15 September 2022
EMA/CHMP/834750/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zynlonta

International non-proprietary name: loncastuximab tesirine

Procedure No. EMEA/H/C/005685/0000

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:	Zynlonta
Applicant:	ADC Therapeutics (NL) B.V. Laarderhoogtweg 25 1101 EB Amsterdam NETHERLANDS
Active substance:	Loncastuximab tesirine
International Non-proprietary Name/Common Name:	loncastuximab tesirine
Pharmaco-therapeutic group (ATC Code):	Antineoplastic and immunomodulating agents, antineoplastic agents, monoclonal antibodies and antibody drug conjugates, other monoclonal antibodies and antibody drug conjugates (ATC L01FX22)
Therapeutic indication(s):	Zynlonta as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy.
Pharmaceutical form(s):	Powder for concentrate for solution for infusion
Strength(s):	10 mg
Route(s) of administration:	Intravenous use
Packaging:	vial (glass)
Package size(s):	1 vial

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List of abbreviations

Abbreviation	Definition
3L	third line
ADA	antidrug antibody
ADC	antibody-drug conjugate
ADCC	antibody-dependent cell-mediated cytotoxicity
ADR	adverse drug reaction
AE	adverse event
AEX	anion exchange chromatography
AlloSCT	allogeneic stem cell transplant
ALT	alanine aminotransferase
AS	active substance
ASCT	autologous stem cell transplant
AST	aggressive salvage therapy
B-ALL	B-cell acute lymphoblastic leukaemia
B-NHL	B-cell lineage non-Hodgkin lymphoma
BOR	best overall response
BR	bendamustine and rituximab
CAR-T	chimeric antigen receptor T-cell
C_{avg}	average serum concentration
CCS	container closure system
CD	human cluster of differentiation
CDC	complement dependent cytotoxicity
CE-SDS	capillary electrophoresis sodium dodecyl sulfate
CEX	cation exchange chromatography
CHO	Chinese hamster ovary
CR	complete response
CRR	complete response rate
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
CYP	cytochrome P450
DAR	drug-to-antibody ratio
DHAP	cisplatin, cytarabine, dexamethasone
DHAX	dexamethasone, cytarabine, oxaliplatin
DLBCL	diffuse large B-cell lymphoma
DoE	design of experiments
DOR	duration of response
ECG	electrocardiogram
ESMO	European Society for Medical Oncology
FL	follicular lymphoma
FMEA	failure mode effect analysis
FP	finished product
GC	gas chromatography
GDP	gemcitabine, dexamethasone, cisplatin
GGT	gamma-glutamyl transferase
FACT-G	functional assessment of cancer therapy-general
FACT-Lym	functional assessment of cancer therapy-lymphoma

HCP	host cell protein
HD	high-dose (chemotherapy)
HPLC	High performance liquid chromatography
HRQoL	health-related quality of life
ICE	ifosfamide, carboplatin, etoposide
ICH	International Conference on Harmonisation
icIEF	imaged capillary isoelectric focusing
ICP-MS	inductively coupled plasma mass spectrometry
IR	infrared spectroscopy
ISS	integrated summary of safety
LFT	liver function test
LT	loncastuximab tesirine
mAb	monoclonal antibody
MCB	master cell bank
MCL	mantle cell lymphoma
MZL	marginal zone lymphoma
NMR	nuclear magnetic resonance
NOR	normal operating ranges
NOS	not otherwise specified
ORR	objective response rate
PAR	proven acceptable ranges
PBD	pyrrolobenzodiazepine
PFS	progression-free survival
Ph. Eur.	European Pharmacopoeia
PPQ	process performance qualification
RH	relative humidity
RMP	risk management plan
R/R	relapsed/refractory
SEC-HPLC	size-exclusion high performance liquid chromatography
SM	starting material
TTC	threshold of toxicological concern
WCB	working cell bank

1. Background information on the procedure

1.1. Submission of the dossier

The applicant FGK Representative Service GmbH (*) submitted on 6 October 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Zynlonta, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

Zynlonta, was designated as an orphan medicinal product EU/3/21/2481 on 20 August 2021 in the following condition: Treatment of diffuse large B-cell lymphoma.

The applicant applied for the following indication:

"Zynlonta is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low grade lymphoma, and high-grade B- cell lymphoma".

The finally approved indication is:

Zynlonta as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy.

(*) During the procedure the applicant changed from FGK Representative Service GmbH to ADC Therapeutics (NL) B.V. Relevant documents for the change of applicant have been provided, validated and agreed.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Zynlonta 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/Zynlonta

1.2. Legal basis, dossier content

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 test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0400/2021 on the granting of deferral and on granting a product-specific waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Applicant's request(s) for consideration

1.5.1. Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation.

1.5.2. New active Substance status

The applicant requested the active substance loncastuximab tesirine 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.

1.6. Protocol assistance

The applicant did not seek Protocol assistance from the CHMP.

1.7. Steps taken for the assessment of the product

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

Rapporteur: Aaron Sosa Mejia Co-Rapporteur: Alexandre Moreau

The application was received by the EMA on	6 October 2021
The procedure started on	28 October 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 January 2022
The CHMP Co-Rapporteur's critique was circulated to all CHMP and PRAC members on	31 January 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	31 January 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 February 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	24 February 2022

The applicant submitted the responses to the CHMP consolidated List of Questions on	30 May 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	27 June 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	07 July 2022
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	21 July 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	12 August 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	31 August 2022
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 Zynlonta on	15 September 2022
The CHMP adopted a report on similarity of Zynlonta with Kymriah, Yescarta, Polivy and Minjuvi	15 September 2022
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	15 September 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The approved indication is:

Zynlonta as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy.

2.1.2. Epidemiology and risk factors

Diffuse large B-cell lymphoma is the most common subtype of NHL and accounts for 25% to 45% of all NHL cases worldwide (Wild et al., 2020; Sant et al., 2014) and comprises 60% of all new lymphomas in the elderly population (Thieblemont and Coiffier, 2007). The disease causes approximately 8500 new cases in Europe (Sant et al. 2010) and an estimated 4000 deaths per year (Marcos-Gragera et al. 2011, De Angelis et al. 2015, Howlader et al. 2016). The incidence of DLBCL increases with age, it is mainly an adult/elderly disease. Based on data from the European HAEMACARE project, the incidence

rises from <1/100,000 in children to 10-15/100,000 in patients aged 65 years and older, with most cases occurring in adults >54 years of age (Sant et al. 2010).

A family history of lymphoma, autoimmune disease, human immunodeficiency virus (HIV) infection, hepatitis C virus (HCV) seropositivity, a high body mass as a young adult and some occupational exposures have been identified as risk factors of DLBCL (Morton el al. 2014).

2.1.3. Biologic features

Non-Hodgkin lymphoma represents a biologically and clinically heterogeneous group of lymphoproliferative malignancies which in 90% of cases are derived from B-cells with DLBCL with distinctive prognostic profiles including cell of origin: germinal centre B-cell (GCB) type or activated B-cell (ABC) type. Identified prognostic factors include expression of MYC, BCL2 and ENO3 genes (Carreras et al. 2020), TP53 deletion or mutation (Tessoulin et al. 2017), and aberrant microRNA expression (Ting et al. 2019). "Double-expression" (overexpression of MYC and BCL2 proteins), "double-hit" (dual translocation of MYC and BCL2 or BCL6) and "triple-hit" (chromosomal alterations in MYC, BCL2, and BCL6) DLBCL are associated with a particularly poor prognosis (Carreras et al. 2020, Xia and Zhang 2020, Rosenthal and Younes 2017). The ABC (non-GCB) type has been associated with worse outcome (Nowakowski et al. 2015, Hans et al. 2004, Lenz et al. 2008). DLBCL have been categorised into different subtypes with different characteristics, such as T-cell/histiocyte-rich B-cell lymphoma, Epstein-Barr virus (EBV)-positive DLBCL, DLBCL not otherwise specified (NOS) and others.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Approximately 25% of DLBCL patients are diagnosed with localised or limited stage disease and typically have a more favourable prognosis; approximately 75% of DLBCL patients present with advanced stage disease, defined as Ann Arbor Stage III and IV or Stage I and II with associated B-symptoms or bulky disease (≥10 cm) (Sehn and Gascoyne, 2015). DLBCL is most frequently diagnosed between the age of 65-74 years, with a median age at diagnosis of 70 years (Smith et al. 2015).

DLBCL is an aggressive disease with short life expectancy if left untreated. With currently available treatments, around 50% of newly diagnosed patients can be cured. DLBCL may arise as de novo, but it can also arise from a prior/existing low-grade (indolent) lymphoma, such as follicular lymphoma (FL) or marginal zone lymphoma (MZL), it is then commonly referred to as transformed lymphoma. Approximately 10% to 15% of patients exhibit primary refractory disease (nonresponse or relapse within 3 months of therapy) and an additional 20% to 25% of patients relapse, usually within the first 2 years, following initial response (Sehn and Gascoyne, 2015).

Salvage therapy, including high-dose chemotherapy and autologous stem cell transplant (HD-ASCT), can be effective treatment and potentially curative for DLBCL patients with chemotherapy-sensitive relapse (Philip et al., 1995). However, over half of the patients treated in this fashion will not have long-term disease control (Gisselbrecht, 2010). The prognosis of patients whose disease is refractory to initial chemotherapy and therefore not eligible for HD-ASCT, or who relapse early after HD-ASCT, is extremely poor. These patients have a poor response to salvage therapy, with an objective response rate of 26% (CR rate 7%) and a median survival of approximately 6 months (Crump, 2017).

2.1.5. Management

In patients progressing or relapsing after first-line treatment, the ultimate goal is salvage chemotherapy mainly with platinum- and/or gemcitabine-based regimens, followed by high-dose

chemotherapy (HDC) with ASCT. Many patients are not fit enough to receive intensive chemotherapy regimens, e.g. because of older age or comorbidities. For these patients, the outcome is dismal with generally no prolonged periods of disease control (Thieblemont and Coiffier 2007).

Treatment options for patients who have relapsed or progressed after second-line treatment of DLBCL are limited, and there is no consensus regarding the optimal treatment. According to guidelines by the European Society of Medical Oncology (ESMO) (Tilly et al. 2015) for patients in more than second relapse, recommendations for fit patients is a second HD-ASCT, allogeneic stem cell transplant (SCT) or participation in clinical trials with novel drugs. For those who are non-fit and transplant –non-eligible, treatment options are participation in clinical studies with novel drugs or palliative care.

Recently other treatment options have become available. There are 2 CD19-directed chimeric antigen receptor T-cell (CAR-T) therapies (axicabtagene ciloleucel [Yescarta SmPC 2021] and tisagenlecleucel [KymriahÒ SmPC, 2021]) approved for the treatment of adult patients with relapsed or refractory DLBCL and primary mediastinal large B-cell lymphoma (Yescarta only) after 2 or more lines of systemic therapy. The ORR for these therapies ranged from 37% to 74%, with a CRR ranging from 28% to 54%. Median duration of response (DOR) was not estimable/not reached (Yescarta/Kymriah, respectively).

Pixantrone (Pixuvri) is approved as monotherapy for the treatment of multiply relapsed or refractory aggressive non-Hodgkin B-cell lymphomas (Pixuvri SmPC, 2020). Fifty-three of the 70 patients enrolled in the pixantrone arm of the study were DLBCL patients. Patients treated with pixantrone showed higher response rates compared to the comparator group (investigator chosen single-agent chemotherapy): best CR (pixantrone, 15.7%; comparator, 0%), and a higher ORR (pixantrone, 40%; comparator, 14.3%). Median PFS for pixantrone was 5.3 versus 2.6 months for the comparator while OS was 10.2 versus 7.6 months (Pixuvri SmPC, 2020).

Polatuzumab vedotin (Polivy) is an anti-CD79b ADC that has been approved in combination with bendamustine and rituximab (BR) for the treatment of relapsed or refractory DLBCL who are not candidates for haematopoietic stem cell transplant (SCT) (Polivy SmPC, 2021). Patients were randomised 1:1 to receive either polatuzumab vedotin in combination with BR or BR alone. Eligible patients were not candidates for HD-ASCT and the study excluded patients who had transformed lymphoma or prior HD-allogeneic SCT (AlloSCT). The best ORR in the experimental arm was 63%, with a CRR of 50%. A DOR of ≥6 months was observed in 64% of patients and ≥12 months in 48% of patients.

Tafasitamab (Minjuvi) is an anti-CD19 antibody that has recently received a conditional marketing authorisation for use in combination with lenalidomide followed by tafasitamab monotherapy in patients with relapsed or refractory DLBCL NOS, including DLBCL arising from low grade lymphoma. The study was a single-arm trial, and patients had to be not eligible for ASCT (Minjuvi SmPC, 2021). Efficacy was evaluated in 81 patients with DLBCL. The combination showed an ORR of 56.8%, with a CRR of 39.5% and a DOR of 43.9 months.

However, all current treatment options in the R/R DLBCL present a substantial degree of toxicity and over half of patients will not have a durable response. Thus, there remains an unmet medical need for patients with relapsed or refractory DLBCL.

2.2. About the product

Loncastuximab tesirine (LT) is an antibody-drug conjugate (ADC) composed of a humanised monoclonal antibody (RB4v1.2) specific for human CD19 of the immunoglobin G1, kappa isotype, conjugated through a cathepsin-cleavable linker to SG3199, a pyrrolobenzodiazepine (PBD) dimer

cytotoxin. The toxin SG3199 attached to the linker is designated as SG3249, also known as tesirine (Tiberghien, 2016). LT binds with picomolar affinity to human CD19. After binding and internalisation, LT is trafficked to the lysosomes, where the protease-sensitive linker is cleaved and the unconjugated PBD dimers (SG3199) are released inside the target cell. The released PBD dimers bind into the minor groove of DNA and form cytotoxic DNA interstrand cross-links. The cross-links result in a stalled DNA replication fork, blocking cell division and causing cell death (Hartley, 2011). The cross-links formed by PBD dimers are relatively nondistorting of the DNA structure, making them hidden to repair mechanisms (Adair et al 2012, Beck et al 2017).

Human CD19 antigen is a 95 kDa type I transmembrane glycoprotein belonging to the immunoglobulin super family (Carter and Barrington, 2004; Tedder, 2009). In normal human tissue, expression of CD19 is restricted to the various stages of B-cell development, from early pre-B stage to mature B-cells, but is lost in terminally differentiated plasma cells (Haas, 2005; Scheuermann and Racila, 1995). Once bound to an antibody, CD19 is rapidly internalised by the cell (Gerber, 2009; Blanc, 2011). It is not shed into the circulation to the extent observed with other CD antigens (Cooper, 2004); therefore, low to no levels of soluble CD19 are present to compete with binding at the target tissue. Expression of CD19 is maintained in B-cell malignancies, including DLBCL, Burkitt's lymphoma, and follicular lymphoma. Additionally, CD19 expression is maintained in B-cell tumors that have lost expression of CD20 after anti-CD20 monoclonal antibody treatment (Anderson, 1984; Scheuermann and Racila, 1995; Wang, 2012).

2.3. Type of Application and aspects on development

The applicant requested consideration of its application for a Conditional Marketing Authorisation based on the following criteria:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data.

  To provide further confirmatory evidence for the efficacy and safety of loncastuximab tesirine, the applicant has initiated the Phase 3 clinical study ADCT-402-311 in March 2021.

  This trial is conducted to confirm post-authorisation the therapeutic value and positive benefit-risk balance of loncastuximab tesirine as a treatment of R/R DLBCL. ADCT-402-311 is a controlled, randomised study of loncastuximab tesirine combined with the well-established CD-20-targeting monoclonal antibody rituximab (Lonca-R) versus standard immunochemotherapy in patients with R/R DLBCL.

  The primary objective of the study is to evaluate the efficacy of Lonca-R compared to standard immunochemotherapy in patients with relapsed or refractory DLBCL not eligible for ASCT. After a safety run-in phase with 20 patients treated with Lonca-R, subsequent patients (approximately 330) will be randomly assigned to either Lonca-R or rituximab / gemcitabine / oxaliplatin (1:1). PFS is the primary endpoint and OS the key secondary endpoint.

- Unmet medical needs will be addressed, as:

  Currently, many patients with R/R DLBCL will receive treatment with chemotherapy regimens which are composed of one or more chemotherapy agents not specifically approved for use in DLBCL. In the European Society for Medical Oncology (ESMO) guidelines treatment options for 3rd line therapy is limited to allogenic transplant (if eligible), clinical trials with novel drugs, or palliative care (Tilly et al 2015). Similarly, the NCCN (National Comprehensive Cancer Network) guidelines for the treatment of B-cell lymphoma list over 20 different combinations that can be

used in R/R DLBCL (NCCN 2021).

However, the response to many of these regimens is low and short-lived. A recent analysis of patients requiring treatment for R/R DLBCL revealed that patients receiving 3rd line treatment had a response rate of 27%, and the ORR was even lower for patients who were refractory (defined as no response to or relapse within 6 months of last treatment) at 21.2%. Response rates were even poorer in patients who received ≥4th line, with <10% of patients responding to therapy (Radford 2019). In addition, the overall survival for these patients is quite short, with a median of approximately 6 months (Radford 2019, Halwani et al 2019).

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

  In view of the substantial and robust anti-tumour activity, the favourable safety profile with no indication of unacceptable toxicities and risks in the broad R/R DLBCL patient population studied, and the limitations of available treatment options, it is considered important to make loncastuximab tesirine available to patients - for some of whom it will be a last treatment option. Loncastuximab tesirine does not only present a positive risk-benefit ratio but, additionally, advantages over available therapies of R/R DLBCL, fulfilling unmet medical needs and providing additional benefit to public health with early market availability although comprehensive and confirmative clinical data are still required.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as powder for concentrate for solution for infusion containing 10 mg of Loncastuximab tesirine as active substance.

Other ingredients are: L-histidine, L-histidine monohydrochloride, polysorbate 20, sucrose.

The product is available in vial made of clear Type 1 glass, closed with a stopper (teflon-coated rubber), with an aluminium seal with plastic flip off cap.

2.4.2. Active substance

Loncastuximab tesirine is a human cluster of differentiation 19 (CD19)-targeted antibody drug conjugate (ADC), consisting of a humanised immunoglobulin G1 (IgG1) kappa monoclonal antibody specific for human CD19 (RB4v1.2 mAb), conjugated to a pyrrolobenzodiazepine (PBD) dimer cytotoxic drug (SG3199) through a protease-cleavable valine-alanine linker. The cytotoxin SG3199 together with the attached linker components is designated as tesirine (also referred to as SG3249 drug linker).

2.4.2.1. Active Substance - tesirine

2.4.2.1.1. General information

The chemical name of tesirine (also referred as SG3249) is [4-[[(2S)-2-[[(2S)-2-[3-[2-[2-[2-[2-[2-[2-[2-[3-(2,5-dioxopyrrol-1-yl)propanoylamino]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy] propanoylamino]-3-methylbutanoyl]amino]propanoyl]amino] phenyl]methyl (6S,6aS)-3-[5-[[(6aS)-2-methoxy-8-methyl-

11-oxo-6a,7-dihydropyrrolo[2,1-c][1,4] benzodiazepin-3-yl]oxy]pentoxy]-6-hydroxy-2-methoxy-8-methyl-11-oxo-6a,7-dihydro-6H-pyrrolo[2,1-c][1,4] benzodiazepine-5-carboxylate, corresponding to the molecular formula $C_{75}H_{101}N_9O_{23}$. It has a relative molecular mass of 1496.7 and the structure shown in Figure 1.

Tesirine comprises the pyrrolobenzodiazepine (PBD) dimer cytotoxic drug (SG3199), para-aminobenzyl carbamate (PABC), a protease sensitive valine-alanine linker (Val-Ala dipeptide), a PEG8 spacer and a maleimide linker.

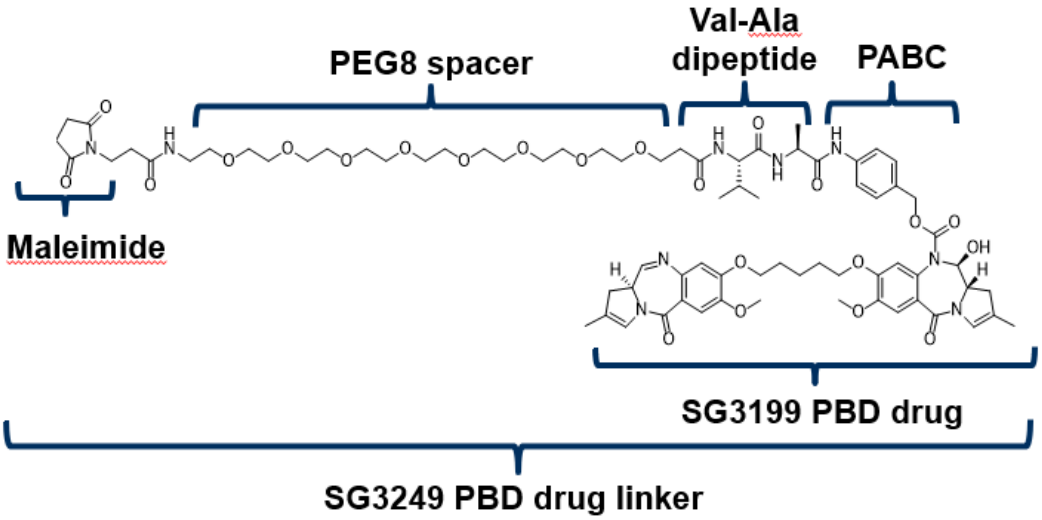


Figure 1. Tesirine chemical structure

The structural characteristics of tesirine (SG3249) have been confirmed by infrared spectroscopy (IR), proton (^1H) and carbon (^{13}C) nuclear magnetic resonance (NMR) spectroscopy, and mass spectrometry. Respective spectra and their interpretation have been presented. No elemental analysis data have been presented, but the justification presented by the applicant was considered acceptable because of the more informative one- and two-dimensional nuclear magnetic resonance (NMR) along with mass spectrometry and infra-red spectroscopy (ATR-FT) that were presented.

Tesirine is white to off-white to yellow to brown hygroscopic solid. It is practically insoluble in water; but very slightly to freely soluble is organic solvents. Polymorphism has not been reported in the literature.

There are five stereocentres however tesirine is manufactured as a single isomer since stereochemistry of the molecule is determined by the stereochemistry of the starting materials and the stereoselective synthetic process. In addition chirality is controlled in the specifications of tesirine.

2.4.2.1.2. Manufacture, characterisation and process controls

Tesirine is manufactured and tested at appropriately authorised sites. Manufacturing steps have been sufficiently described. Detailed description of manufacturing process, with quantities of each reagent used has been presented. For reagents/solvents/process aids specifications have been presented. The input charge amounts of each reagent, with respect to the basis charge for each step, have been presented along with the estimated yields of each reaction. Proven acceptable ranges, which have served to define the quality acceptable ranges (QARs), have been established during process development studies. Design space is not claimed. In-process control specifications as well as intermediates specifications have been presented. Analytical procedures used have been described and

respective validations have been provided. Operations are conducted under nitrogen and protected from light where reasonably possible.

There are four starting materials (SMs). A Major Objection (MO) was raised in relation to the selection of two of the SMs. In their response the applicant further justified the choice of these SMs in line with the ICH Q11 principles. Specifically the origin control and fate of the three chiral centres in the SMs was sufficiently discussed. The syntheses of these two SMs has been presented with all steps covering the introduction of all stereogenic centres. In addition the complete manufacturing process and the detailed SG3249 synthesis pathway that covers introduction of all stereogenic centres was provided. Further information was presented about the two chiral centres formed during the ring formation. The configuration was confirmed by a combination of 1D- and 2D-NMR experiments. Moreover the absolute stereochemistry of tesirine was assessed by comparison of the proposed SMs with their synthetised enantiomers. Finally to ensure the stereochemical configuration of the proposed SMs a chiral HPLC method has been implemented in their specifications. In conclusion these two proposed SMs were considered acceptable in view of the additional information and the MO has been resolved.

The other two SMs were defined as such in response a MO concerning another SM which was originally proposed. This originally proposed SM has been redefined as reaction intermediate and two newly proposed starting materials have been designated. The QP declaration has been appropriately updated following the redefinition of SMs. The information provided after redefinition of the starting materials is acceptable. The CHMP further recommended the applicant to submit a post-approval variation including final control strategy and batch analysis; updating accordingly the manufacturing process to indicate the actual quantities (or ranges) of materials as used; if not otherwise justified, updating the acceptance limits for the newly designated starting material in line with the batch data (REC).

The characterisation of the AS and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Information provided on fate and purge of impurities arising from the synthesis of the starting materials is considered sufficient. Schemes of synthesis of starting materials, as well as specifications, along with analytical procedures description and summary of validation have been presented. Fate and purge of impurities have been also presented.

Process validation has been performed and results were provided albeit not required. It can be concluded that the above campaigns demonstrate a high level of assurance that the SG3249 manufacturing process and associated controls reliably and consistently produce product of appropriate quality.

Extensive, narrative description of the manufacturing process development has also been presented. This section has mainly focused on the fate and purge of possible process impurities. Spiking studies have been performed. The capability of the manufacturing process for impurities removing has also been discussed. Also, non-specified impurities have been characterised. Potential residual solvents have also been mentioned.

The packaging material for tesirine has been sufficiently described and is acceptable.

2.4.2.1.3. Specification

Tesirine (SG3249) intermediate specification includes tests for appearance, identification, assay, purity, and impurities. The proposed specification covers all required attributes. The ICH M7 guideline does not apply to active substances intended for cancer indications. Additionally, as the drug linker is itself genotoxic, the exposure to a mutagenic impurity would not significantly add to the cancer risk of

the active substance. Therefore, impurities could be controlled at acceptable levels for non-mutagenic impurities. A satisfactory discussion on solvent derived genotoxic or potential genotoxic impurities has been provided. Limits for impurities have been sufficiently tightened during the procedure. In addition, the applicant has stated that the specification will be reassessed after data from an additional 15 batches is obtained (for a total of approximately 30 batches).

Analytical methods used in control of tesirine (both release and during stability studies) have been described at the sufficient level of details. All release and stability methods have been validated. Results are within predefined acceptance criteria. Reference standards have been described at the sufficient level of details.

Batch analysis data of several batches of tesirine (SG3249), including toxicology, development, clinical GMP, validation and post-validation batches have been presented. All batches are within limits defined at the time of testing.

2.4.2.1.4. Stability

Stability data for batches stored in the intended commercial packaging for up to 48 months under long-term (≤-65°C (-80°C ± 10°C)), intermediate (-20 ± 5°C), for 6 months under accelerated (5 ± 3°C) and for 1 month in stressed (25 ± 2°C / 60% ± 5% RH) conditions were provided.

Samples were tested for appearance, identity, assay and purity, water content, chiral purity content and impurities. No significant differences are noted between batches stored under long term and accelerated conditions. Results obtained showed no relevant changes under any of the abovementioned conditions and no trends were observed.

Stability studies at intermediate (-20°C ± 5°C), accelerated (+5 ± 3°C) and stressed (+25 ± 2°C / 60% ± 5% RH) conditions in addition to the intended long-term storage temperature (≤-65°C) in order to support short term exposure to higher temperatures during the SG3249 substance manufacturing process and any transient temperature excursions which may occur during shipment between the manufacturing sites.

The demonstrated stability of SG3249 at -20°C and 5°C in the primary stability studies, over periods of up to 12 months and 6 months respectively, and the limited effect of storage at 25°C /60% RH over a 1- to 3-month period contrast with data from the supportive studies where degradation at 5°C and at 25°C / 60% RH was evident in all batches. This difference is attributed to the protective effect of the secondary and tertiary packaging and included desiccant which are designed to prevent water ingress during storage.

In addition, forced degradation studies of SG3249 in acetonitrile with an equal aqueous volume of acid, base or peroxide were performed. SG3249 readily degrades in solution when exposed to acidic, basic, and oxidative conditions. A number of degradation products have been identified. In contrast, there was no reduction in purity or change in the impurity profile of material stored at room temperature for 30 days under an inert atmosphere.

Exposure of SG3249 to light (2.4 million lux hours) resulted in decrease in purity; confirmatory photostability testing of SG3249 (1.2 million lux hours) also resulted in degradation.

It has been further concluded that these studies demonstrate that the HPLC methodology adopted for SG3249 stability studies is stability-indicating and suitable for use.

Overall it has been concluded that the results of stability studies confirm that SG3249 intermediate drug linker is sufficiently stable when the intermediate is stored in the intended packaging. The proposed retest period and storage conditions are acceptable

2.4.2.2. Active Substance – loncastuximab (monoclonal-antibody)

2.4.2.2.1. General information

Loncastuximab (also referred as RB4v1.2), is full-length humanised monoclonal antibody (mAb), produced in Chinese hamster ovary (CHO) cells, and comprises two IgG1 heavy chains and two kappa light chains, directed against the human CD19 antigen. Each heavy chain is composed of 449 amino acids and each light chain contains 211 amino acids. There are two cysteines in the hinge region of each heavy chain capable of forming inter-heavy chain disulfide bonds. There is one disulfide bond forming the covalent attachment between each heavy and light chain. The heavy and light chain amino acid sequences are provided in Figure 2 and Figure 3.

The light chain contains five cysteines. The intrachain disulfide bridges are between C23 – C87 and C131 – C191, with C211 forming the interchain disulfide crosslink with the heavy chain. The interchain cysteine conjugation site is shown in bold and underlined.

```
1   EIVLTQSPAI MSASPGERVT MTCSASSGVN YMHWYQQKPG TSPRRWIYDT SKLASGVPAR
61  FSGSGSGTSY SLTISSMEPE DAATYYCHQR GSYTFGGGTK LEIKRTVAAP SVFIFPPSDE
121 QLKSGTASVV CLLNNFYPRE AKVQWKVDNA LQSGNSQESV TEQDSKDSTY SLSSTLTLSK
181 ADYEKHKVYA CEVTHQGLSS PVTKSFNRGE C
```

Figure 2. Light chain amino acid sequences

The heavy chain sequence contains 11 cysteines. The intrachain cysteine disulfide bridges are between C22 – C96, C147 – C203, C264 – C324, and C370 – C428, with the heavy chain interchain disulfides in the hinge region comprised of residues C229 and C232. The heavy-light interchain disulfide is composed of the heavy chain residue C223 covalently linked to the C211 residue of the light chain. The heavy chain asparagine residue, N300, is post-translationally modified primarily with a complex biantennary core-fucosylated oligosaccharide terminated in N-acetyl glucosamines (G0F). The N-glycosylation site is shown in italic, bold, and underlined. The interchain cysteine conjugation site is shown in bold and underlined.

```
1   QVQLVQPGAE VVKPGASVKL SCKTSGYTFT SNWMHWVKQA PGQGLEWIGE IDPSDSYTNY
61  NQNFQGKAKL TVDKSTSTAY MEVSSLRSDD TAVYYCARGS NPYYYAMDYW GQGTSVTVSS
121 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
181 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG
241 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
301 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE
361 MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW
421 QQGNVFSCSV MHEALHNHYT QKSLSLSPG
```

Figure 3. Heavy chain amino acid sequences

The theoretical light chain molecular weight is approximately 23.0 kilodaltons (kDa) and the theoretical heavy chain molecular weight is approximately 49.2 kDa (without N-linked glycosylation). The glycosylated heavy chain (with N-linked glycosylation predominantly complex biantennary core-fucosylated oligosaccharide ending in terminal N-acetyl glucosamines (G0F)) has a theoretical molecular weight of 50.7 kDa. The average molecular weight of intact RB4v1.2 is approximately 147.3 kDa with predominantly N-linked glycosylation G0F on each heavy chain and cyclisation of the

N-terminal glutamine in the heavy chain to pyroglutamic acid. Complete characterisation including elucidation of higher-order structure is presented in Section 3.2.S.3.1 RB4v1.2.

2.4.2.2.2. Manufacture, characterisation and process controls

Loncastuximab is manufactured and tested by appropriately authorised sites.

Description of manufacturing process and process controls
The manufacturing process of loncastuximab is composed of an upstream cell culture process resulting in the harvest of the cell culture fluid containing loncastuximab and a downstream purification and formulation process resulting in the purified antibody.

The process is typical for monoclonal antibody and involves upstream cell culture process and downstream purification process. Sufficiently detailed information on buffers used in downstream process were provided. Bioburden-control filtrations (0.2 µm filtrations) occur between several of these steps. Reprocessing is not allowed. Refiltration is only allowed in the event of a failed post-use integrity test and/or loss of system integrity (bag leak or tubing rupture).

Virus reduction is achieved with three validated virus inactivation or removal steps.

Control of materials
Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented. No human or animal derived materials are used in the active substance manufacturing process and acceptable documents have been provided for raw materials of biological origin used in the establishment of cell substrate.

The generation of cell line and cell banking system is generally adequately described. RB4v1.2 is a humanised monoclonal antibody of the IgG1, kappa isotype with specific binding to human CD19. RB4v1.2 was derived from the murine anti-CD19 antibody B4 and was humanised by a process called resurfacing and typical molecular engineering procedures. The resulting expression construct sequence is presented in the dossier – presentation of the development of expression vector is found sufficient.

A two-tiered cell banking system is used and sufficient information is provided regarding testing of MCB and WCB and release of future WCBs.

Genotypic characterisation and testing of the cell banks is in line with ICH Q5D and ICH Q5A. Cell bank storage is adequately addressed. A description how stability of the cell banks is routinely monitored was included in the dossier. The requirements for establishment and qualification (retesting scheme with acceptance criteria) of future new WCB were also provided. A summary of analytical methods used to characterise and test MCB and WCBs has been provided.

Genetic stability has been demonstrated for cells at and beyond the limit of cell age according to ICHQ5D. Based on the data, it was concluded that the inserted gene of interest shows consistent gene copy number; relevant results were provided.

Control of critical steps and intermediates
A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the loncastuximab manufacturing process was provided. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests. Actions taken if limits are exceeded are specified. Potential CPPs identified using the Risk Assessment (FMEA) were studied and characterised using a combination of multivariate design of experiments

(DoE) and one-factor-at-a-time (OFAT) approaches to determine the impact of variations of selected process parameters. The outcome of these studies was used to define the list of CPP and respective normal operating ranges (NOR) and proven acceptable ranges (PAR).

