10 December 2020
EMA/CHMP/36661/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lumoxiti

International non-proprietary name: moxetumomab pasudotox

Procedure No. EMEA/H/C/005322/0000

Note

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

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Administrative information

Name of the medicinal product:	Lumoxiti
Applicant:	AstraZeneca AB SE-151 85 Sodertalje SWEDEN
Active substance:	moxetumomab pasudotox
International Non-proprietary Name/Common Name:	moxetumomab pasudotox
Pharmaco-therapeutic group (ATC Code):	other antineoplastic agents, (L01X)
Therapeutic indication:	Lumoxiti as monotherapy is indicated for the treatment of adult patients with relapsed or refractory hairy cell leukaemia (HCL) after receiving at least two prior systemic therapies, including treatment with a purine nucleoside analogue (PNA).
Pharmaceutical form:	Powder for concentrate and solution for solution for infusion
Strength:	1 mg
Route of administration:	Intravenous use
Packaging:	Powder: vial (glass) Stabiliser: vial (glass)
Package sizes:	2 vials + 1 vial and 3 vials + 1 vial

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List of abbreviations

Abbreviation or Specialised Term	Definition
ADA	antidrug antibody(ies)
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AU	Absorbance units
AUC	area under the concentration–time curve
$AUC_{0\text{-last}}$	area under the concentration–time curve from time zero to the last quantifiable concentration
BICR	blinded independent central review
CBC	complete blood count
CD	cluster of differentiation
CI	confidence interval
CL	clearance
CLS	capillary leak syndrome
C_{max}	maximum observed concentration
CPP	Critical Process Parameters
CQA	Critical Quality Attributes
CR	complete response
CRF	case report form
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV%	coefficient of variation
DCO	data cutoff
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DP	Drug Product

Abbreviation or Specialised Term	Definition
DS	Drug Substance
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end of treatment
ESMO	European Society for Medical Oncology
FEV	forced expiratory volume
H&E	haematoxylin & eosin
HBV	hepatitis B virus
HCL	hairy cell leukaemia
HIV	human immunodeficiency virus
HUS	haemolytic uraemic syndrome
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IFN	interferon
IFN-α	Interferon-alpha
IPC	In-process Control
Ig	immunoglobulin
IHC	immunohistochemistry
INR	international normalized ratio
IRB	Institutional Review Board
IRR	infusion-related reaction
ITT	intent to treat
IV	intravenous
IVSS	Intravenous solution stabiliser
LOQ	Limit of Quantification
Max	maximum
MCB	Master Cell Bank
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum

Abbreviation or Specialised Term	Definition
MRD	minimal residual disease
MRI	magnetic resonance imaging
MSD	Meso Scale Discovery
nAb	neutralising anti-drug antibodies
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NK	natural killer
OR	objective response
ORR	objective response rate
PA	Performance Attributes
PD	progressive disease
PE	*Pseudomonas* exotoxin
PFS	progression-free survival
PhEur	European Pharmacopeia
PI	Principal Investigator
PK	pharmacokinetic(s)
PNA	purine nucleoside analog
PPQ	Process Performance Qualification
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
QTcB	Bazett's corrected QT interval
QTcF	Fridericia's corrected QT interval
RV	range of variability
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SE	standard error
SID	subject identification
SOC	System Organ Class

Abbreviation or Specialised Term	Definition
$t_{1/2}$	terminal half-life
T4	thyroxine
TEAE	treatment emergent adverse event
TLS	tumour lysis syndrome
TMA	thrombotic microangiopathy
TOR	Time out of refrigeration
TSH	thyroid stimulating hormone
TTC	Treshold of toxicological concern
TTF	time to treatment failure
ULN	upper limit of normal
V_H	heavy chain variable domain
V_L	light chain variable domain
WCB	Working Cell Bank
WFI	Water for injection

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AstraZeneca AB submitted on 22 November 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Lumoxiti, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 28 February 2019.

Lumoxiti, was designated as an orphan medicinal product EU/3/08/92 on 4 December 2008 in the following condition: treatment of hairy cell leukaemia (EU/3/08/592).

The applicant applied for the following indication:

Lumoxiti is indicated for the treatment of adult patients with relapsed or refractory hairy cell leukaemia (HCL) after receiving at least two prior systemic therapies, including treatment with a purine nucleoside analogue (PNA).

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Lumoxiti as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website:

https://www.ema.europa.eu/en/medicines/human/EPAR/Lumoxiti

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

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

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P0028/2019) on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's requests for consideration

Marketing authorisation under exceptional circumstances

The applicant requested consideration of its application for a marketing authorisation under exceptional circumstances in accordance with Article 14(8) of the above-mentioned Regulation.

New active Substance status

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

Scientific Advice

The applicant received the following Scientific Advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
23 July 2009	EMEA/H/SA/1302/1/2009/PA/III	Prof Andrea Laslop and Prof. Dieter Deforce
27 June 2014	EMEA/H/SA/1302/2/2014/PA/I	Dr Jens Reinhardt and Dr Hans Ovelgönne
28 June 2018	EMEA/H/SA/1302/2/FU/1/2018/PA/I	Dr Walter Janssens and Dr Jens Reinhardt
28 June 2019	EMEA/H/SA/1302/1/FU/1/2018/PA/III	Dr Alexandre Moreau, Dr Jens Reinhardt and Dr Daniel O'Connor

The Scientific Advice pertained to the following non-clinical, quality and clinical aspects of the dossier:

- the overall non-clinical programme, the proposal to revise the repeat-dose monkey toxicity study and to conduct a reproductive toxicity study after marketing authorisation in HCL to support an MAA in the HCL indication;

the plans to support process validation of the intended commercial manufacturing process; the proposed bacteriophage control strategy for commercial manufacture of the product moxetumomab pasudotox;

- the design of the single-arm pivotal study (CD-ON-CAT-8015-1053) and the resulting primary data analysis, together with the proposal of additional data for duration of haematologic remission from onset of CR, to support a MAA under exceptional circumstances.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: Bjorg Bolstad

The application was received by the EMA on	22 November 2019
The procedure started on	2 January 2020

The Rapporteur's first Assessment Report was circulated to all CHMP members on	23 March 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	23 March 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	6 April 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	30 April 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	12 August 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	21 September 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	1 October 2020
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	15 October 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	9 November 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	26 November 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Lumoxiti on	10 December 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The treatment of adult patients with relapsed or refractory hairy cell leukaemia (HCL) after receiving at least two prior systemic therapies, including treatment with a purine nucleoside analogue (PNA).

2.1.2. Epidemiology

Hairy cell leukaemia is a chronic and indolent B-cell malignancy that account for approximately 2% of all leukaemias. The incidence of HCL in the US is approximately 1200 cases per year (Kreitman et al, 2018) whereas in Europe is nearly 1600 cases per year (ESMO guideline, 2015). The incidence is less than 1 per 100 000 persons per year. HCL has a heavy male predominance (4:5). The median age at diagnosis is between 52 (ESMO, 2015) and 55 years (NCCN, 2018). The incidence is elevated among

whites and lower among Asians, Arabians and Africans (Tadmor et al 2015). Environmental and genetic risk factors in HCL is still unclear. Farming, exposure to pesticides and ionizing radiation are identified as risk factors, but not tobacco use.

The exact incidence of the relapsed/refractory population is difficult to be established with certainty; however it is stated in the literature that 30% - 40% of the patients will relapse within 10 years, both after 1st and 2nd line treatment with PNA (Grevet et al, 2011). It is also known that duration of response will decrease with subsequent therapies, and that chemotherapy-related toxicity increases and cumulates (Else et al, Br J Haematol, 2009).

2.1.3. Biologic features

HCL is characterised by clonal proliferation of malignant B-cells. Memory B-cells and possibly splenic marginal zone B-cells are considered as the cell of origin for HCL.

Patients diagnosed with HCL have abnormal circulating lymphocytes, which are notable for their hairy-like projections visible in light microscope. By flow cytometry HCL is typically notable for expression of CD11c, CD19, CD22, CD25, CD103 and CD123, and lack of CD5 and CD101. Almost all cases of classical HCL carry a BRAF V600E mutation that leads to upregulation of the MAP kinase/RAF/MEK/ERK pathway, resulting in enhanced cell proliferation and survival.

A variant of HCL, called HCLv, is more aggressive and is classified as a separate disease (WHO classification of lymphoid neoplasms, 2008- revised in 2016) with separate treatment guidelines (ESMO, 2015). HCLv lack the BRAF V600E mutation and CD25 expression, and accounts for approximately 10% of the total HCL population.

2.1.4. Clinical presentation, diagnosis and prognosis

The median age at diagnosis is 52 to 55 years, and the disease primarily affects men (4-5:1 ratio men vs women) (Monnereau et al 2014; Robak et al 2015). Cytopenias lasting for years can precede the diagnosis. Clinically HCL presents with fatigue, fever, night sweats, infections, weight loss and left upper abdominal pain and bruising. HCL usually develops slowly and kept under control for many years with treatment. The majority of the patients achieve long lasting remissions after both 1st and 2nd line of treatment but will ultimately relapse. Survival data for HCL are available from population-based studies mostly conducted in EU and the US and are consistent across regions and studies. Five-year survival is reported to 80-90%. HCL patients are expected to have a normal length of life if tolerant to therapy and achieving a complete remission (CR) after initial therapy.

Diagnosis of HCL requires a peripheral blood smear showing the hairy cell morphology and immunophenotypic examination of the bone marrow. The immunophenotypic criteria is established by either immunohistochemistry staining (IHS) of a biopsy or flow cytometry of bone marrow aspirate (or peripheral blood). Only the bone marrow biopsy makes it possible to specify degree of tumoral medullary infiltration and the presence of BRAF V600E mutations. For a great deal of the patients, bone marrow biopsy is necessary to obtain the diagnosis due to difficulty in aspirating bone marrow ("dry tap").

The most common indication for treatment has been the presence for at least one cytopenia (neutropenia, anaemia or thrombocytopenia). Other criteria for starting treatment is splenomegaly, enlargement of lymph nodes and frequent infections. These additional criteria are important for patients with HCL following splenectomy and for those with HCLv because these patients typically lack cytopenias, although more advanced disease. Before starting re-treatment of a patient, it is important to determine whether cytopenias are due to chemotherapy toxicity or to relapsed or refractory HCL.

The bone marrow biopsy may show infiltration of HCL in up to 6 months after treatment, so response evaluation should not be performed too early after therapy.

2.1.5. Management

Treatment is reserved for patients that develop significant cytopenias, symptomatic splenomegaly or opportunistic infections. The standard 1st line treatment, which has remained unchanged for the past 25-30 years, is a single agent purine analogue (PNA), either pentostatin or cladribine. The treatment goal is achievement of CR, defined as normalisation of peripheral blood counts, normalisation of organomegaly and disappearance of hairy cells in the bone marrow and peripheral blood. 80-90%of the patients achieve CR and remain relapse-free in median for 16 years (Else et al, 2009). At relapse, treating with the same agent or a different PNA will result in another long-lasting remission in the majority of the patients (70% CR, 11 years median relapse-free survival). Response rates and length of remission progressively decrease with subsequent therapy, however the majority of the patients will reach a natural lifespan without requiring treatment in the 3rd line plus-setting. Patients may experience increased toxicity of the PNAs after more lines of treatment. Some patients are poor responders to PNA and will not reach a CR, and consequently have an early relapse. Others have low tolerance to PNA due to toxicity and/or comorbidity.

In the multiple relapsed/refractory HCL-setting, neither the European (ESMO, 2015) nor the American guidelines (NCCN, 2018) presents a standard of care treatment in the 3rd line and below. Further, "refractory patient" is not clearly defined. "Novel "agents such as vemurafenib, bendamustine, ibritunib and moxetumomab pasudotox in addition to PNA + rituximab are accepted as reasonable treatment options if available. In addition, HCL patients in the multiple relapsed/refractory setting are recommended inclusion in clinical trials. Splenectomy should be considered if symptomatic splenomegaly (> 10 cm) in combination with low-level bone marrow infiltration in refractory patients.

The "novel" 3rd line agents listed in the guidelines are all commercially available, however, only moxetumomab pasudotox have a regulatory approval for the treatment of HCL in the US (FDA). None of the novel agents have regulatory approval in the EU.

About the product

Moxetumomab pasudotox is a CD22 targeted immunotoxin designed to direct the cytotoxic action of the truncated Pseudomonas exotoxin to cells which express the CD22 receptor. CD22 is a B lymphocyte restricted transmembrane protein with a similar or higher receptor density in hairy cell leukaemia (HCL) cells relative to normal B cells. Nonclinical data indicate that the anticancer activity of moxetumomab pasudotox is due to the binding of the immunotoxin to CD22 expressing tumour cells, followed by internalisation of the Lumoxiti CD22 complex and processing to release the active PE38 exotoxin. The exotoxin is translocated to the cytosol where it inactivates elongation factor 2 (EF 2), causing inhibition of protein synthesis leading to apoptotic cell death (SmPC, section 5.1).

The applicant initially requested the approval for the following indication:

Lumoxiti is indicated for the treatment of adult patients with relapsed or refractory hairy cell leukaemia (HCL) after receiving at least two prior systemic therapies, including treatment with a purine nucleoside analogue (PNA).

The final indication applied for by the applicant following CHMP review of this application is:

Lumoxiti as monotherapy is indicated for the treatment of adult patients with relapsed or refractory hairy cell leukaemia (HCL) after receiving at least two prior systemic therapies, including treatment with a purine nucleoside analogue (PNA).

The recommended dose of Lumoxiti is 0.04 mg/kg administered as a 30-minute intravenous infusion on Days 1, 3, and 5 of each 28-day cycle (SmPC, section 4.2) for a maximum of 6 cycles.

Type of Application and aspects on development

The applicant requested consideration of its application for a Marketing Authorisation under exceptional circumstances in accordance with Article 14(8) of the above mentioned Regulation based on the grounds that the indication for which the product in question is intended is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence.

2.2. Quality aspects

2.2.1. Introduction

The finished product Lumoxiti containing moxetumomab pasudotox as active substance is supplied as powder for concentrate and solution for solution for infusion. The product vial (powder) is accompanied by a vial of intravenous solution stabiliser (IVSS) which is to be added to the infusion bag in order to prevent adsorption of the active agent. After reconstitution with water for injection, each vial contains a target of 1mg of moxetumomab pasudotox.

The lyophilised moxetumomab pasudotox finished product (powder) must not be reconstituted with the intravenous solution stabiliser (IVSS).

Other ingredients are:

- Powder for concentrate: sodium dihydrogen phosphate monohydrate, sucrose, glycine, polysorbate 80, sodium hydroxide

- Solution ((stabiliser) (IVSS)): citric acid monohydrate, sodium citrate, polysorbate 80, water for injection.

The finished product and IVSS will be packaged as 2 presentations:

-2:1 pack configuration comprising 2 vials of moxetumomab pasudotox and 1 vial of IVSS

-3:1 pack configuration comprising 3 vials of moxetumomab pasudotox and 1 vial of IVSS

2.2.2. Active Substance

General information

Moxetumomab pasudotox is an approximately 63 kDa recombinant immunotoxin fusion protein targeting the B cell-specific surface antigen cluster of differentiation 22 (CD22). Moxetumomab pasudotox is composed of an immunoglobulin light chain variable domain (VL) and a heavy chain variable domain (VH) genetically fused to a truncated form of Pseudomonas exotoxin, PE38.

Moxetumomab pasudotox specifically binds to the B-lymphocyte-specific adhesion receptor CD22. Following binding of the variable domain (Fv) at the amino terminus of moxetumomab pasudotox to

CD22, the complex is then internalised into the endocytic compartment, where PE38 undergoes reduction of disulfide bond and subsequent cleavage in domain II resulting in separation of the Fv from a 37 kDa carboxyl terminal toxin fragment. This fragment is transported from the Golgi to the endoplasmic reticulum and to the cytosol. In the cytosol, the toxin catalyzes ADP-ribosylation of elongation factor-2, leading to rapid decreases in levels of anti-apoptotic protein Mcl-1, which results in apoptosis and cell death. The biological activity of moxetumomab pasudotox is determined using a cell-based apoptosis bioassay.

Manufacture, characterisation and process controls

All sites involved in the manufacture and testing of the active substance have been listed and are GMP compliant.

Manufacturing process and process controls

A process flow diagram summarizing the manufacturing process, as well as the material inputs, critical and non-critical process parameters and process outputs (in-process controls, microbial controls and performance attributes) has been provided.

The upstream process is a fed-batch process and consists of fermentation and harvest for the two different cell lines, VL and VH-PE38. The upstream processing is performed separately for each cell line and consists of the following steps: vial thaw, shake flask (seed culture 1), seed fermentor (seed culture 2), VL or VH-PE38 in the production fermentor, cell harvest, homogenisation, centrifugation and inclusion body (IB) recovery. After recovery, the IB slurries are stored. Upon thawing, the IB slurries containing the heavy and light chain components are mixed and then further processed together. The downstream purification process starts with the inclusion body thawing and solubilisation, followed by depth filtration, ultrafiltration and refold.

The subsequent purification includes four chromatography steps to remove product and process-related impurities and two intermediate ultrafiltration/diafiltration steps to exchange the buffer between unit operations. A final concentration and diafiltration step followed by a formulation step are used to formulate the active substance at a target concentration. The active substance is stored in sterile bottles.

The manufacturing process and process controls are summarised in flow charts and tables and further described in a process narrative. The process ranges, action limits and acceptance criteria for the process parameters and output parameters have been provided for each step. Conditions for use and reuse of chromatography resins and membranes have been presented, including number of reuse cycles.

The active substance is stored frozen prior to shipment to the finished product manufacturing site for fill and finish. The manufacturing process is generally well described.

VH and VL inclusion bodies are isolated and stored frozen during the active substance manufacturing process and are thus considered to be process intermediates. Sufficient information has been provided for the IBs (specifications, batch analyses and stability data) and this is found acceptable.

The seed media, fermentation media and nutrient feeds are free from animal components. Sufficient information has been provided for the media and the nutrient feeds.

Process parameters are classified as either critical (CPPs) or noncritical (NCPPs). Process outputs are classified in three categories; In-Process Controls (IPCs), Microbial Controls (MCs), and Performance

Attributes (PAs). The classification has been described in more detail in the dossier and is found acceptable.

Proposed hold times are supported by data and are acceptable.

In general, the proposed manufacturing process is supported by the performed process validation and characterisation studies.

Control of materials

Descriptions of raw materials and consumables such as resins have been presented. The information provided is considered sufficient. No animal derived materials were used, some materials of biological origin were sourced from microbial fermentation, plant, yeast, soy or algae. The risk of transmission of TSE from the raw materials is very low, further discussed and assessed in the section for adventitious agents. Raw materials used in the manufacturing process, both compendial and non-compendial are listed, the latter with tests and specifications. Certificates of analysis (CoAs) on materials of biological origin have been provided and also CoAs for excipients used in the final formulation.

Generation of cell substrate and characterisation of cell banks

The characterisation and testing of the gene insert and cell banks was aligned with ICHQ5B and ICHQ5D guidelines. The history and establishment of the research and production cell lines was described. Also, a description and rationale of the gene constructs, the expression plasmids and genetic stability throughout the cell culture production process with plasmid stability was provided. The gene insert region of the plasmid was sequenced for the two master cell banks (MCBs), two working cell banks (WCBs) and extended generation cell banks (EGCB). Information on storage and stability testing with compiled data on cell banks was also provided. Preparation, characterisation and testing of both MCBs and WCBs, from seed stock to EGCB is described. The establishment of the MCB/WCB cell banks for both VL and VH-PE38, adequacy of tests and methods performed with results, are addressed.

A programme for cell bank stability testing has been described and data on storage stability is presented.

Process validation

The process validation studies comprise validation of the commercial production scale, process intermediate hold times, resin sanitisation and storage, resin lifetime and carry over, membrane lifetime, shipping qualification and filter validation.

The process validation of the commercial manufacturing process (process performance qualification) was performed using three consecutive runs. The upstream validation comprised several batches each of VL Inclusion bodies and VH Inclusion bodies. The downstream validation comprised several batches of active substance. Acceptable results of critical and non-critical parameters, performance attributes and in-process controls are presented in tabulated form. The release data for the process validation batches have been also presented. A few deviations were observed during the validation, however these deviations were acceptably investigated and handled. The performed validation demonstrates a robust manufacturing process and is considered acceptable.

Clearance of process-related impurities was demonstrated during process validation, showing acceptable removal capacity.

Adequate removal of product-related impurities was also demonstrated.

Manufacturing process development

Three manufacturing processes have been used for active substance during development; Process 1, Process 2, and Process 3.

The process changes between Process 1 and Process 2 were substantial. The changes between the process versions are in general clearly outlined.

Comparability

Process 1 and Process 2: A comparative analysis comprising characterisation and routine tests were performed using several batches of Process 1 active substance with several batches of Process 2 active substance. The results are presented in the dossier, and according to the applicant's conclusion the data demonstrate that the Process 1 material and Process 2 material are comparable. Although the number of batches in the comparison is found limited, the conclusion can be agreed to.

Process 2 clinical and Process 3 clinical: For the comparison of Process 2 Clinical and Process 3 Clinical batches, characterisation and routine tests as well as evaluation of stability profiles were performed.

Process 3 Clinical and Process 3 Commercial: An extensive comparability exercise was performed between active substance from Process 3 Clinical and Process 3 Commercial. This study comprised several Process 3 clinical and several Process 3 commercial (PPQ) batches. The applicant's conclusion that the comparability results demonstrate that the processes are comparable can be agreed.

Process characterisation

The described overall approach for process characterisation (verification of suitability of scale-down model, risk assessment to define characterisation study design, execution of process characterisation studies and finally determination of CPPs) is endorsed.

Scaled-down models were used for process characterisation. Verification of the predictability of the scale-down models was performed by comparison with commercial scale data and is found acceptable.

The risk assessment methodology used to determine process characterisation study design is sufficiently described and justified.

Control of critical steps and intermediates

To identify the CQAs a severity assessment was performed. Potential impact by quality attributes on safety and efficacy was assessed by assessment of biological activity, pharmacokinetics, immunogenicity and safety. The method to identify the CQAs is found acceptable. The outcome of the severity assessment including the rationale for classification into critical or non-critical is presented for each attribute and is reasonable.

The criticality of process parameters in the manufacturing process that impact product quality attributes was identified based on process characterisation studies and process and theoretical knowledge. A summary of the control strategy showing the various unit operations and control elements that influence the critical quality attributes has been presented and is acceptable.

Characterisation

Comprehensive characterisation studies are presented for moxetumomab pasudotox using state-of-the-art technologies. Characterisation methods are sufficiently described. All peaks are characterised/described and relevant chromatograms are provided. Additional characterisation data from other batches is provided in section S.2.6 in relation to comparability studies performed to support process and manufacturing site changes.

Characterisation and data from manufacturing experience have been presented and include data from all the different active substance manufacturing processes.

The applicant has demonstrated clearance of biologically derived process-related impurities to acceptable and robustly low levels. These impurities are also routinely controlled by the active substance specification.

Small molecules and synthetic macromolecules were evaluated by a safety risk assessment based on quantitative toxicity data and confirmed in process characterisation/validation. The approach is found acceptable.

Specification

The active substance specification has been provided and includes control of identity, purity and impurities, bioactivity and other general tests.

The proposed active substance release and end of shelf life specification is found adequate and acceptably justified in accordance with relevant guidelines. Tightening of limits for some specifications was requested and agreed to during the procedure.

The use of the same limits for release and shelf life where applicable is found reasonable based on the stability data provided for both the active substance and finished product.

Analytical methods

The analytical methods used to test active substance are described and system and sample suitability criteria are adequately defined. the applicant has followed the principles of ICH Q2R1 guideline to demonstrate the validity of the methods. The method descriptions are found acceptable and sufficiently detailed.

Batch analyses

Batch release results from several batches from Process 3 Clinical, and several batches from Process 3 Commercial scale have been presented.

The results comply with the specification in place at the time of testing. All results for Process 3 Commercial batches complies with the proposed active substance specification. The presented batch analyses data demonstrate satisfactory batch-to-batch consistency within each process version.

Reference standards

A two-tiered (primary and working) reference standard system is applied. A portion of the Primary Reference Standard was designated as the first lot of Working Reference Standard. The qualification of the PRS is presented in the dossier. The tests and associated acceptance criteria are described. The protocol for qualification of future reference standards is acceptably described.

Container Closure System

The primary container closure system for active substance comprise a bottle and a cap. The qualitative compositions of the bottle and the cap have been presented, including information with respect to plastic additives. Conformance with the Ph. Eur. requirements for the plastic materials of the bottle and cap has been confirmed. Specifications and a representative Certificates of analysis (CoA) has been provided.

Leachable and extractables studies were performed for the bottle. The results are reported in the dossier and do not give rise to any issues of toxicological concern.

Stability

The stability studies are appropriate and in compliance with the relevant guidelines. The chosen analytical procedures appear adequately stability indicating. Stability data has been provided for several Process 3 clinical batches. Additional data is available for the PPQ batches from active substance process validation.

At the long-term storage condition all results are within specifications at all time points and there are no observable trends.

Photostability of the active substance was evaluated as part of stress studies described in the dossier. Formal photostability studies were performed and reported for the finished product. This is found acceptable.

The proposed shelf life for moxetumomab pasudotox active substance when stored at the recommended long-term storage condition is supported by stability data.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The moxetumomab pasudotox finished product is a sterile lyophilised dosage form intended for intravenous infusion after reconstitution with sterilised water for injections (WFI) and dilution into 0.9% (w/v) saline.

The product vial (powder) is accompanied by a vial of intravenous solution stabiliser (IVSS) which is to be added to the infusion bag in order to prevent adsorption of the active agent.

The finished product and IVSS will be packaged as 2 presentations:

-2:1 pack configuration comprising 2 vials of moxetumomab pasudotox and 1 vial of IVSS

-3:1 pack configuration comprising 3 vials of moxetumomab pasudotox and 1 vial of IVSS

The stabiliser (IVSS) is described in the section - Finished Medicinal Product, solution-stabiliser (IVSS).

Pharmaceutical development

A comprehensive manufacturing process development has been performed which has been adequately described and discussed. The chosen development approach is found appropriate.

Four finished product processes were developed for the clinical and commercial process. Process 1, Process 2, Process 3 clinical and Process 3 commercial. Process 1 and 2 were used for non-clinical and clinical manufacturing. Process 3 was used to manufacture material for Phase 3 clinical studies and is referred to as Process 3 Clinical.

The formulation development has been adequately addressed and the chosen formulation sufficiently justified. The same formulation was used in process 2 and 3. There is no overage of active substance or excipient, only overfill which has been acceptably justified.

The manufacturing process history has been clearly described. A comparability exercise was performed to demonstrate that Process 3 finished product commercial is comparable to the Process 3 finished

product clinical. The results provided demonstrate that material manufactured from the two processes are comparable.

It is noted that there is no comparability exercise performed for the change from process 1 to process 2 and 3. However, the applicant has acceptably justified the absence of comparability studies for these two process changes. Please also see the above discussion on active substance in relation to comparability between process 2 and 3 active substance material.

The process characterisation studies to support the commercial process have been adequately described. The different unit operations have been characterised and the impact of process parameters on product quality and process performance have been acceptably studied.

The Critical Process Parameters (CPP) are listed and sufficiently justified.

The quality impact of manufacturing environmental conditions, including time out of refrigeration, light exposure and product-contacting materials have been satisfactorily addressed.

Furthermore, a leachable assessment on the product contacting materials has been performed and none of the components was found to pose a high risk concerning potential leachables.

Container closure system

The assessment of the suitability of the primary package materials has been acceptably described. The primary packaging materials are in compliance with the compendial requirements of the Ph. Eur. The results from the extractables and leachable assessment support the safety of finished product when stored at the recommended storage conditions.

Compatibility

The finished product is reconstituted in WFI and thereafter diluted into a saline solution. However, prior to finished product dilution into saline an intravenous solution stabiliser (IVSS), supplied with the finished product in a separate vial, is added to the IV bag to prevent adsorption of moxetumomab pasudotox.

The compatibility for the moxetumomab pasudotox in IVSS and saline has been studied when diluted in IV bags. The bags used in the study were selected based on prevalence of use. The proposed in-use stability of 4 hours at room temperature up to 25°C and 24 hours at 2-8°C is found acceptably justified.

Manufacture of the product and process controls

The sites involved in the manufacturing of the finished product are GMP compliant.

Description of manufacturing process and process controls

The manufacturing process and process controls are acceptably described. The manufacturing process for the finished product consists of thawing, pooling, mixing and sterile filtration (two filters) of the active substance followed by aseptic filling, lyophilisation and stoppering. Finally, the finished product is capped, 100% visually inspected, labelled, packaged and stored at 2-8°C.

CPPs, non-critical process parameters and in-process controls have been adequately listed for each process step. The ranges proposed for CPPs and non-CPPs are found acceptably justified.

Satisfactory information on the sterile filter used has been included as well as information on the packing and shipping procedures for the transport of filled bulk vials to the site responsible for the secondary packaging.

Process validation and/or evaluation

The process validation followed a traditional approach and covered several consecutive production scale batches.

The validation results demonstrate that the finished product complies well with the acceptance criteria and specifications and can be consistently manufactured within the defined processing and holding times. Container Closure Integrity Testing (CCIT) was conducted to assure container closure integrity across the sealing force range. All acceptance criteria were met.

In this section of the dossier also, sterilisation of stoppers and crimps is addressed as well as the depyrogenation of the glass vials. These are performed in compliance with Ph. Eur. reference conditions. Information on shipping validation of the transport to the secondary packaging has been provided and is found acceptable to ensure that the transport can be adequately performed.

Product specification

The finished product specification includes control of identity, purity and impurities, bioactivity and other general tests.

The finished product specification, test attributes as well as limits, is at large the same as for the active substance with the exception for the testing only performed on active substance and finished product respectively. The chosen test strategy is found acceptable.

Impurities

In relation to impurities the applicant states that no impurities are introduced during the finished product manufacturing process and therefore not further addressed for the finished product. Furthermore, a summary of the risk assessment for elemental impurities in line with ICH Q3D has been included. The risk assessment did not identify any elemental impurities that are likely to be present at levels approaching the permitted daily exposure (PDE) limits proposed in the guideline. This assessment was confirmed by analytical screening of several lots of moxetumomab finished product.

Upon request, the applicant provided a risk assessment of the potential presence of nitrosamines in moxetumomab finished product. The assessment was based on the risk factors identified within the revised EMA Questions and answers on nitrosamine impurities in human medicinal products (EMA/409815/2020). Based on this assessment the applicant concluded that there is no risk associated with nitrosamines for moxetumomab finished product, and this conclusion can be agreed.

For the finished product specification only justifications in relation to the test attributes pertinent to the finished product were presented. For the chosen approach used to justify the other test attributes and acceptance criteria, reference is given to justifications provided in the dossier for the active substance and this is considered acceptable.

For some quality attributes the acceptance criteria are claimed to be based on manufacturing experience. The justification of specification for these quality attributes of relevance only for the finished product is found acceptable.

Analytical methods

The analytical methods used to test the finished product are described and system and sample suitability criteria are adequately defined. The applicant has followed the principles of ICH Q2R1 guideline to demonstrate the validity of the methods.

Compendial (Ph. Eur.) methods are used and for these methods the suitability of the testing of moxetumomab has been acceptably demonstrated.

Overall, the method descriptions are found acceptable and sufficiently detailed.

Batch analysis

Batch data from the different processes used during product development has been provided. For the commercial process 3, results from the validation batches and additional batches have been provided. The results comply well with the acceptance criteria and demonstrate a satisfactory batch to batch consistency. The results demonstrate that the material from Process 3 finished product commercial is comparable to the Process 3 finished product material used in the pivotal clinical trials.

Stability of the product

A shelf life of 48 months when stored between 2-8°C and protected from light is claimed for the finished product (powder vial).

The applicant has provided stability results from several batches manufactured according to commercial process at the commercial site as well as from the claimed primary stability batches which are clinical batches. Also results from pilot scale batch are provided.

The stability studies are performed in accordance with ICH Q5C Stability Testing of Biotechnological/Biological Products. Long-term studies at 2-8°C are performed and full-time data for the proposed shelf life of 48 months have been provided for the two primary stability batches and the pilot batch. For the four batches manufactured according to commercial process at the commercial site (including the three PPQ batches and one annual commitment) up to 48 months data have been provided.

In addition, results from accelerated and stress studies as well as reconstitution studies have been provided. Also, elemental impurities are studied throughout the shelf life and results up to 24 months have been provided.

All results complied very well with the acceptance criteria and no significant changes were observed for the long-term, accelerated and stressed studies. However, the photostability study verifies the need for the protection from light and that the finished product marketing pack is effective in protecting the finished product from light exposure.

Considering that the stability results demonstrate adequate stability at proposed storage condition, the proposed shelf life of 48 months at 2-8°C when protected from light, is found acceptable. The applicant provided for the process several validation lots 48-month stability data.

The data met the acceptance criteria and no adverse trends were observed. In summary representative lots from process 3 and the commercial filling site demonstrate stability over 48 months.

The proposed 48-months shelf life for the powder vial when stored at 2-8°C are based on sufficient real time data and can be granted.

For Lumoxiti solution (i.e. diluted Lumoxiti concentrate in the prepared infusion bag), chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8°C or 4 hours at room temperature up to 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

Finished Medicinal Product, solution-stabiliser (IVSS)

Description of the product and Pharmaceutical Development

The vialed intravenous solution stabiliser (IVSS) is a sterile liquid dosage form intended to prevent adsorption of moxetumomab pasudotox to contact surfaces during intravenous (IV) infusion. The IVSS is added to the 0.9% (w/v) saline IV bag prior to the addition of the reconstituted moxetumomab pasudotox finished product into the IV bag.

Pharmaceutical development

The IVSS was developed to prevent adsorption of moxetumomab pasudotox to contact surfaces during the addition, dilution, and administration of the finished product. The formulation development has been adequately addressed and the chosen formulation sufficiently justified. A polysorbate 80 concentration was chosen to increase the polysorbate 80 concentration in the IV bag prior to addition of the finished product.

There is no overage of excipient, only overfill which has been acceptably justified.

The manufacturing process development has been adequately described and discussed. The chosen development approach is found appropriate.

The manufacturing process history and rationale for process changes has been acceptably described. There are no major changes in the manufacturing process (clinical through commercial) but the site was changed. No formal analytical comparability exercise was performed. This is found acceptable considering that the formulation was not changed, no major changes to the process were introduced and batch results comply very well with the specifications.

The process characterisation studies support the commercial process and have been adequately described. The different unit operations have been characterised and the impact of process parameters on product quality and process performance have been adequately studied.

The Critical Process Parameters are listed and sufficiently justified.

The quality impact of manufacturing environmental conditions, including time out of refrigeration, light exposure and product-contacting materials have been satisfactorily addressed.

Also, a leachable assessment on the product contacting materials has been performed and none of the components was found to pose a high risk concerning potential leachables.

The assessment of the suitability of the primary package materials has been acceptably described. The primary packaging materials are in compliance with compendial requirements of the Ph. Eur.

The vialed IVSS was evaluated for photostability according to the ICH Guidance. The results from the exposed vials were comparable to the results from the control vials, demonstrating that the IVSS is photostable.

The risk assessment in relation to extractables and leachable support the safety of finished product when stored at the recommended storage conditions.

Manufacture of the product and process controls

Description of manufacturing process and process controls

The manufacturing process and process controls are acceptably described. The manufacturing process for the finished product IVSS consists of formulation, mixing, reduction filtration and sterile filtration (two filters) followed by aseptic filling and stoppering. Finally, the finished product IVSS is capped, 100% visually inspected, labelled, packaged, and stored.

CPP, non-critical process parameters and in-process controls have been adequately listed for each process step.

Vials and stoppers are sterilised as per the reference conditions stated in the Ph. Eur.

Satisfactory information on the sterile filter used is included as well as information on the packing and shipping procedures for the transport of filled bulk vials to the site responsible for the secondary packaging.

Process validation and/or evaluation

The process validation followed a traditional approach and covered three consecutive production scale batches. The validation was run at set points while the ranges of process parameters were challenged during the manufacturing process development.

The process validation batch data demonstrates that the finished product IVSS complies well with the acceptance criteria and specification and can be consistently manufactured within the defined processing and holding times.

Product specification, analytical procedures, batch analysis

Both release and shelf life criteria are given by the final product specification for the IVSS vial and cover relevant test parameters.The general approach, test attributes chosen and limits proposed are acceptably justified. The applicant concludes that no impurities are introduced. Furthermore, a summary of a risk assessment for elemental impurities has been included. This is acceptable.

Analytical methods

Results from the validation of the methods is found adequate. Verification of compliance with the compendial test methods have been acceptably demonstrated.

Batch analyses

The results from batch data for IVSS comply well with the acceptance criteria and demonstrate an acceptable batch to batch consistency.

Stability of the product

A shelf life of 48 months when stored at 2-8°C is claimed for the finished product (IVSS vial).

The applicant has provided stability results from six batches manufactured according to the commercial process at the commercial site and stored up to 36 months at 2-8°C. In addition, supportive data has been provided for three clinical batches.

The studies are performed in accordance with ICH Q5C Stability Testing of Biotechnological/Biological Products. Long-term studies at 2-8°C are performed and until now full-time data for the proposed shelf life of 48 months have only been provided for the three clinical batches using the same package but with a higher fill volume for two of the batches. For the six batches manufactured according to the commercial process at the commercial site (including the three PPQ batches and one annual commitment) up to 36 months data have been provided.

All results comply very well with the acceptance criteria and no significant changes are observed for the long-term, accelerated and photostability studies. The results of the IVSS photostability study have been presented. The results for the IVSS exposed vials were compared to those of the control vials. The results met the acceptance criteria, and the results from the exposed vials were comparable to the results from the control vials, demonstrating that the IVSS is photostable under the exposure conditions described in ICH Q1B.

Although only up to 36 months data are available for the study with batches manufactured at the commercial site, and the study is still on-going, the proposed shelf life of 48 months at 2-8°C for the IVSS vial, is found acceptably justified taken into account the supportive clinical batch data and the fact that no stability trend at all have been shown.

Adventitious agents

Raw materials of biological origin and TSE risk evaluation

No materials of animal origin were used during cell line development, banking or the manufacturing process of moxetumomab pasudotox. The materials were sourced from microbial fermentation, plant, yeast, soy or algae. Considering the EMA/410/01 note for guidance on minimising the risk of transmitting animal spongiform encephalopathy, the risk of transmission of TSE from raw materials of biological origin is very low.

Testing of Master and Working Cell Banks for Microbial Adventitious Agents

The tests, specifications and results for identity and purity showed the cells to be free of contamination of adventitious microbial agents.

Virus safety

The fermentation process of moxetumomab pasudotox is in a serum-free medium. The cells used for production of moxetumomab pasudotox are of bacterial origin. Low levels of endogenous DE3 bacteriophages have been observed in the bacterial cells. A risk assessment was performed.

In summary, the virus safety of moxetumomab pasudotox is found sufficiently demonstrated.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The Lumoxiti dossier is acceptably structured and of acceptable quality.

The active substance manufacture is performed in *E. coli.* Two different production cell lines are used to produce the protein subunits; the VL light chain and the VH-PE38 heavy chain plus toxin fragments, which are isolated as inclusion bodies. The two protein fragments are combined in the refolding step, and the protein is then further purified.

Three active substance manufacturing processes have been used during development; Process 1, Process 2, and Process 3. Process 1 and 2 were used for non-clinical and clinical manufacturing. Furthermore, two different versions of Process 3, referred to as Process 3 Clinical and Process 3 Commercial are described. The changes between the process versions, including the differences between Process 3 Commercial and Process 3 Clinical, are in general clearly outlined.

Appropriate information on development and manufacture of the active substance and the finished product has been presented. The results of tests carried out indicate that both the active substance and the finished product are manufactured in validated and well-controlled processes.

The control of the active substance and finished product has been suitably presented. The stability of the active substance and finished product have been satisfactorily studied and data presented show no significant changes. The product vial (powder) is accompanied by a vial of intravenous solution stabiliser (IVSS) which is to be added to the infusion bag in order to prevent adsorption of active substance. The information on development, manufacture, control and stability of the IVSS has been satisfactorily presented.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Lumoxiti is considered acceptable when used in accordance with the conditions defined in the SmPC.

The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The manufacturing process of the active substance and finished product have been satisfactorily described and validated. The active substance is well characterised and appropriate specifications are set. The quality of the finished product is controlled by adequate test methods and specifications. Adventitious agents' safety including TSE have been sufficiently assured.

In conclusion, based on the review of the quality data provided, this marketing authorisation application for Lumoxiti is considered approvable from the quality point of view.

2.2.6. Recommendations for future quality development

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

2.3. Non-clinical aspects

2.3.1. Introduction

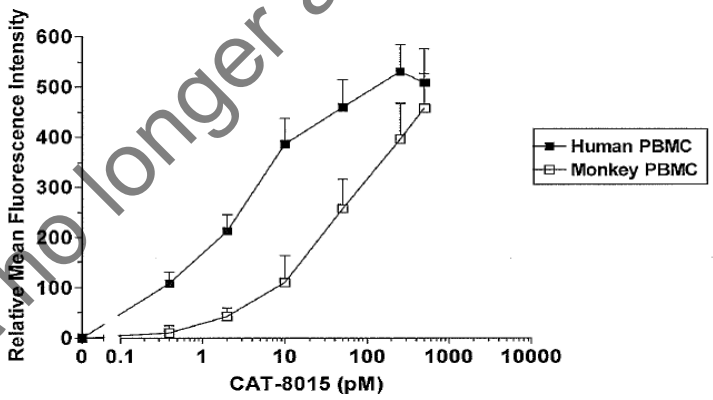
The non-clinical pharmacology programme includes studies conducted by the applicant as well as additional supporting literature publications. The cynomolgus monkey was considered the only pharmacologically relevant species for non-clinical safety evaluation based on a similar binding profile of moxetumomab pasudotox to human and cynomolgus monkey peripheral blood mononuclear cells (PBMCs). The non-clinical programme of pharmacokinetics studies has been carried out with moxetumomab pasudotox in mice, rats and cynomolgus monkeys after a single IV dose. The repeat dose toxicokinetics of moxetumomab pasudotox have been investigated following IV administration to cynomolgus monkeys in one 13-week GLP study (three times weekly dosing) and in one 2-cycle GLP study (three times weekly dosing, every other week for 3 weeks).

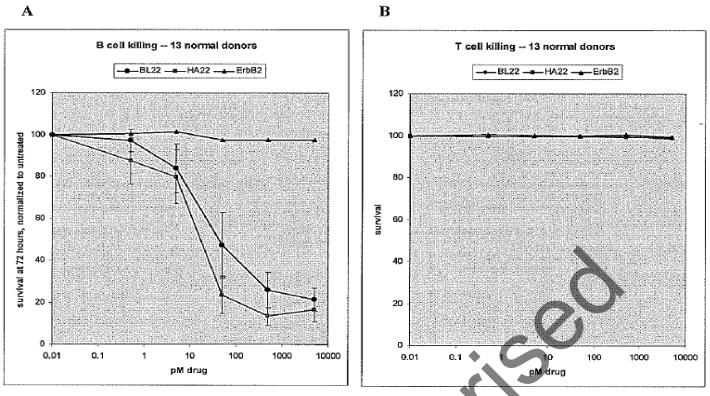
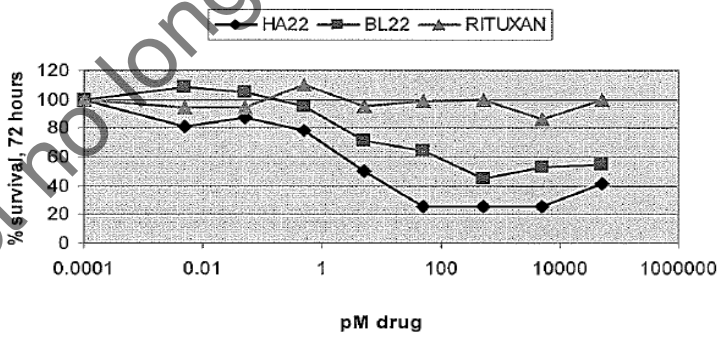
2.3.2. Pharmacology

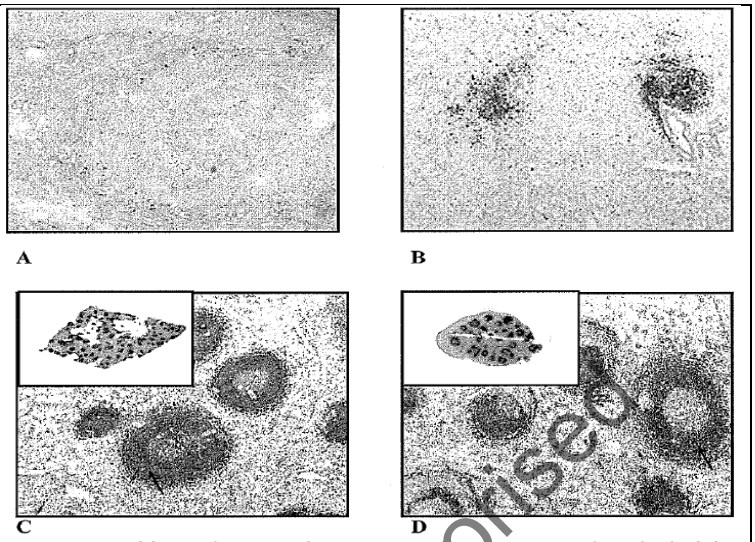
Primary pharmacodynamic studies

A series of *in vitro* and *in vivo* investigations have been conducted in order to characterise the primary pharmacology of moxetumomab pasudotox.

