\text{covbase} \cdot \lambda \cdot t)^{\text{covshape} \cdot \alpha}} \\
 \text{covbase} &= \text{covBMAR} \cdot \text{covCAVG} \cdot \text{covBLDH} \\
 \text{covBMAR} &= e^{-0.0095 \cdot (\text{BMAR} - 76)} \\
 \text{covCAVG} &= \left(\frac{\text{CAVG}}{68.59} \right)^{-0.4063} \\
 \text{covBLDH} &= e^{0.3831 \cdot (\log(\text{BLDH}) - 5.91)}
 \end{aligned}$$

Table 99: Final model parameter estimates for inotuzumab ozogamicin exposure-PFS analysis

Parameter	Value	RSE (%)	95% CI
$\theta_{\text{Base hazard}}$	0.0050	10.48	(0.004 - 0.006)
$\theta_{\text{Shape of hazard}}$	1.3185	6.95	(1.139 - 1.498)
$\theta_{\text{BMAR on base (\%)}}$	-0.0095	-37.94	(-0.017 - -0.002)
$\theta_{\text{CAVG on base (ng/mL)}}$	-0.4063	-22.28	(-0.584 - -0.229)
$\theta_{\text{LBDH on base}}$	0.3831	19.71	(0.235 - 0.531)
OFV	1390.8492	-	-

Exposure-Safety Relationship

Logistic regression was initially performed using a full model approach (including all tested covariates), separately with 8 different exposure parameters: cAUC, log (cAUC), C_{MAX} , log(C_{MAX}), C_{AVG} , log (C_{AVG}), cAUCP1, and log (cAUCP1). The full model was reduced by eliminating covariates that are not statistically significant to yield a final model.

There was no statistically significant positive E-R relationship for Grade 3+ neutropenia, elevated ALT, elevated AST, elevated total bilirubin, investigator-reported VOD/SOS, or hepatic events (defined by a cluster term).

A statistically significant positive E-R relationship was found between Grade 3+ thrombocytopenia and cAUCP1 and between HEAB-assessed VOD/SOS and cAUCP1 (only in patients who did not undergo HSCT post inotuzumab ozogamicin treatment) (**Table 100** and **Figure 22**).

Table 100: Parameter estimates of final exposure-response logistic regression models for thrombocytopenia and HEAB-assessed VOD/SOS

Thrombocytopenia Grade $\geq 3^a$				
Coefficient	Estimate	95% CI ^b	z value	Probability $> z $
Intercept	1.02	[-0.605, 2.7]	1.22	0.221
cAUCP1 (mg•hr/L)	0.0436	[0.00348, 0.0893]	2.01	0.0441
Log(peripheral blast count)	0.0507	[0.00259, 0.101]	2.03	0.0423
Baseline Absolute Platelet Count ($10^9/L$)	-0.0182	[-0.0281, -0.0102]	-4.05	$5.03 \cdot 10^{-5}$
HEAB-Assessed VOD/SOS ^c				
Coefficient	Estimate	95% CI ^b	z value	Probability $> z $
Intercept	-17.9	[-37.2, -7.52]	-2.53	0.0115
Log(cAUCP1) (no post-Inotuzumab ozogamicin HSCT)	4.22	[1.31, 9.24]	2.23	0.0256
Post-Inotuzumab ozogamicin HSCT	16.3	[6.01, 35.6]	2.32	0.0206
Prior HSCT	1.68	[0.215, 3.19]	2.26	0.0241

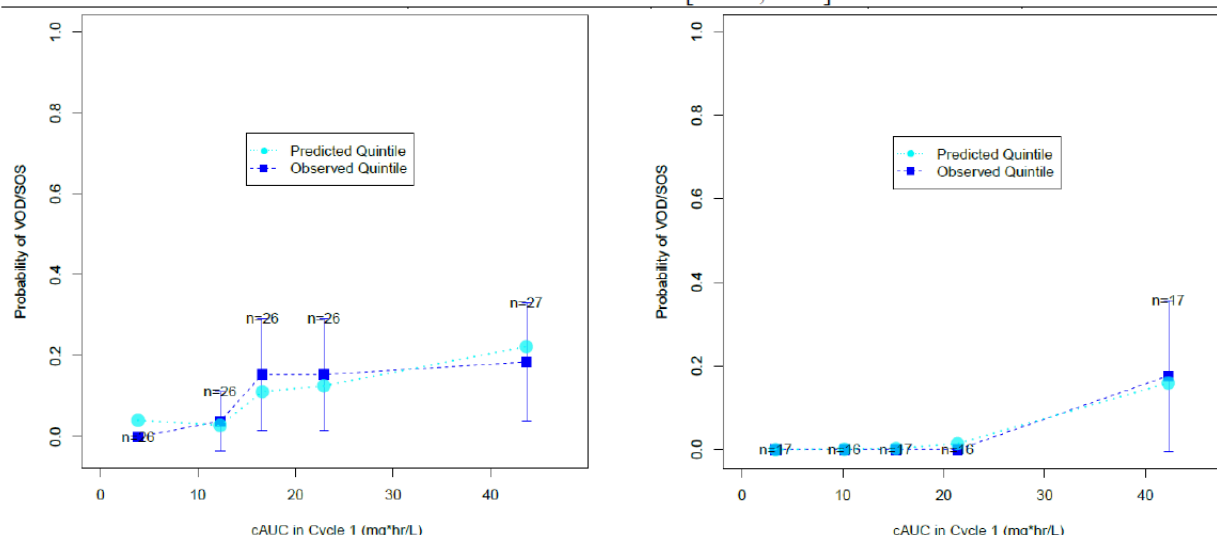


Figure 22: Observed and predicted probability of VOD/SOS (HEAB-assessed) versus cAUCP1 of all patients (Left Panel) and patients without HSCT post-inotuzumab treatment. There was a statistically significant positive ER relationship in patients without HSCT post-inotuzumab. *Source: report PMAR-EQDD-B193a-DP4-205 applicant's exposure-response analysis.*

Reviewer's Analysis

The aim of this analysis is to investigate the possibility that lower doses of inotuzumab ozogamicin may provide a better balance of safety and efficacy. In this exercise, a lower dose of inotuzumab ozogamicin was simulated using the population PK model developed by the Applicant. The dose selected for simulation was 1.2 mg/m² administered according to the schedule highlighted in **Table 9**. This dose level was chosen because it was used in estimating the PK parameters and does not include extrapolation to untested doses.

The individual subject parameters along with subject specific covariates were used to simulate the exposure parameters C_{AVG} (**Figure 23**), cAUCP1 (**Figure 25**), and cAUC for subjects included in study B1931022 and study B1931010. C_{AVG} was calculated at the end of each cycle of treatment for 1.2 mg/m² and 1.8 mg/m² based on the intended dosing regimen. The logistic regression model describing the relationship between C_{AVG} and CR/CRi used to predict the probability of response at each dose level (**Figure 24**). Similarly, simulated cAUCP1 for the two dose levels was used to predict the probability of VOD (**Figure 26**) based on the logistic regression model developed by the applicant.

Conceptually, this simulation exercise supports the idea that a lower dose may decrease the probability of VOD while maintaining efficacy, especially in the patient population with >90% CD22+ where treatment with lower dose appears to achieve the similar probability of CR/CRi by Cycle 4 of treatment.

The predictions of safety and efficacy from this simulation exercise should be interpreted with caution. Primarily, data from the single dose trial (B1931022) preclude thorough characterization of exposure-response relationship. Additionally, confounding factors (e.g., prior treatment regimens and preparatory HSCT treatment) affecting VOD combined low incidence rate further limit the utility of this simulation exercise to recommend an alternate dosing scheme.

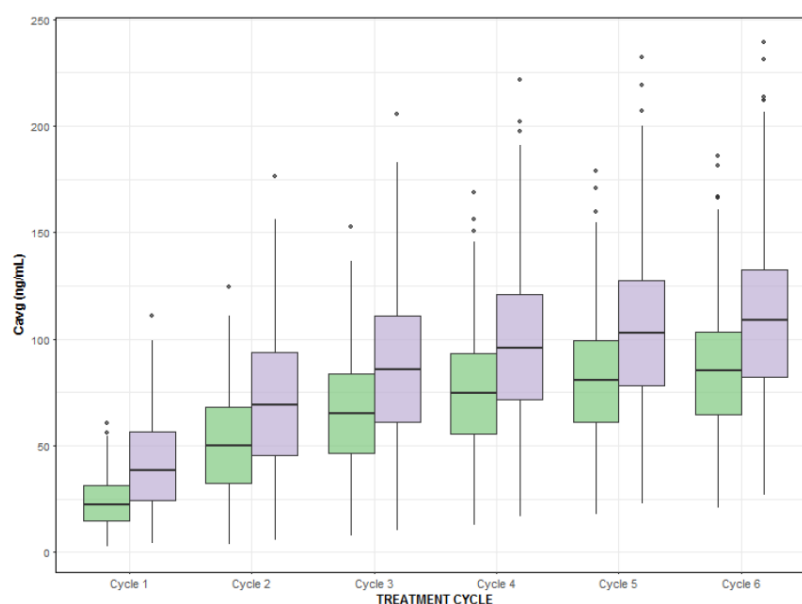


Figure 23: Simulated C_{AVG} at the end of each treatment cycle for 1.2 mg/m² dose (green boxes) and 1.8 mg/m² (purple boxes) for subjects included in study B1931022 and study B1931010.