PPs and CMAs are controlled by NORs and PARs, non-CPPs are controlled by set points target ranges or PARs, and IPCs are controlled by acceptable ranges or action limits. Provided definitions of parameters are in line with ICHQ8. There are no intermediates isolated during the loncastuximab manufacturing process.

The control strategy comprises of routine control measure and also process validation and process verification through lifecycle management. It also considers non-critical quality attributes and process performance. The control strategy is acceptable.

Process validation

The process validation strategy for loncastuximab is based on a traditional approach that includes the process design, process qualification stage and continued process verification. The applicant presented data for process parameters for upstream and downstream process. Process parameters were within acceptable ranges with exception of justified and discussed deviations. The approach generally conforms to the guideline EMA/CHMP/BWP/187338/2014. The overall approach to validation is acceptable. Consistency in production has been shown 3 full scale commercial batches. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces loncastuximab of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

Final filter validation data is presented. Bacterial challenge study results, compatibility study results, extractables study results, specific bubble point study results are provided and can be accepted. Maximum hold times applied to various steps have been sufficiently validated and justified. Chemical and biological stability was confirmed.

The lifetime of resins used in the manufacture of loncastuximab was evaluated. Each resin will be concurrently validated for use in the loncastuximab commercial manufacturing process for a defined number of cycles.

Results of qualification demonstrated that during transport, the shipping container temperature is maintained and container integrity is preserved. No impact to the quality of the mAb intermediate of the shipment conditions from mAb manufacturing site to the conjugation has been confirmed with data**.**

Overall the applicant has provided data to assure that the manufacturing process is appropriately validated and can produce loncastuximab batches of consistent quality. The manufacturing process has been validated adequately.

Manufacturing process development

The commercial active substance manufacturing process was developed in parallel with the clinical development programme.

Toxicology and clinical batches have been manufactured by four processes. Development sites and scale-up has been presented. Process C is the current and validated commercial scale manufacturing process and also the process used for PPQ batches and clinical trial batches.

The development of the cell line was sufficiently described.

The upstream process steps remained almost the same for all four processes; some scale and site changes resulted in differences of operational parameters between processes. The downstream process

steps were the same for the four processes. Development, processes descriptions and changes between manufacturing processes are transparently described in sufficient detail.

For each change, a comparability study has been carried out demonstrating that, apart from some expected differences e.g. in glycosylation, the change did not have a significant influence on the quality of the product.

Comprehensive comparability studies between materials derived from different processes throughout development has been conducted. The provided comparability data and batch data are sufficient to conclude that batches from different processes are of comparable quality. It has been sufficiently justified that any differences seen do not impact the final conclusion of the comparability study**.** Finally a comprehensive comparability study between materials derived from previous process and commercial process material has been conducted. The study included comparative side-by-side release testing and extended characterisation; comparative forced degradation studies, comparison of cell binding. Description of analytical methods is provided, quality attributes chosen for comparability testing are appropriate. All of the comprehensive analytical data obtained during these comparison studies are corroborative, and support the conclusion that loncastuximab manufactured by the commercial process is similar to that from the latest previous process. Comparability exercise is in principle in line with ICHQ5E and the results are found to be comparable.

Overall, the development and comparability data is found acceptable.

Characterisation

Loncastuximab has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of a humanised monoclonal IgG1-type antibody (mAb). The analytical results are consistent with the proposed structure. Furthermore, heterogeneity of the active substance was adequately characterised by analysing size and charge variants, glycosylation and other product-related substances and impurities. Biological characterisation of loncastuximab indicates that this antibody has the ability to bind to human CD19 with high affinity and to specifically bind to Fc neonatal receptor (FcRn) binding activity as expected for a typical IgG1 mAb.

Thus, the primary quality attribute of the loncastuximab portion of the ADC is antigen binding. Loncastuximab tesirine has negligible effector function activity – ADCC and CDC methods were used to characterise potential immunological properties. The cytotoxicity assay was also used to characterise the direct cell killing activity of the antibody.

Adequate and sufficient raw data (chromatograms, results) was provided. Data on qualification of analytical methods used for characterisation, showing these are qualified for intended use are provided.

In summary, the characterisation is considered appropriate for this type of molecule.

Assessment of process-related impurities through manufacturing process validation and intermediate testing demonstrated that these impurities do not pose a safety risk. The loncastuximab manufacturing process has been shown to have a robust capability to effectively and consistently remove process-related impurities. For product related proteins (HMW, charge variants, LMW) no significant changes were seen through the downstream manufacturing process. This is acceptable. The clearance of process-related impurities was consistent across the validation batches with loncastuximab meeting all batch release specifications. Impurity testing of commercial scale batches has confirmed that these impurities are present at low, consistent levels, and in most cases below the detection or quantitation limit.

Product-related impurities such as size variants, charge variants, high molecular weight and low

molecular weight species are controlled through loncastuximab specification. The levels of HMW (dimer and aggregates) and fragments are consistently low.

In-process testing and specification ensure control over potential contaminants and adventitious agents.

The analytical procedures used to test in-process samples for absence of impurities together with qualification status are adequately described in the dossier.

2.4.2.2.3. Specification

The Loncastuximab (RB4v1.2) intermediate specification includes tests for quality, strength, potency, identity, purity and impurities, and safety.

The overall approach to establish and justify the commercial specifications for loncastuximab was based on the knowledge gained from process development and product characterisation studies thus covering the relevant QAs and are in line with ICH Q6B, EMA/CHMP/BWP/532517/2008 and Ph. Eur. and is acceptable. The specifications will be re-evaluated after enough commercial lots are manufactured to provide statistical power for robust analyses.

Analytical methods
The in-house analytical methods were sufficiently described and validated in accordance with ICH Q2 and compendial methods were qualified. The applicant provided full validation reports and method transfers reports.

Potency of the antibody relative to the reference standard is controlled by a cell-based binding immunoassay with electrochemiluminescence (ECL) detection.

Reference standards
A historical overview of the reference standards was presented. Detailed information on the current and previous reference standard lots has been provided. A two-tiered reference standard programme was established from lots representative of production and clinical materials to ensure consistency and continuity of the loncastuximab quality. A protocol for the qualification and characterisation of future primary and working reference standards is included.

Batch analysis data
Batch release data were presented for PPQ batches manufactured according to the intended commercial manufacturing process. In addition, release data were presented for developmental batches manufactured according to the previous processes. All the batches comply with the pre-established specifications valid at the time of testing and demonstrate consistent quality of loncastuximab. The batch release data shows consistent and comparable quality of loncastuximab manufactured with different processes.

Container closure system
The packaging material for the monoclonal antibody has been sufficiently described and is acceptable.

2.4.2.2.4. Stability

Batches manufactured with the commercial process, and batches from earlier processes were placed on stability at the following storage conditions: long-term condition: ≤ -60°C; accelerated condition: -5 ± 3°C; stressed condition: 25 ± 2°C (60 ± 5% RH). At real time storage conditions, the stability data is available for up to 36 months for commercial process batches. The stability programme is in accordance with ICHQ5C. Stability batches were packaged in the proposed closure system.

Samples were tested for quality (appearance, colour/clarity, pH), protein concentration, potency, purity and impurities. There were no significant changes or trends observed in samples stored under long-term and accelerated condition in the quality attributes throughout the study period, including key stability indicating assays. The results meet their specification in each case.

Samples stored under stressed condition demonstrated changes in several parameters but results demonstrated no change in the binding activity of RB4v1.2.

A freeze-thaw (F/T) stress study was conducted on a RB4v1.2 mAb development batch. Three cycles of F/T were performed. The results of the F/T samples were compared to those of the control sample which were taken from release testing. Even after an extended storage at the long-term storage condition, all results of the F/T samples were comparable to test results of the control sample.

There were no significant changes observed in the quality attributes throughout the study period and the results meet their specification intended for the long-term condition.Overall, the provided stability data support the proposed shelf-life at the recommended storage condition, in the proposed container closure system.

2.4.2.3. Active substance - loncastuximab tesirine (antibody-drug conjugate)

2.4.2.3.1. General information

Loncastuximab tesirine (also referred as ADCT-402) is an antibody-drug conjugate (ADC) composed of a CD19-specific humanised IgG1 kappa isotype mAb, RB4v1.2, conjugated through interchain cysteine residues to drug-linker SG3249. The drug-linker SG3249 is comprised of a maleimide linker, a PEG8 spacer, a protease sensitive valine-alanine linker (Val-Ala dipeptide), para-aminobenzyl carbamate (PABC) and the active drug molecule SG3199 that is the PBD dimer drug. RB4v1.2 mAb is produced recombinantly, utilising a mammalian cell line. Briefly, RB4v1.2 mAb comprises two heavy chains (449 amino acids each) and two light chains (211 amino acids each). There is an expected N-linked glycosylation site at Asparagine 300 in each heavy chain. There are 5 cysteine residues in each light chain (LC) and 11 cysteines in each heavy chain (HC), and a total of 32 cysteine residues in the antibody, forming 16 disulfide bonds per molecule.

The chemical name of ADCT-402 is Immunoglobulin Gl, (anti-(human CD19 antigen)) (humanised clone RB4vl.2 γl-chain), disulfide with humanised clone RB4vl.2 κ-chain, dimer, bis (thioether) with N-(31-(2, 5-dihydro-2, 5-dioxo-1H-pyrrol-1-yl)-1, 29-dioxo-4, 7, 10, 13, 16, 19, 22, 25-octaoxa-28-azahentriacont-1-yl]-L-valyl-N-[4-[[[[(11S, 11aS)-8-[[5-[[(l1aS)-5,11a-dihydro-7-methoxy-2-methyl-5-oxo-1H-pyrrolo(2,1-c][1,4] benzodiazepin-8-yl]oxy]pentyl]oxy]-11, 11a-dihydro-11-hydroxy-7-methoxy- 2-methyl-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-10 (5H)-yl]carbonyl] oxy]methyl]phenyl]-L-alaninamide. It has a relative molecular mass 150.8 kDa and its schematic structure is presented in Figure 4.

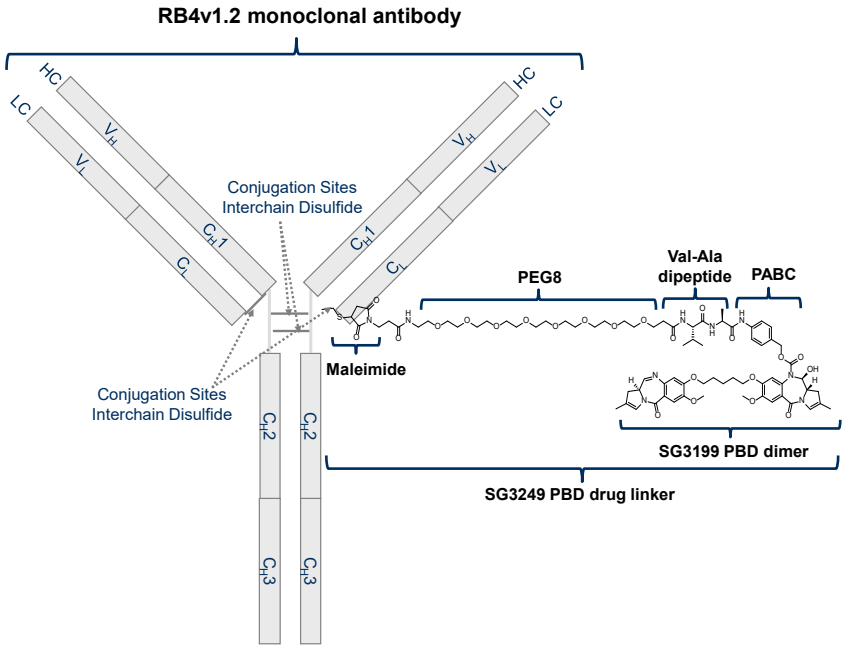


Figure 4. Loncastuximab tesirine schematic structure

The summary of general properties of ADCT-402 AS has been presented (Table 1). The only proven mechanism of action of loncastuximab tesirine is binding to the CD19 antigen on B-cells and PBD dimer drug-induced cell killing.

Table 1. General properties of loncastuximab tesirine

Company Code	ADCT-402 drug substance
Molecule class	ADC directed against human CD19 antigen
Mechanism of Action	Binding to the CD19 antigen on B-cells and PBD dimer drug-induced cell killing
Average DAR	2.3 ± 0.3
Average Molecular Weight	150.8 kDa[a]
Isoelectric Point (pI)	8.6[b]
Extinction Coefficient	1.9 $mL \cdot mg^{-1} \cdot cm^{-1}$ at 280 nm
Appearance	Clear to slightly opalescent and colorless to slightly yellow liquid
Formulation	ADCT-402 in histidine hydrochloride, sucrose, polysorbate 20

ADC = antibody drug conjugate; DAR = drug-to-antibody ratio; PBD = pyrrolobenzodiazepine

a) Corresponding to N-linked glycosylated form of complex biantennary core-fucosylated oligosaccharide ending in terminal N acetyl glucosamines (G0F) at Asparagine 300 of each heavy chain and cyclization of the N-terminal glutamine in the heavy chain to pyroglutamic acid

b) Corresponding to the main isoform of the antibody drug conjugate

ADCT-402 active substance (AS) is presented as a clear to slightly opalescent and colourless to slightly yellow liquid formulated in histidine, sucrose, polysorbate 20.

2.4.2.3.2. Manufacture, characterisation and process controls

The active substance (AS) is manufactured at BSP Pharmaceuticals S.p.A, Via Appia Km 65,561, 04013 Latina Scalo (LT), Italy. Manufacturing and testing takes place at appropriately authorised sites.

Description of manufacturing process and process controls

Manufacturing of loncastuximab tesirine comprises the following steps: thawing and dispensing; antibody pooling and transfer; pH adjustment; antibody reduction; conjugation and quenching; purification and formulation. The batch size has been clearly stated. The manufacturing process is described in sufficient detail. Critical process parameters have been identified by a FMEA study the was performed to assess the risk associated with the execution of the conjugation process for RB4v1.2 mAb with SG3249; the FMEA was executed in a manner that was consistent with ICH Q9. Detailed information is provided on the control of the process. Input and process operating ranges (NORs and PARs) are clearly listed, amounts of added solution are included. The loncastuximab tesirine manufacturing process is a well-controlled process. Hold-times are also provided.

Sufficiently detailed information on buffers used is provided. Reprocessing/re-filtration is not declared. Bioburden-control filtrations (0.2-µm filtrations) occur after several steps (quenching, UF/DF, formulation). The active substance manufacturing process is considered acceptable.

Control of materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented. No human or animal derived materials are used in the active substance manufacturing process. Adequate information about the filters used for ultrafiltration/diafiltration, and 0.2-µm sterile filtration was provided.

Control of critical steps and intermediates

The control strategy is described as set of parameters and controls. A comprehensive description of the control strategy including in-process tests/controls, critical process parameters and critical material attributes, control of process buffers and solutions, and in-process pool hold times employed during manufacture of loncastuximab tesirine to ensure that process performance and product quality are maintained has been provided; the definitions of PARs and CPPs follow ICH Q8. The CQAs were identified in line with ICH Q8, Pharmaceutical Development guideline and ICH Q9.

The potential CPPs for the loncastuximab tesirine manufacturing process were evaluated or characterised through process characterisation studies designed to identify the final list of CPPs. Scale-down models' qualification data is provided. Results of these small-scale studies - process characterisation studies - supporting the process risk assessment are provided. The impact of investigated CPPs on a chosen CQAs is shown and evaluated (in graphic format with plots too). List of CPPs together with NORs has been included for all steps. The identified CPPs are typical for conjugation process. The test procedures are appropriately qualified. Actions foreseen in case NORs excursions were also described.

The control strategy comprises of routine control measure and also process validation and process verification through lifecycle management. The control strategy also considers non-critical quality attributes and process performance.

In summary, the control strategy was developed on principles of ICH Q11, is clearly set out in sufficient detail and consistently described and is thus satisfactory.

Process validation

The process validation strategy for loncastuximab tesirine is based on a traditional approach that includes the process design, process validation stage and continued process verification.

Consecutive PPQ batches were used to produce material for clinical programme and for commercial

use. All PPQ batches were manufactured with use of antibody from the commercial process. The manufacturing process was qualified at the commercial scale.

All performance parameters results were within their respective acceptable ranges, in-process controls were within acceptance criteria, final AS batches met release specification requirements. No deviations for parameters that were outside of acceptable ranges or release specification were reported. The results for the PPQ batches, along with an evaluation against the pre-defined acceptance criteria support the commercial scale manufacturing process.

Several additional validation studies were performed concerning specific steps of the process; results and range of these studies are acceptable. The approach conforms to the guideline EMA/CHMP/BWP/187338/2014 and is acceptable. Overall, the applicant has provided data to assure that the manufacturing process is appropriately validated and can produce AS batches of consistent quality.

Manufacturing process development

The applicant clearly described the development of the manufacturing processes. Loncastuximab tesirine is commercially manufactured according to the current Process. This active substance was the active ingredient in the product used in the late phase clinical trials.

A comprehensive comparability study between materials derived from the different processes used throughout development has been conducted. The provided comparability data and batch data are sufficient to conclude that batches from different processes are comparable. Any observed differences have been justified and do not affect the conclusion that batches from different processes are comparable. A comprehensive comparability study between materials derived from previous process and the commercial process material has been also conducted. No significant differences were observed. Some minor differences were observed but the impact assessment performed concluded that these minor differences have no impact on the biological activity of the AS nor in the safety and efficacy of the AS. Comparability exercise is in principle in line with ICHQ5E. All of the analytical data obtained during these comparability studies are corroborative and support the conclusion that loncastuximab tesirine manufactured in the commercial process is similar to that from earlier processes.

Overall, process control strategy development and comparability data is found acceptable.

Characterisation

The aim of the structural characterisation was to confirm the primary structure and the higher order structure of loncastuximab tesirine. Additionally, the molecule heterogeneity was defined and characterised. Various orthogonal analytical techniques were used to characterise the primary structure, carbohydrate structure, mass heterogeneity, drug load distribution, disulfide bridge patterns, size heterogeneity, charge heterogeneity, biological functions and degradation pathways. Adequate and sufficient raw data (chromatograms, results) were provided. The side-by-side characterisation of AS and the source antibody intermediate mAb was also performed to evaluate the impact of conjugation on the physicochemical and biological activities of the antibody. The final CQAs of loncastuximab tesirine were presented in characterisation section together with their control strategy. The choice of the characterisation analytical methods for the ADC is adequate.

The molecular weight and drug load distribution were confirmed. All conjugate species were confirmed at the expected target conjugation sites. No off-target conjugation was detected.

The N-linked glycosylation profile of the AS was confirmed and is consistent with that of the mAb intermediate material so it was properly concluded that the AS manufacturing process doesn’t impact the glycosylation profile of the intermediate mAb.

The amino acid sequence of loncastuximab in the AS was verified. The structural integrity of loncastuximab tesirine was further demonstrated by disulfide bonds analysis.

Molecular size variants were characterised through orthogonal methods.

The charge heterogeneity was sufficiently (quantitatively) assessed. Batch analysis demonstrated consistency of this quality attribute.

A set of suitable characterisation methods was applied to evaluate the higher order structure of loncastuximab tesirine.

The only known mechanism of action of loncastuximab tesirine is to target through loncastuximab binding and kill CD19-expressing malignant B-cells through PBD-induced cytotoxicity. Loncastuximab tesirine has negligible effector function activity. The cytotoxicity potency assay was used to characterise the direct cell killing activity of the antibody.

The final method for antigen binding potency is a cell-based competitive ECLIA assay format. Relative binding potency of DS is measured through competitive binding to CD19. These cytotoxicity and antigen binding assays are relative potency assays based on dose response curves of the reference standard.

Evaluation of MoA and effector functions and development of potency assays is sufficient.

Loncastuximab tesirine samples were exposed to stress conditions to evaluate the potential degradation pathways and stability-indicating properties of analytical methods. The AS shows potential increases in aggregation, fragmentation, acidic variants, degradation of drug-linker and increase of free drug species. The changes on the antibody don't significantly impact the antigen binding potency. The degradation of drug-linker was determined and it is concluded that the linker hydrolysis doesn't impact cytotoxicity, but other degradations of drug-linker potentially reduce the cytotoxicity of AS.

Finally the stability indicating character of the methods used was demonstrated in line with ICHQ5C. Data on qualification of analytical methods used for characterisation, showing these are qualified for intended use are provided.

Overall, the characterisation of loncastuximab tesirine is adequate for this type of molecule.

Process-related impurities are introduced into the AS process either directly or from the antibody and drug linker. Any impurities originating from the intermediates that are of potential concern are controlled in the manufacturing processes of the intermediates. Product-related impurities are controlled in the AS specification.

A risk assessment was performed for evaluation of extractables and leachables on all product contacting material used during manufacturing process. All identified compounds were determined to be either below the AET, below the identified substance PDE or below the TTC.

In-process testing and AS specification ensure control over potential contaminants and adventitious agents.

2.4.2.3.3. Specification

The Loncastuximab tesirine active substance specification includes tests for identity, quantity, purity, potency, and microbial safety.

The proposed list of tests included in the loncastuximab tesirine specification cover identity, quantity, purity, potency, and microbial safety. Overall, the list of tests is in line with ICH Q6A, ICH Q6B,

EMA/CHMP/BWP/532517/2008 and Ph. Eur. The overall approach to establish and justify the commercial specifications for loncastuximab tesirine were based on reference and compendial requirements, the knowledge gained from process development and product characterisation studies. The proposed limits have been revised during the procedure and are considered justified and acceptable.

All analytical procedures used for AS release and shelf-life analysis have been well described. In-house methods have been reliably validated in accordance with ICH Q2 and compendial methods were qualified.

Batch analysis data has been provided for batches used throughout development, toxicological, clinical studies and PPQ batches. All batches were within specification and the data is consistent across manufacturing runs. A two-tiered reference standard programme was established from lots representative of production and clinical materials to ensure consistency and continuity of the loncastuximab tesirine quality.

Preparation and qualification of the current working reference standard as well as new primary reference standard are provided. PRS and WRS are well-characterised and qualified by testing according to the release specification and extensive structural characterisation tests. A summary of the qualification strategy for future primary and working reference standards are included in the dossier. The packaging material for the AS has been sufficiently described and is acceptable. The applicant declares in the dossier that container fulfils Ph. Eur. standards**.**

2.4.2.3.4. Stability

The primary stability study comprises batches manufactured with commercial process batches; supportive stability batches include batches representative for earlier processes. All batches were placed on stability at the following storage conditions: long-term condition: ≤ -60°C; accelerated condition: 5 ± 3°C; stressed condition: 25 ± 2°C /60 ± 5% RH. At real time storage conditions, the stability data is available for up to 24 months for commercial process batches and for up to 36 months for earlier process batches. Stability batches were packaged in the proposed closure system. The stability programme is in accordance with ICHQ5C.

In the samples stored under long-term and accelerated condition, there were no changes or trends observed in the quality attributes throughout the study period including stability indicating methods. The results of all methods meet their specification in each case. The results meet their specification in each case and are consistent between primary and supportive batches.

Samples stored under stressed condition demonstrated changes similar to the supportive lots with changes in certain test parameters. The results were consistent between primary and supportive batches.

A photostability study was performed on a primary stability, commercial scale, batch to determine the effect of light intensity, as specified in ICH Q1B (option 2). Results indicate that that ADCT-402 is negatively impacted by light when directly exposed to the level as specified in ICH Q1B (option 2), which is significantly more light compared to room light during manufacturing operations, leading to major degradation which is detected by almost all test methods. In addition, test results of the dark control suggest that ADCT-402 is sensitive to the heat generated in the photostability chamber. Therefore, it is recommended that ADCT-402 AS be protected from long-term exposure to light during storage.

A freeze-thaw (F/T) study was performed on a primary stability, commercial scale, batch to determine the impact of temperature cycling on the quality of ADCT-402. The results demonstrated that there are

no significant changes or trends no impact to product quality when ADCT-402 underwent three cycles of F/T.

The proposed shelf-life and storage conditions are supported by real-time stability data and are acceptable.

2.4.3. Finished medicinal product

2.4.3.1. Description of the product and pharmaceutical development

Loncastuximab tesirine (ADCT-402) finished product (FP), 10 mg/vial powder for concentrate for solution for infusion, is a sterile, white to off-white lyophilised, preservative-free cake or powder in a single-use vial for reconstitution. Loncastuximab tesirine is administered as an intravenous (IV) infusion.

In the composition of the applied product only compendial excipients are used and are controlled in line with respective Ph.Eur. monograph. An overfill is implemented to ensure that the labelled amount of the active ingredient is applied.

Loncastuximab tesirine (ADCT-402) finished product has the same formulation as ADCT-402 active substance. The active ingredient (loncastuximab tesirine [ADCT-402]) is formulated at 5.0 mg/mL with the excipient's histidine, sucrose and polysorbate 20. Properties of each used excipient have been briefly described**.** The formulation used in the early clinical development (Phase 1) and during Phase 2 clinical studies have been described. The suitability of the lyophilised formulation was tested as a liquid aqueous formulation as well as a lyophilised formulation. Two studies evaluated the robustness of the formulation by modifying excipient concentrations and pH during accelerated stability studies. The pH of the formulation was optimised to achieve a good balance between competing degradation mechanisms. In general, sucrose was identified as a stabilising formulation component with higher concentrations providing better stability. It was concluded from the lyophilised stability study that there is minimal degradation after lyophilisation. Challenges of storage and shipment of this type of product necessitated the development of a lyophilised formulation. Comparability between lyophilised powder and frozen liquid formulations and the corresponding AS and FP manufacturing processes was demonstrated and discussed in the dossier.

The applicant has presented a narrative history of the manufacturing process and associated development studies. A risk assessment was performed on each process parameter in order to determine parameter criticality. CPPs have been presented in a tabular summary for each process step, together with normal operating ranges were given; this is acceptable.

The development of container closure system (CCS) has been presented and updated during the procedure. It has been stated that the Type I glass vial, rubber stopper, and flip-off cap container-closure configuration is designed to maintain a sterile product and prevent microbial contamination. Detailed discussion of the extractables and leachables studies for the CCS has been provided. Container and extractable volume test have been performed to demonstrate that the required volume can be delivered. A compatibility study for ADCT-402 was performed. It has been concluded that if the FP reconstituted solution is compatible with the evaluated material type, the use of all commercially available materials in that category may be allowed.

Dose solutions with different concentrations were prepared in IV bags. No significant changes in product quality attributes were observed for loncastuximab tesirine FP from either a clinical lot or a commercial lot after 4 hours' storage at both 5°C and 25°C post-reconstitution as reflected in SmPC

section 6.3. Different diluents were evaluated for loncastuximab tesirine administration. The data confirmed compatibility of the applied product only with D5W and this is reflected in SmPC section 6.6.

In-line filter is referred as required in the dossier and was part of the compatibility studies. ADCT-402 is compatible with PES in-line filter. Zynlonta must be administered using a dedicated infusion equipped with a sterile, non-pyrogenic, low-protein binding in-line or add-on filter (0.2 or 0.22 micrometre pore size) and catheter).

2.4.3.2. Manufacture of the product and process controls

Finished product manufacture and quality control testing are performed at appropriately authorised site. The manufacturing process consists of the following main steps: Thawing of the active substance, pooling and mixing of BDS, sterile filtration, aseptic filling and partial stoppering, lyophilisation, crimping, external vial washing, visual inspection, vial Labelling and secondary packaging.

A detailed description of manufacturing process has been presented including proven acceptable ranges (PARs) for each CPP. Analytical methods used during IPC have been described and validated.

The batch size has been clearly stated. Process validation data (PPQ) have been presented for commercial scale batches. The PPQ results met acceptance criteria predetermined for each process step. Validation of holding time is acceptable as is the transport validation data. Overall, the presented data demonstrates that the manufacturing process is well-controlled and capable of consistently producing FP that meets the acceptance criteria.

2.4.3.3. Product specification

The finished product release and end of shelf-life specification, includes tests for general quality parameters, strength, potency, identity, purity and impurities, and safety. The specification was set in accordance with ICH Q6B. AS and FP data were pooled to establish acceptance criteria. This is justified since AS and FP have identical composition. Overall, the proposed specification is acceptable. The impurities that are present in the FP are primarily identical to the impurities in the AS. However, additional investigations with respect to potential FP impurities were performed. Elemental impurities testing and risk assessment was performed per the ICH Q3D (R1) guideline. Elemental impurities to be considered for parenteral applications plus those metals considered potential issues based on the equipment of manufacture were tested in the three batches of the FP. Extractable and leachable studies were performed on manufacturing components, storage containers and final container closure system. No reportable compounds were found in the simulated leachable study. Overall, no risks have been identified.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been initially performed and updated during the procedure in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). The data presented are acceptable. Based on this information it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary. The analytical methods for the FP that are also used for the AS testing are described above. The product-specific, non-compendial analytical methods used for batch release and stability were validated consistent with ICH Q2 (R1). Compendial methods used for batch release and stability testing of the FP were verified in compliance with the requirements defined

in each method compendial monograph. Reference standards are identical for FPS and AS; this is acceptable.

Batch analysis data have been presented. Batch data were also presented for batches manufactured as frozen formulation. All batches were within specification and the data is consistent across manufacturing runs.

The finished product is packaged in clear Type 1 glass vial closed with a stopper (teflon-coated rubber), with an aluminium seal with plastic flip-off cap. Specifications and representative certificates of analyses for each element of primary packaging has been presented. The outer packaging consists of a cardboard carton.

2.4.3.4. Stability of the product

The primary stability study comprises commercial scale batches stored under long term conditions (5 ± 3°C) for up to 24 months, accelerated (25°C / 60% RH) for up to 6 months and under stressed conditions (40°C / 75% RH) for three months. Stability batches were packaged in the proposed closure system. The stability programme is in accordance with ICHQ5C.

In addition supportive stability data has been provided for development batches stored for up to 48 months under the same long term conditions, for six months under accelerated and 3 months under stressed conditions. Based on the accepted comparability exercise, the supportive batches are considered as comparable to the commercial batches.

There were no changes or trends observed in the quality attributes throughout the study period under the long term conditions. The results comply with the specification for both primary and supportive batches.

Primary stability batches under accelerated conditions were also consistent with the supportive stability data exhibiting no significant changes for any of the stability tests except for an increasing trend in moisture content (but still within the specification limits) when stored for 6 months at the accelerated storage condition.

A thermal cycling study was performed on a primary PPQ batch to evaluate the impact of repeated thermal stress on the FP. Based on the temperature cycling stability data obtained from the study, there was no impact to product quality when loncastuximab tesirine lyophilised product underwent three cycles of thermal stress. No significant changes were observed in any quality attributes outside of method variability when compared to results of the control sample.

A photostability study was performed on a primary PPQ batch to determine the effect of light intensity, as specified in ICH Q1B (option 2). Based on the results, it is concluded that FP is negatively impacted by light when a naked vial is directly exposed to the level as specified in ICH Q1B (option 2) leading to major degradation which is detected by almost all test methods. However, the effect of light exposure on the quality of product when packaged in a carton (without a label or insert) was only minimal and met all specifications, indicating the package offers protection of the loncastuximab tesirine FP from exposure to intense light. The commercial package which includes a label and insert would further protect the drug product from light exposure.

The compatibility/clinical in-use study results exhibited acceptable stability post-reconstitution, compatibility, in use stability and recovery of dose solutions. Furthermore, loncastuximab tesirine FP did not promote microbial growth, which supports storage for 8 hours at room temperature and up to 24 hours in total. The in-use stability recommendation as stated in the SmPC section 6.3 are supported by data and are considered acceptable.

Taken together, the presented stability data sufficiently support a shelf life of 3 years and the proposed storage conditions "Store in a refrigerator (2 °C – 8 °C)", "Do not freeze", "Keep the vial in the outer carton in order to protect from light" + as stated in SmPC section 6.3 and 6.4.

2.4.3.5. Post approval change management protocols

A post-approval change management protocol (PACMP), developed per EMA/CHMP/CVMP/QWP/586330/2010 has been submitted for the addition of a new manufacturer. Upon completion of the agreed PACMP and demonstration of comparability, it is proposed that the implementation will be submitted under the relevant variation category; this is accepted.

2.4.3.6. Adventitious agents

Controlled sourcing of raw materials is the primary defence against introducing causative agents of TSE and BSE in the manufacturing process. The use of animal materials (no animal derived materials except cell line) is compliant with the effective version of EMA/410/01. Intermediates, AS and FP therefore pose minimal/negligible risk for transmission of TSE and BSE.

Extensive testing for endogenous and adventitious viral agents has been conducted for the expression cell lines, MCBs and WCBs and EOPCB to ensure that the cell banks are free from detectable adventitious viral contamination.

Bulk harvest is tested for the absence of mycoplasma, adventitious viruses (using several *in vitro* virus assay indicator cell clines) and minute virus of mice (MVM). This is in line with ICHQ5A.

Bulk testing is performed on the production bioreactor as an in-process control during production of each lot confirmation of the presence of infectious adventitious agent will lead to lot rejection. The loncastuximab purification process includes several steps for virus reduction. Overall, these data support the viral safety of Zynlonta for commercial use is according to ICHQ5A.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The AS loncastuximab tesirine is a human (CD19)-targeted antibody drug conjugate, consisting of a humanised immunoglobulin G1 (IgG1) kappa monoclonal antibody specific for human CD19 (RB4v1.2 mAb), conjugated to a pyrrolobenzodiazepine dimer cytotoxic drug via a linker. During the procedure, two MOs were raised on the suitability of the starting materials used in the synthesis of the tesirine. Both MOs were resolved by provision of additional information supporting the selected starting materials or redefining them as appropriate. Detailed and satisfactory information has been presented for all three components of the AS. The finished product has the same formulation as the AS.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain to updating the manufacturing process of SG3249 for Step1 and Step 2 and are put forward and agreed as recommendations for future quality development.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.4.6. Recommendation for future quality development

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

- to submit post-approval variation including final control strategy and batch analysis, the requested manufacturing process updates and the requested starting material specifications updates.