Table 1 In vitro pharmacodynamic studies with moxetumomab pasudotox (CAT-8015, GCR-8015*)*

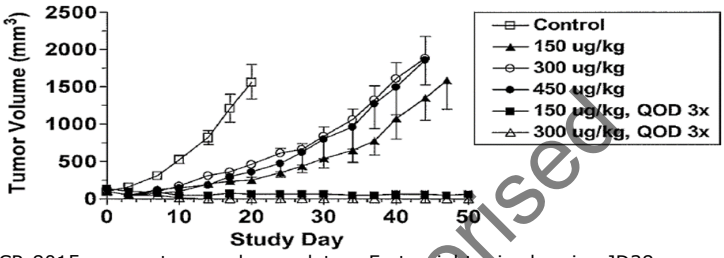
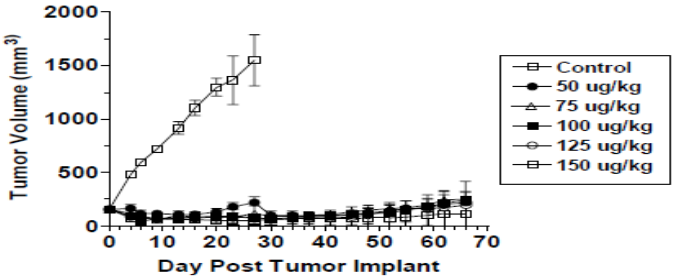
Study	***Setup***	***Objectives and results***
In vitro / ex vivo Binding studies (non-GLP) Study No: NRT0019	Human and cynomolgus monkey PBMCs obtained from human and cynomolgus whole blood (n=4). Flow cytometry Methods: Purified PBMCs were stained with biotinylated moxetumomab pasudotox (GCR-8015, Lot 10309005) at 0.001 to 500 pM, washed with PBS, treated with streptavidin FITC, and analyzed by FACS.	Objective: To characterise the binding of GCR-8015 to cynomolgus monkey peripheral blood B-cells as compared with human B-cells. Results: **Comparison of GCR-8015 Binding to Human and Cynomolgus Monkey PBMCs**  Peripheral blood mononuclear cell (PBMC) mean fluorescence of human (n = 4) and cynomolgus monkey (n = 4) PBMCs stained with biotinylated CAT-8015 (also referred to as GCR-8015 or moxetumomab pasudotox) followed by FITC-labeled streptavidin. - The binding of moxetumomab pasudotox to human PBMCs saturated at 250 pM, 531 mean fluorescence intensity units (MFI) units. At the highest concentration tested (500 pM), the level of moxetumomab pasudotox binding to cynomolgus monkey PBMCs was 457 MFI. - Overall, the profile of moxetumomab pasudotox binding to human and cynomolgus monkey PBMCs seems to be similar, albeit the binding curve was shifted towards higher concentrations (~ 10x) for cynomolgus monkey PBMC.
In vitro Expression studies (non-GLP) Study No: NRT0018	Purified PBMCs and viable human leukaemia and lymphoma cell lines were stained with an anti-CD22 antibody (RFB4) labeled with Alexa Fluor 488. Fluorescence was measured by FACS.	Objective: To establish the method for CD22 quantitation and to survey a limited panel of cell lines for CD22 receptor numbers. Results: - All of the B-cell lines examined expressed CD22, where Daudi cells were consistently the highest CD22 expressing cells. - In the B-cell lines tested, the number of CD22 sites/cell ranged from 214 (Granta cells) to 10,397 (Daudi cells). In human PBMCs, the number of CD22 sites/cell ranged from 2,025 to 5,275 with a mean of 3,169 sites/cell.
Ex vivo Cytotoxicity studies (non-GLP)	Human bone marrow and human and cynomolgus monkey PBMCs *ex vivo*, FACS Methods:	Objective: To develop a flow cytometric assay to measure B-cell cytotoxicity induced by the CD22-targeted immunotoxins GCR-8015 and GCR-3888 Results

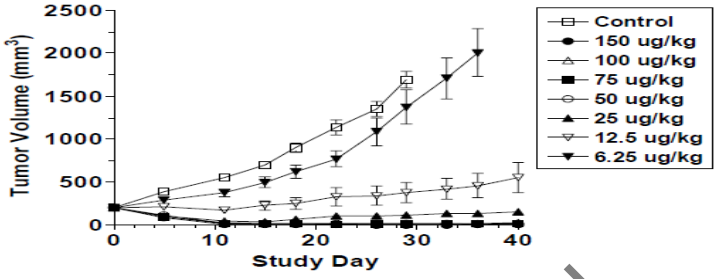
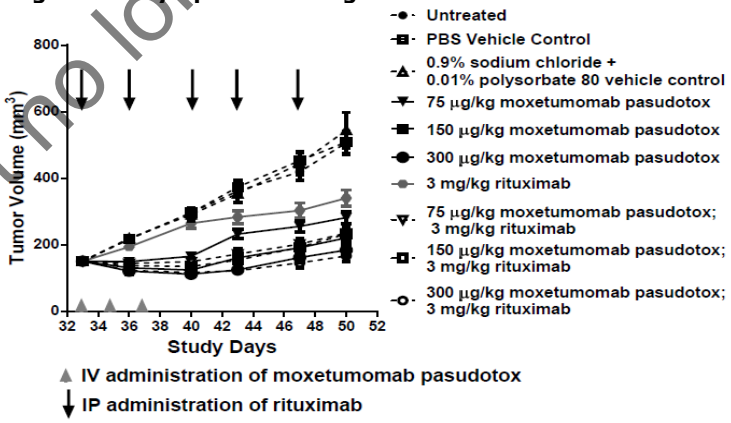
Study No: NRT0006	Human whole blood collected from normal donors (n=13) and Cynomolgus monkey blood (n=4). Moxetumomab pasudotox and anti-ERBB2-PE38 antibody were serially diluted (10-fold) into culture medium starting at 5 or 50 nM for PBMCs and bone marrow, respectively. Cells were treated with CD19, annexin V-FITC, and propidium iodide and analyzed by FACS. Cytotoxicity was measured as the change in frequency of apoptotic B-cells normalised to untreated cells.	**1. Human B-cell (A) and T-cell (B) Survival after Incubation with GCR-3888 (BL22), GCR-8015 (moxetumomab pasudotox) or ErbB2-PE38 immunotoxins**  GCR-8015, HA22 = moxetumomab pasudotox; GCR-3888, BL22 = CAT-3888. Peripheral blood mononuclear cell (A) or T cells (B) from normal human donors (n = 13) were incubated for 72 hours with immunotoxin HA22, BL22 or ErB2-PE38. Values represent the percent of non-apoptotic B-cells (CD19-positive) or T-cells (CD3-positive) normalised to untreated cells. (A) Dose-dependent responses were observed with moxetumomab pasudotox and BL22 but not with ErB2-PE38. (B) Immunotoxin treatment did not result in T-cell cytotoxicity **2. Human Bone Marrow B-cell Survival Following Treatment with GCR-8015 (HA22 or moxetumomab pasudotox), GCR-3888 (BL22) or Rituximab®**  Human bone marrow cells were incubated with immunotoxins GCR-8015 (HA22 or moxetumomab pasudotox), GCR-3888 (BL22 or CAT-3888) or rituximab (Rituxan®) for 72 hours at 37°C at the concentrations shown above. Cytotoxicity was evaluated as the change in frequency of apoptotic B cells normalised to untreated cells. Cytotoxic effects were observed with the CD22-targeting immunotoxins, but not with rituximab. -In human B cells, the IC50 for moxetumomab pasudotox was approximately 7 pM. Moxetumomab pasudotox was cytotoxic to B-cells derived from human bone marrow or peripheral blood. - No data (e.g. IC50 values) for moxetumomab pasudotox was reported in monkey B-cells. - In summary, in assays using human PBMCs or bone marrow cells, a dose-dependent cytotoxicity response was observed following treatment with moxetumomab pasudotox (GCR-8015).
In vitro Binding studies (non-GLP) Study No: NRT0017	Frozen rhesus monkey, cynomolgus monkey, and human spleen sections and rhesus and cynomolgus monkey PBMCs *ex vivo*, IHC, FACS Methods: Spleen sections were fixed in acetone, air dried, and treated with 25 µg/mL RFB4-phycoerythrin (anti-CD22) or mouse IgG1 isotype control.	Objective: To determine if the mouse anti-human CD22 antibody, RFB4, cross-reacted with cynomolgus, rhesus or human CD22 expressed on lymphatic tissue (spleen). Binding to cynomolgus and rhesus monkey peripheral blood B-cells was also determined. Results: **Immunohistochemical Staining by Anti-human CD22 Antibody RFB4 on Human and Monkey Frozen Spleen Tissue**

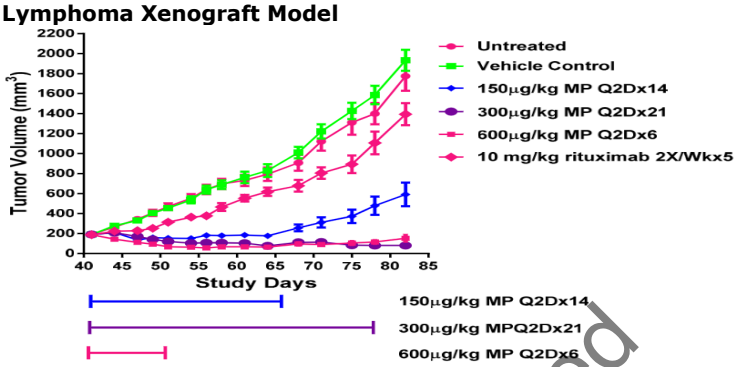
	Sections were examined by light microscopy. Peripheral blood from rhesus and cynomolgus monkeys was stained for CD22-positive B-cells using standard immunophenotyping protocols employing FACS. Briefly, 50 µL fresh blood was aliquoted into tubes and 10 µL RFB4-phycoerthyrin was added to the cells and incubated on ice for 20 minutes. Red blood cells were lysed with annnonium chloride, washed in PBS, and analyzed by FACS.	 IHC staining of frozen human spleen tissue with isotype control antibody (A) and RFB4 anti-human CD22 antibody (B) is shown compared to RFB4 anti-human CD22 staining of rhesus monkey (C) and cynomolgus monkey (D) frozen spleen tissue. Arrows in C and D show staining of B-cells in the mantle cell areas. -The staining profile for RFB4 on human spleen tissue was considered qualitatively similar to that observed in cynomolgus monkey and rhesus monkey sections. - FACS analysis of RFB4-phycoerythrin binding to cell-surface CD22 molecules on PBMCs from cynomolgus and rhesus monkeys resulted in the resolution of the B cell component from monocytes and T cells. - In summary, based on the IHC and FACS analysis, the mouse anti-human CD22 antibody RFB4 was observed to cross-react with rhesus, cynomolgus and human CD22 expressed on splenic tissues, as well as on monkey peripheral blood B-cells.
In vitro IHC expression study (CD22) (non-GLP) Study No: NRT0016	B cell leukaemia and lymphoma frozen human tissue panels *ex vivo*, IHC Methods: Samples were sectioned, fixed in 4% paraformaldehyde, IHC stained, and treated with AHS2202 or mouse IgG1 (0.5 µg/mL)	Objective: To characterise a commercially available monoclonal antibody to CD22 using imunohistochemical methods. Results: -CD22 is expressed in many histopathologically defined tumour cells in B-cell lymphomas. Four MCL samples stained strongly (intensity of 2+ to 3+) in 75% to 100% of tumour cells. Nine of 15 (94%) FL samples showed strong positive staining (2+ to 3+) and 1 samples showed dim staining in only 25% of tumour cells. - Expression data suggest that CD22-expressing B cell malignancies represent potential targets for anti-CD22 recombinant immunotoxins.

The anti-tumour activity of moxetumomab pasudotox was evaluated in xenograft models of B-cell malignancies *in vivo*.

Table 2 In vivo pharmacodynamic studies with moxetumomab pasudotox (CAT-8015, GCR-8015)

Study	***Setup***	***Objectives and results***
In vivo cytotoxic activity (non-GLP) Study No: NRT0015	CD22 expressing Burkitt's lymphoma (JD38) subcutaneous xenograft tumour model. Female athymic nude mice, n=8/group Tumour model: Tumour cells (JD38) were implanted subutenously Doses: Moxetumomab pasudotox single bolus: 150, 300, and 450 µg/kg; IV Moxetumomab pasudotox QOD x 3: 150 and 300 µg/kg; IV Vehicle (aqueous buffer containing 1.7 mM KH2P04, 5 mM NazHP04, 0.5 M NaCl, pH 7.4) Endpoints: Every 3 to 4 days, the body weights were recorded and the tumours were measured on two axes with calipers.	Objective: To determine the cytotoxic activity of GCR-8015 (HA22, CAT-8015) *in vivo* using a CD22 expressing Burkitt's lymphoma (JD38) subcutaneous xenograft tumour model. Results: **Effect of GCR-8015 on the Growth of JD38 Tumours in NCr Athynic Nude Animals**  GCR-8015 = moxetumomab pasudotox; Forty-eight mice bearing JD38 subcutaneous xenograft tumours in NCr athymic female nude mice were inoculated subcutaneously with 10 million JD38 cells and were randomised into groups on Study Day 0, when tumours were approximately 100 mm3, with 8 mice per group. Following randomisation, the mice were then treated either one time with moxetumomab pasudotox at 150, 300 or 450 µg/kg or were treated QOD x 3 with moxetumomab pasudotox at 150 or 300 µg/kg. The data points represent the Mean ± standard error of the mean (SEM). Mice receiving vehicle were treated one time. Tumours of mice receiving a single dose of moxetumomab pasudotox showed evidence of a slower growth profile. Tumours of mice receiving either 150 or 300 µg/kg moxetumomab pasudotox remained in regression with no evidence of regrowth for a period of 50 days. -A tumour growth inhibition by moxetumomab pasudotox was shown in a JD38 xenograft model with increased tumour growth inhibition with QOD x 3 schedule. -When administered as a single IV bolus dose, moxetumomab pasudotox suppressed the growth of JD38 tumours. -When administered QOD (IV bolus) for 3 days, moxetumomab pasudotox induced tumour regression and, based on the absence of regrowth after 50 days, tumour cell death.
In vivo cytotoxic activity (non-GLP) Study No: NRT0007	CD22 expressing Burkitt's lymphoma (JD38) subcutaneous xenograft tumour model. Female athymic nude mice, n=8/group Tumour model: Tumour cells (JD38) were implanted subutenously Doses: Moxetumomab pasudotox QOD x 3: 50, 75, 100, 125, 150 µg/kg; IV Vehicle (aqueous buffer containing 1.7 mM KH2P04, 5 mM Na2HP04, 0.5 M NaCl, pH 7.4) Endpoints: Every 3 to 4 days, the body weights were recorded and the tumours were measured on two axes with calipers.	Objective: To evaluate the cytotoxic activity of GCR-8015 (HA22, CAT-8015) in JD38 tumours *in vivo*. Results: **Effect of GCR-8015 on the Growth of JD38 Tumours in NCr athymic Nude Mice**  GCR-8015 = moxetumomab pasudotox. Mice bearing JD38 subcutaneous tumours were randomised into groups (n = 8) on Study Day 0. Mice were treated with moxetumomab pasudotox every other day for 3 doses. The data points represent the Mean ± standard error of the mean (SEM). Tumours in mice treated with ⩾ 75 µg/kg moxetumomab pasudotox had an initial dose-dependent decrease in tumour volumes. Tumour volumes remained suppressed for an extended interval, with growth rebounding by Study Day 66. - A inhibition of tumour growth was shown with moxetumomab pasudotox, at doses ≥ 75 µg/kg, in a JD38 xenograft model. - Tumour suppression occurred until Study Day 66.
In vivo cytotoxic activity	CD22 expressing Burkitt's lymphoma (JD38)	Objective: To investigate the effect of GCR-8015 (CAT-8015, HA22) on the *in vivo* growth of JD38 SC tumours.

(non-GLP) Study No: NRT0020	subcutaneous xenograft tumour model. Female athymic nude mice, n=8-10/group Tumour model: Tumour cells (JD38) were implanted subutenously Doses: Moxetumomab pasudotox QOD x 3: 6.25, 12.5, 25, 50, 75, 100, 125, 150 µg/kg; Vehicle (aqueous buffer containing 1.7 mM KH2P04, 5 mM Na2HP04, 0.5 M NaCl, pH 7.4) Endpoints: Every 3 to 4 days, the body weights were recorded and the tumours were measured on two axes with calipers.	Results: **Effect of GCR-8015 on the Growth of JD38 Subcutaneous Xenograft Tumours in NCr Athymic Nude Mice**  Tumour-bearing mice were randomised into groups based on tumour size on Study Day 0. Following randomisation, the mice were then treated QOD x 3 with the indicated doses of GCR-8015 (moxetumomab pasudotox). The data points represent the mean ± SEM (n = 8 -10 mice per group). -A dose-dependent inhibition of tumour growth was shown in a JD38 xenograft model with moxetumomab pasudotox, with significant tumour growth inhibition demonstrated at doses of 12.5 µg/kg or greater.
In vivo Anti-tumour efficacy (non-GLP) Study No: ONC8015-0005	Karpas422, a human DLBCL xenograft model in SCID mice Female CB17 SCID mice, n=10/group IV (GCR-8015) and IP (rituximab) Tumour model: Human Karpas422 diffuse large B-cell lymphoma cancer cells (1×10^7 Karpas422 cells (100 µLvolume, SC)) were implanted subcutaneously in female CB-17 SCID mice Doses: Moxetumomab pasudotox QOD x 3: 75, 150 300 µg/kg; Rituximab: 1.5, 3.0 mg/kg Moxetumomab pasudotox QOD x 3: 75, 150, 300 µg/kg + 3 mg/kg rituximab; Vehicle (.9% sodium chloride, 0.01% polysorbate 80) Untreated Endpoints: Tumour volumes (electronic caliper) and body weight measurements were recorded twice a week.	Objective: To evaluate anti-tumour efficacy of moxetumomab pasudotox as a monotherapy and in combination with rituximab in Karpas422, a human DLBCL xenograft model in SCID mice. Results: **Efficacy of Moxetumomab Pasudotox or Rituximab® as Single Agents and in Combination in a Karpas422 Diffuse Large B-cell Lymphoma Xenograft Model**  Mice bearing Karpas422 xenografts were randomised into groups by tumour size on Day 32. Treatment with vehicle, or moxetumomab pasudotox or rituximab started on Day 32 at the doses indicated. On Day 50, differences in tumour volumes compared to control mice were compared. There was significant tumour growth inhibition as compared to control mice for all groups. - Dose-dependent inhibition of Karpas422 DLBCL xenograft tumour growth was demonstrated by moxetumomab pasudotox administered QOD x 3 at doses of 75, 150 or 300 µg/kg, IV. - Rituximab administered twice weekly for 5 doses at 1.5 or 3 mg/kg, IP resulted in slight inhibition in tumour growth. - Combination treatment of moxetumomab pasudotox at doses of 75, 150 or 300 µg/kg with rituximab at 3 mg/kg demonstrated tumour growth inhibition equivalent to moxetumomab pasudotox alone, with no significant benefit of combination.
In vivo Anti-tumour efficacy (non-GLP) Study No:	Karpas422, a human DLBCL xenograft model in SCID mice Female CB17 SCID mice, n=10/group IV (GCR-8015) and IP (rituximab)	Objective: To Evaluate the antitumour efficacy and tolerability of moxetumomab pasudotox when administered at different dose levels and schedules in subcutaneous Karpas422 diffused large B-cell lymphoma xenograft model Results:

ONC8015-0007	Tumour model: Human Karpas422 diffuse large B-cell lymphoma cancer cells (1 × 10^7 Karpas422 cells (100 µLvolume, SC)) were implanted subcutaneously in female CB-17 SCID mice Doses: Moxetumomab pasudotox at 150 µg/kg, 300 µg/kg, and 600 µg/kg dosed on schedules of 3 types: daily (qd) (150 and 300 µg/kg), every other day (qod) (all dose levels) and qod with a 6 day dosing holiday (150 µg/kg, 300 µg/kg). Rituximab was dosed at 10 mg/Kg twice weekly for 5 doses. Endpoints: Tumour volumes (electronic caliper) and body weight measurements were recorded twice a week.	**Efficacy of Moxetumomab Pasudotox at the every other day dose schedule in a Karpas422 Diffuse Large B-cell Lymphoma Xenograft Model**  - Comparable regressions of tumour growth were observed with every other day dosing at 300 µg/kg for 21 doses (delta TGI 107%), and at 600 µg/kg qod for 9 doses (delta TGI 102%). - Results indicate that in this model, dosing at 300 µg/kg was superior to 150 µg/kg on the schedules compared, with 300 µg/kg delivered for 21 doses qod resulting in the greatest delta TGI

A summary of supportive literature publications describing *in vitro* and *in vivo* studies of primary pharmacodynamics with moxetumomab pasudotox are listed in ***Table 3***.

Table 3 Supportive pharmacodynamic studies with moxetumomab pasudotox

Key Data	Literature Reference
Binding affinity of moxetumomab pasudotox to recombinant CD22 or malignant B-cells	Salvatore et al 2002; Ho et al 2005
CD22 expression on B-cell tumour cell lines	Alderson et al 2009
CD22 expression on HCL tumour cells	D'Arena et al, 2000; Jasper et al, 2011; Olejniczak et al, 2006; Robbins et al, 1993; Shao et al, 2013; Dorken et al, 1986
CD22 expression on normal B-cells	Jasper et al, 2011
Cytotoxicity of moxetumomab pasudotox on patient-derived malignant cells	HCL: Weldon et al, 2015; Salvatore et al, 2002 CLL: Weldon et al, 2009; Salvatore et al,2002 ALL: Mussai et al, 2010; Hansen et al, 2010; Mueller et al, 2016
Cytotoxicity of moxetumomab pasudotox on B-cell malignant cell lines	Salvatore et al, 2002; Bang et al, 2005; Ho et al, 2005; Alderson et al 2009; Weldon et al, 2009; Mueller et al, 2016
Specificity of cytotoxicity of moxetumomab pasudotox on non-CD22-expressing cell lines	Salvatore et al, 2002; Bang et al, 2005; Hoet al, 2005
ADP ribosylation of EF2 by moxetumomab pasudotox	Bang et al, 2005; Ho et al, 2005
Protein synthesis inhibition by moxetumomab pasudotox	Salvatore et al, 2002; Bang et al, 2005; Ho et al, 2005; Weldon et al, 2009; Alderson et al 2009; Hu et al, 2013; Wei et al, 2012; Wei et al, 2013; Mueller et al, 2016
Tumour xenograft growth inhibition by moxetumomab pasudotox	Bang et al, 2005; Alderson et al 2009; Weldon et al 2009; Hansen et al, 2010
Binding of moxetumomab pasudotox to human and cynomolgus PBMC	Alderson et al 2009
In vivo cytotoxicity on B-cells of moxetumomab pasudotox treated cynomolgus monkeys	Wang et al, 2013

ADP = adenosine diphosphate; ALL = acute lymphoblastic leukaemia; CD22 = cluster of differentiation 22; CLL= chronic lymphocytic leukaemia; EF2 = elongation factor 2; HCL = hairy cell leukaemia; PBMC = peripheral blood mononuclear cells.

Secondary pharmacodynamic studies

No specific secondary pharmacodynamics studies have been conducted with moxetumomab pasudotox (see discussion on non-clinical aspects).

Safety pharmacology programme

Safety pharmacology endpoints were incorporated into the design of toxicology studies. Potential effects following single and repeated dosing with moxetumomab pasudotox in cynomolgus monkeys on the cardiovascular system were evaluated by performing electrocardiograms (ECGs), measuring blood pressure, heart rate and capillary refill times, effects on the respiratory system were evaluated by measurement of respiratory rate and effects on the central nervous system (CNS) were evaluated by daily clinical cage side observations and by measurement of rectal body temperature.

Table 4 Safety pharmacology studies with moxetumomab pasudotox (CAT-8015)

Type of study, GLP, Study no	Species, Gender and no/grp	Method of Admin, Duration of dosing	Doses (mg/kg)	Safety pharmacology findings
CV/CNS/Respiratory GLP	Cynomolgus monkeys	13-Week Repeat-Dose IV Bolus Toxicity, Toxicokinetics, and	0, 0.135, 0.405 & 1.35	Cardiovascular:

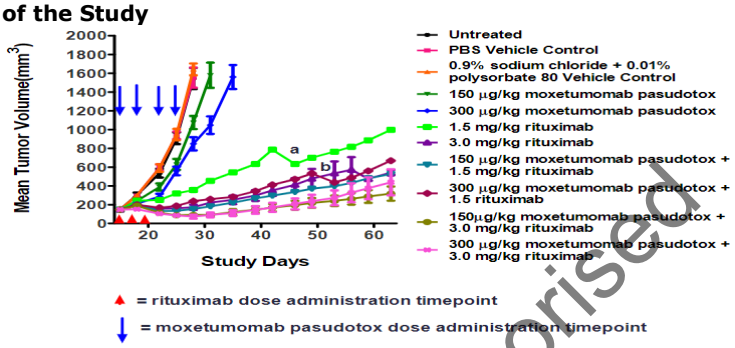
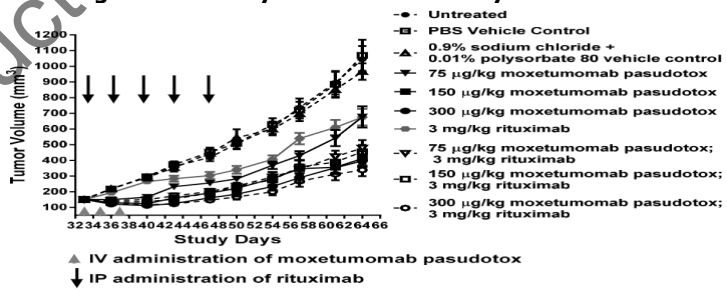
Type of study, GLP, Study no	Species, Gender and no/grp	Method of Admin, Duration of dosing	Doses (mg/kg)	Safety pharmacology findings
Study 20009858	5/sex/group Anesthetised	Pharmaco-dynamics Study with moxetumomab pasudotox in cynomolgus monkeys with 6-Week Recovery Period Methods: 6-lead ECG recordings were obtained during the predose period; on Day 1: 15 minutes (± 1 0 min.) postdose and Day 87: 15 minutes (± 10 min.) postdose. Endpoints: Veterinary Physical Examinations Respiratory rates, heart rate, body temperature on predose period, Days 3, 14, and 88, and conducted for recovery animals on Day 130.; Clinical observations were recorded daily during the dosing phase	mg/kg, 3 X/week, IV	No CAT-8015-related changes in blood pressure parameters occurred during the dosing phase of the study. One 0.405 mg/kg male (Animal No. 3004) had infrequent ventricular premature complexes on Day 1 (2 ventricular premature complexes) and Day 87 (5 ventricular premature complexes) of the dosing phase at 15 minutes postdose. The ventricular premature complexes in this single animal were considered likely a spontaneous normal variant; there were no histopathologic changes in the heart. No other abnormalities in rhythm and no other electrocardiographic changes were found in this study <u>CNS:</u> Neurological examinations were conducted on Day 14 and two findings were noted. One 1.35 mg/kg female (Animal No. 4502) was noted with moderate generalised tremors, which were also noted in clinical observations and considered related to CAT-8015. Another 1.35 mg/kg female (Animal No. 4501) had decreased visual placing reactions in both legs, but normal postural reactions in proprioceptive positioning and tactile placing reactions. The findings in this animal were not considered related to CAT-8015. <u>Clinical observations:</u> Animal No. 3703 (0.405 mg/kg) was observed as thin on Days 14 and 88 and had a decreased body temperature on Day 88 which correlated with the low food consumption, hunched appearance, and body weight loss observed in this animal within the last 18 days of the study. The findings in this animal were considered related to CAT-8015. On Day 14, Animal No. 4605 (1.35 mg/kg) had slight skin sloughing of all digits on the feet (similar to two early necropsy 1.35 mg/kg animals) which was considered related to CAT-8015 administration; however, this effect was transient. <u>Respiratory:</u> There were no moxetumomab pasudotox-related findings in these evaluations at doses up to 1.35 mg/kg. <u>Plasma exposure:</u> Day 1 Cmax was 3.31 ± 0.296 µg/mL for the 0.135 mg/kg dose, 10.5 ± 1.44 µg/mL for the 0.405 mg/kg dose, and 34.0 ± 4.58 µg/mL for the 1.35 mg/kg dose. Day 1 AUC(0-inf) were 3.19 ± 1.04, 13.2 ± 9.07, and 23.5 ± 4.72 µg·hr/mL for the 0.135, 0.405, and 1.35 mg/kg dose, respectively. Clinical Cmax: 435 ng/mL

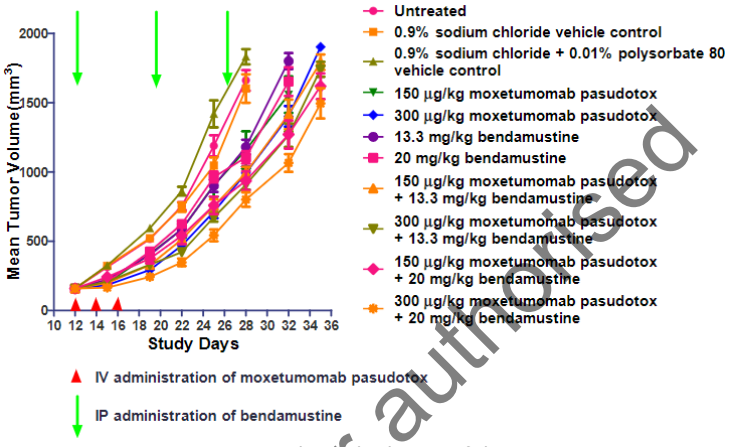
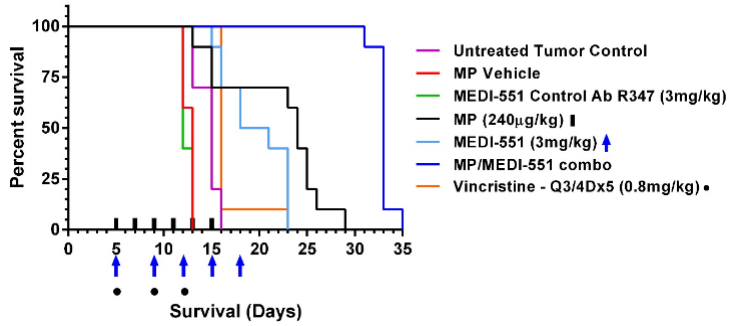
Type of study, GLP, Study no	Species, Gender and no/grp	Method of Admin, Duration of dosing	Doses (mg/kg)	Safety pharmacology findings
				Clinical ($AUC_{0\text{-last}}$): 820 ng·hr/mL Exposure margins: 24-fold at dose 0.405 mg/kg on day 1
CV/CNS/Respiratory GLP Study ACY00040 (GRT0001) On this GLP study, toxicokinetic and anti-drug antibody bioanalyses were not conducted in accordance with GLP regulations.	Cynomolgus monkeys 3-5 /sex/group	2-cycle IV toxicity study with moxetumomab pasudotox in cynomolgus monkeys Methods: 6-lead ECG recordings were obtained prior to treatment, at Day 19 (all animals), within 1 hour of dosing, and prior to necropsy on Day 47. Endpoints Veterinary Physical Examinations Respiratory rates, heart rate, body temperature on predose period, Day 20 and Day 48 for recovery animals prior to necropsy. Clinical observations were recorded daily during the dosing phase	0, 0.135, 0.405 & 1.35 mg/kg, 3 X/week in Week 1 and Week 3 with a 28-day recovery; IV	There were no moxetumomab pasudotox-related effects upon physical (including a record of general condition, rectal body temperature, respiratory rate, heart rate), ophthalmic, or electrocardiographic examinations through the highest dose tested (1.35 mg/kg, IV) Plasma exposure: Day 1 Cmax was 4.86 ± 0.513 µg/mL for the 0.135 mg/kg dose, 11.11 ± 1.47 µg/mL for the 0.405 mg/kg dose, and 22.96 ± 4.22 µg/mL for the 1.35 mg/kg dose. Day 19 Cmax was 3.79 ± 0.77 µg/mL for the 0.135 mg/kg dose, 9.81 ± 3.43 µg/mL for the 0.405 mg/kg dose, and 16.92 ± 6.37 µg/mL for the 1.35 mg/kg dose. Clinical Cmax:435 ng/mL Exposure margins: >52-fold at dose 1.35 mg/kg on day 19

Pharmacodynamic drug interactions

Four *in vivo* studies in three xenograft mouse models were conducted to evaluate the anti-tumour activity of moxetumomab pasudotox in combination with rituximab, an anti-CD20 antibody with ADCC activity, or an investigational anti-CD19 monoclonal antibody targeting another B-cell marker, or bendamustine, an alkylating agent used for the treatment of CLL and lymphomas.

Table 5 *Pharmacodynamic drug interaction studies with moxetumomab pasudotox (CAT-8015, GCR-8015*

Study	Setup	Objectives and results
In vivo Anti-tumour activity (non-GLP) Study No: ONC8015-0003	Daudi human Burkitt's lymphoma CB17 SCID mouse xenograft tumour model. Female SCID mice, n=10/group Tumour model: SCID mice were each injected subcutaneously in the right flank with 1 × 10^7 Daudi cells (100 µL) Doses: Moxetumomab pasudotox single bolus: 150, 300 µg/kg; IV, every other day for a total of 3 doses. Rituximab intraperitoneally (IP) 1.5 or 3 mg/kg, twice a week for a total of 4 doses Vehicle: PBS control Endpoints: Tumour volumes and body weight measurements were recorded twice a week.	Objective: Evaluate the antitumour efficacy of moxetumomab pasudotox when administered either as monotherapy or in combination with rituximab in Daudi, a human Burkitt's lymphoma xenograft model, in SCID mice. Results: **Efficacy of Moxetumomab Pasudotox in Combination with Rituximab in the Daudi Burkitt's Lymphoma Xenograft Model Including the Recovery Phase of the Study**  Data points represent mean and the error bars represent the standard error of the mean. PBS = phosphate buffered saline. -The combination of moxetumomab pasudotox with rituximab resulted in tumour regressions in 10-20% of mice, while no regressions were observed when either agent was used alone. - At Day 28, the combination of 3 doses of moxetumomab pasudotox administered QOD with 1.5 mg/kg rituximab at doses of 150 µg/kg or 300 µg/kg increased the percent dTGI to 99.5% and 93.6%, respectively, from a dTGI of 34.1% and 50.2%, respectively for moxetumomab pasudotox treatment alone and a dTGI of 85.2% with 1.5 mg/kg rituximab alone.
In vivo Anti-tumour activity (non-GLP) Study No: ONC8015-0005	Karpas422 DLBCL xenograft model in SCID mice Female CB17 SCID mice, n=10/group Tumour model: Human Karpas422 diffuse large B-cell lymphoma cancer cells were injected SC (1 × 10^7 Karpas422 cells, 100 µL) Doses: Moxetumomab pasudotox QOD x 3: 75, 150, 300 µg/kg; IV Rituximab 3 mg/kg, IP, twice per week, for a total of 5 doses Vehicle: 0.9% sodium chloride + 0.01% polysorbate 80 or PBS Endpoints: Tumour volumes and body weight measurements were recorded twice a week.	Objective: Evaluate anti-tumour efficacy of moxetumomab pasudotox as a monotherapy and in combination with rituximab in Karpas422, a human diffuse large B-cell lymphoma, xenograft model in SCID mice Results: **Efficacy of Moxetumomab Pasudotox in Combination with Rituximab in the Karpas422 Human Diffuse Large B-cell Lymphoma Xenograft Model Including the Recovery Phase of the Study**  Data points show mean and standard error of the mean.IP = intraperitoneal; IV= intravenous; PBS = phosphate buffered saline. - A dose-dependent inhibition of tumour growth was shown with both moxetumomab pasudotox and CAT-3888 in a JD38 xenograft model. - In the moxetumomab pasudotox dose groups, at doses≥ 75 µg/kg, there was a dose-dependent decrease in tumour volume and tumour suppression occurred until Study Day 66. - No additional benefit of treatment with the combination of moxetumomab pasudotox with rituximab was observed.

Study	Setup	Objectives and results
In vivo Anti-tumour activity (non-GLP) Study No: ONC8015-0004	CA46 Burkitt's lymphoma xenograft model. Female CD17 SCID mice, n=10/group Tumour model: Human CA46 Burkitt's lymphoma cancer cells, SC injection of 1 × 10^7 CA46 cells (100 µL) Doses: Moxetumomab pasudotox QOD x 3: 150, 300 µg/kg; IV Bendamustine 13.3 or 20 mg/kg mg/kg, IP, once a week, for a total of 3 doses Vehicle: 0.9% sodium chloride + 0.01% polysorbate 80 or PBS Endpoints: Tumour volumes and body weight measurements were recorded twice a week.	Objective: Evaluate the antitumour efficacy of moxetumomab pasudotox when administered either as monotherapy or in combination with bendamustine in CA46, a human Burkitt's lymphoma xenograft model, in SCID mice. Results: **Efficacy of Moxetumomab Pasudotox in Combination with Bendamustine in the CA46 Burkitt's Lymphoma Xenograft Model Including the Recovery Phase of the Study**  Data points represent mean and standard error of the mean. IP = intraperineal; IV = intravenous - At Day 28, the end of the dosing phase treatment with 150 µg/kg or 300 µg/kg moxetumomab pasudotox resulted in a dTGI of 30.7% (p = 0.018) and 42.3% (p < 0.001), respectively in comparison to the 0.9% sodium chloride vehicle control - In comparison to the 0.9% sodium chloride vehicle control, monotherapy with either 13.3 mg/kg or 20 mg/kg bendamustine resulted in similar dTGI of 29.3% (p = 0.005) and 34.4% (p < 0.001), respectively - The combination of moxetumomab pasudotox and bendamustine showed no significant difference in tumour growth inhibition or delay of tumour re-growth for the combination compared to what was observed when administered as single agents.
In vivo Anti-tumour efficacy (non-GLP) Study No: ONC8015-0010	Disseminated 697 ALL NOD.Cg-Prkdcscid Il2rgtm1Wjl/SzJ (NSG) mouse xenograft model Female NSG mice, n=10/group Tumour model: human 697 ALL cell line was injected IV with 200ul (1x10^7 cells). Doses: Moxetumomab pasudotox QOD x 6: 240 µg/kg; IV MEDI-551: 3 mg/kg, IP, twice weekly for total 5 doses (human anti-CD19 mAb) Endpoints: Median survival time	Objective: T Evaluate the antitumour efficacy of moxetumomab pasudotoxboth alone and in combination with MEDI-551 in the disseminated 697 acute lymphoblastic leukaemia (ALL) model Results: **Efficacy of moxetumomab pasudotox as survival of NSG mice bearing the disseminated 697 ALL model following treatment with a combination of moxetumomab pasudotox and MEDI551.**  Data points represent the survival of individual subjects(n=10)within the study.MP =moxetumomab pasudotox. - The combination treatment of moxetumomab pasudotox with MEDI-551 resulted in significantly increased survival (p<0.0001) when compared to either the moxetumomab pasudotox or MEDI-551 single agent treatment groups

2.3.3. Pharmacokinetics

Single dose pharmacokinetics

Single-dose PK of moxetumomab pasudotox has been investigated in non-GLP studies following iv administration to non-tumour-bearing and JD38 CD22-expressing tumour-bearing Ncr athymic nude mice, Sprague Dawley rats and Cynomolgus monkeys. Results are presented in ***Table 6***.

Table 6: Single iv bolus dose pharmacokinetic parameters of moxetumomab pasudotox (ELISA)

Species/ Study ID	Dose (mg/kg)	AUC0-inf (µg.h/mL)	AUC0-last (µg.h/mL)	Cmax (µg/ml)	C0 (µg/ml)	Cl (ml/min)	T1/2 (h)	Vss (ml)
Non-tumour mice **Tumour-mice** NRT0012/ GCOR-05-043-0184	0.5	4.37	4.22	7.28	7.63	0.040	0.42	1.37
		4.57	4.32	8.22	9.19	0.038	0.48	1.49
SD Rat NRT0013/ GCOR-05-044	0.25	4.12	4.08	5.57	5.93	0.228	0.609	10.6
Cynomolgus monkey NRT0003/NRT000/ 7043-101	0.1	2.03	1.92	2.78	2.92	2.39	0.563	107
	0.5	8.13	8.05	11.7	12.4	2.83	0.621	131
	2	32.2	32.1	42.5	44.7	3.26	1.20	182

Mouse: Moxetumomab pasudotox exhibited a monophasic disposition profile in mice. The PK profiles of moxetumomab pasudotox were similar in non-tumour- and tumour-bearing mice, suggesting the implanted tumour had no impact on the distribution and elimination of moxetumomab pasudotox in this model. The t1/2 was approximately 0.45 hours. The Vss approximated the plasma volume, suggesting restricted tissue distribution of moxetumomab pasudotox.

Rat: Moxetumomab pasudotox disposition in rats was monophasic (samples measurable for 4 hours postdose) with limited tissue distribution. The total body CL of moxetumomab pasudotox was 0.23 mL/min and the plasma t1/2 was 0.6 hours.

Cynomolgus monkey: Analysis of moxetumomab pasudotox concentration-time data showed that plasma moxetumomab pasudotox disposition was biphasic in cynomolgus monkeys. The PK exposure was slightly under dose proportional, and the Vss (107 to 182 mL) was close to the plasma volume. The systemic CL of moxetumomab pasudotox was 2.4 to 3.3 mL/min with t1/2 ranging from 36 to 72 minutes. There was no observed gender difference in drug exposure.

Immmunogenicity assessments were only performed in the 2 mg/kg dose group. In this group, all animals had a positive ADA-response 10 days postdose. The immune response was specific for moxetumomab pasudotox, with immunodepletion values > 79% for all 4 animals. ADA titres were relatively low, ranging from 1:90 to 1:484, but were increased compared to predose. One of 4 monkeys tested positive for neutralising antibodies.

Repeat dose pharmacokinetics

The repeat-dose toxicokinetics of moxetumomab pasudotox have been investigated following iv administration to cynomolgus monkeys in the two cycle GLP study (three times weekly dosing, every other week for 3 weeks) and the 13-week GLP study (three times weekly dosing). The study designs and toxicokinetic results are presented and discussed in repeat dose toxicity studies section.

In general, exposure values in monkeys increased with increasing doses, suggesting linear PK within the tested dose range (0.135-1.35 mg/kg/dose). Mean terminal elimination half-life values were approximately 1.02 to 2.77 in the 13-week study. Plasma concentrations of moxetumomab pasudotox declined after repeated dosing, in correlation with monkeys developing neutralising ADAs. There were no quantifiable concentrations of moxetumomab pasudotox detected during the post-dose observation periods.

Comparability of PK and PD parameters for process 1 and process 2 manufactured material in cynomolgus monkey (AAO00109)

A study was conducted in cynomolgus monkeys following iv administration (n=12 per group) to compare the moxetumomab pasudotox materials manufactured from Process 1 and Process 2. A 1 mg/kg dose of each process material was administered via slow bolus iv injection on Day 1, 3 and 5. The animals were evaluated for clinical signs, cage side observations and food consumption, and changes in body weight (Days -8 and -1, and weekly thereafter starting on Day 7), serum chemistry parameters (Day -14), and haematology and flow cytometry parameters (Days -14, -7, 1, 2, 3, 5, 8, 15, 22, 29, and 32). Blood samples were collected for PK and PD (CD22) analysis at various time points after dosing on Days 1, 3, and 5 and later in the study. Moxetumomab pasudotox and ADAs were analysed using the validated ECL assays. Animals were continued on study without further dosing and then released from the study on Day 33.

The mean non-compartmental PK parameter values were similar for animals receiving Process 1 or Process 2 of moxetumomab pasudotox (***Table 7***). The t1/2 of moxetumomab pasudotox was 1 hour and thus similar to t1/2 after a single dose to cynomolgus monkeys. Since the 90% confidence intervals of Cmax, AUC0-t, and AUC0-inf geometric mean ratios were all within the 80% to 125% range, the PK of Process 1 and Process 2 moxetumomab pasudotox were considered comparable in cynomolgus monkeys. On Day 32, all animals dosed with Process 1 or 2 moxetumomab pasudotox were immunopositive against moxetumomab pasudotox.

Table 7: Comparability of PK parameters for process 1 and process 2 manufactured material in cynomolgus monkey (AAO00109)

Parameters	Moxetumomab pasudotox Material	Geometric Mean (% CV)	Ratio of Geometric Mean (%) [90% CI]
C_{max} (ng/mL)	Process 1	19200 (11.9)	102 [94.8-110]
	Process 2	19600 (8.79)	
AUC_{0-t} (ng•h/mL)	Process 1	14600 (13.6)	101 [91.1-111]
	Process 2	14700 (14.7)	
AUC_{0-inf} (ng•h/mL)	Process 1	14700 (13.4)	100 [91.4-111]
	Process 2	14800 (13.9)	

Parameter values rounded to 3 significant figures

AUC_{0-inf} = area under concentration time curve from time zero to infinity; AUC_{0-t} = area under concentration time curve from time zero to last timepoint; C_{max} = maximum observed concentration; CI = confidence interval; CV = coefficient of variation.

On Day 1, at the 24-hour post dose time point, total lymphocyte counts had decreased by 46% and 55% compared to Day 1 predose levels for animals dosed with Processes 1 and 2 of moxetumomab pasudotox, respectively. There were moxetumomab pasudotox -related decreases in CD20+ and CD22+ lymphocyte counts after each day of dosing for both groups. Lymphocyte counts and CD20+ and CD22+ lymphocyte counts returned to prestudy levels by Day 22 for both groups.

Organ distribution studies have not been conducted. From the single dose pharmacokinetic studies, the Vss suggested restricted tissue distribution of moxetumomab pasudotox.

No studies on metabolism and on excretion have been conducted. Non-clinical pharmacokinetic drug interaction studies have not been conducted.

2.3.4. Toxicology

Single dose toxicity

No single-dose toxicity studies were conducted with moxetumomab pasudotox, and toxicity after a single dose was evaluated as part of repeat-dose toxicity studies.

Repeat dose toxicity

The repeat-dose toxicity of moxetumomab pasudotox was evaluated following IV administration in 3 studies conducted in cynomolgus monkeys. These included a non-GLP range-finding study (Report ACY00039); a study to determine potential toxicity of 2 cycles of moxetumomab pasudotox when administered via IV with a 28-day recovery period (Report ACY00040); and a 13-week repeat-dose (three times per week [TIW]) IV bolus toxicity, toxicokinetics (TK), and pharmacodynamics study with moxetumomab pasudotox with a 6-week recovery period (Report 20009858). These latter 2 studies are GLP-compliant studies that are considered pivotal studies for First in Human clinical trials and moxetumomab pasudotox registration, respectively.

Table 8 Non-pivotal repeat dose toxicity study

Study Title/Study No./ Testing Facility	Type of Study/ GLP	Species/Strain (Sex and N)	Doses (mg/kg)/ Duration of Dosing/ ROA	Noteworthy Findings
A Pilot Dose Escalation Range-Finding Study of GCR-8015 and GCR-3888 in Cynomolgus Monkeys NRT0008 Charles River Laboratories Worcester, MA, USA	Repeat-dose toxicology range-finding study Non-GLP	Cynomolgus monkey Group 1: N = 2M&2F Group 2: N = 1M&1F	Group 1: GCR-8015 at 0.12, 0.36, 1.2, 2.4, and 4.8 Group 2: GCR-3888 (BL22) at 0.12, 0.36, 1.2, 2.4, and 4.8 Escalating doses were administered as a slow IV bolus injection (over 1 minute) on Days 1, 3, 5, 8 and 11	Only slight differences between animals treated with GCR-3888 (BL22) and GCR-8015 in terms of clinical observations, food consumption, body weights, and haematological and serum chemistry endpoints Clinical observations of dry flaky and erythemic skin, and lethargy or hunched posture were only observed after dosing with 2.4 mg/kg of either test article and considered possibly related to test article administration. Test article-related changes in haematology (increases in WBC, neutrophils and large unstained cells) and serum chemistry parameters (marked increases in transanimases and triglycerides) observed on Day 14 (72 hours after dosing with 4.8 mg/kg of either test article) and decreases in albumin and albumin to globulin ratios. LDH increases relative to baseline were seen but there were no effects upon troponin suggesting the increases were not related to the damage of heart tissue. Changes in clinical pathology parameters, specifically increases in APLY counts and decreases in ALB levels.

ALB = albumin; APLY = absolute polymorphonuclear neutrophil; F = female; GCR-3888 or BL22 = CAT-3888; GCR-8015 = moxetumomab pasudotox; GLP = Good Laboratory Practice; IV = intravenous; LDH = lactate dehydrogenase; M = male; ROA = route of administration; WBC = white blood cell.

Pivotal studies

- **A Study to Determine the Potential Toxicity of Two Cycles of as and GCR-8015 and GCR-3388 (BL22) When Administered to Cynomolgus Monkeys via Intermittent IV Injections with a 28-day Recovery Period**

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOAEL (mg/kg/day)
GRT0001 GLP (not TK and ADA bioanalysis)	Cynomolgus 3M/3F per group +2M/2F for recovery	moxetumomab pasudotox 0 0.135 mg/kg/dose 0.405 mg/kg/dose 1.35 mg/kg/dose GCR-3388 1.35 mg/kg/dose IV bolus 3x per week every other week for 3 weeks (6 doses in total	28 days 28 days recovery	0.135 mg/kg

Noteworthy findings

Plasma concentrations: All animals in treatment groups were exposed to moxetumomab pasudotox during the study. C_{max} values increased with increasing doses. Moxetumomab pasudotox concentrations were similar in male and female animals. Mean C_{max} values were similar throughout the study; however, individual concentrations in many animals decreased over time. A trend toward decreased C_{max} values after repeated administration of was observed following Day 5.

ADA: Positive antibody responses were seen by Day 20 in virtually all treated monkeys by Day 20. Binding of the test article to its ligand (CD22) was inhibited in the majority of animals by Day 20 at doses > 0.405 mg/kg and this neutralisation response was time and concentration dependent. On Day 20 in monkeys treated at doses > 0.405 mg/kg, drug-induced WBC and neutrophil increases (seen on Day 6) were usually not evident in those animals with clearly positive neutralisation responses.

PD results: Flow cytometry analyses revealed dose-dependent reductions in $CD3^{-}CD22^{+}$ and $CD3^{-}CD20^{+}$ lymphocytes. The effects were most prominent on Day 6 of the treatment period and were reversible following the recovery period. Accordingly, most evident in high-dose GCR-815 females, the relative diminution of the magnitude of reductions in these parameters on Day 20 versus Day 6 was often correlated with the presence of a neutralising antibody response.

Clinical observations: Increased incidence of dry flaky skin and mild skin erythema at all doses. Slight body weight reductions (males at ≥0.405 mg/kg, females at 1.35 mg/kg.

Haematology: Slight to moderate, transient reductions in one or more red blood cell parameters (statistically significant in males and females at doses of > 0.135 mg/kg) and absolute and/or relative lymphocytes (statistically significant in males at all dose levels and females at doses of ≥ 0.405 mg/kg). Increase in total WBC and neutrophil counts, correlating with the formation of ADA. Reduction in haemoblogin in females at 1.35 mg/kg. No remarkable haematology findings after recovery period.