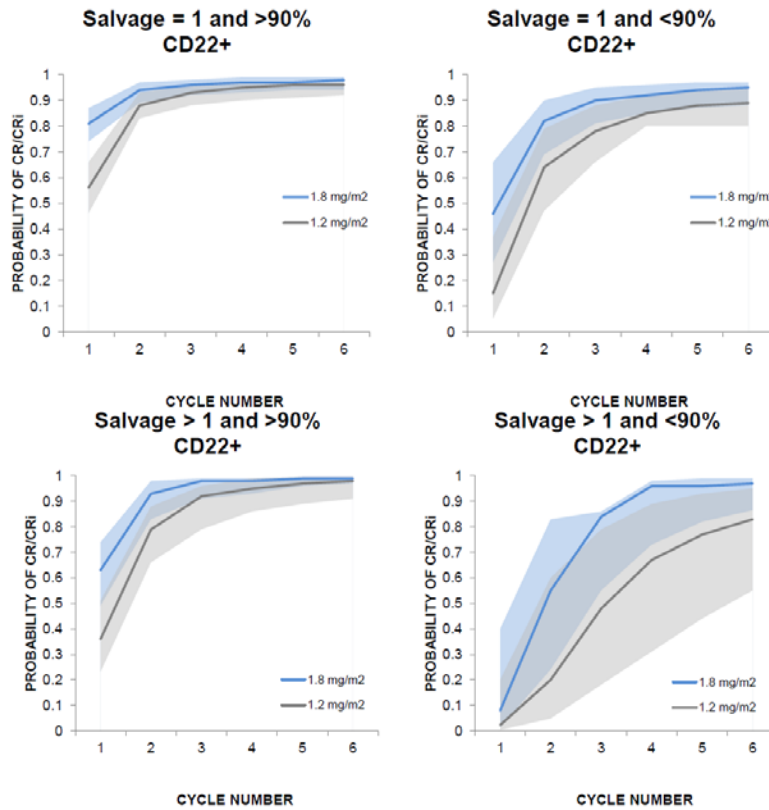


Figure 24: Predicted probability of CR/CRi for the 1.8 mg/m² and 1.2 mg/m² doses at each treatment cycle. The predicted probabilities are stratified by salvage treatment and percent CD22+, both which are statistically significant covariates.

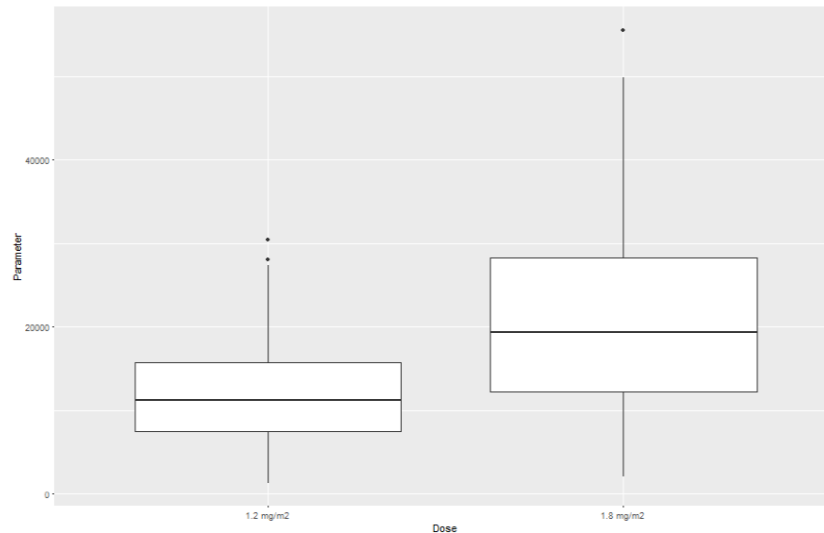


Figure 25: Predicted cAUCP1 for the 1.2 mg/m² dose (left box) and the 1.8 mg/m² dose (right box).

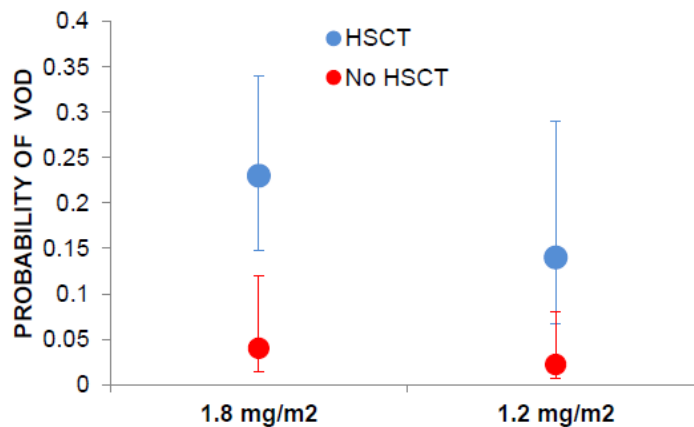


Figure 26: Predicted probability of VOD for patients proceeding to HSCT and patients not proceeding to HSCT. Error bars represent the 95% confidence interval of the model prediction.

13.4.2. Population PK Analysis

Background

The Applicant used population PK modeling to characterize the effect of intrinsic/extrinsic factors, concomitant medications, and organ impairment on the pharmacokinetics of inotuzumab ozogamicin. The objectives of the modeling effort, according to the Applicant, are:

- (1) to develop a model that describes inotuzumab ozogamicin PK following administration of 1.2-1.8 mg/m² administered over 2 or 3 doses given weekly to patients with relapsed

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or refractory B-cell ALL or as a single dose (0.4 – 2.4 mg/m²) given on Day 1 or Day 2 of each cycle to patients with relapsed refractory NHL

- (2) to identify potential covariates that may be important predictors of variability in inotuzumab ozogamicin distribution and elimination

Data

The population PK analysis was based on pooled PK data from the two studies in patients with relapsed or refractory ALL (B1931010 and B1931022) and nine studies in patients with relapsed or refractory NHL as described in **Table 101**.

Table 101: Summary of PK information from clinical studies of inotuzumab ozogamicin

Study	Design	Inotuzumab Ozogamicin Dosing	Total No. of Patients Treated With Inotuzumab Ozogamicin (Included in PK Analysis)	PK Sampling
Patients With ALL Who Received Single-Agent Inotuzumab Ozogamicin				
B1931022	Phase 3, global, multicenter, 2-arm, randomized	Arm A (n=141 randomized [139 treated]) Inotuzumab ozogamicin 1.8 mg/m ² /21-28 day cycle (0.8, 0.5, and 0.5 mg/m ² on Days 1, 8 and 15) Arm B (n=138 randomized [120 treated]) FLAG, cytarabine plus mitoxantrone, or HIDAC (21-28 day cycle)	139 (133)	Sparse PK Cycles 1, 2, and 4
B1931010	Phase 1/2, open-label, single arm, dose-escalation	Phase 1 dose finding: 1.2 mg/m ² /28 day cycle (0.8 and 0.4 mg/m ² on Days 1 and 15, n=3) 1.6 mg/m ² /28 day cycle (0.8, 0.4, and 0.4 mg/m ² on Days 1, 8 and 15, n=12) 1.8 mg/m ² /28 day cycle (0.8, 0.5, and 0.5 mg/m ² on Days 1, 8 and 15, n=9) Phase 1 dose expansion: 1.8 mg/m ² /28 day cycle (0.8, 0.5, and 0.5 mg/m ² on Days 1, 8 and 15, n=13)	72 (72)	Sparse PK Cycles 1, 2, and 4
Patients With NHL Who Received Single-Agent Inotuzumab Ozogamicin				
B1931002	Phase 1, FIH, open-label, multicenter, dose-escalation	Phase 1 0.4 mg/m ² q3w (n=2) 0.8 mg/m ² q3w (n=5) 1.34 mg/m ² q3w (n=11) 1.8 mg/m ² q3w (n=6) 2.4 mg/m ² q3w (n=6) Phase 2 1.8 mg/m ² q4w (n=49)	79 (59)	Full PK Cycles 1, 2, 3, and 4
B1931016	Phase 1, dose-escalation	1.3 mg/m ² q4w (n=3) 1.8 mg/m ² q4w (n=10)	13 (13)	Full PK Cycles 1, 2, and 3; Sparse PK, Cycle 4
B1931007	Phase 2, single arm	1.8 mg/m ² q4w	81 (75)	Sparse PK Cycles 1, 3, 4, and 6
Patients With NHL Who Received Inotuzumab Ozogamicin in Combination With Rituximab				

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B1931005	Phase 1, open-label, multicenter	Inotuzumab ozogamicin 1.8 mg/m ² q4w Rituximab 375 mg/m ² q4w	10 (10)	Full PK; Cycles 1, 2, and 3
B1931004	Phase 1/2, open-label, dose-escalation	Part 1: Inotuzumab ozogamicin 0.8 mg/m ² (n=5) 1.3 mg/m ² (n=3) 1.8 mg/m ² (n=7) plus rituximab 375 mg/m ² q4w Part 2: Inotuzumab ozogamicin 0.8 mg/m ² plus rituximab 375 mg/m ² q4w (n=104)	118 (118)	Full PK; Cycles 1, 2, and 3
B1931001	Phase 2, open-label, multicenter	Inotuzumab ozogamicin 1.8 mg/m ² q3w Rituximab 375 mg/m ² q3w	61 (53)	Sparse PK; Cycles 1, 2, and 4
B1931006	Phase 3, open-label, randomized (1:1), active-comparator	Arm 1 (n=15): Inotuzumab ozogamicin 1.8 mg/m ² q4w Plus Rituximab 375 mg/m ² q4w Arm 2 (n=14) ^c : R-CVP or R-FND	15 (14)	Sparse PK; Cycles 1, 2, 3, and 4
B1931008	Phase 3, multicenter, randomized 1:1, active-comparator	Arm 1 (n=166 randomized [164 treated]): Inotuzumab ozogamicin (1.8 mg/m ²) on Day 2 of a 4 week cycle, plus rituximab 375 mg/m ² on Day 1 of a 4 week cycle Arm 2 (n=172 randomized [167 treated]) ^d : Rituximab 375 mg/m ² on Day 1 + bendamustine 120 mg/m ² on Days 1 and 2 in of a 4 week cycle or rituximab 375 mg m ² on Days 1, 8, 15 and 22 of Cycle 1 and on Day 1 for all other cycles, + gemcitabine 1000 mg/m ² on Days 1, 8 and 15 of 4 week cycle	164 (145)	Sparse PK; Cycles 1, 3, and 4
Patients With NHL Who Received Inotuzumab Ozogamicin Combination With Rituximab Plus Chemotherapy				
B1931003	Phase 1, open-label, multicenter, 1-arm, dose-finding	Arm 1 (n=48): Inotuzumab ozogamicin (0.4, 0.8, 1.3 mg/m ²) + R-CVP ^e Arm 2 (n=55): Inotuzumab ozogamicin (0.8 mg/m ²) + R-GDP ^f	103 (44)	Sparse PK; Cycles 1, 3, and 4

Base Model

The applicant developed a population PK model to describe inotuzumab ozogamicin only. Unconjugated calicheamicin was below the limit of quantitation in 752 (98.4%) of the total 764 samples.