2.5. Non-clinical aspects

2.5.1. Introduction

Loncastuximab tesirine (designated as ADCT-402 or RB4v1.2-SG3249) is an antibody-drug conjugate (ADC) with an established pharmacologic class of CD19-directed antibody and alkylating agent conjugate. The humanised antibody component (RB4v1.2) of loncastuximab tesirine is an IgG1 kappa isotype. The antibody is conjugated (at the inter-chain cysteine residues) to a protease cleavable valine-alanine linker-payload designated as SG3249 (tesirine).

SG3249 contains the payload SG3199, a pyrrolobenzodiazepine (PBD) dimer cytotoxic agent, a para-aminobenzyl carbamate (PABC) moiety, and a maleimide polyethylene glycol (PEG) moiety. PBD monomers bind in the DNA minor groove and form a single covalent aminal linkage to the exocyclic N2 amino group of guanine within purine-guanine-purine sequences. PBDs are a class of naturally occurring anti-tumour antibiotics found in Streptomyces spp. PBD dimers, obtained by joining two PBD monomers together via an appropriate polymethylene tether, have the ability to produce two covalent bonds forming highly cytotoxic DNA interstrand cross-links.

Cluster of differentiation (CD) 19 is a 95 kilodalton (kDa) type I transmembrane glycoprotein belonging to the immunoglobulin Ig super family. It is expressed on all types of B-lymphocytes except plasma cells, thereby representing a potentially attractive target for treatment of B-cell leukaemia or non-Hodgkin lymphomas of B-cell origin. Expression of CD19 is maintained in hematologic B-cell malignancies, including leukaemias (pre-B-cell acute lymphoblastic leukaemia [pre-B ALL], B ALL, hairy cell leukaemia and NHLs (Burkitt's lymphoma], follicular lymphoma, diffuse large B-cell lymphoma.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Loncastuximab tesirine binds to cell surface CD19 and is internalised. Once inside the cell, the cytotoxic drug (SG3199) is released, forming DNA crosslinks and leading to cell death. The submitted pharmacology studies suggest CD19 binding and expression is an important determinant for the cytotoxic activity of loncastuximab tesirine. The monoclonal antibody (mAb) component of

loncastuximab tesirine, RB4v1.2, is selective for human CD19 and not cross-reactive with CD19 from any nonclinical species.

The primary pharmacology studies included *in vitro* cell binding studies, *in vitro* cytotoxicity studies using CD19-positive human cell lines and *in vivo* tumour growth inhibition studies using several CD19-positive xenograft murine models. The applicant has presented a number of aspects regarding the biology of CD19 and mode-of-action of ADCT-402, the preclinical models used, and the translation of the nonclinical data to the clinical setting to provide sufficient evidence of the validity of the preclinical evaluation of ADCT-402. The nonclinical studies conducted with ADCT-402 using a panel of cell lines derived from lymphoma and leukaemia patients have supported the clinical testing of loncastuximab tesirine in patients. Findings from these nonclinical studies support the use of cancer cell lines for nonclinical studies with ADCs. PBD-based ADCs have shown potent and specific activity, *in vitro* and *in vivo*, in cancer cell lines and in primary patient samples, including primary paediatric samples. In both cell lines and patient-derived material, PBD-based ADCs have shown activity across the entire cytogenetic risk spectrum, different molecular abnormalities and independently from Multiple Drug Resistance (MDR) positivity status.

In vitro studies

In a flow cytometric analysis, the apparent KD of RB4v1.2 for CD19-positive cell lines was within a range of 206 pM – 790 pM and a competitive Ramos cell-based binding assay showed that the relative binding of RB4v1.2 and ADCT-402 to cell-bound CD19 were similar, indicating that conjugating RB4v1.2 to the drug-linker SG3249 did not alter its binding affinity for CD19. ADCT-402 was shown not to be cross-reactive to cynomolgus monkey CD19 expressed on PBMCs in a flow cytometry assay.

The *in vitro* cytotoxicity of ADCT-402 was assessed in CD19-positive human cell lines (Daudi, DOHH-2, GRANTA-519, MEC-2, NALM-6, NAMALWA, Ramos, and SU-DHL-4). In study No. SIR041 it was observed that at the highest concentration of ADCT-402 tested (67 nM), some cell lines appeared to retain resistant populations of cells, as evidenced by less than 90% total cell killing. The two CD19-positive cell lines that had some residual surviving cells when tested with the highest concentration of ADCT-402 were Granta 519 and Mec2. These two cell lines grew in culture as large aggregates of cells and had the lowest percentage of single cells. It was noted in the discussion of study No. SIR041 that cell growth as aggregates could hinder diffusion of an ADC and reduce exposure to the ADC by the cells in the core, thus relatively protecting them from the ADC cytotoxic activity. The phenomenon of the presence of some residual surviving Granta 519 and Mec2 cells after exposure to ADCT-402 is probably related to the different growth pattern of these two cell lines.

The single cell gel electrophoresis (comet assay) was used to measure the interstrand cross-links induced in the DNA by the released PBD dimer toxin following ADCT-402 binding, internalisation and trafficking to the lysosomes. Cross-link formation was dose-dependent and the peak of cross-linking occurred between eight to 12 hours after a two-hour exposure of the cells to ADCT-402. ADCT-402 was shown to moderately target CD19-negative cells in co-culture experiments with CD19-positive and CD19-negative cells and to mediate bystander killing of CD19-negative cells via conditioned-medium transfer from ADCT-402-treated, CD19-positive cells. The ability of ADCT-402 to induce bystander killing of neighbouring CD19-negative tumour cells is of potential benefit for the clinical setting. Although CD19 has a broad and homogenous expression profile in the majority of DLBCL and B-cell NHL cases, there is a proportion of lymphoma patients with heterogeneous CD19 expression(Masir et al., 2006). For these patients, the ability of ADCT-402 to mediate bystander killing of CD19-negative tumour cells is expected to be beneficial as it would allow ADCT-402 to kill both CD19-positive and CD19-negative tumour cells and at the same time to reduce the chance of relapse via CD19-negative clonal expansion. The bystander effect may be a contributor to the efficacy of loncastuximab tesirine,

including the durable responses which continue beyond the end of treatment in patients who achieve a response.

In vivo studies

The *in vivo* pharmacological activity of ADCT-402 was characterised in immunodeficient mice using two human Burkitt's lymphoma (BL) models (Ramos and Daudi), a human DLBCL model (WSU-DLCL-2), a disseminated Ramos model and a pre-B acute lymphoblastic leukaemia-derived model (NALM-6). ADCT-402 was tested in combination with rituximab, a CD20-specific mAb or with the anti-metabolite chemotherapeutic drug gemcitabine in the WSU-DLCL2 xenograft model and with the pan-class I PI3K inhibitor copanlisib in the TMD8 xenograft model.

ADCT-402 demonstrated dose-dependent anti-tumour activity in CD19-positive Burkitt's and DLBCL-derived xenograft mouse models.

In a comparative study involving ADCT-402 and RB4v1.2-DM4 and hBU12-vc-PAB-MMAF, two different CD19 targeting ADCs with a tubulin inhibitor as payload, ADCT-402 showed superior anti-tumour activity in the Ramos s.c. xenograft model.

In a disseminated Ramos xenograft mouse model, ADCT-402 caused a significant increase in survival compared to both vehicle-treated and isotype control ADC-treated mice when tested as a single-dose at 0.33 mg/kg or 1 mg/kg.

2.5.2.2. Secondary pharmacodynamic studies

No secondary pharmacology studies were conducted with ADCT-402 or SG3199.

2.5.2.3. Safety pharmacology programme

No dedicated safety pharmacology studies were conducted with ADCT-402 or SG3199, however, in accordance with ICH S6(R1) safety pharmacology endpoints, including neurobehavioural and cardiovascular endpoints (8-lead electrocardiogram measurement and blood pressure) and assessment of the respiratory rate, were included in the repeat-dose toxicity studies with ADCT-402. There were no treatment-related findings.

Consistent with International Council for Harmonization (ICH) S6(R1), no stand-alone safety pharmacology studies were conducted with loncastuximab tesirine, and safety pharmacology endpoints were evaluated as part of the GLP-compliant 4- and/or 13-week repeat-dose toxicity studies in cynomolgus monkeys. Parameters evaluated included cardiovascular endpoints (8-lead electrocardiogram (ECG) [heart rate, RR-, PR-, QRS-, QT, and QT corrected by Bazett's formula [QTcB]-interval] and blood pressure), respiratory rate, and neurobehavioral assessments (general assessment of sensorimotor function and a standard observation battery [modified Irwin]). No loncastuximab tesirine-related effects were noted on any endpoint studied.

2.5.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were conducted with loncastuximab tesirine. Due to the high binding specificity of loncastuximab tesirine to human CD19, a transmembrane protein expressed on the surface of cells of B-lineage origin, it is stated to be unlikely that loncastuximab tesirine has pharmacodynamic interactions with co-administered drugs.

2.5.3. Pharmacokinetics

Analytical methods were developed to determine ADCT-402, total RB4v1.2 antibody or SG3199 in rat and cynomolgus monkey serum or for determination of SG3199 in *in vitro* metabolism studies. Validated methods were used in the GLP-compliant repeat-dose toxicity studies in the rat and cynomolgus monkey. In addition, in order to determine the formation of ADA in cynomolgus monkey serum, a validated method was developed. The validations of the analytical methods included: determination of assay range, inter-assay and intra-assay precision and accuracy, selectivity, specificity, bench top stability, long-term stability, freeze-thaw stability, hook (prozone) effect. The studies have all been conducted in test facilities and sites that belong to national compliance programs and had been inspected for their GLP compliance in the time of the conductance of the studies.

The studies are mostly GLP compliant except:

Study No. 8303115: the phase reports on dosage of RB4V1.2 and RB4V1.2 conjugate state that long-term stability data were not available to confirm the dosage results at the time of the completion of the study. With the response of day 120 the applicant amended the final toxicology study report of Study 8303115 with the final bioanalysis reports containing the long-term stability data and included a statement in the final toxicology study report to indicate that TK parameters determined after the second dose are likely impacted by the lack of supporting long term storage stability data and may underestimate drug exposure, in particular in the animals assigned to the recovery phase.

Study No. 8374716: the phase report on dosage of conjugated RB4V1.2 states that long-term stability data were not available to confirm the dosage results for concentrations <650 ng/mL. With responses to day 120 the applicant submitted additional data. Long-term storage stability data for the conjugate-specific assay showed that for samples with ADCT-402 conjugate concentrations ≥650 ng/mL storage stability at -70°C was 365 days, whilst for samples with ADCT-402 conjugate concentrations <650 ng/mL storage stability at -70°C of only 105 days. The concentrations <650 ng/mL were defined as For Information Purpose Only (FIPO) and were not intended for inclusion in the TK analysis.

Study No. 8374716: Some of the analysed concentrations for formulations were out of range (below LOD), therefore not valid and the analytical method used for those analysis was not validated. The applicant was requested to justify why those deviations to GLP do not jeopardise the validity of the study. Mean Cmax values for the sexes combined at 0.075, 0.15 and 0.3 mg/kg of 2.26, 4.40 and 10.87 µg/mL following dosing on Day 1, and of 2.80, 5.35 and 10.6 µg/mL demonstrate dose-dependent exposure over the intended dose range. Dose-related effects such as skin effects, nephropathy and testicular changes were observed in toxicology studies. These results indicate the correct dosage.

Absorption studies were not conducted with ADCT-402 or SG3199. All *in vivo* studies with ADCT-402 or SG3199 used the IV route of administration, the intended clinical route of administration for ADCT-402.

No distribution studies were conducted with ADCT-402. Given its molecular size, ADCT -402 would be expected to be largely confined to the plasma space, similar to the endogenous antibodies and monoclonal antibodies. This was confirmed by the TK analyses from 4- and 13 – week repeat dose toxicity studies in cynomolgus monkeys, which indicated that the volume of distribution (Vz) was generally similar to the plasma volume.

No metabolism studies were performed on ADCT -402. Monoclonal antibodies are expected to be metabolised in the same manner as endogenous antibodies. This is acceptable according to ICHS6(R1).

In vitro studies indicated that SG3199 is not a potent inhibitor of cytochrome P450 (CYP) enzymes. CYP induction studies showed that SG3199 did not induce CYP2B6- or CYP3A4-mediated enzyme

activity or mRNA expression in human hepatocytes *in vitro*, whilst a >2-fold increase in CYP1A2 mRNA expression (without corresponding increase in enzyme activity) was observed. These data indicate that SG3199 is unlikely to induce CYP2B6 or CYP3A4 *in vivo* and therefore the potential for producing clinically relevant CYP induction related drug-drug interactions is considered to be low. However, based on the *in vitro* data SG3199 may be an inducer of CYP1A2 *in vivo*.

Comparable metabolite profiles were observed upon incubation with rat, cynomolgus monkey or human hepatocytes and liver microsomes. Biotransformation by human liver microsomes and hepatocytes resulted in ether hydrolysis, amide hydrolysis, various oxygenation biotransformations and O-demethylation, or a combination thereof. Results from two approaches to reaction phenotyping (recombinant human CYP enzymes and chemical inhibition) indicated potential involvement of CYP3A4/5 in the metabolism of SG3199. In addition, based on the extent of substrate loss in the absence of NADPH when SG3199 was incubated with human liver microsomes, non-CYP mediated metabolism of SG3199 is indicated.

No nonclinical excretion studies were conducted with the ADCT – 402 antibody part, as it will undergo normal protein metabolism.

Excretion of [3H]-SG3199 was mainly via the faeces, biliary route (97.5±3.0%), with minor urinary excretion (3.8±0.3%). Excretion was rapid, with most radioactivity (83.5±5.8%) recovered 24 h post dose.

Loncastuximab tesirine was cleared slowly in animals with the half-life ranging from 8 to 17 days in monkeys. Exposures to loncastuximab tesirine generally increased dose proportionally with an increase in dose level. There were no major differences in plasma exposure between males and females and no evidence of accumulation with repeated dosing. Maximal serum concentrations were generally reached within 1.5 hours of dosing. Plasma concentrations were overall comparable between loncastuximab tesirine and the monoclonal antibody component, and the level of deconjugated SG3199 was below the lower limit of quantitation at most timepoints and dose levels in the 13-week repeat-dose study in monkeys. Plasma stability studies combined with the toxicokinetic data in monkeys suggest the ADC is stable and, when free, SG3199 is highly protein bound in rat, cynomolgus monkey and human plasma (approximately 97%, 93%, and 94%, respectively). [3H]-SG3199 distribution was rapid and widespread with the majority of tissues reaching maximum radioactivity at 2 hours post dose, the first sampling time point. There was no apparent distribution of SG3199 to melanin-containing tissues or the brain or spinal cord. Linear clearance profiles for loncastuximab tesirine were noted across the dose range studied (0.075-0.9 mg/kg), indicative of a lack of target-mediated drug disposition (TMDD) and consistent with the lack of cross-reactivity of RB4v1.2 to cynomolgus monkey CD19.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

At single dose 0.5 mg/kg there was no evidence of effects of ADCT-402 on haematology parameters or gross pathology. The MTD for ADCT-402 in female Sprague Dawley rats was considered to be the 2 mg/kg dose.

Single IV doses of 50 or 100 µg/kg SG3199 were not tolerated and associated with adverse clinical signs, early terminations and death, and exceeded the MTD in male Sprague Dawley rats.

2.5.4.2. Repeat dose toxicity

Loncastuximab tesirine-related toxicities were seen in the kidneys, liver, lungs, male reproductive organs, organs of the hematopoietic system, gastrointestinal tract, skin, salivary gland, and urinary bladder. Inappetence, body weight loss, and immunosuppression were dose limiting with the ADC in rats and skin toxicity (lesions) was dose limiting with the ADC in monkeys. Liver toxicity (jaundice) in rats and inappetence and body weight loss in Beagle dogs were dose limiting for SG3199. Decreased prothrombin time, increased platelets and fibrinogen, and haemorrhage were observed mainly in monkeys after repeated doses with loncastuximab tesirine. Minor changes in coagulation parameters were observed in rats following repeated doses of SG3199. Toxicity findings with loncastuximab tesirine in monkeys were generally reversible at tolerated doses, except for black spots on the skin and the effects on male reproductive organs. Also present during recovery at low incidence were organ haemorrhages and oedema and myocardial degeneration. Some monkeys with these histopathological findings also displayed changes in haematology and clinical pathology parameters associated with inflammation. Treatment of monkeys with loncastuximab tesirine resulted in pro-inflammatory responses as indicated by increases in the white blood cells (WBCs) and/or differentials, increased fibrinogen, and histopathology observations (multi-organ inflammation, particularly the lung, kidney, or injection site). Pro-inflammatory findings with loncastuximab tesirine are consistent with findings in a meta-analysis of PBD-containing ADCs. Several of the findings with loncastuximab tesirine were observed in studies conducted with the free payload in pilot or GLP toxicology studies. In the 13-week toxicity study with ADCT-402 in cynomolgus monkeys (Study 8374716), red discolouration of all lung lobes was observed at necropsy in 1 recovery male (P0303). There is no evidence of this being associated with fluid build-up in the thoracic cavity during necropsy. This finding correlated with increased lung weight, and, in microscopic pathology evaluations, with moderate alveolar haemorrhage, without evidence of inflammatory cell infiltration or erythrophagocytosis. Taking into account the incidental nature of this finding in a single animal ~90 days after the last ADCT-402 dose and also the lack of evidence of tissue repair, and the difference in anatomic location vs pleural effusions it seems unlikely that the finding in animal P0303 is representative of pleural effusions as seen in individual patients.

In repeat-dose IV toxicity studies in cynomolgus monkeys, ADCT-402 exhibited linear PK/TK without evidence of TMDD, consistent with lack of cross-reactivity to cynomolgus monkey CD19. Exposures increased in a dose-proportional manner, with a mean half-life of ~8 to 17 days.

Due to rapid clearance, SG3199 TK parameters could not be accurately determined, however, based on the available data in the GLP 4-week repeat-dose toxicity study in the rat, systemic exposure upon daily IV administration increased with dose, without evidence of gender-related differences or accumulation, and a half-life ranging approximately 8 to 41 min.

2.5.4.3. Genotoxicity

No genotoxicity studies were conducted with ADCT-402.

SG3199 was genotoxic in GLP *in vitro* studies (*in vitro* micronucleus assay and the chromosome aberration assay in human lymphocytes from whole blood). A GLP bacterial reverse mutation assay (Ames test) was also conducted; however, mutagenicity could not be assessed due to cytotoxicity at all concentrations tested. In pharmacology studies and other toxicity studies, the applicant demonstrated that SG3199 crosslinks DNA and causes double strand breaks. The results of these studies indicate that loncastuximab tesirine will cause chromosomal damage; therefore, the wait times for contraception will be T1/2 (half-life) + three months for males and 5 x T1/2 + six months for females after the last dose.

2.5.4.4. Carcinogenicity

In accordance with ICH S9, ICH S6(R1) and ICH S1A (Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals) no carcinogenicity studies were conducted or are planned with ADCT-402 or SG3199 given the genotoxic mode of action of SG3199 (covalent DNA crosslinking/ alkylating agent) and the intended clinical use in patients with advanced cancer.

2.5.4.5. Reproductive and developmental toxicity

Given that SG3199 is genotoxic and that ADCT-402/SG3199 target actively dividing cells, in accordance with ICH S9 no reproductive and developmental toxicity studies were conducted or are planned with ADCT-402 or SG3199.

Results from repeat-dose toxicity studies with intravenous administration of loncastuximab tesirine in cynomolgus monkeys indicate the potential for impaired male reproductive function and fertility. Administration of loncastuximab tesirine to cynomolgus monkeys every 3 weeks at 0.6 mg/kg for a total of 2 doses, or every 3 weeks at 0.3 mg/kg for 13 weeks resulted in adverse findings that included decreased weight and/or size of the testes and epididymis, atrophy of the seminiferous tubules, germ cell degeneration, and/or reduced sperm content. The dose of 0.3 mg/kg in animals results in an exposure (AUC) that is approximately 3 times the exposure at the maximum recommended human recommended dose [MRHD] of 0.15 mg/kg. These findings were not reversible at the end of the 12-week recovery period following 4 or 13 weeks of dosing. The animal: human safety margin was determined from a human exposure (AUC) of 26,518 day.ng/mL (or 636 hr.µg/mL) at the maximum recommended human dose (MRHD) of 0.15 mg/kg every 3 weeks and the Day 43 AUC from the 13-week general toxicology study in monkeys was 1830 hr*µg/mL at 0.3 mg/kg.

2.5.4.6. Toxicokinetic data

In repeat-dose IV toxicity studies in cynomolgus monkeys, ADCT-402 exhibited linear PK/TK without evidence of TMDD, consistent with lack of cross-reactivity to cynomolgus monkey CD19. Exposures increased in a dose-proportional manner, with a mean half-life of ~8 to 17 days.

Due to rapid clearance, SG3199 TK parameters could not be accurately determined, however, based on the available data in the GLP 4-week repeat-dose toxicity study in the rat, systemic exposure upon daily IV administration increased with dose, without evidence of gender-related differences or accumulation, and a half-life ranging approximately 8 to 41 min.

2.5.4.7. Local tolerance

Local tolerance upon IV administration of ADCT-402 was evaluated as part of repeat-dose toxicity studies in cynomolgus monkeys.

No standalone local tolerance studies were conducted with SG3199, and injection sites were evaluated as part of single and repeat-dose toxicity studies in Sprague Dawley rats.

Findings in the pivotal 13-week repeat-dose toxicity study of ADCT-402 included dose-related black skin discoloration, which correlated microscopically with minimal-to-moderate epidermal hyperpigmentation. These findings were still present with reduced incidence by the end of the 12-week recovery phase, indicating a trend towards reversibility.

Due to the low incidence and severity of injection site findings in studies with SG3199, these findings were considered procedural, although a relationship to treatment with SG3199 could not be excluded.

2.5.4.8. Other toxicity studies

Tissue cross-reactivity study was conducted with ADCT-402 using normal human tissues and blood smears. The panel of 37 frozen human tissues used as the test system was considered consistent with the tissues recommended in Annex II of Directive 75/318/EEC. Specific, membranous to cytoplasmic, staining was observed in mononuclear and/or stellate cells within the majority of human tissue specimens. In tissues of the lymphoreticular system (lymph node, gut-associated lymphoid tissue, mucosa-associated lymphoid tissue, spleen, thymus and tonsil), positive cells were organised into distinct regions, for example coalescing foci within the germinal follicles of the tonsil and extensive aggregates throughout the medullary regions of the thymus. This was considered to reflect the immunoregulatory function of these organs/tissues and the prominent role of CD19-expressing cells in these processes.

In neuronal tissue, including components of the central (cerebrum, cerebellum and spinal cord) and peripheral (peripheral nerve, optic nerve and retina) nervous systems, positive mononuclear and/or stellate cells were located in all regions, including the white/grey matter of the central nervous tissues and the endoneurium of the peripheral nervous tissues. This was considered indicative of the presence of immunomodulatory CD19-positive cells amongst the neuroglial and/or resident inflammatory cell population. Within lymphoreticular, neuronal and the majority of other tissues, there were scattered and individualised positive mononuclear and/or stellate cells located throughout the parenchyma. These were of variable staining intensity and considered to reflect the relative abundance of static and circulatory CD19-positive cells, including B-lymphocytes and cells of follicular dendritic lineage, within normal tissue.

A package of phototoxicity studies was performed to determine the effects of SG3199 on supercoiled pUC19 plasmid DNA when analysed on 1% agarose gels with or without exposure to visible light, UVA or UVB radiation. The potential effects of visible light on the ability of SG3199 to mediate DNA crosslinking and double-strand breaks was evaluated. Similar to UV light, exposure to visible light markedly enhanced the ability of SG3199 to induce DNA crosslinking and double-strand breaks. Furthermore, similar to UVB, pre-exposure did not affect the intrinsic ability of SG3199 to mediate DNA crosslinking and double-strand breaks, and similar enhancement was seen upon re-exposure. SG3199 is photoreactive, and the exposure to visible light, UVA or UVB radiation enhance its ability to mediate DNA crosslinking and double-strand breaks.

2.5.5. Ecotoxicity/environmental risk assessment

The PECsw for loncastuximab tesirine is around 100-fold below the trigger value of 0.01 µg/L. The PECsw for SG3199, which presents approximately 1% of the total ADC, is even further below the trigger value. Hence, further investigations on the environmental fate and effects detailed in Phase II Tier A of the EMEA guidance document are not considered required. Experimental log P values of 0.94 and 1.00 for acidic and neutral conditions were obtained for SG3199 and whilst they are indicative of its lipophilic nature, they are far below the trigger value for PBT assessment.

2.5.6. Discussion on non-clinical aspects

Loncastuximab tesirine binds to cell surface CD19 and is internalised. Once inside the cell, the cytotoxic drug (SG3199) is released, forming DNA crosslinks and leading to cell death. The submitted pharmacology studies suggest CD19 binding and expression is an important determinant for the cytotoxic activity of loncastuximab tesirine. The monoclonal antibody (mAb) component of

loncastuximab tesirine, RB4v1.2, is selective for human CD19 and not cross-reactive with CD19 from any nonclinical species.

The primary pharmacology studies included *in vitro* cell binding studies, *in vitro* cytotoxicity studies using CD19-positive human cell lines and *in vivo* tumour growth inhibition studies using several CD19-positive xenograft murine models The applicant has presented a number of aspects regarding the biology of CD19 and mode-of-action of ADCT-402, the preclinical models used, and the translation of the nonclinical data to the clinical setting to provide sufficient evidence of the validity of the preclinical evaluation of ADCT-402. The nonclinical studies conducted with ADCT-402 using a panel of cell lines derived from lymphoma and leukaemia patients have supported the clinical testing of loncastuximab tesirine in patients. Findings from these nonclinical studies support the use of cancer cell lines for nonclinical studies with ADCs. PBD-based ADCs have shown potent and specific activity, *in vitro* and *in vivo*, in cancer cell lines and in primary patient samples, including primary paediatric samples. In both cell lines and patient-derived material, PBD-based ADCs have shown activity across the entire cytogenetic risk spectrum, different molecular abnormalities and independently from Multiple Drug Resistance (MDR) positivity status.

Cell-binding studies showed that the relative binding of RB4v1.2 and ADCT-402 to CD19 was similar, indicating that the binding affinity of the RB4v1.2 monoclonal antibody (mAb) was unaffected upon conjugation of the SG3249 payload.

The *in vitro* cytotoxicity of ADCT-402 was assessed in CD19-positive human cell lines (Daudi, DOHH-2, GRANTA-519, MEC-2, NALM-6, NAMALWA, Ramos, and SU-DHL-4).

In study No. SIR041 it was observed that at the highest concentration of ADCT-402 tested (67 nM), some cell lines appeared to retain resistant populations of cells, as evidenced by less than 90% total cell killing in these cell lines. The phenomenon of the presence of some residual surviving Granta 519 and Mec2 cells after exposure to ADCT-402 is probably related to the different growth pattern of these two cell lines. In view of the above explanations, the issue is not further pursued.

The *in vivo* pharmacological activity was characterised in immunodeficient mice using two human Burkitt's lymphoma (BL) models (Ramos and Daudi), a human DLBCL model (WSU-DLCL-2), a disseminated Ramos model and a pre-B acute lymphoblastic leukaemia-derived model (NALM-6).

Moreover, ADCT-402 was tested in combination with rituximab, a CD20-specific mAb or with the anti-metabolite chemotherapeutic drug gemcitabine in the WSU-DLCL2 xenograft model and with the pan-class I PI3K inhibitor copanlisib in the TMD8 xenograft model.

ADCT-402 was shown to moderately target CD19-negative cells in co-culture experiments with CD19-positive and CD19-negative cells and to mediate bystander killing of CD19-negative cells via conditioned-medium transfer from ADCT-402-treated, CD19-positive cells. The bystander effect may be a contributor to the efficacy of loncastuximab tesirine, including the durable responses which continue beyond the end of treatment in patients who achieve a response.

Analytical methods were developed to determine ADCT-402, total RB4v1.2 antibody or SG3199 in rat and cynomolgus monkey serum or for determination of SG3199 in *in vitro* metabolism studies. Validated methods were used in the GLP-compliant repeat-dose toxicity studies in the rat and cynomolgus monkey. In addition, in order to determine the formation of ADA in cynomolgus monkey serum, a validated method was developed. The validations of the analytical methods included: determination of assay range, inter-assay and intra-assay precision and accuracy, selectivity, specificity, bench top stability, long-term stability, freeze-thaw stability, hook (prozone) effect. The incurred sample reproducibility evaluation could not be found in any study. ISR analyse performed in support of the GLP-compliant 4- and 13-week studies with ADCT-402 in cynomolgus monkeys (Study

8303115 and Study 8374716) and the GLP-compliant 4-week study with SG3199 in rats (Study 527042) met predefined reproducibility criteria for all assays in all studies.

Absorption studies were not conducted with ADCT-402 or SG3199. All *in vivo* studies with ADCT-402 or SG3199 used the IV route of administration, the intended clinical route of administration for ADCT-402.

No distribution studies were conducted with ADCT-402. Given its molecular size, ADCT -402 would be expected to be largely confined to the plasma space, similar to the endogenous antibodies and monoclonal antibodies. This was confirmed by the TK analyses from 4- and 13 – week repeat dose toxicity studies in cynomolgus monkeys, which indicated that the volume of distribution (Vz) was generally similar to the plasma volume.

No metabolism studies were performed on ADCT-402. Monoclonal antibodies are expected to be metabolised in the same manner as endogenous antibodies. This is acceptable according to ICHS6(R1).

In vitro studies indicated that SG3199 is not a potent inhibitor of cytochrome P450 (CYP) enzymes. CYP induction studies showed that SG3199 did not induce CYP2B6- or CYP3A4-mediated enzyme activity or mRNA expression in human hepatocytes *in vitro*, whilst a >2-fold increase in CYP1A2 mRNA expression (without corresponding increase in enzyme activity) was observed. These data indicate that SG3199 is unlikely to induce CYP2B6 or CYP3A4 *in vivo* and therefore the potential for producing clinically relevant CYP induction related drug-drug interactions is considered to be low. However, based on the *in vitro* data SG3199 may be an inducer of CYP1A2 *in vivo*.

Comparable metabolite profiles were observed upon incubation with rat, cynomolgus monkey or human hepatocytes and liver microsomes. Biotransformation by human liver microsomes and hepatocytes resulted in ether hydrolysis, amide hydrolysis, various oxygenation biotransformations and O-demethylation, or a combination thereof. Results from two approaches to reaction phenotyping (recombinant human CYP enzymes and chemical inhibition) indicated potential involvement of CYP3A4/5 in the metabolism of SG3199. In addition, based on the extent of substrate loss in the absence of NADPH when SG3199 was incubated with human liver microsomes, non-CYP mediated metabolism of SG3199 is indicated.

No nonclinical excretion studies were conducted with ADCT-402, which is acceptable for the antibody part as it will undergo normal protein metabolism.

Excretion of [3H]-SG3199 was mainly via the faeces, biliary route (97.5±3.0%), with minor urinary excretion (3.8±0.3%). Excretion was rapid, with most radioactivity (83.5±5.8%) recovered 24 h post dose.

Loncastuximab tesirine was cleared slowly in animals with the half-life ranging from 8 to 17 days in monkeys. Exposures to loncastuximab tesirine generally increased dose proportionally with an increase in dose level. There were no major differences in plasma exposure between males and females and no evidence of accumulation with repeated dosing. Maximal serum concentrations were generally reached within 1.5 hours of dosing. Plasma concentrations were overall comparable between loncastuximab tesirine and the monoclonal antibody component, and the level of deconjugated SG3199 was below the lower limit of quantitation at most timepoints and dose levels in the 13-week repeat-dose study in monkeys. Plasma stability studies combined with the toxicokinetic data in monkeys suggest the ADC is stable and, when free, SG3199 is highly protein bound in rat, cynomolgus monkey and human plasma (approximately 97%, 93%, and 94%, respectively). [3H]-SG3199 distribution was rapid and widespread with the majority of tissues reaching maximum radioactivity at 2 hours post dose, the first sampling time point. There was no apparent distribution of SG3199 to melanin-containing tissues or the brain or spinal cord. Linear clearance profiles for loncastuximab tesirine were noted across the

dose range studied (0.075-0.9 mg/kg), indicative of a lack of target-mediated drug disposition (TMDD) and consistent with the lack of cross-reactivity of RB4v1.2 to cynomolgus monkey CD19.

The cynomolgus monkey was subsequently selected by the Sponsor as the species for nonclinical safety evaluation of ADCT-402, in light of the general suitability of this species for nonclinical safety evaluation of ADCs, and the fact that the potential human PK parameters and the toxicities associated with SG3199 are adequately predicted in this species to allow for calculation of safe clinical starting doses. Potential on-target toxicity could not be evaluated in this species, however, there is extensive nonclinical and clinical experience with selective CD19 and CD20 depletion with ADCs and mAbs that alleviates potential on-target toxicity concerns.

In repeat-dose toxicity studies in cynomolgus monkeys, loncastuximab tesirine exhibited a safety profile consistent with SG3199-mediated effects on the skin (epidermal hyperpigmentation with hyperplasia/hyperkeratosis), bone marrow (hypocellularity associated with regenerative anaemia), kidney (nephropathy–degeneration and hyperplasia/hypertrophy of distal tubules and collecting ducts, mainly in the cortico-medullary junction) and testis (testicular atrophy with reduced spermatogenesis). The majority of these findings were considered to be reversible, although (full) reversibility was not always demonstrated in the context of completed studies. The nonclinical toxicity of SG3199 was predominantly evaluated in the rat, with the toxicity profile characterised by myelosuppression, increased liver enzymes/liver toxicity, and inflammation of the gastrointestinal tract with epithelial degeneration.