Serum chemistry: Slight increase in APTT (females 1.35 mg/kg). Reduction in albumin and A/G ratio. Elevations in LDH and globulin (females >0.405 mg/kg). Transient increases in ALT, AST and total LDH activity, most prevalent in animals receiving ≥0.405 mg/kg. No remarkable serum chemistry alterations at the end of recovery period.

Urinalysis: Largely unremarkable. Large amounts of urinary glucose and urinary protein in one high-dose female administered GCR-815 that exhibited moderate renal tubular necrosis and minimal renal tubular apoptosis at necropsy.

Gross pathology and organ weights: No findings

Microscopic pathology:Increase in apoptosis of the renal proximal tubular epithelial cells (≥0.405 mg/kg). Acute tubular necrosis (one female at 1.35 mg/kg).

- **A 13-week Repeat-dose (TIW) IV bolus Toxicity, Toxicokinetics, and Pharmacodynamics Study with Moxetumomab Pasudotox in Cynomolgus Monkeys with a 6-week Recovery Period**

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOAEL (mg/kg/day)
20009858 GLP	Cynomolgus 3M/3F per group +2M/2F for recovery	moxetumomab pasudotox 0.135 mg/kg/dose 0.405 mg/kg/dose 1.35 mg/kg/dose IV bolus 3x per week	13 weeks 6 week recovery	0.135 mg/kg

Noteworthy findings

Toxicokinetics

Dose (mg/kg):	Control	0.135 mg/kg/dose	0.405 mg/kg/dose	1.35 mg/kg/dose
TK Parameters [a]				
Day 1				
C_{max} (µg/mL)	BLQ	3.31 ± 0.296	10.5 ± 1.44	34.0 ± 4.58
$AUC_{0\text{-}inf}$ (µg·h/mL)	BLQ	3.19± 1.04	13.2 ± 9.07	23.5 ± 4.72

Day 22				
C_{max} (µg/mL)	BLQ	0.572 ± 0.440	5.07 ± 2.88	24.4 ± 9.66
$AUC_{0\text{-}inf}$ (µg·h/mL)	BLQ	0.726 ± 0.514	9.51 ± 9.48	57.9 ± 30.4
Day 85				
C_{max} (µg/mL)	BLQ	0.0267 ± 0.0553	2.55 ± 3.42	10.2 ± 15.9
$AUC_{0\text{-}inf}$ (µg·h/mL)	BLQ	NR	49.7	234

Human exposure: In study CD-ON-CAT-8015-1053 following IV administration of the third dose (Day 5) in Cycle 1, the mean (standard deviation) Cmax and area under the curve from time zero to the last measurable concentration (AUC0-last) values were 435 ng/mL (233) and 820 ng·hr/mL (721), respectively

Exposure margin at NOAEL (0.135 mg/kg):

	Cmax	AUC
Day 1	7.6	3.9
Day 22	1.3	0.89

ADA

Almost all serum samples (including from controls and predose samples) tested positive for ADA. The positive ADA signals most likely resulted from pre-existing antibodies directed against the PE domain of moxetumomab pasudotox. Prior exposure of study animals to PE was expected, but an increase in assay signal compared with baseline was observed in samples from treated animals after repeat dosing, which is consistent with the development of an ADA response. The results suggested that moxetumomab pasudotox was immunogenic when given TIW to cynomolgus monkeys.

PD results: Pharmacodynamic analyses showed dose-independent drug-related decreases in B-lymphocyte (CD3-/CD20+) and T-lymphocyte (CD3+/CD20-) values at 4 hrs post dosing on Days 1 and 22, with predose values on Days 22 and 29 trending towards recovery to baseline values.

Mortalities: One female dosed at 0.405 mg/kg was euthanised on Day 5 after two doses and replaced. This animal had clinical signs of decreased activity, lethargy, hunched appearance and tremors in the left leg. During veterinary evaluation on Day 4 low body temperature, excessive urination and red stained urine was observed. Review of pre-dosing records revealed that this animal had approximately 30 days of persistent bleeding in the peri-vaginal area and pre-existing urinary tract disease was suspected. Occult blood and RBC were noted in the pre-dosing and Day 5 urinalysis for this animal. Postmortem during gross examination a large bladder stone was observed within the urethral outflow tract causing obstruction and ureter dilation. Microscopically there were findings in the kidneys, urinary bladder and vagina consistent with chronic outflow obstruction and irritation from the bladder stone that were not considered related to moxetumomab pasudotox administration. Evaluation of blood smears from this animal revealed a concomitant infection with Plasmodium.

Four cynomolgus monkeys dosed at 1.35 mg/kg including one male and 3 females were euthanised on Days 63, 35, 37, and 63, respectively. Clinical signs in these animals included decreased activity, hunched appearance, low food consumption, favoring legs, tremors in feet and/or legs, toes in flexion, poor coordination, and/or general body tremors. Increased clinical chemistry enzymes (AST, ALT, ALP, and/or LDH) indicative of striated muscle and/or liver injury were considered moxetumomab pasudotox-related. For the haematologic parameters, decreases in platelet counts were considered to be moxetumomab pasudotox-related. Decreases in red cell mass in 2 animals was considered to have an equivocal relationship to moxetumomab pasudotox administration based on concurrent Plasmodium infection. Mildly increased white blood cell (WBC) and neutrophil counts and fibrinogen and decreased albumin were attributed to an inflammatory response. The albumin and albumin to globulin (A/G) ratio were moderately decreased and the globulin increased indicative of an acute-phase protein response. In addition, there was a marked decrease in the platelet count with a responsive megakaryocytic

hyperplasia suggestive of increased platelet destruction/utilisation. There was a moderate decrease in WBC and neutrophil counts in one male animal which were considered to have an uncertain relationship to moxetumomab pasudotox administration. Glycosuria without concomitant hyperglycemia suggestive of renal tubular injury was considered to be moxetumomab pasudotox-related. Minimal to mild prolongations of the coagulation parameters, prothrombin time and/or activated partial thromboplastin time (APTT) were considered to have an uncertain relationship to moxetumomab pasudotox administration.

Clinical observations: Tremors in the legs, arms, or whole body within 30 minutes post dose in all 10 animals at 1.35 mg/kg, 6 of 10 animals at 0.405 mg/kg, and 3 of 10 animals at 0.135 mg/kg. In the majority of cases, the tremors showed reduced incidence when antihistamine (diphenhydramine) administration was administered pre dose. Body weight loss (M 1.35 mg/kg). Reduced food consumption (1.35 mg/kg). Transient occurrences of poor coordination, favouring or disuse of legs/feet, toes held in flexion, decreased activity and hunched appearance (predominantly in the higher dose groups).

There were no drug-associated changes in ophthalmology, electrocardiography, blood pressure measurements, clinical pathology parameters (coagulation and urinalysis), and organ weights.

Haematology: Mild to moderate decrease in the mean lymphocyte counts. Dose-dependent mild to moderate increase in mean neutrophil counts. Minimal changes in the albumin, A/G ratio, and/or globulin consistent with an acute-phase protein response to inflammation during the treatment period.

Microscopic pathology: Minimal to moderate myocardial degeneration, necrosis and/or haemorrhages in the heart. Increased injection site inflammation and/or haemorrhage, and minimal to marked decreased size of lymphoid follicles within the spleen, mesenteric and mandibular lymph nodes, and Peyer's patches. All the animals had liver findings consisting of degeneration/regeneration, diffuse rarefaction, or necrosis of hepatocytes. Other treatment- associated findings occurred sporadically in the early termination animals and included hypercellular gray matter in the brains of two animals, characterised by gliosis in both, minimal infiltrates of neutrophils and apoptotic/necrotic cell debris in one animal, and lymphocytic infiltrates in the other.

Effects on reproductive organs: All male and female animals assigned to the study were sexually mature cynomolgus monkeys based on evaluation of the femoral physis and histopathological evaluation of reproductive tract. Following 3 months of dosing, there were no moxetumomab pasudotox-related adverse effects on male or female reproductive organs, the surrogate endpoint for fertility.

Genotoxicity

Genotoxicity studies with moxetumomab pasudotox were not performed (see discussion on non-clinical aspects).

Carcinogenicity

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

Reproduction Toxicity

Dedicated studies to evaluate potential adverse effects of moxetumomab pasudotox on fertility and early embryonic development, embryofetal development, prenatal and postnatal development (including maternal function) have not been conducted. The applicant has proposed a waiver for conducting either an embryofetal developmental (EFD) or an enhanced pre- and postnatal developmental (ePPND) toxicity study.

In lieu of either of these developmental toxicity studies an alternative assessment of risk for developmental toxicity of moxetumomab pasudotox was provided that was based on consideration of 1) the patient population; 2) the absence of findings in reproductive organs and tissues of sexually mature cynomolgus monkeys treated with moxetumomab pasudotox for 13 weeks; 3) the results of a tissue cross reactivity study with moxetumomab pasudotox using panels of human and cynomolgus monkey tissue; 4) the biophysical properties of moxetumomab pasudotox and impact on placental transfer; 5) salient published non-clinical data related to CD22 knock-out mice; 6) CD22 expression during B cell maturation in the embryo/fetus, and 7) an orphan indication (data not shown).

For fertility evaluations, the potential for adverse effects of moxetumomab pasudotox on male and female fertility was assessed by evaluation of the reproductive tract (organ weights and histopathological evaluations) of sexually mature male and female cynomolgus monkeys in the 13-week repeat-dose toxicology study (Report 20009858). Histopathological evaluation of the reproductive tract confirmed that all male and female animals assigned to the study were sexually mature cynomolgus monkeys. Following up to 3 months of dosing, histopathological evaluation of male and female reproductive organs including mammary gland; epididymis, prostate, seminal vesicle, and testis; and cervix, ovary, oviduct, uterus and vagina revealed no effects on reproductive organs or tissues due to moxetumomab pasudotox administration at doses up to 1.35 mg/kg.

Toxicokinetic data

Toxicokinetic data was included in the pivotal toxicology studies.

Local Tolerance

Local tolerance was assessed by irritation score (Draize) evaluations and histological evaluation of moxetumomab pasudotox iv administration sites in the repeat dose toxicity studies.

There were no moxetumomab pasudotox-related injection site changes during the dosing phase. Histopathology post-mortem revealed slightly increased inflammation, muscular degeneration, and haemorrhages at injection site compared to vehicle. Changes were reversible and considered non-adverse.

Other toxicity studies

Study to assess the potential cross reactivity of moxetumomab pasudotox with a selected panel of human and cynomolgus tissues (2563/001 (GRT0003), GLP)

The objective of the study was to assess using immunohistochemical techniques, the potential cross-reactivity of moxetumomab pasudotox, with histologically prepared acetone fixed cryosections The human tissue panel used 3 donors per tissue and included cryosections of all tissues recommended in the 1997 United States Food and Drug Administration "Points to Consider in the Manufacture and Testing of Monoclonal Products for Human Use" and in Annex II of the European Union's Committee for

Medicinal Products for Human Use Guideline "Production and Quality Control of Monoclonal Antibodies." Similarly, the cynomolgus monkey tissue panel used 3 donors per tissue and included cryosections of the same tissues found in the human tissue panel with the exception of placenta. Concentrations of moxetumomab pasudotox tested were 3.85, 7.7, and 15.4 µg/ml.

In human tissues only there was specific diffuse positive staining of individual cells of undetermined cell type in the pituitary.

In both human and cynomolgus monkey tissues specific positive staining of B cells in many tissues was observed. In addition, some diffuse non-granular staining within the white matter of brain (cortex and cerebellum) and spinal cord disuse samples, which was considered non-specific.

Limited Tissue Cross-Reactivity Study of CAT-8015 with Normal Human Pituitary Tissue (IM1426, GLP)

The objective of the study was to further evaluate the potential cross-reactivity of moxetumomab pasudotox with cryosections of normal human pituitary gland tissue (4 human donors). Concentrations of moxetumomab pasudotox tested: 3 and 30 µg/ml. Moxetumomab pasudotox was compared to two other mouse antibodies targeted at B-cells, a mouse anti-human CD19 antibody and mouse anti-human CD22 antibody. Tonsils were used as the positive and negative control tissue for this study because it contained both CD22-positive lymphocytes as well as CD22-negative stromal fibroblasts. An assay control slide, where the primary antibody was omitted, was used as the negative control.

No moxetumomab pasudotox-specific staining was present in the limited human pituitary tissue panel. Commercial anti-CD22 or anti-CD19 antibodies did not stain pituitary tissue. Intense staining of CD22-expressing lymphocytes by moxetumomab pasudotox, mouse anti- CD19 and anti-CD22 antibodies was observed in cryosections of human tonsils.

2.3.5. Ecotoxicity/environmental risk assessment

No ERA was submitted (see discussion on non-clinical aspects).

2.3.6. Discussion on non-clinical aspects

The non-clinical studies were, in general, performed in accordance with legal requirements and available guidelines. Scientific advice on non-clinical developmental aspects has been received and the CHMP advice have been sufficiently followed.

Pharmacology

Limited *in vitro* and *in vivo* studies were conducted to pharmacologically characterise moxetumomab pasudotox. During the development of moxetumomab pasudotox three different process materials have been used. It is unclear when the manufacturing changes of the product occurred and, in the context of the non-clinical safety evaluation, whether the process development affected the target specificity and biological activity of the different moxetumomab pasudotox batches. Although a discussion on the comparability between Process 1 and 2 (used in the non-clinical studies) and commercial clinical Process 3 material would have been expected, additional information is not requested considering that an expected pharmacological activity (e.g. depletion of CD22 expressing B-cells) is demonstrated in the pivotal toxicity studies, indicating that the animals were sufficiently exposed (see also Quality section).

The applicant originally claimed that CD22 is a B-lymphocyte restricted transmembrane protein with a higher receptor density in hairy cell leukaemia (HCL) cells relative to normal B cells. This is supported by publications by D'Arena et al (2000) and Jasper et al (2011). In study NRT0018, however, CD22

expression on cells from HCL patients (HC-1 cells) were comparable to expression on human donor PBMCs. Further, in a publication by Olejniczak et al (2006), CD22 expression levels on HCL-cells were significantly below normal B-cell levels. The applicant was asked to consider the findings in study NRT0018, and the CD22 expression levels reported by Olejniczak et al.

Taken together, with a CD22 expression level in HCL cell samples (n=9) similar to normal levels in the publication by Olejniczak et al and in study NRT0018, and expression levels above normal B cells in other publications (D'Arena et al 2000, Jasper et al 2011, Stetler-Stevenson and Tembhare 2011), the wording in section 5.1 of the SmPC was amended to reflect these findings as follows: CD22 is a B-lymphocyte restricted transmembrane protein with similar or higher receptor density in hairy cell leukaemia (HCL) cells relative to normal B cells.

No studies have been conducted by the applicant demonstrating pharmacodynamics effects on HCL-cells (including cells from HCL patients after receiving at least two prior systemic therapies). Hairy cell do express CD22, and in a publication by Weldon et al (2009) moxetumomab pasudotox was cytotoxic to cells from HCL patients (IC50 0.165-5.2 ng/ml). Although similar range of cytotoxicity was observed in Daudi cells *in vitro* (IC50 0.27 ng/ml, Weldon et al, 2009), Daudi tumours were less sensitive than JD38- and Karpas422-tumours *in vivo*. Thus, although binding of CD22 by moxetumomab pasudotox is required for activity, the overall response *in vivo* is neither directly correlated with CD22 expression levels, nor with *in vitro* cytotoxicity. The applicant proposes that the pharmacodynamics is likely influenced by downstream processes such as internalisation of moxetumomab pasudotox, processing to the active PE38 toxin, ADP-ribosylation of EF2, and inhibition of protein synthesis. The applicant was asked to provide a thorough discussion on these potential downstream processes leading to different susceptibility. Further, the applicant was asked to justify the lack of *in vivo* studies with tumour models with HCL cells, considering the apparent lack of correlation between CD22 expression levels, and the moderate effects observed in the Daudi model in spite of apparent potency *in vitro*, making extrapolation from *in vitro* to *in vivo* data more challenging. The applicant submitted a discussion on the downstream processes following binding to CD22, clarifying potential causes for difference in overall response to moxetumomab pasudotox between cells. In conclusion, it is acknowledged that the overall response *in vivo* is not only directly correlated with CD22 expression levels but is likely also influenced by the capacity and performance of downstream processes, such as internalisation of moxetumomab pasudotox, processing to the active PE38 toxin by furin, transport and transfer of PE38 into cytosol, ADP-ribosylation of EF2, and inhibition of protein synthesis.

Data from *in vivo* HCL models would have been preferred. But based on the relative *in vitro* activity in agreement with activity *in vivo* in other models, and considering lack of established HCL-models, the chosen approach is considered acceptable.

Secondary pharmacodynamics studies of moxetumomab pasudotox have not been conducted. Since moxetumomab pasudotox is an immunotoxin that inhibit protein synthesis, a variety of potential off-target adverse effects may occur due to e.g. cross-reactivity to a different target or non-specific uptake into cells by pinocytosis, which in turn may lead to off-target activity. The applicant was initially asked to provide a discussion on possible secondary pharmacodynamic effects of moxetumomab pasudotox. There is a lack of cytotoxic activity in CD22 non-expressing cells in *ex vivo* and *in vitro* including primary human umbilical vein endothelial cells. Therefore, *in vitro* testing may not be sensitive enough to detect cell death induced by moxetumomab pasudotox in CD22 negative cells. In the *in vivo* setting, moxetumomab pasudotox may be internalised by either the target mediated endocytosis or non-CD22 mediated pinocytosis leading release of PE38 and induction of apoptosis. The applicant considers that there is a limited risk of pinocytosis in CD22 negative cells *in vivo* due to the short half-life of moxetumumab pasudotox. However, non-target mediated toxicity has been observed in the non-clinical toxicology studies and clinical trials (kidney toxicity). It could be possible that the

observed kidney findings in humans are related to non-specific uptake by kidney tubule cells. This issue is further discussed in the toxicology section.

Dedicated studies on safety pharmacology have not been performed. Appropriate endpoints were however investigated without findings in toxicology studies. This is considered acceptable. Overall, there were no apparent safety signals from the core battery of studies in major organ systems of cynomolgus monkeys apart from clinical signs of tremors and moderate generalised tremors noted in one female animal at the highest dose tested (1.35 mg/kg, IV, 78-fold above clinical Cmax). CNS related side effects were also observed in the repeat-dose toxicity studies in monkeys which included clinical signs of decreased activity, hunched appearance, tremors and poor coordination.

Pharmacokinetics

Overall, the scope of pharmacokinetic programme is considered adequate. The non-clinical programme of pharmacokinetics studies has been carried out with moxetumomab pasudotox in mice, rats and cynomolgus monkeys after a single IV dose. The repeat dose toxicokinetics of moxetumomab pasudotox have been investigated following IV administration to cynomolgus monkeys in one 13-week GLP study (three times weekly dosing) and in one 2-cycle GLP study (three times weekly dosing, every other week for 3 weeks). Toxicokinetics was included in the pivotal toxicology studies.

Methods of analysis for determination of moxetumomab pasudotox and ADAs are in general adequate and of sufficient quality. In one of the pivotal toxicology studies in monkeys, the bioanalytical method used for toxicokinetic evaluation was not in accordance with GLP regulation. The applicant was asked to clarify on the aspects that were not according to GLP and the impact on the toxicokinetic evaluation in the GLP compliant toxicity study (ACY00040; GRT0001). Only the ECL based assays were fully validated and GLP compliant. These methods were used in the toxicokinetic part of the GLP 13-week monkey repeat dose toxicity study (20009858). The applicant commented on the GLP aspects of the bioanalytical methods used in the 3-week toxicity study (study ACY00040; GRT0001), confirming that the used method was validated according to GLP compliance. In addition, there were no GLP-compliant issues regarding the pivotal 13-week repeat-dose study (study 20009858) and the exposure data was comparable between the two GLP toxicity studies in monkeys.

In the animal PK studies only total antibody-immunotoxin complex has been measured in plasma or serum and the presence of free active toxin in plasma has not been analyzed. This issue was also raised in a CHMP scientific advice. Therefore, the fate of the moxetumomab pasudotox complex *in vivo* was further addressed. The applicant was asked to discuss the possibility of generation of active free toxin levels in the systemic circulation after administration of moxetumomab pasudotox and its potential clinical consequences for both safety and efficacy. The applicant presented a brief discussion on the possible generation of free active toxin levels in the systemic circulation after administration of moxetumomab pasudotox. In the *in vivo* setting, moxetumomab pasudotox may be internalised by either the target mediated endocytosis or non-CD22 mediated pinocytosis leading to release of PE38 and induction of apoptosis. There is a limited risk of pinocytosis in CD22 negative cells *in vivo* due to the short half-life of moxetumumab pasudotox and expected low systemic exposure. In addition, the risk for humans associated with circulating PE38 fragments is considered low since such toxin fragments lack the cell binding (Fv fragment) and membrane translocation domains (Domain II) that are required for cell killing. This question was not further pursued from a non-clinical pharmacokinetic point of view. The fate of active free toxin levels in the systemic circulation after administration of moxetumomab pasudotox and its potential clinical consequences is further discussed in the toxicology section.

It is unknown what kind of ADAs that were triggered in monkeys by treatment with moxetumomab pasudotox, since methods used for analysis could not discriminate. Neutralising effect of ADAs targeting the CD22 binding domain of moxetumomab pasudotox is established, but whether ADAs

targeting the PE-part of moxetumomab pasudotox can neutralise the pharmacodynamic effect (e.g. by reducing internalisation) is unknown. Both ADA targeting the CD22-binding domain of moxetumomab pasudotox, and ADA targeting the PE38 domain, can neutralise the pharmacodynamic effect of moxetumomab pasudotox. Neutralisation by blocking of the CD22 binding site directly, or by steric hindrance of CD22 binding, will interact with analysis of moxetumomab pasudotox in monkey plasma (capture on CD22-covered plates). In theory, neutralising ADA targeting the catalytic domain in the PE38 region may not have an impact on CD22 binding. However, this type of ADA will probably interact with the detection step in the analysis of moxetumomab pasudotox (use of ruthenium-conjugated PE-toxin antibody). Taken together, it has been clarified that ADA targeting the PE-part of moxetumomab pasudotox can be expected to be neutralising. Most likely, both ADA to CD22-binding domain and ADA to the PE38 domain will interact with detection of moxetumomab pasudotox in monkey plasma.

Toxicology

A series of repeat-dose toxicity studies have been performed in cynomolgus monkeys. Cynomolgus is a pharmacologically relevant model, as demonstrated by the reduction of CD22+ B-cells in treated animals. Two GLP compliant toxicity studies have been provided, a study with 2 cycles of treatment (3 doses per week in week 1 and 3) 13-week study with 3 doses/week. The 2-cycle study was performed with drug substance produced with an early manufacturing process (Process 1) where comparability to the commercial material has not been demonstrated. In addition, in this study the toxicokinetics analysis was not GLP compliant. The 13-week study was performed with material from Process 2. In comparison to the commercial material produced with Process 3, there is a higher amount of inactive deamidated immunotoxin in the Process 2 material. This is not considered of importance for the safety evaluation and the 13-week study is deemed as the pivotal toxicity study for this application.

In the 2-cycle study, toxicity was less severe, with histopathological findings limited to renal tubular apoptosis and necrosis. Moxetumomab pasudotox was studied in cynomolgus monkeys for 13 weeks. At doses ≥10 times the human recommended dose, minimal to moderate degeneration of heart tissue was observed microscopically without corresponding changes in ECG. At doses of approximately 34 times the human recommended dose, microscopic evidence of gliosis and axonal degeneration was observed in the brain and spinal cord, respectively, along with observations of body tremors.

The immunotoxin is immunogenic. In humans and to a lesser extent in the cynomolgus, antibodies to the toxin are present due to previous plasmodium infections. Upon treatment, the antibody titres are increasing. Since the toxin acts intracellularly, all modes for cellular uptake are important for the safety. The intended route, binding to CD22 and uptake in B-cells and B-cell derived tumours, is unlikely to be the only uptake route. The presence of ADA could provide an alternative uptake opportunity. Formation of immune complexes may lead to uptake by cells in the reticuloendothelial system. Uptake in these cells could explain some of the toxicological findings where there was evidence for both vascular involvement and an inflammatory response. An ADA-dependent mode of action may also explain the worse outcome in the 13-week study when compared to the shorter 2-cycle study.

Off-target toxicity from the uptake of the exotoxin in other cells than the target cells (CD22-expressing tumour cells and B-cells) is considered most important for the clinical safety profile. Unspecific uptake through pinocytosis is a possibility and it is plausible that the observed kidney findings are related to such uptake by kidney tubule cells. The possibility of FcR-mediated uptake of the antibody, predominantly when part of an immune complex, is acknowledged. Such possibility suggests that presence of ADA and formation of antibodies could be a driver for toxicity. No correlation between ADA levels and toxicity was observed in clinical trials. However, this analysis was not considered conclusive, due to the common presence of antibodies to the toxin before treatment.

The applicant has provided a justification for not providing data on developmental toxicity, based on a number of factors. It is agreed that the patient population is of low risk for pregnancy. Also, the information value of an EFD or ePPND toxicity study in cynomolgus is considered limited. Moreover, moxetumomab pasudotox is a large molecule and it lacks the Fc part which for monoclonal antibodies mediate placental transfer. Therefore, foetal exposure is considered unlikely. Any risk to the foetus would come from maternal effects. Nevertheless relevant warnings have been included in the SmPC as follows:

Women of childbearing potential should use effective contraception during treatment with moxetumomab pasudotox and for at least 30 days after the last dose (SmPC, section 4.6).

There are no human or animal data to assess the risk of moxetumomab pasudotox use during pregnancy. Based on its mechanism of action and observed adverse reactionseffects of moxetumomab pasudotox in non-pregnant female monkeys including body weight loss, moxetumomab pasudotox may be expected to cause maternal and embryofetal toxicity when administered to a pregnant woman. Moxetumomab pasudotox should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus (SmPC, section 4.6).

There is no information regarding the presence of moxetumomab pasudotox in human milk, the absorption and effects on the breast-fed child, or the effects on milk production. A risk to the breast-fed child cannot be excluded. A decision must be made whether to discontinue breast feeding or to discontinue Lumoxiti therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman (SmPC, section 4.6).

Animal fertility studies have not been conducted with moxetumomab pasudotox. In a 3 month repeat dose toxicity study using sexually mature cynomolgus monkeys, no adverse effects on male or female reproductive organs were observed at doses approximately 34 times the human recommended dose (SmC, section 5.3). There are no data available to directly determine the potential effects on human fertility (see section 4.6).

Moxetumomab pasudotox is a recombinant immunotoxin composed of an immunoglobulin light chain variable domain (VL) and a heavy chain variable domain (VH) genetically fused to a truncated form of Pseudomonas exotoxin, PE38. Moxetumomab pasudotox is considered to be a non-hazardous, biodegradable product. As such, the environmental risk in terms of use and disposal is considered to be negligible and in accordance with the guideline (CHMP 2006) ERA studies are not submitted. Furthermore, the assessment performed does not indicate a requirement to take special precautions during the release to the environment that will result from use in patients or disposal of the product. Therefore, it is not considered necessary to include warnings or precautions within the product information in relation to environmental risks.

2.3.7. Conclusion on the non-clinical aspects

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

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 9. Summary of study design and objectives of studies CAT-8015-1053 and CD-ON-CAT-8015-1001

Type of Study	Study Identifier/ Location of Study Report	Objectives of the Study	Study Design and Type of Control	Test Product; Dosage Regimen; Route of Administration	No. of Subjects Dosed	Population	Duration of Treatment	Study Status; Type of Report
Safety and Efficacy	CD-ON-CAT-8015-1053 [a] / 5.3.5.2	Safety and Efficacy	Phase 3, multicenter, open label, single-arm	Moxetumomab pasudotox (Process 3) 40 µg/kg D1, 3, 5 of each 28-day cycle; IV	80 total	Relapsed or refractory HCL ≥ 18 years	Until CR or for up to 6 cycles, PD, initiation of alternative anticancer therapy, unacceptable toxicity	Complete; Full CSR
Safety and Efficacy	CAT-8015-1001/ 5.3.5.2	Safety/Tolerability, PK, Immunogenicity, Pharmacodynamics, and Antitumor Activity	Phase 1, open label, non-controlled, multicenter, interpatient dose escalation and dose expansion	Moxetumomab pasudotox: (Process 1, 2) 5 µg/kg 10 µg/kg 20 µg/kg 30 µg/kg 40 µg/kg 50 µg/kg D1, 3, 5 of each 28-day cycle; IV	49 total 3 3 3 3 4 33	Relapsed or refractory HCL ≥ 18 years	Until CR, PD, initiation of alternative anticancer therapy, unacceptable toxicity, development of nAbs, or other reasons to discontinue therapy	Complete; Full CSR

2.4.2. Pharmacokinetics

The clinical pharmacology of moxetumomab pasudotox has been investigated in patients from 9 clinical studies. Two studies were conducted in adult patients with relapsed/refractory HCL (CAT-8015-1001 and CD-ON CAT-8015-1053). The remainder of the studies were conducted in other CD22-expressing B-cell malignancies including 2 studies in paediatric patients with acute lymphoblastic leukaemia.

Only clinical pharmacology data from studies CAT 8015 1001 and CD-ON-CAT-8015-1053 are assessed since PK from HCL indications differs from other indications since hairy cells express 10–20 times higher levels of CD22 compared to other indications (eg, ALL and CLL). Also for ADA, there are differences in patient immune status, ADA methods, and inclusion/exclusion criteria in the remaining studies that make the ADA data from other diseases not relevant to HCL.

Three manufacturing processes have been used during the development of moxetumomab pasudotox. Process 1 (frozen) and Process 2 (lyophilised) were used for nonclinical and clinical manufacturing, and both materials were administered in the Phase 1 HCL study (CAT-8015-1001). Process 3 material has higher bioactivity relative to Process 2 material. Process 3 material was used in the pivotal Phase 3

HCL study (CD-ON-CAT-8015-1053). Because of the higher bioactivity and reduction in deamidation of Process 3 material compared with Process 2 material, a dose adjustment was implemented to ensure that a similar amount of biologically equipotent active product would be delivered to patients receiving Process 3 material compared to patients receiving Process 2 material.

- *Analytical methods*

Analysis of moxetumomab pasudotox

Two sandwich ELISA methods (one at Quest Pharmaceutical Services and one at Intertek) were set-up and validated for quantifying moxetumomab pasudotox in human K2EDTA plasma. In addition, one non-validated biological assay was used at National Cancer Institute for analysis of moxetumomab pasudotox.

The analytical method at Intertek was used for analysis of plasma samples from the phase 3 study CD-ON-CAT-8015-1053. Plasma concentrations of moxetumomab pasudotox (CAT8015) were determined with a sandwich ELISA method. Standards, controls and test samples are incubated with CAT8015 anti-ID Antibody (G09.4) which has been immobilised on a 96-Well Plate. After incubation, unbound material is washed away and CAT8015 is detected with anti-CAT8015 (IP-49) biotinylated antibody. Following incubation, unbound antibody is washed away and allowed to bind to streptavidin HRP. The colour development visualised with tetramethylbenzidine (TMB) is proportional to the concentration of CAT8015. Selectivity was acceptable in normal human plasma samples but not acceptable in plasma samples from individuals with HCL. Pre-existing anti-PE-antibodies present in drug naïve plasma interfered with moxetumomab pasudotox measurement leading to low recovery in samples with high signals. Satisfactory between- and within-run accuracy and precision were shown for LLOQ, low, medium and high QC sample concentrations (40, 75, 250 and 1000 ng/ml). The calibration curve consisted of six standard points in duplicate (range 40-1200 ng/ml) and two anchor points (20 and 2400 ng/ml). Dilution linearity was evaluated for dilution factors up to 2500. Long-term stability data in plasma (for 743 days at –70°C and 92 days at –20°C) was referred to a previous study (QPS project number 244-1001) and no long-term stability was tested in this study. Parallelism between the calibration curve and serially diluted study samples have not been evaluated. Satisfactory method performance during study sample analysis in study CD-ON-CAT 8015-1053 was demonstrated. Incurred sample reanalysis was not performed.

Immunogenicity methods

In the phase III Study CD-ON-CAT-8015-1053, results from three assays (screening, neutralising antibody, specificity) and titres were reported. The applicant used a tiered strategy for immunogenicity testing with first an ADA screening of samples using a meso-scale discovery (MSD)-based electrochemiluminescent (ECL) bridging immunoassay. ADA positive samples were subsequently evaluated in a cell-based neutralisation assay (nAb). nAb positive samples were further characterised for ADA titres and specificity (CD22 or PE38).

- **Pharmacokinetic data analysis**

Non-compartmental analyses

Non-compartmental pharmacokinetic data analysis (NCA) was performed with moxetumomab pasudotox plasma concentrations determined with the MedImmune assay. Due to sparse PK sampling in **study 1053**, the terminal phase parameters was allowed to be estimated by linear regression using only two log concentrations versus time, of which one could be the maximum concentration (C_{max}).

- **Evaluation and Qualification of models**

Population pharmacokinetic analysis

Methods

The objectives of this analysis were to characterise the PK of moxetumomab pasudotox in adult patients with relapsed/refractory HCL, evaluate the potential impact of covariates, and assess the potential relationships between moxetumomab pasudotox exposure and efficacy and safety endpoints.

All individual concentrations from study CAT-8015-1001 and study CD-ON-CAT-8015-1053 were pooled along with moxetumomab pasudotox dosing information and covariates. Population modelling was performed using NONMEM v. 7.3. The covariate-PK relationships were then assessed with the stepwise covariate model (SCM)– a forward inclusion phase (if $p<0.01$) and a backward elimination phase (if $p<0.001$). The first PK measurement after Cmax that was reported below the LLOQ for the PK assay, was set to 0.5*LLOQ and included in the modelling. The rest was discarded.

Additional post-hoc analysis was conducted on phase 3 PK data (CD-ON-CAT-8015-1053) to evaluate the impact of covariates that were missing, not usable or not evaluated in phase 1 study but were available for phase 3 study. The impact of covariates including ADA titre was evaluated on clearance after the first dose (CL2). Baseline CD19+B-cell counts were not available for ~21 percent of patients evaluated in the post-hoc analysis. The relationship between patient baseline CD19+B-cell counts and moxetumomab pasudotox clearance on cycle 1 day 1 (CL1) was assessed graphically instead.

Results

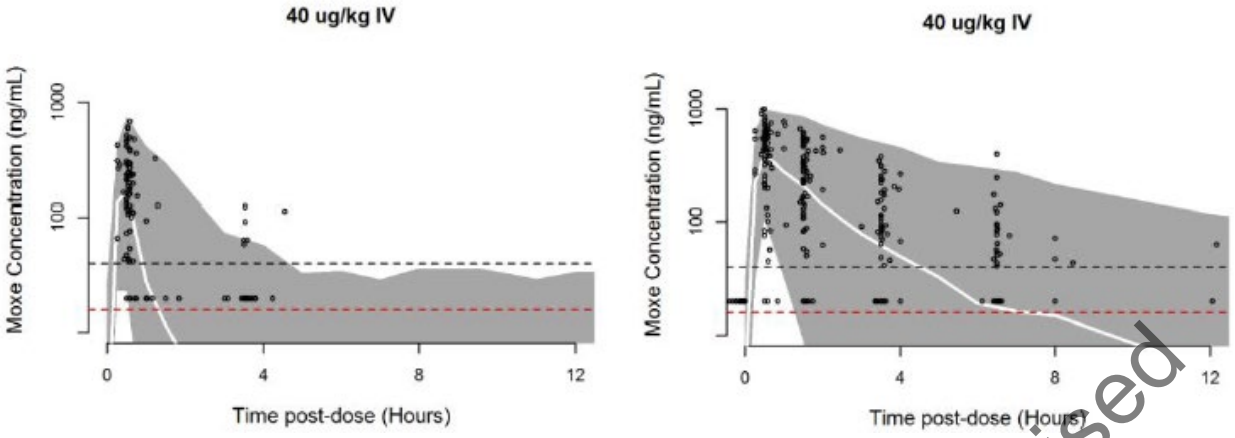
The data set included 4639 moxetumomab pasudotox concentrations from 49 subjects in the Phase 1 study and 1055 concentrations from 74 subjects in the Phase 3 study. Of these, 40% were below the quantification limit.

A one-compartment linear model with separate clearance parameters for the first dose and subsequent doses was used to describe the data. None of the covariates tested (body weight, age, race, gender, process material, immunogenicity, baseline spleen size, baseline bone marrow involvement, previous rituximab use) were identified as significant in the covariate analysis, therefore the final model was same as the base model (***Table 10***). Visual predictive check plots of the final PK model versus time after previous dose on C1D1, C1D5, C2D1, and C3D1 are presented in ***Figure 1***.

Table 10. Summary of PK parameters from the base and final PK model

Parameters	Point Estimate	Standard Error	%RSE
Systemic Clearance 1 (CL_1) (L/hr)	24.7	3.71	15.0%
Systemic Clearance 2 (Cl_2) (L/hr)	3.76	0.601	16.0%
Volume of Distribution (V) (L)	6.51	0.357	5.48%
Variance (CL_1)	1.34 (CV = 116%)	0.228	17.0%
Variance (CL_2)	1.19 (CV = 109%)	0.189	15.9%
Variance (V)	0.140 (CV = 37.4%)	0.0207	14.8%
Covariance (CL_1 and CL_2)	0.910 (R = 0.721)	0.202	22.2%
Covariance (CL_1 and V)	0.294 (R = 0.679)	0.0652	22.2%
Covariance (CL_2 and V)	0.355 (R = 0.870)	0.0566	15.9%
Additive Error (MEDI Assay) (ng/mL)	20.5	0.461	2.25%
Additive Error (NCI Assay) (ng/mL)	8.95	0.359	4.01%
Proportional Error	0.414	0.00297	0.717%

%RSE is percent relative standard error (100% x SE/EST), CV: coefficient of variation, SD: standard deviation.



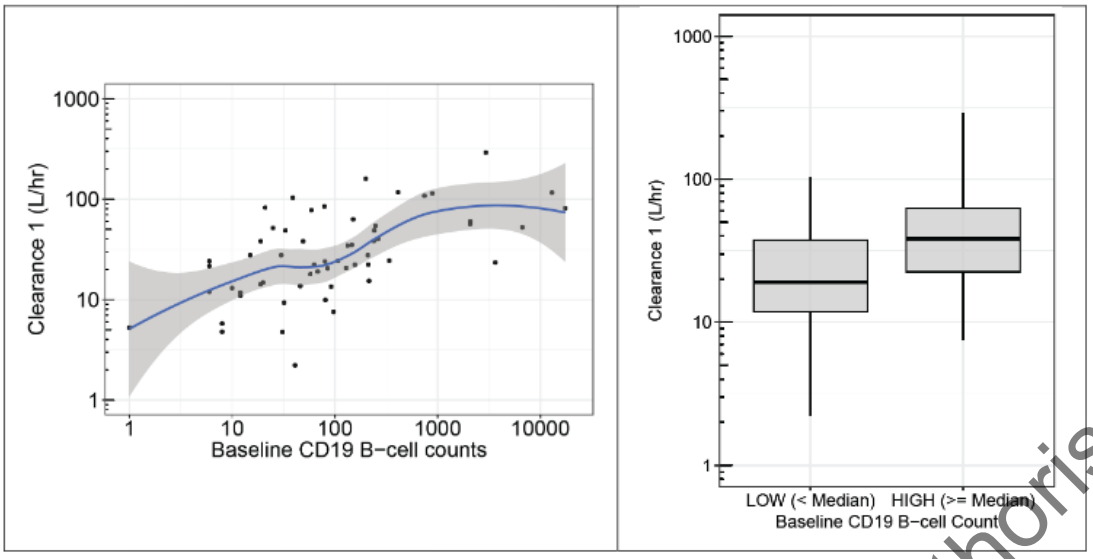
Black and red dashed lines represent the LLOQ for MEDI assay (LLOQ=40 ng/mL) and NCI assay (LLOQ=16 ng/mL), respectively. The grey shaded area represents the area between the 5th and 95th percentiles from the simulations. The solid white line represents the 50th percentile of the simulations.

Figure 1. Visual predictive check of the final PK model versus time after previous dose on for Cycle 1 Day 1 (left) and for Cycle 1 Day 5 (right), shown for the proposed dose level only (40 µg/kg).

Post-hoc analysis of data from Study CAT-8015-1053

A high prevalence of ADA and nAb to moxetumomab pasudotox was observed in subjects with HCL. In study CD-ON-CAT-8015-1053, the ADA prevalence rate was 87.5% (70/80 subjects) with nAbs against moxetumomab pasudotox detected in 67 (83.8%) of 80 subjects. Among these 67 subjects, ADAs were 98.5% specific to the PE38 binding domain and 53.7% specific to the CD22 binding domain. The ADA incidence rate (treatment-emergent ADA) was 65.8%. Titres were generally low at baseline but markedly increased after multiple dosing over time. Baseline CD19+B-cell counts were not available for ~21 percent of patients in study CD-ON-CAT-8015-1053.

The previously established model structure in the pooled analysis was adopted for the post-hoc analysis. The parameter estimates of CL1 and V were fixed to those previously estimated (see ***Table 10***). The final model for the post-hoc analysis included ADA titre >10240 as a covariate on CL2. The typical value of CL2 was estimated to be 4.69L/hr. The NAb positive patients with ADA titre that exceeded 10240 showed ~4-fold increase in moxetumomab pasudotox clearance. The IIV of moxetumomab pasudotox remained high for clearance estimates.



The solid blue line represents the loess smoothing line and the grey shaded area represents the 95% confidence interval.

Figure 2. Relationship between model predicted moxetumomab pasudotox clearance from first dose (CL1) and baseline CD-19+B cells

Absorption

Not applicable since moxetumomab pasudotox is administered intravenously.

Distribution

In the population PK analysis based on pooled phase 1 and phase 3 data the volume of distribution was estimated to be 6.5L with 37.4% inter-patient variability, however, the population PK model is currently considered inadequate. Plasma protein binding studies have not been performed.

In the population PK analysis including pooled phase 1 and phase 3 (which currently is not considered adequate), the clearances were estimated to be 24.7L/hr and 3.76L/hr with their corresponding inter-patient variability, as 116% and 109% respectively.

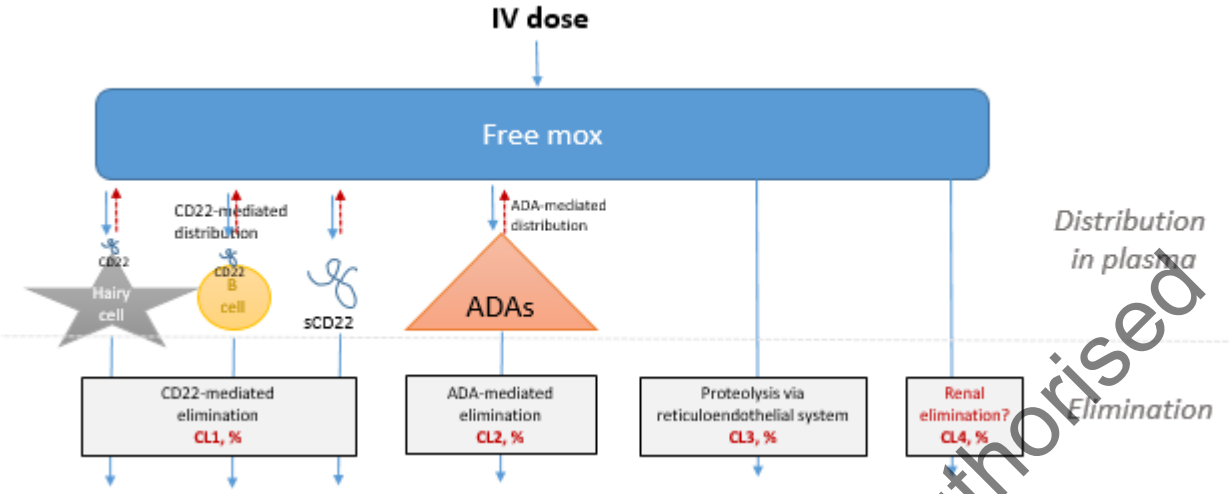
Elimination

The exact pathway through which moxetumomab pasudotox is metabolised has not been characterised. The distribution and elimination pathways of moxetumomab pasudotox have neither been characterised. Based on its mechanism of action and molecular size (63 kDa), elimination pathways were presumed by the applicant to include target-mediated drug disposition (TMDD) via CD22 and proteolysis via the reticuloendothelial system. When ADA developed post-treatment, the presence of ADA was associated with reduced concentration levels.

Moxetumomab pasudotox is above the typical limit for when protein drugs are expected not to undergo renal excretion (~60 kDa), and specific studies on renal excretion were not performed.

A schematic diagram of the current understanding of the disposition of moxetumomab pasudotox has been illustrated in the figure below. Missing key components are marked in red and include the binding kinetics and relative affinities to hairy cell- and B-cell bound CD22, soluble CD22 and ADAs,

approximate relative contributions of the various elimination pathways (CL1-4) to the total clearance of moxetumomab pasudotox, and how these change over time.



Dose proportionality and time dependencies

Table 11. Summary of PK parameters following IV administration of moxetumomab pasudotox in HCL subjects in study CAT-8015-1001.

Cohort	5 µg/kg		10 µg/kg		20 µg/kg		30 µg/kg		40 µg/kg		50 µg/kg	
	Day 1	Day 5	Day 1	Day 5	Day 1	Day 5	Day 1	Day 5	Day 1	Day 5	Day 1	Day 5
n	3	3	3	3	3	3	2	3	4	4	12	12
T_{max} (hr)	0.508 (0.383-0.633)	0.500 (0.250-0.550)	0.467 (0.450-0.483)	0.467 (0.417-0.483)	0.367 (0.233-0.500)	0.250 (0.250-0.533)	0.467 (0.417-0.517)	0.517 (0.417-0.617)	0.267 (0.250-0.417)	0.475 (0.417-1.00)	0.417 (0.250-0.500)	0.417 (0.283-0.517)
C_{max} (ng/mL)	77.5 (70.0)	103 (40.5)	86.3 (41.9)	135 (49.1)	49.4 (43.3)	161 (136)	443	420 (384)	290 (107)	701 (328)	435 (260)	738 (316)
$AUC_{0\text{-last}}$ (hr·ng/mL)	75.5 (71.6)	179 (155)	31.0 (20.9)	90.2 (52.3)	72.4 (96.0)	93.2 (113)	897	909 (861)	183 (146)	1640 (1270)	511 (585)	1920 (1290)
CL (mL/kg/hr)	32.6	13.3	NA	68.9	49.1	66.3	43.9	18.7	91.8	45.5 (47.6)	106 (80.2)	33.3 (37.5)
$t_{1/2}$ (hr)	0.643	2.20	NA	0.369	3.77	0.404	1.00	1.86	0.375	1.66 (0.928)	0.799 (0.755)	2.06 (0.980)
AUC AR	2.62 (1.22-4.02)		3.08 (2.61-3.39)		3.09 (0.0328-6.15)		1.93 (1.20-2.66)		12.4 (1.99-25.0)		3.63 (1.73-21.8)	
C_{max} AR	1.11 (0.934-1.29)		1.73 (1.39-1.73)		2.12 (0.839-3.40)		1.48 (1.30-1.66)		2.51 (1.47-3.26)		1.58 (1.09-3.94)	

AR=accumulation ratio; $AUC_{0\text{-last}}$=area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration; CL=systemic clearance; C_{max}=maximum observed concentration; HCL=hairy cell leukemia; n=sample size; NA=not applicable; $t_{1/2}$=half-life.

Notes: PK parameters are listed as mean (standard deviation); T_{max} (time of maximum observed concentration) is listed as hours after dosing and as median (range); AR are listed as median (range). Standard deviation is reported only when n≥3; range is only reported when n≥2.
Source: Section 5.3.5.2, CAT-8015-1001 CSR, Appendix 16.1.13

Time dependency within Cycle 1

The average peak plasma concentration was approximately 2-fold higher on Cycle 1 Day 5 (third dose) compared with Cycle 1 Day 1 (***Figure 3***).