The inotuzumab ozogamicin PK was described using 2-compartment model with linear and time-dependent clearance components. The time dependent clearance model is:

$$CL = CL_1 + CL_t$$

$$CL_t = CL_2 \cdot e^{(-k_{des} \cdot Time)}$$

Where total clearance (CL) was a sum of time-dependent clearance (CL_t) and linear clearance (CL_1), and K_{des} is the decay coefficient of the time-dependent clearance. The selected model structure improved the fit and minimized the objective function compared to 1-compartment model and 2-compartment model with only linear elimination.

The effect of disease and analytical method (ALL and HPLC-MS/MS vs NHL and ELISA) on the CL_1 , CL_2 , and K_{des} were investigated. Patients with ALL had lower CL_1 and K_{des} compared to patients with NHL. Hence, this model structure was carried forward.

IIV in the PK parameters was modeled using multiplicative exponential random effects. The stability of the model was improved when random effects on peripheral compartment parameters (V_2 and Q) were removed. OMEGA block structure for CL_1 , V_1 , and CL_2 was found to increase model stability and minimize objective function value.

Two residual errors were included in the model, where inotuzumab ozogamicin PK concentrations were analyzed using the ELISA and HPLC/MS/MS methods for NHL and ALL, respectively. Residual variability was modeled additively based on log-transformed observation data using thetazied variance-covariance matrix of the intra-individual random effects.

Inotuzumab ozogamicin PK data < LLOQ was included in the final model using a likelihood-based approach where concentrations $\geq$ LLOQ and < LLOQ were treated as continuous-type and categorical-type data, respectively. Visual predictive check confirmed the superiority of the likelihood approach compared to omitting BLQ data. The eta-shrinkage was substantially lower with likelihood approach. The final parameters estimates and model performance are summarized in Table 102 and Figure 27.

Table 102: Population PK model parameter estimates

Parameter	NONMEM Results OFV = 1560.354				Nonparametric Bootstrap Results		
	Estimate	95% CI ^a		Shrinkage %	Estimate (Median)	95% CI ^b	
		Lower	Upper			Lower	Upper
CL_1 (L/h)	0.118	0.111	0.125	--	0.118	0.109	0.130
ALL on CL_1 ^c	-0.716	-0.748	-0.684	--	-0.718	-0.751	-0.676
CL_2 (L/h)	0.368	0.324	0.412	--	0.371	0.333	0.418
V_1 (L)	6.64	6.32	6.96	--	6.62	6.34	6.92
k_{des} (h^{-1})	0.0322	0.0229	0.0415	--	0.0315	0.0219	0.0426
ALL on k_{des} ^c	-0.830	-0.879	-0.781	--	-0.824	-0.867	-0.742
Q (L/h)	0.0398	0.0343	0.0453	--	0.0405	0.0346	0.0485
V_2 (L)	5.47	4.91	6.03	--	5.45	3.22	8.61
$CL_1 \omega^2$ (%CV)	0.258 (50.8)	0.216	0.300	14.6	0.264 (51.4)	0.172	0.381
$CL_2 \omega^2$ (%CV)	0.601 (77.5)	0.490	0.712	20.2	0.586 (76.6)	0.352	1.14
$V_1 \omega^2$ (%CV)	0.206 (45.4)	0.179	0.233	13.5	0.202 (44.9)	0.165	0.242
$k_{des} \omega^2$ (%CV)	0.255 (50.5)	0.181	0.329	59.1	0.247 (49.7)	0.129	0.447
CL_1 - $V_1 \omega$ (covariance)	0.216 ^d	0.187	0.245	--	0.214	0.167	0.274
CL_1 - $CL_2 \omega$ (covariance)	0.327 ^d	0.280	0.374	--	0.317	0.220	0.437
CL_2 - $V_1 \omega$ (covariance)	0.291 ^d	0.250	0.332	--	0.278	0.206	0.361
Res Prop Err - NHL ^e	0.453	0.447	0.459	18.7	0.452	0.400	0.502
Res Prop Err - ALL ^e	0.641	0.634	0.648	--	0.634	0.572	0.704

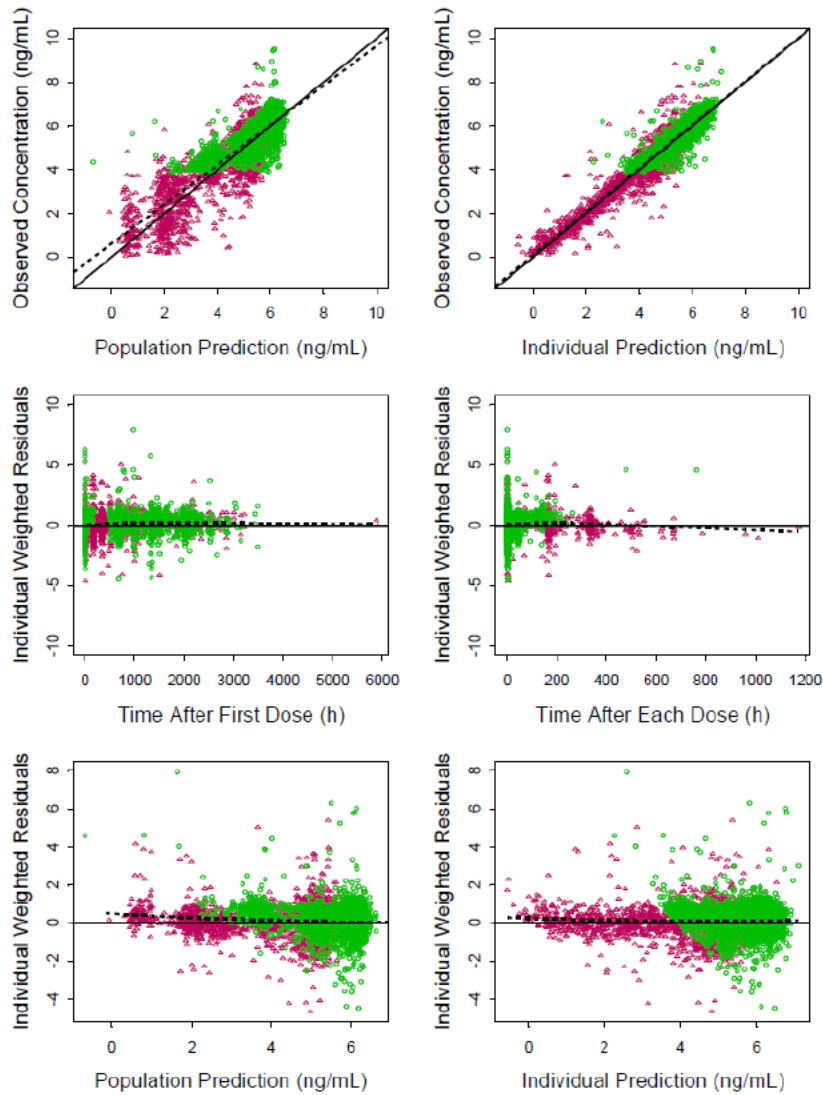


Figure 27: Base model prediction vs observed (top panels), weighted residuals vs time (middle panels), and weighted residuals vs concentration (bottom panels) for population (left) and individual (right) predictions. *Source: report PMAR-EQDD-B193a-DP4-202 applicant’s population PK analysis.*

Covariate Analysis

The model building process included the evaluation of covariate effects. The baseline covariates (categorical and continuous) of subjects included in the PK analysis are summarized in **Table 103** and **Table 104**.