The majority of the toxicities observed in the 4-week study were also observed in the 13-week study, with progression of some findings to lower doses with longer periods of dosing. For example, the incidence of black spots that correlated microscopically with epidermal hyperpigmentation observed at 0.6 mg/kg q3w in the 4-week study was comparable to the incidence at the 0.3 mg/kg dose in the 13-week study. Statistically significant decreases in haematocrit and haemoglobin were observed only at 0.6 mg/kg in the 4-week study and were observed at ≥ 0.15 mg/kg on Day 92 of the 13-week study. Creatinine elevations in the 4-week study were only observed at 0.6 mg/kg and during the recovery phase; in the 13-week study they were observed during the main study phase in females at doses ≥ 0.15 mg/kg. Microscopic findings of nephropathy (characterised by tubular degeneration and dilatation) were observed at 0.6 mg/kg in the 4-week study and are observed at doses ≥ 0.075 mg/kg in the 13-week study. In one 0.6 mg/kg female, slight fibrosis (pleural/subpleural) of the lungs was observed only in the recovery phase in the 4-week study; in the 13-week study, minimal to moderate fibrosis (pleural/ subpleural) of the lungs was observed at doses ≥ 0.15 mg/kg during the dosing phase. In the 13-week study, multifocal oedema, acute inflammation, and necrosis were observed in the lung, but were not present or were reduced in severity by the end of the 12-week recovery phase. Taking into account the incidental nature of alveolar haemorrhage in a single animal ~90 days after the last ADCT-402 dose and also the lack of evidence of tissue repair, and the difference in anatomic location vs pleural effusions it seems unlikely that the finding in animal P0303 is representative of pleural effusions as seen in individual patients.

Also, adverse findings in male reproductive organs were present at 0.6 mg/kg only in the 4-week study and at all doses (≥ 0.075 mg/kg) in the 13-week study.

SG3199 was clastogenic in both the *in vitro* micronucleus assay and the chromosome aberration assay in human lymphocytes from whole blood. The clastogenicity was observed in the presence and absence of metabolic activation (S9 mix). In the chromosome aberration assay, statistically significant and concentration-dependent increases in chromosomal aberrations were observed and were comprised mainly of broken segments (gaps or breaks) of one or both chromatids that are aligned or unaligned; a single, usually circular, part of a chromatid lacking a centromere; an exchange(s) between two or more chromosomes resulting in the formation of a tri- or more-armed configuration; and miscellaneous

aberrations. Some aberrations exceeded the positive control range. A GLP bacterial reverse mutation assay (Ames test) was also submitted; however, mutagenicity could not be assessed due to cytotoxicity at all concentrations tested.

Given that SG3199 is a potent genotoxicant, in accordance with ICH S9 and ICH S6(R1), no reproductive and developmental toxicity studies were conducted with loncastuximab tesirine, and, based on the mode of action of SG3199, reproductive and developmental toxicity is expected. With regard to fertility, the potential for effects of loncastuximab tesirine on male and female fertility was assessed in the pivotal repeat-dose toxicity study in sexually mature cynomolgus monkeys by evaluation of the reproductive tract (organ weights and histopathological evaluation) as outlined in ICH S6(R1). In males, marked testicular toxicity (testicular atrophy with reduced spermatogenesis) was observed. These findings are consistent with the pharmacological activity of ADCT-402 and were not reversible after a 12-week treatment-free period corresponding to 2 spermatogenic cycles (42 days in Cynomolgus monkeys). Therefore, SPC 4.6 should be amended to state that men being treated with this medicine are advised to have sperm samples preserved and stored before treatment (OC). In females, no effects were reported on reproductive organs. There was no fresh corpus luteum in one high dose female at 0.3 mg/kg in the 13-week monkey study. The relationship of this finding to loncastuximab tesirine is uncertain due to the low incidence in the 13-week monkey study and the lack of the finding at higher doses in other studies. Therefore, at this time, this finding and a potential for loncastuximab tesirine to impair female reproductive function is not included in labelling.

Based on nonclinical genotoxicity findings and the mechanism of action of loncastuximab tesirine, the applicant states that there is a risk of embryo-foetal toxicity during pregnancy. There are no data on loncastuximab tesirine exposure in pregnant women. Therefore, women of childbearing potential should use effective contraception during treatment with Zynlonta and for 9 months after the last dose. Similarly, male patients with female partners of childbearing potential should use effective contraception during treatment with Zynlonta, and for 6 months after the last dose. There is no sufficient human experience and a relevant risk from non-clinical studies suggest a suspected risk to the developing embryo/fetus. Findings in the pivotal 13-week repeat-dose toxicity study of ADCT-402 included dose-related black skin discoloration, which correlated microscopically with minimal-to-moderate epidermal hyperpigmentation. These findings were still present with reduced incidence by the end of the 12-week recovery phase, indicating a trend towards reversibility.

Due to the low incidence and severity of the local tolerance findings, these were considered procedural, although a relationship to treatment with SG3199 could not be excluded.

The PECsw for loncastuximab tesirine is around 100-fold below the trigger value of 0.01 µg/L. The PECsw for SG3199, which presents approximately 1% of the total ADC, is even further below the trigger value. Hence, further investigations on the environmental fate and effects detailed in Phase II Tier A of the EMEA guidance document are not considered required. Experimental log P values of 0.94 and 1.00 for acidic and neutral conditions were obtained for SG3199 and whilst they are indicative of its lypophilic nature, they are far below the trigger value for PBT assessment. The applicant used *in silico* evaluation to predict the Log P of SG3199. According to the ERA guideline the octanol /water partition coefficient Kow should be determined experimentally with regards to GLP compliance. Taking into account the low risk due to the negligible release of SG3199 in the environment, an additional determination of log Kow is not warranted, and the costs associated with such a determination do not weigh up against the very limited impact the results of such a determination would have on the overall risk assessment. Therefore loncastuximab tesirine is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

Overall, loncastuximab tesirine is considered approvable from a nonclinical point of view.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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.

Table 2 Tabular overview of clinical studies

Study Number	Study Design	Objectives	N	Treatment Regimen
ADCT-402-101	Open-label, Phase 1 study of loncastuximab tesirine in patients with relapsed or refractory B-cell lineage non-Hodgkin lymphoma	Safety and tolerability and determine the MTD of loncastuximab tesirine (Part 1, dose escalation part); RP2D for Part 2 (dose expansion part); Safety and tolerability in Part 2 at the dose level recommended in Part 1. Characterize the PK (total antibody, PBD-conjugated antibody, and free cytotoxic agent SG3199) and immunogenicity (ADA) profile of loncastuximab tesirine.	183	15, 30, 60, 90 µg/kg IV, Q3W; 120, 150, 200 µg/kg IV, Q3W or Q6W.
ADCT-402-201	Open-label, Phase 2 single-arm study of loncastuximab tesirine in patients with relapsed or refractory diffuse large B-cell lymphoma	Evaluate the efficacy and safety of loncastuximab tesirine. Characterize the PK (total antibody, PBD-conjugated antibody, and free cytotoxic agent SG3199) and immunogenicity (ADA) profile of loncastuximab tesirine.	145	150 µg/kg IV, Q3W ×2 followed by 75 µg/kg IV, Q3W on subsequent treatment cycles.
ADCT-402-102	Open-label, Phase 1 study of loncastuximab tesirine in patients with relapsed or refractory B-cell lineage acute lymphoblastic leukaemia	Evaluate safety and tolerability, and determine the MTD (Part 1, dose escalation part), of loncastuximab tesirine. Determine RP2D for Part 2 (dose expansion part). Safety and tolerability in Part 2 at the RP2D. Characterize the PK (total antibody, PBD-conjugated antibody, and free cytotoxic agent SG3199) and immunogenicity (ADA) profile of loncastuximab tesirine.	35	15, 30, 60, 90, 120, 150 µg/kg IV, Q3W. Weekly dosing on Days 1, 8, and 15 of each 3-week treatment cycle: 50 µg/kg IV

Source: ADCT-402-101 CSR, ADCT-402-201 CSR, and ADCT-402-102 CSR
ADA = anti-drug antibody; IV = intravenous; MAA = Marketing Authorisation Application; MTD = maximum tolerated dose; N = number of patients; PBD = pyrrolobenzodiazepine; PK = pharmacokinetic(s); Q3W = every 3 weeks; Q6W = every 6 weeks; RP2D = recommended Phase 2 dose.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Loncastuximab tesirine (LT), is a CD19-targeted antibody-drug conjugate (ADC), consisting of a humanised IgG1 kappa monoclonal antibody (mAb) specific for human CD19, conjugated to SG3199, a pyrrolobenzodiazepine (PBD) dimer cytotoxic drug, through a protease-cleavable valine-alanine linker. SG3199 attached to the linker is designated SG3249 (also known as tesirine). LT has an average of approximately 2.3 SG3199 molecules attached per antibody. LT is intended for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy. The proposed dose regimen for LT is 0.15 mg/kg every 3 weeks (Q3W) for the first 2

cycles, then a dose of 0.075 mg/kg Q3W thereafter, as an IV infusion. The dose regimen was chosen to minimise the potential for a drug holiday, to mitigate onset and severity of adverse events, and to ensure that efficacious drug levels could be maintained.

Studies providing data for the clinical pharmacology evaluation consist of the ongoing pivotal Phase 2 study ADCT-402-201, and in the completed Phase 1 studies ADCT-402-101 and ADCT-402-102. Details of the clinical studies can be found in table above. The pivotal Phase 2 study was conducted in patients with DLBCL, supportive studies are the Phase 1 study ADCT-402-101 in patients with B-cell lineage non-Hodgkin lymphoma (NHL) (B-NHL) and the phase 1 study ADCT-402-102 in patients with B-cell lineage acute lymphoblastic leukaemia (B-ALL) in ADCT-402-102.

Dose rationale: The dose escalation of LT started with a dose of 15 µg/kg Q3W in patients with NHL. In absence of DLTs in Cycle 1, as dose escalation proceeded to the 200 µg/kg dose level, the MTD was not established during the trial. Cumulative toxicity was substantially increased at the 200 µg/kg dose compared to lower dose levels. After induction doses of 150 µg/kg Q3W ×2, a 50% dose reduction to 75 µg/kg Q3W thereafter was instituted in the Phase 2 study to rapidly achieve steady state exposure and to mitigate cumulative toxicities. Based on ORR, the proposal to apply the dose reduction regimen for patients with DLBCL appeared justified. PBD-conjugated Ab C_{avg} and C_{min} levels monitored early in treatment during Cycles 1 and 2 were significantly associated with OR, and C_{avg} was prognostic for association with OS and PFS. The choice of a Q3W dose regimen was based on animal studies and the expectation that this interval would result in efficacious drug levels while reducing adverse events.

Bioanalysis: Three analytes in serum were measured to characterise the pharmacokinetics of LT: total (unconjugated and conjugated) Ab, PBD-conjugated Ab, and free cytotoxic agent SG3199. Anti-drug Ab (ADA) against LT in serum was measured from the collected samples.

The total Ab (conjugated and unconjugated) and PBD-conjugated Ab of LT in serum were measured using 2 validated electro-chemiluminescence immunoassays (ECLIAs) with lower limits of quantitation (LLOQs) of 20 and 5.06 ng/mL, respectively. A validated liquid chromatography-tandem mass spectrometric (LC-MS/MS) assay was used to measure SG3199 serum concentration with LLOQ of 25 pg/mL. Screening, confirmation, and titration of anti-LT ADA were performed using a validated bridging ECLIA assay. Pre-treatment samples from 7 of the 363 patients treated in total were confirmed as ADA positive (1.9% overall of pre-treatment samples).

PopPK analyses: The population PK of Loncastuximab tesirine total antibody and conjugated antibody was described by a 2-compartment linear model with linear clearance and time-dependent clearance in parallel and an additive residual error model. A one-compartment model with linear clearance was integrated into the model with a linear deconjugation clearance from the central deconjugated antibody compartment to account for the formation of free warhead SG3199.

Table 3 **Bootstrap Validation of Population Pharmacokinetics Parameters of loncastuximab tesirine PBD-Conjugated Antibody and Total Antibody (run235Tbs)**

Parameters [a]	Symbol	Estimate (%RSE) [b]	Bootstrap Median (95% CI) [c]
CL (L/day)	θ1	0.224 (4.7)	0.223 (0.194 - 0.250)
WT on CL	θ10	0.531 (36.5)	0.531 (0.190 - 0.735)
ECOG on CL	θ13	0.246 (0)	0.246 (0.0882 - 0.406)
ALBU on CL	θ14	-0.536 (56.9)	-0.536 (-1.03 - -0.0235)
SEX on CL	θ20	-0.161 (46.7)	-0.157 (-0.261 - 0.0326)
V1 (L)	θ2	4.02 (4.6)	3.995 (3.69 - 4.19)
WT on V1	θ15	0.568 (27.3)	0.568 (0.383 - 0.743)
SEX on V1	θ21	-0.108 (53.9)	-0.0975 (-0.187 - 0.0524)
CL_{dec} (L/day)	θ3	0.043 (10.9)	0.0430 (0.0371 - 0.0491)
V2 (L)	θ4	3.53 (fixed)	3.53 (fixed)
DELT (L/day)	θ5	0.103 (19.3)	0.103 (0.072 - 0.129)
PTST on DELT	θ18	10.1 (30)	10.23 (4.23 – 19.51)
ALBU on DELT	θ28	-5.36 (17.3)	-5.37 (-7.89 - -3.58)
Q (L/day)	θ6	1.16 (fixed)	1.16 (fixed)
Kdes (1/day)	θ7	0.0505 (16.9)	0.0505 (0.0310 - 0.0725)
BSV of CL (%CV)	η1	45.4 (8.6)	45.3 (30.3 – 54.8)
BSV of V1 (%CV)	η2	33.8 (10.2)	33.7 (22.5 – 40.5)
BSV of CL_{dec} (%CV)	η3	87.6 (16.8)	87.5 (38.6 – 128.9)
BSV of V2 (%CV)	η4	50.1 (10.4)	50.1 (40.5 – 61.2)
BSV of DELT (%CV)	η5	154.6 (13.4)	151.7 (127.7 – 153.7)
BSV of Q (%CV)	η6	128.1 (12.1)	128.4 (110.6 – 153.7)
BSV of Kdes (%CV)	η7	112.2 (29.3)	109.3 (80.1 – 130.2)
BOV of CL (%CV)	η8	25.7 (fixed)	25.7 (fixed)
BOV of V1 (%CV)	η11	33.2 (fixed)	32.7 (fixed)
BOV of CL_{dec} (%CV)	η14	57.4 (fixed)	57.1 (fixed)
BOV of V2 (%CV)	η17	24.9 (fixed)	24.9 (fixed)
ADD ERR1 (%CV)	θ8	21.3 (0.5)	20.4 (17.3 - 24.4)
ADD ERR2 (%CV)	θ9	22.4 (0.5)	21.8 (18.0 – 25.7)

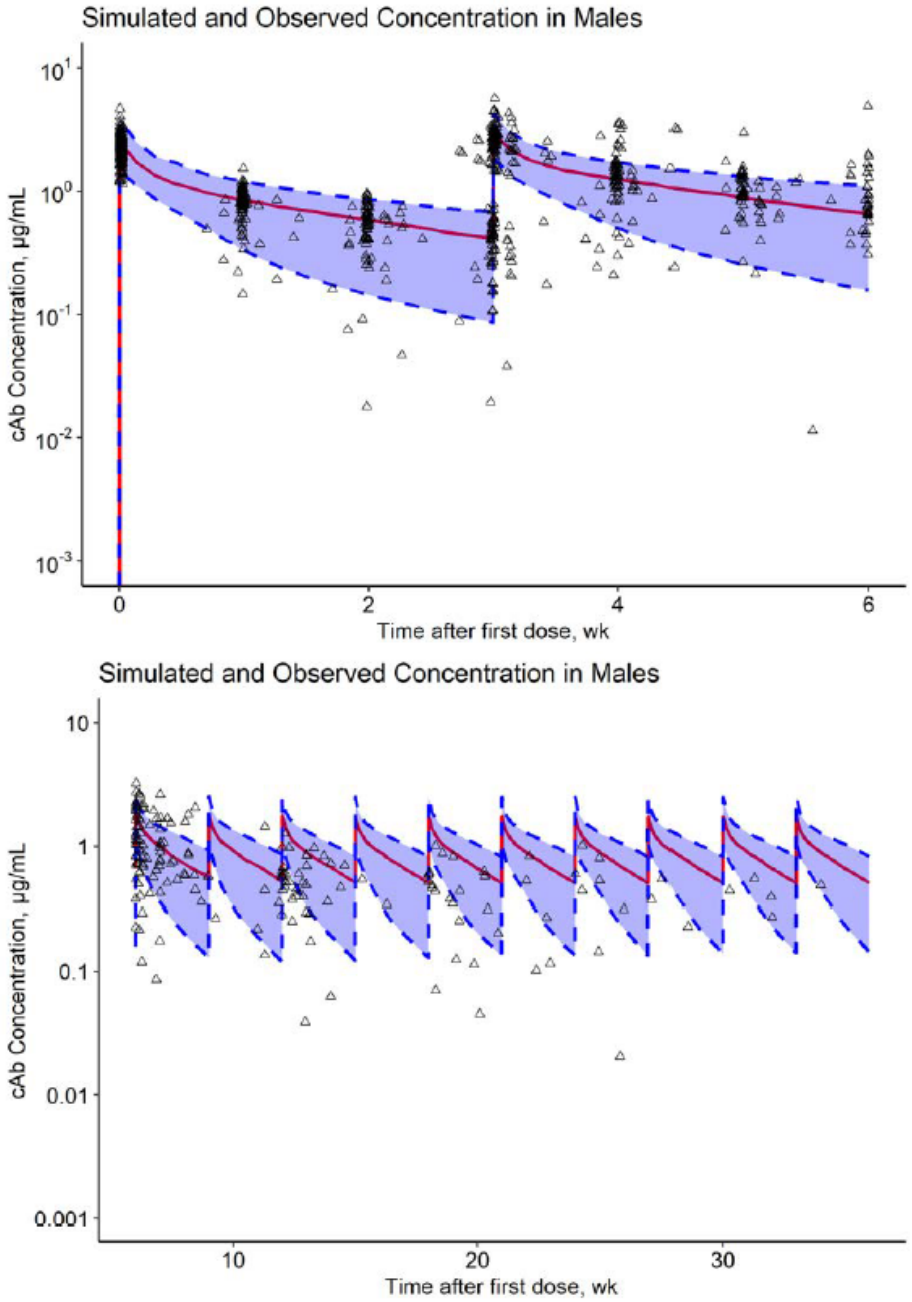
[a] Definition of covariate factors are listed in Section 4.5
[b] run235T
[c] run235Tbs bootstrap replicated at least 100 times.

Note: The objective function value = -15,131.5. Condition number = 270.8. Condition number was calculated as the ratio of the largest to smallest eigenvalue of correlation matrix of estimate. The typical values (TV) of pharmacokinetic parameters, $TVCL = 0.224 \cdot \left(\frac{WT}{78.0}\right)^{0.531} \cdot \left(\frac{ALBU}{40.0}\right)^{-0.536} \cdot ECOG_{CL} \cdot SEX_{CL}$, where $ECOG_{CL}$ is a shift factor of 1 for ECOG = 1 patients, and 1+0.246 for ECOG >0 patients, and SEX_{CL} is a shift factor of 1 for male patients, and 1 - 0.161 for female patients. $TVV1 = 4.02 \cdot \left(\frac{WT}{78.0}\right)^{0.568} \cdot SEX_{V1}$, where SEX_{V1} is a shift factor of 1 for male patients and 1 - 0.108 for female patients. $TVDELT = 0.103 \cdot \left(\frac{ALBU}{40.0}\right)^{-5.36} \cdot PTST_{DELT}$, where $PTST_{DELT}$ is a shift factor of 1 for DLBCL patients, and 1+10.1 for non-DLBCL patients.
ADD ERR1 = additive error of PBD-conjugated antibody on a log scale; ADD ERR2 = additive error of total antibody on a log scale; ALBU = albumin; BSV = between-subject variability; CL = linear clearance; CL_{dec} = deconjugation clearance; CV% = percent coefficient of variation; ECOG = Eastern Cooperative Oncology Group; K_{des} = time-dependent clearance rate constant; PTST = disease subtype; Q = inter-compartmental clearance; RSE% = percent relative standard error; V_1 = volume of distribution in the central compartment; V_2 = volume of distribution in the peripheral compartment; WT = body weight.

The final model was evaluated by means of bootstrap analysis, goodness-of-fit plots and visual predictive checks. The precision of structural model parameters and random variance terms were

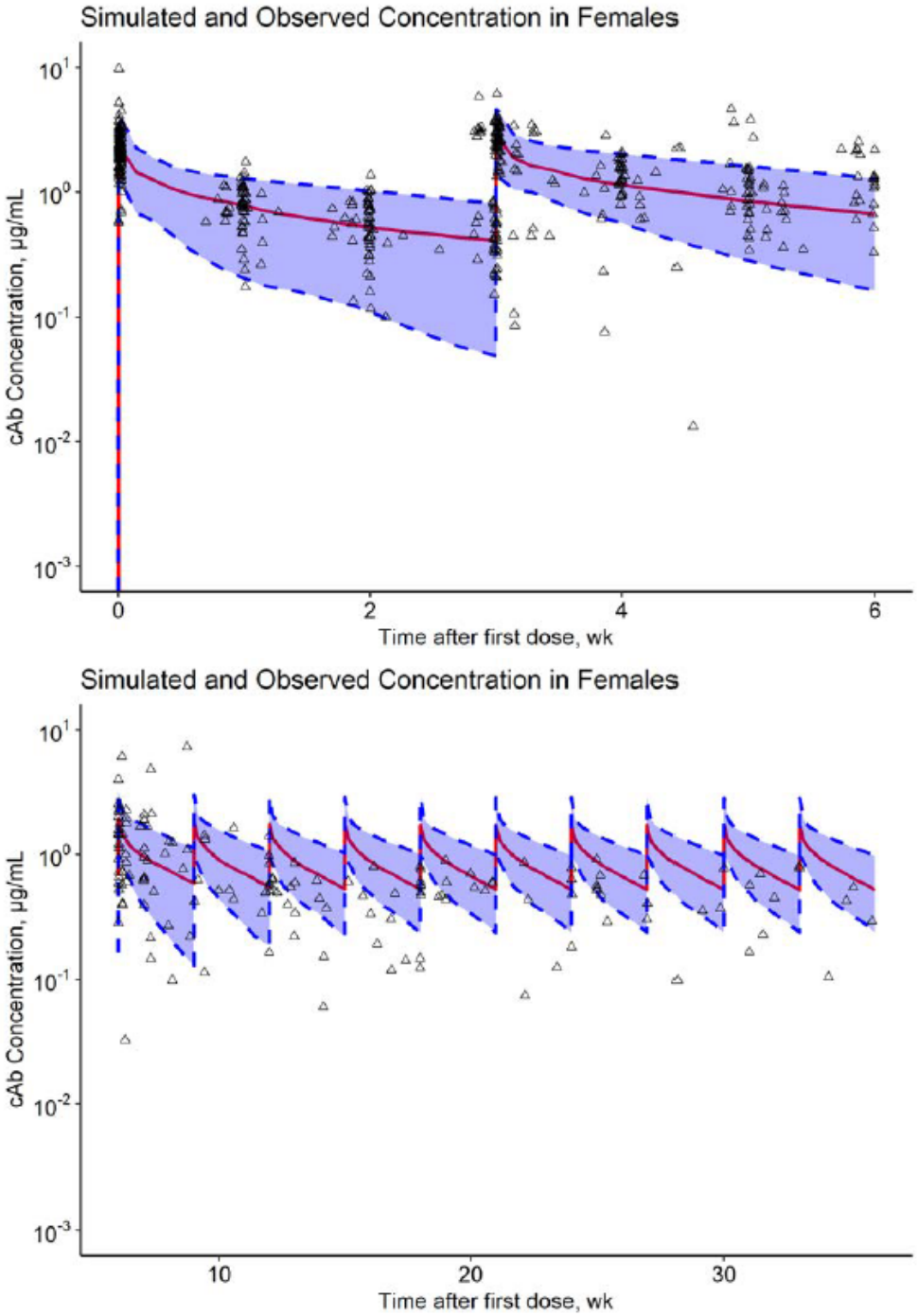
estimated with adequate precision (relative standard error less than 25%), whereas covariate effects were estimated with relatively high imprecision.

Figure 5. **Visual Predictive Check; Study ADCT-402-201 Model-Predicted and Observed Serum conjugated Anti-body Concentrations for the Final PPK Model by Sex (continued)**



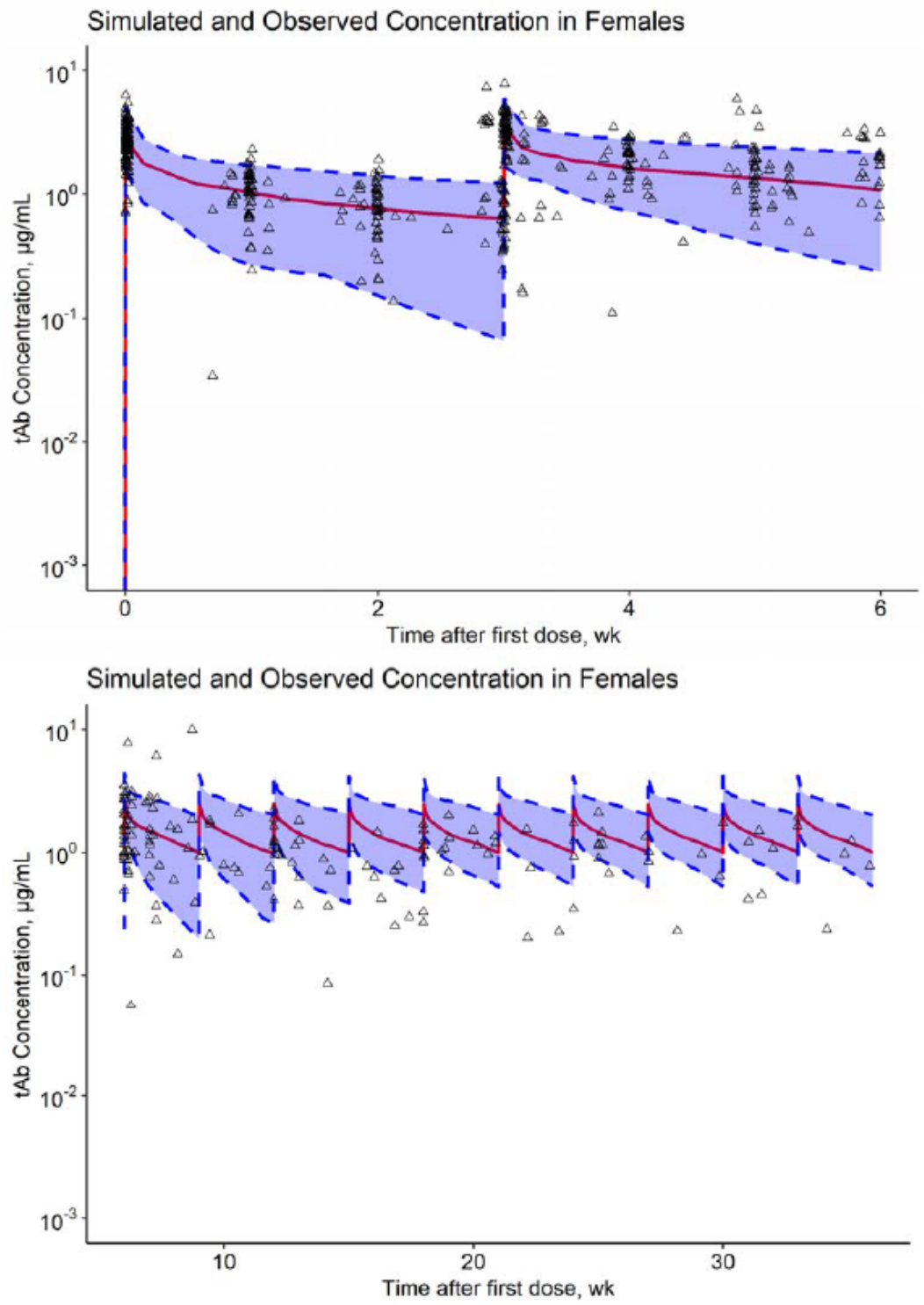
* The solid red line represents the median model-predicted values, and the dashed blue line indicate the model-predicted 95% confidence interval. The black triangle markers represent observed PK data. Study ADCT-402-201 has the dose regimen of 150 µg/kg per Q3W cycle x2, then reduced to 75 µg/kg Q3W.

Figure 6. **Visual Predictive Check; Study ADCT-402-201 Model-Predicted and Observed Serum conjugated Anti-body Concentrations for the Final PPK Model by Sex (run235T)**



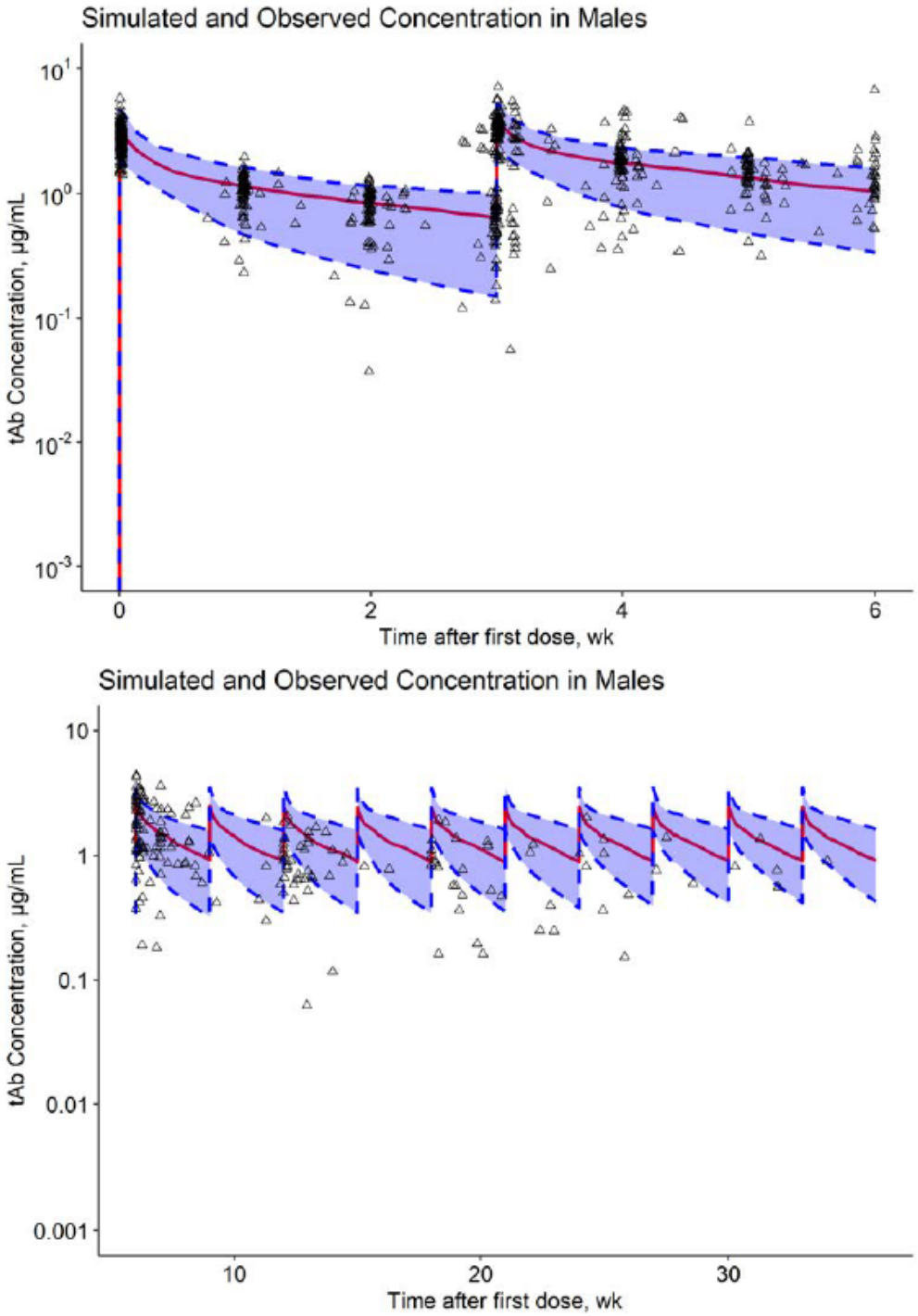
* The solid red line represents the median model-predicted values, and the dashed blue line indicate the model-predicted 95% confidence interval. The black triangle markers represent observed PK data. Study ADCT-402-201 has the dose regimen of 150 µg/kg per Q3W cycle x2, then reduced to 75 µg/kg Q3W.