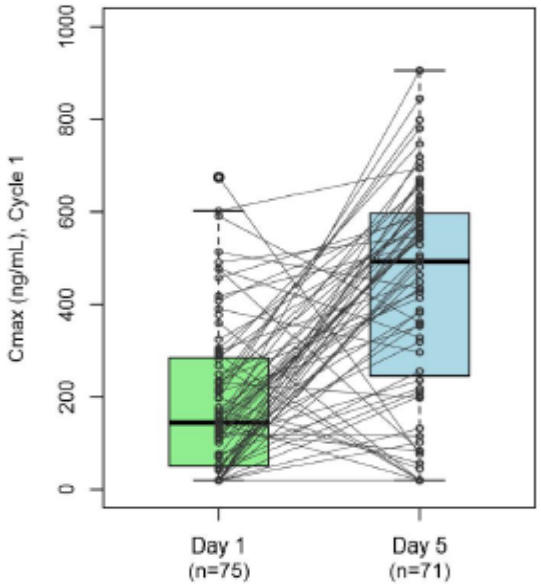


Figure 3. Moxetumomab pasudotox exposure comparison between the first (Day 1) and third dose (Day 5) of Cycle 1 in Study 1053.
Round symbols represent individual values; solid black lines connect respective individual values as observed on Days 1 and 5. Upper and lower boxplot whiskers indicate Q3+1.5 x IQR and Q1– 1.5 x IQR, respectively, where IQR is the interquartile range (Q3 – Q1).

Time dependency after Cycle 1

After the third dose (Cycle 1 Day 5), mean peak moxetumomab pasudotox levels were generally consistent between dosing intervals as expected due to the short $t_{1/2}$. Mean C_{max} (standard deviation) was estimated at 192 ng/mL (162), 435 ng/mL (233), 379 ng/mL (262), 366 ng/mL (289), and 315 ng/mL (340) for Cycle 1 Day 1, Cycle 1 Day 5, Cycle 2 Day 1, Cycle 3 Day 1, and Cycle 5 Day 1, respectively (see ***Figure 4***).

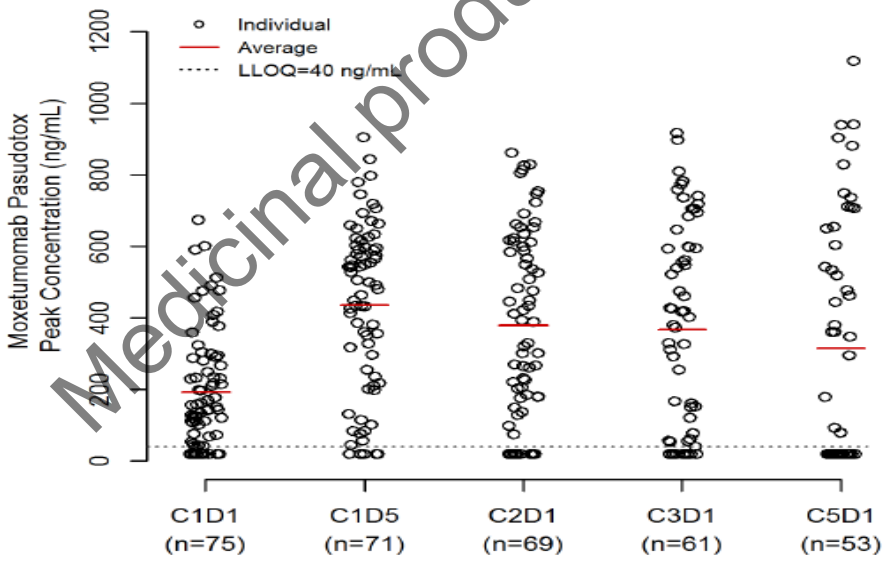


Figure 4. Mean peak concentration levels of moxetumomab pasudotox after each cycle in Study 1053

The presence of ADAs post baseline was associated with statistically significant ($p<0.05$) changes in PK exposure (Cmax) at later cycles (Cycle 3 and beyond), which is consistent with increasing titre levels.

As shown in ***Figure 5***, ADA-positive patients in Cycles 3 and 5 exhibited approximately 4- and 26-fold lower median Cmax, respectively, compared to ADA-negative patients.

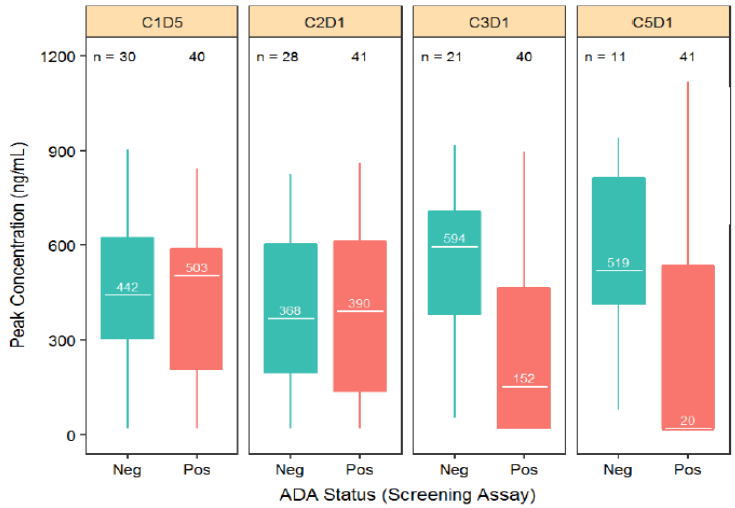


Figure 5. Effect of post-baseline ADA status by cycle on moxetumomab pasudotox exposure in Study 1053
IQR=interquartile range (Q3 – Q1, Neg=ADA negative; Pos=ADA positive.Note: ADA category represents patient's ADA status at each cycle. Upper and lower boxplot whiskers indicate Q3+1.5×IQR and Q1–1.5×IQR, respectively.

Special populations

The number of elderly subjects (aged 65 years and above) that contributed PK data from the Pivotal Phase 3 study CD-ON-CAT-8015-1053 is presented in ***Table 12.***

Table 12. Elderly subjects contributing pharmacokinetic data

	Age 65-74 (n=30)	Age 75-84 (n=10)	Total (N=129)
Trials contributing PK data			
Study CD-ON-CAT-8015-1053 (N=80)	22	9	31

HCL=hairy cell leukaemia; ISS=Integrated Summary of Safety; PK=pharmacokinetic.
Note: There were no patients aged 85 years and above in the 2 HCL studies contributing PK data.

Dedicated studies in subjects with renal or hepatic impairment have not been conducted. The Phase 3 study included 50 patients (63%) with normal renal function, 26 patients (35%) with mild renal impairment and 4 patients (5%) with moderate renal impairment (according to creatinine clearance calculated using the Cockcroft-Gault formula). All patients had normal hepatic function, except 10 patients (12.5%) with mild hepatic impairment (according to the National Cancer Institute Organ Dysfunction Working Group criteria).

The impact of renal and hepatic impairment, gender, race, age and weight on the PK of moxetumomab pasudotox was not significant when using the population PK model based on the pooled data from the Phase 1 and Phase 3 studies.

Most subjects had normal renal function, and no subject had creatinine clearance ≤29 mL/min. Hepatic impairment was investigated in terms of single hepatic function markers and not classified according to Child-Pugh.

The applicant assesed the impact of weight (median 80 kg, range 42-123 kg) on CL2 in the population PK model, however failed due to rounding errors and did not pursue this covariate further. The relationships between body weight and NCA-derived PK parameters were assessed graphically (Day 121 response) and showed that exposure (Cmax and AUC_{0-3h}) generally increased with increasing body weight in males (***Figure 6***). In females, there were too limited data to assess any trend.

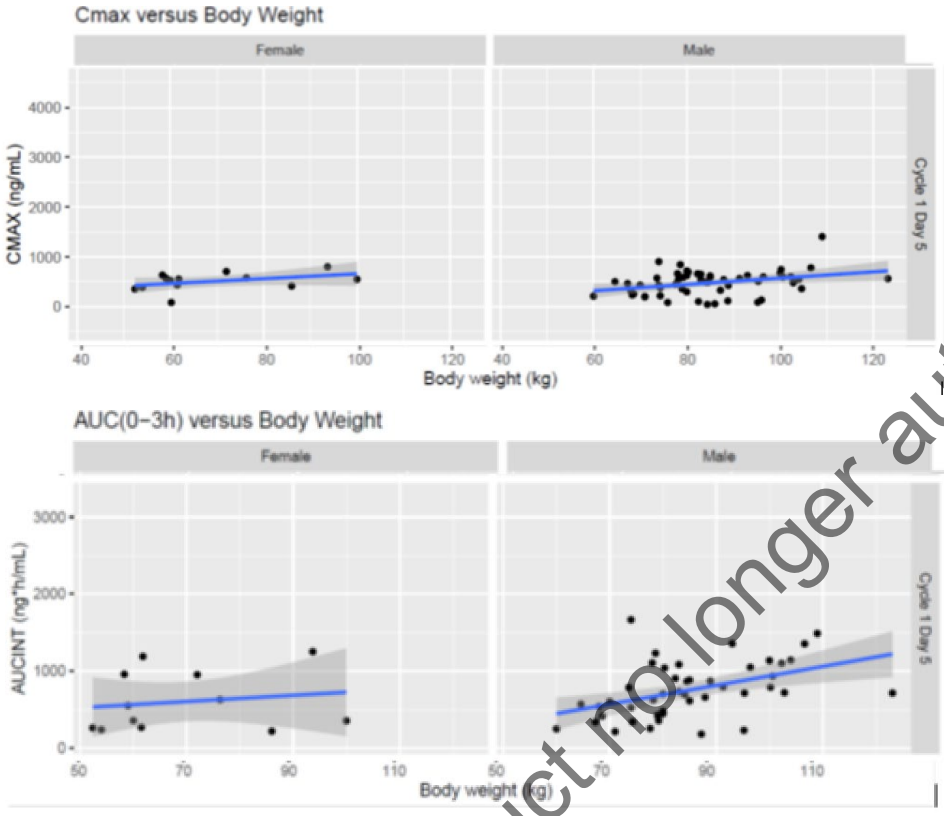


Figure 6. Body weight vs Cmax and AUC(0-3h) at Cycle 1, Day 5. The graph is stratified by gender.

Pharmacokinetic interaction studies

No pharmacokinetic interaction studies have been conducted.

Pharmacokinetics using human biomaterials

Not applicable.

2.4.3. Pharmacodynamics

The pharmacodynamic effects of moxetumomab pasudotox on CD22 expression on HCL cells in whole blood or in bone marrow (study CAT-8015-1001), soluble CD22 in serum (study CAT-8015-1001), and circulating T, B, and natural killer (NK) cells in whole blood (study CD-ON-CAT-8015-1053) were investigated. CD22 expression was investigated at 2 facilities in the US. In the latter facility the assay was not validated. Also, analysis of soluble CD22 in serum was not validated. However, the used methods are considered adequate.

- CD22 expression

At one of the US facilities, flow cytometry was used to quantify CD22 expression levels on circulating CD11c-positive, CD19-positive HCL cells. For validation, blood samples of normal donors were first used to assess the saturating concentration of moxetumomab pasudotox in order to block the CD22 binding sites. Also, stability of the assay up to 3 days was assessed. Finally, blood samples from patients with malignancies were used to confirm intra- and inter-assay precision. Samples from 3 HCL patients were analysed showing < 7% coefficient of variation for both CD22 MESF and percent saturation in intra-assay variability. The inter-assay variability was < 20 % CV for CD22 MESF and percent saturation. The preceding validation assays with blood from normal donors showed in part very high CV, due to very low values. Nevertheless, assay design is acceptable and in general, the obtained values are comparable.

- T, B, and NK Assay

A flow cytometric assay was introduced to quantify the numbers of T-cell, B-cells and NK-cells in peripheral blood. Whole blood was stained with antibody cocktails (CD3, CD4, CD8, CD16/CD56, CD19, CD45). Stability of the samples was tested. However, 20 % and 30 % of the samples had a CV >20 % after 2 and 3 days, respectively, indicating that a stability of 2 days is not guaranteed for all samples. Intra-assay precision variability is acceptable. Regarding inter-assay precision, blood from the same donor was analysed on three different collection days with at least 3-5 days apart. The inter-assay precision was quite high (CV ≤25%) and 30 % of the samples had a higher CV.

Mechanism of action

CD22 is a B-lymphocyte lineage-restricted 135-kDa transmembrane sialoglycoprotein. HCL tumour cell expression of CD22 has been reported to be approximately equal to or higher than CD22 expression on normal B cells. Moxetumomab pasudotox is a CD22-targeted immunotoxin composed of an immunoglobulin light chain variable domain (VL) and a heavy chain variable domain (VH) genetically fused to a truncated form of Pseudomonas exotoxin (PE38). Following binding to CD22, the complex is rapidly internalised and processed to release the exotoxin (PE38) which catalyses ADP-ribosylation of elongation factor-2 (EF-2), leading to apoptotic cell death. The mechanism of action has been supported by literature references and non-clinical *in vitro* and *in vivo* studies.

Primary and Secondary pharmacology

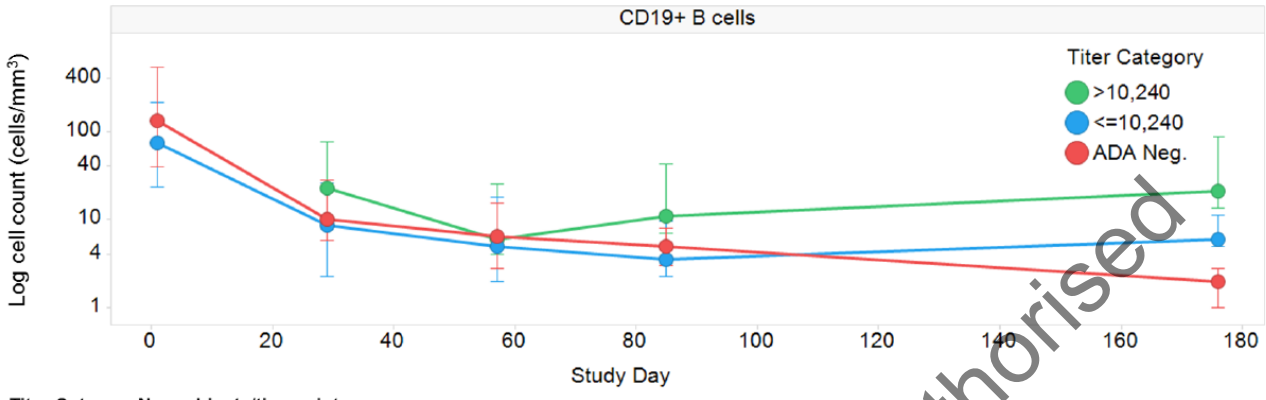
Primary pharmacology

The clinical pharmacodynamic properties of moxetumomab pasudotox have been investigated in two clinical studies conducted in adult patients with relapsed/refractory HCL. PD endpoints included lymphocyte counts in the phase III study (study 1053, process 3 product), and CD22 expression and soluble CD22 measurements in the Phase I study (study 1001, process 1 and 2 product).

Due to different PD parameters evaluated in the two studies, potential process-related effects on pharmacodynamics cannot be assessed. However, the differences between the two processes in deamidation and conformational changes within the catalytic domain of PE38 is related to different potency of moxetumomab pasudotox, without affecting binding to CD22 and internalisation.

In study 1053, median B cell quantities were reduced by 89% (<20 cells/mm3) on study day 8, remained significantly reduced throughout six treatment cycles, and returned to baseline at 181 days post-EOT. When stratified by ADA titres, the B cell counts in patients with ADA titres above 10,240 started to increase from the third treatment cycle. In ADA negative and low-titre patients, however,

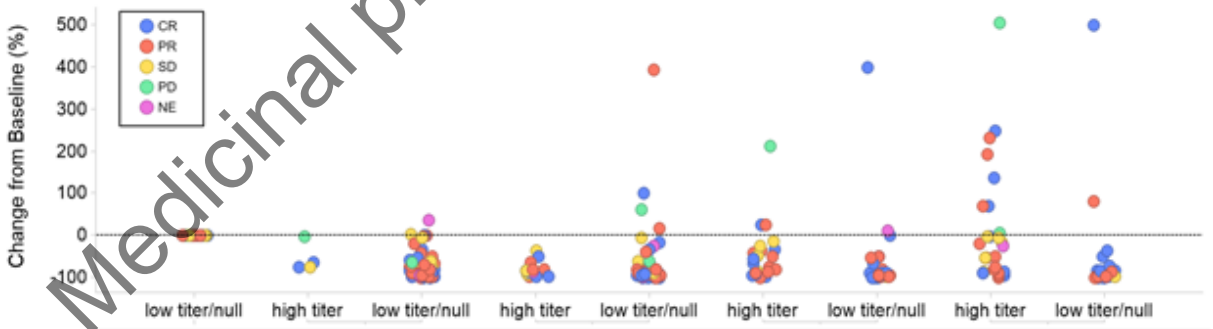
the B-cell counts remained low (low-titre) or decreased further (ADA negative) throughout the six treatment cycles (***Figure 7***). High titre ADA levels are also correlated with substantial reduction in moxetumomab pasudotox exposure levels, leading to exposure levels close to or below LoQ following repeated cycles.



Titer Cat.	No. subjects/timepoint				
>10,240	0	4	13	22	27
<=10,240	34	30	25	18	18
ADA Neg.	28	24	20	11	8

Figure 7: Median (Q3,Q1) CD19+ B cell counts stratified by ADA status over time
Cat.=category, No.= number, ADA= anti-drug antibodies >10,240 titre category includes results from ADA positive patients with nAb titre >10,240; <=10,240 titre category includes ADA positive patients with nAb titre <=10,240 and ADA positive patients that are nAb negative; ADA Neg. titre category includes results from ADA and nAb negative patients; data plotted only for patients from which ADA and CD19+ B cell data are available

When normalised by baseline CD19+ B cell values (***Figure 8***), subjects with high ADA titre demonstrated lower reduction magnitudes compared with subjects with low ADA titre/null at Cycle 5 Day 1 and EOT. However, the majority of subjects with high ADA titre continued to demonstrate CD19+ B-cell reductions below baseline at these time points (19/22 and 19/26 on Cycle 5 Day 1 and EOT, respectively). In addition, of those subjects with high-titre ADA who demonstrated CD19+ B-cell increases above baseline at EOT, 6 of 7 were confirmed complete or partial responders (CR or PR).



	Cycle 1 Day 1	Cycle 2 Day 1		Cycle 3 Day 1		Cycle 5 Day 1		End of Treatment	
	low titer/null	high titer	low titer/null	high titer	low titer/null	high titer	low titer/null	high titer	low titer/null
Count	62	4	50	13	41	22	25	26	22
Q3	0	-47.6649	-60.5992	-79.4393	-61.5145	-32.0175	-66.6667	54.1529	-83.3333
Median	0	-68.6228	-81.3793	-84.6154	-85	-52.3196	-93.3333	-20.9058	-93.75
Q1	0	-74.8168	-96.8521	-91.0377	-95.2941	-87.1872	-97.3373	-83.9379	-96.7677

Figure 8: Baseline-normalised B-cell counts stratified by ADA status (high titre or low titre/null) ADA=anti-drug antibody; CR=complete response; NE=not evaluable; PD=progressive disease; PR=partial response; Q=quartile; SD=stable disease.

In study 1001, PD parameters included CD22 expression levels on leukemic cells by flow cytometry and soluble CD22 (sCD22) quantification, to investigate the potential of biomarkers to predict any therapeutic or toxic response.

When stratified upon overall response, the CD22 expression level in peripheral blood cells appears relatively higher in subjects with CR as compared to subjects with PR, SD. However, due to small sample sizes, pooling of data across dose groups, and higher level in subjects with SD than subjects with PR in peripheral blood and bone marrow samples, a potential relation between baseline CD22 expression and overall response cannot be addressed.

CD22 is shed into the peripheral blood, and it has been suggested that soluble CD22 (sCD22) levels could be a tumour marker for HCL and treatment outcome (Matsushita et al, 2008). In a study on NHL and CLL patients (study MI-CP218), there was a clear positive correlation between sCD22 and B cell counts ($p < 0.0001$). In study 1001, baseline and pre-cycle sCD22 were reported. Due to low exposure levels for moxetumomab pasudotox shortly after dosing, pre-cycle sCD22 analyses are not expected to be hampered by circulating active substance.

When evaluated for clinical response by baseline sCD22 levels (45 patients), most of the patients with CRs and PRs had low baseline sCD22 levels. Further, percentage change from baseline to pre-Cycle 3 sCD22 (32 patients) was largest in patients with CR (mean reduction of 92.4%, range 100% to 74%), and less inn patients with PR (mean reduction of 63.5%, range 100% - 53%) and SD (mean reduction of 50.2%, range 95% - 12%). Thus, there is a potential correlation between overall response and sCD22 levels.

Secondary pharmacology

No thorough QT study has been performed.

Genetic differences in PD response

CD22 polymorphism is suggested related to autoimmune diseases, and polymorphism is also seen within HCL.

Analysis of a cohort of 126 Japanese patients with systemic sclerosis (SSc) revealed an association between a synonymous SNP in exon 13 in patients with the limited cutaneous form of SSc (Hitomi et al. 2007). The presence of this polymorphism was associated with an average 17% decrease in CD22 expression levels on B cells in these patients. Hairy cells have been reported to express higher levels of CD22 than normal B cells. Thus, if this polymorphism were present in patients with HCL, it would be unlikely to affect moxetumomab pasudotox pharmacokinetics or pharmacodynamics.

In the leukaemia literature, Uckun et al. (Uckun et al. 2010) observed that primary leukaemia cells derived from infants with B-precursor leukaemia (BPL) expressed a truncated version of CD22 that was largely devoid of the intracytoplasmic domain, termed CD22ΔE12. RNA from three adult patients indicate that only a minority of clones (<20%) were found to harbour this polymorphism.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

The PK of moxetumomab pasudotox in HCL patients has been studied in two studies (study CAT-8015-1001 (phase I) and study CD-ON-CAT-8015-1053 (pivotal Phase III)). As in study CAT-8015-1001 validation methods, were questioned and patients received drug from different processes. Only PK based on results from study CD-ON-CAT-8015-1053 are described.

The intended mechanism of action of moxetumomab pasudotox is apoptosis and cell death due to PE38 toxin which catalyzes ADP-ribosylation of elongation factor-2, leading to rapid decreases in levels of anti-apoptotic protein Mcl-1 specifically. The apoptosis of cells might result in release of the PE38 toxin portion. It is noted that the *Pseudomonas* exotoxin cell-binding region (Domain Ia) is deleted from the expression construct and therefore internalisation is prevented. An assay for free PE38 toxin was not developed but the lack of the assay was justified by discussing several aspects addressing the potential safety risk for patients. The most convincing argument is that that the ADP ribosyl transferase enzyme domain (III) alone does not retain cell killing activity *in vitro*. Based on the provided risk assessment it is considered acceptable to measure solely the intact immunotoxin.

The PK sampling strategy in study 1053 was not optimally designed, however, the resulting estimates are overall, considered acceptable for descriptive purposes.

The population PK models presented deficiencies related to the use of pooled data from the PK studies however, with the PK having relatively low impact in the application, the popPK analysis was not further pursued.

ADME

The distribution and elimination pathways of moxetumomab pasudotox have not been well characterised. Moxetumomab pasudotox appears to bind to blood components that mediate distribution and elimination, including CD22-expressing cells (including hairy cells and B-cells) and soluble CD22 receptors. Additionally, proteolysis is expected to represent an important elimination pathway. In addition to the elimination pathways described above, antidrug antibodies (ADAs) develop over time in the majority of patients and result in titre-dependent decreases in moxetumomab pasudotox exposure.

CD22-expressing B-cells and soluble CD22 receptors represent off-target binding sites that may reduce the amount of drug available for the intended target. Soluble CD22 was measured only in the Phase 1 study, and not in Study 1053. Correlation analyses for CD19+ B-cell count vs. NCA-derived exposure metrics indicate that exposure to free moxetumomab pasudotox decreases with increasing number of CD19+ B-cells. As CD19+ B-cell count is partly reflecting CD22 (target) availability, this is as expected. However, there is no clear trends of relationships with clinical outcomes. Thus, dosing based on B-cell count is not considered warranted based on the current information.

The applicant claims that no renal elimination is expected for moxetumomab pasudotox due to its molecular size (63 kDa). However, published studies of the renal excretion of PE38-based recombinant immunotoxins of the same size as moxetumomab pasudotox (63 kDa), including BL22 (a parental molecule for moxetumomab pasudotox differing by three amino acids), have shown that intact immunotoxin was found in the urine of patients (Traini and Kreitman Bioconjug Chem 2011;22:736). Thus, renal excretion cannot be excluded. However, renal excretion is not expected to be a major elimination pathway.

Dose proportionality

Lack of dose proportionality data is considered acceptable since the only proposed and possible dose to administer is 0.04 mg/kg and no dose adjustments are proposed other than to withhold and/or discontinue treatment to manage AEs.

Time dependency

In the majority of patients, exposure *increased* considerably within Cycle 1 from the first to the third dose (Day 5), with an average peak concentration approximately doubled at Day 5. This may be due to reduction in the CD22-expressing B-cell pool.

Over the first 2-3 cycles, ADAs develop in the majority of patients and become the primary determinant of moxetumomab pasudotox disposition. In patients with ADA titre >10,240, moxetumomab pasudotox concentrations apparently become undetectable in a considerable number of subjects. However, due to the analytical method for moxetumomab pasudotox not being valid at high ADA titres, the results are not conclusive.

Inter- and intra-individual variability

Inter-individual variability in free moxetumomab exposure was extensive for moxetumomab pasudotox. No information on intra-patient (inter-occasion) variability has been provided, but this was considered acceptable and not furthered pursued.

Special populations

Renal excretion cannot be excluded but is not expected to be a major elimination pathway due to the molecular size. Because no reliable popPK analysis was presented, NCA-derived exposure data (Day 5 and Day 29) were compared for patients from study 1053 with normal renal function vs. renal impairment as well as with normal hepatic function vs. hepatic impairment. The results overall indicated lower exposure in patients with organ dysfunction. However, due to the small numbers, uncertainties in the NCA-derived exposure metrics and potential confounding factors not being accounted for, no conclusions could be derived. There is no clear mechanistic basis to expect that mild organ impairment would cause reduced moxetumomab pasudotox exposure. Thus, dose adjustments are not considered warranted in these subpopulations. Moxetumomab pasudotox has not been studied in patients with moderate or severe hepatic impairment and moderate or severe renal impairment (creatinine clearance <60 mL/min, n=3).

It is not expected that covariates such as sex and race will impact PK of moxetumomab pasudotox.

The scatterplot of body weight vs. NCA-derived Cmax and $AUC_{0\text{-}3h}$ indicated increasing exposure with increasing body weight after dose administration proportional to body weight. A flat dose could potentially be preferred. However, this is not pursued as there is no established relationship between free exposure and clinical outcomes. These findings are reflected in section 5.2 (special population) in the SmPC. No dose adjustments are recommended for these demographics.

Pharmacodynamics

The clinical pharmacodynamic properties of moxetumomab pasudotox have been investigated in two clinical studies conducted in adult patients with relapsed/refractory HCL. PD endpoints included lymphocyte counts in the phase III study (Study 1053, process 3 product), and CD22 expression and soluble CD22 measurements in the Phase I study (Study 1001, process 1 and 2 product).

In the Phase III study, median B cell quantities were reduced by 89% (<20 cells/mm3) on study day 8, remained significantly reduced throughout six treatment cycles ($p< 0.01$), and returned to baseline at 181 days post-EOT. When stratified by ADA titres the B cell counts in patients with ADA titres above 10,240 started to increase from the third treatment cycle. In ADA negative and low-titre patients, however, the B-cell counts remained low (low-titre) or decreased further (ADA negative) throughout the six treatment cycles. High titre ADA levels are also correlated with substantial reduction in moxetumomab pasudotox exposure levels, leading to exposure levels close to or below LoQ following repeated cycles. Thus, continued pharmacodynamic effect in high-titre ADA patients following the first 2-3 treatment cycles were questioned.

In order to better address potential effects of high-titre ADAs on B-cell counts, and due to the wide range of B-cell counts observed among subjects at baseline, the applicant provided baseline-normalised values, and compared CD19+ B cell percent change from baseline values stratified by high titre and or low/null titre ADA In the presented plot, it is shown that a number of patients with high ADA titres do have reduced B-cell counts at Cycle 5 Day 1 and at EOT. Further, although some patients do develop B-cell levels significantly above baseline at EOT, these also comprise patients with CR and PR.

Taken together, a mechanistic rationale for beneficial effects of continued treatment in high-titre patients with low or undetectable moxetumomab pasudotox exposure levels has not been provided. However, additional beneficial effects despite low exposure levels cannot be excluded. Only free moxetumomab pasudotox in plasma has been measured, which may not be well reflecting pharmacologically active drug. The key safety concerns CLS and HUS, as well as infusion-related reactions, typically occurred prior to increases in ADA titre and corresponding reductions in moxetumomab pasudotox concentration levels.

Thus, continued treatment after high-titre ADA development and lowered moxetumomab pasudotox exposure is considered acceptable from a pharmacological point of view, despite not having explicitly demonstrated continued pharmacodynamic effects in patients with low or undetectable exposure.

Although the mechanism of action for moxetumomab pasudotox indicate selective effects upon B cells, significant reductions (20% to 47%) in median baseline-normalised quantities were observed for CD3+, CD4+, CD8+ T, and NK cell populations on Day 8 following the first 3 doses ($p < 0.01$). Similar findings have been reported for rituximab targeting CD20, and it is suggested that this is caused by loss of B cells that secrete T cell–stimulating cytokines and chemokines (Mélet et al. 2013; Fillatreau 2018). At subsequent time points, the T- and NK-cell populations were returned to, or significantly above baseline, with CD4+ T-cells and NK-cells remaining significantly increased at 181 days post-EOT. Baseline T- and NK-cell levels were lower than expected ranges in healthy subjects, and an apparent rebound effect in later cycles leads to cell levels within expected ranges, possibly related to reduced tumour load.

Baseline sCD22 data stratified upon overall response in the Phase 1 study indicate that sCD22 may be a relevant marker for HCL and for potential treatment outcome, in line with findings by Matsushita et al (2008). However, due to small sample sizes and pooled data from a range of doses, the finding could not be further analysed. Unfortunately, neither sCD22 nor CD22 were measured in the Phase 3 study.

Secondary pharmacology

Considering the limited size of the safety data base and the fact that a QTcF change from baseline >30 ms was observed in 18% of the patients in the Phase III study, the applicant was requested to perform a concentration-QT modelling analysis based on the available data. A model was submitted, however, the PK and ECG data available for analyses were not time-matched and were overall highly sparse. Furthermore, the exposure range studied was relatively narrow as all subject received the same weight-adjusted dose.

Genetic differences in PD response

The SNP in exon 13 was associated with an average 17% decrease in CD22 expression levels on B cells. The applicant claims that, due to higher expression levels of CD22 in hairy cells than in normal B cells, a 17% decrease in CD22 expression would still mean targetable levels in excess of normal B cell levels. At expression levels similar to normal B cells, a 17% decrease is not considered sufficient to prevent pharmacodynamic effects.

Potential effects of mutated CD22ΔE12 on CD22 internalisation are not known. If a truncated CD22 could prevent or reduce internalisation of moxetumomab pasudotox, this may lead to reduced B cell clearance and concomitant slower elimination rates. In a paper by Uckun et al (2010), RNA samples from primary leukemic cells from 3 adults with HCL demonstrated that only a minority of PCR clones harboured CD22ΔE12 (6 of 49 clones). Thus, if this low occurrence of mutated CD22ΔE12 is representative for the HCL patient population, only a minor reduction in clearance or pharmacodynamic effect of moxetumomab pasudotox is expected.

Exposure-response relationships

Exploratory analyses of exposure-response relationships for efficacy and safety have been submitted. However, there were several limitations with these analyses that hamper their interpretation, including reliable PK data being available only from the Phase 3 study in which only one dose level was tested, and PK was sparsely sampled. Further, PK exposure metrics were predicted using an unqualified popPK model and only free moxetumomab pasudotox concentrations were measured. Exposure-efficacy analyses are also prone to confounding because increasing exposure over time is considered to partly reflect treatment response due to lowered target-mediated drug disposition, while exposure-safety analyses are hampered by low frequencies of adverse events. Conclusions cannot be drawn from the limited and uncertain data available and new analyses are therefore not requested.

2.4.5. Conclusions on clinical pharmacology

Despite several noted deficiencies the overall clinical pharmacology programme can be considered adequate.

The relevant information has been included in the SmPC sections 4.2 and 5.2.

2.5. Clinical efficacy

2.5.1. Dose response study

One dose-finding study (Study 1001) has been performed to determine the dose for the pivotal study (Study 1053). Study 1001 was a multicentre, dose-finding, open-label, Phase 1 study, which used a 3+3 design with an expanded MTD cohort, to assess safety and antitumour activity of moxetumomab pasudotox at the MTD (or RP2D) in patients with relapsed or refractory HCL.

For all doses, moxetumomab pasudotox was administered as an intravenous (IV) infusion over 30 minutes on Days 1, 3, and 5 of every 28-day cycle. Subjects were to receive cycles of moxetumomab pasudotox every 4 weeks until CR, PD, initiation of alternative anticancer therapy, unacceptable toxicity, development of neutralising antibodies, or another reason to discontinue therapy intervened.

A total of 18 subjects (3 subjects in each of the 5, 10, 20, 30, 40, and 50 µg/kg cohorts, respectively) were included in the evaluable population for DLT for MTD evaluation. An MTD was not determined and no DLTs were observed at any dose level tested. Based on the absence of DLTs, observed haematologic improvement in the first 3 subjects after Cycle 1 at the 50 µg/kg dose level, and anticipated worsening of treatment-attributable toxicity for dose escalation beyond 50 µg/kg (as indicated by preclinical toxicology studies), further escalation to a dose of 60 µg/kg was not recommended by the Dose Escalation Committee. The 50 µg/kg dose level cohort was therefore expanded to treat additional subjects (for a total of 33 subjects) and was considered the recommended dose for further testing.

The main reason for treatment discontinuation was development of neutralising antibodies to moxetumomab pasudotox (57.1%). The median number of cycles across all dose levels was 4 (range 1 to 16). Disease response by dose group is shown in Table 13. There was no apparent dose-response relationship, possibly due to limited sample size.

Table 13. Disease response by dose group, Study 1001

Parameter	Moxetumomab Pasudotox						Total (N = 49)
	5 µg/kg (N = 3)	10 µg/kg (N = 3)	20 µg/kg (N = 3)	30 µg/kg (N = 3)	40 µg/kg (N = 4)	50 µg/kg (N = 33)	
Best overall response, n (%)							
Complete response	0	2 (66.7)	2 (66.7)	1 (33.3)	2 (50.0)	21 (63.6)	28 (57.1)
MRD-positive (by flow cytometry)	0	1 (33.3)	1 (33.3)	1 (33.3)	0	9 (27.3)	12 (24.5)
MRD-negative (by flow cytometry)	0	0	0	0	1 (25.0)	11 (33.3)	12 (24.5)
Unknown MRD status	0	1 (33.3)	1 (33.3)	0	1 (25.0)	1 (3.0)	4 (8.2)
Partial response	3 (100)	1 (33.3)	0	1 (33.3)	1 (25.0)	8 (24.2)	14 (28.6)
Stable disease	0	0	1 (33.3)	1 (33.3)	0	4 (12.1)	6 (12.2)
Progressive disease	0	0	0	0	1 (25.0)	0	1 (2.0)
ORR (CR or PR)	3 (100)	3 (100)	2 (66.7)	2 (66.7)	3 (75.0)	29 (87.9)	42 (85.7)
95% CI [a]	29.2 – 100	29.2 – 100	9.4 – 99.2	9.4 – 99.2	19.4 – 99.4	71.8 – 96.6	72.8 – 94.1
Time to complete response [b]							
Median time (months) [c]	NA	2.53	9.56	3.71	2.53	3.94	3.56
95% CI of median time [c]	NA	2.30 – 2.76	4.11 – 15.01	NE	2.27 – 2.79	2.30 – 6.31	2.69 – 5.22
Min – Max	NA	2.30 – 2.76	4.11 – 15.01	3.71 – 3.71	2.27 – 2.79	0.95 – 25.30	0.95 – 25.30
Time to OR [d]							
Median time (months) [c]	3.02	1.12	8.2	8.18	1.08	1.05	1.15
95% CI of median time [c]	2.04 – 4.80	0.92 – 2.76	1.38 – 15.01	1.87 – 14.49	0.95 – 2.79	0.92 – 1.58	1.02 – 1.87
Min – Max	2.04 – 4.80	0.92 – 2.76	1.38 – 15.01	1.87 – 14.49	0.95 – 2.79	0.23 – 14.00	0.23 – 15.01
Duration of CR, months							
Loss of CR, n (%) [e]	–	1 (50.0)	1 (50.0)	1 (100.0)	0	9 (42.9)	12 (42.9)
Median time (months) [c]	NA	NE	25.89	70.34	NE	42.35	70.34
95% CI of median time [c]	NA	17.97 – NE	NE	NE	NE	17.45 – NE	19.09 – NE
Min – Max	NA	17.97 – 61.47	8.77 – 25.89	70.34 – 70.34	55.23 – 77.34	0.03 – 72.08	0.03 – 77.34
Duration of OR, months							
Loss of CR/PR [f]	1 (33.3)	1 (33.3)	1 (50.0)	1 (50.0)	0	6 (20.7)	10 (23.8)
Median time (months)	8.34	84.44	80.95	78.29	NE	NE	80.95
95% CI of median time	NE	NE	NE	NE	NE	52.11 – NE	78.29 – 84.44
Min – Max	0.72 – 8.34	0.03 – 84.44	8.77 – 80.95	66.00 – 78.29	11.10 – 78.52	0.03 – 73.49	0.03 – 84.44

CI = confidence interval; CR = complete response; MRD = minimal residual disease; NA = not applicable; NE = not estimable; OR = objective response; ORR = objective response rate; PR = partial response.

[a] Two-sided CI was calculated using the exact probability method based on the binomial distribution.

[b] Time to CR and duration of CR was calculated for the subgroup of subjects with CR.

[c] Median time and its 95% CI were estimated using Kaplan-Meier method (Min/Max was estimated using simple statistics).

[d] Time to objective disease response and duration of objective response were calculated for the subgroup of subjects with confirmed CR/PR.

[e] Loss of CR was calculated based on the subgroup of subjects with CR.

[f] Loss of CR/PR was calculated based on the subgroup of subjects with objective response.

Source: Section 14.2, Table 7.2

2.5.2. Main study

Study CD-ON-CAT-8015-1053

Title of study

Study CD-ON-CAT-8015-1053 was a pivotal Phase 3, multicentre, open-label, single-arm study to evaluate efficacy, safety, immunogenicity and PK of moxetumomab pasudotox monotherapy in adults with relapsed or refractory HCL.

Methods

Study Participants

Patients meeting the following criteria were eligible for enrolment:

Inclusion criteria

1. Subjects must have had histologically confirmed HCL or HCL variant with a need for therapy based on at least one of the following criteria:
    a. neutrophils < 1.0 × 109/L
    b. platelets < 100 × 109/L
    c. haemoglobin < 10 g/dL
    d. symptomatic splenomegaly
2. Subjects must have been *Pseudomonas*-immunotoxin naive
3. Subjects must have received at least 2 prior systemic therapies, including 2 courses of a PNA, or 1 course of either rituximab or BRAF inhibitor following a single prior course of PNA
4. Men or women age ≥ 18 years. Because this disease does not generally occur in children, children were excluded from this study
5. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
6. Subjects must have had adequate organ function as defined below:
    a. total bilirubin ≤ 1.5 mg/dL, unless consistent with Gilbert's (ratio between total and direct bilirubin > 5)
    b. aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3× upper limit of normal (ULN)
    c. alkaline phosphatase < 2.5× ULN
    d. serum creatinine ≤ 1.5 mg/dL or creatinine clearance ≥ 60 mL/min as estimated by the Cockcroft-Gault equation
7. Prothrombin time (PT)/international normalised ratio (INR) or partial thromboplastin time < 2.5 ULN, fibrinogen ≥ 0.5 lower limit of normal; if on warfarin, INR < 3.5, if on any other anticoagulation, PT < 2.5× baseline
8. Ability to understand and the willingness to sign a written informed consent document.
9. Life expectancy ≥ 6 months
10. Females of childbearing potential who were sexually active with a non-sterilised male partner must have agreed to use a highly effective method of contraception

11. Nonsterilised males who were sexually active with a female partner of childbearing potential must have agreed to use an effective method of contraception.

Exclusion criteria

1. Subjects who had chemotherapy, immunotherapy, or radiotherapy within 4 weeks prior to initiation of treatment
2. Subjects who were receiving any other investigational agents
3. Subjects with known brain metastases were excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other AEs
4. Subjects with retinal or choroidal detachment identified during the screening ophthalmologic evaluation
5. Pregnant or breastfeeding females
6. Positive for hepatitis B core antibody or surface antigen unless the subject was on lamivudine or entecavir and hepatitis B viral DNA load was < 2000 IU/mL
7. Active second malignancy requiring treatment other than minor resection of indolent cancers like basal cell and squamous skin cancers
8. Uncontrolled intercurrent illness, including but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, uncontrolled hypertension, cardiac arrhythmia, malaria infection, or psychiatric illness/social situations that would limit compliance with study requirements.
9. Known human immunodeficiency virus (HIV)-positive subjects unless taking appropriate anti-HIV medications with a CD4 count of > 200. Otherwise, there may have been increased risk of lethal infections when temporarily suppressing normal B-cells.
10. History of allogeneic bone marrow transplant
11. Subjects with history of both thromboembolism and known congenital hypercoagulable conditions.
12. Uncontrolled pulmonary infection, pulmonary oedema
13. Oxygen saturation at rest < 88% measured by pulse oximetry or partial pressure of oxygen ≤ 55 mmHg
14. Serum albumin < 2 g/dL
15. Radioimmunotherapy within 2 years prior to enrolment in the study
16. Absolute neutrophil count (ANC) < 1.0 × 109/L, or platelet count < 50 × 109/L, unless judged by the investigator to be due to underlying disease (ie, potentially reversible with anti-neoplastic therapy). A subject will not be excluded because of pancytopenia ≥ Grade 3, or erythropoietin dependence, if due to disease, based on the results of bone marrow studies
17. Subjects with < 50% of predicted forced expiratory volume (FEV) or < 50% of predicted diffusing capacity for carbon monoxide, corrected for haemoglobin concentration and alveolar volume. Note: Subjects with no prior history of pulmonary illness were not required to have pulmonary function testing. FEV was assessed after bronchodilator therapy. Subjects with history of thrombotic microangiopathy or thrombotic microangiopathy/haemolytic uraemic syndrome (HUS)

18. Subjects with history of thrombotic microangiopathy or thrombotic microangiopathy/haemolytic uraemic syndrome (HUS)
19. Subjects with corrected QT interval (Friderica) elevation > 500 msec (manually over-read by medically qualified person) based on at least two separate 12-lead electrocardiograms (ECGs).
20. Subjects on high dose estrogen (defined as > 0.625 mg/day of an estrogen compound)
21. Subjects with clinical evidence of disseminated intravascular coagulation (Grade 3–4)

Treatments

Eighty subjects received treatment with moxetumomab pasudotox (40 µg/kg) by intravenous (IV) infusion over 30 ± 10 minutes on Days 1, 3, and 5 of each 28-day cycle for up to 6 cycles, until documentation of CR, PD, initiation of alternate therapy, or unacceptable toxicity.

The patients received prophylaxis for renal insufficiency (fluids and low dose aspirin) and hypersensitivity reactions (hydroxyzine, acetaminophen, and ranitidine).

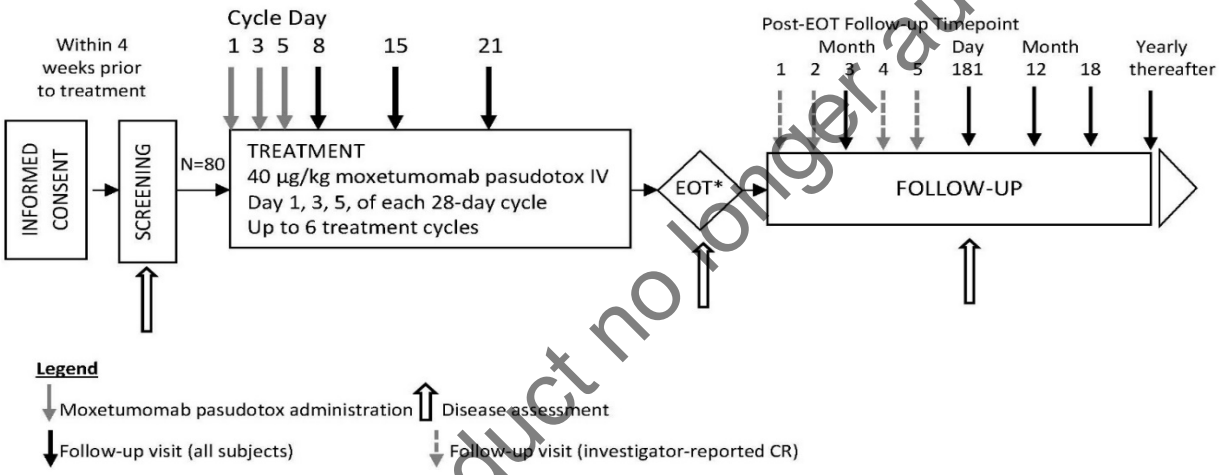


Figure 9 - Study CD-ON-CAT-8015-1053

No dose reductions for moxetumomab pasudotox were allowed according to the study protocol. Toxicity was managed through either treatment delay or discontinuation. The use of steroids was not routinely recommended to prevent CLS or fever; however, secondary prophylaxis for IRRs with dexamethasone 4 mg IV or oral could be administered at the investigator's discretion.

Blinded independent central review determined disease response and minimal residual disease (MRD) status.

Objectives

Primary objective

Efficacy: Determine the rate of durable complete response (CR) in multiple relapsed HCL with moxetumomab pasudotox.

Secondary objectives

Efficacy: Determine the ORR, PFS, TTF, and duration of response (CR and PR)

Safety: Confirm the tolerability and safety of moxetumomab pasudotox in subjects with HCL

Pharmacokinetic: Evaluate pharmacokinetics (PK) of moxetumomab pasudotox

Immunogenicity: Evaluate immunogenicity of moxetumomab pasudotox.

Outcomes/endpoints

The primary efficacy endpoint was durable complete response (CR; see below for definition) based on CR assessed per blinded independent central review (BICR).

Response criteria included 3 components: Pathology (routine haematoxylin and eosin (H & E) staining) of bone marrow;Imaging (computerised tomography or magnetic resonance imaging) of liver, spleen and lymph nodes; Haematology laboratory assessment

Secondary efficacy endpoints were CR, time to CR, duration of CR, duration of haematological remission from onset of haematological remission, time to haematologic remission (HR), objective response (OR), time to OR, duration of OR, progression-free survival (PFS) and time to treatment failure (TTF). Primary and secondary endpoints are listed in the table below.

Complete Response:

- No evidence of leukemic cells by routine H&E staining of peripheral blood and bone marrow aspirate and biopsy
- No hepatomegaly, splenomegaly, or lymphadenopathy by physical examination and/or appropriate radiographic techniques
- Normal CBC as exhibited by haematologic remission (defined below) without transfusions or growth factors for at least 4 weeks. After this 4-week period, the bone marrow biopsy and CT was to be performed to confirm CR. The bone marrow biopsy and aspirate did not need to be performed at the beginning of this 4-week interval.

Durable CR:

Proportion of subjects with durable CR defined as CR per blood, bone marrow, and imaging criteria for CR, with haematologic remission [HR] lasting >180 days.

At the final analysis, an analysis of CR with HR ≥ 360 days was performed.

Haematologic remission was defined as follows:

- Neutrophils > 1,5 x 10^9/L
- Platelets > 100 x 10^9/L
- Haemoglobin > 11,0 g/L
- Haematologic remission duration is not interrupted by transient decreases in normal blood counts.

Minimal residual disease (MRD)

MRD was assessed in subjects at study sites per local protocols by flow cytometry conducted on peripheral blood and/or bone marrow aspirate and by IHC on bone marrow biopsy. Local MRD status was assessed centrally by dedicated, blinded MRD pathology reviewer based on immunohistochemistry (IHC) evidence of HCL in the bone marrow biopsy, and locally by each site, based on flow cytometric evidence of HCL in blood or bone marrow aspirates using local protocols. If baseline bone marrow

aspirates were not available, screening results from peripheral-blood flow cytometry could be used as the baseline for bone marrow aspirate for MRD analysis by flow cytometry instead. A validated central laboratory flow cytometry MRD assay was not available.

MRD negativity: HCL phenotype not evident in bone marrow biopsy (IHC) or in bone marrow aspirate or blood (flow cytometry).