Table 103: Categorical covariates investigated in the model

Covariate	Category	ALL Total N = 234	NHLTotal N = 531	Overall Total N = 765
Gender	Male	141 (60.3%)	317 (59.7%)	458 (59.9%)
	Female	93 (39.7 %)	214 (40.3%)	307 (40.1%)
Race	Caucasian	165 (70.5%)	369 (69.5%)	534 (69.8%)
	Black	6 (2.56%)	14 (2.64%)	20 (2.61%)

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Baseline ECOG Performance Score	Asian ^a	24 (10.3%)	30 (5.65%)	54 (7.06%)
	Japanese	13 (5.56%)	88 (16.6%)	101 (13.2%)
	Other	23 (9.83%)	30 (5.65%)	53 (6.93%)
	Unknown	3 (1.28%)	0 (0.00%)	3 (0.392%)
	0	74 (31.6%)	282 (53.1%)	356 (46.5%)
	1	120 (51.3%)	199 (37.5%)	319 (41.7%)
	2	37 (15.8%)	37 (6.97%)	74 (9.67%)
	3	3 (1.28%)	9 (1.69%)	12 (1.57%)
Baseline NCI ODWG Criteria for Hepatic Impairment	Unknown	0 (0.00%)	4 (0.753%)	4 (0.523%)
	A (normal)	167 (71.4%)	443 (83.4%)	610 (79.7%)
	B1 (mild)	58 (24.8%)	75 (14.1%)	133 (17.4%)
	B2 (mild)	8 (3.42%)	9 (1.69%)	17 (2.22%)
	C (moderate)	1 (0.427%)	2 (0.377%)	3 (0.392%)
Prior Radiotherapy	D (severe)	0 (0.00%)	1 (0.188%)	1 (0.131%)
	Unknown	0 (0.00%)	1 (0.188%)	1 (0.131%)
Salvage Line	No	177 (75.6%)	397 (74.8%)	574 (75.0%)
	Yes	57 (24.4%)	134 (25.2%)	191 (25.0%)
Combination Therapy With Rituximab	Salvage 1	128 (54.7%)	NA	128 (16.7%)
	Salvage 2	77 (32.9%)	NA	77 (10.1%)
	Salvage 3+	27 (11.5%)	NA	27 (3.53%)
	Unknown	2 (0.855%)	531 (100%)	533 (69.7%)
Combination Treatment ^b	No	234 (100%)	147 (27.7%)	381 (49.8%)
	Yes	0 (0.00%)	384 (72.3%)	384 (50.2%)
Stimulatory Treatment ^c	No	166 (70.9%)	157 (29.6%)	323 (42.2%)
	Yes	68 (29.1%)	374 (70.4%)	442 (57.8%)
Concomitant Hydroxyurea	No	148(63.2%)	434 (81.7%)	582 (76.1%)
	Yes	86 (36.8%)	97 (18.3%)	183 (23.9%)
P-glycoprotein Inhibitors ^d	No	221 (94.4%)	531 (100%)	752 (98.3%)
	Yes	13 (5.56%)	0 (0.00%)	13 (1.70%)
	No	187 (79.9%)	439 (82.7%)	626 (81.8%)
	Yes	47 (20.1%)	92 (17.3%)	139 (18.2%)

Table 104: Continuous covariates investigated in the model

	ALL Overall N = 234	NHL Overall N = 531	Total Overall N = 765
Covariate	Median (Range)	Median (Range)	Median (Range)
Age (y)	46.0 (20.0-79.0)	65.0 (18.0-92.0)	61.0 (18.0-92.0)
Body Weight (kg)	74.0 (30.9-154)	73.2 (33.5-148)	73.3 (30.9-154)
Body Surface Area (m ²)	1.86 (1.27-2.81)	1.83 (1.13-2.56)	1.84 (1.13-2.81)
Creatinine Clearance (mL/min)	122 (29.4-368)	81.8 (18.2-264)	93.1 (18.2-368)
Albumin (g/dL)	3.80 (1.80-4.93)	4.00 (2.20-5.20)	3.92 (1.80-5.20)
Aspartate Aminotransferase (U/L)	26.0 (5.00-187)	24.5 (7.00-163)	25.0 (5.00-187)
Alanine Aminotransferase (U/L)	33.0 (5.00-161)	20.4 (3.00-236)	22.0 (3.00-236)
Total Bilirubin (mg/dL)	0.500 (0.100-2.16)	0.499 (0.100-3.90)	0.499 (0.100-3.90)
Absolute Blast Counts in Peripheral Blood (× 10 ⁹)	0.823 (0.00-254)	NA	0.823 (0.00-254)
Absolute CD22+ Blast Counts in Peripheral Blood (× 10 ⁹)	0.442 (0.00-252)	NA	0.442 (0.00-252)
Blasts in Peripheral Blood (%)	4.00 (0.00-100)	NA	4.00 (0.00-100)

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Blasts that are CD22+ in Peripheral Blood (%)	98.7 (11.4-100)	NA	98.7 (11.4-100)

Renal function using baseline creatinine clearance (BCCL) – normal (n = 377), mild (n=234), moderate (n =121), and severe (n=4) – was tested as a covariate in the model. Similarly, hepatic function using baseline laboratory values of baseline alanine aminotransferase, baseline aspartate aminotransferase, and baseline total bilirubin, and baseline NCI ODWG criteria for hepatic impairment were tested as covariate in the model. The Applicant conducted generalized additive model with the covariates listed in the **Table 105**.

Table 105: Covariates tested with the population PK parameter

Parameter	Covariate
CL ₁ and CL ₂	PTST (disease or analytical assay method, i.e., NHL or ELISA vs ALL or HPLC/MS/MS), SEX, BHGRADE (NCI ODWG classification for hepatic impairment), RITX (combined rituximab treatment), PGP = P-glycoprotein inhibitors, COMB (concomitant treatment for the first 2 cycles), GCSF (GCSF treatment), HYDR (hydroxyurea treatment), RADIO (prior radio therapy), ASIA (non-Asian versus Asian), SALV (salvage therapy), AGE, BBSA (baseline body surface area), BWT (baseline bodyweight), BCCL (baseline creatinine clearance), BALB (baseline albumin), BALT (baseline alanine aminotransferase), BAST (baseline aspartate aminotransferase), BBIL (baseline total bilirubin), BLSTABL (baseline absolute blast counts in peripheral blood), CD22BLST (baseline absolute absolute CD22+ blast counts in peripheral blood), BLSTPB (baseline percent of blast in peripheral blood), CD22PPB (baseline percent of blast counts in peripheral blood), BLSTPB (baseline percent of blast in peripheral blood), CD22PPB (baseline percent blasts that are CD22+ in peripheral blood_
V ₁	SEX, ASIA, AGE, BBSA, and BWT
K _{des}	PTST, SEX, ASIA, SALV, BBSA, BLSTABL, BLSTPB, CD22BLST, and CD22PPB

The GAM analysis results included the following potential covariates selected to test for statistical significance:

- CL₁: RITX, HYDR, BBSA, BALB, BBIL, BLSTPB, and CD22PPB
- CL₂: BBSA and BALB
- V₁: BBSA
- K_{des}: SALV, BBSA, and BLSTPB

BBSA was found to be a statistically significant covariate for CL₁ (power model), CL₂ (power model), and V₁ (linear). BLSTPB was found to be a statistically significant covariate for K_{des}. The equations below describe the final model estimation of typical values of CL₁, CL₂, V₁, and k_{des} in NHL patients:

$$CL_1 = 0.113 \text{ L/h} \cdot (1 - 0.745 \cdot PTST_{ALL}) \cdot (BBSA / 1.84 \text{ m}^2)^{1.54} \cdot (1 + 0.155 \cdot RITX)$$

$$CL_2 = 0.369 \text{ L/h} \cdot (BBSA / 1.84 \text{ m}^2)^{1.64}$$

$$V_1 = 6.70 \text{ L/h} \cdot (1 + 0.774 \cdot [BBSA - 1.84 \text{ m}^2])$$

$$k_{des} = 0.0337 \text{ h}^{-1} \cdot (1 - 0.860 \cdot PTST_{ALL}) \cdot (BLSTPB / 5.25 \%)^{-0.0401}$$

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The final model estimation of typical values of CL_1 , CL_2 , V_1 , and k_{des} in ALL patients are represented with the following equations:

$$CL_1 = 0.0333 \text{ L/h} \cdot (\text{BBSA}/1.84 \text{ m}^2)^{1.54}$$

$$CL_2 = 0.369 \text{ L/h} \cdot (\text{BBSA}/1.84 \text{ m}^2)^{1.64}$$

$$V_1 = 6.70 \text{ L/h} \cdot (1 + 0.774 \cdot [\text{BBSA} - 1.84 \text{ m}^2])$$

$$k_{des} = 0.00472 \text{ h}^{-1} \cdot (\text{BLSTPB}/5.25 \%)^{-0.0401}$$

The parameter estimates of the final covariate model are summarized in Table 106 and the visual predictive check of the final model with covariates is illustrated in Figure 28 and Figure 29.

Table 106: Population PK final model parameter estimates

Parameter	Final Model (M3 Method, Include Data <LLOQ) for Supplemental Analysis						
	NONMEM Results OFV = 1450.357				Nonparametric Bootstrap Results		
	Estimate	95% CI ^a		Shrinkage %	Estimate (Median)	95% CI ^b	
		Lower	Upper			Lower	Upper
CL_1 (L/h)	0.113	0.106	0.120	--	0.114	0.104	0.124
ALL on CL_1 ^c	-0.745	-0.778	-0.712	--	-0.747	-0.777	-0.712
BBSA (m^2) on CL_1	1.54	1.20	1.87	--	1.52	1.18	1.88
RITX on CL_1	0.155	0.0464	0.264	--	0.152	0.0565	0.266
CL_2 (L/h)	0.369	0.332	0.406	--	0.373	0.338	0.420
BBSA (m^2) on CL_2	1.64	1.08	2.20	--	1.66	1.08	2.17
V_1 (L)	6.70	6.40	7.00	--	6.69	6.43	6.96
BBSA (m^2) on V_1	0.774	0.620	0.928	--	0.774	0.657	0.887
k_{des} (h^{-1})	0.0337	0.0251	0.0423	--	0.0336	0.0249	0.0447
ALL on k_{des} ^c	-0.860	-0.897	-0.823	--	-0.859	-0.893	-0.806
BLSTPB (%) on k_{des}	-0.0401	-0.0545	-0.0257	--	-0.0392	-0.0589	-0.0230
Q (L/h)	0.0405	0.0349	0.0461	--	0.0418	0.0355	0.0507
V_2 (L)	5.10	4.60	5.60	--	4.88	3.02	7.62
$CL_1 \omega^2$ (%CV)	0.179 (42.3)	0.147	0.211	18.9	0.170 (41.2)	0.113	0.258
$CL_2 \omega^2$ (%CV)	0.451 (67.2)	0.370	0.533	23.2	0.443 (66.6)	0.281	0.783
$V_1 \omega^2$ (%CV)	0.170 (41.2)	0.150	0.190	15.8	0.169 (41.1)	0.129	0.209
$k_{des} \omega^2$ (%CV)	0.207 (45.5)	0.137	0.277	57.1	0.197 (44.4)	0.114	0.347
CL_1 - $V_1 \omega$ (covariance)	0.156 ^d	0.133	0.179	--	0.151	0.112	0.203
CL_1 - $CL_2 \omega$ (covariance)	0.213 ^d	0.175	0.251	--	0.208	0.136	0.298
CL_2 - $V_1 \omega$ (covariance)	0.222 ^d	0.191	0.253	--	0.218	0.160	0.291
Res Prop Err - NHL ^e	0.453	0.447	0.459	18.5	0.450	0.402	0.501
Res Prop Err - ALL ^e	0.619	0.612	0.626		0.611	0.555	0.684