Figure 7. **Visual Predictive Check; Study ADCT-402-201 Model-Predicted and Observed Serum loncastuximab tesirine Total Anti-body Concentrations for the Final PPK Model by Sex (run235T)**



* The solid red line represents the median model-predicted values, and the dashed blue line indicate the model-predicted 95% confidence interval. The black triangle markers represent observed PK data. Study ADCT-402-201 has the dose regimen of 150 µg/kg per Q3W cycle x2, then reduced to 75 µg/kg Q3W

Figure 8. **Visual Predictive Check; Study ADCT-402-201 Model-Predicted and Observed Serum loncastuximab tesirine Total Anti-body Concentrations for the Final PPK Model by Sex (continued)**

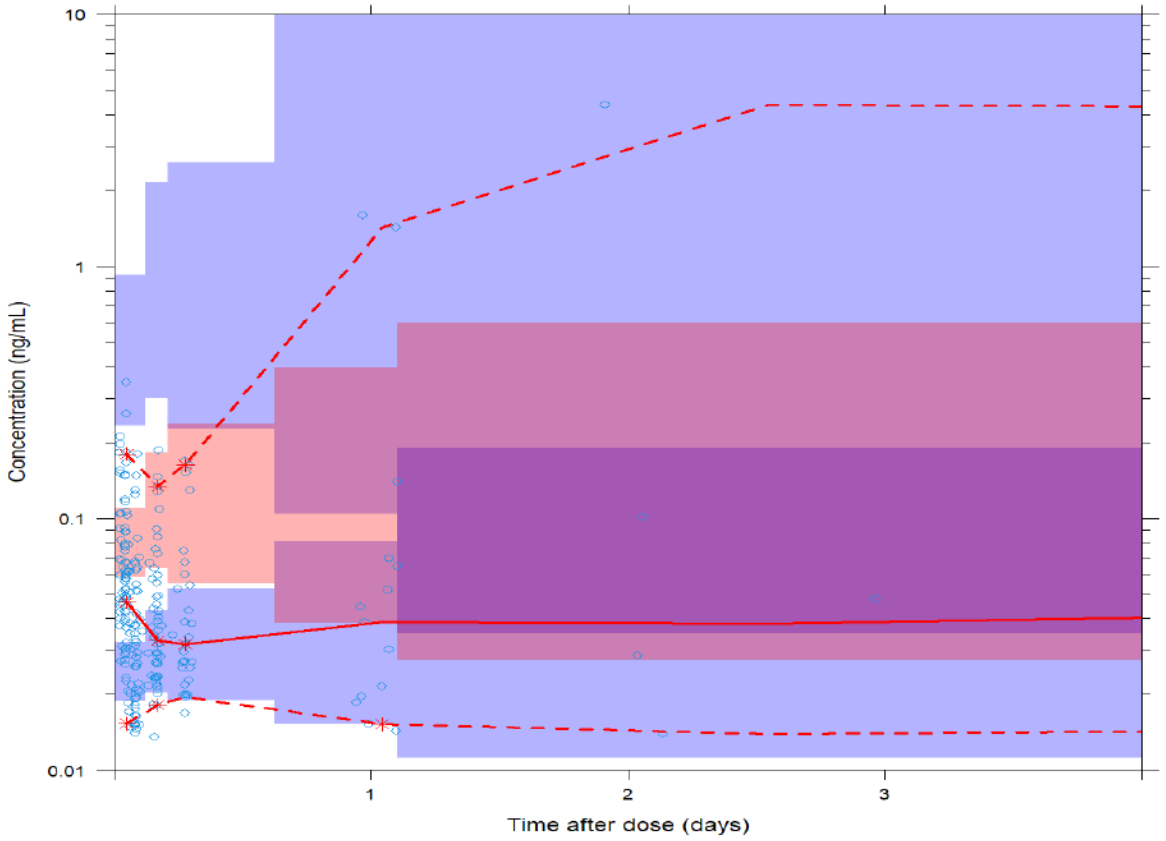


* The solid red line represents the median model-predicted values, and the dashed blue line indicate the model-predicted 95% confidence interval. The black triangle markers represent observed PK data. Study ADCT-402-201 has the dose regimen of 150 µg/kg per Q3W cycle x2, then reduced to 75 µg/kg Q3W

Model predictability of total antibody and PBD-conjugated antibody was demonstrated for the VPC which showed the majority of the observed concentrations were contained within the 95% prediction interval bands. VPC of SG3199 model (Figure below) indicates that the model overpredicts SG3199

serum concentrations but this is likely due to the model being based on very few data points as the majority of patients had concentrations below LLOQ.

Figure 9. **Visual Predictive Check; Model-Predicted and Observed Serum SG3199 Concentrations for the PPK Model (run301A)**



CI = confidence interval; DV = dependent variable (usually observation); pcVPC = prediction corrected VPC; PPK = population pharmacokinetic.
Note: The pcVPC plots show the median (solid red line) and spread (5^{th} to 95^{th} percentiles; dashed red line) of the DV in all participants. The red area is the 95% CI of the simulated median, and the blue area is the 95% CI of the simulated 5^{th} and 95^{th} percentiles.

Table 4 Population Pharmacokinetic Parameter Estimates of the Final Model for ADCT-402 SG3199 (run301A)

Parameter	Parameter Description	Estimates [RSE %]	CV (%)	Shrinkage
th29	CL (L/day)	1.94 [21.5]	NA	NA
th30	V (L)	0.0456 [19.6]	NA	NA
th31	Additive error (µg/mL)	0.452 [5.6]	NA	NA
om20	IIV on CL (L/day)	1.56 [23.2]	125	56.1

CL = elimination clearance of SG3199; CV = coefficient of variation; IIV = inter-individual variability; NA = not applicable; RSE = relative standard error; V = volume of distribution for metabolite SG3199. Source: Data on file.

Absorption

The product is administered as an intravenous infusion. In ADCT-402-101 and ADCT-402-201, with the Cycle 1 dose of 150 µg/kg, the geometric mean time to reach Cmax (Tmax) was 1.92 and 1.39 h for PBD-conjugated Ab, 1.87 and 1.44 h for total Ab, and 2.16 and 2.52 h for SG3199, respectively. The time to maximum concentration was close to the end of infusion or shortly after the end of infusion.

Using drug accumulation by Cycle 2 as a guide, exposures to LT PBD-conjugated Ab and total Ab after the 150 µg/kg Q3W doses were increased compared to Cycle 1 (AI = 1.65 and 2.07, respectively).

PK parameters observed in the target population in studies ADCT-402-101 and ADCT-402-201 are found tables below for PBD-conjugated Ab and free SG3199. For SG3199, the majority of time points and patients had data that were largely below the LLOQ. Non-compartmental steady state PK data for SG3199 have not been provided, which is acceptable since the majority of the sample data had measurements below LLOQ.

Steady state values of Cmax and AUC for LT were calculated from the final popPK model, these data are presented in section 5.2 of the SmPC.

Table 5 **Pharmacokinetic Parameters of PBD-conjugated Antibody after Loncastuximab Tesirine Dose of 150 µg/kg Q3W, by Study**

Study	Cycle	N	C_{max} (ng/mL)	AUC* (ng*day/mL)	T_{half} (day)	CL* (L/day)	V* (L)	AI
ADCT-402-101	1	88	2841 (57.7)	7361 (188)	4.46 (129)	1.36 (181)	6.37 (59.3)	-
	2	72	3258 (53.7)	18049 (106)	9.77 (82.2)	0.516 (99.2)	6.62 (52.5)	1.41 (24.6)
ADCT-402-102	1	6	2145 (49.1)	486 (53.4)	0.713 (83.6)	27.4 (45.2)	34.2 (104)	-
	2	4	3033 (48.1)	7444 (11.2)	3.99 (18.1)	1.57 (46.2)	9.45 (55.7)	1.03 (1.81)
ADCT-402-201	1	144	2436 (38.8)	19775 (53.7)	8.85 (53.5)	0.459 (48.3)	4.26 (40.3)	-
	2	118	2736 (35.6)	26902 (33.4)	15.3 (31.7)	0.331 (32.0)	6.42 (36.7)	1.65 (18.5)

Source: ADCT-402-101 CSR Tables 11-5 and 11-6; ADCT-402-102 CSR Tables 5, 7, 14.7.66 and 14.7.87; Module 5, Section 5.3.5.3, Table 14.4.6.1

Note: Data were presented as geometric mean (CV%) for ADCT-402-101 and ADCT-402-201, and as arithmetic mean (CV%) for ADCT-402-102.

AI = accumulation index; AUC* = area under the serum concentration-time curve from time 0 to infinity (AUC_{inf}) for Cycle 1 and area under the serum concentration-time curve from time 0 to end of dosing interval (AUC_{tau}) for Cycle 2; CL* = apparent clearance for Cycle 1 and apparent clearance at steady state for Cycle 2; C_{max} = maximum serum concentration; CV% = percent coefficient of variation; PBD = pyrrolobenzodiazepine; Q3W = every 3 weeks; T_{half} = apparent terminal half-life; V* = apparent volume of distribution at steady state (V_{ss}) for ADCT-402-101 and ADCT-402-201, and apparent volume of distribution at terminal phase ($V_{dβ}$) for ADCT-402-102; - = not available.

Table 6 **PK Parameters of SG3199 after Loncastuximab Tesirine Dose of 150 µg/kg Q3W in ADCT-402-101, ADCT-402-102 and ADCT-402-201**

Study	Cycle	N	C_{max} (ng/mL)	T_{max} (day)	AUC_{last} (ng*day/mL)	AUC* (day*ng/mL)	T_{half} (day)	CL* (L/day)	V_{ss} (L)
ADCT-402-101	1	28	0.0480 (59.3)	0.0900 (66.9)	0.00500 (436)	0.154 (-)	0.418 (-)	627 (-)	335 (-)
	2	15	0.0400 (56.1)	0.0980 (277)	0.00300 (311)	-	-	-	-
ADCT-402-102	1	6	0.0907 (55.2)	0.395 (197)	0.0338 (44.2)	-	-	-	-
	2	2	0.0550 (50.4)	0.0600 (47.1)	0.00927 (95.1)	-	-	-	-
ADCT-402-201	1	9	0.0390 (55.2)	0.105 (561)	0.0040 (474)	-	-	-	-
	2	5	0.0490 (78.8)	0.0360 (104)	0.00100 (204)	-	-	-	-

Source: ADCT-402-101 CSR Tables 14.4.6.5 and 14.4.6.6; ADCT-402-102 CSR Tables 14.7.81 and 14.7.104; Module 5, Section 5.3.5.3, Table 14.4.6.1

Note: Data were presented as geometric mean (CV%) for ADCT-402-101 and ADCT-402-201, and as arithmetic mean (CV%) for ADCT-402-102.

AUC* = area under the serum concentration-time curve from time 0 to infinity (AUC_{inf}) for Cycle 1 and area under the serum concentration-time curve from time 0 to end of dosing interval (AUC_{tau}) for Cycle 2; AUC_{last} = area under the serum concentration-time curve from time 0 to last measurable timepoint in respective cycle; CL* = apparent clearance for Cycle 1 and apparent clearance at steady state for Cycle 2; C_{max} = maximum serum concentration; CV% = percent coefficient of variation; Q3W = every 3 weeks; T_{half} = apparent terminal half-life; T_{max} = time to reach C_{max}; V* = apparent volume of distribution at steady state (V_{ss}) for ADCT-402-101 and ADCT-402-201, and apparent volume of distribution at terminal phase ($V_{dβ}$) for ADCT-402-102; - = not available.

Distribution

SG3199 is highly protein bound in human plasma (94%). In the SmPC, the Vd of LT is stated to be 7.14 L.

Elimination

The elimination route in humans has not been investigated in detail due to the nature of the product. This is acceptable considering the nature of the product. The immunoglobulin part is not expected to be eliminated differently than other endogenous immunoglobulins.

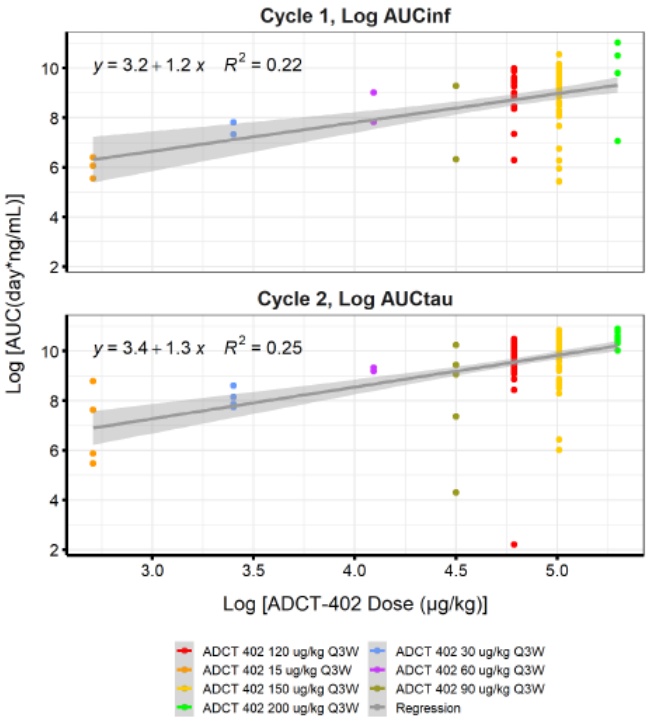
In a rat study, the elimination of SG3199 was mainly via biliary excretion and faeces (97.5±3.0%), and an *in vitro* study using recombinant CYP enzymes indicated that CYP3A4/5 is potentially involved in the metabolism of SG3199. In the metabolism studies using liver microsomes and hepatocytes from different species, no human-specific or disproportionate SG3199 metabolites were detected, with the rat and cynomolgus monkey hepatocyte metabolite profiles most closely matching the human hepatocyte metabolite profile. Two out of three SG3199 metabolites identified would likely still be able to bind DNA, as this is a generic property of PBDs, but as they are monomers rather than dimers they would no longer be able to cross-link DNA and would therefore be expected to be less cytotoxic than SG3199.

Via population PK analysis, the CL of LT is estimated to be 0.2 L/day, which is typical for monoclonal Abs. Data on the variability in CL for the active moiety SG3199 has been provided. The CV% for IIV is 125.

Dose proportionality and time dependencies

Multiple ascending doses of 15, 30, 60, 90, 120, 150 and 200 µg/kg of LT were evaluated in ADCT-402-101. The PK exposure (C_{max} and AUC) of PBD-conjugated Ab and total Ab appeared to increase with dose. The dose proportionality analyses were performed using a power model based on linear regression with log-transformed values. Dose proportionality in the dose range of 15 to 200 µg/kg has been shown for AUC (both in cycle 1 and 2) and for Cmax in cycle 2. For Cmax in cycle 1, dose linearity was only shown in the dose range of 120 to 200 µg/kg, which could be attributed to the small number of patients in the lower dose cohorts.

Figure 10. **Log AUC_{inf} (Cycle 1, Upper Panel) and Log AUC_{tau} (Cycle 2, Lower Panel) for PBD-conjugated Antibody Versus Log of Dose in the Dose Range of 15 to 200 µg/kg Q3W in ADCT-402-101**



Source: ADCT-402-101 Figures 14.4.15.1 and 14.4.15.7
Note: A linear regression model was used with natural logarithm of dose (Cycle 1) as the independent variable and natural logarithm of AUC_{inf} (Cycle 1) as the dependent variable. The estimated slope (standard error) was 1.16 (0.255), and 90% confidence interval was (0.735, 1.59). A linear regression model was used with natural logarithm of Dose (Cycle 2) as the

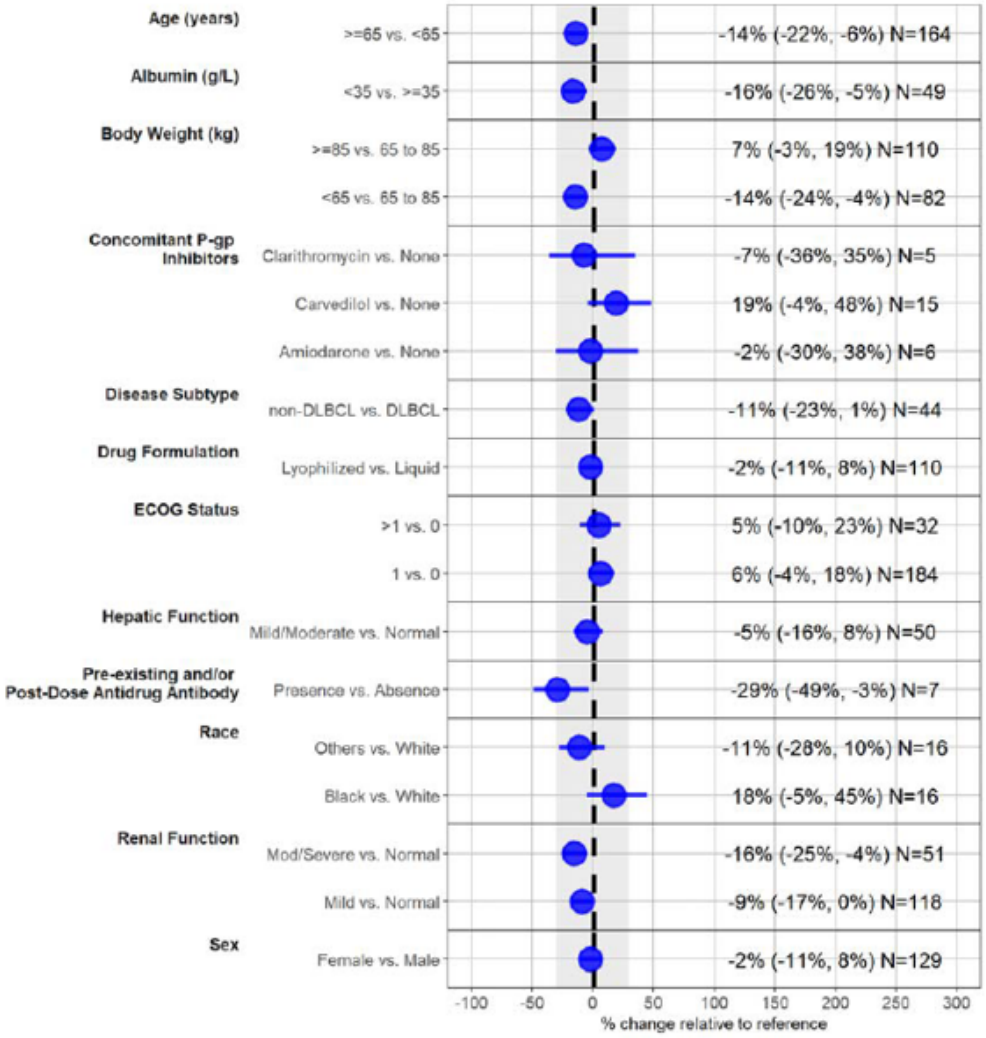
Time dependency: In the popPK analysis, the half-life of LT was 14.6 days at Cycle 1 and 20.6 days at steady state. This increase in half-life could be attributed to a decrease in tumour burden and therefore in target-mediated disposition.

Interindividual variability: Based on the population PK analysis, after adjusting for significant covariates, the inter-individual variability for CL and V_1 of PBD-conjugated Ab was 45.4% and 33.8%, respectively.

Special populations

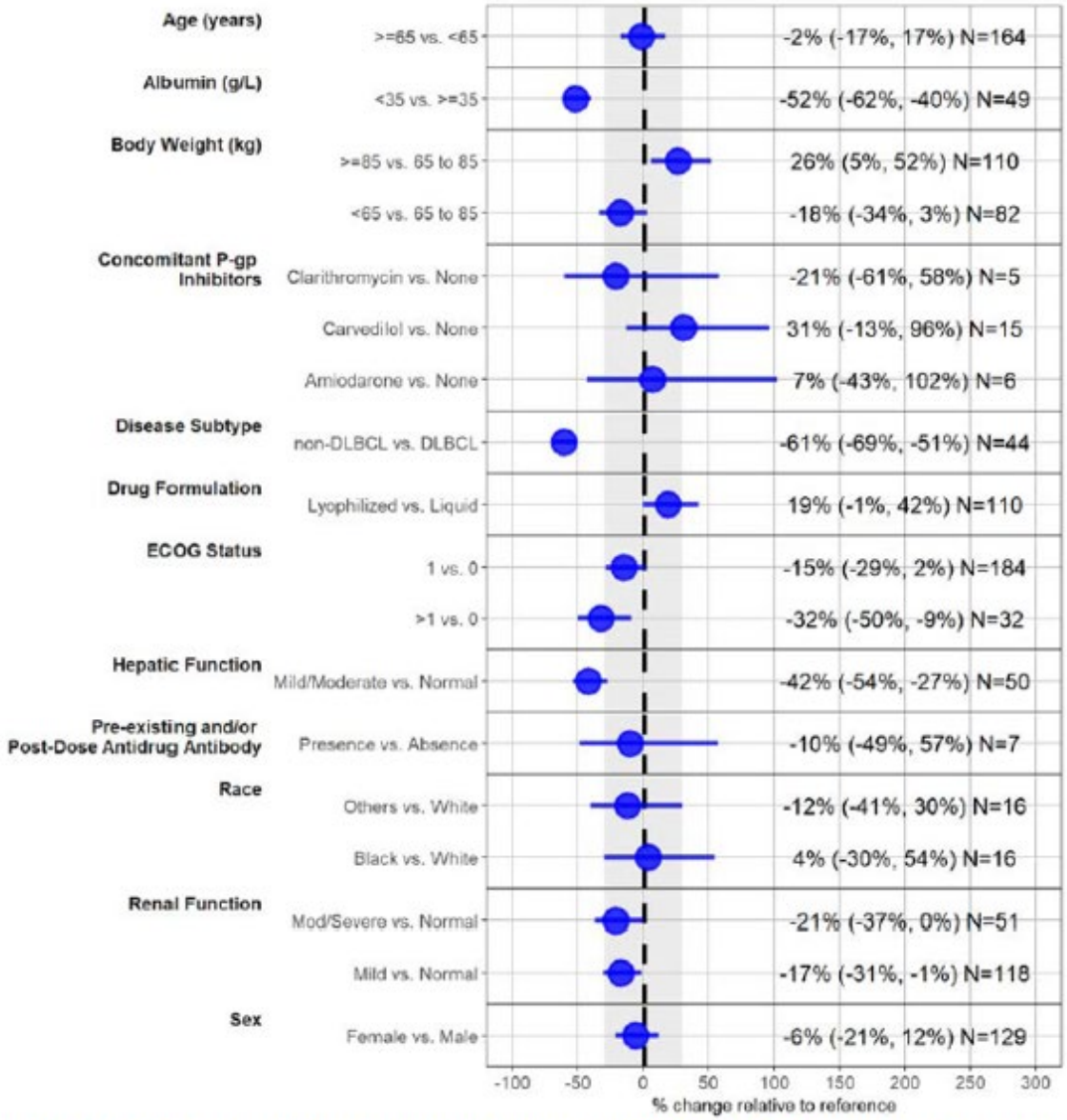
Population PK analyses were conducted by pooling data from studies ADCT-402-101 and ADCT-402-201 to characterise the PK disposition for a typical patient and to identify intrinsic and extrinsic sources of exposure variability. The impact of age, race, sex, baseline body weight, baseline lab measurements, baseline disease characteristics, ADA, formulation, and selected concomitant agents on the PK of LT was evaluated in the population PK analysis. The effects of the selected covariates on LT PK are shown as forest plots below.

Figure 11. Forest Plot Analyses on Percent Change Relative to Reference Value of Model Predicted Cycle One Peak loncastuximab tesirine PDB-Conjugated Antibody Concentration



Key: Solid blue circle represents mean and error bar represents 95% confidence interval. Dashed line represents reference value of 0. Numbers represent ratio, confidence interval, and number of patients in the comparison groups. Gray shaded region represents ±30% from reference value. ECOG=Eastern Cooperative Oncology Group disease status at the baseline; DLBCL= Diffuse Large B-cell Lymphoma. Note: Analyses assumed that all patients received 150 µg/kg loncastuximab tesirine 30 min IV infusion once every 3 weeks. Peak concentration was derived as the post-infusion concentration of the 1th dose. The number of patients in the reference group for each covariate: normal renal function (N=159); normal hepatic function (N=277); age <65 yr (N=164); male (N=199); white (N=294); body weight from 65 to 85 kg (N=136); DLBCL (N=284); ECOG=0 (N=112); albumin from 35 to 52 g/L (N=279); liquid drug form (N=218); absence of anti-drug antibody (N=305); no concomitant P-gp inhibitors (N=302). Three body weight subgroups are 42.1 to 65 kg, 65 to 85 kg, and 85 to 160.5 kg. Two albumin subgroups are 17 to 34 g/L, 35 to 52 g/L.

Figure 12. Forest Plot of Subgroup Analyses on Percent Change Relative to Reference Value of Model Predicted Cycle One C_{avg} Loncastuximab tesirine PDB-Conjugated Antibody Concentration



Key: Solid blue circle represents mean and error bar represents 95% confidence interval. Dashed line represents reference value of 0. Numbers represent ratio, confidence interval, and number of patients in the comparison groups. Gray shaded region represents ±30% from reference value. ECOG=Eastern Cooperative Oncology Group disease status at the baseline; DLBCL= Diffuse Large B-cell Lymphoma. Note: Analyses assumed that all patients received 150 µg/kg loncastuximab tesirine 30 min IV infusion once every 3 weeks. The number of patients in the reference group for each covariate: normal renal function (N=159); normal hepatic function (N=277); age <65 yr (N=164); male (N=199); white (N=294); body weight from 65 to 85 kg (N=136); DLBCL (N=284); ECOG=0 (N=112); albumin from 35 to 52 g/L (N=279); liquid drug form (N=218); absence of anti-drug antibody (N=305); no concomitant P-gp inhibitors (N=302). Three body weight subgroups are 42.1 to 65 kg, 65 to 85 kg, and 85 to 160.5 kg. Two albumin subgroups are 17 to 34 g/L, 35 to 52 g/L.

Impaired renal function: The impact of renal impairment was evaluated in the population PK analysis that included patients with normal renal function, and with mild renal impairment or moderate/severe renal impairment. The analyses of the impact of mild, moderate, and severe renal impairment comprised 118 patients, 51 patients, and one patient, respectively. Hence, no conclusion can be drawn for patients with severe renal impairment. The pattern of decreased exposure to LT with renal impairment could be explained by kidney-related factors associated with the underlying disease

e.g. increased glomerular permeability or an increased catabolic state with increased IgG and albumin degradation in the renal impairment groups.

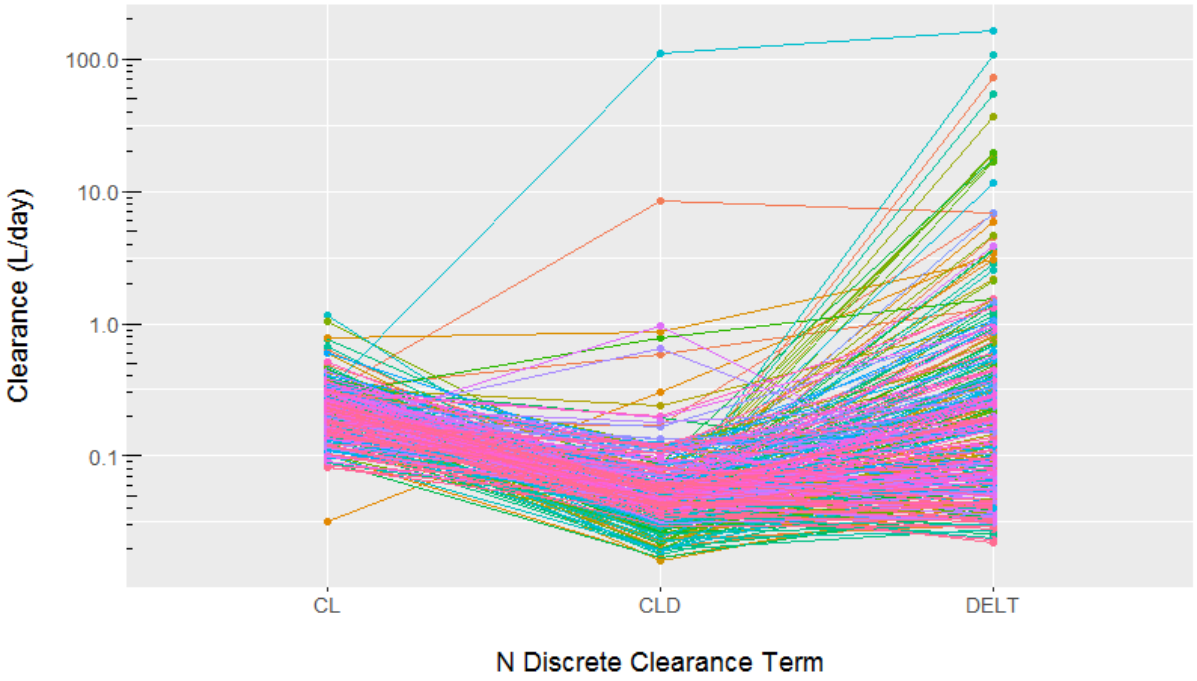
Table 7 **Clearance of PBD-conjugated Antibody in Patients with Baseline Normal Renal Function or Mild/Moderate/Severe Renal Impairment during Loncastuximab Tesirine Clinical Studies**

Renal Function	N	Creatinine Clearance* Mean (StDev) (mL/min)	PBD-conjugated Ab Clearance# Median (Range) (L/day)	PBD-conjugated Ab Clearance# Mean (StDev) (L/day)
Normal (CLCR ≥90 mL/min)	158	128 (35.9)	0.511 (0.149, 54.5)	1.30 (4.81)
Mild Renal Impairment (CLCR ≥60-<90 mL/min)	118	75.2 (8.27)	0.478 (0.143, 273)	5.25 (27.8)
Moderate/Severe Renal Impairment (CLCR ≥15-<60 mL/min)	52	48.2 (8.01)	0.391 (0.164, 37.1)	1.91 (5.76)

Source: Population PK Report Attachment 28
Ab = antibody; CLCR = creatinine clearance; PBD = pyrrolobenzodiazepine; StDev = standard deviation.
*: Creatinine clearance was calculated from the baseline serum creatinine, age, sex, and body weight using the Cockcroft-Gault equation. CLCR = (140-Age in year) x (Weight in kg) x (1.23 for Male, 1.04 for Female)/(Serum creatinine in µmol/L).
#: PBD-conjugated Ab clearance was derived from the population pharmacokinetic modelling, with total clearance = linear clearance + deconjugation clearance + time-dependent clearance at time 0.

The substantial variability in CL reported in Table 5 above is attributed to variability in time-dependent clearance and in deconjugation clearance, which is apparent from Figure below. The applicant argues that the skewness may, in part, be due to insufficiency of observations for fully characterising the non-linear aspects of clearance in some patients.

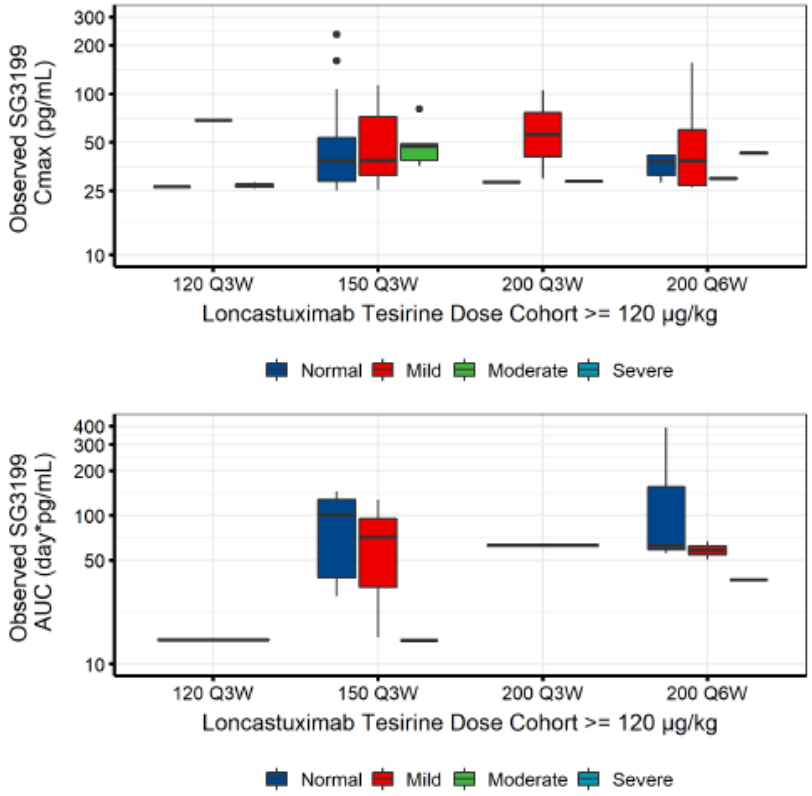
Figure 13. Loncastuximab Tesirine Individual Predictions for Discrete Clearance Terms by Patient



CL = linear clearance; CLD = dissociation clearance; DELT = time-dependent clearance.
Source: Data on file.

For SG3199, the available measurable serum concentrations were compared across dose cohorts between normal renal function and renal impairment subgroups. There was no sign of association between the baseline renal function and SG3199 PK exposure (Figure 12).

Figure 14. **C_{max} (Upper Panel) and AUC (Lower Panel) of SG3199 (Cycle 1) in Different Baseline Renal Function Subgroups by Dose Cohort in ADCT-402-101 and ADCT-402-201**



Source: Population PK Report Attachment 29
Note: Pharmacokinetic data were derived from integrated pooling of data from non-compartmental analysis.
AUC = area under the concentration-time curve from time 0 to the last quantifiable concentration; C_{max} = maximum serum concentration; Q3W = every 3 weeks; Q6W = every 6 weeks.

Impaired hepatic function: According to the NCI Organ Dysfunction Working Group classification, patients treated with LT were grouped into different baseline hepatic function subgroups as shown Table below. The majority of patients included in the population PK analysis had normal hepatic function (n = 278) or mild hepatic impairment (n = 49); 1 patient had moderate hepatic impairment. The moderate hepatic impairment and mild hepatic impairment subgroups were merged into 1 category. An unexpected pattern of decreased exposure to LT (42% lower Cavg, Figure below) has been presented, which, according to the applicant, potentially could be clinically relevant.