MRD positivity: HCL phenotype cells evident in bone marrow, bone marrow aspirate or blood (by IHC or flow cytometry as described above)

Partial Response

Partial response required all of the following for a period of at least 4 weeks (Note: PR did not require bone marrow examination). The subject must fulfill the following criteria (if abnormal prior to treatment):

- ≥ 50% decrease or normalisation (< 5.0 × 10^9/L) in peripheral blood lymphocyte count from the pretreatment baseline value
- ≥ 50% reduction in lymphadenopathy by CT or magnetic resonance imaging (MRI), based on sum of products of perpendicular diameters, or resolution to size consistent with CR
- ≥ 50% reduction in abnormal hepatosplenomegaly by CT or MRI, or resolution to size consistent with CR
- Neutrophils ≥ 1.5 × 10^9/L or 50% improvement over baseline without growth factors for at least 4 weeks
- Platelets ≥ 100 × 10^9/L or 50% improvement over baseline, and
- Haemoglobin ≥ 11.0 g/dL or 50% improvement over baseline without transfusions or growth factors for at least 4 weeks. For subjects who were transfusion-dependent at baseline, a haemoglobin of ≥ 9.0 g/dL without transfusions or growth factors for at least 4 weeks.

  The beginning of PR was considered as the beginning of the 4-week duration of required blood counts meeting PR criteria.

Progressive Disease

Progressive disease was defined by at least one of the following compared with pretreatment:

- ≥ 25% increase in the sum of the products of the greatest perpendicular dimensions of at least 2 lymph nodes by CT or MRI on 2 consecutive examinations at least 2 weeks apart (at least 1 node must be ≥ 2 cm in minimum length) or appearance of new palpable lymph nodes
- ≥ 50% increase in the absolute number of circulating lymphocytes, on 2 consecutive examinations showing abnormal lymphocytosis at least 2 weeks apart
- ≥ 25% decrease in haemoglobin (must have been <11 g/dL), platelets (must have been <100 × 10^9/L), or ANC (must be <1.5 × 10^9/L) unless these were judged to be effects of treatment.

Stable Disease

SD was characterised by not meeting the criteria for CR, PR, or PD as outlined above.

Relapse

- Relapse from CR: Loss of criteria needed for CR, excluding transient decrease in lab values below criteria for CR

- Relapse from PR: Loss of criteria needed for PR, excluding transient decrease in lab values below criteria for PR
- Relapse from SD: Subjects who met above criteria for PD when compared with measurements after the end of therapy.

Duration of follow up

Patients who are in CR will be followed until clinical relapse (defined as loss of HR, development of disease related symptoms, or organomegaly), subsequent therapy, death, or withdrawal of consent. Patients in CR should not receive any anti-cancer therapies for remission maintenance. Patients removed from study for unacceptable AEs will be followed until resolution or stabilisation of the AE.

Response assessments

Bone marrow examination, blood smear/aspirate slide examination, full haematologic blood count and radiographic disease assessment by BICR were performed at screening, end of treatment (EOT), and 6 months after EOT. The BICR assessment was conducted by 5 independent reviewers (a radiologist, 2 pathologists, minimally, and 3 pathologists if there were discordance, and one oncologist). If during treatment and prior to completion of 6 cycles of therapy blood counts were consistent with CR for at least 4 weeks, then the interim disease assessment could be performed at the discretion of the Investigator. If a CR with MRD negativity is documented, treatment could be discontinued. For any other response, treatment was continued to complete 6 cycles of therapy with the full disease assessment repeated EOT.

Sample size

The sample size was estimated based on the assumptions that the historical durable CR rate in the study population is ≤ 13%, and at least 28% for moxetumomab pasudotox. Using the exact binomial test, a total of 77 subjects was calculated to provide 90% power to detect a difference in these CR rates at a 2-sided significance level of 0.05.

Randomisation

Not applicable.

Blinding (masking)

Not applicable.

Statistical methods

Analysis populations

Intent to treat (ITT) Population: Subjects who were entered into the study and received treatment with moxetumomab pasudotox

Safety Population: Subjects who received at least 1 dose of moxetumomab pasudotox

Efficacy Evaluable Population: Subjects who received at least 1 dose of moxetumomab pasudotox, had a baseline with at least one indication for treatment (neutropenia [ANC < 1000 cells/μL], anaemia [haemoglobin < 10 g/dL], thrombocytopenia [platelets < 100,000/μL], or symptomatic splenomegaly), had one baseline bone marrow biopsy and/or aspirate and cross sectional imaging and at least one

post baseline disease assessment including both bone marrow examination and cross sectional imaging, or had not died within 30 days after last dose.

PK Population: All subjects who received at least 1 dose of moxetumomab pasudotox and provided at least 1 baseline and post-baseline concentration-time data point.

Hypothesis and primary efficacy analysis

The primary efficacy analysis of the primary endpoint, durable CR based on CR assessed per BICR, was performed in the ITT population. Durable CR rate was calculated, and the 95% CI of durable CR was estimated using the exact probability method (Clopper and Pearson). If the lower bound of the 95% CI was above 13%, it was to be concluded that the durable CR rate in this subject population is significantly higher than the historical control value of 13%.

An interim analysis for futility was planned to take place when 25 subjects were evaluable for durable CR, and the trial would stop accrual if two or less of these subjects showed durable CR. Alternatively, if three or more patients prior to when 25 subjects were response evaluable showed durable CR the trial would continue.

The duration of CR was censored according to rules summarised in Table 14, and two sensitivity analyses to assess the impact of censoring were performed, with rules summarised in Table 15 and Table 16.

Table 14. Summary of censoring guidelines for duration of haematologic remission

Situation	Date of Event or Censoring	Outcome
Loss of haematologic remission (without more than one consecutive missed or non-evaluable haematologic assessments or without initiation of alternative anticancer therapy)	Date of the first haematologic assessment with abnormal blood count	Event
Haematologic remission prior to initiation of alternative anticancer therapy	Date of CR or last evaluable haematologic assessment demonstrating haematologic remission prior to initiation of alternative anticancer therapy, whichever occurred last	Censored
Loss of haematologic remission immediately after ≥ 2 consecutive missed or non-evaluable haematologic assessments	Date of CR or last evaluable haematologic assessment demonstrating haematologic remission prior to missed or non-evaluable haematologic assessments, whichever occurred last	Censored
Haematologic remission (without alternative anticancer therapy)	Date of last evaluable haematologic assessment demonstrating haematologic remission	Censored

Table 15. Summary of censoring guidelines for duration of haematologic remission - sensitivity analysis 1

Situation	Date of Event or Censoring	Outcome
Haematologic remission prior to initiation of alternative anticancer therapy	One day after date of CR or one day after last evaluable haematologic assessment showing haematologic remission prior to initiation of alternative anticancer therapy, whichever occurred last	Event

Situation	Date of Event or Censoring	Outcome
Loss of haematologic remission (without more than one consecutive missed or non-evaluable haematologic assessments or without initiation of alternative anticancer therapy)	Date of the first haematologic assessment with abnormal blood count	Event
Haematologic remission (without more than one consecutive missed or non-evaluable haematologic assessments or without initiation of alternative anticancer therapy)	Date of last evaluable haematologic assessment showing haematologic remission	Censored
Loss of haematologic remission immediately after more than one consecutive missed or non-evaluable haematologic assessments	One day after date of CR or one day after last evaluable haematologic assessment showing haematologic remission prior to missed or non-evaluable haematologic assessments, whichever occurred last	Event
Haematologic remission followed by more than one consecutive missed or non-evaluable haematologic assessments without additional follow up data prior to data cutoff	One day after date of CR or one day after last evaluable haematologic assessment showing haematologic remission prior to missed or non-evaluable haematologic assessments, whichever occurred last	Event
Haematologic remission after more than one consecutive missed or non-evaluable haematologic assessments	Date of last evaluable haematologic assessment showing haematologic remission	Censored

Table 16. Summary of censoring guidelines for duration of haematologic remission – sensitivity analysis 2

Situation	Date of Event or Censoring	Outcome
Loss of haematologic remission	Date of the first haematologic assessment with abnormal blood count regardless of whether a patient initiates any alternative anticancer therapy or has more than one consecutively missed or non-evaluable haematologic assessment	Event
Haematologic remission	Date of CR or last evaluable haematologic assessment showing haematologic remission, whichever occurred last, regardless of whether a patient initiates any alternative anticancer therapy or has more than one consecutively missed or non-evaluable haematologic assessment	Censored

Results

Participant flow

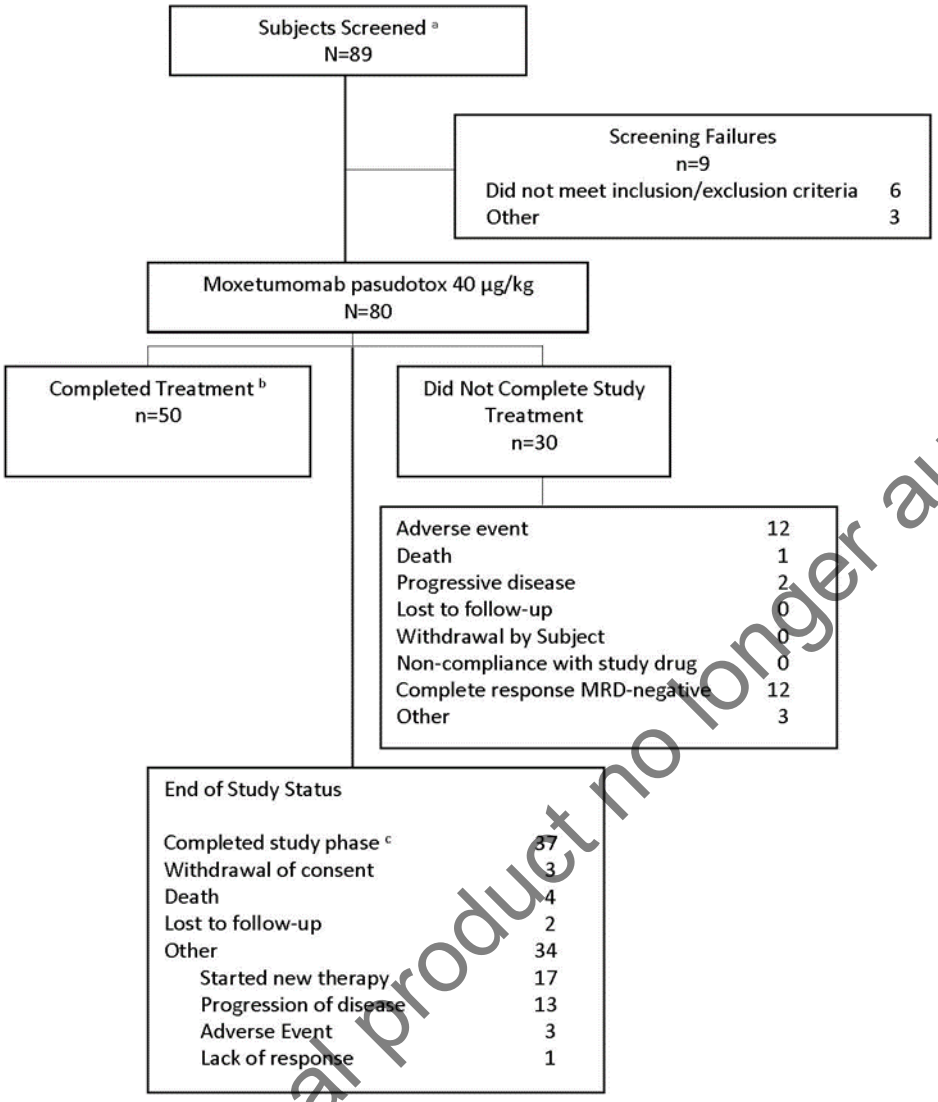


Figure 10 Subject disposition diagram- Study CD-ON-CAT-8015-1053

MRD = minimal residual disease. [a] Informed Consent Form signed. [b] Completion of protocol treatment is defined as 6 cycles of therapy. [c] Completion of study phase is defined as being followed through the Day 181 post-end of treatment visit, regardless of the number of doses of investigational product received.

Recruitment

A total of 80 subjects were treated with moxetumomab pasudotox at 32 sites located in 14 countries in the US, Canada, Europe and Israel.

The first subject received the first dose of moxetumomab pasudotox on 2 May 2013, and the last subject received the first dose on 30 May 2016. The last subject, last visit, corresponding to final data cut-off, occurred on 29 April 2019.

Conduct of the study

Protocol Amendments

The original protocol was dated 14 February 2013. The study was revised a total of 9 times between activation and the data cut-off date 24 May 2017. Key protocol revisions are listed as follows:

Protocol Amendment 1 (26 March 2013):

- stopping rules updated for when subjects redevelop > 3 grade 3 non-haematologic toxicities after withholding study drug and re-challenge.
- exclusion criteria added for subjects with clinically significant ophthalmologic findings during screening.

Protocol Amendment 2 (1 November 2013 and 20 February 2014):

- included dexamethasone to be used as secondary prophylaxis for infusion related reactions (IRR) at the investigator's discretion.
- subjects with grade 4 CLS and grade 3 HUS to be taken off treatment instead of off study.
- Comprehensive AEs and potential risks list for moxetumomab pasudotox were updated.

Protocol Amendment 3 (9 June 2014):

- eligibility criteria modified to clarify that subjects with HCL-V are eligible for enrollment.
- The study population was widened to include patients who had received at least 1 prior treatment with PNA and 1 prior treatment with BRAF inhibitor or rituximab.
- The treatment plan was updated to indicate guidelines for fluid and antihistamine administration and to allow flexibility in and\ministration of medications/collection of vital signs
- Following sentence added to concomitant medication: "Use of NSAIDs is not permitted from the first dose of the cycle through 7 days after the last dose of the cycle".

Protocol Amendment 4 (12 August 2014):

- A maximum of 6 treatment cycles established
- Day 181 disease assessment was changed to 181 days after EOT (earlier 181 days after start of CR)
- Added optional interim disease assessment to be performed at the discretion of the investigator during treatment and prior to completion of 6 cycles of therapy. Treatment delay was specified as > 2 weeks.
- Included instruction stating treatment should be suspended for HUS of any grade until resolution of all laboratory abnormalities and should only be resumed if the maximum grade was ≤ 2 and after consultation and agreement with the sponsor.

Protocol Amendment 5 (2 October 2014):

- Added that subjects should not begin a subsequent cycle of moxetumomab if there is active infection requiring treatment.

Protocol Amendment 6 (22 January 2015):

- HUS/thrombotic microrangiopathy updated from i*mportant potential risk* to *identified risk.*

- Added wording regarding HUS-like event and CLS diagnoses warranting PK collection within 24 hours.

Protocol Amendment 7 (23 April 2015):

- Exclusion criterion 1 was changed from "…prior entering the study" to "….prior to initiation of treatment". Prior splenectomy and lymph nodes > 4 cm were removed from the list of exclusion criteria (previously exclusion criterion 7)

Protocol Amendment 8 (6 January 2017):

- Requirement for CR +/- MRD that need to be present was changed to require "no evidence of leukemic cells in the peripheral blood and/or by routine H/E staining of bone marrow".
- Added censoring rules for duration of haematologic remission separate from duration of CR
- Definition of PFS clarified
- Duration of OR clarified

Protocol deviations

A total of 23 subjects (28.8%) had important protocol deviations. The most common category of important protocol deviations pertained to informed consent (9 subjects [11.3%]).

Table 17 Important protocol deviations – ITT population- Study CD-ON-CAT-8015-1053

Important Protocol Violations/Deviations	**40 µg/kg N=80 No. of subjects (%)**
Any subject with important protocol deviations	23 (28.8)
Inclusion and exclusion criteria	2 (2.5)
Study drug	5 (6.3)
Assessment – safety	3 (3.8)
Lab/Endpoint data	1 (1.3)
Visit window	7 (8.8)
Informed consent	9 (11.3)
Other	4 (5.0)

Baseline data

Baseline characteristics of patient in study 1053 are summarised in **Table 18**. The median age was 60 years (min 34, max 84 years) and the majority were male (78.8%, 63/80) and white (93.5%, 72/80).

Table 18 Demographics – ITT population - Study CD-ON-CAT-8015-1053

Parameter	**Moxetumomab pasudotox 40 µg/kg N = 80**
Age (years)	
Median	60.0
Min, max	34, 84
Age group (years), n (%)	
< 65	49 (61.3)
≥ 65	31 (38.8)
Gender, n (%)	
Male	63 (78.8)
Female	17 (21.3)
Race, n (%) [a]	
White [b]	72 (93.5)
Other	3 (3.9)

Parameter	Moxetumomab pasudotox 40 µg/kg N = 80
Black or African American	1 (1.3)
Asian	1 (1.3)
Information missing	3 (3.9)

ITT = intent to treat; max = maximum; min = minimum.

Table 19 Baseline disease characteristics – ITT population- Study CD-ON-CAT-8015-1053

Parameter	Moxetumomab pasudotox 40 µg/kg N = 80
Spleen size by BICR (cm), n (%)[a]	
N	74
Median	3.29
Min, max	8.9, 24.7
< 14 cm	46 (57.5)
≥ 14 cm	28 (35.0)
Missing	6 (7.5) [d]
< 17 cm	60 (75.0)
≥ 17 cm	14 (17.5)
Missing	6 (7.5)[d]
HCL type, n (%)	
HCL	77 (96.3)
Variant HCL	3 (3.8)
Time from initial diagnosis to study entry (months)	
Median	133.33
Min, Max	7.3, 367.7
Time from last prior treatment to study entry (months)	
Median	25.0
Min-Max	2–111
Haemoglobin (g/dL)	
Median	11.10
Min, Max	6.5, 16.3
Platelets (10^3/µL)	
Median	68.00
Min, Max	6.0, 350.0
Neutrophils (10^3/µL)	
Median	0.810
Min, Max	0.13, 6.21
Leukaemia cells present in bone marrow biopsy / aspirate by investigator, n (%)	
Yes	76 (95.0)
No	4 (5.0)
ECOG, n (%)	
0	49 (61.3)
1	29 (36.3)
2	2 (2.5)
Unfit for PNA, n (%)	
Total unfit for PNA	30 (37.5)
At risk of infection[b]	20 (25.0)
Active infection[c]	19 (23.8)

ANC = absolute neutrophil count; BICR = blinded independent central review; DCO = data cutoff; ECOG = Eastern Cooperative Oncology Group; HCL = hairy cell leukaemia; ITT = intent to treat; max = maximum; min = minimum; PNA = purine nucleoside analog. [a]Measurement by scan. [b]At risk of infection includes subjects whose baseline ANC was < 0.5 × 10^9/L. [c]Active infection includes subjects whose medical history included at least Grade 3 infection or febrile neutropenia, which was marked as "ongoing" or ended after the first dose of moxetumomab pasudotox. Five subjects had splenectomy (reported in medical history; see Listing 16.2_4.5) and 1 subject's (Subject 1010007) spleen size by scan was not reported because scans were not provided to the independent radiologist prior to DCO

Table 20 Prior cancer treatment – ITT population- Study CD-ON-CAT-8015-1053

Parameter	Moxetumomab pasudotox 40 µg/kg N = 80
Number of prior systemic therapies	
Mean (standard deviation)	4.1 (2.1)
Median	3.0
Both cladribine and pentostatin	32 (40.0%)
Pentostatin only	3 (3.8%)
Cladribine only	45 (56.3%)
Median number of lines (min, max)	2.0 (1, 6)
Rituximab, n (%)	60 (75.0%)
Monotherapy	41 (51.3%)
Combination with PNA	23 (28.8%)
BRAF inhibitor, n (%)	14 (17.5%)
Interferon-α, n (%)	20 (25.0%)
Other, n (%) [a]	8 (10.0%)
Number of prior PNA, n (%)	
1	10 (12.5%)
2	30 (37.5%)
> 2	40 (50.0%)
Refractory to prior PNA, n (%) [b]	39 (48.8%)
PNA monotherapy [c]	29 (36.3%)
PNA + rituximab [d]	15 (18.8%)

HCL = hairy cell leukaemia; ITT = intent to treat; max = maximum; min = minimum; OR = objective response; PNA = purine nucleoside analog. [a] Six subjects were treated with other prior cancer therapies including bendamustine (3), bendamustine and ibrutinib (1), bendamustine and dexamethasone (1), ibrutinib and fludarabine (1) [b] Includes subjects who had HCL that was refractory to any line of PNA. Note: A subject can be counted as having HCL refractory to PNA monotherapy and also PNA + rituximab. [c] Subjects who did not achieve an OR, or achieved an OR (or OR with unknown interval to subsequent therapy) lasting < 1 year. [d] Subjects who did not achieve an OR, or achieved an OR (or OR with unknown interval to subsequent therapy) lasting < 2 years.

Table 21 Best response to last prior cancer treatment – ITT population

Parameter	Moxetumomab pasudotox 40 µg/kg N = 80
Complete response	18 (22.5%)
Partial response	21 (26.3%)
Stable disease	5 (6.3%)
Progressive disease	2 (2.5%)
Not available	34 (42.5%)

ITT = intent to treat

Numbers analysed

Table 22 Analysis populations – All subjects- Study CD-ON-CAT-8015-1053

Population	Moxetumomab pasudotox 40 µg/kg
Intent to treat Population	80
Safety Population	80
Efficacy Evaluable Population	65
Pharmacokinetic Population	77

Outcomes and estimation

The final analysis of efficacy was performed based data cut-off 29 April 2019.

Primary efficacy endpoint: durable CR rate

The durable CR rate assessed by BICR in the ITT Population was 36.3% (29 of 80 subjects; 95% CI: 25.8%, 47.8%). Results were updated to include 5 additional subjects who met the primary endpoint criteria following the primary analysis.

The duration of haematologic remission from onset of CR as assessed by BICR was evaluated for subjects in the ITT Population. With a median follow-up duration of 24.6 months the median duration of haematologic remission from onset of CR (by BICR) was 62.8 months (95% CI: 35.7, 62.8). Landmark rates of duration of haematologic remission at 6, 12, and 24 months after onset of CR were 93.5%, 90.0%, and 82.6%, respectively.

An additional post hoc analysis to estimate the BICR-reported CR rate with haematologic remission of ≥360 days was assessed in the ITT Population for the final study analysis. Twenty-six subjects (32.5%; 95% CI: 22.4%, 43.9%) who achieved CR as assessed by BICR maintained haematologic remission for ≥360 days.

Table 23. Durable complete response and duration of haematologic remission from onset of complete response assessed by BICR – ITT population

Parameter	**Moxetumomab pasudotox 40 µg/kg N = 80**
Durable CR, n (%)	29 (36.3)
95% CI	(25.8%, 47.8%)
CR, n (%)	33 (41.3)
Duration of haematologic remission from onset of CR (months)[a]	
Loss of haematologic remission, n (%)	7 (21.2)
Median (95% CI)	62.8 (35.7, 62.8)
(Min, max)	(0.1+, 62.8)
Landmark rate at 6 months, %	93.5 (95% CI: 76.6%, 98.3%)
Landmark rate at 12 months, %	90.0 (95% CI: 71.9%, 96.7%)
Landmark rate at 18 months, %	86.4 (95% CI: 67.5%, 94.7%)
Landmark rate at 24 months, %	82.6 (95% CI: 63.0%, 92.4%)
Landmark rate at 36 months, %	74.3 (95% CI: 48.2%, 88.6%)
Landmark rate at 48 months, %	74.3 (95% CI: 48.2%, 88.6%)
Landmark rate at 60 months, %	74.3 (95% CI: 48.2%, 88.6%)
CR with haematologic remission ≥360 days, n (%)	26 (32.5)
95% CI	(22.4%, 43.9%)

BICR = blinded independent central review; CI = confidence interval; CR = complete response; ITT = intent to treat; max = maximum; min = minimum. [a] Median duration of response was assessed by the Kaplan-Meier method.

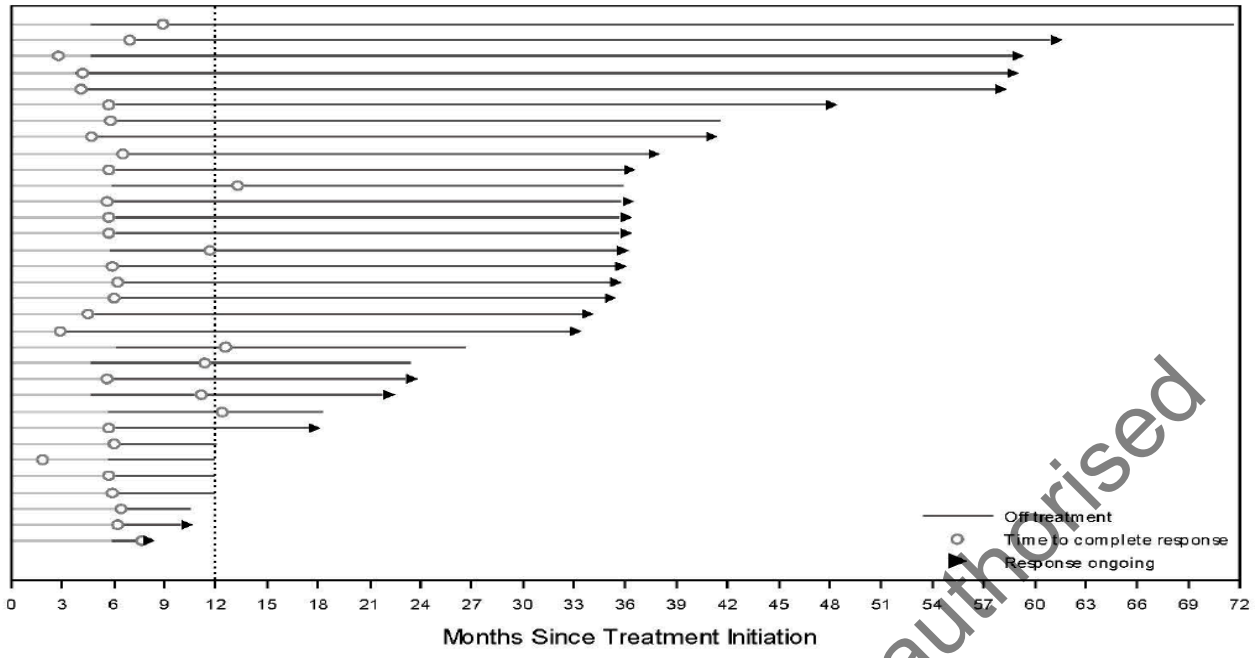


Figure 11. Duration of complete response assessed by BICR – Complete responders

BICR = blinded independent central review.

Secondary efficacy analysis

Best overall response

33 subjects (41.3%, 95% CI: 30.4%, 52.8%) had CR assessed by BICR in the ITT population. 27 of the 33 subjects had MRD-negative CR as assessed by the second blinded central pathologist ITT Population.

27 subjects (33.8%) had a PR assessed by BICR in the ITT Population. The ORR assessed by BICR in the ITT Population was 75% (60 subjects; 95% CI: 64.1%, 84.0%). Additionally, 12 subjects (15.0%) had SD and 2 subjects (2.5%) had PD.

42 subjects (52.5%, 95% CI: 41.0%, 63.8%) had CR by investigator's assessment in the ITT population (Table 24) including 26 subjects (32.5%) with MRD-negative CR. 21 subjects (26.3%) had a PR by investigator's assessment, including 1 subject (1.3%) with MRD-negative PR. The ORR by investigator's assessment was 78.8% (95% CI: 68.2%, 87.1%). Additionally, 9 subjects (11.3%) had SD, and 3 subjects (3.8%) had PD. The investigator-assessed best overall response was based on either clinical response assessment or full disease assessment.

The disease response assessed by investigator and by BICR are summarised in Table 24 and Table 25, respectively.

Table 24. Disease response by investigator's assessment – ITT population

Parameter	**Moxetumomab pasudotox 40 µg/kg N = 80**
Complete response n (%)	42 (52.5%)
95% CI	(41.0%, 63.8%)
Minimal residual disease negative [a], n (%)	26 (32.5%)
95% CI	(22.4%, 43.9%)
Minimal residual disease positive [a], n (%)	6 (7.5%)
95% CI	2.8%, 15.6%
Minimal residual disease unknown, n (%)	10 (12.5%)

Parameter	Moxetumomab pasudotox 40 µg/kg N = 80
95% CI	(6.2%, 21.8%)
Partial response	21 (26.3%)
Minimal residual disease negative [a], n (%)	1 (1.3%)
Minimal residual disease positive [a], n (%)	14 (17.5%)
Minimal residual disease unknown, n (%)	6 (7.5%)
Stable disease n (%)	9 (11.3%)
Progressive disease n (%)	3 (3.8%)
Not evaluable n (%)	5 (6.3%)
Objective response rate, n (%)	63 (78.8%)
95% CI	(68.2%, 87.1%)

CI = confidence interval; HCL = hairy cell leukaemia; ITT = intent to treat. [a] Study sites used a variety of approaches to identify and quantitate HCL cells including flow cytometry and/or analysis of peripheral blood and/or bone marrow aspirate.

Table 25. disease response assessed by BICR – ITT population

Parameter	Moxetumomab pasudotox 40 µg/kg N = 80
Complete response, n (%)	33 (41.3%)
95% CI [a]	(30.4%, 52.8%)
Minimal residual disease negative [b], n (%)	27 (33.8%)
95% CI	(23.6%, 45.2%)
Minimal residual disease positive [b], n (%)	6 (7.5%)
95% CI	(2.8%, 15.6%)
Partial response	27 (33.8%)
Minimal residual disease negative [b], n (%)	4 (5.0%)
Minimal residual disease positive [b], n (%)	20 (25.0%)
Minimal residual disease not evaluable/not done, n (%)	3 (3.8%)
Objective response rate, n (%)	60 (75.0%)
95% CI [a]	(64.1%, 84.0%)
Stable disease, n (%)	12 (15.0%)
Progressive disease, n (%)	2 (2.5%)
Not evaluable [c], n (%)	6 (7.5%)

BICR = blinded independent central review; CI = confidence interval; IHC = immunohistochemistry; ITT = intent to treat. [a] Two-sided CI was calculated using the exact probability method based on the binomial distribution. [b] Determined by IHC. [c] No data post baseline were available for disease or clinical response assessments.

Comparison Best overall response between investigator's and BICR assessment

The best overall response comparison between investigator's and BICR assessment for the ITT population is presented in Table 26. Among 33 BICR-assessed CRs, 29 were also investigator-assessed CRs, including 28 durable CRs. 13 investigator-assessed CRs were not reported as CR by BICR. Discrepancy arose in instances where the investigator reported a pre-cycle clinical response based on haematology data with or without physical examination only, which was not confirmed by a full disease assessment (including bone marrow H&E stain, imaging, and haematology).

Table 26. Best overall response comparison – Investigator's assessment vs BICR – ITT population

Investigator's Assessment	BICR				
	CR	**PR**	**SD**	**PD**	**NE**
CR	**29**	10	3	-	-
PR	4	**15**	2	-	-
SD	-	2	**3**	2	2
PD	-	-	3	-	
NE	-	-	1	-	**4**

BICR = blinded independent central review; CR = complete response; ITT = intent to treat; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease. Note: bold numbers indicate concordance between the independent reviewer and the investigator.

BICR assessment (by IHC) confirmed eradication of MRD in 46 of 80 subjects (57.5%). Of those with an MRD-negative BICR assessment, 100% had CR as assessed by the investigator.

Table 27. Analysis of investigator-reported disease response by BICR IHC bone marrow MRD status - ITT population

Investigator Disease Response Assessment, n (%)	BICR MRD Assessment (IHC)		
	MRD Positive N = 46	**MRD Negative N = 33**	**MRD NE / Not Done N = 1**
CR	9 (19.6)	33 (100)	0
PR	21 (45.7)	0	0
SD	8 (17.4)	0	1 (100)
PD	3 (6.5)	0	0
NE	5 (10.9)	0	0

BICR = blinded independent central review; CR = complete response; IHC = immunohistochemistry; MRD = minimal residual disease; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Time to CR and duration of CR

The median time to CR was 5.9 months (95% CI: 5.7, 6.2) for subjects assessed by BICR in the ITT Population. With a median follow-up duration of 24.6 months, the median duration of CR was 62.8 months (95% CI: 35.7, 62.8; min, max: 0.1+, 62.8). Any evidence of not meeting CR criteria was considered as loss of CR and relapse, even if the subject was still asymptomatic and did not require alternative therapy. With this definition, 11 subjects had loss of BICR-assessed CR; 4 of 11 subjects with loss of CR maintained haematologic remission.

The median time to CR was 4.8 months (95% CI: 2.8, 5.7) for subjects assessed by investigators in the ITT Population. The median duration of CR was 56.6 months (95% CI: 35.7, 69.0). The time to CR and duration of CR assessed by BICR and investigators respectively is summarised in Table 28.

Table 28. Time to complete response and duration of complete response by BICR and investigator's assessment – ITT population

Parameter	**Moxetumomab pasudotox 40 µg/kg N = 80**	
	BICR	**Investigator's Assessment**
Subjects with CR	33	42
Time to CR (months)		
Median	5.9	4.8
95% CI	(5.7, 6.2)	(2.8, 5.7)
(min, max)	(1.8, 13.2)	(1.0, 35.4)
Duration of CR (months)		
Median	62.8	56.6
95% CI	(35.7, 62.8)	(35.7, 69.0)
(min, max)	(0.1+, 62.8)	(0.0+, 69.0)
Landmark rate at 6 months, n (%)	29 (93.5%)	37 (92.5%)

BICR = blinded independent central review; CI = confidence interval; CR = complete response; ITT = intent to treat; max = maximum; min = minimum.

Table 29. Haematologic remission from onset of haematologic remission – ITT population

Parameter	Moxetumomab pasudotox 40 µg/kg N = 80
Haematologic remission	
n (%)	64 (80.0%)
95% CI	(69.6%, 88.1%)
Time to haematologic remission (months)[a]	
Median	1.1
95% CI	(1.0, 1.2)
(Min, Max)	(0.2, 12.9)
Duration of haematologic remission from onset of haematologic remission (months)[a]	
Median [a]	45.8
95% CI	(25.9, 71.5)
(Min, Max)	(0.3, 71.5)
Landmark rate at 6 months, n (%)[b]	58 (93.8%)
Loss of haematologic remission, n (%)	28 (43.8%)

BICR = blinded independent central review; CI = confidence interval; ITT = intent to treat; max = maximum; min = minimum. [a] Median time to response and median duration of response were assessed by the Kaplan-Meier method. [b] Landmark rate was assessed using the Kaplan Meier method.

39 subjects had abnormal haemoglobin levels at baseline; among these subjects, 30 (76.9%) reported normalisation of haemoglobin after treatment with moxetumomab pasudotox with median time to normalisation of 1.6 months. 65 subjects had abnormal neutrophil counts at baseline; among these subjects 55 (84.6%) reported normalisation of neutrophils with median time to normalisation of 1 month. 67 subjects had abnormal platelet counts at baseline; among these subjects, 55 (82.1%) reported normalisation of platelets with median time to normalisation of 0.5 months.

Table 30. Haematologic remission for subjects with complete response per BICR or investigator's assessment – ITT population

	Moxetumomab pasudotox 40 µg/kg N = 80	
Parameter	**BICR**	**Investigator's Assessment**
Number of subjects with CR, n	33	42
Time to haematologic remission (months)		
Median	1.0	1.0
95% CI	(1.0, 1.1)	(1.0, 1.2)
(Min, Max)	(0.3, 2.2)	(0.2, 3.0)
Duration of haematologic remission from onset of CR (months)		
Median	62.8	69.0
95% CI	(35.7, 62.8)	(NE, NE)
(Min, Max)	(0.1+, 62.8)	(0.0+, 69.0)
Landmark rate at 6 months, n (%)	29 (93.5%)	39 (100.0%)

BICR = blinded independent central review; CI = confidence interval; CR = complete response; ITT = intent to treat; max = maximum; min = minimum; NE = not estimable.

Time to objective response (OR) and duration of OR

Objective response was determined by BICR and by investigator's assessment for subjects in the ITT population. Median duration of follow-up was 24.6 months. 23 patients lost OR assessed by BICR, 29 patients lost OR assessed by investigators.

Table 31. Analysis of objective response per BICR or investigator assessment – ITT population

Parameter	Moxetumomab pasudotox 40 µg/kg N = 80	
	BICR	**Investigator's Assessment**
Subjects with OR	60	63
Time to OR (months)		
Median	5.7	4.5
95% CI	(5.7, 5.9)	(2.8, 5.6)
(Min, Max)	(1.8, 12.9)	(0.9, 8.0)
Duration of OR (months)		
Median	66.7	42.1
95% CI	(25.4, 66.7)	(17.8, 69.0)
(Min, Max)	(0.0+, 66.7)	(0.0+, 69.0)

BICR = blinded independent central review; CI = confidence interval; ITT = intent to treat; max = maximum; min = minimum; OR = objective response.

Progression- free survival

The median PFS per BICR in the ITT Population was 41.5 months (95% CI: 28.1, 71.7; min, max: 0.0+, 71.7 months). The median PFS per investigator assessment in the ITT population was 35.8 months (95% CI: 17.3, 58.4; min, max: 0.0+, 71.7 months).

Time to treatment failure

The median TTF assessed by BICR for subjects in the ITT population was 41.5 months (95% CI: 28.1, 71.7; min, max: 0.0+, 71.7 months). The median TTF by investigator's assessment for subjects in the ITT population was 35.8 months (95% CI: 17.4, 71.7; min, max: 0.0+, 71.7 months).

Subgroup analysis of complete response rate

MRD-status: The CR rate was summarised by subgroup for the subjects assessed by BICR in the ITT population. Subjects who were MRD-negative (33 patients) had a higher CR rate; 78.8 (95% CI 61.1%-91%) than subjects who were MRD-positive (6 patients); 6.5 (95% CI; 1.4%-17.9%).

Age: The CR rate was lower, 19.4 (95% CI; 7.5%-37.5%) for subjects aged ≥65 years compared with subjects aged <65 years; 46.9 (95% CI; 32.5%-61.7%).

Disease response by MRD status

Table 32. Disease response assessed by BICR in MRD-negative subjects - ITT population

Parameter	MRD-negative N = 33
Durable CR, n (%) [95% CI] [a]	26 (78.8) [61.1, 91.0]
CR with haematologic remission ≥360 days, n (%) [95% CI] [a]	23 (69.7) [51.3, 84.4]
CR, n (%) [95% CI] [a]	27 (81.8) [64.5, 93.0]
OR, n (%) [95% CI] [a]	31 (93.9) [79.8, 99.3]

BICR = blinded independent central review; CR = complete response; CI = confidence interval; ITT = intent to treat; MRD = minimal residual disease; OR = objective response. Two-sided CI was calculated using the exact probability method based on the binomial distribution

Disease response by PNA refractoriness, prior PNA therapy and PNA-unfit status

Table 33. BICR-assessed disease response based on prior PNA therapy and fitness for PNA – Study CD-ON-CAT-8015-1053

Parameter	Moxetumomab pasudotox, 40 µg/kg						
	ITT Population	PNA Refractory [a]	Prior PNA Treatment, Number of Lines			PNA Unfit [b]	PNA Unfit and/or Refractory
	N = 80	N = 39	1 Line N = 10	2 Lines N = 30	> 2 Lines N = 40	N = 30	N = 53
Durable CR, n (%) (95% CI) [c]	29 (36.3) (25.8, 47.8)	14 (35.9) (21.2, 52.8)	3 (30.0) (6.7, 65.2)	14 (46.7) (28.3, 65.7)	12 (30.0) (16.6, 46.5)	12 (40.0) (22.7, 59.4)	20 (37.7) (24.8, 52.1)
CR with HR ≥360 days, n (%) (95% CI) [c]	26 (32.5) (22.4, 43.9)	12 (30.8) (17.0, 47.6)	3 (30.0) (6.7, 65.2)	12 (40.0) (22.7, 59.4)	11 (27.5) (14.6, 43.9)	10 (33.3) (17.3, 52.8)	17 (32.1) (19.9, 46.3)
CR, n (%) (95% CI) [c]	33 (41.3) (30.4, 52.8)	15 (38.5) (23.4, 55.4)	4 (40.0) (12.2, 73.8)	16 (53.3) (34.3, 71.7)	13 (32.5) (18.6, 49.1)	12 (40.0) (22.7, 59.4)	21 (39.6) (26.5, 54.0)
CR with MRD negative by IHC, n (%) (95% CI) [c]	27 (33.8) (23.6, 45.2)	12 (30.8)	4 (40.0)	12 (40.0)	11 (27.5)	11 (36.7)	17 (32.1)
OR, n (%) (95% CI) [c]	60 (75.0) (64.1, 84.0)	27 (69.2) (52.4, 83.0)	6 (60.0) (26.2, 87.8)	26 (86.7) (69.3, 96.2)	28 (70.0) (53.5, 83.4)	20 (66.7) (47.2, 82.7)	36 (67.9) (53.7, 80.1)

BICR = blinded independent central review; CI = confidence interval; CR = complete response; IHC = immunohistochemistry; ITT = intent-to-treat; MRD = minimum residual disease; OR = objective response; PNA = purine nucleoside analog. [a] Includes PNA monotherapy refractory and/or PNA + rituximab refractory. [b] PNA unfit defined as either at risk of infection or with active infection at baseline. [C] Two-sided CI was calculated using the exact probability method based on the binomial distribution.

Ancillary analyses

- *Sensitivity analyses*

Two pre-specified sensitivity analyses were performed to assess the impact of censoring rules on the duration of haematologic remission in determining the durable CR rate for subjects in the ITT Population. The durable CR rates from Sensitivity Analyses 1 and 2 were both 36.3% (95 CI: 25.8%, 47.8%). The outcomes from the primary endpoint analysis and two sensitivity analyses were consistent and identical with the exception of loss of haematologic remission, i.e. 7 subjects [21.2%] in the primary endpoint analysis and 8 subjects [24.2%] in the sensitivity analyses.

- *Additional data: Literature review and meta-analyses*

The literature review was conducted to provide historical data on available therapies (none of which are both approved and recommended in the ESMO guidelines for use in the 3rd-line and beyond treatment setting) to put into context the efficacy data for moxetumomab pasudotox in adult HCL patients available from the 2 single-arm studies CD-ON-CAT-8015-1053 and CAT-8015-1001.

The initial systematic literature review and meta-analysis was conducted in November 2017 at the request of the United States (US) Food and Drug Administration (FDA) to support the Biologics License Application (BLA) for moxetumomab pasudotox. The current review and meta-analysis document was prepared in order to address a recommendation from the Committee for Human Medicinal Products (CHMP) in their final advice letter dated 28 June 2018 (EMEA/H/SA/1302/1/FU/1/2018/PA/III) for a supportive comprehensive meta-analysis of all relevant historical studies with comparable patient populations in order to validate historical CR rates appropriately. The current review and meta-analysis

included therapies summarised in the National Comprehensive Cancer Network (NCCN) HCL guidelines (NCCN 2019) used to support the BLA, and those summarised in the European Society of Medical Oncology (ESMO) Clinical Practice Guidelines for HCL.

Methodology

The primary objective was to conduct a literature review and meta-analysis to evaluate the historical CR rate in patients with HCL treated in the relapsed or refractory setting and specifically in the 3rd-line and beyond setting, corresponding to the indication sought for moxetumomab. Secondary objectives included evaluation of duration of CR and the proportion of patients who achieved eradication of minimal residual disease (MRD) based on the literature review.

Sensitivity meta-analyses (SMAs) were performed around the primary endpoint of CR rate to address differences in study design (both prospective clinical studies and retrospective data); number of prior lines of treatment (given that the trials of relapsed/refractory HCL could include either or both first relapse and multiply-relapsed patients in the same study); and the type of treatment (given that multiple single agent and combination treatment reports were available). Also review articles were included in the review.

Meta-analysis

Fixed and random effect meta-analyses (DerSimonian and Laird 1986) were performed to integrate the quantitative findings from separate studies and provide an estimate of CR rate and confidence interval. Statistical heterogeneity was assessed using the *I2* test. A random effect model was used in order to account for heterogeneity within the data and provide more robust estimates. A random-effects meta-analysis takes into account that the observed estimates of CR rate could vary across studies because of differences in the CR rate in each study as well as sampling variability.

The primary meta-analysis was conducted based on the publications that were most relevant to the indication sought for moxetumomab pasudotox: prospectively-conducted trials in the 3rd line + monotherapy and combination therapy. Four sensitivity meta-analysis (SMAs) were conducted also for the retrospective and prospective trials in the 3rd L+ setting, two SMAs for the 2nd L+ setting. No SMA was performed for prospective studies for 3rd-line and beyond combination therapy because this subgroup consisted of only one publication. Three subgroup meta-analysis were performed to evaluate the effect of rituximab, vemurafenib and bendamustine + rituximab (retrospective studies in the 3rd L+).

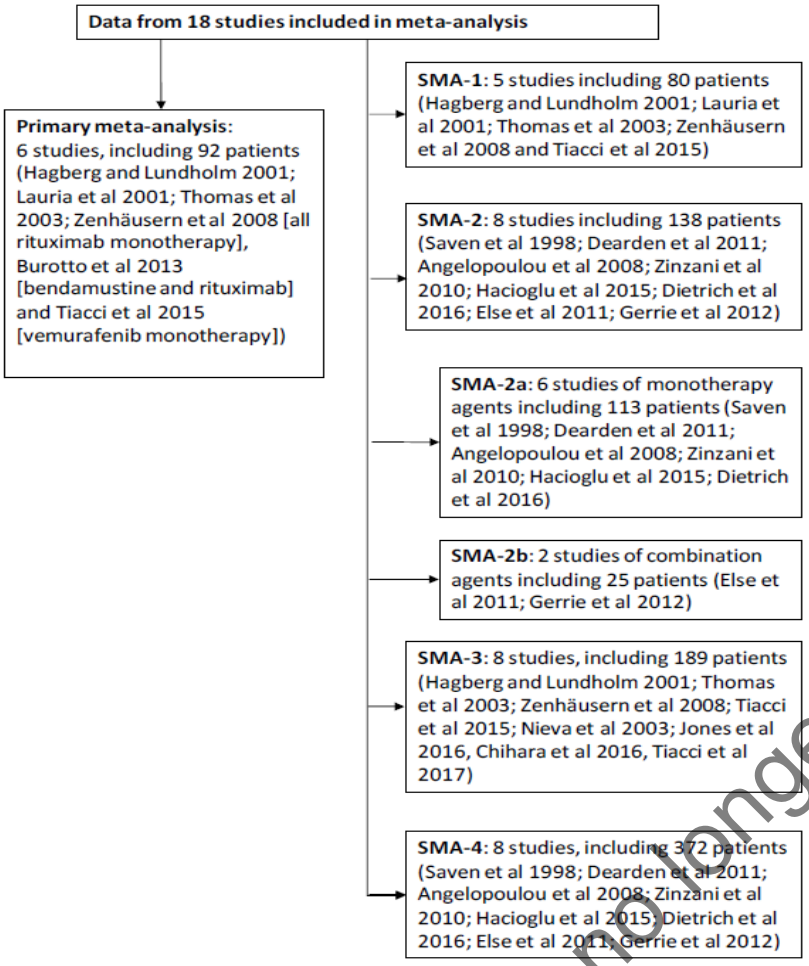


Figure 12. Flow diagram for meta-analyses

SMA = sensitivity meta-analysis.
SMA-1: Prospective studies for 3rd-line and beyond monotherapy.
SMA-2: Retrospective studies for 3rd-line and beyond monotherapy and combination therapy.
SMA-2a: Retrospective studies for 3rd-line and beyond monotherapy.
SMA-2b: Retrospective studies for 3rd-line and beyond combination therapy.
SMA-3: Prospective studies for 2nd-line and beyond monotherapy and combination therapy.
SMA-4: Retrospective studies for 2nd-line and beyond monotherapy and combination therapy.