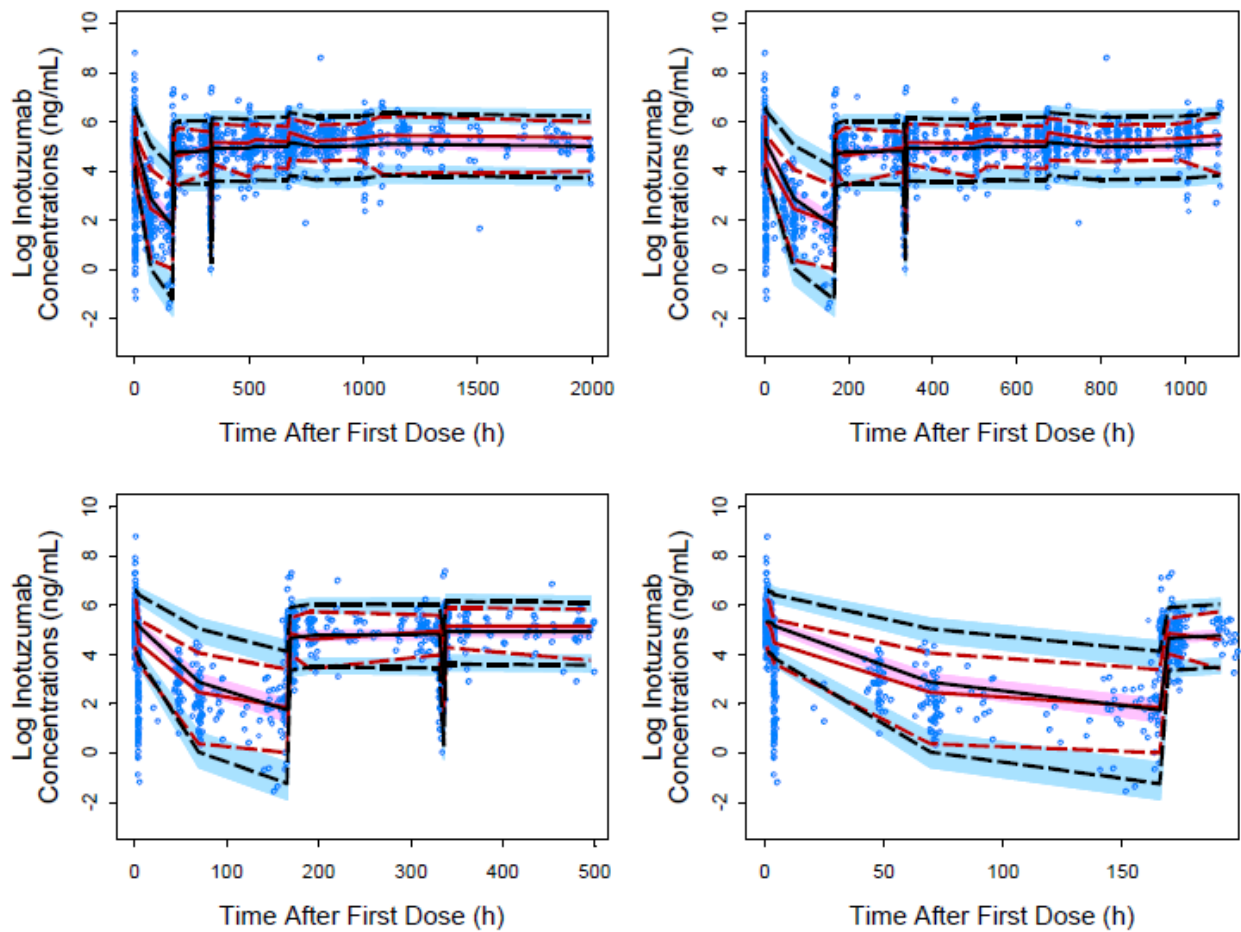


Figure 28: Visual Predictive Check for the final model for relapsed or refractory patients with ALL over a range of timescales. *Source: report PMAR-EQDD-B193a-DP4-202 applicant's population PK analysis.*

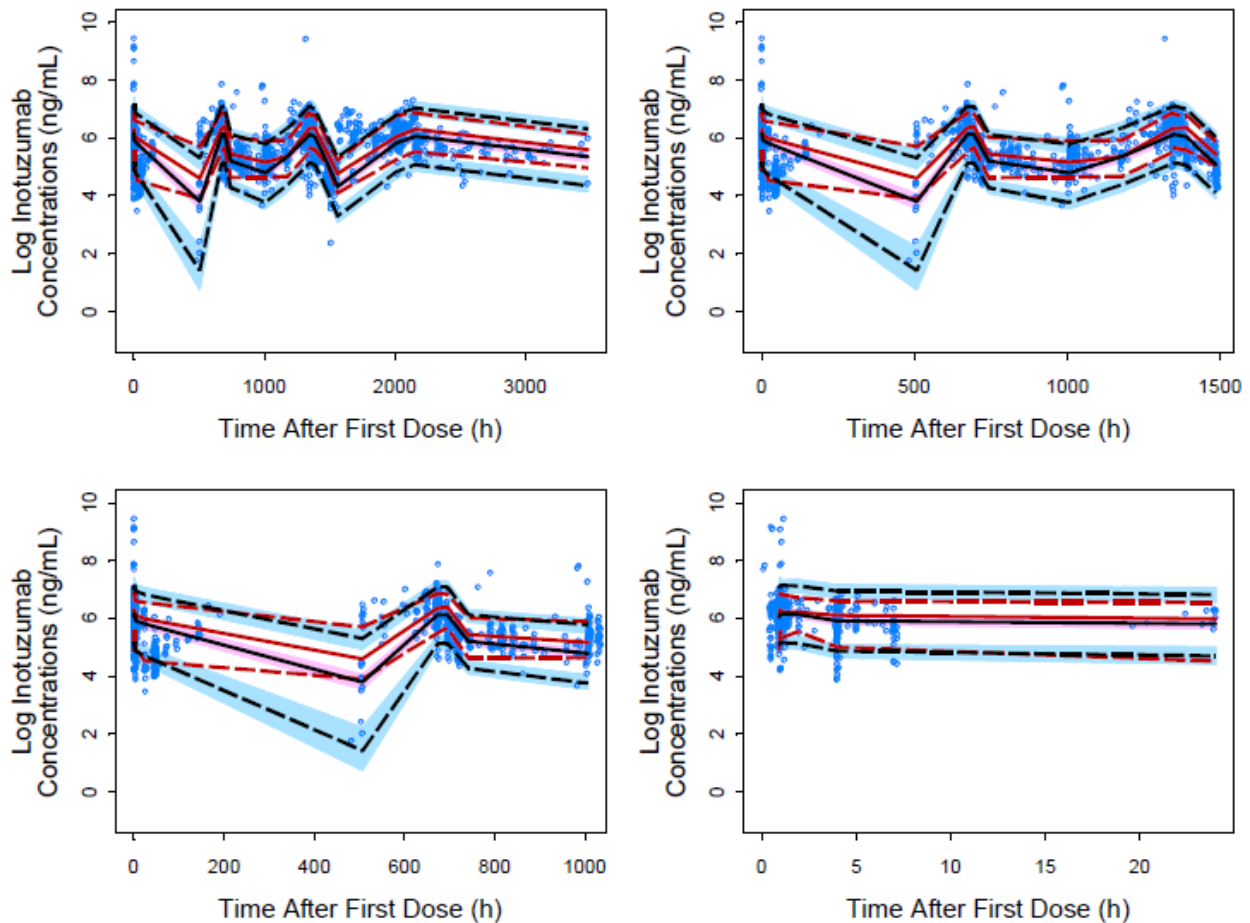


Figure 29: Visual Predictive Check for the final model for relapsed or refractory patients with NHL over a range of timescales. *Source: report PMAR-EQDD-B193a-DP4-202 applicant's population PK analysis.*

Intrinsic Factors

Age, Gender, and Race

During GAM analyses, the effect of age on PK parameters was not significant. Gender and race (Asian vs non-Asian) were found to be correlated with BBSA (**Figure 30**). Therefore, inclusion for BBSA in the final model accounted for differences based on gender and race.