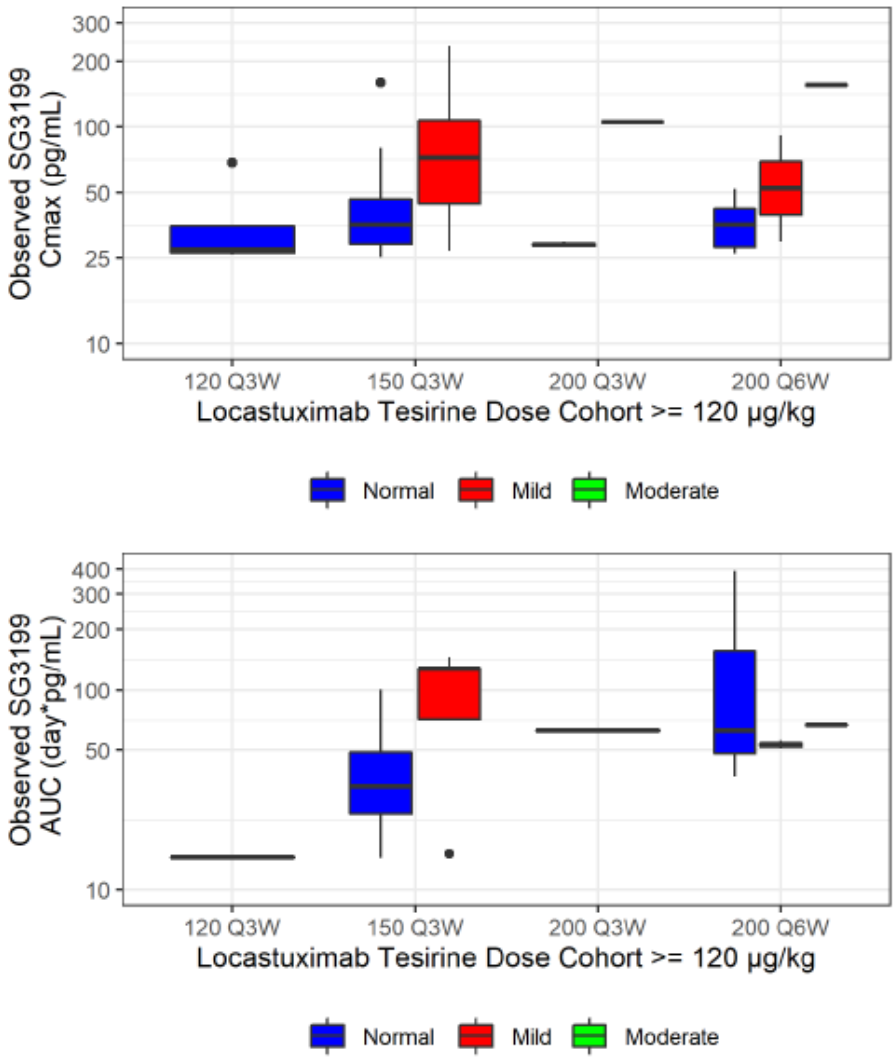
Table 8 **Clearance of PBD-conjugated Antibody in Patients with Baseline Normal Hepatic Function or Mild/Moderate/Severe Hepatic Impairment during Loncastuximab Tesirine Studies**

Hepatic Function	Hepatic Function Criteria	N	PBD-conjugated Ab Clearance# (Median [Range]) (L/day)	PBD-conjugated Ab Clearance# (Mean [StDev]) (L/day)
Normal	TB ≤ULN & AST ≤ULN	278	0.453 (0.143, 273)	2.21 (16.9)
Mild/Moderate Hepatic Impairment	TB >1.0-1.5 x ULN or AST >ULN (Mild) TB >1.5-3 x ULN & AST any level (Moderate)	50	0.763 (0.172, 109)	6.19 (18.6)

Source: Population PK Report Attachment 28
Ab = antibody; AST = aspartate transaminase; PBD = pyrrolobenzodiazepine; StDev = standard deviation; TB = total bilirubin; ULN = upper limit of normal.
#: PBD-conjugated Ab clearance was derived from the population pharmacokinetic modelling, with total clearance = linear clearance + deconjugation clearance + time-dependent clearance at time 0.

According to the applicant, the mean clearance reported in Table above (2.21 L/day) represents the total mean clearance as defined as the sum of linear clearance + deconjugation clearance + time-dependent clearance at time 0, which decreases over time due to a decrease in the time-dependent clearance.

Figure 15. **C_{max} (Upper Panel) and AUC (Lower Panel) of SG3199 (Cycle 1) in Different Baseline Hepatic Function Subgroups by Dose Cohort in ADCT-402-101 and ADCT-402-201**



Source: Population PK Report Attachment 30
Note: Pharmacokinetic data were derived from integrated pooling of data from non-compartmental analysis.
AUC = area under the concentration-time curve from time 0 to the last quantifiable concentration; C_{max} = maximum serum concentration; Q3W = every 3 weeks; Q6W = every 6 weeks.

Gender: Based on popPK analyses, gender did not have a clinically relevant effect on the exposure to LT. Females had slightly lower exposure than males, probably reflecting an averagely lower dose received.

Race: Based on popPK analyses, race did not have a clinically relevant effect on the exposure to LT.

Weight: Based on popPK analyses, body weight did not have a clinically relevant effect on the exposure to LT. The evaluated weight range was 42-160 kg. The reference weight range was 65-85 kg.

Higher weight resulted in slightly higher exposure, and lower weight in slightly lower exposure, reflecting the weight-based dose regimen.

Age: Based on popPK analyses, age did not have a clinically relevant effect on the exposure to LT. Age <65 years resulted in a 14% decrease in Cmax and a 2% decrease in Cavg.

Table 9 Number of subjects in the different age categories

	Age 65-74 (Older subjects' number /total number)	**Age 75-84 (Older subjects' number /total number)**	**Age 85+ (Older subjects' number /total number)**
PK Trials	109/328 (33.23%)	48/328 (14.63%)	7/328 (2.13%)

Pharmacokinetic interaction studies

SG3199 is *in vitro* a substrate of P-gp. Concomitant medication with P-gp inhibitors was included in a post-hoc pop PK covariate analysis. Data are limited but no trend of a change in the exposure to SG3199 was observed. Based on the provided data, a clinical study with P-gp inhibitors is not warranted. In various *in vitro* test systems, the transporter inhibition of SG3199 was examined and most IC50 values were above 10 µM. The IC50 value for MATE2-K was the lowest with 3.25 µM, which is far above the typical clinical plasma exposure.

No dedicated clinical DDI studies have been performed. Based on the nature of the product (ADC molecule), the low plasma concentration of SG3199, and the *in vitro* investigations, this is acceptable.

Pharmacokinetics using human biomaterials

See above.

Immunogenicity

Immunogenicity against LT was evaluated in all clinical studies of ADCT-402-101, ADCT-402-201, and ADCT-402-102. Data for studies ADCT-402-101 and ADCT-402-201 are summarised below.

Out of 7 patients with ADA response occurring at any time, ADA-positivity occurred in 1 patient at the post-dose timepoint and 6 patients had pre-existing ADA response (**Table below**).

Table 10 Anti-drug Antibody Response to Loncastuximab Tesirine

Study	Number of Patients Tested for ADA	Confirmed Positive ADA Predose N (%)	Confirmed Positive ADA Postdose Only N (%)	Confirmed Positive ADA Anytime N (%)	Confirmed Positive ADA Before and After Dose N (%)
ADCT-402-101	183	5 (2.73%)	1 (0.546%)	6 (3.28%)	2 (1.09%)
ADCT-402-201	145	1 (0.689%)	0 (0%)	1 (0.690%)	0 (0.0%)
Total	328	6 (1.83%)	1 (0.305%)	7 (2.13%)	2 (0.610%)

Source: Module 5, Section 5.3.5.3, Table 14.4.7.1x
ADA = anti-drug antibody.

The incidence of ADAs against LT seems to be low, and an impact of ADA positivity on the exposure of LT was not apparent in studies 101 and 201. However, based on the low number of ADA positive patients (n=7), firm conclusions cannot be made.

2.6.2.2. Pharmacodynamics

Mechanism of action

LT is an antibody-drug conjugate. The mechanism of action of LT consists of a multi-step process. After intravenous (IV) administration, LT binds to CD19, then undergoes receptor-mediated internalisation and subsequent lysosomal degradation, which results in the intracellular release of PBD dimer cytotoxin (SG3199). Binding of SG3199 to DNA results in the formation of inter-strand cross-links, relatively non-distorting DNA structure, which makes them hidden to DNA`s repair mechanisms and subsequently causes cell death.

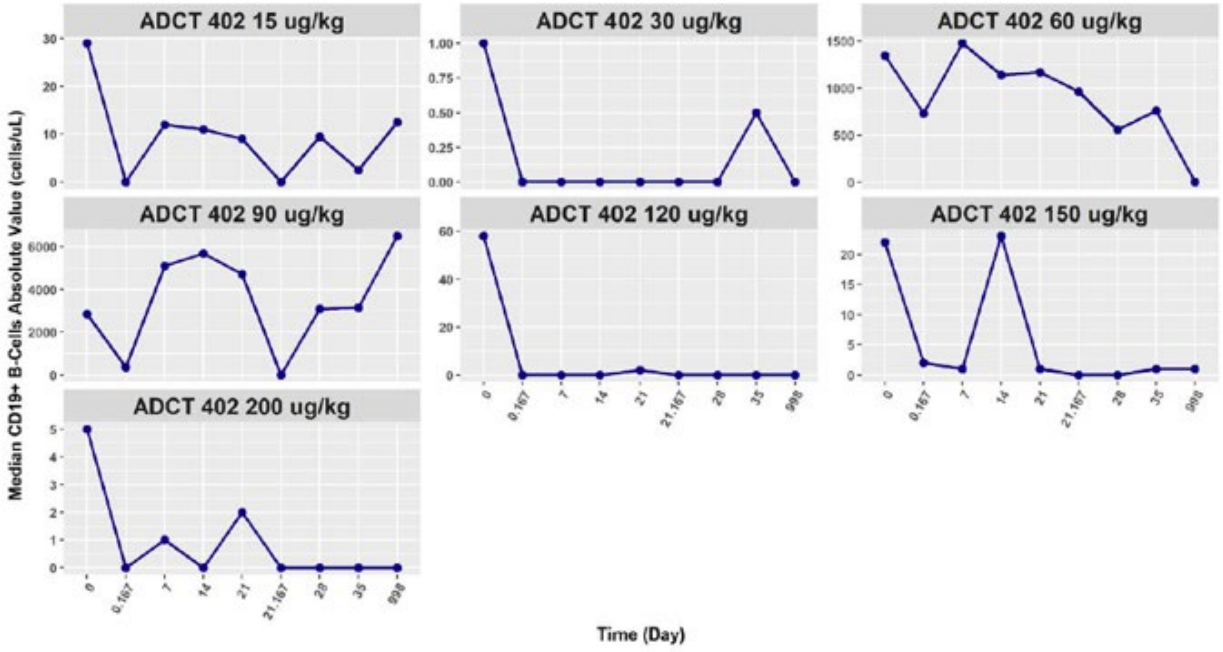
Although LT is a CD19 directed antibody and depletion of CD19+ B cells is the primary pharmacodynamic effect of LT, CD19 as a biomarker was only sparsely investigated and reported.

Assessment of an exposure-efficacy relationship was conducted using overall response rate (ORR), progression-free survival (PFS), overall survival (OS) and the duration of response (DOR) as efficacy parameters. For assessment of an exposure-safety relationship, skin and nail reactions, oedema-effusion, fatigue, pain, gamma-glutamyltransferase (GGT) increased, group liver function test (LFT) abnormalities, neutrophil decreased, and platelet decrease-related toxicities were used as safety parameters.

Primary and Secondary pharmacology

In study 101, change in CD19+ cells were monitored and loncastuximab tesirine has been shown to decrease median CD19+ cells by 100% after infusion at the intended starting dose of 150 µg/kg. Data are less clear at 60 and 90 µg/kg (Figures below).

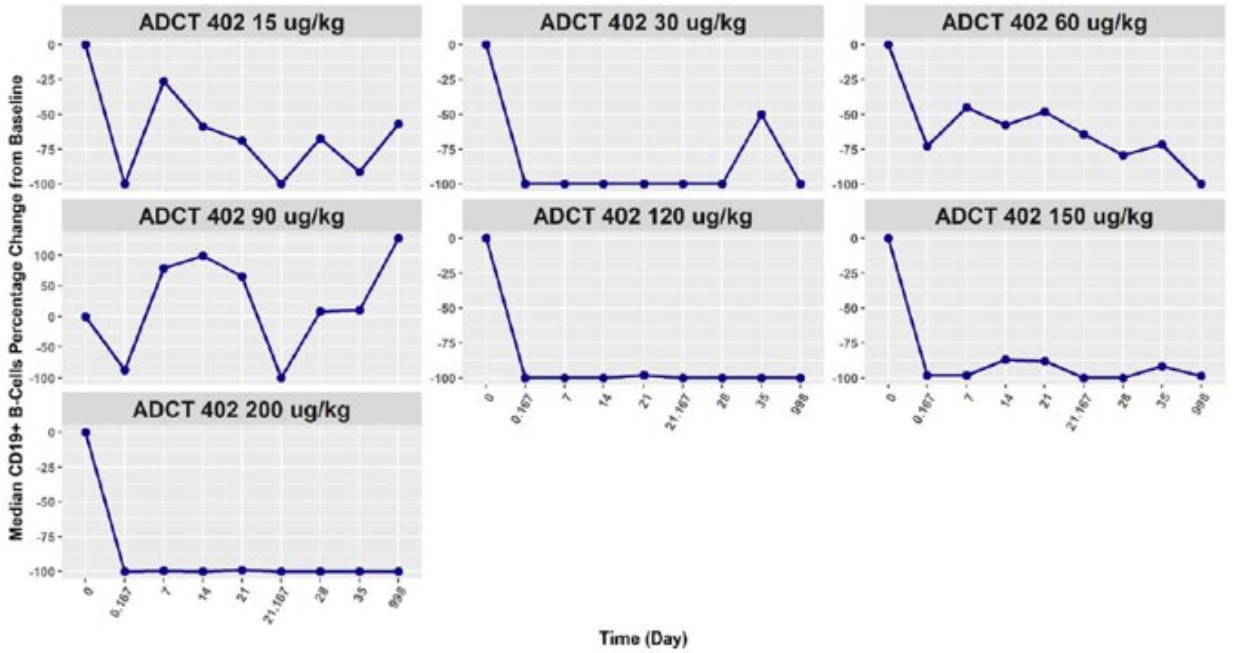
Figure 16. Median CD19+ B-Cells Absolute vs Time by Dose Cohort



Footnote: 998(Time)=End of Treatment (EOT);Graphics denote absolute value and the original value was reported as CD19+ B-cells (cells/uL).

A:\Clinical Pharmacology\ADCT-402\ADCT-402-101_PKPD Analysis_PD CSR\PD_Figures\Rcoding\Summary_*R version 3.5.1*_f14_4_12_x_mean_pd_time.Rmd 8/30/2019 4:35 PM

Figure 17. Median CD19+ B-cells Percentage Change from Baseline vs Time by Dose Cohort

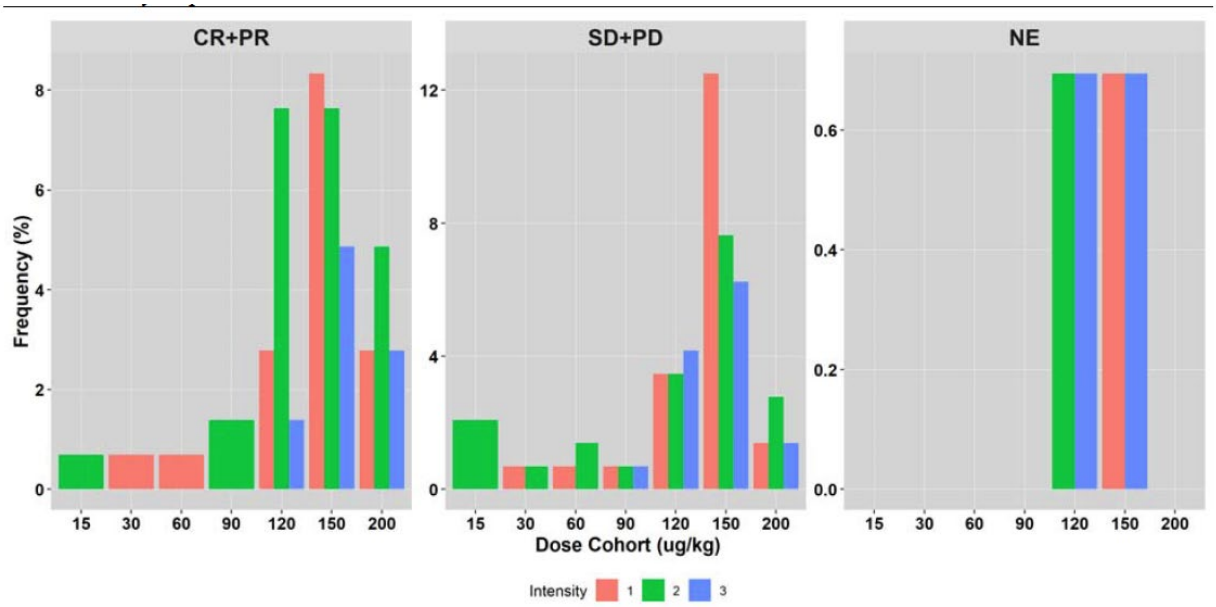


Footnote: 998(Time)=End of Treatment (EOT);Graphics denote percentage change in the baseline value and the original value was reported as CD19+ B-cells (cells/uL).

A:\Clinical Pharmacology\ADCT-402\ADCT-402-101_PKPD Analysis_PD CSR\PD_Figures\Rcoding\Summary_*R version 3.5.1*_f14_4_12_x_mean_pd_time.Rmd 8/30/2019 4:35 PM

According to data issued from study 101, level of CD19 at baseline does not seem to correlate with clinical response. **Figure below** describes response according to CD19 tumour expression suggests that there is no difference in categories (CR+PR) and (SD+PD) in function of percentage of CD19+ cells in the tumour. Moreover, the applicant analysed CD-19 expression according to 3 classes of increasing intensity (+1, +2 and +3 intensity) in responders (CR+PR) and non-responders (SD+PD). At the intended posology, frequency of the +3 intensity was similar in responders and non-responders.

Figure 18. **Frequency vs. Dose Cohort by Best Response and Tumor CD19 Expression (Categorical Intensity) in Archival/Pretreatment Tumor Samples**



LT impact on QTc

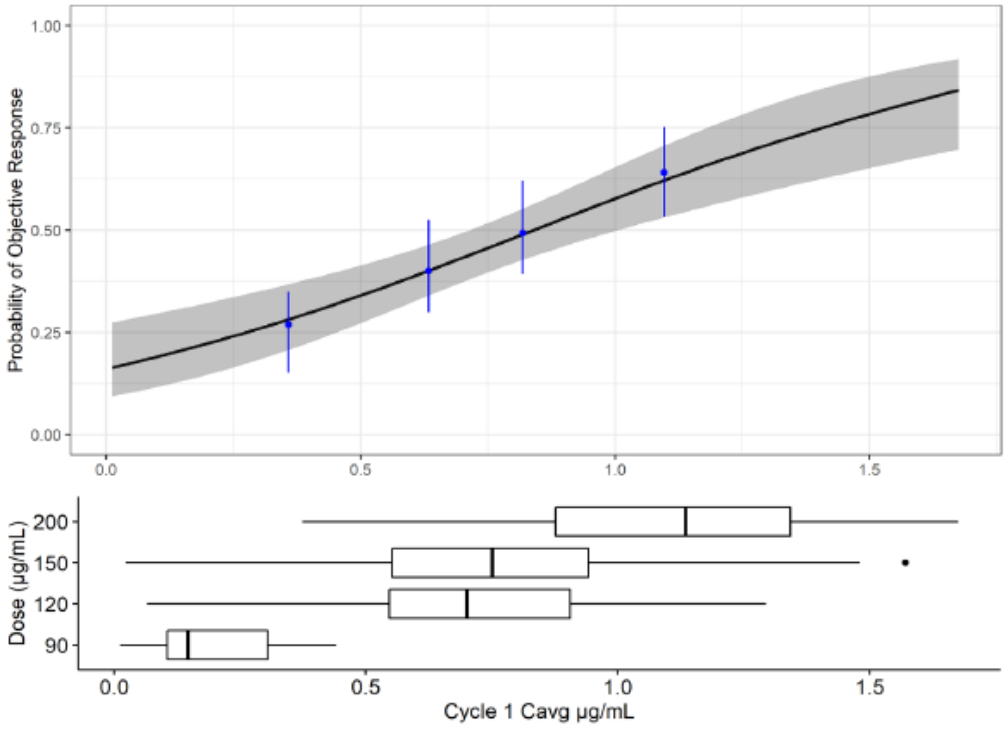
In a concentration-QTcF analysis on data from patients with DLBCL, no evidence of QTc prolongation at the recommended LT dose was found. The effect on ΔQTcF for the 150 µg/kg dose was predicted to be < 5 ms in both cycle 1 and 2.

Exposure-efficacy relationships

Overall response rate (ORR)

The primary efficacy endpoint used to support the MAA application was ORR in studies ADCT-402-101 and ADCT-402-201. ORR was defined as the proportion of patients with a best overall response (BOR) of CR or PR. The correlation between population PK-predicted PBD-conjugated Ab exposure and the ORR was evaluated in patients with DLBCL from both studies. Univariate logistic regression analyses were performed to evaluate the probability of OR in association with the exposure to PBD-conjugated Ab. A significant relationship between Cycle 1 Cavg and the OR was identified ($p < 0.001$) (**Figure below**).

Figure 19. **Observed and Model-predicted Overall Response Rate from the Logistic Regression Base Model by PBD-conjugated Antibody Cycle 1 C_{avg} and the Distribution of PBD-conjugated Antibody Cycle 1 C_{avg} (µg/mL) by Dose Level in Patients with DLBCL**



Source: Exposure-response Analysis Report Figure 8
Note: The solid blue circles (vertical line segments) represent the observed ORR (95% confidence interval, Clopper-Pearson method) for each quartile of Cycle 1 C_{avg}. The solid black line and shaded grey area represent the predicted ORR (95% CI) from a univariate logistic regression using individual patient level Cycle 1 C_{avg}. The quartiles for Cycle 1 C_{avg} were: 1st quartile (0.0120 to 0.516 µg/mL), 2nd quartile (0.517 to 0.728 µg/mL), 3rd quartile (0.729 to 0.942 µg/mL), and 4th quartile (0.943 to 1.68 µg/mL).
C_{avg} = average serum concentration; DLBCL = diffuse large B-cell lymphoma; ORR = objective response rate; PBD = pyrrolobenzodiazepine.

In a multivariate logistic regression analysis (full model), the baseline covariates of sex, age, race, weight, body surface area, body mass index (BMI), baseline renal/hepatic functions, immunogenicity parameters, baseline disease characteristics, elapsed time of initial diagnosis, ECOG performance status, selected high risk disease phenotype, bulky disease, prior chemotherapy response, prior stem cell therapy, DLBCL diagnosis at baseline, dexamethasone concomitant medication, and study were included.

A stepwise reduction was performed from the full logistic regression model until the Akaike information criterion no longer decreased. Backward elimination was further used to retain the significant covariates based on α = 0.05 and 95% CI of odds ratios that included 1. The final model included Cycle 1 Cavg, baseline tumour sum of area, and disease phenotype as significant predictors of ORR (**Table below**). The odds of ORR increased by 6.095-fold for a 1 µg/mL increase in Cycle 1 Cavg (1.198-fold for a 0.1 µg/mL increase). The odds of ORR decreased by 0.985-fold for 1 cm2 increase in baseline tumour sum of area, and 0.48-fold for selected high risk disease phenotype. This ORR analysis provides direct evidence for a significant E-R relationship.

Table 11 **Estimates of Odds Ratio (95% CI) from the Final Logistic Regression Model for Overall Response Rate with PBD-conjugated Antibody Cycle 1 C_{avg}**

	Estimate	Odds Ratio (95% CI)	*p*-value
Intercept	-0.746	-	-
Cycle 1 C_{avg} (µg/mL)	1.807	6.095 (2.647, 14.749)	0.0000350
Baseline tumour sum of area (cm^2)	-0.015	0.985 (0.977, 0.992)	0.0000813
Selected high risk disease phenotype	-0.733	0.48 (0.268, 0.847)	0.01218

Source: Exposure-response Analysis Report Table 13
Note: Akaike information criterion = 346.
C_{avg} = average serum concentration; CI = confidence interval.

The number of responders seemed to increase for higher values of Cavg and Cmin in Cycles 1 and 2, exhibiting a positive trend between exposure and overall response rate (ORR) as supported by **Table below**. Overall response rate was 64.5% of patients who had drug exposure in the highest quartile (Q4) of Cycle 1 Cavg, in comparison to only 25% response in patients from the lowest quartile (Q1).

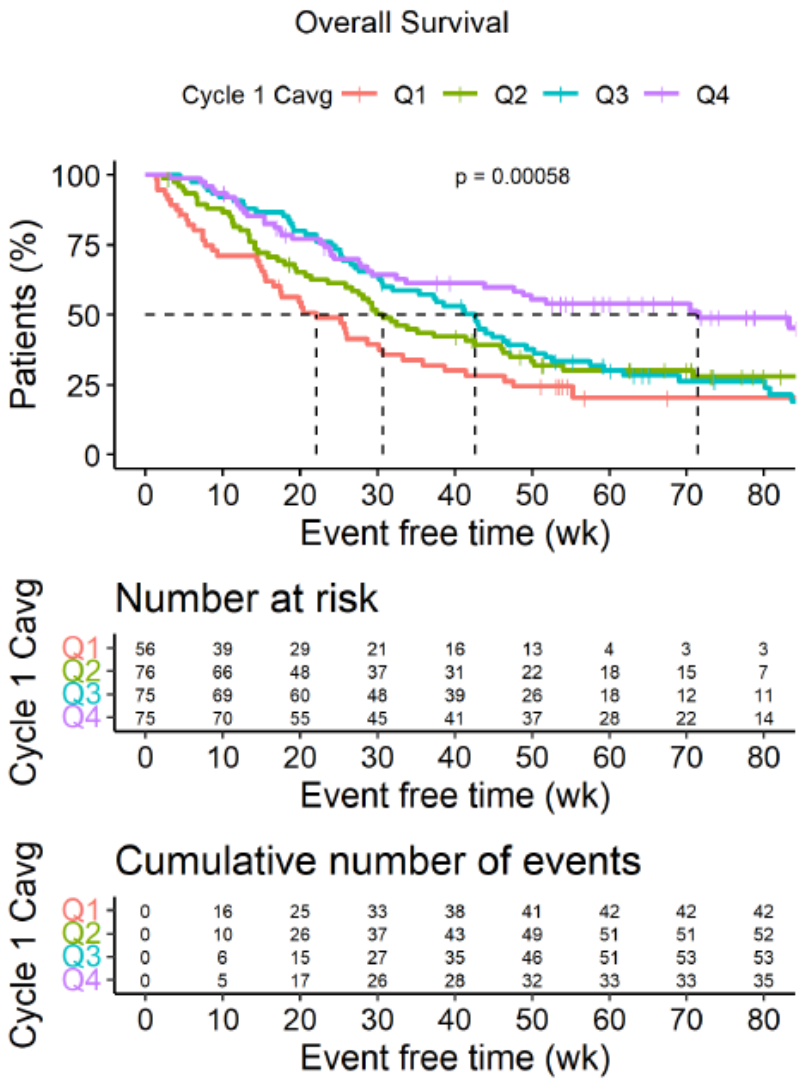
Table 12 **Overall Response Rate by Cycle and Exposure Quartiles of PBD-Conjugated Ab**

		Q1	Q2	Q3	Q4
Cycle 1	C_{ave} (µg/mL)	25	35.5	50	64.5
	C_{min} (µg/mL)	20.4	30.3	50.6	71.4
Cycle 2	C_{avg} (µg/mL)	25	50.8	58.7	74.6
	C_{min} (µg/mL)	23.1	41.9	66.2	73.8

Overall survival (OS)

OS was a secondary efficacy endpoint in ADCT-402-101 and ADCT-402-201. Population PK-predicted PBD-conjugated Ab exposure of LT and OS were used to establish the correlation in DLBCL patients from both studies. For exploratory analysis, Kaplan-Meier analyses were generated, stratified by quartiles of estimated PBD-conjugated Ab Cavg values of 0.0120 to 0.516 µg/mL, 0.517 to 0.728 µg/mL, 0.729 to 0.942 µg/mL and 0.943 to 1.68 µg/mL. Increasing exposures of PBD-conjugated Ab were associated with longer OS (**Figure below**), with a significant difference in survival determined between the different Cavg quartile subgroups (log rank test p = 0.00057911).

Figure 20. **Kaplan-Meier Survival Curves (p <0.05) for Overall Survival by C_{avg} of PBD-conjugated Antibody in Cycle 1 of Patients with DLBCL in ADCT-402-101 and ADCT-402-201**



Source: Exposure-response Analysis Report Figure 2
Note: The solid lines represent the Kaplan-Meier survival curves for quartile groups of PBD-conjugated Ab exposure. Right-censoring is indicated by the vertical ticks on the survival curves. Median event-free times, if reached, are indicated with black dashed lines. Log rank test was used to test for significant differences between Kaplan-Meier curves (p <0.05).
C_{avg} = average serum concentration; DLBCL = diffuse large B-cell lymphoma; PBD = pyrrolobenzodiazepine; Q = quartile; wk = week.

Given Kaplan–Meier analysis was a univariate analysis and the difference in survival in these exposure quartiles may be confounded by other covariates, Cox proportional hazard (CPH) regression models were generated to obtain the hazard ratio of each covariate tested. The effects of covariates were evaluated through separate univariate Cox regressions, which evaluated the following significant covariates (α = 0.05) for entry into the full model: Cycle 1 Cavg, baseline albumin, baseline AST, baseline ALKP, hepatic function (mild/moderate impairment versus normal), baseline LDH, baseline tumour sum of area, ECOG performance status, disease phenotype (selected high risk versus other), bulky disease, prior chemotherapy response, and clinical study (ADCT-402-101 versus ADCT-402-201).

Estimates from the final CPH model for OS are presented in **Table below**. The hazard of death decreased by 4.96% for 0.1 µg/mL increase in Cycle 1 Cavg and 7% for 1 g/L increase in baseline

albumin. The hazard of death increased by 212% with bulky tumour, and 69% with mild/moderate hepatic impairment. Patients in the 50th and 75th percentiles of Cycle 1 Cavg (0.726 and 0.942 µg/mL, respectively) had a risk of death reduced by approximately 39% and 46% relative to patients with the minimum Cycle 1 Cavg (0.0120 µg/mL).

Table 13 **Parameter Estimates from the Final Cox Proportional Hazards Model for Overall Survival with PBD-conjugated Antibody Cycle 1 C_{avg} in Patients with DLBCL**

Predictor	Predictor Statistic	HR (95% CI)	*p*-value	HR P05: Median (95% CI)	HR P95: Median (95% CI)
Cycle 1 C_{avg} (µg/mL)	0.726 (0.156-1.3)	0.601 (0.378, 0.954)	0.0307838	0.748 (0.575, 0.973)	1.33 (1.02, 1.74)
Baseline albumin (g/L)	40 (31.1-48)	0.925 (0.896, 0.955)	0.00000134	0.535 (0.416, 0.690)	2.01 (1.514, 2.669)
Hepatic function	Mild/Moderate Impairment:Normal (n = 44:237)	1.693 (1.159, 2.473)	0.0064587	-	-
Bulky disease	Bulky:Other (n = 26:256)	3.124 (2.008, 4.862)	4.41E-7	-	-

Source: Exposure-response Analysis Report Table 11
C_{avg} = average serum concentration; CI = confidence interval; DLBCL = diffuse large B-cell lymphoma; HR = hazard ratio; P05 = 5th percentile; P95 = 95th percentile; PBD = pyrrolobenzodiazepine.
Note: Likelihood ratio test, *p*-value <0.001. Median (P05-P95) is presented for continuous predictors and count of comparator:reference is provided for categorical predictors under Predictor Statistic.

Exposure-safety relationships

Population PK predicted PBD-conjugated Ab exposure and the safety endpoints were used to establish correlations in patients with B-NHL from ADCT-402-101 and with DLBCL from ADCT-402-201. Exploratory analysis of SG3199 in correlation with safety endpoints was also performed in all patients from both studies.

The safety endpoints for AEs included skin and nail reactions, oedema-effusion, fatigue, pain, gamma-glutamyltransferase (GGT) increased, group liver function test (LFT) abnormalities, neutrophil decreased, and platelet decrease-related toxicities. Grade ≥2 AEs were investigated for the correlation with the exposure to LT. This level of toxicity severity was chosen to provide a reasonable representation of event frequencies for characterisation. The univariate logistic regression analysis was used to establish the correlation between PK exposure of PBD-conjugated Ab and all the listed Grade ≥2 AEs. For skin and nail reactions, LFT abnormalities, GGT increased and pain, there were significant relationships observed for Cavg and Cmin for Cycles 1, 2, and 3. Based upon the lowest p value of the model, GGT increased (Grade ≥2) in relationship with Cycle 1 Cavg was selected for further investigation.

Cycle 1 Cavg was significantly correlated with the Grade ≥2 GGT increased (p <0.001). Given a statistically significant effect of exposure was observed, a covariate analysis was conducted using the multivariate logistic regression analysis. In the final model, Cycle 1 Cavg, baseline ALT, bulky disease (bulky versus non-bulky), race (non-white vs. white) and response to prior chemotherapy (BOR of CR or PR versus other) were predictors of the probability of increased GGT (Grade ≥2). The odds ratios (95% CI) for each predictor in the final model are presented in **Table below**. The odds of having

increased GGT (Grade ≥2) increased by 3.68-fold for a 1 µg/mL increase in Cycle 1 Cavg (1.139-fold for a 0.1 µg/mL increase).