Table 34. Studies included in the meta-analysis

Study type	Patient population	Agents Studied	Reference	3rd-line and beyond setting			2nd-line and beyond setting	
				No. of evaluable patients	Analysis		No. of evaluable patients	Analysis
Prospective	At least 2nd-line, but with specific information for 3rd-line and beyond	**Bendamustine + Rituximab**	**Burotto et al 2013**	**12**	Primary meta-analysis (N=92 patients)		-	
		Rituximab	Lauria et al 2001	10		SMA-1 (N=80 patients)	-	SMA-3 (N=189 patients)
			Hagberg and Lundholm 2001	7			8	
			Thomas et al 2003	8			15	
			Zenhäusern et al 2008	10			25	
		Vemurafenib	Tiacci et al 2015	45			50	
	At least 2nd-line, but no specific information for 3rd-line and beyond	Rituximab	Nieva et al 2003	unk	Analysis not possible		24	
		Ibrutinib	Jones et al 2016	unk			28	
		Sequential Cladribine→ Rituximab	**Chihara et al 2016[a]**	**0**	Analysis not possible		**14**	
		Vemurafenib + Rituximab	**Tiacci et al 2017[a]**	**unk**			**25**	
Retrospective	At least 2nd-line, (some with specific information for 3rd-line and beyond)	Cladribine or Pentostatin	Saven et al 1998	14	SMA-2 (N=138 patients)	SMA-2a (N=113 patients)	67	SMA-4 (N=372 patients)
			Dearden et al 2011	16			104	
			Hacioglu et al 2015	6			26	
		Cladribine, Pentostatin, Interferon, or Rituximab; ± splenectomy	Angelopoulou et al 2008	2			11	
		Rituximab	Zinzani et al 2010	59			112	
		Vemurafenib	Dietrich et al 2016	16			19	
		Cladribine or Pentostatin + Rituximab	**Else et al 2011**	**13**		SMA-2b (N=25 patients)	**18**	
		Fludarabine + Rituximab	**Gerrie et al 2012**	**12**			**15**	

SMA = sensitivity meta-analysis; No. = number; unk = unknown. SMA-1: Prospective studies for 3rd-line and beyond monotherapy. SMA-2: Retrospective studies for 3rd-line and beyond monotherapy and combination therapy. SMA-2a: Retrospective studies for 3rd-line and beyond monotherapy. SMA-2b: Retrospective studies for 3rd-line and beyond combination therapy. SMA-3: Prospective studies for 2nd-line and beyond monotherapy and combination therapy. SMA-4: Retrospective studies for 2nd-line and beyond monotherapy and combination therapy

Response criteria

The response criteria (specifically CR) in most studies were based on the consensus resolution proposed for the evaluation of response to the treatment of HCL, which are similar to those used in Study CD-ON-CAT-8015-1053. None of the publications evaluated an efficacy endpoint of 'durable CR', which was a novel composite endpoint specific to Study CD-ON-CAT-8015-1053. No published studies included blinded independent central review (BICR) assessment of response data.

Duration of CR was not consistently reported across the identified publications. There were differences in the criteria for relapse assessment across studies. It was not possible to conduct a meta-analysis for MRD status due to the paucity of data available in the available publications.

Meta-analysis results

25 publications were initially assessed as meeting the eligibility criteria. Eighteen studies were included from the medical review in the meta-analysis and are summarised in Table 34.

The primary meta-analysis consisted of totally six prospective studies; four studies of rituximab monotherapy, one of bendamustine + rituximab and one of vemurafenib monotherapy.

It was not possible to conduct a meta-analysis for duration of CR due to the paucity of the data available and differences in the way relapse and/or response durations were defined. 4 of 6 prospective studies in the 3rdL+ setting reported duration of response data. Duration of CR data for the retrospectively conducted combination therapy studies were generally not reported by line of therapy; however, a median duration of response in the 3rd-line only treatment setting.

Table 35. Overview of meta-analysis results (random effect model)

	Prospective Studies		Retrospective Studies	
	CR Rate (95% CI)	**# of Patients (# of Studies)**	**CR Rate (95% CI)**	**# of Patients (# of Studies)**
3rd-line and beyond				
Overall 3rd-line and beyond	Primary meta-analysis 36.9% (20.3%; 53.4%)	92 (6)	SMA-2 42.9% (24.6%; 61.2%)	138 (8)
Monotherapy with 3rd-line and beyond	SMA-1 32.7% (15.6%; 49.7%)	80 (5)	SMA-2a 38.6% (19.1%; 58.1%)	113 (6)
Combination therapy with 3rd-line and beyond	N/A	N/A	SMA-2b 55.3% (0; 100.0%)	25 (2)
2nd-line and beyond				
Overall 2nd-line and beyond	SMA -3 50.9% (20.6%; 81.2%)	189 (8)	SMA-4 55.4% (42.1%; 68.7%)	372 (8)

CI = confidence interval; CR = complete response; N/A = not available; SMA = sensitivity meta-analysis.
SMA-1: Prospective studies for 3rd-line and beyond monotherapy.
SMA-2: Retrospective studies for 3rd-line and beyond monotherapy and combination therapy.
SMA-2a: Retrospective studies for 3rd-line and beyond monotherapy.
SMA-2b: Retrospective studies for 3rd-line and beyond combination therapy.
SMA-3: Prospective studies for 2nd-line and beyond monotherapy and combination therapy.
SMA-4: Retrospective studies for 2nd-line and beyond monotherapy and combination therapy.

Summary of main efficacy results

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

Table 36. Summary of efficacy for trial CD-ON-CAT-8015-1053

Title: A Pivotal Multicenter Trial of Moxetumomab Pasudotox in Relapsed/Refractory Hairy Cell Leukemia		
Study identifier	CD-ON-CAT-8015-1053	
Design	Multicentre, open-label, single-arm Phase 3 study of moxetumomab pasudotox in subjects with relapsed or refractory hairy cell leukaemia (HCL). Patients must have received at least 2 prior systemic therapies, including 2 courses of a purine nucleoside analogue (PNA) therapy (cladribine or pentostatin), or 1 course of either rituximab or BRAF inhibitor following a single prior course of PNA.	
	Duration of main phase: Duration of run-in phase: Duration of extension phase:	49 months (23 April 2013 to 24 May 2017; Primary Analysis) Not applicable 23 months (Final Analysis: 29 April 2019)
Hypothesis	The durable complete response (CR) rate was tested to reject the null hypothesis of durable	

	CR is less than 13%.		
Treatments groups	Single arm study (active treatment)		moxetumomab pasudotox iv infusion at a dose of 40 µg/kg on Days 1, 3, and 5 of each 28-day cycle for up to 6 cycles, until documentation of CR, progressive disease (PD), initiation of alternate therapy, or unacceptable toxicity. 80 patients were enrolled and treated (ITT)
Endpoints and definitions	Primary endpoint	Durable CR (by BICR)	Proportion of subjects with durable CR (defined as CR per blood, bone marrow, and imaging criteria for CR, with haematologic remission [HR] lasting >180 days)
	Secondary endpoints	CR	Complete responses, by investigator assessment and BICR
		Time to CR	Time to complete response
		Duration of CR	Duration of complete response
		Duration of HR from onset of HR	Duration of haematologic remission from onset of haematologic remission
		Time to HR	Time to haematologic remission
		ORR	Objective response rate
		Time to OR	Time to objective response
		Duration of OR	Duration of objective response
		PFS	Progression-free survival
		TTF	Time to treatment failure
Database lock	24 May 2017 (Primary Analysis); 29 April 2019 (Final Analysis)		

Results and Analysis

Analysis description	**Primary Analysis**	
Analysis population and time point description	Intent to treat (subjects who were entered into the study and received treatment with moxetumomab pasudotox). The Primary Analysis of efficacy and safety was performed based on a data cut-off (DCO) of 24 May 2017, the date by which all patients had had the opportunity to complete at least 6 months of post-treatment follow-up.	
Descriptive statistics and estimate variability	Treatment group	Moxetumomab pasudotox (40 µg/kg, single arm)
	Number of subjects	80
Primary endpoint	Durable CR by BICR, n (%) (95% CI)	24 (30.0%) (20.3%, 41.3%)
Effect estimate per comparison	Not applicable (single-arm study; historical control)	

Analysis description	**Final Analysis**	
Analysis population and time point description	Intent to treat (subjects who were entered into the study and received treatment with moxetumomab pasudotox).	
Descriptive statistics and estimate variability	Treatment group	Moxetumomab pasudotox (40 µg/kg, single arm)
	Number of subjects	80
Primary endpoint	Durable CR by BICR, % (95% CI)	36.3 (25.8, 47.8)
	CR by BICR with HR ≥360 days, % (95% CI); (post-hoc analysis) [a]	32.5 (22.4, 43.9)
	Duration of HR from onset of CR in months, median (95% CI), (range) [b]	62.8 (35.7, 62.8) (min 0.1+, max 62.8)
Secondary endpoints	**CR, time to CR, duration of CR**	
	CR by BICR, % (95% CI)	41.3 (30.4, 52.8)
	CR by investigator assessment,	52.5 (41.0, 63.8)

	% (95% CI)		
	CR by BICR, MRD negative by IHC, % (95% CI) [c]		33.8 (23.6, 45.2)
	Time to CR by BICR in months, median (95% CI), (range)		5.9 (5.7, 6.2) (min 1.8, max 13.2)
	Duration of CR by BICR in months, median (95% CI), (range)		62.8 (35.7, 62.8) (min 0.1+, max 62.8)
	Duration of HR and time to HR		
	HR rate, % (95% CI) [d]		80.0 (69.6, 88.1)
	Duration of HR from onset of HR in months, median (95% CI), (range)		45.8 (25.9, 71.5) (min 0.3, max 71.5)
	Time to HR in months, median (95% CI), (range)		1.1 (1.0, 1.2) (min 0.2, max 12.9)
	OR, time to OR, duration of OR		
	ORR by BICR, % (95% CI)		75.0 (64.1, 84.0)
	Time to OR by BICR in months, median (95% CI), (range)		5.7 (5.7, 5.9) (min 1.8, max 12.9)
	Duration of OR by BICR in months, median (95% CI), (range)		66.7 (25.4, 66.7) (min 0.0+, max 66.7)
	Time to progression, time to treatment failure		
	PFS by BICR in months, median (95% CI), (range)		41.5 (28.1, 71.7), (min 0.0+, max 71.7)
	TTF by BICR in months, median (95% CI), (range)		41.5 (28.1, 71.7), (min 0.0+, max 71.7)
Notes	a. CR with HR ≥ 360 days: proportion of subjects who achieved a CR by BICR and maintained haematologic remission ≥ 360 days (post-hoc analysis). b. Duration of HR from onset of CR by BICR (variable supporting the primary endpoint). c. CR by BICR with MRD negative by IHC: proportion of subjects who achieved a complete response by BICR with MRD negative status as assessed by immunohistochemistry (variable supporting the secondary endpoint) d. HR rate: proportion of subjects who achieved haematologic remission (variable supporting the secondary endpoint) Median durations for CR and HR from onset of CR (by BICR) were not reached at the primary analysis.		
Subgroup analyses (pre-specified)	Durable CR by prior PNA therapy, % (95% CI)	1 prior treatment with PNA (N=10)	30.0 (6.7, 65.2)
		2 prior treatments with PNA (N=30)	46.7 (28.3, 65.7)
		>2 prior treatments with PNA (N=40)	30.0 (16.6, 46.5)
	Durable CR by prior rituximab therapy, % (95% CI)	Prior rituximab (N=60)	36.7 (24.6, 50.1)
		No prior rituximab (N=20)	35.0 (15.4, 59.2)
	Durable CR by prior BRAF inhibitor therapy, % (95% CI)	Prior BRAF (N=14)	42.9 (17.7, 71.1)
		No prior BRAF (N=66)	34.8 (23.5, 47.6)
	Durable CR in PNA refractory patients, % (95% CI)	All PNA refractory (N=39)	35.9 (21.2, 52.8)
	Durable CR in PNA unfit patients, % (95% CI)	All PNA unfit (N=30)	40.0 (22.7, 59.4)

Analysis performed across trials (pooled analyses and meta-analysis) Not applicable.

Clinical studies in special populations

Table 37 Subjects in moxetumomab pasudotox studies by age

	Age 65-74 (Older subjects number)	**Age 75-84 (Older subjects number)**
HCL population		
Study CD-ON-CAT-8015-1053 (N=80)	22	9

Table 37 Subjects in moxetumomab pasudotox studies by age

	Age 65-74 (Older subjects number)	Age 75-84 (Older subjects number)
Study CAT-8015-1001 (N=49)	8	1
Other tumour types:		
Non-controlled trials (other); (N=36)	14	1

Note; no patients were aged ≥85 years.

Non-controlled trials (other) includes all adult patients who received any dose of moxetumomab pasudotox in Studies CAT-8015-1002 (CLL, PLL, SLL), CAT-8015-1003 (NHL), and MI-CP218 (B-cell CLL or NHL).

CLL = chronic lymphocytic leukaemia; HCL = hairy cell leukaemia; NHL = non Hodgkin lymphoma; PLL = prolymphocytic leukaemia; SLL = small lymphocytic lymphoma.

Supportive study

Study CAT-8015-1001 (described under the section *Dose response study*) was a multicentre, open-label, dose-finding Phase 1 study, which used a 3+3 design with an expanded maximum tolerated dose cohort, to assess safety and antitumour activity of moxetumomab pasudotox. This study was conducted in adult patients with relapsed or refractory HCL who had received at least 2 prior systemic therapies with PNA or 1 prior systemic therapy with PNA if the response duration lasted < 2 years, or if the patient had unacceptable toxicity to PNA. Moxetumomab pasudotox was administered as an IV infusion at doses of 5, 10, 20, 30, 40, or 50 µg/kg on Days 1, 3, and 5 of each 28-day cycle. This study was completed after 49 patients had been enrolled and treated.

Efficacy results

All 49 patients treated in this study were evaluable for response. The median duration of follow-up was 75 months for the overall population, and 61 months for the 33 patients at the 50 µg/kg dose level. The investigator-assessed ORR (CR or PR) in the overall population was 85.7% (95% CI: 72.8%, 94.1%), with 57.1% of patients achieving a CR. In patients at the 50 µg/kg dose level, the ORR was 87.9% (95% CI: 71.8%, 96.6%) with 63.6% (95% CI: 45.1%, 79.6%) of patients achieving a CR. The median duration of a CR was 70.34 months (95% CI: 19.09 months, not reached) and the median duration of OR was 80.95 months.

Of the 49 patients treated on this supportive study, 37 patients were evaluated for BICR IHC MRD. All BICR-assessed IHC MRD-negative patients in the 50 µg/kg dose cohort achieved an investigator-assessed CR (12/12, 100%)

An integration/pooling of efficacy data from the 2 HCL studies was not performed for this application because of key differences between the studies in the primary endpoint (durable CR vs antitumour activity) and how it was assessed (BICR- vs investigator-assessed). Best overall response rates were assessed by the investigator for both the pivotal and the supportive study, allowing for direct comparison.

The investigator-assessed CR rate for the pivotal study (52.5%; 42/80 patients) was similar to those reported for the supportive study: 50 µg/kg dose cohort, 63.6%, 21/33 patients.

For the pivotal study, 79% (33/42) of patients with investigator-assessed CR had also achieved IHC MRD negativity as assessed by BICR, and for the supportive study, 63% (17/27) of patients with investigator-assessed CR had also achieved IHC MRD negativity as assessed by BICR.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of Lumoxiti is based upon study 1053 titled "a pivotal multicenter trial of moxetumomab pasudotox in relapsed/refractory hairy cell leukemia".

Study 1053 was conducted in patients with histologically confirmed HCL or HCL variant in need of therapy based on presence of cytopenias or splenomegaly and who had received prior treatment with at least 2 systemic therapies, including 1 purine nucleoside analog (PNA). Eligible patients had serum creatinine ≤ 1.5 mg/dL or creatinine clearance ≥ 60 mL/min as estimated by the Cockcroft Gault equation.

A total of 80 patients were enrolled; 77 with classic HCL and 3 with HCL variant. The median age was 60 years (range: 34 to 84, with 39% ≥65 yo), 79% were male, and 94% were Caucasian. At baseline, 98% of patients had an ECOG performance status of 0 or 1. The median number of prior treatments was 3 (range: 2 to 11); all patients received prior PNA therapy, including 29% in combination with rituximab. The most common other prior treatment regimens were rituximab monotherapy (51%), interferon-alpha (25%), and a BRAF inhibitor (18%). At baseline, 33% (26/80) of patients had low haemoglobin (< 10 g/dL), 68% (54/80) of patients had neutropenia (<1.0 × 109/L), and 84% (67/80) patients had baseline platelet counts <100 × 109/L. Moreover, 35% of patients had enlarged spleens (≥14 cm, assessed by BICR) at baseline.

Patients received moxetumomab pasudotox 40 µg/kg as an intravenous infusion over 30 minutes on days 1, 3, and 5 of each 28-day cycle for a maximum of 6 cycles or until documentation of complete response (CR), disease progression, or unacceptable toxicity. This is identical to the dose and posology recommended under 4.2. of the SmPC. The median duration of follow-up was 24.6 months.

Efficacy data and additional analyses

The primary endpoint, durable complete response (>180 days) rate by BICR was met and was observed in 29/80 patients (36.3%). Of those, 26 were MRD negative responses by central pathology review; 23/26 MRD negative patients had a CR with haematologic remission >360 days. Two sensitivity analyses showed no change in the durable CR rate.

The outcomes of the secondary endpoints support the primary endpoint results.

ORR (BICR) was observed in 60/80 patients, 75% (95% CI 64.1, 84): CR 41.3%, PR 33.8%, SD 15% and PD 2.5%. Among the 60 patients who achieved an objective response, 31 (51.7%) were MRD negative by BICR-assessed IHC (27 CR and 4 PR patients). The time to objective response was 5.7 months. The median duration of CR by KM analysis was 62.8 months (95% CI 35.7. 62.8). Among the 3 patients with HCL-v (which is considered a separate clinical entity from classical HCL), 2 achieved a PR and 1 SD (note however that SD is not an acceptable treatment outcome, since therapy is directed to improve haematologic parameters or disease-related symptoms).

Haematologic remission (normalisation of haematologic parameters without growth factors or transfusions in 4 weeks) was observed in 64/80 patients (80%) (95% CI: 69.6%, 88.1%) with a clinically meaningful median time to HR of 1.1 months (0.2, 12.9) and a median duration of HR of 45.8 months (95% CI: 25.9, 71.5). Fifty-eight out of 64 patients remained in haematologic remission 6 months after the onset of HR.

There were no meaningful differences in the CR rate or ORR based on the number of PNA previous lines; PNA refractory, PNA unfit and the overall ITT population. However, response rates were higher in patients who did not have splenomegaly or splenectomy (which was associated with high disease burden in the bone marrow; 4 of the 5 patients had 100% involvement at baseline). Three patients with HCL variant were enrolled; all had high disease burden (all had splenomegaly >17 cm and two had lymphocytosis >20/nL) and did not achieve complete response. It may be advisable to initiate moxetumomab pasudotox treatment earlier in relapse when possible in patients with very high disease burden.

Thirty PFS events (BICR) were reported in the ITT population with a mPFS of 41.5 months (28.1; 71.7). A sensitivity analysis applying more conservative censoring rules, in which initiation of alternative therapy, death or PR/relapse after ≥2 consecutive missed visits were considered an event, was requested and lowered the PFS estimate by BICR to 30.3 months (95% CI 18.2-71.7), as expected in such a small study population. Overall survival was not a pre-specified secondary endpoint and no updates are available past EOT.

The pivotal trial data showed a tendency towards inferior efficacy among the older (≥65 years) patients, both through primary and secondary endpoints. The applicant has provided subgroup analysis of haematologic remission rate, time to haematologic remission and duration of haematologic remission according to age vs the ITT population. The haematologic remission rate (67.7%) is still high and the time to haematologic remission is short (median 1.5 months) in the older population. As haematologic remission is the most clinically relevant secondary endpoint, one could conclude that there is clinical benefit in the oldest population, although less durable.

Additional efficacy data needed in the context of a MA under exceptional circumstances

The CHMP agreed that the applicant is unable to provide comprehensive data on the efficacy and safety under normal conditions of use because the indication is too rare. Therefore, the CHMP recommended that a marketing authorisation under "exceptional circumstances" be granted due to the rarity of the disease. In this context, the applicant is required to submit the results from a non-interventional post-authorisation study based on data from a disease registry in HCL patients.

2.5.4. Conclusions on the clinical efficacy

Study CD-ON-CAT-8015-1053 has provided convincing evidence of clinical efficacy of moxetumomab pasudotox in terms of the primary endpoint (durable complete response) in patients with relapsed or refractory HCL after receiving at least two prior systemic therapies, including treatment with a PNA.

The outcomes of pivotal trial 1053 consist of a remarkably short time to haematologic response (improvement of low blood counts in the absence of transfusions and growth factors) followed by a long duration of response; a short time to CR (which, importantly, is similar to the time to achieve a complete response in prior lines of treatment), where notably the majority of the complete responses are MRD negative.

The outcomes of the secondary endpoints support the primary endpoint results.

These outcomes inform of improvement in the biological parameters and disease-related symptoms, which, taken together, define the clinical benefit of moxetumomab pasudotox in 3L RR HCL. The CHMP agreed that the applicant is unable to provide comprehensive data on the efficacy and safety under normal conditions of use because of the rarity of the disease. In the context of marketing authorisation

under exceptional circumstances, the applicant is required to submit the results from a non-interventional post-authorisation study based on data from a disease registry in HCL patients.

2.6. Clinical safety

Safety data is presented based on the populations described below.

- Primary HCL Population (HCL studies CD-ON-CAT-8015-1053 [pivotal Phase 3] and CAT-8015-1001 [Phase 1]; N=129): This population (target population) consists of all adult patients in the 2 HCL studies who have received at least 1 dose of moxetumomab pasudotox at any dose level. Both studies had an open-label, single-arm design with treatment being administered on Days 1, 3, and 5 of each 28-day cycle.

- Pivotal HCL Population (Study CD-ON-CAT-8015-1053; N=80): This population consists of all patients in the pivotal Phase 3 study who received at least 1 dose of moxetumomab pasudotox at the intended dose level of 40 µg/kg administered on Days 1, 3, and 5 of each 28 day cycle for a maximum of 6 cycles.

- Adult Population (All 5 adult sponsored studies; N=165): This population consists of all patients in the pooled adult studies who have received at least 1 dose of moxetumomab pasudotox at various dose levels (all administered on Days 1, 3, and 5 of each 28 day cycle) and treatment durations, and across multiple haematologic malignancy indications. While this pool includes populations other than the HCL patient population, the applicant considered that the safety profile of moxetumomab pasudotox in adult patients with relapsed/refractory HCL would be similar to that in adult patients with other relapsed/refractory haematologic B-cell malignancies. For completeness, tables with all three populations submitted by the MAH are shown.

However, the safety assessment focuses on the patients treated at the proposed SmPC dose and duration in the pivotal study 1053 due to issues related to different manufacture processes in the phase 1 trial and the phase 3 trial (for details, see Quality section).

Patient exposure

Table 38 Extent of exposure to moxetumomab pasudotox – across adult populations

Parameter	Primary HCL Population All Doses (N=129)	Pivotal HCL Population P3_40 µg/kg (N=80)	Adult Population All Doses (N=165)
Duration of exposure (months)			
Mean	4.62	4.98	4.12
Median	4.93	5.65	4.27
Min, Max	0.9, 16.2	0.9, 6.7	0.2, 16.2
<1 month	1 (0.8%)	1 (1.3%)	3 (1.8%)
1 to <2 months	14 (10.9%)	8 (10.0%)	35 (21.2%)
2 to <6 months	97 (75.2%)	58 (72.5%)	108 (65.5%)
6 to <9 months [a]	16 (12.4%)	13 (16.3%)	17 (10.3%)
9 to <12 months [a]	0	0	1 (0.6%)
≥12 months [a]	1 (0.8%)	0	1 (0.6%)
Duration of exposure (cycles)[b]			
Mean	4.7	5.1	4.2
Median	5.0	6.0	4.0
Min, Max	1, 16	1, 7	1, 16
1-3 cycles	35 (27.1%)	13 (16.3%)	62 (37.6%)
4-6 cycles	89 (69.0%)	66 (82.5%)	96 (58.2%)
7-9 cycles	4 (3.1%)	1 (1.3%)	6 (3.6%)
10-12 cycles	0	0	0
13-16 cycles	1 (0.8%)	0	1 (0.6%)
>16 cycles	0	0	0
Relative dose intensity (%)[c]			
Mean	97.80	96.47	97.71
Median	99.95	100.00	99.95
Min, Max	33.2,104.9	33.2, 103.7	33.2, 105.8
<90%	6 (4.7%)	6 (7.5%)	10 (6.1%)
90% - 110%	123 (95.3%)	74 (92.5%)	155 (93.9%)
>110%	0	0	0

HCL=hairy cell leukaemia; ISS=Integrated Summary of Safety; Max=maximum; Min=minimum; P3=Process 3.

a Patients treated for >6 cycles were enrolled in Study CAT-8015-1001, except for 1 patient from Study CD-ON-CAT-8015-1053 who received 7 cycles of study drug due to having been enrolled and treated prior to implementation of the protocol amendment (CD-ON-CAT-8015-1053 Protocol Amendment 4 dated 12Aug2014) that established a maximum of 6 treatment cycles.
b Duration of exposure (cycles) was defined as the number of cycles during which patients received at least 1 dose of moxetumomab pasudotox
c Dose intensity of moxetumomab pasudotox (%) = (total dose received/total dose intended based on the last day of the last cycle in which a patient receives study treatment) ×100. Source: Section 5.3.5.4, ISS Table 7.1.

Treatment modifications

Reasons for dose delays within a treatment cycle were collected in the Phase 3 study only, whereas reasons for cycle delay were collected for all studies. Dose interruptions and reasons for dose interruptions were based on reported events.

A total of 48 patients (60.0%) in the Pivotal HCL Population experienced a dose delay. Of these patients, most (77.1%) had 1 or 2 dose delays, and the median length of delay was 4.0 days (range 1

to 14 days). The most common reasons for delaying a dose were other reasons (33 patients, 47.8%) and scheduling conflict (26 patients, 37.7%). Other reasons were most often logistical issues or holidays. Twelve patients (15.0%) delayed a dose due to an AE. Six patients (7.5%) required a dose interruption (i.e., the dose was stopped, either temporarily or permanently, in the middle of the infusion); these were due to AEs and other reasons (3 patients each).

Adverse events

For the integrated analyses, AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) v19.0 and assigned grades based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.03. A treatment-emergent adverse event (TEAE) was defined as any AE that occurred on or after the date of initial receipt of study treatment. The analysis of AEs was limited to TEAEs.

A rate summary of AEs in the safety populations is given in Table 39.

Table 39 Rate summary of adverse events – across adult populations

Subjects with	Primary HCL Population All Doses (N=129)	Pivotal HCL Population P3_40 µg/kg (N=80)	Adult Population All Doses (N=165)
At least 1 event	128 (99.2%)	79 (98.8%)	164 (99.4%)
At least 1 related event	120 (93.0%)	72 (90.0%)	147 (89.1%)
At least 1 event of Grade 3-4 severity	96 (74.4%)	54 (67.5%)	115 (69.7%)
At least 1 related event of Grade 3-4 severity	35 (27.1%)	24 (30.0%)	43 (26.1%)
At least 1 event resulting in death (Grade 5)[a]	2 (1.6%)	2 (2.5%)	6 (3.6%)
At least 1 related event resulting in death (Grade 5)	0	0	0
At least 1 serious event	34 (26.4%)	28 (35.0%)	47 (28.5%)
At least 1 related serious event	16 (12.4%)	14 (17.5%)	21 (12.7%)
At least 1 event leading to study drug discontinuation	15 (11.6%)	12 (15.0%)	25 (15.2%)
At least 1 related event leading to study drug discontinuation	10 (7.8%)	8 (10.0%)	16 (9.7%)
At least 1 event leading to dose interruption	4 (3.1%)	3 (3.8%)	7 (4.2%)
At least 1 related event leading to dose interruption	3 (2.3%)	3 (3.8%)	5 (3.0%)
At least 1 event leading to dose delay	12 (9.3%)	12 (15.0%)	12 (7.3%)
At least 1 related event leading to dose delay	4 (3.1%)	4 (5.0%)	4 (2.4%)
At least 1 event leading to dose omission	5 (3.9%)	5 (6.3%)	5 (3.0%)
At least 1 related event leading to dose omission	2 (1.6%)	2 (2.5%)	2 (1.2%)
At least 1 event leading to dose interruption, dose delay, or dose omission	20 (15.5%)	19 (23.8%)	23 (13.9%)
At least 1 related event leading to dose interruption, dose delay, or dose omission	9 (7.0%)	9 (11.3%)	11 (6.7%)

AE=adverse event; HCL=hairy cell leukaemia; ISS=Integrated Summary of Safety; P3=Process 3; PID=patient identification.
a The events resulting in death presented in this table include only those AEs with onset within 30 days after the last dose of study drug. In addition to the deaths due to AE reported above, there was 1 patient (PID 8352001) in the pivotal study (CD-ON-CAT-8015-1053) who experienced an AE of Grade 4 sepsis syndrome starting 3 days after the last dose of study drug and whose death was reported as due to the AE of sepsis syndrome and the underlying disease of HCL >30 days after the last dose of study drug, and 1 patient (PID 8337003) in the pivotal study (CD-

ON-CAT-8015-1053) who discontinued study due to an AE of Grade 4 glioblastoma; the investigator reported that the patient subsequently died approximately 67 days after the last dose of study drug (

Common Adverse Events and Adverse Events of Grade 3 or 4 in Severity

Rates of common (frequency ≥10% in any population) AEs (any grade), AEs of Grade 3 or 4 severity, and treatment-related AEs by PT across the adult populations are shown in the table below.

Table 40 Common adverse events (frequency ≥10% in any population) by preferred term – across adult population

Preferred Term[a] (MedDRA v19.0)	Any Grade (Regardless of Causality)			Grade 3-4 (Regardless of Causality)			Treatment-related (Any Grade)		
	Primary HCL Population All Doses (N=129)	Pivotal HCL Population P3_40 µg/kg (N=80)	Adult Population All Doses (N=165)	Primary HCL Population All Doses (N=129)	Pivotal HCL Population P3_40 µg/kg (N=80)	Adult Population All Doses (N=165)	Primary HCL Population All Doses (N=129)	Pivotal HCL Population P3_40 µg/kg (N=80)	Adult Population All Doses (N=165)
Patients with at least 1 AE	128 (99.2%)	79 (98.8%)	164 (99.4%)	96 (74.4%)	54 (67.5%)	115 (69.7%)	120 (93.0%)	72 (90.0%)	147 (89.1%)
Oedema peripheral	53 (41.1%)	31 (38.8%)	67 (40.6%)	0	0	0	42 (32.6%)	21 (26.3%)	52 (31.5%)
Hypoalbuminaemia	51 (39.5%)	16 (20.0%)	57 (34.5%)	1 (0.8%)	0	1 (0.6%)	46 (35.7%)	12 (15.0%)	52 (31.5%)
Alanine aminotranferase increased	50 (38.8%)	17 (21.3%)	54 (32.7%)	4 (3.1%)	1 (1.3%)	4 (2.4%)	46 (35.7%)	15 (18.8%)	48 (29.1%)
Pyrexia	49 (38.0%)	25 (31.3%)	54 (32.7%)	3 (2.3%)	1 (1.3%)	4 (2.4%)	37 (28.7%)	16 (20.0%)	38 (23.0%)
Aspartate aminotranferase increased	46 (35.7%)	15 (18.8%)	50 (30.3%)	0	0	0	44 (34.1%)	14 (17.5%)	46 (27.9%)
Nausea	46 (35.7%)	28 (35.0%)	57 (34.5%)	2 (1.6%)	2 (2.5%)	2 (1.2%)	38 (29.5%)	22 (27.5%)	43 (26.1%)
Headache	45 (34.9%)	26 (32.5%)	54 (32.7%)	0	0	0	35 (27.1%)	17 (21.3%)	39 (23.6%)
Fatigue	41 (31.8%)	27 (33.8%)	53 (32.1%)	0	0	0	28 (21.7%)	14 (17.5%)	36 (21.8%)
Myalgia	39 (30.2%)	11 (13.8%)	42 (25.5%)	1 (0.8%)	0	1 (0.6%)	30 (23.3%)	10 (12.5%)	33 (20.0%)
White blood cell count decreased	33 (25.6%)	8 (10.0%)	34 (20.6%)	28 (21.7%)	7 (8.8%)	29 (17.6%)	6 (4.7%)	2 (2.5%)	6 (3.6%)
Hypocalcaemia	32 (24.8%)	19 (23.8%)	36 (21.8%)	1 (0.8%)	0	2 (1.2%)	4 (3.1%)	4 (5.0%)	5 (3.0%)
Hypophosphataemia	30 (23.3%)	19 (23.8%)	32 (19.4%)	11 (8.5%)	8 (10.0%)	12 (7.3%)	6 (4.7%)	6 (7.5%)	6 (3.6%)
Lymphopenia	30 (23.3%)	1 (1.3%)	30 (18.2%)	27 (20.9%)	1 (1.3%)	27 (16.4%)	4 (3.1%)	1 (1.3%)	4 (2.4%)
Chills	27 (20.9%)	15 (18.8%)	30 (18.2%)	0	0	0	23 (17.8%)	12 (15.0%)	25 (15.2%)
Hyperglycaemia	27 (20.9%)	8 (10.0%)	29 (17.6%)	1 (0.8%)	1 (1.3%)	2 (1.2%)	2 (1.6%)	1 (1.3%)	2 (1.2%)
Lymphocyte count decreased	27 (20.9%)	16 (20.0%)	28 (17.0%)	26 (20.2%)	16 (20.0%)	27 (16.4%)	6 (4.7%)	6 (7.5%)	6 (3.6%)
Constipation	26 (20.2%)	18 (22.5%)	32 (19.4%)	0	0	1 (0.6%)	6 (4.7%)	4 (5.0%)	6 (3.6%)
Diarrhoea	24 (18.6%)	17 (21.3%)	32 (19.4%)	0	0	0	10 (7.8%)	6 (7.5%)	13 (7.9%)
Blood creatinine increased	22 (17.1%)	9 (11.3%)	26 (15.8%)	0	0	1 (0.6%)	17 (13.2%)	8 (10.0%)	19 (11.5%)
Hypertriglyceridaemia	22 (17.1%)	2 (2.5%)	27 (16.4%)	1 (0.8%)	0	2 (1.2%)	1 (0.8%)	0	1 (0.6%)
Hyponatraemia	21 (16.3%)	9 (11.3%)	26 (15.8%)	5 (3.9%)	3 (3.8%)	7 (4.2%)	0	0	0
Arthralgia	19 (14.7%)	13 (16.3%)	21 (12.7%)	0	0	0	7 (5.4%)	2 (2.5%)	8 (4.8%)
Vomiting	19 (14.7%)	15 (18.8%)	24 (14.5%)	1 (0.8%)	1 (1.3%)	1 (0.6%)	13 (10.1%)	9 (11.3%)	16 (9.7%)
Hypotension	18 (14.0%)	6 (7.5%)	22 (13.3%)	0	0	1 (0.6%)	17 (13.2%)	5 (6.3%)	19 (11.5%)
Neutrophil count decreased	18 (14.0%)	6 (7.5%)	22 (13.3%)	14 (10.9%)	5 (6.3%)	16 (9.7%)	3 (2.3%)	2 (2.5%)	4 (2.4%)
Platelet count decreased	18 (14.0%)	9 (11.3%)	23 (13.9%)	12 (9.3%)	5 (6.3%)	15 (9.1%)	7 (5.4%)	5 (6.3%)	9 (5.5%)
Anaemia	17 (13.2%)	17 (21.3%)	24 (14.5%)	8 (6.2%)	8 (10.0%)	11 (6.7%)	5 (3.9%)	5 (6.3%)	7 (4.2%)
Cough	17 (13.2%)	8 (10.0%)	25 (15.2%)	0	0	0	2 (1.6%)	0	3 (1.8%)
Dizziness	17 (13.2%)	8 (10.0%)	22 (13.3%)	0	0	0	13 (10.1%)	6 (7.5%)	16 (9.7%)
Dyspnoea	17 (13.2%)	9 (11.3%)	25 (15.2%)	1 (0.8%)	0	3 (1.8%)	6 (4.7%)	4 (5.0%)	9 (5.5%)
Hypokalaemia	17 (13.2%)	13 (16.3%)	20 (12.1%)	2 (1.6%)	2 (2.5%)	2 (1.2%)	2 (1.6%)	1 (1.3%)	2 (1.2%)
Oedema	17 (13.2%)	4 (5.0%)	19 (11.5%)	0	0	0	15 (11.6%)	3 (3.8%)	15 (9.1%)
Pain in extremity	17 (13.2%)	12 (15.0%)	21 (12.7%)	0	0	1 (0.6%)	4 (3.1%)	3 (3.8%)	6 (3.6%)
Back pain	16 (12.4%)	12 (15.0%)	21 (12.7%)	1 (0.8%)	1 (1.3%)	2 (1.2%)	6 (4.7%)	2 (2.5%)	6 (3.6%)
Capillary leak syndrome	16 (12.4%)	7 (8.8%)	21 (12.7%)	2 (1.6%)	2 (2.5%)	3 (1.8%)	15 (11.6%)	7 (8.8%)	19 (11.5%)
Hypermagnesaemia	16 (12.4%)	3 (3.8%)	17 (10.3%)	2 (1.6%)	1 (1.3%)	2 (1.2%)	2 (1.6%)	1 (1.3%)	2 (1.2%)
Hypomagnesaemia	16 (12.4%)	6 (7.5%)	16 (9.7%)	1 (0.8%)	1 (1.3%)	1 (0.6%)	1 (0.8%)	1 (1.3%)	1 (0.6%)
Haemoglobin decreased	15 (11.6%)	0	19 (11.5%)	6 (4.7%)	0	6 (3.6%)	1 (0.8%)	0	1 (0.6%)
Haptoglobin decreased	15 (11.6%)	6 (7.5%)	16 (9.7%)	4 (3.1%)	0	4 (2.4%)	5 (3.9%)	3 (3.8%)	6 (3.6%)
Decreased appetite	14 (10.9%)	11 (13.8%)	20 (12.1%)	0	0	0	8 (6.2%)	5 (6.3%)	12 (7.3%)
Hypertension	14 (10.9%)	12 (15.0%)	17 (10.3%)	6 (4.7%)	6 (7.5%)	6 (3.6%)	6 (4.7%)	4 (5.0%)	6 (3.6%)

Preferred Term[a] (MedDRA v19.0)	Any Grade (Regardless of Causality)			Grade 3-4 (Regardless of Causality)			Treatment-related (Any Grade)		
	Primary HCL Population All Doses (N=129)	Pivotal HCL Population P3_40 µg/kg (N=80)	Adult Population All Doses (N=165)	Primary HCL Population All Doses (N=129)	Pivotal HCL Population P3_40 µg/kg (N=80)	Adult Population All Doses (N=165)	Primary HCL Population All Doses (N=129)	Pivotal HCL Population P3_40 µg/kg (N=80)	Adult Population All Doses (N=165)
Rash	14 (10.9%)	4 (5.0%)	16 (9.7%)	1 (0.8%)	1 (1.3%)	1 (0.6%)	1 (0.8%)	0	2 (1.2%)
Face oedema	13 (10.1%)	11 (13.8%)	18 (10.9%)	0	0	0	12 (9.3%)	10 (12.5%)	15 (9.1%)
Hyperkalaemia	13 (10.1%)	6 (7.5%)	15 (9.1%)	1 (0.8%)	1 (1.3%)	1 (0.6%)	3 (2.3%)	2 (2.5%)	3 (1.8%)
Insomnia	13 (10.1%)	8 (10.0%)	15 (9.1%)	0	0	0	0	0	0
Rhinitis	13 (10.1%)	4 (5.0%)	14 (8.5%)	0	0	0	2 (1.6%)	1 (1.3%)	2 (1.2%)
Weight increased	13 (10.1%)	6 (7.5%)	14 (8.5%)	0	0	0	11 (8.5%)	4 (5.0%)	12 (7.3%)
Anxiety	12 (9.3%)	9 (11.3%)	14 (8.5%)	0	0	0	1 (0.8%)	0	1 (0.6%)
Abdominal pain	11 (8.5%)	7 (8.8%)	17 (10.3%)	1 (0.8%)	0	2 (1.2%)	4 (3.1%)	2 (2.5%)	5 (3.0%)
Abdominal distension	10 (7.8%)	10 (12.5%)	13 (7.9%)	0	0	0	6 (4.7%)	6 (7.5%)	7 (4.2%)
Asthenia	10 (7.8%)	10 (12.5%)	11 (6.7%)	1 (0.8%)	1 (1.3%)	1 (0.6%)	7 (5.4%)	7 (8.8%)	8 (4.8%)

AE=adverse event; HCL=hairy cell leukaemia; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; P3=Process 3; PT=preferred term.
a Patients are counted once for each PT regardless of the number of events.

Adverse Drug Reactions

To identify any additional ADR, a detailed review of AEs reported in each of the 2 clinical studies of moxetumomab pasudotox in the population with relapsed or refractory HCL (pivotal Phase 3 study CD-ON-CAT-8015-1053 and phase 1 study, CAT-8015-1001) was conducted. These data were then compared with the AE data from the overall Adult Population. The initial step of ADR identification included review of the most frequent AEs (≥10% of patients) in either of the studies. Many of these were either most commonly associated with underlying disease of HCL (*Quest and Johnston, 2015; Tadmor and Polliack, 2015*), or considered by the investigator mostly as not related to study drug and/or generally confounded by alternate risk factors. TEAEs occurring in <10% of patients in study CD-ON-CAT-8015-1053 and ≥10% of patients in study CAT-8015-1001 were also reviewed. The review of AEs with frequency <10% in either HCL study was conducted if relatedness of these events to moxetumomab pasudotox by the investigator was ≥50%.

Table 41 Adverse drug reactions primary HCL population

Adverse Drug Reaction System Organ Class Preferred Term (MedDRA v19.0)	Primary HCL Population All Doses (N = 129)	
	Any Grade	Grade 3-4
Any AE	109 (84.5%)	12 (9.3%)
Blood and lymphatic system disorders	**9 (7.0%)**	**5 (3.9%)**
Haemolytic uraemic syndrome[a]	9 (7.0%)	5 (3.9%)
Gastrointestinal disorders	**46 (35.7%)**	**2 (1.6%)**
Nausea	46 (35.7%)	2 (1.6%)
General disorders and administration site conditions	**69 (53.5%)**	**0**
Oedema peripheral[b]	69 (53.5%)	0
Injury, poisoning and procedural complications	**32 (24.8%)**	**2 (1.6%)**
Infusion related reaction[c]	32 (24.8%)	2 (1.6%)
Investigations	**60 (46.5%)**	**4 (3.1%)**
Alanine aminotransferase increased/ Aspartate aminotransferase increased	51 (39.5%)	4 (3.1%)
Blood creatinine increased	22 (17.1%)	0
Metabolism and nutrition disorders	**54 (41.9%)**	**1 (0.8%)**
Hypoalbuminaemia[d]	54 (41.9%)	1 (0.8%)
Vascular disorders	**17 (13.2%)**	**2 (1.6%)**
Capillary leak syndrome[e]	17 (13.2%)	2 (1.6%)

AE = adverse event; HCL = hairy cell leukaemia; ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Activities; P3 = Process 3.

a Haemolytic uraemic syndrome included investigator-reported and sponsor-adjudicated haemolytic uraemic syndrome; b Oedema peripheral included oedema peripheral, oedema, localised oedema, face oedema, periorbital oedema, peripheral swelling; c Infusion related reaction included infusion-related reaction, co-occurrence of 2 or more typical symptoms of infusion-related reaction: headache, dizziness, hypotension, myalgia, pyrexia, chills, nausea, and/or vomiting on the day of study drug infusion; d Hypoalbuminemia included hypoalbuminemia, and blood albumin decreased; e Capillary leak syndrome included investigator-reported and sponsor-adjudicated capillary leak syndrome.