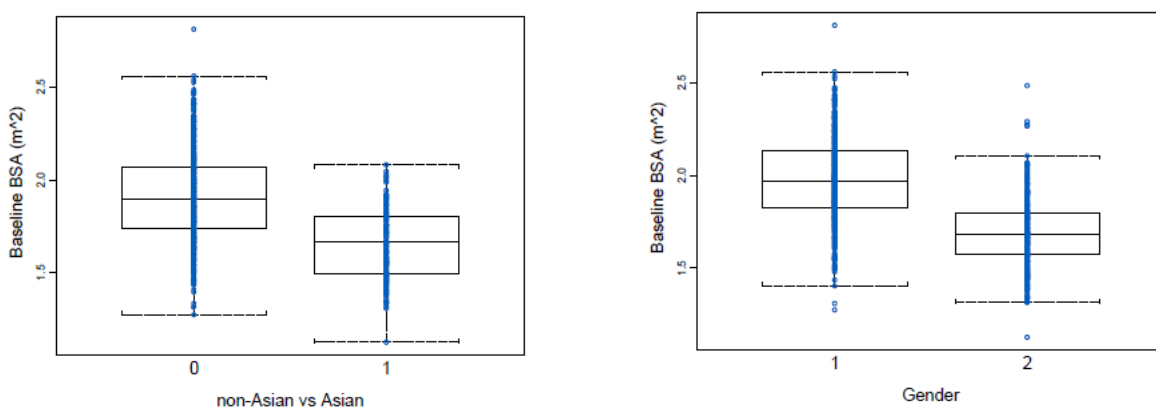


Figure 30: Relationship between gender or race (Asian vs non-Asian) and race and BSA. Both covariates were not included in the final model due to their correlation with BSA. *Source: report PMAR-EQDD-B193a-DP4-202 applicant's population PK analysis.*

Final model comparisons of ETAs (on CL_1 , CL_2 , and V_1) show that there are no differences in the distributions between genders or races after correcting for BSA.

Baseline Body Surface Area

Increasing BBSA was correlated with an increase in CL_1 , CL_2 , and V_1 . The value of CL_1 and CL_2 increased by approximately 36% for BBSA of 2.21 m² and decreased by 24% at BBSA of 1.56 m², relative to the typical value at 1.84 m². Similarly, the value of V_1 increased by 28.8% for BBSA of 2.21 m² and decreased by 21.6% at BBSA of 1.56 m², relative to the typical value at 1.84 m². The final model accounts for BBSA effect on final model ETAs on CL_1 , CL_2 , and V_1 (i.e., ETAs centered on zero) as shown in **Figure 31**.

Renal Impairment

The effect of renal function on the PK of inotuzumab ozogamicin was evaluated using BCCL (Table 107: Baseline CLCR in NHL and ALL patients included in the population PK analysis **Table 107**). Base model diagnostic plots showed no visible changes in inotuzumab ozogamicin PK with BCCL and this trend was reflected in the GAM analysis where BCCL was not a significant covariate on CL_1 or CL_2 . The PK data set in both NHL and ALL included 4 patients with severe (BCCL 15-29 mL/min), 121 patients with moderate (BCCL 30-59 mL/min), 234 patients with mild (BCCL 60-89 mL/min), and 377 patients with normal (BCCL $\geq$ 90 mL/min). There was no correlation between inotuzumab ozogamicin clearance estimates and the impairment of renal function (**Figure 32**).

Hepatic Impairment

The impact of hepatic function on inotuzumab clearance was evaluated using the NCI ODWG criteria for hepatic impairment (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 (**Table 108**). Base model diagnostic plots showed no visible changes with inotuzumab ozoagamicn PK with baseline NCI ODWG criteria for hepatic impairment or with any of the

baseline laboratory values (**Figure 33**). This observed trend was reflected in the GAM analysis where hepatic function was a statistically significant covariate.

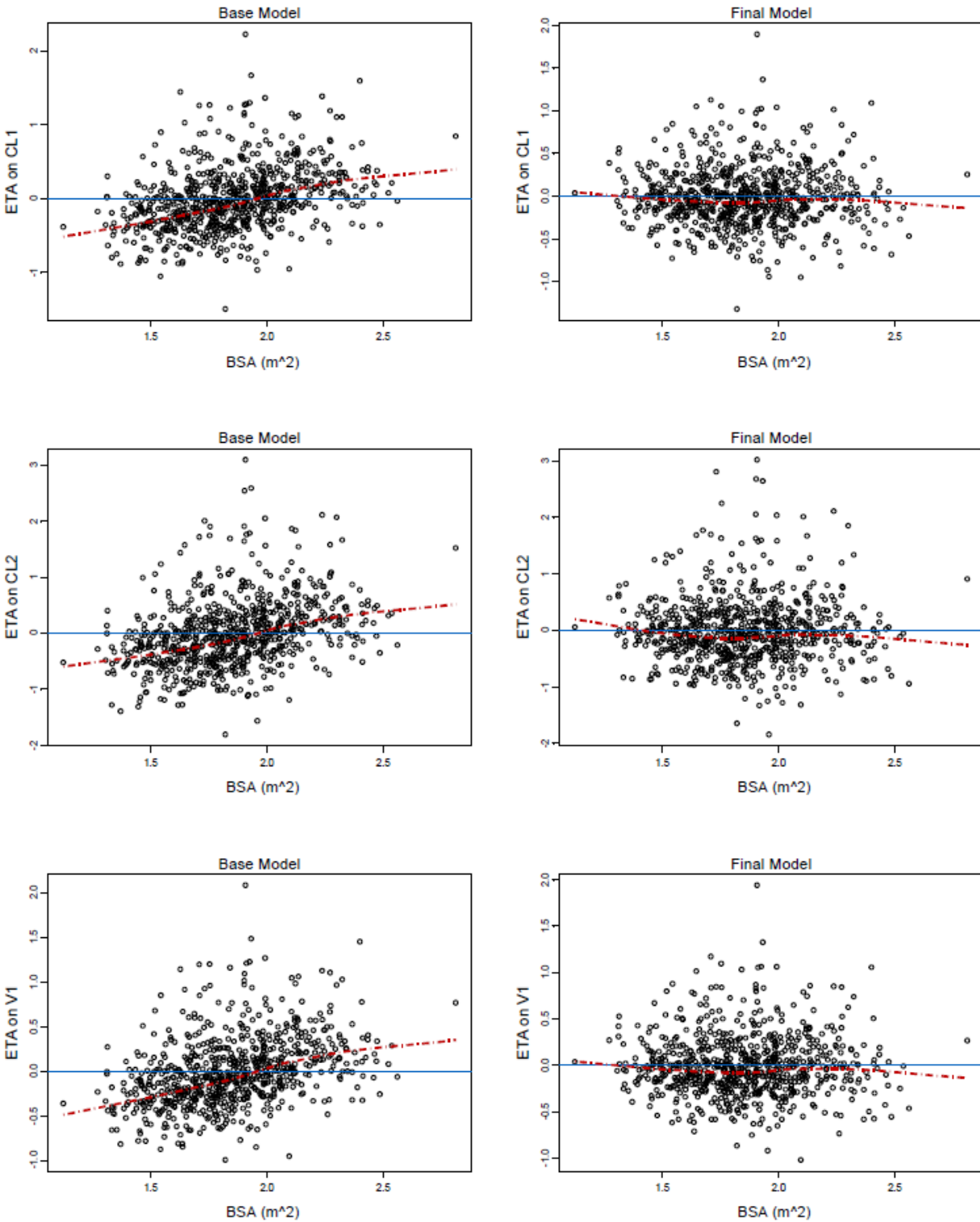


Figure 31: ETAs centered on zero for CL₁, CL₂, and V₂ in the final model when BBSA was included as a covariate. Source: report PMAR-EQDD-B193a-DP4-202 applicant's population PK analysis.

Table 107: Baseline CL_{CR} in NHL and ALL patients included in the population PK analysis

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

Table 108: Hepatic function of NHL and ALL patients included in the population PK analysis

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

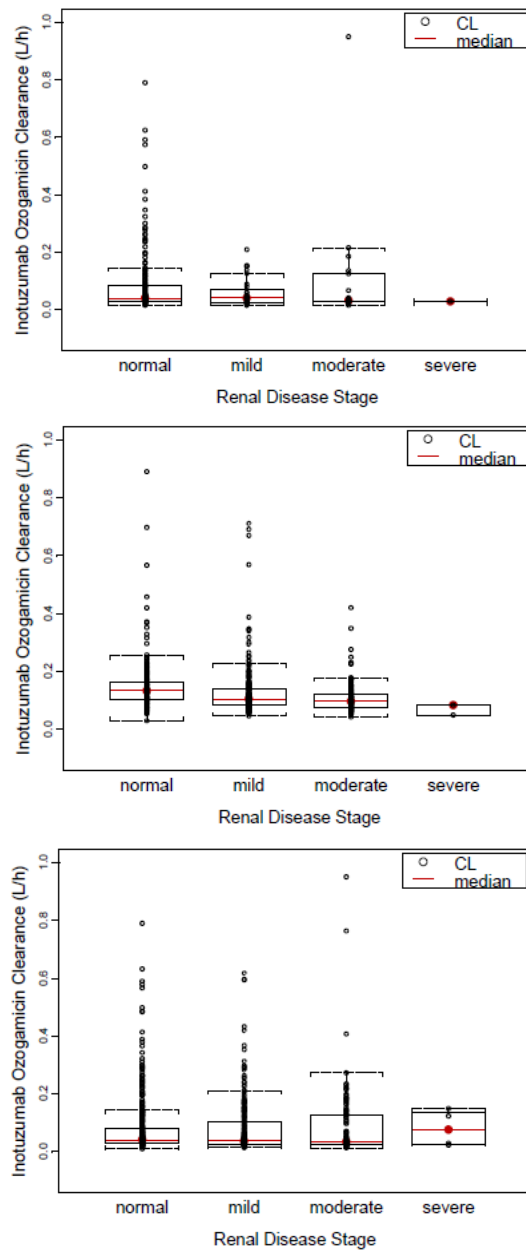


Figure 32: Estimate of clearance in ALL patients (top panel), NHL patients (middle panel), and combined patients stratified by renal disease stage. *Source: report PMAR-EQDD-B193a-DP4-202 applicant's population PK analysis.*