Table 14 **Estimates (95% CI) from the Final Logistic Regression Model for Loncastuximab Tesirine Exposure–response Relationship with GGT Increased (Grade ≥2)**

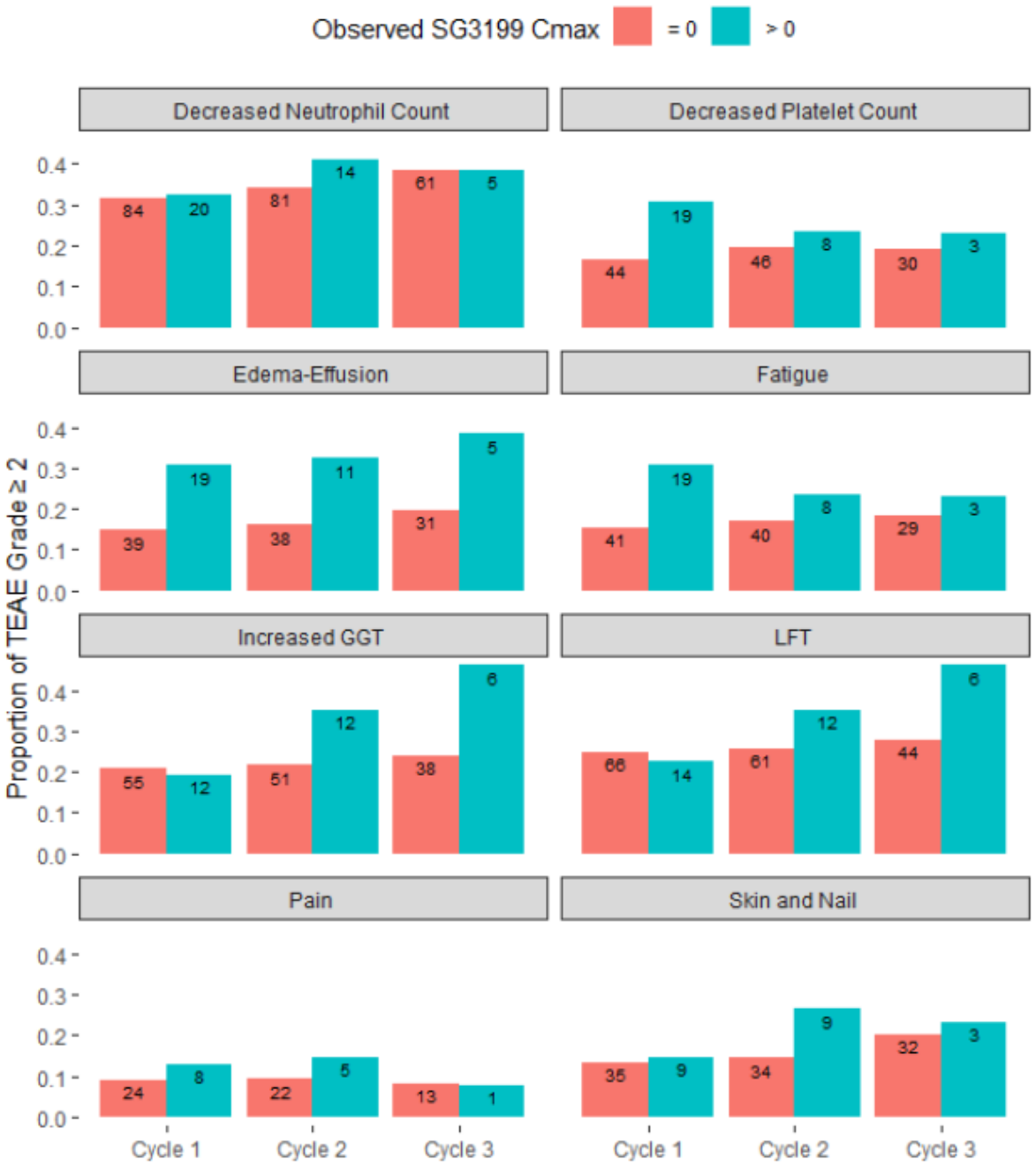
	Estimate	Odds Ratio (95% CI)	*p*-value
Intercept	-4.3	-	-
Cycle 1 C_{avg} (µg/mL)	1.3	3.68 (1.63, 8.6)	0.002039
Race category	1.02	2.76 (1.17, 6.28)	0.016746
Alanine aminotransferase (U/L)	0.0206	1.02 (1.01, 1.04)	0.005563
Bulky disease	0.99	2.7 (1.1, 6.36)	0.024864
Prior chemotherapy response	1.41	4.1 (1.61, 13)	0.006952

Source: Exposure-response Analysis Report Table 15
Note: Akaike information criterion = 311.
C_{avg} = average serum concentration; CI = confidence interval.

Exploratory SG3199 analysis

The lower limit of quantification (LLOQ) is 0.025 ng/mL for SG3199 metabolite. Approximately 96% of SG3199 samples were below the LLOQ. An exploratory comparison of TEAEs (grade 2 or more) between patients with measurable SG3199 concentrations in Cycles 1, 2 and 3 and patients without detectable SG3199 indicates that a higher concentration of the cytotoxic agent leads to more adverse reactions (**Figure below**).

Figure 21. **Proportion of Patients with TEAE (Grade 2 or more) by SG3199 Exposure and Cycle in Studies ADCT-402-101 and ADCT-402-201**



Note: Proportion of patients is defined by cycle and by two observed SG3199 C_{max} groups, non-measurable (= 0) and measurable (> 0).

Impact of immunogenicity on efficacy and safety

The number of ADA positive patients is very small so definitive conclusions cannot be made. Presence of ADAs do not seem to negatively affect the efficacy or safety associated with the treatment with LT.

2.6.3. Discussion on clinical pharmacology

Loncastuximab tesirine (LT), is a CD19-targeted antibody-drug conjugate (ADC), consisting of a humanised IgG1 kappa monoclonal antibody (mAb) specific for human CD19, conjugated to SG3199, a pyrrolobenzodiazepine (PBD) dimer cytotoxic drug, through a protease-cleavable valine-alanine linker. SG3199 attached to the linker is designated SG3249 (also known as tesirine). Zynlonta as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy.

The clinical pharmacology programme assessed the PK, PD, and immunogenicity of LT in two clinical phase 1 studies and in a clinical phase 2 study. In addition, population PK/PD analyses have been performed. LT has not been administered to healthy subjects.

The total Ab (conjugated and unconjugated) and PBD-conjugated Ab of LT in serum were measured using 2 validated electro-chemiluminescence immunoassays (ECLIAs) with lower limits of quantitation (LLOQs) of 20 and 5.06 ng/mL, respectively. A validated liquid chromatography-tandem mass spectrometric (LC-MS/MS) assay was used to measure SG3199 serum concentration with LLOQ of 0.025 ng/mL. Screening, confirmation, and titration of anti-LT ADA were performed using a validated bridging ECLIA assay.

The population PK of LT total antibody and conjugated antibody was described by a 2-compartment linear model with linear clearance and time-dependent clearance in parallel. The following covariates were identified as statistically significant and included in the final model: body weight, Eastern Cooperative Oncology Group (ECOG) performance status, albumin and sex on CL; body weight and sex on V1; disease subtype (PTST) and albumin on time-dependent clearance (DELT). A one-compartment model with linear clearance was integrated into the model with a linear deconjugation clearance from the central deconjugated antibody compartment to account for the formation of SG3199.

The proposed dose regimen for LT is 0.15 mg/kg every 3 weeks (Q3W) for the first 2 cycles, then a dose of 0.075 mg/kg Q3W thereafter, as an IV infusion.

The product is intended for intravenous administration and the bioavailability is therefore 100% and Cmax is reached at the end of infusion. The accumulation index for LT between cycle 1 and 2 is 1.65 and the Vd of LT is 7.14L.

Based on modelling, steady state of LT is reached after cycle 3. As for SG3199, the majority of samples showed concentration data that were below the LLOQ. Non-compartmental steady state PK data for SG3199 have not been provided, which is acceptable since the majority of the sample data had measurements below LLOQ.

The elimination route in humans has not been investigated in detail. This is acceptable considering the nature of the product. The immunoglobulin part is not expected to be eliminated differently than other endogenous immunoglobulins. In a rat study, the elimination of SG3199 was mainly via biliary excretion and faeces (97.5±3.0%), and an *in vitro* study using recombinant CYP enzymes indicated that CYP3A4/5 is potentially involved in the metabolism of SG3199. Via population PK analysis, the CL of LT is estimated to be 0.2 L/day, which is typical for monoclonal Abs.

The lack of information on the PK characteristics of free tesirine is adequately reflected in the SmPC.

In the popPK analysis, the half-life of LT was 14.6 days at Cycle 1 and 20.6 days at steady state. This increase in half-life could be attributed to a decrease in tumour burden and therefore in target-mediated disposition. The interindividual variability of PBD-conjugated Ab for CL and central volume of distribution (V1) was up to 45% which is considered moderate. The inter-individual variability for CL of SG3199 is 125%.

Based on popPK analyses, demographic covariates, such as body weight, sex, age, and race did not have clinically relevant effects on the exposure to LT. The impact of mild and moderate hepatic impairment on LT PK was evaluated in 49 patients and 1 patient, respectively. Hence, no conclusion can be drawn for patients with moderate hepatic impairment. An unexpected pattern of decreased exposure to LT (42% lower Cavg) has been presented, which, according to the applicant, potentially could be clinically relevant. At the same time, the exposure to SG3199 seems to increase with hepatic impairment but SG3199 measurements are not robust due to low plasma concentrations. As for renal impairment, an extreme variability in CL of LT was observed. Based on the available data, no dose adjustment is considered necessary for any of the covariates. The PK of SG3199 could be better characterised in patients with renal and hepatic impairment and this is reflected in the SmPC.

SG3199 is *in vitro* a substrate of P-gp. Concomitant medication with P-gp inhibitors was included in a post-hoc pop PK covariate analysis. Data are limited but no trend of a change in the exposure to SG3199 was observed. Based on the provided data, a clinical study with P-gp inhibitors is not warranted. In various *in vitro* test systems, the transporter inhibition of SG3199 was examined and most IC50 values were above 10 µM. The IC50 value for MATE2-K was the lowest with 3.25 µM, which is far above the typical clinical plasma exposure. No dedicated clinical DDI studies have been performed, which is acceptable.

Immunogenicity against LT was evaluated in all clinical studies. The incidence of ADAs against LT seems to be low, and an impact of ADA positivity on the exposure of LT was not apparent in studies 101 and 201. However, based on the low number of ADA positive patients (n=7), firm conclusions cannot be made.

In a concentration-QTcF analysis on data from patients with DLBCL, no evidence of QTc prolongation at the recommended LT dose was found. The effect on ΔQTcF for the 150 µg/kg dose was predicted to be < 5 ms in both cycle 1 and 2.

Assessment of an exposure-efficacy relationship was conducted using overall response rate (ORR), progression-free survival (PFS), overall survival (OS) and the duration of response (DOR) as efficacy parameters. A significant relationship between cycle 1 Cavg of LT and ORR and OS has been demonstrated. The odds of ORR increased 20% with a 0.1 µg/mL increase in Cycle 1 Cavg, and the HR for death decreased 4.96% when Cycle 1 Cavg increased 0.1 µg/mL.

As for exposure-safety relationships, a significant correlation was observed between exposure of PBD-conjugated Ab (Cavg and Cmin for Cycles 1, 2, and 3) and skin and nail reactions, LFT abnormalities, GGT increased, and pain. In the final multivariate regression model, the odds of having increased GGT (Grade ≥2) increased 14% with a 0.1 µg/mL increase in Cycle 1 Cavg. Approximately 96% of SG3199 samples were below the LLOQ. An exploratory comparison of TEAEs (grade 2 or more) between patients with measurable SG3199 concentrations in Cycles 1, 2 and 3 and patients without detectable SG3199 indicates that a higher concentration of the cytotoxic agent leads to more adverse reactions, which is to be expected.

The number of ADA positive patients is very small so definitive conclusions cannot be made. Presence of ADAs do not seem to negatively affect the efficacy or safety associated with the treatment with LT.

2.6.4. Conclusions on clinical pharmacology

The clinical pharmacology package for LT consists of data from three clinical studies and pop PK analyses. Considering the nature of the product (ADC molecule) and the fact that the plasma concentration of the toxic moiety is very low and below LLOQ in most samples, the pharmacology package is considered adequate. The proposed dose regimen of LT seems appropriate. Relevant information on clinical pharmacology has been appropriately reflected in the SmPC.

2.6.5. Clinical efficacy

Table 15 **Summary of Clinical Studies with Loncastuximab Tesirine to Support the MAA Application**

Study Number	Study Design	Objectives	N	Treatment Regimen
ADCT-402-101	Open-label, Phase 1 study of loncastuximab tesirine in patients with relapsed or refractory B-cell lineage non-Hodgkin lymphoma	Safety and tolerability and determine the MTD of loncastuximab tesirine (Part 1, dose escalation part); RP2D for Part 2 (dose expansion part); Safety and tolerability in Part 2 at the dose level recommended in Part 1. Characterize the PK (total antibody, PBD-conjugated antibody, and free cytotoxic agent SG3199) and immunogenicity (ADA) profile of loncastuximab tesirine.	183	15, 30, 60, 90 µg/kg IV, Q3W; 120, 150, 200 µg/kg IV, Q3W or Q6W.
ADCT-402-201	Open-label, Phase 2 single-arm study of loncastuximab tesirine in patients with relapsed or refractory diffuse large B-cell lymphoma	Evaluate the efficacy and safety of loncastuximab tesirine. Characterize the PK (total antibody, PBD-conjugated antibody, and free cytotoxic agent SG3199) and immunogenicity (ADA) profile of loncastuximab tesirine.	145	150 µg/kg IV, Q3W ×2 followed by 75 µg/kg IV, Q3W on subsequent treatment cycles.
ADCT-402-102	Open-label, Phase 1 study of loncastuximab tesirine in patients with relapsed or refractory B-cell lineage acute lymphoblastic leukaemia	Evaluate safety and tolerability, and determine the MTD (Part 1, dose escalation part), of loncastuximab tesirine. Determine RP2D for Part 2 (dose expansion part). Safety and tolerability in Part 2 at the RP2D. Characterize the PK (total antibody, PBD-conjugated antibody, and free cytotoxic agent SG3199) and immunogenicity (ADA) profile of loncastuximab tesirine.	35	15, 30, 60, 90, 120, 150 µg/kg IV, Q3W. Weekly dosing on Days 1, 8, and 15 of each 3-week treatment cycle: 50 µg/kg IV

Source: ADCT-402-101 CSR, ADCT-402-201 CSR, and ADCT-402-102 CSR
ADA = anti-drug antibody; IV = intravenous; MAA = Marketing Authorisation Application; MTD = maximum tolerated dose; N = number of patients; PBD = pyrrolobenzodiazepine; PK = pharmacokinetic(s); Q3W = every 3 weeks; Q6W = every 6 weeks; RP2D = recommended Phase 2 dose.

2.6.5.1. Dose response study(ies)

The ADCT-402-101 study is a phase 1, first in human, open-label, dose escalation (Part 1) and expansion (Part 2) study of loncastuximab tesirine (LT) as monotherapy in patients with relapsed or refractory B NHL (including DLBCL). The ADCT-402-101 study evaluated the safety and efficacy of LT and characterised the PK profile of LT.

LT was administered IV at different dose levels of 15 µg/kg to a maximum of up to 200 µg/kg once every 3 weeks. Based on the safety, efficacy and the PK data, the doses and schedules selected for Part 2 (expansion) were: 120 µg/kg every 3 weeks and 150 µg/kg every 3 weeks. Some patients in this group had their dose reduced to 75 µg/kg every 3 weeks after 3 cycles at 150 µg/kg.

The ADCT-402-101 study evaluated the activity of LT in 137 previously treated patients. The majority of patients had subtype DLBCL (76.0%), of these 26.6% with transformed DLBCL and 16.5% with double-hit or triple-hit disease, and the majority having Ann Arbor Stage IV. The majority of patients were white (90.6%), 57.6% were male with a median age of 63.0 years (range 20 to 86 years). ECOG scores included ECOG 0 (23.7%), ECOG 1 (61.9%) and ECOG 2 (12.9%). The median number of prior lines of systemic therapy was 3 (range: 1 to 10), and 39.6% had received ≥4 prior lines and 19.4%

had prior SCT. For patients with DLBCL, 94.3% of patients were in 3L+ setting consistent with the intended indication.

Half of the patients withdrew due to progressive disease, followed by adverse events, physician decision, other and death. Of 20 patients who withdrew for "other" reasons 14 had DLBCL. Of these 14 patients, six patients withdrew to undergo a transplant, two due to progression, one due to deterioration, one had CR but decided to withdraw due to fatigue, one patient was elected to withdraw and it was patient's decision for the three remaining patients.

Table 16 Overall Response Rate – Patients with DLBCL (Efficacy Analysis Set)

	15 µg/kg	30 µg/kg	60 µg/kg	90 µg/kg	120 µg/kg			150 µg/kg			200 µg/kg	
	Part 1 (N=2)	Part 1 (N=3)	Part 1 (N=3)	Part 1 (N=2)	Part 1 (N=11)	Part 2 (N=21)	Part 1+2 (N=32)	Part 1 (N=15)	Part 2 (N=55)	Part 1+2 (N=70)	Part 1 (N=25)	All Doses (N=137)
Best Overall Response												
Complete response	0	1 (33.3)	0	0	4 (36.4)	2 (9.5)	6 (18.8)	5 (33.3)	10 (18.2)	15 (21.4)	10 (40.0)	32 (23.4)
Partial response	0	0	0	1 (50.0)	2 (18.2)	6 (28.6)	8 (25.0)	4 (26.7)	10 (18.2)	14 (20.0)	3 (12.0)	26 (19.0)
Stable disease	1 (50.0)	0	0	1 (50.0)	3 (27.3)	4 (19.0)	7 (21.9)	0	12 (21.8)	12 (17.1)	2 (8.0)	23 (16.8)
Not evaluable	0	0	0	0	0	1 (4.8)	1 (3.1)	0	1 (1.8)	1 (1.4)	0	2 (1.5)
Progressive disease	1 (50.0)	2 (66.7)	3 (100)	0	2 (18.2)	8 (38.1)	10 (31.3)	6 (40.0)	22 (40.0)	28 (40.0)	10 (40.0)	54 (39.4)
ORR (CR + PR)	0	1 (33.3)	0	1 (50.0)	6 (54.5)	8 (38.1)	14 (43.8)	9 (60.0)	20 (36.4)	29 (41.4)	13 (52.0)	58 (42.3)
95% CI for ORR	-	(0.8, 90.6)	-	(1.3, 98.7)	(23.4, 83.3)	(18.1, 61.6)	(26.4, 62.3)	(32.3, 83.7)	(23.8, 50.4)	(29.8, 53.8)	(31.3, 72.2)	(33.9, 51.1)

CI=confidence interval; CR=complete response; DLBCL=diffuse large B-cell lymphoma; ORR=overall response rate; PR=partial response
200 µg/kg includes patients treated every 3 weeks and every 6 weeks
Note: Best overall response is the best visit response, based on the 2014 Lugano Classification criteria.
Source: Table 14.2.1.1.2

In the DLBCL Efficacy Analysis Set, the median treatment duration (all dose levels combined) was 64 days (range: 22 to 277 days) and the mean number of treatment cycles administered was 3.1.

Regarding efficacy, results from 137 previous-treated patients, showed an ORR of 42.3% (95%CI: 33.9, 51.2) (all doses) and CR of 23.4%, this is considered clinical meaningful and encouraging in a heavily pre-treated population as well as a median DOR of 4.47 months.

Overall the efficacy data from the ADCT-402-101 study was considered supportive for the initiation of the pivotal trial. In conclusion, the recommended dose is 150 µg/kg every 3 weeks for two doses followed by 75 µg/kg every 3 weeks for subsequent doses. The dose reduction after 2 cycles was based on the fact that a substantial portion of patients treated on the Phase 1 trial required dose reduction after 2 or more cycles, usually as a result of prolonged dose delays because of adverse events (AEs). Decreasing the dose after 2 cycles was intended to reduce the incidence of dose delay and decrease the need for further dose reduction. The choice of a Q3W dose regimen was based on animal studies and the expectation that this interval would result in efficacious drug levels while reducing adverse events.

2.6.5.2. Main study(ies)

ADCT-402-201 is an ongoing Phase 2, multicentre, open-label, single-arm study of the efficacy and safety of loncastuximab tesirine in patients with relapsed or refractory DLBCL. This report presents data collected from study initiation (01 Aug 2018) up to and including 01 Mar 2021. The primary analysis date was 15 May 2020.

Methods

- **Study Participants**

Main inclusion criteria:

Each patient had to meet the following criteria to be eligible for the study:

1. Male or female patient aged ≥ 18 years.

2. Pathologic diagnosis of DLBCL, as defined by the 2016 World Health Organization (WHO) classification, to include: DLBCL not otherwise specified (NOS); primary mediastinal large B-cell lymphoma; and high-grade B-cell lymphoma, with MYC and B-cell lymphoma 2 apoptosis regulator (BCL2) and/or B-cell lymphoma 6 transcription repressor (BCL6) rearrangements.

3. Relapsed or refractory disease following two or more multi-agent systemic treatment regimens.

4. Measurable disease as defined by the 2014 Lugano classification and availability of formalin-fixed paraffin-embedded tumour tissue block (or minimum 10 freshly cut unstained slides if block was not available). If several samples, the most recent was preferred.

5. ECOG performance status 0 to 2.

6. Adequate organ function as pre-defined by screening tests.

Exclusion Criteria

Patients who met any of the following criteria were not eligible for participation in the study:

1. Previous treatment with loncastuximab tesirine.

2. Known history of hypersensitivity to or positive serum human ADA to a CD19 antibody.

3. Pathologic diagnosis of Burkitt's lymphoma, bulky disease, defined as any tumor ≥10 cm in longest dimension (added in Protocol Amendment 2).

4. Active second primary malignancy other than nonmelanoma skin cancers, nonmetastatic prostate cancer, in situ cervical cancer, ductal or lobular carcinoma in situ of the breast, or other malignancy that the Sponsor's medical monitor and Investigator agreed and document should not be exclusionary.

5. Autologous SCT or allogeneic SCT within 30 days or 60 days respectively prior to start of study drug (Cycle 1, Day 1).

6. Active graft-versus-host disease.

7. Posttransplant lymphoproliferative disorders.

8. Active autoimmune disease, including motor neuropathy considered of autoimmune origin and other central nervous system (CNS) autoimmune disease.

9. Known seropositive and requiring antiviral therapy for human immunodeficiency virus, hepatitis B virus (HBV), or hepatitis C virus.

10. History of Stevens-Johnson syndrome or toxic epidermal necrolysis.

11. Lymphoma with active CNS involvement at the time of screening, including leptomeningeal disease

12. Clinically significant third space fluid accumulation (ie, ascites requiring drainage or pleural effusion that either required drainage or was associated with shortness of breath).

13. Significant medical comorbidities, such as uncontrolled hypertension (BP ≥160/100 mmHg repeatedly), unstable angina, congestive heart failure (New York Heart Association class II > II), electrocardiographic evidence of acute ischemia, coronary angioplasty, or myocardial infarction

within 6 months prior to screening, uncontrolled atrial or ventricular cardiac arrhythmia, poorly controlled diabetes, or severe chronic pulmonary disease.

14. Major surgery, radiotherapy, chemotherapy, or other antineoplastic therapy within 14 days prior to start of study drug (Cycle 1, Day 1), except shorter if approved by the Sponsor.

15. Use of any other experimental medication within 14 days prior to start of study drug (Cycle 1, Day 1).

16. Planned live vaccine administration after starting study drug (Cycle 1, Day 1).

17. Failure to recover to Grade ≤1 (Common Terminology Criteria for Adverse Events version [CTCAE] version 4.0) from acute nonhematologic toxicity (Grade ≤2 neuropathy or alopecia) due to previous therapy prior to screening.

18. Congenital long QT syndrome or a corrected QT (QTc) using Fridericia's correction (QTcF) interval of >480 ms at screening (unless secondary to pacemaker or bundle branch block).

19. Any other significant medical illness, abnormality, or condition that would have, in the Investigator's judgment, made the patient inappropriate for trial participation or put the patient at risk.

- **Treatments**

Loncastuximab tesirine (LT) was administered as an IV infusion over 30 minutes on Day 1 of each cycle (Q3W) at a dose of 150 µg/kg for 2 cycles and then 75 µg/kg for subsequent cycles. The study included a screening period (of up to 28 days), a treatment period (cycles of 3 weeks) for up to 1 year or until progressive disease (PD), unacceptable toxicity, or other discontinuation criteria, whichever occurred first and a follow-up period. Disease assessments were performed at baseline and 6 and 12 weeks after Cycle 1, Day 1, then every 9 weeks during the treatment period and at end of treatment (EOT).

Dexamethasone (4 mg orally) as premedication was administered twice daily the day before LT administration (if possible), the day of LT administration (given at least 2 hours prior to administration when not given the day before; otherwise, any time prior to administration), and the day after LT administration.

- **Objectives**

Table 17 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
Evaluate the efficacy of single-agent loncastuximab tesirine in patients with relapsed or refractory DLBCL	ORR according to the 2014 Lugano classification (Cheson et al 2014) as determined by central review in all-treated patients; ORR was defined as the proportion of patients with a best overall response (BOR) of CR or PR
Secondary	
Further evaluate the efficacy of loncastuximab tesirine	DOR defined as the time from first documentation of tumor response to disease progression or death
	CR rate (CRR) defined as the percentage of treated patients with a BOR of CR
	Relapse-free survival (RFS) defined as the time from the documentation of CR to disease progression or death
	PFS defined as the time between start of treatment and the first documentation of recurrence, progression, or death
	OS defined as the time between the start of treatment and death from any cause
Characterize the safety profile of loncastuximab tersine	Frequency and severity of AEs and SAEs
	Changes from baseline of safety laboratory variables, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, and 12-lead ECGs
Characterize the pharmacokinetic (PK) profile of loncastuximab tesirine	Concentrations and PK parameters of loncastuximab tesirine total antibody, PBD-conjugated antibody, and unconjugated warhead SG3199. (These data will be analyzed and reported separately).
Evaluate the immunogenicity of loncastuximab tesirine	Antidrug antibody (ADA) titers and, if applicable, neutralizing activity to loncastuximab tesirine after treatment with loncastuximab tesirine. (These data will be analyzed and reported separately).
Objectives	**Endpoints**
Evaluate the impact of loncastuximab tesirine treatment on health-related quality of life (HRQoL)	Change from baseline in HRQoL as measured by EuroQol 5 Dimensions-5 Levels (EQ-5D-5L) and Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym)
Exploratory	
Characterize the exposure-response relationship between loncastuximab tesirine exposure and measures of efficacy and safety	Relation between exposure (loncastuximab tesirine dose, PK metrics) and selected efficacy and safety endpoints. (These data will be analyzed and reported separately).
Explore correlations between clinical activity or tolerability and tumor and/or blood biomarkers, including pharmacogenetic markers	Relation between tumor and/or blood biomarkers and selected efficacy and safety endpoints. (These data will be analyzed and reported separately).

Imaging by PET-CT was performed in all patients, the screening imaging (PET-CT) was to be performed within 4 weeks prior to Cycle 1 Day 1. The median time from the baseline scan to the start of treatment was 11 days.

- **Outcomes/endpoints**

Please refer to the section above

- **Sample size**

The sample size of 140 patients was defined based on the assumption that a response rate of 20% would be a clinically meaningful option for this patient population. Patients with DLBCL who have failed second line therapy have a very poor prognosis, with response to second-line salvage therapy ranging from 14-26%, with a median survival of 6.1 months (Seshadri et al., 2008; Crump et al., 2017).

The primary hypothesis is that the ORR based on central review for patients treated with loncastuximab tesirine is significantly greater than 20% (i.e., H0: $p \leq 0.2$ vs. Ha: $p > 0.2$). This hypothesis will be tested at type I error of 0.05 (two sided).

The publications referred to by the applicant to justify the objective rate of 20% dated 2008 (Seshadri *et al.*) and 2017 (Crump *et al.*) are both retrospective studies. It was a retrospective study in patients with DLBCL refractory to one treatment line. The publication states that the objective response rate was 26% (complete response rate, 7%) to the next line of therapy, and the median overall survival was 6.3 months.

It is to be noted that Yescarta and Kymriah were both authorised in 2018 and tafasitamab was authorised in 2021. The ORR for Yescarta (68% at 24-months analysis) and Kymriah (53%) appear to be far above the plan target of 20%. However, the objective of 20% was used only for the sample size calculation, and the applicant does not propose to include the "p" value in the SmPC.

Using nQuery exact test for single proportion, a sample size of 140 patients has >99% power to achieve a 1-sided significance level of 0.025 (2-sided significance level of 0.05). This sample size will provide adequate precision for observed ORR in the expected range.

Of note, the sample size calculation description was different in the protocol version 1, where a Simon's 2-stage design was implemented with 2 different cohorts (without / with bulky disease). The total number of patients was also 140. In the overall summary and rationale for changes from Protocol v 1 (protocol amendment 1, page 127 / 411), the applicant claimed that the changed in the study design were performed according to suggestions from the FDA.

- **Randomisation and Blinding (masking)**

Not applicable since it is a single arm study.

- **Statistical methods**

<u>Efficacy analysis populations</u>

All-Treated Population: All patients who received at least one dose of loncastuximab tesirine. This population was used in the primary analyses of efficacy and safety. This is not endorsed since the intention to treat principle requires to include all enrolled patients. However, since all enrolled patients were treated, sensitivity analyses are not required.

Per-Protocol Population: All patients in the All-Treated Population who met the inclusion/exclusion criteria, did not take a prohibited concomitant treatment, and did not have other protocol deviation that could have had a major impact on efficacy results.

SCT Population: All patients who responded to loncastuximab tesirine and underwent SCT (either autologous or allogeneic) after permanent discontinuation of loncastuximab tesirine treatment without any intervening anticancer therapy. (This population was introduced in the Statistical Analysis Plan [SAP] and was not specified in the protocol).

Primary endpoint ORR

The ORR and the corresponding 95% two-sided exact CI were presented. The overall response category was derived based on response assessment performed on or before the start of subsequent anticancer therapy/procedure. Patients without documented subsequent anticancer therapy and/or with missing start date of anticancer therapy were considered as not having received subsequent anticancer therapy.

A BOR of SD could only be made after the patient was on study for a minimum of 35 days after the first dose of loncastuximab tesirine. Any tumor assessment indicating SD before this time period was considered as NE for BOR if no assessment after this time period was available.

Sensitivity analyses

ORR determined by the independent reviewer's evaluation for the Per-Protocol Population. ORR determined by investigators.

Secondary endpoints

Duration of response will be estimated and displayed for the all-treated population using Kaplan-Meier methods.

Censoring rules

Patients who have the event after the start of subsequent anticancer therapy/procedure, or are progression-free and alive at the time of clinical cut-off, or have unknown status, will be censored at the last valid tumour assessment on or before the start of subsequent anticancer therapy/procedure or clinical cut-off time.

When a subsequent anticancer therapy is used and progressive disease (based on radiographic or clinical progression at EOT/EOS) is observed within 6 days, they will be considered as the same visit (within the protocol specified +/-6 days visit window) and the patient will be counted as having an event (losing the response). Patients with no post-baseline disease assessment will be censored on Day 1.

Sensitivity analyses

A sensitivity analysis of DOR will be conducted in which the DOR for patients undergo SCT will not be censored at SCT. A sensitivity analysis of DOR per investigator assessments will also be conducted. Clinical progression at EOT/EOS without radiographic assessment could be considered as an event in a sensitivity analysis.

Complete response rate (CRR), RFS, PFS and OS

CRR will be analysed as described for ORR. The same methods described for DOR were implemented for the analysis of RFS and PFS. OS was estimated and displayed for the All-Treated Population using Kaplan-Meier methods. For OS, patients who were known to be alive as of their last known status were censored at their date of last contact, and Patients who were lost to follow-up were censored at the date the patient was last known to have been alive.

Interim Analyses and multiplicity control

An interim analysis for futility was performed when the first 52 patients dosed had two tumor assessments (approximately 12 weeks after start of loncastuximab tesirine). The ORR and the corresponding 95% CI were reported. Enrollment continued during the interim analysis. If <10 patients responded the study enrollment was to be halted. Other analyses such as DOR, PFS, CR rate, RFS, OS, and safety analyses may have been performed if necessary. A futility interim analysis is not expected to inflate the type I error. The applicant presented the response results: 23 patients had complete or partial response and therefore the study was not halted due to futility.

One primary endpoint was defined (ORR) as the first testing endpoint. A strategy to control for multiple secondary endpoints was not found. Therefore, the p-values corresponding to the secondary endpoints cannot be interpreted.

Changes to the Planned Statistical Analyses

1. There were two patient populations added to the SAP that were not previously described in the protocol:

• SCT Population

• PRO Analysis Population

2. A PK Population was defined in the protocol as being performed in the Per-Protocol Population. This was changed to the All-Treated Population.

3. An additional efficacy analysis; time to tumour response, was conducted although it was not previously described in the protocol:

• Time to tumour response was evaluated for the subset of patients who achieved a CR or PR as BOR before the start of subsequent anticancer therapy or procedure from the time of first dose to the initial documented response. For this subset of patients, time to tumour response was summarised using descriptive statistics.

The current version of the SAP is version 2.0 dated 2 Mar 2020.

The applicant defined additional populations in the SAP and incorporated a secondary endpoint "Time to tumor response".

Results

- **Participant flow**

Overall, 145 patients were treated and included in the All-Treated Population of pivotal study ADCT-402-201. Although data for the supportive phase 1 ADCT-402-101 trials are also presented in the tables, comments are related to the pivotal study.

Table 18 **Patient Disposition**

	ADCT-402-201 (All-Treated Population) (N=145)	ADCT-402-101 DLBCL (all dose levels) (Safety Analysis Set) (N=139)
Primary reason for treatment withdrawal	145 (100)	139 (100)
Progressive disease	82 (56.6)	71 (51.1)
Unacceptable toxicity	32 (22.1)	0
Adverse event	0	25 (18.0)
Withdrawal by subject	9 (6.2)	1 (0.7)
Non-compliance including lost to follow-up	0	1 (0.7)
Protocol deviation	0	0
Physician decision	4 (2.8)	20 (14.4)
Study terminated by Sponsor	0	0
Transplant	7 (4.8)	0
Pregnancy	0	0
Death	9 (6.2)	7 (5.0)
Other	2 (1.4)	14 (10.1)
Primary reason for discontinuation from study	108 (74.5)	139 (100)
Death	96 (66.2)	92 (66.2)
Withdrawal by subject	7 (4.8)	4 (2.9)
Physician/Sponsor decision	1 (0.7)	0
Lost to follow-up	4 (2.8)	1 (0.7)
Completed	0	31 (22.3)
Other	0	11 (7.9)

Source: Module 5, Section 5.3.5.2.2, Table 14.1.1.1; ADCT-402-101 CSR Table 14.1.1.2
DLBCL = diffuse large B-cell lymphoma

Table 19 **Patient Analysis Sets (All-Enrolled Patients)**

	All-Treated Population (N=145)
Patients enrolled [n]	145
Patients treated, All-Treated Population [n(%)[a]]	145 (100)
Patients enrolled but not treated [n(%)[a]]	0
Per-Protocol Population	121 (83.4)
Patient-reported Outcomes Population [n(%)[a]]	130 (89.7)
Stem Cell Transplant Population [n(%)[a]]	10 (6.9)

[a]Percent is based on all-enrolled patients
Source: Table 14.1.1

- **Recruitment**

Study initiation date was 01 Aug 2018, the initial data cut-off date (DCO) was 06 Apr 2020, but updated data were submitted during the procedure with cut-off date 01 Mar 2021. Unless otherwise specified, the data presented in this report correspond to the latest data cut-off.