Adverse events of special interest

Table 42 Adverse events of special interest and Important Potential Risks by Group Term and PT – Across Adult Populations

Group Term[a] Preferred Term (MedDRA v19.0)	Regardless of Causality, Any Grade			Regardless of Causality, Grade 3-4			Treatment-related, Any Grade		
	Primary HCL Population All Doses (N = 129)	Pivotal HCL Population P3_40 µg/kg (N = 80)	Adult Population All Doses (N = 165)	Primary HCL Population All Doses (N = 129)	Pivotal HCL Population P3_40 µg/kg (N = 80)	Adult Population All Doses (N = 165)	Primary HCL Population All Doses (N = 129)	Pivotal HCL Population P3_40 µg/kg (N = 80)	Adult Population All Doses (N = 165)
Patients with at least 1 event	78 (60.5%)	49 (61.3%)	92 (55.8%)	21 (16.3%)	18 (22.5%)	30 (18.2%)	62 (48.1%)	36 (45.0%)	71 (43.0%)
Adverse Events of Special Interest									
HUS/HUS-like/TMA	**9 (7.0%)**	**7 (8.8%)**	**10 (6.1%)**	**5 (3.9%)**	**5 (6.3%)**	**6 (3.6%)**	**9 (7.0%)**	**7 (8.8%)**	**10 (6.1%)**
Haemolytic uraemic syndrome (investigator-reported)	8 (6.2%)	6 (7.5%)	8 (4.8%)	4 (3.1%)	4 (5.0%)	4 (2.4%)	8 (6.2%)	6 (7.5%)	8 (4.8%)
Sponsor-adjudicated	1 (0.8%)	1 (1.3%)	2 (1.2%)	1 (0.8%)	1 (1.3%)	2 (1.2%)	1 (0.8%)	1 (1.3%)	2 (1.2%)
CLS	**17 (13.2%)**	**7 (8.8%)**	**23 (13.9%)**	**2 (1.6%)**	**2 (2.5%)**	**4 (2.4%)**	**16 (12.4%)**	**7 (8.8%)**	**21 (12.7%)**
Capillary leak syndrome (investigator-reported)	16 (12.4%)	7 (8.8%)	21 (12.7%)	2 (1.6%)	2 (2.5%)	3 (1.8%)	15 (11.6%)	7 (8.8%)	19 (11.5%)
Sponsor-adjudicated	1 (0.8%)	0	2 (1.2%)	0	0	1 (0.6%)	1 (0.8%)	0	2 (1.2%)
Blood Creatinine Increased	**22 (17.1%)**	**9 (11.3%)**	**26 (15.8%)**	**0**	**0**	**1 (0.6%)**	**17 (13.2%)**	**8 (10.0%)**	**19 (11.5%)**
Blood creatinine increased	22 (17.1%)	9 (11.3%)	26 (15.8%)	0	0	1 (0.6%)	17 (13.2%)	8 (10.0%)	19 (11.5%)
Hepatic Function Abnormality	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Potential Hy's law[b]	0	0	0	0	0	0	0	0	0
Ocular Events	**10 (7.8%)**	**10 (12.5%)**	**14 (8.5%)**	**0**	**0**	**0**	**3 (2.3%)**	**3 (3.8%)**	**5 (3.0%)**
Vision blurred	7 (5.4%)	7 (8.8%)	10 (6.1%)	0	0	0	3 (2.3%)	3 (3.8%)	5 (3.0%)
Visual acuity reduced	2 (1.6%)	2 (2.5%)	2 (1.2%)	0	0	0	0	0	0
Vitreous floaters	1 (0.8%)	1 (1.3%)	2 (1.2%)	0	0	0	0	0	0
Pulmonary Oedema	**1 (0.8%)**	**1 (1.3%)**	**3 (1.8%)**	**0**	**0**	**0**	**0**	**0**	**0**
Pulmonary ooedema	1 (0.8%)	1 (1.3%)	1 (0.6%)	0	0	0	0	0	0
Acute respiratory distress syndrome	0	0	1 (0.6%)	0	0	0	0	0	0
Pulmonary congestion	0	0	1 (0.6%)	0	0	0	0	0	0
Important Potential Risks									
Nephrotoxicity	**37 (28.7%)**	**18 (22.5%)**	**46 (27.9%)**	**2 (1.6%)**	**2 (2.5%)**	**4 (2.4%)**	**30 (23.3%)**	**14 (17.5%)**	**35 (21.2%)**
Blood creatinine increased	22 (17.1%)	9 (11.3%)	26 (15.8%)	0	0	1 (0.6%)	17 (13.2%)	8 (10.0%)	19 (11.5%)
Proteinuria	10 (7.8%)	1 (1.3%)	10 (6.1%)	0	0	0	10 (7.8%)	1 (1.3%)	10 (6.1%)
Haematuria	6 (4.7%)	6 (7.5%)	10 (6.1%)	0	0	0	3 (2.3%)	3 (3.8%)	5 (3.0%)
Haemoglubinuria	5 (3.9%)	2 (2.5%)	5 (3.0%)	0	0	0	4 (3.1%)	2 (2.5%)	4 (2.4%)
Acute kidney injury	3 (2.3%)	3 (3.8%)	4 (2.4%)	2 (1.6%)	2 (2.5%)	3 (1.8%)	2 (1.6%)	2 (2.5%)	3 (1.8%)
Renal failure	3 (2.3%)	3 (3.8%)	4 (2.4%)	0	0	1 (0.6%)	3 (2.3%)	3 (3.8%)	4 (2.4%)

Group Term[a] Preferred Term (MedDRA v19.0)	Regardless of Causality, Any Grade			Regardless of Causality, Grade 3-4			Treatment-related, Any Grade		
	Primary HCL Population All Doses (N = 129)	Pivotal HCL Population P3_40 µg/kg (N = 80)	Adult Population All Doses (N = 165)	Primary HCL Population All Doses (N = 129)	Pivotal HCL Population P3_40 µg/kg (N = 80)	Adult Population All Doses (N = 165)	Primary HCL Population All Doses (N = 129)	Pivotal HCL Population P3_40 µg/kg (N = 80)	Adult Population All Doses (N = 165)
Protein urine present	2 (1.6%)	0	3 (1.8%)	0	0	0	2 (1.6%)	0	3 (1.8%)
Renal impairment	2 (1.6%)	2 (2.5%)	2 (1.2%)	0	0	0	1 (0.8%)	1 (1.3%)	1 (0.6%)
Haemoglobin urine present	1 (0.8%)	0	1 (0.6%)	0	0	0	1 (0.8%)	0	1 (0.6%)
Urine output decreased	0	0	1 (0.6%)	0	0	0	0	0	0
Severe Infections	**17 (13.2%)**	**14 (17.5%)**	**23 (13.9%)**	**16 (12.4%)**	**13 (16.3%)**	**21 (12.7%)**	**2 (1.6%)**	**2 (2.5%)**	**2 (1.2%)**
Pneumonia	3 (2.3%)	1 (1.3%)	6 (3.6%)	2 (1.6%)	0	3 (1.8%)	0	0	0
Erysipelas	2 (1.6%)	2 (2.5%)	2 (1.2%)	2 (1.6%)	2 (2.5%)	2 (1.2%)	0	0	0
Lung infection	2 (1.6%)	2 (2.5%)	4 (2.4%)	2 (1.6%)	2 (2.5%)	3 (1.8%)	1 (0.8%)	1 (1.3%)	1 (0.6%)
Upper respiratory tract infection	2 (1.6%)	2 (2.5%)	2 (1.2%)	2 (1.6%)	2 (2.5%)	2 (1.2%)	0	0	0
Clostridium difficile colitis	1 (0.8%)	1 (1.3%)	1 (0.6%)	1 (0.8%)	1 (1.3%)	1 (0.6%)	0	0	0
Clostridium difficile infection	1 (0.8%)	1 (1.3%)	1 (0.6%)	1 (0.8%)	1 (1.3%)	1 (0.6%)	0	0	0
Infection	1 (0.8%)	1 (1.3%)	3 (1.8%)	1 (0.8%)	1 (1.3%)	3 (1.8%)	0	0	0
Neutropenic infection	0	0	1 (0.6%)	0	0	1 (0.6%)	0	0	0
Opportunistic infection	1 (0.8%)	0	1 (0.6%)	1 (0.8%)	0	1 (0.6%)	0	0	0
Pneumonia fungal	1 (0.8%)	1 (1.3%)	1 (0.6%)	1 (0.8%)	1 (1.3%)	1 (0.6%)	0	0	0
Respiratory tract infection	1 (0.8%)	1 (1.3%)	1 (0.6%)	1 (0.8%)	1 (1.3%)	1 (0.6%)	0	0	0
Sepsis syndrome	1 (0.8%)	1 (1.3%)	1 (0.6%)	1 (0.8%)	1 (1.3%)	1 (0.6%)	0	0	0
Septic shock	1 (0.8%)	1 (1.3%)	1 (0.6%)	0	0	0	0	0	0
Sinusitis	1 (0.8%)	1 (1.3%)	1 (0.6%)	1 (0.8%)	1 (1.3%)	1 (0.6%)	0	0	0
Tooth infection	1 (0.8%)	1 (1.3%)	1 (0.6%)	1 (0.8%)	1 (1.3%)	1 (0.6%)	0	0	0
Urinary tract infection	1 (0.8%)	1 (1.3%)	1 (0.6%)	1 (0.8%)	1 (1.3%)	1 (0.6%)	1 (0.8%)	1 (1.3%)	1 (0.6%)
Acute pulmonary histoplasmosis	0	0	1 (0.6%)	0	0	1 (0.6%)	0	0	0
Histoplasmosis	0	0	1 (0.6%)	0	0	1 (0.6%)	0	0	0
TLS Events	**1 (0.8%)**	**1 (1.3%)**	**2 (1.2%)**	**1 (0.8%)**	**1 (1.3%)**	**2 (1.2%)**	**1 (0.8%)**	**1 (1.3%)**	**2 (1.2%)**
Tumour lysis syndrome	1 (0.8%)	1 (1.3%)	2 (1.2%)	1 (0.8%)	1 (1.3%)	2 (1.2%)	1 (0.8%)	1 (1.3%)	2 (1.2%)
CRS and Severe Hypersensitivity	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
IRR[c]	**32 (24.8%)**	**20 (25.0%)**	**32 (19.4%)**	**2 (1.6%)**	**2 (2.5%)**	**2 (1.2%)**	**29 (22.5%)**	**18 (22.5%)**	**29 (17.6%)**
Chills	14 (10.9%)	9 (11.3%)	14 (8.5%)	0	0	0	12 (9.3%)	7 (8.8%)	12 (7.3%)
Nausea	13 (10.1%)	7 (8.8%)	13 (7.9%)	0	0	0	10 (7.8%)	5 (6.3%)	10 (6.1%)
Pyrexia	13 (10.1%)	7 (8.8%)	13 (7.9%)	1 (0.8%)	1 (1.3%)	1 (0.6%)	11 (8.5%)	6 (7.5%)	11 (6.7%)
Myalgia	8 (6.2%)	2 (2.5%)	8 (4.8%)	0	0	0	7 (5.4%)	2 (2.5%)	7 (4.2%)
Hypotension	7 (5.4%)	3 (3.8%)	7 (4.2%)	0	0	0	7 (5.4%)	3 (3.8%)	7 (4.2%)
Infusion related reaction	7 (5.4%)	7 (8.8%)	7 (4.2%)	1 (0.8%)	1 (1.3%)	1 (0.6%)	7 (5.4%)	7 (8.8%)	7 (4.2%)
Vomiting	7 (5.4%)	5 (6.3%)	7 (4.2%)	0	0	0	4 (3.1%)	3 (3.8%)	4 (2.4%)
Dizziness	6 (4.7%)	2 (2.5%)	6 (3.6%)	0	0	0	5 (3.9%)	2 (2.5%)	5 (3.0%)
Headache	6 (4.7%)	3 (3.8%)	6 (3.6%)	0	0	0	5 (3.9%)	2 (2.5%)	5 (3.0%)

Group Term[a] Preferred Term (MedDRA v19.0)	Regardless of Causality, Any Grade			Regardless of Causality, Grade 3-4			Treatment-related, Any Grade		
	Primary HCL Population All Doses (N = 129)	Pivotal HCL Population P3_40 µg/kg (N = 80)	Adult Population All Doses (N = 165)	Primary HCL Population All Doses (N = 129)	Pivotal HCL Population P3_40 µg/kg (N = 80)	Adult Population All Doses (N = 165)	Primary HCL Population All Doses (N = 129)	Pivotal HCL Population P3_40 µg/kg (N = 80)	Adult Population All Doses (N = 165)

ADR=adverse drug reaction; CLS=capillary leak syndrome; CRS=cytokine-release syndrome; HCL=hairy cell leukaemia; HUS=haemolytic uraemic syndrome; IRR=infusion-related reaction; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; P3=Process 3; PT=preferred term; TLS=tumour lysis syndrome; TMA=thrombotic microangiopathy.
A Patients are counted once for each group term and PT regardless of the number of events.
B IRRs are included in this table as they used to be considered important potential risks. However, based on a comprehensive review of available data in 2017, the status of IRRs was changed by the Sponsor from important potential risk to identified risk and an ADR. IRRs are described in the ADR section.

- *Haemolytic Uraemic Syndrome (HUS) (Including HUS-like and TMA)*

In the combined safety database of patients with HCL treated with Lumoxiti, HUS occurred in 7.0% (9/129) of patients, including Grade 3 in 3.1% (4/129) and Grade 4 in 0.8% (1/129).

The median time to first onset of HUS was 36 days (range: 9 115) and may occur during any cycle of treatment with Lumoxiti. Most cases of HUS occurred in the first 9 days (range: 1 to 16) of a treatment cycle. The median time to resolution of HUS was 11.5 days (range: 2-44). All cases resolved, including those who discontinued Lumoxiti.

In study 1053, the median end of treatment creatinine clearance (as estimated by Cockcroft Gault) was higher among patients without HUS (89 mL/min, range 42 to 195) compared to patients with HUS (76 mL/min, range 19 to 96) (SmPC, section 4.8).

Six patients (4.7%; 4 of whom were in the pivotal study) with investigator-reported HUS had concurrent investigator-reported CLS. All of these events were considered to be treatment related.

- *Capillary Leak Syndrome*

In the combined safety database of patients with HCL treated with Lumoxiti, CLS occurred in 13.2% (17/129) of patients, the majority were Grade 2. There were 1.6% (2/129) Grade 4 events.

The median time to onset of CLS was 34 days (range: 5-215) and may occur during any cycle of treatment. Most cases of CLS occurred in the first 8 days (range: 1 to 19) of a treatment cycle. All CLS resolved, with a median time to resolution of 12 days (range: 1-53) (SmPC, section 4.8).

- *Nephrotoxicity*

In the Primary HCL Population, 37 of 129 patients (28.7%) had at least 1 event in the group nephrotoxicity. The majority of the nephrotoxicity events were of Grade 1 or 2 severity and considered by the investigator to be treatment related. SAEs of nephrotoxicity included an isolated event of Grade 2 renal failure, an event of Grade 3 acute kidney injury increased that co-occurred with Grade 3 TLS and Grade 3 urinary tract infection, an event of Grade 1 blood creatinine increased occurring during an AE of CLS, and events of Grade 1 blood creatinine increased, Grade 3 blood creatinine increased and Grade 1 haematuria that were associated with adjudicated HUS-like events.

The rates of nephrotoxicity events that led to moxetumomab discontinuation were similar across 3 adult population (range, 2.3% to 3.8%) and occurred in 3 patients in Primary HCL Population, 3 patients in Pivotal HCL Population and 4 patients in the Adult Population; 2 of these patients discontinued due to co-occurring events of HUS. None of the nephrotoxicity events resulted in death. The vast majority (73.9%) of the nephrotoxicity events resolved.

In the combined safety database of patients with HCL treated with Lumoxiti, nephrotoxicity events of acute kidney injury (2.3%), renal failure (2.3%), renal impairment (1.6%), serum creatinine increased (17.1%), proteinuria (7.8%), haematuria (4.7%), and haemoglobinuria (3.9%) were reported. Grade 3 acute kidney injury occurred in 1.6% (2/129) of patients.

At baseline, 63.6% (82/129) of patients had normal renal function and 33.3% (43/129) of patients had mild renal impairment (creatinine clearance 60-89 mL/min). During treatment, creatinine increased by two or more grades from baseline in 22.4% (29/129) of patients, including increases of Grade 3 in 1.6% (2/129) of patients. At the end of treatment, serum creatinine levels remained elevated at 1.5 to 3 times the upper limit of normal in 5% of patients, with no Grade 3 elevations (SmPC, section 4.8).

- *Increased Blood Creatinine*

In the Primary HCL Population, 22 of 129 patients (17.1%) had at least 1 AESI of increased blood creatinine. All patients had events of Grade 1 or 2 severity, and a majority (17 of 22) were considered by the investigator to be treatment-related events. Two patients (both in the pivotal study) with increased blood creatinine (serious Grade 1 and non-serious Grade 1, respectively) permanently discontinued treatment with moxetumomab pasudotox due to the events (these events were associated with HUS/HUS-like events, which also contributed to treatment discontinuation); both events resolved. None of the blood creatinine increased AESIs resulted in death.

The incidence of Grade 3 or 4 events (< 1%) and events resulting in discontinuation of study drug (≤ 2.5%) was low and similar across the 3 adult populations. The median time to onset of increased blood creatinine was 38.0, 36.5, and 57.0 days for the Pivotal HCL Population, the Adult Population, and the Primary HCL Population, respectively. All but 2 patients with increased blood creatinine recovered with normalisation or return to baseline of creatinine values (one discontinued due to HUS, no information on the second case).

Based on laboratory data at baseline, 109 of 129 patients (86%) in the Primary HCL Population had normal blood creatinine, and 18 patients (4.2%) had Grade 1 elevation based on CTCAE 4.03 upper limit of normal (ULN)-based grading criteria. During treatment, 29.1% of the patients in the Primary HCL Population worsened from normal to Grade 1, with 1.6% worsening from normal to Grade 3 (both of these patients experienced elevated creatinine during an SAE of HUS). Comparing blood creatinine toxicity grade (based on ULN) at EOT vs baseline, 81.7% remained normal, 15.9% worsened, and 2.4% improved.

In study 1053, increases in creatinine up to a maximum of 3 times the upper limit of normal were reported in 11.3% (9/80) of patients. At the end of treatment, serum creatinine levels were within normal limits for the majority (82.5%) of patients. Serum creatinine levels remained elevated above Grade 2 in 5% of patients (4/80), two of these patients had Grade 3 or 4 HUS (SmPC, section 4.8).

- *Hepatic Function Abnormality (Potential Hy's Law)*

AESIs of hepatic function abnormality are defined as any increase in ALT or AST greater than 3 × ULN and concurrent (within 8 days) increase in bilirubin greater than 2 × ULN. Patients meeting these criteria were evaluated for the presence or absence of confounding and alternate aetiologies, which could have included progression of malignant disease in the liver, other disease processes with known hepatic injury, or use of concomitant medications with the potential for hepatotoxicity.

Two patients were considered to have met potential Hy's Law criteria.

- *Ocular Events*

Ocular AESIs are defined as any clinically significant change (as determined by the investigator) in vision, retinal abnormalities, or choroidal disturbance that occurs during the course of each study. Retinal damage may occur in association with HUS.

In the Primary HCL Population, 10 of 129 patients (7.8%) had at least 1 AESI in the group Ocular Events, the PTs reported were Vision Blurred (5.4%), Visual Acuity Reduced (1.6%), and Vitreous Floaters (0.8%). All patients had events of Grade 1 or 2 severity, and 3 patients had treatment-related events of Grade 1 vision blurred. None of the ocular events resulted in permanent discontinuation of moxetumomab pasudotox, dose delay/interruption, or death. The median time to onset of the ocular events was 8.0 days (range 5 to 104 days). Of the 10 patients with ocular events, 9 patients recovered, and 1 patient did not recover.

- *Pulmonary Oedema*

Overall, the rate of AESIs in the pulmonary oedema group was low and consistent across the 3 adult populations (range, 0.8% to 1.8%). None of the events were considered to be treatment-related and all but 1 event (Grade 5 ARDS) were of Grade 1 or 2 severity.

- *Severe Infections*

In the Primary HCL Population, 17 of 129 patients (13.2%) had at least 1 AESI in the group severe infections (defined as Grade 3 or higher). PTs reported in > 1 patient each were pneumonia (3 patients, 2.3%), and erysipelas, lung infection, and upper respiratory tract infection (2 patients, 1.6% each). Few patients (2 of 17) had treatment-related events. Two patients (1.6%) had treatment-related Grade 3 events of lung infection and urinary tract infection; both events resolved. There were no treatment-related Grade 4 events. Three patients (2.3%) permanently discontinued treatment with moxetumomab pasudotox due to events of Grade 5 pneumonia, Grade 3 respiratory tract infection, and Grade 4 sepsis syndrome, respectively; none of these events were considered to be treatment related. The event of respiratory tract infection resolved. The patient with sepsis syndrome subsequently died due to this event.

- *Tumour Lysis Syndrome*

In the Primary HCL Population, 1 of 129 patients (0.8%) experienced a nonserious, treatment-related Grade 3 TLS 9 days after start of treatment with moxetumomab pasudotox; the event resolved 13 days after onset.

- *Cytokine Release Syndrome and Severe Hypersensitivity*

Due to the mechanism of action of moxetumomab and the pharmacological class (immunotoxins) as well as the potential for life-threatening and fatal outcome associated with CRS and severe hypersensitivity reactions, these events are considered important potential risks of moxetumomab pasudotox. However, as of 1 July 2019, no such events have been identified in the moxetumomab pasudotox clinical programme.

- *Infusion-related Reactions*

Infusion-related reactions as reported by investigator or retrospectively defined as two or more symptoms of headache, dizziness, hypotension, myalgia, pyrexia, chills, nausea, and/or vomiting on the day of treatment with study drug occurred in 25% of patients, including Grade 3 in 2.5% of patients. Infusion related reactions may occur during any cycle of treatment with Lumoxiti (SmPC, section 4.8).

In the Primary HCL Population, 7 patients (all in the Phase 3 study) had a PT of IRR reported by the investigator. Most patients with IRR had several non-serious Grade 1 or 2 events that were considered related to moxetumomab pasudotox by the investigator; there was 1 Grade 3 event and 2 SAEs. Time to onset was variable (occurring between Cycle 1, Day 1 and Cycle 5, Day 5); 1 event was associated with the first dose. The most commonly reported signs and symptoms associated with the IRR were chills and pyrexia. One event of infusion-related reaction led to dose interruption; the infusion was resumed and the full prescribed dose was administered. One patient experienced recurrent IRR in a setting where secondary prophylaxis was not instituted after the initial IRR. In other cases, there was no recurrent IRR either in the setting of no secondary prophylaxis (3 of 7) or with institution of secondary prophylaxis (3 of 7).

Serious adverse event/deaths/other significant events

Serious Adverse Events

The frequency of SAEs and treatment related SAEs by SOC and PT across the adult populations is summarised in Table 43.

Table 43 Serious adverse events by SOC and PT – across adult populations

System Organ Class[a] Preferred Term (MedDRA v19.0)	Regardless of Causality			Treatment-related		
	Primary HCL Population All Doses (N=129)	Pivotal HCL Population P3_40 µg/kg (N=80)	Adult Population All Doses (N=165)	Primary HCL Population All Doses (N=129)	Pivotal HCL Population P3_40 µg/kg (N=80)	Adult Population All Doses (N=165)
Patients with at least 1 SAE	34 (26.4%)	28 (35.0%)	47 (28.5%)	16 (12.4%)	14 (17.5%)	21 (12.7%)
Blood and lymphatic system disorders	**12 (9.3%)**	**8 (10.0%)**	**13 (7.9%)**	**8 (6.2%)**	**6 (7.5%)**	**8 (4.8%)**
Febrile neutropenia	4 (3.1%)	2 (2.5%)	5 (3.0%)	0	0	0
Haemolytic uraemic syndrome	8 (6.2%)	6 (7.5%)	8 (4.8%)	8 (6.2%)	6 (7.5%)	8 (4.8%)
Cardiac disorders	**1 (0.8%)**	**1 (1.3%)**	**1 (0.6%)**	**0**	**0**	**0**
Left ventricular dysfunction	1 (0.8%)	1 (1.3%)	1 (0.6%)	0	0	0
Eye disorders	**0**	**0**	**1 (0.6%)**	**0**	**0**	**1 (0.6%)**
Optic ischaemic neuropathy	0	0	1 (0.6%)	0	0	1 (0.6%)
Gastrointestinal disorders	**2 (1.6%)**	**2 (2.5%)**	**2 (1.2%)**	**1 (0.8%)**	**1 (1.3%)**	**1 (0.6%)**
Diarrhoea	1 (0.8%)	1 (1.3%)	1 (0.6%)	1 (0.8%)	1 (1.3%)	1 (0.6%)
Nausea	1 (0.8%)	1 (1.3%)	1 (0.6%)	1 (0.8%)	1 (1.3%)	1 (0.6%)
Neutropenic colitis	1 (0.8%)	1 (1.3%)	1 (0.6%)	0	0	0
Vomiting	1 (0.8%)	1 (1.3%)	1 (0.6%)	1 (0.8%)	1 (1.3%)	1 (0.6%)
General disorders and administration site conditions	**9 (7.0%)**	**8 (10.0%)**	**9 (5.5%)**	**3 (2.3%)**	**3 (3.8%)**	**3 (1.8%)**
Fatigue	1 (0.8%)	1 (1.3%)	1 (0.6%)	1 (0.8%)	1 (1.3%)	1 (0.6%)
Multiple organ dysfunction syndrome	1 (0.8%)	1 (1.3%)	1 (0.6%)	0	0	0
Pain	1 (0.8%)	1 (1.3%)	1 (0.6%)	0	0	0
Pyrexia	6 (4.7%)	5 (6.3%)	6 (3.6%)	2 (1.6%)	2 (2.5%)	2 (1.2%)
Infections and infestations	**10 (7.8%)**	**9 (11.3%)**	**15 (9.1%)**	**0**	**0**	**0**
Acute pulmonary histoplasmosis	0	0	1 (0.6%)	0	0	0
Clostridium difficile colitis	1 (0.8%)	1 (1.3%)	1 (0.6%)	0	0	0

System Organ Class[a] Preferred Term (MedDRA v19.0)	Regardless of Causality			Treatment-related		
	Primary HCL Population All Doses (N=129)	Pivotal HCL Population P3_40 µg/kg (N=80)	Adult Population All Doses (N=165)	Primary HCL Population All Doses (N=129)	Pivotal HCL Population P3_40 µg/kg (N=80)	Adult Population All Doses (N=165)
Erysipelas	1 (0.8%)	1 (1.3%)	1 (0.6%)	0	0	0
Infection	1 (0.8%)	1 (1.3%)	3 (1.8%)	0	0	0
Lung infection	1 (0.8%)	1 (1.3%)	2 (1.2%)	0	0	0
Pneumonia	2 (1.6%)	1 (1.3%)	5 (3.0%)	0	0	0
Pneumonia fungal	1 (0.8%)	1 (1.3%)	1 (0.6%)	0	0	0
Sepsis syndrome	1 (0.8%)	1 (1.3%)	1 (0.6%)	0	0	0
Septic shock	1 (0.8%)	1 (1.3%)	1 (0.6%)	0	0	0
Upper respiratory tract infection	2 (1.6%)	2 (2.5%)	2 (1.2%)	0	0	0
Injury, poisoning and procedural complications	**2 (1.6%)**	**2 (2.5%)**	**2 (1.2%)**	**2 (1.6%)**	**2 (2.5%)**	**2 (1.2%)**
Infusion related reaction	2 (1.6%)	2 (2.5%)	2 (1.2%)	2 (1.6%)	2 (2.5%)	2 (1.2%)
Investigations	**3 (2.3%)**	**2 (2.5%)**	**5 (3.0%)**	**1 (0.8%)**	**1 (1.3%)**	**2 (1.2%)**
Blood calcium increased	0	0	1 (0.6%)	0	0	0
Blood creatinine increased	2 (1.6%)	1 (1.3%)	3 (1.8%)	1 (0.8%)	1 (1.3%)	2 (1.2%)
Haptoglobin decreased	1 (0.8%)	1 (1.3%)	1 (0.6%)	1 (0.8%)	1 (1.3%)	1 (0.6%)
Neutrophil count decreased	1 (0.8%)	1 (1.3%)	1 (0.6%)	0	0	0
Platelet count decreased	1 (0.8%)	1 (1.3%)	1 (0.6%)	1 (0.8%)	1 (1.3%)	1 (0.6%)
Weight increased	1 (0.8%)	1 (1.3%)	1 (0.6%)	1 (0.8%)	1 (1.3%)	1 (0.6%)
Metabolism and nutrition disorders	**0**	**0**	**1 (0.6%)**	**0**	**0**	**1 (0.6%)**
Tumour lysis syndrome	0	0	1 (0.6%)	0	0	1 (0.6%)
Musculoskeletal and connective tissue disorders	**1 (0.8%)**	**1 (1.3%)**	**2 (1.2%)**	**0**	**0**	**0**
Back pain	0	0	1 (0.6%)	0	0	0
Rhabdomyolysis	1 (0.8%)	1 (1.3%)	1 (0.6%)	0	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**1 (0.8%)**	**1 (1.3%)**	**3 (1.8%)**	**0**	**0**	**0**
Diffuse large B-cell lymphoma	0	0	1 (0.6%)	0	0	0
Glioblastoma	1 (0.8%)	1 (1.3%)	1 (0.6%)	0	0	0
Tumour associated fever	0	0	1 (0.6%)	0	0	0
Psychiatric disorders	**1 (0.8%)**	**1 (1.3%)**	**1 (0.6%)**	**0**	**0**	**0**
Mental status change	1 (0.8%)	1 (1.3%)	1 (0.6%)	0	0	0
Renal and urinary disorders	**3 (2.3%)**	**3 (3.8%)**	**4 (2.4%)**	**3 (2.3%)**	**3 (3.8%)**	**4 (2.4%)**
Acute kidney injury	1 (0.8%)	1 (1.3%)	2 (1.2%)	1 (0.8%)	1 (1.3%)	2 (1.2%)
Haematuria	1 (0.8%)	1 (1.3%)	1 (0.6%)	1 (0.8%)	1 (1.3%)	1 (0.6%)
Renal failure	1 (0.8%)	1 (1.3%)	1 (0.6%)	1 (0.8%)	1 (1.3%)	1 (0.6%)
Respiratory, thoracic and mediastinal disorders	**7 (5.4%)**	**5 (6.3%)**	**10 (6.1%)**	**0**	**0**	**1 (0.6%)**
Acute respiratory distress syndrome	0	0	1 (0.6%)	0	0	0
Bronchospasm	1 (0.8%)	0	1 (0.6%)	0	0	0
Cough	1 (0.8%)	1 (1.3%)	1 (0.6%)	0	0	0
Dyspnoea	2 (1.6%)	1 (1.3%)	3 (1.8%)	0	0	1 (0.6%)
Hypoxia	3 (2.3%)	2 (2.5%)	3 (1.8%)	0	0	0
Obstructive airways disorder	0	0	1 (0.6%)	0	0	0
Pharyngeal cyst	1 (0.8%)	1 (1.3%)	1 (0.6%)	0	0	0
Pulmonary embolism	1 (0.8%)	0	1 (0.6%)	0	0	0
Respiratory failure	1 (0.8%)	1 (1.3%)	1 (0.6%)	0	0	0
Tachypnoea	1 (0.8%)	1 (1.3%)	1 (0.6%)	0	0	0
Skin and subcutaneous tissue disorders	**1 (0.8%)**	**1 (1.3%)**	**1 (0.6%)**	**0**	**0**	**0**
Rash	1 (0.8%)	1 (1.3%)	1 (0.6%)	0	0	0
Vascular disorders	**4 (3.1%)**	**4 (5.0%)**	**6 (3.6%)**	**4 (3.1%)**	**4 (5.0%)**	**6 (3.6%)**
Capillary leak syndrome	4 (3.1%)	4 (5.0%)	6 (3.6%)	4 (3.1%)	4 (5.0%)	6 (3.6%)

HCL=hairy cell leukaemia; HUS=haemolytic uraemic syndrome; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; P3=Process 3; PT=preferred term; SAE=serious adverse event; SOC=system organ class. Note: Co-occurring SAEs of increased blood creatinine, haptoglobin decreased, haemoglobinuria, platelet count decreased, and increased weight were considered as a HUS-like event based on Sponsor adjudication.[a] Patients are counted once for each SOC and PT regardless of the number of events.

Deaths

Across the adult populations, there were 20 deaths on-study (12.1%); most of these deaths (14 deaths, 8.5%) were due to underlying disease. The incidence of death due to AEs was similar across the 3 adult populations (Primary HCL Population: 1.6% [2 patients]; Pivotal HCL: 2.5% [2 patients]; Adult Population: 3.0% [5 patients]). Five patients in the Adult Population, of whom 1 was in the Primary HCL Population, had AEs that resulted in death within 30 days of the last dose of study drug. None of the deaths due to AEs were considered related to treatment by the investigator. One patient with FL in Study MI-CP218 experienced a Grade 5 event of ARDS that was initially considered by the investigator as not related to moxetumomab pasudotox as the autopsy revealed underlying PJP infection. However, the possibility of CLS in the development of ARDS could not be ruled out, and the assessment of death by the Sponsor was made as possibly related to moxetumomab pasudotox.

Table 44 Summary of deaths – across adult populations

Population	Primary HCL Population All Doses (N=129)	Pivotal HCL Population P3_40 µg/kg (N=80)	Adult Population All Doses (N=165)
Deaths	**8 (6.2%)**	**4 (5.0%)**	**20 (12.1%)**
≤30 days post-last dose	1 (0.8%)	1 (1.3%)	5 (3.0%)
>30 days post-last dose	7 (5.4%)	3 (3.8%)	15 (9.1%)
Due to study disease	**6 (4.7%)**	**2 (2.5%)**	**14 (8.5%)**
Due to AE[a]	**2 (1.6%)**	**2 (2.5%)**	**5 (3.0%)**
Related to treatment	0	0	0
Other	0	0	1 (0.6%)

AE=adverse event; EOT=end of treatment; HCL=hairy cell leukaemia; ISS=Integrated Summary of Safety; p3=Process 3; PID=patient identification.
a The deaths "due to AE" presented in this table include only those AEs with onset within 30 days after the last dose of study drug. In addition to the deaths due to AE reported above, there was one patient (PID 8352001) in the pivotal study (CD-ON-CAT-8015-1053) who experienced an AE of Grade 4 sepsis syndrome starting 3 days after the last dose of study drug and whose death was reported as due to the AE of sepsis syndrome and the underlying disease of HCL >30 days after last dose of study drug, and one patient (PID 8337003) in the pivotal study (CD-ON-CAT-8015-1053)who discontinued study due to an AE of Grade 4 glioblastoma; the investigator reported that the patient subsequently died approximately 67 days after the last dose of study drug.

Laboratory findings

Haematology parameters

Change from Baseline in Haematology Laboratory Values and Haematology Toxicity Grades: Primary Populations

In the Primary HCL Population, median haemoglobin, platelet, and neutrophil levels were higher than baseline levels both at the last record and during treatment.

Of the patients in the Primary HCL Population with any grade worsening in haematology variables, any worsening to Grade 3 or 4 was most commonly (> 30% of patients) observed for lymphocyte count decreased (65.9%), WBC count decreased (54.7%), and neutrophil count decreased (36.7%).

Platelet count and anaemia decreased to grade 3 or 4 was seen for 21.1% and 20.3%, respectively.

The median time to onset of these events was 3 to 4 days. A majority of the Grade 3 or 4 haematologic abnormalities resolved. The median time to resolution was 3 days for anaemia, 4 days

for decreased platelet count, 8 days for decreased neutrophil count, 20 days for decreased WBC count, and 40 days for decreased lymphocyte count.

For all haematology parameters, patients who had worsening grades on treatment generally improved by EOT.

Table 45 Any grade and grade 3 or 4 worsening in haematology toxicity grade – across adult populations

Laboratory Test	Any Grade Worsening			Any Worsening to Grade 3 or 4		
	Primary HCL Population All Doses (N=129)	Pivotal HCL Population P3_40 µg/kg (N=80)	Adult Population All Doses (N=165)	Primary HCL Population All Doses (N=129)	Pivotal HCL Population P3_40 µg/kg (N=80)	Adult Population All Doses (N=165)
Lymphocyte count decreased	n=129	n=80	n=164	n=129	n=80	n=164
	102 (79.1%)	58 (72.5%)	108 (65.9%)	85 (65.9%)	44 (55.0%)	91 (55.5%)
White blood cell decreased	n=128	n=79	n=162	n=128	n=79	n=162
	78 (60.9%)	42 (53.2%)	86 (53.1%)	70 (54.7%)	38 (48.1%)	71 (43.8%)
Neutrophil count decreased	n=128	n=79	n=162	n=128	n=79	n=162
	58 (45.3%)	33 (41.8%)	71 (43.8%)	47 (36.7%)	25 (31.6%)	57 (35.2%)
Platelet count decreased	n=128	n=79	n=163	n=128	n=79	n=163
	34 (26.6%)	17 (21.5%)	47 (28.8%)	27 (21.1%)	12 (15.2%)	34 (20.9%)
Anaemia	n=128	n=79	n=163	n=128	n=79	n=163
	67 (52.3%)	34 (43.0%)	85 (52.1%)	26 (20.3%)	12 (15.2%)	32 (19.6%)
Lymphocyte count increased	n=129	n=80	n=164	n=129	n=80	n=164
	2 (1.6%)	1 (1.3%)	9 (5.5%)	1 (0.8%)	0	3 (1.8%)

HCL=hairy cell leukaemia; ISS=Integrated Summary of Safety; P3=Process 3. Note: Laboratory tests are sorted by frequency in the Primary HCL Population.

CD4+ T-cell counts were assessed in the pivotal study (CD-ON-CAT-8015-1053). Median CD4+ T-cell count decreased on Cycle 1 Day 8 by 38.5/µl. At all subsequent time points, median CD4+ T-cell counts were at or above baseline, and at EOT, median counts had increased from baseline by 86.5/µL. Toxicity grade shifts from baseline to EOT in CD4 lymphocytes are summarised in

Table 46.

Table 46 Toxicity grades/shifts from baseline to EOT in CD4 lymphocytes – pivotal HCL population (Study CD-ON-CAT-8015-1053; N=80)

Baseline[a]	EOT CD4 Lymphocytes Decrease				
	Normal/ Grade 1	Grade 2	Grade 3	Grade 4	Total
Normal/Grade 1	9 (15.5%)	1 (1.7%)	0	0	10 (17.2%)
Grade 2	9 (15.5%)	24 (41.4%)	1 (1.7%)	0	34 (58.6%)
Grade 3	0	6 (10.3%)	7 (12.1%)	0	13 (22.4%)
Grade 4	0	0	1 (1.7%)	0	1 (1.7%)
Total	18 (31.0%)	31 (53.4%)	9 (15.5%)	0	58 (100%)

Baseline[a]	EOT CD4 Lymphocytes Decrease				
	Normal/ Grade 1	Grade 2	Grade 3	Grade 4	Total
Missing	4	3	0	0	7

EOT=end of treatment; HCL=hairy cell leukaemia.

Note: Normal or Grade 1 is defined as: ≥500/µL; Grade 2 decreased is defined as: <500 – 200/µL; Grade 3 decreased is defined as <200 – 50/µL; Grade 4 decreased is defined as: <50/µL.

[a] Baseline is defined as the last nonmissing value before initial administration of moxetumomab pasudotox.

Abnormal Haematology Values Recorded as Adverse Events

In the Primary HCL Population, the most common (> 10% of patients) abnormal haematology values recorded as Grade 3 or 4 AEs were WBC count decreased (21.7%), lymphopenia (20.9%), lymphocyte count decreased (20.2%), and neutrophil count decreased (10.9%).

Clinical Chemistry

Of the patients in the Primary HCL Population with any grade worsening in chemistry variables, worsening to Grade 3 or 4 was most commonly (>5% of patients) observed for hyperglycemia (6.2%), and increased ALT and hyponatremia (5.5% each). Of note, the incidence of any worsening to Grade 3 or 4 was low for increased creatinine and increased AST (1.6% each). Change for select chemistry parameters (increased creatinine, increased ALT, increased AST, increased blood bilirubin, and hypoalbuminemia) across the adult populations are briefly discussed below.

AST/ALT/bilirubin

During treatment, 2-grade or higher shifts from baseline in ALT or AST occurred in 17 patients (13.4%) and 13 patients (10.2%), respectively. At the EOT, there were no 2 grade or higher shifts in increased ALT or AST. During treatment, 2-grade or higher shifts from baseline in blood bilirubin occurred in 8 patients (6.2%). At the EOT, there were no 2 grade or higher shifts in increased blood bilirubin.

Increased creatinine (grading based on baseline serum creatinine value)

Mean creatinine levels increased from baseline over the course of the study with the highest levels reported at EOT and last record on study.

During treatment, 2-grade or higher shifts from baseline occurred in 29 patients (22.8%); 27 patients (21.3%) worsened from normal to Grade 2 and 2 patients (1.6%) worsened to Grade 3. At the EOT, 2-grade or higher shifts from baseline were experienced by 8 patients (6.3%) who worsened from normal to Grade 2. There were no shifts to Grade 4 on treatment, and no shifts to Grade 3 or 4 at EOT.

Albumin

During treatment, 2-grade or higher shifts from baseline in hypoalbuminemia occurred in 33 patients (25.6%): 30 patients (23.3%) worsened from normal to Grade 2, 2 patients (1.6%) worsened from normal to Grade 3, and 1 patient (0.8%) worsened from Grade 1 to Grade 3. At the EOT, 2-grade shifts in hypoalbuminemia were experienced by 2 patients (1.6%); an additional 4 patients (3.1%) worsened from Grade 1 to Grade 2 at EOT. There were no shifts to Grade 3 or higher in hypoalbuminemia at EOT.

Electrocardiogram findings

Table 47 Number and percentage of patients meeting criteria for notable central ECG internal values – Study CD-ON-CAT-8015-1053

Parameters/ Criteria	Moxetumomab Pasudotox P3_40 µg/kg (N=80)
QTcF value (n=74)	
>450 ms	3 (4.1%)
>480 ms	1 (1.4%)
>500 ms	2 (2.7%)
QTcF change from baseline (n=74)	
>30 ms	12 (16.2%)
>90 ms	1 (1.4%)
QTcB value (n=74)	
>450 ms	7 (9.5%)
>480 ms	1 (1.4%)
>500 ms	2 (2.7%)
QTcB change from baseline (n=74)	
>30 ms	14 (18.9%)
>90 ms	1 (1.4%)
QT value (n=74)	
>450 ms	6 (8.1%)
>500 ms	2 (2.7%)
QT change from baseline (n=74)	
>30 ms	21 (28.4%)
>90 ms	3 (4.1%)

ECG=electrocardiogram; P3=Process 3; QTcB=QTc corrected by Bazett's formula; QTcF=QTc corrected by Fridericia's formula.

Abnormal Chemistry Values Recorded as Adverse Events

In the Primary HCL Population, the most common (>2% of patients) abnormal chemistry values recorded as Grade 3 or 4 AEs were hypophosphatemia (8.5%), hyponatremia (3.9%), and increased ALT (3.1%). No Grade 3 or 4 increased blood creatinine events were reported in the Primary HCL Population. However, the 2 patients with abnormal chemistry values reported as SAEs had events of Grade 1 increased blood creatinine (both associated with HUS). Two patients permanently discontinued treatment with moxetumomab pasudotox due to increased blood creatinine. None of the abnormal chemistry values reported as AEs resulted in death.

Safety in special populations

- **Age**

Table 48 Overall summary of treatment-emergent adverse events by age subgroup - primary HCL population

Subjects[a] with	Age <65 years N = 89	Age ≥65 to <75 years N = 30	Age ≥75 years N = 10
At least one event	88 (98.9%)	30 (100%)	10 (100%)
At least one moxetumomab pasudotox-related event	84 (94.4%)	26 (86.7%)	10 (100%)
At least one event of grade 3-4 severity[b]	66 (74.2%)	23 (76.7%)	7 (70.0%)
At least one moxetumomab pasudotox-related event of grade 3-4 severity[b]	23 (25.8%)	11 (36.7%)	1 (10.0%)
At least one moxetumomab pasudotox-related event resulting in Death (grade 5 severity[b])	0	0	0
At least one serious[c] event	21 (23.6%)	12 (40.0%)	1 (10.0%)
At least one event resulting in death (grade 5 severity[b])	0	1 (3.3%)	1 (10.0%)
Requiring inpatient hospitalisation	19 (21.3%)	8 (26.7%)	1 (10.0%)
- Requiring prolongation of existing hospitalisation	4 (4.5%)	7 (23.3%)	0
- Life-threatening	3 (3.4%)	4 (13.3%)	0
- Persistent or significant disability/incapacity	0	0	0
Important medical event	1 (1.1%)	0	0
At least one moxetumomab pasudotox-related serious[c] event	7 (7.9%)	8 (26.7%)	1 (10.0%)
At least one event leading to discontinuation of moxetumomab pasudotox[d]	6 (6.7%)	7 (23.3%)	2 (20.0%)
At least one moxetumomab pasudotox-related event leading to discontinuation of moxetumomab pasudotox	4 (4.5%)	6 (20.0%)	0
At least one event leading to dose interruption	3 (3.4%)	0	1 (10.0%)
At least one moxetumomab pasudotox-related event leading to dose interruption	2 (2.2%)	0	1 (10.0%)
At least one event leading to dose delay	7 (7.9%)	5 (16.7%)	0
At least one moxetumomab pasudotox-related event leading to dose delay	2 (2.2%)	2 (6.7%)	0
At least one event leading to dose omission	2 (2.2%)	3 (10.0%)	0
At least one moxetumomab pasudotox-related event leading to dose omission	2 (2.2%)	0	0
At least one event leading to dose interruption or dose delay or dose omission	12 (13.5%)	7 (23.3%)	1 (10.0%)
At least one moxetumomab pasudotox-related event leading to dose interruption or dose delay or dose omission	6 (6.7%)	2 (6.7%)	1 (10.0%)
AEs by SOC			
Accidents and injuries	0	0	0
Anticholinergic syndrome	0	0	0
Cardiac disorders	15 (16.9%)	4 (13.3%)	4 (40.0%)
Cerebrovascular disorders	0	0	0

Subjects[a] with	Age <65 years N = 89	Age ≥65 to <75 years N = 30	Age ≥75 years N = 10
Infections and infestations	43 (48.3%)	15 (50.0%)	6 (60.0%)
Nervous system disorders	47 (52.8%)	12 (40.0%)	7 (70.0%)
Psychiatric disorders	18 (20.2%)	3 (10.0%)	3 (30.0%)
Renal and urinary disorders	17 (19.1%)	12 (40.0%)	4 (40.0%)
Vascular disorders	32 (36.0%)	14 (46.7%)	3 (30.0%)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures[e]	13 (14.6%)	4 (13.3%)	3 (30.0%)
Dizziness	11 (12.4%)	4 (13.3%)	2 (20.0%)
Pubis fracture	0	0	1 (10%)
Presyncope	2 (2.2%)	0	0

AE=adverse event; HCL=hairy cell leukaemia; SOC=System Organ Class.

[a] Subjects are counted once for each category regardless of the number of events.

[b] Grade 3: Severe, Grade 4: Life-threatening, Grade 5: Fatal

[c] Serious adverse event criteria: death, life-threatening, required inpatient hospitalisation, prolongation of existing hospitalisation, persistent or significant disability/incapacity, important medical event, congenital anomaly/birth defect (in the offspring of the subject).

[d] Includes subjects with an AE resulting either discontinued from the study or study drug discontinued.

[e] There were no events of postural hypotension, falls, black outs, syncope, loss of consciousness, or ataxia.

Notes: Primary HCL Population includes all subjects in the two HCL studies 1053 and 1001 who received any dose of moxetumomab pasudotox. There are no subjects age >84 years.

- **Gender (male, female)**

The incidence of AEs was generally similar between female (n=25) and male (n=104) patients with HCL for all AE categories. There were no appreciable differences between these subgroups for any of the AEs or AESIs.

- **Race (White, non-white)**

The number of patients with HCL in the non-Caucasian group (n=4) was too small to allow for reliable comparison with the Caucasian group (n=118) and meaningful interpretation of the results.

- **Baseline ECOG PS (0, 1, 2)**

The number of patients with HCL with an ECOG PS of 2 was very small (n=4); therefore, the interpretation of baseline performance status results focuses on any differences seen between patients with an ECOG PS of 0 (n=71) or 1 (n=54).

Notable differences at the PT level are summarised in the table below.

Table 49 Notable differences in adverse events by baseline ECOG performance status – primary HCL population

Preferred Term (MedDRA v19.0)	ECOG PS 0 (N=71)	ECOG PS 1 (N=54)
Any AE		
Aspartate aminotransferase increased	20 (28.2%)	25 (46.3%)
Hypoalbuminaemia	20 (28.2%)	29 (53.7%)
Lymphopenia	9 (12.7%)	20 (37.0%)
Diarrhoea	9 (12.7%)	15 (27.8%)

Preferred Term (MedDRA v19.0)	ECOG PS 0 (N=71)	ECOG PS 1 (N=54)
Weight increased	3 (4.2%)	8 (14.8%)
Hypercholesterolaemia	2 (2.8%)	7 (13.0%)
Grade 3-4 AE		
Lymphopenia	7 (9.9%)	19 (35.2%)
Treatment-related AE		
Aspartate aminotransferase increased	18 (25.4%)	25 (46.3%)
Hypoalbuminaemia	18 (25.4%)	26 (48.1%)

AE=adverse event; ECOG=Eastern Cooperative Oncology Group; HCL=hairy cell leukaemia; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; PS=performance status.

- **Refractory to Purine analogues (PNA)**

The incidence of AEs was similar between PNA-refractory (n = 58) and non PNA-refractory (n = 71) patients with HCL for all AE categories. At the PT level, the only appreciable differences between the subgroups were anaemia (20.7% vs 7.0%), which occurred at a higher rate in patients with PNA-refractory disease, and fatigue (39.4% vs 22.4%) and myalgia (40.8% vs 17.2%), both of which occurred at higher rates in patients with non-PNA- refractory disease.

- **Unfit for PNA – analysed only in study 1053**

At the PT level, the only appreciable difference between the subgroups was abdominal distension (23.3% vs 6.0%) and IRR (14.0% vs 0%), which occurred at a higher rate in patients who were unfit versus fit for PNA therapy. The proportion of patients who reported febrile neutropenia or any AE related to infections and infestations was similar between patients who were unfit versus fit for PNA therapy.

The moxetumomab pasudotox safety profile was also assessed in relation to the following extrinsic factors:

- **Time from last line of PNA to first dose (<12, ≥12 months)**

The frequency of AEs was generally similar between patients who received their last line of PNA therapy <12 months (n=15) or ≥12 months (n=114) prior to first dose for all AE categories.

- **Time from last line of PNA + rituximab to first dose (<24, ≥24 months**

The incidence of AEs was generally comparable between patients who received their last line of PNA + rituximab therapy <24 months (n=10) and ≥24 months (n=18) prior to the first dose. However, treatment-related AEs resulting in discontinuation of study drug occurred at a notably higher rate in patients who received their last line of PNA + rituximab therapy <24 months prior to the first dose (30.0% vs 0%). At the PT level, there were no clinically meaningful differences between the 2 subgroups for any of the AEs or AESIs.

- **Geographic region (US, non-US)**

The incidence of AEs was generally comparable between patients with HCL in the US (n=82) and non-US (n=47) for all AE categories except Grade 3 or 4 AEs (87.8% vs 51.1%, respectively), which occurred at a notably higher rate in US versus non-US patients. At the PT level, some notable differences in AE rates were observed between the US and non-US regions. A majority of the rate differences, nearly all of which were higher in the US region, were seen for events associated with laboratory abnormalities. According to the applicant, this discrepancy could be partially attributed to the fact that most patients enrolled in study CAT-8015-1001 were from the US, and most centres who

participated in that study reported any laboratory abnormality as an AE, irrespective of whether or not the abnormality was clinically significant. Overall, the population of patients enrolled at non-US sites was rather small and nearly 2-fold smaller than the population of patients enrolled in the US.

Immunological events

Moxetumomab pasudotox (CAT-8015) is a recombinant fusion protein or immunotoxin, comprised of a murine anti-CD22 immunoglobulin light chain variable domain and a PE38 (a domain of Pseudomonas Exotoxin A) domain.

Immunogenicity was investigated in two studies; a phase 1 PK study (CAT-8015-1001) and a phase 3 efficacy/safety/immunogenicity study in subjects with relapsed or refractory Hairy Cell Leukaemia (HCL)(CAT-8015-1053)(Table 50).

Phase 1 study - CAT-8015-1001

Immunogenicity studies were to include screening, titre, specificity, and neutralising antibody assays. Patients were required to be neutralising antibody (NAb)-negative at screening and were removed from treatment when developing neutralising ADAs. Subjects testing positive for NAbs were deemed ineligible to either begin treatment with moxetumomab pasudotox, or if already on study, to receive the next cycle of therapy.

Phase 3 study - CAT-8015-1053

Immunogenicity subpopulation studied: ADA positive at any time; ADA always negative; ADA positive subjects who are NAb positive at any visit (ADA+/NAb+); CD22 specificity positive any time of subjects who are ADA+/NAb+; mPE38 specificity positive any time of subjects who are ADA+/NAb+; Titres greater than median of subjects who are ADA+/NAb+.

In Study CD-ON-CAT-8015-1053, there were no immunogenicity criteria for screening or off-treatment decisions; patients could participate in the study regardless of their ADA results at screening and could stay on the study regardless of ADA results during treatment.

In the CSR for the CAT-8015-1001 study, it is stated that samples ADA-positive in the screening assay were subsequently analysed to evaluate the presence of neutralising ADAs against the CD22 binding of moxetumomab pasudotox.