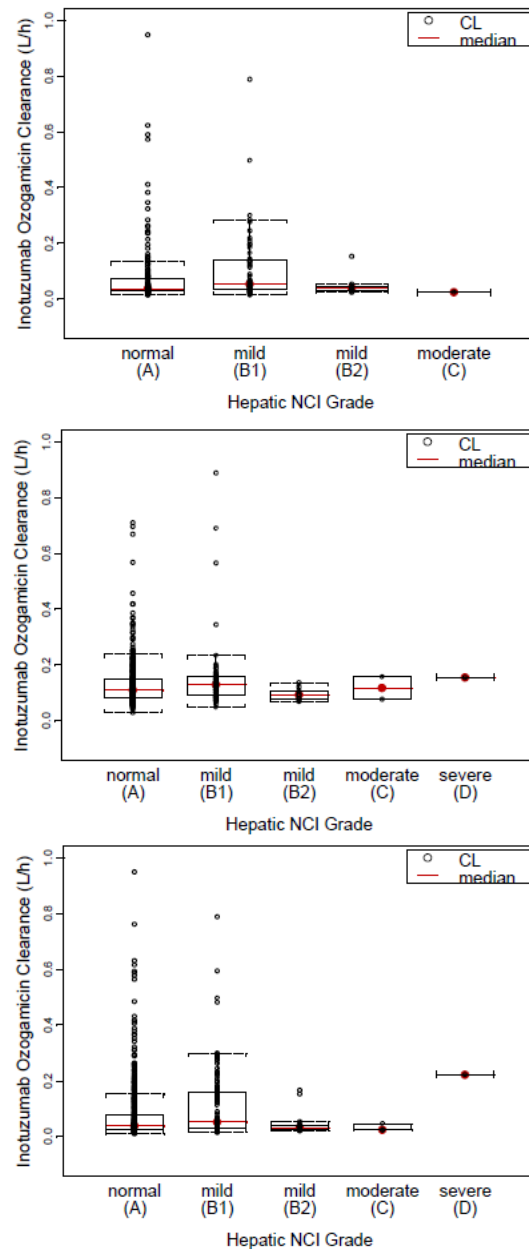


Figure 33: Estimate of clearance in ALL patients (top panel), NHL patients (middle panel), and combined patients stratified by hepatic function. *Source: report PMAR-EQDD-B193a-DP4-202 applicant's population PK analysis.*

Extrinsic Factors

The effects of concomitant medications on inotuzumab ozogamicin PK were tested in GAM. There were varying numbers of patients taking P-glycoprotein (PGP) inhibitors (17%), granulocyte colony stimulating factor (GCSF, 22.6%), hydroxyurea (HYDR, 1.63%), inotuzumab ozogamicin given with concomitant treatment for first 2 cycles (COMB, 59.6%), prior radiotherapy (RADIO, 52.2%), and salvage therapy (SALV, Salvage 1 = 53.2%, Salvage 2 = 33.3%, and Salvage 3+ = 13.2%). For HYDR, patients were all from the ALL studies and for RITX, patients

were all from the NHL studies. GAM results showed no significant effects of PGP, GCSF, COMB, and RADIO on CL_1 and CL_2 ; however, SALV was significant on K_{des} , and HYDR and RITX were significant on CL_1 . After testing the covariates in the stepwise covariate modeling, RITX was retained as the only significant covariate on CL_1 . Hence, PGP, GCSF, HYDR, COMB, RADIO, and SALV were concluded to have no effect on inotuzumab ozogamicin PK.

In the final model, the effect of RITX (patients without Rituximab) was estimated to increase clearance by 16% (95% CI: 5.47%-26.5%). The final model did not fully account for the effects of rituximab, where ETA on CL_1 was not centered at zero (**Figure 34**). The applicant stated that the use of concomitant rituximab treatment may have some confounding factors as the NHL patients took rituximab in combination with other concomitant medications or with chemotherapy.

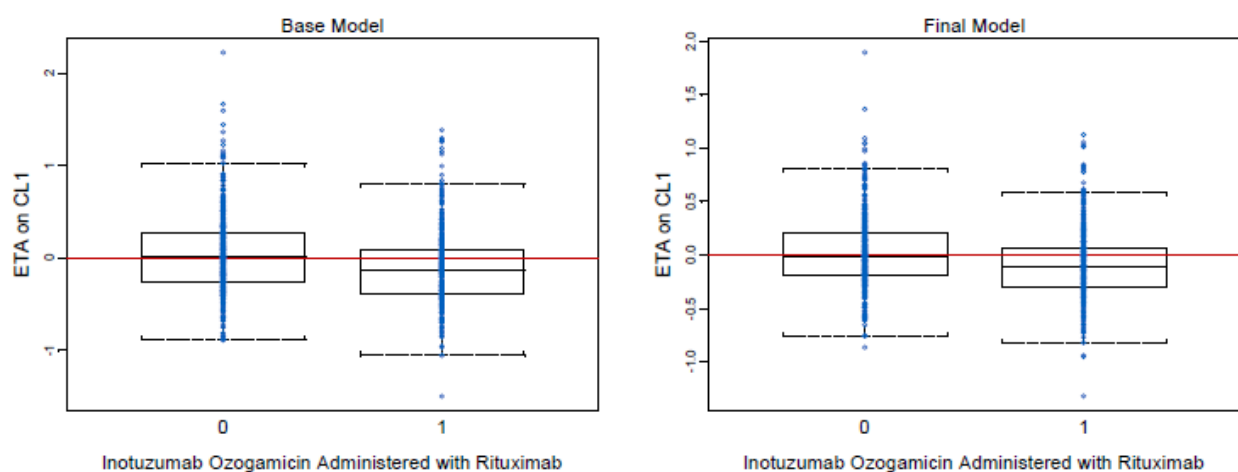


Figure 34: Rituximab treatment inclusion as a covariate in the model did not account rituximab effects on ETA. Source: report PMAR-EQDD-B193a-DP4-202 applicant's population PK analysis.

The applicant's analyses followed a reasonable and thorough approach in describing the pharmacokinetics of inotuzumab ozogamicin. The applicant's model selection and validation criteria are acceptable. To that end, the reviewer agrees with the applicant's conclusions regarding lack of effect of intrinsic (other than BSA) and extrinsic factors on the pharmacokinetics of inotuzumab ozogamicin. However, the conclusions regarding the lack of effect are only supportive in nature due to the fact that the timing and administration of concomitant medications was not included in the model.

13.4.3. Bioanalytical Method Report

HPLC/MSMS Assay (Study B1931010 and B1931022)

Total Calicheamicin

In this assay, an aliquot of study sample was initially extracted with methyl tert-butyl ether (MTBE) to separate unconjugated calicheamicin from inotuzumab ozogamicin. The MTBE layer containing unconjugated calicheamicin was discarded, and the remaining aqueous layer

containing intact inotuzumab ozogamicin was fortified with internal standard (IS) N-propionyl- γ -calicheamicin and treated with dithiothreitol, resulting in the release of conjugated N-acetyl- γ -calicheamicin DMH by disulfide bond reduction and its intramolecular rearrangement to N-acetyl- ε -calicheamicin (the IS converted to N-propionyl- ε -calicheamicin). N-acetyl- ε -calicheamicin (along with an IS) was then extracted by MTBE and measured as surrogate analyte for inotuzumab ozogamicin using reverse phase chromatography and positive ion electrospray tandem mass spectrometry. The method parameters for total calicheamicin are summarized in **Table 109**.

Table 109: HPLC/MSMS method parameters and validation summary of total calicheamicin

Parameter	Details
Method	HPLC/MS-MS
Analyte	Inotuzumab Ozogamicin measured as N-acetyl- ε -calicheamicin
Internal Standard	N-propionyl- γ -calicheamicin DMH measured as N-propionyl- ε -calicheamicin
Calibration Range	1.00 to 500 ng/mL
VQC Concentrations	1.00, 2.50, 25.0, 200, 375, and 1000 (dilution VQC) ng/mL
Intra-Batch Precision (%CV)	LLOQ QC: <15.3%; remaining QC samples: < 16.3%
Intra-Batch Accuracy (%RE)	LLOQ QC: -13.7% to 6.19%; remaining QC samples: -6.8% to 17.2%
Inter-Batch Precision (%CV)	LLOQ QC: 16.3%; remaining QC samples: 8.29% to 10.5%
Inter-Batch Accuracy (%RE)	LLOQ QC: 0.821%; remaining QC samples: 1.65% to 10.2%
Dilution Factor	Demonstrated for 10-fold
Analyte Recovery	49.2% average across low, mid, high VQC
IS Recovery	126%
Selectivity	No detectable response at analyte and IS MRM transitions and retention times in 10 of 10 individual normal human serum lots
Stability	
Primary Stock Solution	Demonstrated for 272 days at -80 °C for 1.00 mg/mL in water and at room temperature for 6 hours
IS Stock Solution	Demonstrated for 66 days at -80 °C for 5.00 mg/mL in methanol
IS Working Solution	Demonstrated for 60 minutes on ice and at room temperature for 10 ng/mL in 50:50 isopropanol:water
Ambient Temperature Matrix Stability	Demonstrated for 24 hours at room temperature
Refrigerated Matrix Stability	Demonstrated for 24 hours at 2 to 8 °C
Frozen Storage Matrix Stability	297 days at -20 °C and -80 °C and for 8 cycles at -70 °C
Extract Stability	Demonstrated for 129 hours at 2 to 8 °C in reconstitution solution
Freeze/Thaw Matrix Stability	Demonstrated for 5 cycles at -20 °C and -80 °C and for 8 cycles at -70 °C
Re-injection	Demonstrated for 143 hours at 2 to 8 °C in reconstitution solution

Reproducibility	

Unconjugated Calicheamicin

Concentrations of unconjugated calicheamicin (as N-acetyl- γ -calicheamicin DMH) in serum were measured using an HPLC/MS-MS method. Study samples were fortified with an IS (N-propionyl- γ -calicheamicin) and underwent solid-phase extraction followed by reverse-phase chromatography with positive ion electrospray tandem mass spectrometric detection. The method parameters for unconjugated calicheamicin are summarized in **Table 110**.

Table 110: HPLC/MSMS method parameters and validation summary of unconjugated calicheamicin

Parameter	Details
Method	HPLC/MS-MS
Analyte	N-acetyl- γ -calicheamicin DMH
Internal Standard	N-propionyl- γ -calicheamicin DMH
Calibration Range	0.05 to 10.0 ng/mL
VQC Concentrations	0.05, 0.15, 7.50, and 20.0 (dilution VQC) ng/mL
Intra-Batch Precision (%CV)	LLOQ QC: <12.1%; remaining QC samples: < 6.71%
Intra-Batch Accuracy (%RE)	LLOQ QC: -9.83% to 4.87%; remaining QC samples: -10.3% to 5.62%
Inter-Batch Precision (%CV)	LLOQ QC: 10.0%; remaining QC samples: 4.81% to 8.26%
Inter-Batch Accuracy (%RE)	LLOQ QC: 2.68%; remaining QC samples: -8.02% to 2.68%
Dilution Factor	Demonstrated for 5-fold
Analyte Recovery	48.6% average across low, mid, high VQC
IS Recovery	67.7%
Selectivity	No detectable response at analyte and IS MRM transitions and retention times in 10 of 10 individual normal human serum lots
Stability	
Primary Stock Solution	Demonstrated for 245 days at -70 °C for 100 μ g/mL in methanol and at room temperature (ambient and yellow light) for 6.2 hours
IS Stock Solution	Demonstrated for 66 days at -70 °C for 5.00 mg/mL in methanol
IS Working Solution	Demonstrated for 60 minutes on ice and at room temperature for 10 ng/mL in 50:50 isopropanol:water
Ambient Temperature Matrix Stability	Demonstrated for 4 hours at room temperature (yellow light)
Refrigerated Matrix Stability	Demonstrated for 3.18 hours on wet ice (yellow light)
Frozen Storage Matrix Stability	803 days at -70 °C
Freeze/Thaw Matrix Stability	Demonstrated for 3 cycles at -70 °C
Extract Stability	Demonstrated for 56.85 hours at 2 to 8 °C

Re-injection Reproducibility	Demonstrated for 55 hours at 2 to 8 °C

Electrochemiluminescence Assay (Anti-Drug Antibody Measurement)

The potential for immunogenicity to inotuzumab ozogamicin was measured using a bridging ECL assay. This assay was used to detect and measure the titer of serum immunoglobulins that specifically bind to inotuzumab ozogamicin (Table 111). All patient samples that tested positive in the ECL bridging assay were further tested using a cell-based nAb assay because a polyclonal antibody response to a drug product may result in both non-neutralizing and nAb (Table 112).

Table 111: ELISA validation assay for detection of ADA against inotuzumab ozogamicin

Parameter	Details		
Method Description			
Method	ELISA		
Biological Matrix	Serum		
Minimum Required Dilution	1:25		
Capture Antibody	CMC-544		
Secondary Antibody	Biotinylated CMC-544		
Diluent Solution	PBST		
Detection Method	Avidin-HRP conjugate with TMB substrate		
Quantification	OD at 450 nm		
Positive Control	PC1: Rabbit anti-G544 polyclonal antibody PC2: Rabbit anti-calicheamicin polyclonal antibody		
Negative Control	Pooled normal human serum		
Intra-Assay Precision (n = 4) %CV of End point log ₁₀ Titer %CV of OD (At maximum OD for PC1 and PC2)	PC1	PC2	NC
	≤1.8%	N/A	N/A
	≤8.3%	≤3.7%	≤6.8%
Intra-run Precision (n=4) %CV of End Point log ₁₀ Titer %CV of OD (Multiple Dilutions for PC1 and PC2) %CV of Cut Point	PC1	PC2	NC
	1.3%	N/A	N/A
	≤10.8	≤9.1%	N/A
	N/A	N/A	2.5%
Dilutional Linearity	PC1: Demonstrated linearity over 25-, 75-, 225-, and 675-fold dilutions (%CV = 1.5% across the 4 dilutions)		
Cut Point			
Screening and Titer Assays Cut Point	2 x mean OD of NC		
Sensitivity (Based on Affinity Purified Rabbit Polyclonal Antibody)	663 ng/mL (low titer) and 224 ng/mL (high titer) in human serum		
Drug Interference	PC1: Detected in presence of up to 0.01 □g/mL CMC-544: Detected in presence of up to 1000 □g/mL		

	rituximab PC2: Detected in presence of up to 1000 □g/mL rituximab
Matrix Reactivity	Response in 54 and 54 individual human serum lots was below cut point OD (defined as 2 x mean OD of NC)
Plate Specificity	Responses of PC1, PC2, and NC in section of plate coated with buffer were below cut point OD
Stability (PC1 and PC2)	PC1 and PC2: No significant effect on performance after 3 hours ambient temperature
	PC1 and PC2: No significant effect on performance after 3 freeze/thaw cycles (-70°C)

Table 112: Cell-based luminescence assay for the detection of neutralizing antibodies

Parameter	Details
Method Description	
Method	Cell-based assay
Positive Control	Rabbit Polyclonal antibody against G544
Cell Line	RS4; 11
Biological Matrix	Serum
Minimum Dilution	1:10
Mean Intra-Assay Precision (%CV of End Point log ₁₀ Titer)	6.1%
Inter-Assay Precision (%CV of End Point log ₁₀ Titer)	9.3%
Cut Point	
Screening Assay Cut Point	1.24 x mean OD of NC
Screening and Titration Cut Point Factor	1.24
Sensitivity (Using Affinity Purified Antibody)	58.3 ng/mL
Drug Interference	PC at 1:250 antibody dilution was detected in the presence of 1 µg/mL
Matrix Selectivity (Recovery) With PC1	100% of the lots have recovery between 70% and 130%
Stability	21 hours at room temperature
	5-cycle freeze (-20°C)/thaw (ambient temperature)
	5-cycle freeze (-70°C)/thaw (ambient temperature)
Cell Line Passage Stability	Assay performance up to cell passage number 22 was acceptable

14 Division Director (DHOT)

Deputy Division Director
Haleh Saber, PhD

15 Division Director (OCP)

NAM Atiqur Rahman, PhD

16 Division Director (OB)

Rajeshwari Sridhara, Ph.D.

17 Division Director (Clinical)

- I recommend approval of inotuzumab ozogamicin based on substantial evidence of effectiveness for the treatment of adult patients with relapsed or refractory precursor B-cell ALL. The Applicant conducted an adequate and well-controlled randomized phase 3 trial in patients aged 18 years of age or older with relapsed or refractory ALL. The endpoints of CR and duration of response in the first 218 randomized patients were used for the regulatory decision making process. As noted earlier, CR was achieved by 39/109 (36%) patients (95% CI: 27%, 46%) in the inotuzumab ozogamicin arm versus 19/109 (17%) patients (95% CI: 11%, 26%) in the investigator's choice of chemotherapy arm. This result was statistically significant. Additionally the responses were durable with estimated median duration of CR of 8 months (95% CI: 5, 10 months) in the inotuzumab ozogamicin arm. The durable complete response/remission results are supported by the achievement of MRD negativity in patients who achieved CR: 35/39 (90%) in inotuzumab ozogamicin arm compared to 6/19 (32%) in investigator's choice of chemotherapy arm. Also the results were consistent with the analysis of the full intent-to-treat (ITT) population (N=326) and consistent across the subpopulations tested. The second primary endpoint was overall survival; however, an improvement in overall survival based on the ITT population was not demonstrated. Additional support for approval is the fact that more patients in the inotuzumab ozogamicin arm received a potentially curative procedure (transplantation) compared with the investigator's choice arm. A competing risk analysis based on patients who proceeded to subsequent hematopoietic stem cell transplantation, showed an increase in non-relapse mortality in the inotuzumab ozogamicin arm of 38% compared with 24% in the investigator's choice arm. Hepatic VOD was the main contributing factor for the increase in non-relapse mortality in the inotuzumab ozogamicin arm. A boxed warning in labeling describes risk of VOD and recommends if a patient develops VOD that the patient stop taking Besponza and initiate treatment for VOD. Besides VOD, other safety concerns were myelosuppression, infection, hemorrhage, pyrexia, and elevated liver function tests. In summary the data show a favorable risk-benefit for inotuzumab ozogamicin.

Ann. T. Farrell, M.D.

18 Office Director (or designated signatory authority)

This application was reviewed under the auspices of the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. The risk-benefit profile was also assessed by Drs. Farrell, De Claro and Wroblewski who recommend approval. I also recommend approval of this application. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

Richard Pazdur, MD

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RACHEL S MCMULLEN
08/16/2017

TANYA M WROBLEWSKI
08/16/2017

MICHAEL L MANNING
08/16/2017

CHRISTOPHER M SHETH
08/16/2017

HALEH SABER
08/17/2017

SALAHELDIN HAMED
08/17/2017

BAHRU A HABTEMARIAM
08/17/2017

NAM ATIQRUR RAHMAN
08/17/2017
I concur.

QING XU
08/17/2017

YUAN L SHEN
08/17/2017

RAJESHWARI SRIDHARA
08/17/2017

ROMEO A DE CLARO

08/17/2017

ANN T FARRELL

08/17/2017

RICHARD PAZDUR

08/17/2017