The protocol for the CAT-8015-1053 study describes specificity tests of neutralising activities to both parts of moxetumomab pasudox.

Table 50. Overview of PK and immunogenicity assessments in moxetumomab pasudotox HCL clinical studies

Protocol	PK Sampling Schedule	ADA Sampling Schedule
CD-ON-CAT-8015-1053	Cycle 1 Day 1: Pre, end infusion, 3 hr Day 5: Pre, end infusion, 1, 3, 6 hr Cycle 2 Day 1: Pre, end infusion, 3 hr Cycles 3 and 5 Day 1: Pre, end infusion	Before each treatment cycle After treatment was completed (4 to 6 weeks after last dose) At future follow-up visits to end of study Testing for ADA, nAbs, titers, and specificity
CAT-8015-1001	Cycles 1 and 2 Day 1: Pre, during (15 min), end infusion, 1, 1.5, 2, 4, 8 and 12 hr Day 3: Pre, end of infusion Day 5: Pre, during (15 min), end infusion, 1, 1.5, 2, 4, 8, 12 hr Cycles 3, 5 and subsequent alternate cycles Day 1: Pre, end infusion, 2, 4, 8 hr Day 5: Pre, end infusion, 2, 4, 8 hr	Prior to enrollment Before each treatment cycle Once, after treatment was completed Testing for ADA and nAbs

ADA=antidrug antibodies; HCL=hairy cell leukemia; hr=hour; nAb=neutralizing antibody.
Note: Moxetumomab pasudotox was administered in a 30-minute intravenous infusion in all studies.

PK sampling for both studies were according to protocol. A full sampling schedule was supposed be followed for the first two cycles of moxetumomab. On cycles three, five, and alternate cycles thereafter, samples were going be drawn prior to dosing, immediately before the end of the infusion (0.5 H) and at 2h, 4h, and 8h after the first and third doses of the cycle.

The presence of ADAs was assessed in samples taken from all subjects prior to the start of Cycles 1, 2, 3, and 5, and at the end of treatment (4–6 weeks after the last dose).

In the CAT 8015-1001 study, dosing was to end after ten cycles. In the CAT 8015-1053 study, firstly, there were no limitations regarding treatment cycles, however, until a maximum of six cycles were introduced in amendment six (4) of the protocol.

Bioanalytical methods

The moxetumomab pasudotox screening assay was a validated ELISA that measured antimoxetumomab pasudotox antibodies in human K2-EDTA plasma. The ADA screening assay developed at MedImmun represent an ECL method. The assay cutpoint was determined from a set of individual plasma samples immunodepleted with CAT-8015, which is justified due to the high prevalence of pre-existing antibodies. The assay is characterised by high sensitivity. The drug tolerance is considered acceptable. After transfer of the assay to MedImmune's Mountain View, CA, USA facility the cross-validation data indicate comparable assay performance.

The moxetumomab pasudotox NAb assay performed at CentraLabs was a solid phase ELISA that measured the NAbs that inhibited the binding of moxetumomab pasudotox to CD22. The detection of nAbs against moxetumomab pasudotox in human heparin plasma was done using a cell-based assay. The assay measured neutralisation of moxetumomab pasudotox-induced cytotoxicity in the B-cell lymphoma cell line Raji. The assay detected NAbs to both domains of moxetumomab pasudotox: the CD22 binding and/or the PE38 domains. ADAs with specificity towards CD22-binding domain (ADA1) were determined by percentages of inhibition in the presence of ADA1-specific inhibitor D1, and ADAs with specificity to PE38 domain (ADA2) were determined by percentages of inhibition in the presence of ADA2-specific inhibitor D2.

<u>Immunogenicity results</u>

CAT-8015-1001- study

Subjects with >50% neutralisation of moxetumomab pasudotox based on the NCI neutralising antibody bioassay were excluded from the study. Development of ADA was common in the overall study population, with 50% of subjects developing neutralising antibodies. The neutralisation test regarding ADAs developed at CentraLabs were specific only towards the CD22-part of the immunotoxin. Development of ADA was a criterion for treatment discontinuation, so the impact of ADA on moxetumomab pasudotox exposures is unknown according to the applicant. Subjects developing ADA were less likely to achieve CR and had shorter CR duration than subjects without ADA, however, several patients with high titre ADAs still had considerable response (28% regarding complete response).

CAT-8015-1053 study

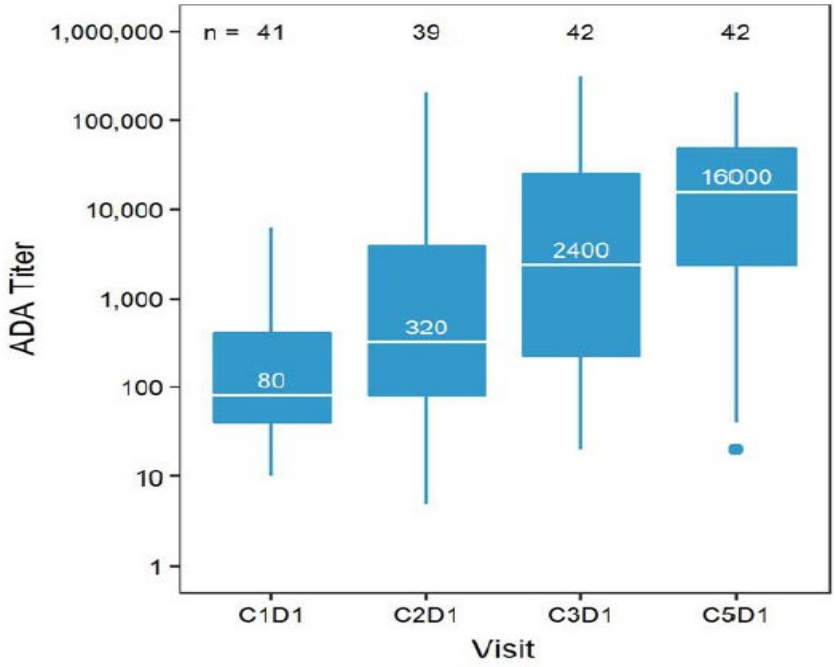
In this study, subjects with ADAs and/or Nabs were not excluded, neither at baseline nor post-treatment. Samples for immunogenicity assessment were available from all 80 treated subjects in the safety populations. Seventy-seven patients with baseline ADA results, 58.4% tested positive for ADAs prior to any treatment with moxetumomab pasudotox. Following moxetumomab pasudotox treatment, 49 of 74 patients (66.2%) with both baseline and post-baseline results developed treatment-emergent ADAs. The ADA prevalence rate was 87.5% (70/80 patients), with NAbs detected in 67 of 80 patients (83.8%). Among the 67 patients who tested NAb positive, the ADAs were 98.5% specific (66/67 patients) to the PE38-binding domain and 55.2% specific (37/67 patients) to the CD22-binding domain. ADA titres were measured for patients with positive NAb results. Titres were generally low at baseline with median titres of 80 (range 10 to 6400), and increased after multiple dosing, where median titres in Cycles 2, 3, and 5 were 320, 2400, and 16000, respectively. The presence of post-baseline ADA was associated with reduced PK exposure at later cycles (Cycle 3 and beyond), consistent with increasing ADA titre levels.

Table 51. Anti-drug antibody responses, safety population, study CD-ON-CAT-1053

ADA Category	Result
Any ADA result	80
ADA+ at any visit	70 (87.5%)
ADA+ patients who are nAb positive at any visit (ADA+/nAb+)	67 (83.8%)
Median of maximum titer[a]	12800.0
(25th percentile, 75th percentile)	(320-51200)
(Min, Max)	(10-512000)
Specificity CD22 positive of ADA+/nAb+ at any visit[g]	37 (55.2%)
Specificity PE38 positive of ADA+/nAb+ at any visit[g]	66 (98.5%)
Baseline ADA result	77
ADA+ at baseline	45 (58.4%)
ADA+ at baseline only	4 (5.2%)
ADA+/nAb+ at baseline only	4 (5.2%)
Median of maximum titer[a]	50.0
(25th percentile, 75th percentile)	(15-120)
(Min, Max)	(10-160)
Post-baseline ADA result	77
ADA+ post-baseline	66 (85.7%)
ADA+ post-baseline only	25 (32.5%)
Persistent Positive[b]	62 (80.5%)
Transient Positive[c]	4 (5.2%)
ADA+/nAb+ at post-baseline only	23 (29.9%)
Median of maximum titer[a]	6400.0
(25th percentile, 75th percentile)	(800-25600)
(Min, Max)	(10-204800)

ADA Category	Result
Baseline and post-baseline ADA result	74
ADA+ post-baseline and positive at baseline	41 (55.4%)
Treatment-boosted[d]	26 (35.1%)
Treatment-induced[e]	23 (31.1%)
ADA incidence[f]	49 (66.2%)
ADA+/nAb+ positive at both baseline and post-baseline	36 (48.6%)
Median of maximum titer[a]	38400.0
(25th percentile, 75th percentile)	(4800-102400)
(Min, Max)	(20-512000)

ADA=antidrug antibodies; nAb=neutralising antibodies.
a Includes ADA+ assessments with reportable ADA titre results.
b Persistent positive is defined as positive at ≥2 post-baseline assessments (with ≥16 weeks between first and last positive) or positive at last post-baseline assessment.
c Transient positive is defined as having at least one post-baseline ADA positive assessment and not fulfilling the conditions of persistently positive.
d Treatment-boosted is defined as baseline positive ADA titre that was boosted to a 16-fold or higher level following drug administration.
e Treatment-induced is defined as ADA negative at baseline and ADA positive post-baseline at any time.
f ADA incidence (Treatment-emergent ADA) is defined as sum of treatment-induced (post-baseline ADA positive only) or treatment-boosted ADA.
g The percentage is based on ADA+ patients who are nAb positive at any visit (ADA+/nAb+)



ADA=antidrug antibody; C=cycle; D=day; HCL=hairy cell leukaemia; IQR=interquartile range (Q3 – Q1); n=number of observations. Notes: Y-axis was log-transformed for visualisation purposes.
Data below the assay cut-point (<10) were presented at 1/2 cut-point for illustration only. Numbers inside boxes represent median values. Upper and lower boxplot whiskers indicate Q3+1.5×IQR and Q1– 1.5×IQR, respectively.

Figure 13. ADA titres in HCL patients with positive neutralising ADA results, Study CD-ON-CAT-8015-1053.

There is a high level of ADAs produced against moxetumomab in treated patients, both baseline (pre-existing) and treatment-emergent. Approximately 30% of patients have neutralising antibodies post-baseline and as many as 81% are persistent positive regarding ADAs.

ADA effects on pharmacokinetics

To evaluate the potential impact of pre-existing antibodies on PK exposures, cycle 1 PK data were compared based on the ADA status at baseline. Peak moxetumomab pasudotox concentrations were also compared according to the ADA category (positive versus negative) at each cycle.

The presence of ADAs post-baseline was associated with statistically significant ($p<0.05$) changes in PK exposure (C_{max}) at later cycles (Cycle 3 and beyond), which is consistent with increasing titre levels. ADA-positive patients in Cycles 3 and 5 exhibited approximately 4- and 26-fold lower median C_{max}, respectively, compared to ADA-negative patients. Moreover, PK exposure (C_{max}) in patients with HCL was inversely related to the ADA titres. Thus, patients with high titres showed reduced PK exposures. Patients who were ADA-positive with high titres had reduced PK exposure compared to ADA-negative patients. In addition, although high titres usually occurred at later time points, patients with high titres were observed at earlier time points as well. For those patients, PK exposures were also lower.

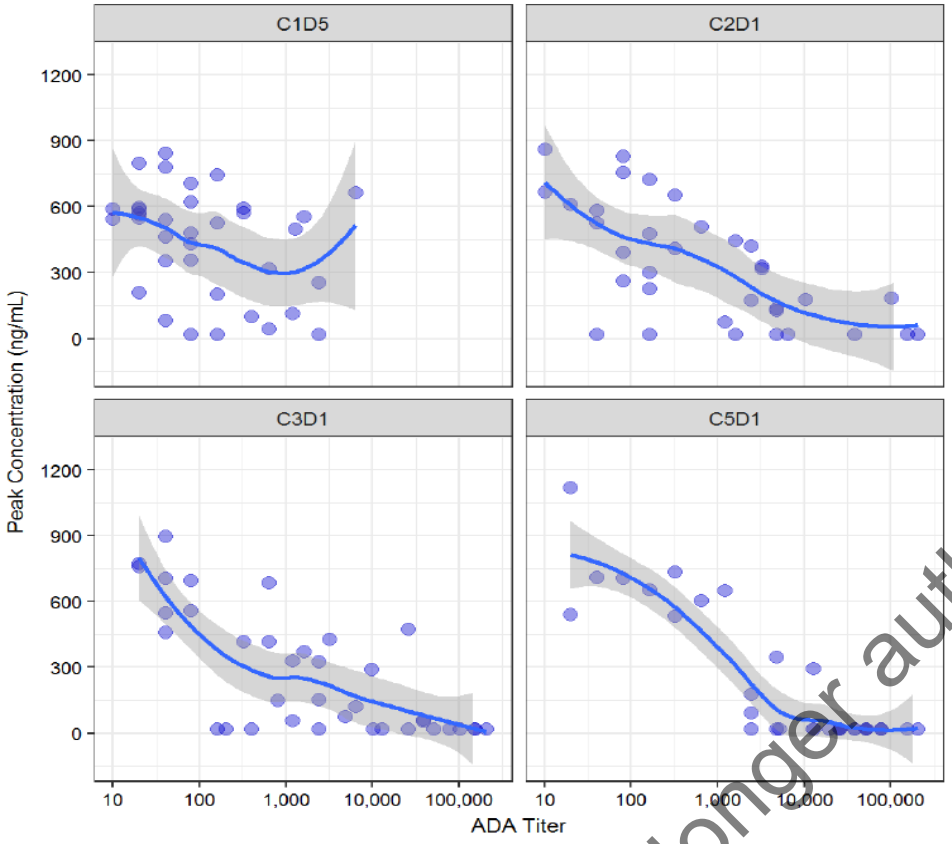


Figure 14. Individual titres vs. moxetumomab pasudotox exposure by cycle

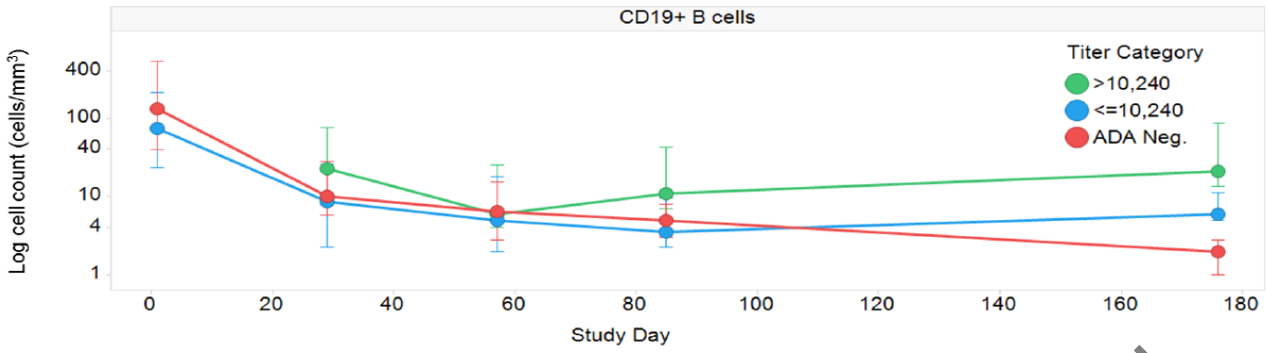
Plasma concentrations of moxetumomab decreased quickly after subsequent ongoing treatment cycles, i.e. in many patients the exposure was reduced to non-detectable levels. Post-treatment, there was a clear correlation between ADA positivity and exposure, and the higher the titre of anti-drug antibodies, the lower exposure of moxetumomab (Figure 14).

ADA effects on pharmacodynamics

Analysis of median baseline (Cycle 1 Day 1 pre-dose) normalised CD19+ B-cell quantities revealed statistically significant reductions at all post-baseline time points up to and including EOT. Median baseline normalised CD19+ B cell quantities returned to baseline levels at 181 days post-EOT. Patients with best overall responses of CR and PR demonstrated a trend of increased durations of median B-cell reductions from baseline compared to patients with stable disease and PD responses.

To assess the effect of ADA on the magnitude of CD19+ B-cell reduction, patients in Study CD-ON-CAT-8015-1053 were assigned to 1 of 3 categories: ADA negative, ADA positive with titres ≤10,240, and ADA positive with no detectable NAbs or ADA positive with titres >10,240. CD19+ B-cell quantities were reduced to equivalent levels among the three categories on Study Days 29, 57, and 85. However, on EOT Study Day 176, the reduction magnitudes were greatest for patients who were ADA negative, followed by ADA-positive patients with titres ≤10,240. Patients with ADA titres >10,240 exhibited the highest CD19+ B-cell counts on study Day 176.

The effects of ADA titre on B-cell quantities post-end-of-treatment are unknown as no ADA samples were collected subsequent to this time point according to the CSR.



Titer Cat.	No. subjects/timepoint				
>10,240	0	4	13	22	27
<=10,240	34	30	25	18	18
ADA Neg.	28	24	20	11	8

Figure 15. Median CD19+ B-cell counts stratified by ADA status over time, study CD-ON-CAT-8015-1053

ADA=antidrug antibody; Cat=category; nAb=neutralising antibody; No.=number.
Notes: >10,240 titre category includes results from ADA-positive patients with nAb titre >10,240; ≤10,240 titre category includes ADA-positive patients with nAb titre ≤10,240 and ADA-positive, nAb negative patients; ADA Neg. titre category includes results from ADA-negative and nAb-negative patients. Median ± 25th-75th percentiles plotted.

The magnitude of CD19+ B-cell reduction was used as PD biomarker on potential influence of ADAs. The applicant also states that the ADA–B cell data (Figure 15) indicate that the magnitude and duration of CD19+ B cell reductions may function as pharmacodynamic markers of moxetumomab pasudotox activity in patients with HCL.

ADA effect on efficacy

Subgroup analysis to correlate disease response and immunogenicity was conducted for the intent-to-treat (ITT) population for Study CD-ON-CAT-8015-1053 (Figure 16 and Figure 17). The durable CR rate as assessed by blinded independent central review (BICR) was 36% (29/80 patients). The CR rate as assessed by BICR is 41.3 % (33/80 patients). Among 10 patients whose ADA status was always negative, six of 10 patients (60%) had CR. Among 32 patients with ADA titres greater than the median, 9 of 32 patients (28.1%) had CR. In patients with high ADA titre, numerically lower CR and durable CR rates were seen, but also in patients with high titre ADAs, a CR on 36% and durable CR on 28% were observed.

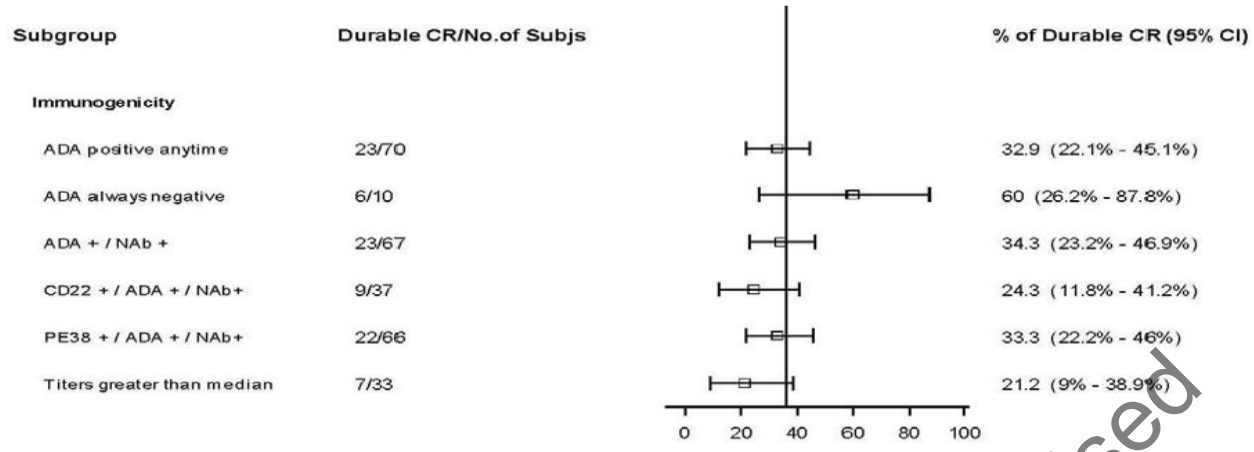


Figure 16. Forest plot of durable CR by immunogenicity status, study CD-ON-CAT-8015-1053

ADA=antidrug antibody; CI=confidence interval; CR=complete response; nAb=neutralising antibody; Subjs=subjects; ITT=intend-to-treat; Vertical line=BICR-assessed durable CR of 30%, for overall ITT population. Source: Section 5.3.5.2, Study CD-ON-CAT-8015-1053 CSR Section 14, Figure 14.2_1.404f

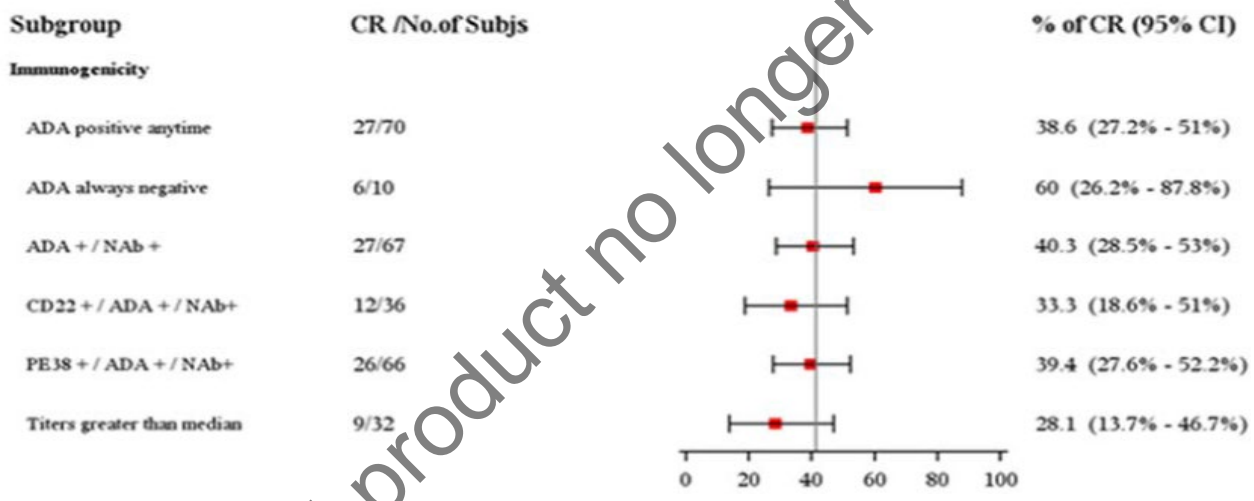


Figure 17. Forest plot of CR by immunogenicity status, study CD-ON-CAT- 8015-1053

ADA=antidrug antibody; CI=confidence interval; CR=complete response; NAb=neutralising antibody; Subjs=subjects; Vertical line=BICR-assessed CR rate of 41.3 %, for overall ITT population. Source: Section 5.3.5.2, Study CD-ON-CAT-8015-1053 CSR Section 14, Figure 14.2_1.403

The forest plots on CR and durable CR show an apparent difference in response between ADA positive patients and ADA negative patients. Sixty percent of ADA negative patients are obtaining a CR, while only 28% of patients with increasing or higher ADA titres are obtaining a CR, which reflects influence of ADAs on the effect of moxetumomab in HCL. However, the results from the ADA-response analyses also indicate that some patients can derive benefit from moxetumomab pasudotox treatment despite high ADA titres.

ADA effects on safety

Subgroup analyses to correlate safety parameters and immunogenicity was conducted for the safety population in Study CD-ON-CAT-8015-1053 (

Table 52). The analyses of safety events by immunogenicity status did not show evidence of correlation between ADA positivity and proportion of patients who developed treatment-related TEAEs of ≥Grade 3 or AEs of HUS/HUS-like, CLS, blood creatinine increased or infusion-related reaction.

However, 70 patients (87.5%) were ADA positive at any time, and only 10 patients (12.5%) were always ADA negative. Because of the low prevalence of ADA-negative patients and limited number of patients with HUS/HUS-like, CLS, and infusion-related reactions, the relationship between ADA status and safety is inconclusive according to the applicant.

A table correlating immunogenicity with safety (same groups as in the table) per cycle, like for efficacy, was adequately received as asked for. However, an explanation on inconsistencies in the numbers compared to a previous table have been requested.

Table 52. Subgroup analysis of safety parameters–Immunogenicity, Safety Population, Study CD-ON-CAT- 8015-1053

Safety Parameter	ADA Positive at Any Time (n=70)	ADA Always Negative (n=10)	ADA-positive Patients who are nAb Positive at Any Visit (ADA+/nAb+) (n=67)	CD22 Specificity Positive at Any Time of Patients Who are ADA+/nAb+ (n=37)	PE38 Specificity Positive Any Time of Patients Who are ADA+/nAb+ (n=66)	Titers > Median of Patients Who are ADA+/nAb+ (n=33) [a]
HUS/HUS-like	5 (7.1%)	1 (10.0%)	5 (7.5%)	1 (2.7%)	5 (7.6%)	1 (3.0%)
CLS	7 (10.0%)	0	7 (10.4%)	4 (10.8%)	7 (10.6%)	1 (3.0%)
Both HUS/HUS-like and CLS	4 (5.7%)	0	4 (6.0%)	1 (2.7%)	4 (6.1%)	0
Infusion-related reaction	7 (10.0%)	0	7 (10.4%)	5 (13.5%)	7 (10.6%)	4 (12.1%)
Severe hypersensitivity reactions to include anaphylaxis and serious allergic reactions	0	0	0	0	0	0
Treatment related TEAE (≥ Grade 3)	22 (31.4%)	2 (20.0%)	21 (31.3%)	11 (29.7%)	21 (31.8%)	7 (21.2%)
Creatinine increased [a]	19 (27.1%)	4 (40.0%)	19 (28.4%)	6 (16.2%)	18 (27.3%)	4 (12.1%)

Safety related to drug-drug interactions and other interactions

No formal drug interaction studies have been conducted with moxetumomab pasudotox.

Discontinuation due to adverse events

In the Primary HCL Population, 15 patients (11.6%) had at least 1 AE that resulted in permanent discontinuation of moxetumomab pasudotox. AEs resulting in permanent discontinuation of moxetumomab pasudotox in >1 patient each were HUS (6 patients, 4.7%), blood creatinine increased and CLS (2 patients, 1.6% each).

Ten patients (7.8%) had treatment-related AEs resulting in permanent discontinuation of moxetumomab pasudotox as assessed by the investigator. Treatment-related AEs occuring in ≥ 1 patient each were HUS (6 patients, 4.7%), blood creatinine increased and CLS (2 patients, 1.6% each). With exception of 1 case of Grade 2 HUS from Pivotal HCL Population, all patients who developed HUS were permanently discontinued.

Post marketing experience

Moxetumomab pasudotox was approved by the US Food and Drug Administration (FDA) on 13 September 2018 at the dose of 40 µg/kg for the treatment of adult patients with relapsed or refractory HCL who received at least 2 prior systemic therapies, including treatment with a PNA. Approximately 42 patients have been exposed to moxetumomab pasudotox in the post-approval setting as of 01 July 2019.

Ten case reports that contained 1 or more SAEs from spontaneous and solicited sources, to include the patient support programme, were received post-launch from 13 September 2018 to 1 July 2019.

There have been post marketing case reports of serious HUS, CLS, relapsed HCL/malignant neoplasm progression and death of unknown causality. Serious events of renal impairment/failure were reported in 3 patients with reported HUS and/or CLS. One serious event of pneumonia and 1 serious event of acute kidney infection was reported in 1 patient each with reported HUS and CLS, respectively. No reports of drug interactions were reported during this time period.

2.6.1. Discussion on clinical safety

In the pivotal study, the median duration of exposure to moxetumomab pasudotox was 5.65 months (min, max: 0.9, 6.7). The majority of patients were exposed for 6 to < 12 months. The median number of treatment cycles was 6. Fifty-four subjects (67.5%) received the maximum of 6 cycles of treatment. The median relative dose intensity was 100% (min, max: 33.2, 103.7).

Overall, 79 subjects (98.8%) experienced at least one AE. The most common AEs were peripheral oedema, nausea, fatigue, headache, and pyrexia. Moxetumomab pasudotox-related AEs were reported in 72 subjects (90%). The most common related AEs were nausea, peripheral oedema, headache, pyrexia, and increased alanine aminotransferase.

SAEs were reported in 28 patients (35%). The most common SAEs were decreased lymphocyte count, anaemia, and hypophosphatemia. Moxetumomab pasudotox related SAEs were reported in 14 patients (17.5%).

Grade 3 or 4 AEs were reported in 54 patients (67.5%); moxetumomab pasudotox related gr 3 or 4 AEs occurred in 24 patients (30%). Grade 3 or 4 infections were reported in 13 patients (16.3%), with no particular type of infection being the most common. Moxetumomab pasudotox-related gr 3 or 4 infections were reported in 2 patients.

A total of 19 patients (23.8%) had at least one event leading to dose interruption, dose delay, or dose omission. Nine patients (11.3%) had at least one moxetumomab pasudotox-related AE leading to dose interruption, dose delay, or dose omission.

Twelve patients (15%) experienced at least one AE leading to discontinuation. Eight patients (10%) had at least one moxetumomab pasudotox-related AE leading to the discontinuation, including 4 HUS and 2 CLS events.

Deaths reported for 2 patients were attributed to AEs that occurred during the AE reporting period; one of these deaths occurred within 30 days of receiving the last dose of moxetumomab pasudotox (septic shock). No moxetumomab pasudotox-related deaths were reported.

Haemolytic uraemic syndrome (HUS) has been reported in patients treated with Lumoxiti and is characterised by the triad of microangiopathic haemolytic anaemia, thrombocytopenia, and progressive renal failure (SmPC, section 4.4).

Lumoxiti should be avoided in patients with prior history of severe thrombotic microangiopathy (TMA) or HUS. Prophylactic fluids are recommended during treatment with Lumoxiti (see section 4.2). In Study 1053, patients with a platelet count ≥100,000/mm3 received low-dose aspirin on Days 1 through 8 of each 28 day cycle for prophylaxis of renal insufficiency (SmPC, section 4.4).

Blood chemistry and complete blood counts should be monitored prior to each dose and as clinically indicated during treatment. Monitoring mid cycle is also recommended. Diagnosis of HUS should be considered in patients who develop haemolytic anaemia, worsening or sudden onset of thrombocytopenia, worsening of renal function, elevation of bilirubin and/or LDH, and have evidence of haemolysis based on peripheral blood smear schistocytes (SmPC, section 4.4).

The events of HUS may be life-threatening if treatment is delayed with increased risk of progressive renal failure requiring dialysis. If HUS is suspected appropriate supportive measures including fluid repletion and haemodynamic monitoring should be initiated, and hospitalisation as clinically indicated should be considered. For Grade 2 HUS, treatment with Lumoxiti should be withheld until resolution, and permanently discontinued for Grade ≥3 HUS (SmPC, section 4.4).

Capillary leak syndrome (CLS) has been reported among patients treated with Lumoxiti and is characterised by hypoalbuminaemia, hypotension, symptoms of fluid overload and haemoconcentration (SmPC, section 4.4).

The important identified risks of CLS and HUS events were generally manageable and reversible with the implementation of supportive care (including adequate hydration and close monitoring of blood pressure, body weight, blood creatinine level, and numbers of schistocytes in peripheral blood smear) and treatment discontinuation. There were no Grade 5 events of CLS or HUS.

Patient weight and blood pressure should be monitored prior to each Lumoxiti infusion and as clinically indicated during treatment. Patients should be assessed for signs and symptoms of CLS including weight gain (≥10% from Day 1 of current cycle), hypotension, peripheral oedema, shortness of breath or cough, and pulmonary oedema and/or serosal effusions. In addition, the following changes in laboratory parameters may help identify CLS: hypoalbuminemia, elevated haematocrit, leucocytosis and thrombocytosis (SmPC, section 4.4).

CLS may be life-threatening or fatal if treatment is delayed. Patients should be advised to seek immediate medical attention should signs or symptoms of CLS occur at any time. Patients who develop CLS should receive appropriate supportive measures, including concomitant oral or IV corticosteroids, and hospitalisation as clinically indicated. For Grade 2 CLS, treatment with Lumoxiti should be withheld until resolution, and permanently discontinued for Grade ≥3 CLS (SmPC, section 4.4).

Nephrotoxicity has been reported in patients treated with Lumoxiti therapy (SmPC, section 4.4).

Patients who experience HUS, those ≥65 years of age, or those with baseline renal impairment may be at increased risk for worsening of renal function following treatment with Lumoxiti. Treatment with Lumoxiti is not recommended in patients with pre-existing severe renal impairment (creatinine clearance ≤29 mL/min) (SmPC, section 4.4).

Renal function should be monitored prior to each infusion of Lumoxiti, and as clinically indicated throughout treatment. Lumoxiti dosing should be delayed in patients with Grade ≥3 elevations in creatinine, or upon worsening from baseline by 2 or more grades (SmPC, section 4.4).

Haematology parameters of haemoglobin, neutrophil count, and platelet counts improved during and after treatment with moxetumomab pasudotox.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say it is essentially 'sodium-free' (SmPC, section 4.4).

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded (SmPC, section 4.4).

There is no specific treatment for moxetumomab pasudotox overdose. In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment should be instituted immediately (SmPC, section 4.7).

In the Pivotal Study CD-ON-CAT-8015-1053, 13 subjects had at least 1 QTcF measurement that showed an increase from baseline by >30 msec. Of the 13 subjects, 1 subject experienced a QTcF increase by >60 msec from baseline. For 11 of the 13 subjects with a change in the QTcF interval from

baseline >30 msec, the change was temporary and followed by a reduction in QTcF interval on consecutive visits.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

Additional safety data needed in the context of a MA under exceptional circumstances

The CHMP agreed that the applicant is unable to provide comprehensive data on the efficacy and safety under normal conditions of use because the indication is too rare. Therefore, the CHMP recommended that a marketing authorisation under "exceptional circumstances" be granted due to the rarity of the disease. In this context, the applicant is required to submit the results from a non-interventional post-authorisation study based on data from a disease registry in HCL patients.

2.6.2. Conclusions on the clinical safety

The safety profile is consistent with what could be expected from a product containing an immunotoxin, however it appears to be manageable in the small RR HCL population it was studied.

The CHMP agreed that the applicant is unable to provide comprehensive data on the efficacy and safety under normal conditions of use because of the rarity of the disease. In the context of marketing authorisation under exceptional circumstances, the applicant is required to submit the results from a non-interventional post-authorisation study based on data from a disease registry in HCL patients.

2.7. Risk Management Plan

Safety concerns

Table 53: **Summary of the safety concerns**

Important identified risks	HUS CLS
Important potential risks	Nephrotoxicity Severe infections CRS
Missing information	None

CLS = capillary leak syndrome; CRS = cytokine release syndrome; HUS = haemolytic uraemic syndrome.

Pharmacovigilance plan

Table 54: **Ongoing and planned additional pharmacovigilance activities**

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Planned safety disease registry study	Primary: To further evaluate the safety concerns (important identified and important potential safety risks) of moxetumomab pasudotox in the treatment of patients with relapsed or refractory HCL who have received at least 2 prior systemic therapies, including prior treatment with a PNA. Secondary: To further evaluate effectiveness of moxetumomab pasudotox among patients with relapsed or refractory HCL under conditions of routine clinical care	Important identified risks: HUS, CLS Important potential risks: Nephrotoxicity, severe infections, CRS	Draft protocol Annual reports Final study report	Within 4 months of approval Annually

CLS = capillary leak syndrome; CRS = cytokine release syndrome; HCL = hairy cell leukaemia; HUS = haemolytic uraemic syndrome; PNA = purine nucleoside analogue.

Risk minimisation measures

Table 55: **Summary table of pharmacovigilance activities and risk minimisation activities by safety concern**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
HUS	Routine risk minimisation measures: • SmPC Sections 4.2, 4.4, and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for spontaneous reports Additional PV: PASS (disease registry study)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
CLS	Routine risk minimisation measures: • SmPC Sections 4.2, 4.4, and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for spontaneous reports Additional PV: PASS (disease registry study)
Nephrotoxicity	Routine risk minimisation measures: • SmPC Sections 4.2, and 4.4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for spontaneous reports Additional PV: PASS (disease registry study)
Severe infections	None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for spontaneous reports Additional PV: PASS (disease registry study)
Cytokine release syndrome	None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for spontaneous reports Additional PV: PASS (disease registry study)

AE = adverse event; CLS = capillary leak syndrome; HUS = haemolytic uraemic syndrome; PASS = post authorisation safety study; SmPC = Summary of Product Characteristics.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.3, dated 30th October 2020, is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

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

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

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

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

2.10. Product information

2.10.1. User consultation

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

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Lumoxiti (moxetumomab pasudotox) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU and it is approved under exceptional circumstances [REG Art 14(8), DIR Art (22)].

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

Lumoxiti as monotherapy is for the treatment of adult patients with relapsed or refractory hairy cell leukaemia (HCL) after receiving at least two prior systemic therapies, including treatment with a purine nucleoside analogue (PNA).

3.1.1. Disease or condition

Hairy cell leukaemia is an indolent chronic B-cell malignancy with multiple treatment options, including several that are investigational and not approved for use in HCL. Patients present with progressive pancytopenia, splenomegaly and abnormal circulating lymphocytes. Treatment is reserved for patients that develop significant cytopenias, symptomatic splenomegaly or opportunistic infections. Though nearly all patients respond to initial therapy, ultimately, these patients will relapse. Patients achieving CR and that are fit for further PNA treatment are at good prognosis; a normal lifespan is expected.

HCL is a rare disease worldwide, with an incidence of less than 1 per 100.000 persons per year. Median age at presentation is 52 years in Europe, and it is 3-4 times more frequent in males (Tadmor et al, 2015).

A variant HCL (HCLv) accounts for approximately 10% of the total HCL population. According to WHO, HCLv is classified as a separate disease (WHO classification of lymphoid neoplasms, 2008- revised in 2016) and the guidelines give separate treatment recommendations for this variant. It is documented in the literature that HCLv has a poorer prognosis than classical HCL.

3.1.2. Available therapies and unmet medical need

The European (ESMO) and American (NCCN) guidelines both clearly recommend PNA with or without rituximab in 1st and 2nd line therapy. Refractory patients are not clearly defined in the guidelines, however it is reasonable to interpret refractory patients as patients not achieving remission (complete or partial) after PNA treatment (in any line) and/or an early relapse after PNA treatment. Another designation for refractory is therapy resistant. Both European and American guidelines have in common that there is no standard of care for multiple relapsed HCL patients or HCL patients refractory to PNA treatment.

With the PNAs, 80-90% of the patients reach a complete response and remain disease free for many years; median relapse-free survival is 16 years (Else et al, Br J Haematol- 2009). At relapse, treating with the same agent or a different PNA will result in another remission in the majority of the patients. However, the duration of the CR decreases after 2nd line treatment with a PNA; relapse-free survival is 11 years (Else et al, 2009). After 3rd line therapy with PNA, CR rate declines to approximately 50% with a relapse-free survival of 6.5 years. There are no published results from prospective clinical studies of 3L+ treatment with PNA or in patients with HCL that was reported as refractory to prior PNA.

Despite most patients achieving a second CR, response rates and length of remission decrease with subsequent therapies. In addition, patients treated with more than one line of PNA therapy, may potentially develop enhanced PNA-related toxicities, i.e. bone marrow depression followed by risk of infections, bleeding and anaemia. Thus, stating an unmet medical need for the HCL population refractory to PNA or multiple relapsed with PNA-related toxicity, is acknowledged.

3.1.3. Main clinical studies

The clinical package of moxetumomab pasudotox was primarily supported by data from a Phase 3, multicentre, open-label, single-arm study intended to evaluate efficacy, safety, immunogenicity and PK of moxetumomab pasudotox monotherapy in adults with relapsed or refractory HCL (Study CD-ON-CAT-8015-1053).

3.2. Favourable effects

The primary endpoint for the pivotal trial 1053, durable complete response (>180 days) rate by BICR was met and was observed in 29/80 patients (36.3%). Of those, 26 were MRD negative responses by central pathology review; 23/26 MRD negative patients had a CR with haematologic remission >360 days.

The outcomes of the secondary endpoints support the primary endpoint results:

- ORR (BICR) was observed in 60/80 patients, 75% (95% CI 64.1, 84): CR 41.3%, PR 33.8%, SD 15% and PD 2.5%. Among the 60 patients who achieved an objective response, 31 (51.7%) were MRD negative by BICR-assessed IHC (27 CR and 4 PR patients). The time to objective response was 5.7 months. The median duration of CR by KM analysis was 62.8 months (95% CI 35.7. 62.8).

Haematologic remission (normalisation of haematologic parameters without growth factors or transfusions in 4 weeks) was observed in 64/80 patients (80%) with a median time to HR of 1.1 months and a median duration of HR of 45.8 months. There were no meaningful differences in the CR rate or ORR based on the number of PNA previous lines; PNA-refractory, PNA-unfit and the overall ITT population.

- Thirty PFS events (BICR) were reported in the ITT population with a mPFS of 41.5 months (28.1; 71.7).

The results with moxetumomab pasudotox in 3rd line are numerically superior to the last prior cancer treatment in the ITT population.

3.3. Uncertainties and limitations about favourable effects

The application is based on a single arm trial of very limited size (in a rare cancer). Point estimates of efficacy are uncertain. Furthermore, the impact of patient selection on efficacy is not fully understood. Furthermore, there are no data to isolate drug effects on PFS and OS.

In addition, overall survival data have not been presented. The disease registry in HCL patients that will be conducted post-authorisation is expected to gather additional efficacy data, including overall survival.

3.4. Unfavourable effects

- AEs were reported in 79 patients (98.8%). The most common AEs were peripheral oedema, nausea, fatigue, headache, and pyrexia. Moxetumomab pasudotox-related AEs were reported in 72 patients (90%). The most common related AEs were nausea, peripheral oedema, headache, pyrexia, and increased alanine aminotransferase.

- SAEs were reported in 28 patients (35%). The most common SAEs were decreased lymphocyte count, anaemia, and hypophosphatemia. Moxetumomab pasudotox related SAEs were reported in 14 patients (17.5%).

- Grade 3-4 AEs were reported in 54 patients (67.5%); moxetumomab pasudotox related gr 3 or 4 AEs occurred in 24 patients (30%).

- Grade 3 or 4 infections were reported in 13 patients (16.3%), with no particular type of infection being the most common. Moxetumomab pasudotox-related gr 3 or 4 infections were reported in 2 patients.

- Treatment discontinuation due to moxetumomab pasudotox related AEs was reported in 8 patients (10%), including 4 HUS and 2 CLS.

- Deaths attributed to AEs were reported for 2 patients; one of these deaths occurred within 30 days of receiving the last dose of moxetumomab pasudotox (septic shock). No moxetumomab pasudotox-related deaths were reported.

- The important identified risks of CLS and HUS events were generally manageable and reversible with the implementation of supportive care. There were no gr 5 events of CLS or HUS.

3.5. Uncertainties and limitations about unfavourable effects

The uncertainties about unfavourable effects are related to the limited number of patients treated with moxetumomab pasudotox in 3rd line RR HCL, and the single arm nature of the study. Long-term safety data are not available, however this issue is perhaps partially mitigated by the fact that the administration of the product is limited to a maximum of 6 cycles of therapy (or less, depending on response). The disease registry in HCL patients that will be conducted post-authorisation is expected to gather long-term safety data.

3.6. Effects Table

Table 56. Effects table for Lumoxiti in HCL (data cut-off: April 2019).

Effect	Short description	Unit	Treatment	Result	Uncertainties / Strength of evidence	References
Favourable Effects						
Durable CR by BICR	Defined as CR per blood, bone marrow, and imaging criteria for CR, with HR lasting >180 days.	Percentage (%)	Moxetumomab pasudotox (40 µg/kg)	36.3 (25.8, 47.8)	Single arm trial of very limited size / (95% CI)	Study CD-ON-CAT-8015-1053

Effect	Short description	Unit	Treatment	Result	Uncertainties / Strength of evidence	References
CR by BICR with HR ≥360 days; post-hoc analysis [a]	Defined as CR per blood, bone marrow, and imaging criteria for CR, with HR ≥360 days	Percentage (%)	Moxetumomab pasudotox (40 µg/kg)	32.5 (22.4, 43.9)	95% CI	
Duration of HR from onset of CR, median [b]		Months (range)	Moxetumomab pasudotox (40 µg/kg)	62.8 (35.7, 62.8) (min 0.1+, max 62.8)	95% CI	
Unfavourable Effects						
Any AEs	Incidence as percentage of patients involved	Percentage (%)		98.8%; Grade 3-4: 67.5%		
AEs related to treatment	Incidence as percentage of patients involved	Percentage (%)		90%; SAEs: 30%		
SAEs At least 1 SAE		Percentage (%)		35%: CLS 4 pt (5%); HUS 6 pt (7.5%); infections: 9 pt (11.3%)		
Treatment-related SAEs				17.5%: CLS 4 pt; HUS 6 pt; pyrexia 2 pt; IRR 2 pt		

Abbreviations: AE: adverse event, BICR: blinded independent central review, CI: confidence interval, CLS: capillary leak syndrome, CR: complete response, HR: haematologic remission, HUS: haemolytic uraemic syndrome, SAE: serious adverse event

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

HCL patients receive treatment when in need of therapy, regardless of treatment line, otherwise the strategy is "watch and wait". The patients included in the study 1053 were all in need of treatment, i.e. in haematologic relapse, with declining haematologic parameters (low counts) requiring intervention (transfusions; growth factors); or having symptoms related to reoccurrence of the disease. Prompt and durable improvement of these mentioned parameters defines clinical benefit, together with adequate complete response rates (especially MRD-negative CR), durable CR rates and high ORRs.

The safety profile is consistent with what could be expected from a product containing an immunotoxin, however moxetumomab pasudotox appears to have a manageable safety profile in the small RR HCL population it was studied.

3.7.2. Balance of benefits and risks

The durable CR rate (36.3%) reported in the pivotal phase 3 study is of clinical relevance since the long lasting haematologic remission implicated by this endpoint must be interpreted as advantageous for these patients for whom cytopenias are the main challenge in everyday life. Furthermore, long lasting haematologic remission could be considered a clinical benefit irrespective of achieving CR. Phase 3 study 1053 showed clinical benefit of moxetumomab pasudotox as durable and deep complete responses, with a manageable safety profile.

3.7.3. Additional considerations on the benefit-risk balance

Marketing authorisation under exceptional circumstances

As comprehensive data on the product are not available due to the rarity of the disease, a marketing authorisation under exceptional circumstances was requested by the applicant in the initial submission.

The incidence of HCL is less than 1 per 100 000 persons per year. The exact incidence of the relapsed/refractory population is difficult to be established with certainty; however, it is stated in the literature that 30-40% of the patients will relapse within 10 years.

The CHMP considers that the applicant has sufficiently demonstrated that it is not possible to provide comprehensive data on the efficacy and safety under normal conditions of use, because the indication applied for is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence. In this context, the applicant is required to submit the results from a non-interventional post-authorisation study based on data from a disease registry in HCL patients.

Therefore, recommending a marketing authorisation under exceptional circumstances is considered appropriate.

3.8. Conclusions

The overall B/R of Lumoxiti is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Lumoxiti is favourable in the following indication:

Lumoxiti as monotherapy is indicated for the treatment of adult patients with relapsed or refractory hairy cell leukaemia (HCL) after receiving at least two prior systemic therapies, including treatment with a purine nucleoside analogue (PNA).

The CHMP therefore recommends the granting of the marketing authorisation under exceptional circumstances subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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

Specific Obligation to complete post-authorisation measures for the marketing authorisation under exceptional circumstances

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
Non-interventional post-authorisation safety study (PASS): In order to further evaluate the safety and efficacy of moxetumomab pasudotox under routine clinical practice for the treatment of patients with relapsed or refractory HCL (who have received at least 2 prior systemic therapies, including prior treatment with a PNA), the MAH should conduct and submit the results of a study based on data from a disease registry in HCL patients according to an agreed protocol.	Annually as part of the annual reassessment

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

Not applicable.

New Active Substance Status

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