The study has completed enrolment and 145 patients were enrolled at 16 centres in the US, 6 centres in the United Kingdom (UK), 5 centres in Italy and 1 centre in Switzerland.

The main reason for exclusion during screening was lack of adequate organ function (16/37) followed by ECOG score above 2 (5/37), lack of measurable disease (4/37), and bulky disease ≥10 cm (3/37). According to the patient disposition table above, the primary reasons for treatment withdrawal were PD (n=82, 56.6%) and unacceptable toxicity (n= 32, 22.1%). Although the toxicity rate may be considered relatively high, the PD rate is as expected in a R/R DLBCL setting. 108 patients (74.5%) discontinued from the study, the most common reason was death (n=96, 66.2%). The number of patients lost to follow-up is low (4 subjects). Seven patients are listed as withdrawal by subject and two due to other reasons. The applicant has also provided narratives for the patients withdrawing due to "Other reasons" or "Withdrawal by subject". As expected, elderly patients with adverse events severely affecting quality of life regularly choose to withdraw although the study rules did not request them to discontinue.

- **Conduct of the study**

The original protocol was dated 09 Mar 2018 and was amended before implementation in response to US FDA recommendations.

Amendment 1, 05 Apr 2018:

• The study design was changed to a single cohort with the primary endpoint being ORR in all-treated patients, resulting in changes to primary and secondary objectives and endpoints, and statistical considerations.

• For eligibility, pathologic diagnosis was clarified to align with the 2016 WHO classification, the requirement for patients to be ineligible or have failed SCT was removed (as the FDA felt that loncastuximab tesirine was potentially suitable for third line therapy in patients who were potentially eligible for SCT), and the specific requirement for rituximab therapy was deleted as it was expected that all patients would have received this in at least one prior line of therapy.

• For patients whose disease was not PET-avid, bone marrow biopsy was added as part of baseline staging and disease assessment if clinically appropriate to fully align with the 2014 Lugano Classification.

• Safety follow-up was extended to 180 days after transplant for patients who had responded to loncastuximab tesirine and gone on to SCT to monitor for possible increased transplant-related toxicity in patients who had been treated with loncastuximab tesirine.

• The exposure relationship to blood biomarkers was removed because there was no plan to perform this against the pharmacogenetic measures.

Amendment 1.1 UK 28 Jun 2018 and Amendment 1.1 SZ 20 Jul 2018 allowed patients who were clinically benefiting of the study to continue treatment beyond one year.

Amendment 2, 24 Sep 2018: The purposes of the amendment were the following:

• Patients with bulky disease (defined as at least one lymph node ≥10 cm in longest diameter) were excluded based on analysis of Phase 1 data showing that these patients had an ORR of 11%. Based on an interim analysis this was the ORR at the time of this analysis.

• The inclusion criterion regarding hepatic function was revised to no longer allow patients with ALT, AST, and GGT ≤5×ULN if there was liver involvement, to be consistent with the requirement to hold the dose of loncastuximab tesirine for patients with Grade ≥2 liver function test abnormalities.

• A definition of overdose and instructions for reporting overdoses were added.

• Patients who were clinically benefiting were allowed to continue treatment beyond 1 year with Sponsor review and approval.

• A requirement for dose discontinuation for dose delays >5 weeks due to toxicity at least possibly related to loncastuximab tesirine was added.

• The requirement for IV contrast for PET-CT was removed and the type and timing of efficacy assessments were removed.

Amendment 3, 07 Jun 2019: was approved internally by ADC Therapeutics. This amendment was not submitted to any study sites, regulatory agencies, or ethics committees. All changes from amendment 2 are included in amendment 4 (below). The modifications aimed to improve the safety of participants or to allow for capture of response information and adverse events for patients who received subsequent CAR-T therapy.

Amendment 4, 09 Jul 2019:

• The text was updated to include information regarding monitoring for extravasation during or after loncastuximab tesirine infusion because of updated safety information.

• The instructions for dose delays and modifications for nonhematologic and hematologic toxicities were clarified and updated.

• Efficacy assessments were updated to allow for capture of response information during the follow-up period for patients who received CAR-T therapy after loncastuximab tesirine treatment.

• AE/SAE reporting requirements for patients who received CAR-T therapy after loncastuximab tesirine discontinuation were added.

• Editorial corrections and clarifications were applied throughout.

Protocol deviations

Important deviations were identified, these deviations excluded patients from the Per-Protocol Population. Overall, there were 11 patients with an important CSR-reportable protocol deviation.

Eight patients had inclusion or exclusion criteria deviations:

- Three patients had elevated GGT levels (inclusion criterion #8c), 1 patient did not have results available for AST at screening so results were not confirmed before dosing (inclusion criterion #8c)
- Three patients tested positive for hepatitis virus and were receiving antiviral therapy (protocol amendment #2, exclusion criterion #11)
- One patient was enrolled with bulky disease (Protocol Amendment #2, exclusion criterion #4)
- One patient received a prohibited concomitant therapy (radiation therapy for lytic lesion on C5 vertebrae).
- Two patients had study drug deviations:
    - One patient with a BMI >35 was administered loncastuximab tesirine based on actual weight instead of ABW for the first infusion that was 19.6% higher than per-protocol planned dose according to ABW.
    - One patient was administered study drug that was 18% lower than the planned dose according to ABW for all 3 cycles.

- **Baseline data**

In the following, comments are related to the pivotal study, ADC-402-201, unless otherwise specified.

Table 20 Demographic and Baseline Characteristics

	ADCT-402-201 (All-Treated Population) (N=145)	ADCT-402-101 DLBCL (all dose levels) (Safety Analysis Set) (N=139)
Sex [n (%)]		
Female	60 (41.4)	59 (42.4)
Male	85 (58.6)	80 (57.6)
Race [n (%)]		
White	130 (89.7)	126 (90.6)
Black or African American	5 (3.4)	7 (5.0)
Asian	3 (2.1)	3 (2.2)
American Indian or Alaskan Native	1 (0.7)	0
Native Hawaiian or Pacific Islander	1 (0.7)	0
Other	5 (3.4)	2 (1.4)
Missing	-	1 (0.7)
Ethnicity [n (%)]		
Hispanic or Latino	13 (9.0)	6 (4.3)
Not Hispanic or Latino	132 (91.0)	133 (95.7)
Age (years)		
n	145	139
Mean	62.7	61.4
std	13.63	15.24
Median	66.0	63.0
Min, Max	23, 94	20, 86
Age Group [n (%)]		
<65 years	65 (44.8)	73 (52.5)
≥65 to <75 years	59 (40.7)	37 (26.6)
≥75 years	21 (14.5)	29 (20.9)

	ADCT-402-201 (All-Treated Population) (N=145)	ADCT-402-101 DLBCL (all dose levels) (Safety Analysis Set) (N=139)
Body Mass Index (kg/m²)		
n	144	138
Mean	26.93	27.70
std	5.728	6.956
Median	25.97	26.90
Min, Max	17.2, 50.5	16.5, 50.1
ECOG Performance Status [n (%)]		
Grade 0	58 (40.0)	33 (23.7)
Grade 1	78 (53.8)	86 (61.9)
Grade 2	9 (6.2)	18 (12.9)
Grade 3	-	2 (1.4)
Country		
US	59 (40.7)	NA
UK	31 (21.4)	NA
Italy	53 (36.6)	NA
Switzerland	2 (1.4)	NA

Source: Module 5, Section 5.3.5.2.2, Table 14.1.3.1.1, ADCT-402-101 CSR Table 14.1.3.1.2
DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; max = maximum; min = minimum, NA = not applicable, std = standard deviation

Cancer history

Table 21 **Cancer History and Pre-treatment Disease Characteristics**

	ADCT-402-201 (All-Treated Population) (N=145)	ADCT-402-101 DLBCL (all dose levels) (Safety Analysis Set) (N=139)
Primary Category		
DLBCL	145 (100)	139 (100)
DLBCL NOS	127 (87.6)	134 (96.4)[a]
High-grade B-cell Lymphoma	11 (7.6)	3 (2.2)[a]
DLBCL, Primary Mediastinal	7 (4.8)	2 (1.4)[a]
DLBCL Additional Subtype		
Cell of Origin		
Germinal centre B-cell subtype	48 (33.1)	ND
Activated centre B-cell subtype	23 (15.9)	ND
Transformed DLBCL		
Transformed Follicular	25 (17.2)	26 (18.7)
Transformed MZBCL	1 (0.7)	2 (1.4)
Transformed Lymphoplasmacytic	1 (0.7)	1 (0.7)
Trans. Nodular Lymphocyte predominant Hodgkin's Lymphoma	0	2 (1.4)
Richter's Transformation	2 (1.4)	6 (4.3)
Other	0	38 (27.3)
Bulky Disease		
Yes	8 (5.5)	19 (13.7)
No	137 (94.5)	120 (86.3)
DLBCL Double/Triple Expressor		
Double Expressor	18 (12.4)	8 (5.8)
Triple Expressor	2 (1.4)	2 (1.4)
DLBCL Double/Triple-Hit		
Double-Hit	12 (8.3)	20 (14.4)
Triple-Hit	3 (2.1)	3 (2.2)
Disease Stage (Ann Arbor Criteria)		
Stage I	10 (6.9)	7 (5.0)
Stage II	23 (15.9)	20 (14.4)
Stage III	19 (13.1)	23 (16.5)
Stage IV	93 (64.1)	89 (64.0)

Source: Module 5, Section 5.3.5.2.2, Table 14.1.4; Table 14.1.7; ADCT-402-101 CSR Table 14.1.4.1; Table 14.1.7.2; ISS Table 1.1.3

[a]percentages were manually calculated using a denominator of 139.

DLBCL = diffuse large B-cell lymphoma; MZBCL = marginal zone B-cell lymphoma; ND = not done; NOS = not otherwise specified

The IPI scores and LDH levels at baseline were provided and showed that the large majority of patients had an LDH >normal (70.2%) and that 57.2% of patients had an IPI score ≤ 2 i.e. considered low or low-intermediate risk categories. These characteristics are considered in the provided matching-adjusted indirect comparison (MAIC) in an attempt to compare loncastuximab tesirine to other available treatments in 3L+.

Prior Anticancer Therapy

Table 22 Prior Anti-cancer Procedure or Therapy

	ADCT-402-201 (All-Treated Population) (N=145)	ADCT-402-101 DLBCL (all dose levels) (Safety Analysis Set) (N=139)
Lines of Prior Systemic Therapies [n (%)]		
2 prior lines	63 (43.4)	-
3 prior lines	35 (24.1)	-
≥3 prior lines	47 (32.4)	-
≤3	-	84 (60.4)
4 to 6	-	48 (34.5)
7 to 10	-	7 (5.0)
Number of Lines of Prior Systemic Therapies		
n	145	139
Mean	3.1	3.5
std	1.27	1.66
Median	3.0	3.0
Min, Max	2, 7	1, 10
Prior Radiotherapies [n (%)]		
Yes	53 (36.6)	52 (37.4)
No	92 (63.4)	87 (62.6)
Prior Stem Cell Transplant [n (%)]		
Yes	24 (16.6)	27 (19.4)
No	121 (83.4)	112 (80.6)
Type of Stem Cell Transplant [n (%)]		
Autologous	21 (14.5)	22 (15.8)
Allogeneic	2 (1.4)	2 (1.4)
Both	1 (0.7)	2 (1.4)
Unknown	0	1 (0.7)
First Line Prior Systemic Therapy Response Group [n (%)]		
Relapse	99 (68.3)	90 (64.7)
Refractory	29 (20.0)	30 (21.6)
Other	17 (11.7)	19 (13.7)
Last Line Prior Systemic Therapy Response Group [n (%)]		
Relapse	44 (30.3)	49 (35.3)
Refractory	88 (60.7)	83 (59.7)
Other	13 (9.0)	7 (5.0)
Prior CAR-T Therapy		
Yes	13 (9.0)[a]	NA
No	132 (91.0)[a]	NA

Source: Module 5, Section 5.3.5.2.2, Table 14.1.5; Table 14.2.1.1.18; ADCT-402-101 CSR Table 14.1.5.2
[a]percentages were manually calculated.

CAR-T = chimeric antigen receptor T-cell; DLBCL = diffuse large B-cell lymphoma; max = maximum; min = minimum, NA = not applicable; std = standard deviation.

Following the first relapse of DLBCL, the most significant treatment approach in medically fit patients is to achieve long-term disease control or cure by intensive salvage chemotherapy followed by SCT.

A tabulated summary of post-treatment anticancer therapy and procedure follows:

Table 23 **Study ADCT-402-201: Outcome at Last Follow-up**

Post-treatment anticancer therapy	N	Outcome at last follow-up			
		Alive	Died of progressive disease	Died of other/unknown cause	Withdrawn from study
SCT	15	8	2	4	1
CAR-T	16	6	9	1	0
Non-cellular systemic therapies	41	5	26	8	2
Radiotherapy alone	4	1	3		

CAR-T = chimeric antigen receptor t-cell; SCT = stem cell transplantation.
Source: Module 5.3.5.2, Study ADCT-402-201, Listing 16.1.12

- **Numbers analysed**

The pivotal study included 145 treated patients in the All-Treated Population and 121 patients (83.4%) were included in the Per-Protocol Population. The supportive data from 137 patients from the phase 1 Study ADCT-402-101 are presented in Section 3.2 and the pharmacokinetic part.

- **Outcomes and estimation**

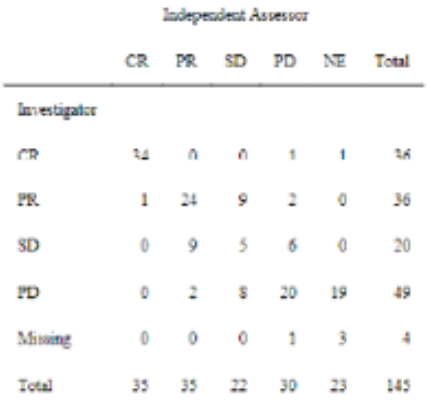
Primary endpoint- overall response rate

Table 24 **Best Overall Response and Overall Response Rate**

	ADCT-402-201 (All-Treated Population) (N=145)	ADCT-402-101 DLBCL (all dose levels) (Efficacy Analysis Set) (N=137)
Best Overall Response		
Complete response	36 (24.8)	32 (23.4)
Partial response	34 (23.4)	26 (19.0)
Stable disease	22 (15.2)	23 (16.8)
Not evaluable	23 (15.9)	2 (1.5)
Progressive disease	30 (20.7)	54 (39.4)
ORR (CR+PR)	70 (48.3)	58 (42.3)
95% CI for ORR	(39.9, 56.7)	(33.9, 51.1)

Source: Module 5, Section 5.3.5.2.2, Table 14.2.1.1.1; ADCT-402-101 CSR Table 14.2.1.1.2
Note: Best overall response is the best visit response, based on the 2014 Lugano Classification criteria.
Note: For ADCT-402-201, not evaluable included patients without any scan to the independent reviewer (even clinical progressive disease) or patients whose scan was determined as not evaluable by the independent reviewer.
Note: For ADCT-402-101, patients were considered not evaluable if they had only 1 valid disease assessment which was stable disease and the assessment was within 35 days after the first dose.
CI = confidence interval; CR = complete response; DLBCL = diffuse large B-cell lymphoma; ORR = overall response rate; PR = partial response

Figure 22 **Best Overall Response by Independent Reviewer versus Investigator Assessment**



	Independent Assessor					
	CR	PR	SD	PD	NE	Total
Investigator						
CR	34	0	0	1	1	36
PR	1	24	9	2	0	36
SD	0	9	5	6	0	20
PD	0	2	8	20	19	49
Missing	0	0	0	1	3	4
Total	35	35	22	30	23	145

CR=complete response; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease

ORR as assessed by independent review, the primary endpoint of study of study ADCT-402-201 was 48.3% (70/145 patients; 95% CI: 39.9, 56.7) and endorsed by the supportive study ADCT-402-101. ORR by Investigator assessment was 49.7% (72/145 patients; 95% CI: 41.3, 58.1).

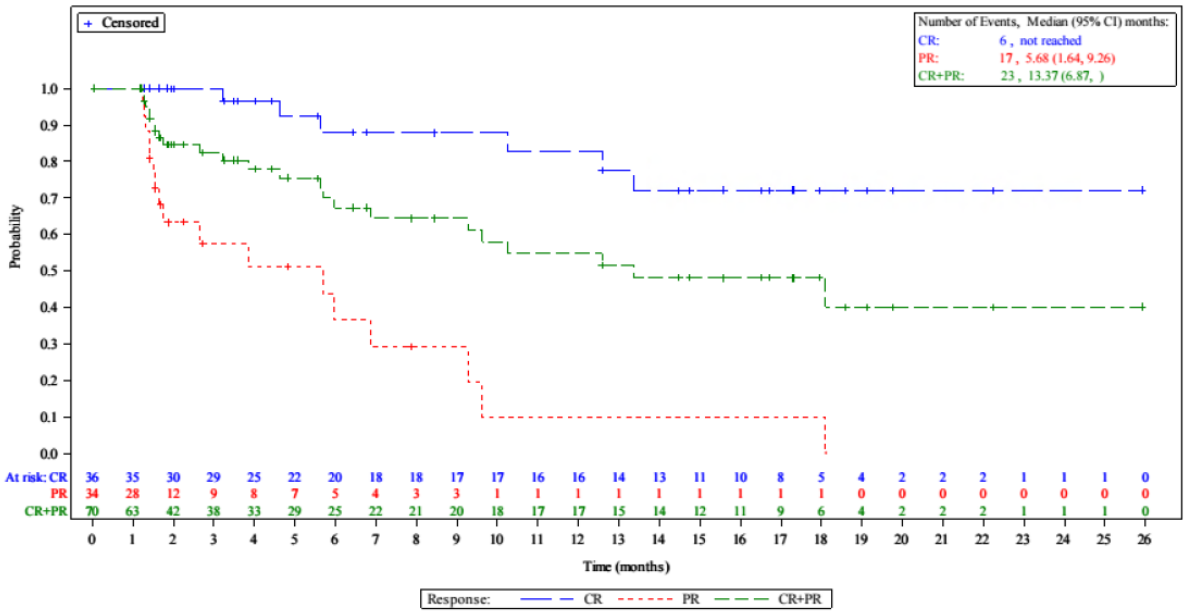
Complete response rate was observed for 24.8% (36/145 patients, 95% CI:18.0, 32.7). The CR rate is considered clinically relevant as a potential surrogate endpoint of PFS in high-grade R/R DLBCL. Updated ORR data for the pivotal study ADCT-402-201 with a data cut-off date of 01 March 2021 showed an ORR of 48.3% (70/145 patients, 95% CI: 39.9, 56.7– see Table 24 above). The applicant has compared LT to approved and recommended therapies in r/r DLBCL utilizing an MAIC with historical data.

Secondary endpoint – Duration of response

Table 25 Summary of Duration of Response by Independent Reviewer All-Treated Population

Parameter	150 µg/kg (N=145)
Total number of patients	70
Number of events	23
Number of censored	47
25 percentile of DOR (95% CI) (month)	5.62 (1.64, 9.26)
50 percentile of DOR (95% CI) (month)	13.37 (6.87,)
75 percentile of DOR (95% CI) (month)	not reached
Probability to maintain the response for 6 months (95% CI)	67.3 (51.6, 78.9)
Probability to maintain the response for 9 months (95% CI)	64.4 (48.3, 76.6)
Probability to maintain the response for 12 months (95% CI)	54.7 (37.9, 68.8)

Figure 23. **Kaplan-Meier Plot of Duration of Response by Independent Reviewer by Best Overall Response (All-Treated Population)**



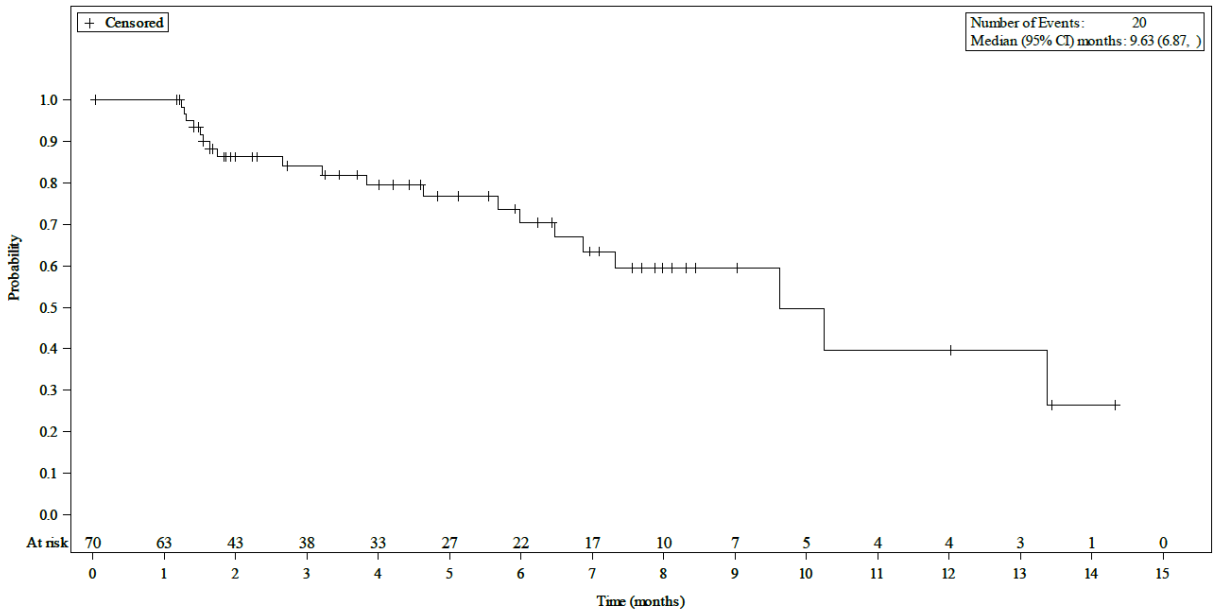
Source: Module 5.3.5.2 Study ADCT-402-201, Section 14 – Updated Tables and Figures, Batch 1, 2021, Figure 14.2.1.9.10 (01 March 2021)

The median duration of response (DOR) for the 70 responding subjects was 13.37 months (95% CI: 6.87, NE). Median DoR was not reached for CR patients, and was 5.68 months (95% CI: 1.64, 9.26) for PR patients.

The median DOR for patients with SCT not censored was also 13.37 months (95% CI: 6.87, NE).

ADCT402-201 - Cut off date 06Apr2020

Figure 24. Kaplan-Meier Plot of Duration of Response by Independent Reviewer with Stem Cell Transplant not Censored
All-Treated Population



Based on independent reviewer data, including death as event. The patients are not censored by transplant.
Dataset: adtte, adsl
Program: f-km.sas, Output: f14_2_1_9_4_km_dorircsc_eff.rtf, Generated on: 04JUN2020 10:31

There were two different formulations administered during LT clinical development (lyophilised and liquid formulation). The applicant provided efficacy results according to the formulation administered. Overall, although the small number of patients who received the liquid formulation do not allow a firm conclusion, it is agreed that especially for ORR, no major difference was observed.

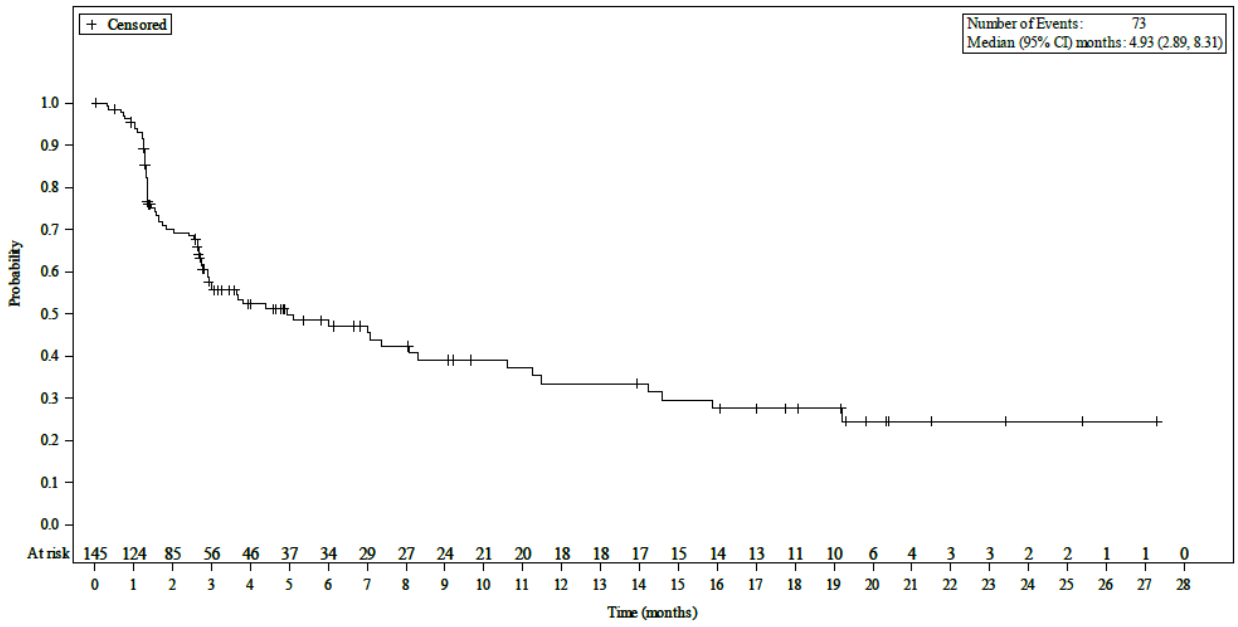
The protocol of the pivotal phase II study ADCT-402-201 recommends a dose delay in case of toxicities followed by dose reduction if the toxicity require more than a 3-week delay. In addition, the dose may also be reduced upon investigator's decision for any grade ≥3 toxicity (≥2 for oedema, effusion, or increased AST/ALT/GGT) possibly related to LT even if it does not result in dosing delay of more than 3 weeks. However, no efficacy analysis is provided in such case.

With regards to the recommendations of the SmPC (suspension with further dose reduction by 50% if dosing is delayed by more than 3 weeks), the applicant was required to provide an efficacy analysis for patients who had a dose reduction subsequently to dose delay at 50% of the initial dose, and for patients with a dose delay which did not require dose reduction.

Secondary endpoint – Progression-free Survival

The median PFS in the All-Treated Population was 4.93 months (95% CI: 2.89, 8.31) with SCT not censored. With clinical progression imputed as an event, median PFS was 4.40 months (95% CI: 2.76, 8.08).

Figure 25. Kaplan-Meier Plot of Progression-free Survival by Independent Reviewer
All-Treated Population

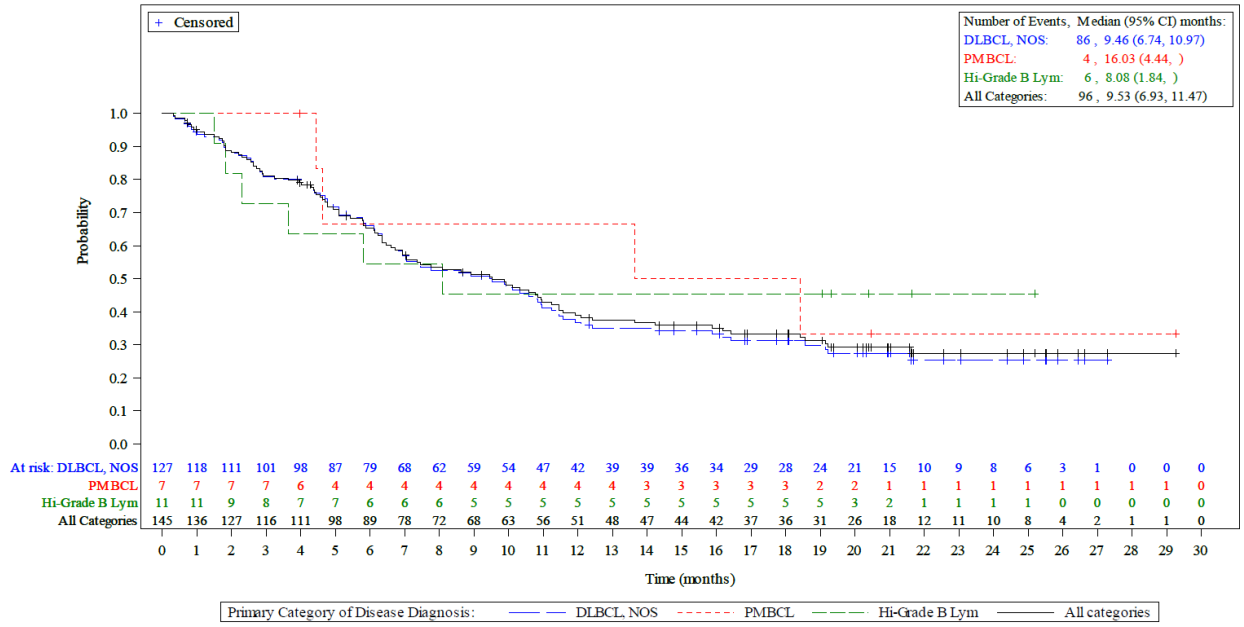


Based on independent reviewer data, including death as event
Dataset: adtte, adsl
Program: f-km.sas, Output: f14_2_1_6_1_km_pfs_eff.rtf, Generated on: 15APR2021 15:05

Secondary endpoint – Overall Survival

Of the 145 patients in the All-Treated Population, the median OS was 9.53 months (95% CI: 6.93, 11.47).

Figure 26. Kaplan-Meier Plot of Overall Survival by Primary Category of Disease Diagnosis
All-Treated Population



Dataset: adtte, adsl
Program: f-km-bywhocat.sas, Output: f14_2_1_8_3_km_os_bywhocat_eff.rtf, Generated on: 15APR2021 15:11

The median time to response (CR or PR) in the pivotal study ADCT-402-201 was 41.0 days (range: 35 -247 days), similarly 43.0 days (range 31-323) for the supportive study ADCT-402-101, indicating that most responders had a response after 2 doses of the study drug.

The median duration of response (DOR) for the 70 responding subjects was 13.37 months (95% CI: 6.87, NE) in the pivotal study, this is considered highly clinical meaningful. But for the supportive Study, ADCT-402-101, median DOR was 4.47 months (95% CI: 3.94 to 9.46).

Similarly, a difference was noted between the PFS results for the pivotal and the supportive study. In the Study ADCT-402-201, the median PFS was 4.93 months (95% CI: 2.89, 8.31) compared with 2.83 months (95% CI: 1.91, 3.75) in the Study ADCT-402-101.

Median OS for the 145 patients in Study ADCT-402-201 was 9.53 months (95% CI: 6.93, 11.47) and 7.46 months (95% CI: 5.95 to 9.79 months) in the Study ADCT-402-101.

Health-related Quality of Life

The PRO/HRQoL were collected using the EQ-5D-5L and FACT-Lym questionnaires in the PRO population which included 130 patients. The patients were classified as improved/deteriorated based on minimally clinically important differenced for EQ-5D-5L score and FACT-Lym.

EQ-5D-5L

A total of 97.2% of patients completed the baseline EQ-5D-5L assessment. The completion rate among patients who were treated at each visit was ≥92% up to Cycle 9. After Cycle 9, <20 patients were treated.

The mean (std) EQ-5D-5L VAS score was 71.4 (19.1) at baseline. During the course of treatment, 41.4% of patients showed improvement at one or more visits by at least 7 points, 39.6% showed deterioration at one or more visits by at least 7 points, and 65.8% remained stable (change <7 points) across visits. When averaging the change from baseline scores for each patient across visits during the course of treatment, 27.9% of the patients showed improvements by at least 7 points, 20.7% showed

deterioration, and 51.4% remained stable. The mean VAS change score showed a trend of improvement on overall health over time.

FACT-Lym

The completion rate for FACT-Lym subscale and composite scores in the PRO-Population was 93.8% at baseline, and ≥88% of patients at each visit completed the FACT-Lym subscale and composite scores up to Cycle 9. After Cycle 9, there were <20 patients in treatment.

During the course of the treatment, 42.5% of the patients showed improvement for one or more visits by at least 3 points, 43.4% showed deterioration for one or more visits by at least 3 points, and 60.2% remained stable (change less than 3 points) in all visits. When averaging the change from baseline scores for each patient across visits during the course of the treatment, 26.5% of patients showed improvement by at least 3 points, and 27.4% showed deterioration by at least 3 points, and approximately half showed no change. Mean changes in all FACT-Lym subscale and composite scores were generally stable over time. Mean changes in all FACT-Lym subscale and composite scores were generally stable over time.

FACT-Lym subscales that showed a trend of improvement from baseline over time were emotional well-being (except Cycle 15 Day 1) and LymS (except Cycle 15 Day 1). The subscales of PWB and functional well-being (except Cycle 15 Day 1) were relatively stable from baseline over time and the subscale of social/family well-being showed a trend of deterioration from baseline over time.

- **Ancillary analyses**

ADCT402-201 - Cut off date 01Mar2021

Figure 27. Forest Plot of Overall Response Rate by Subgroup
All-Treated Population

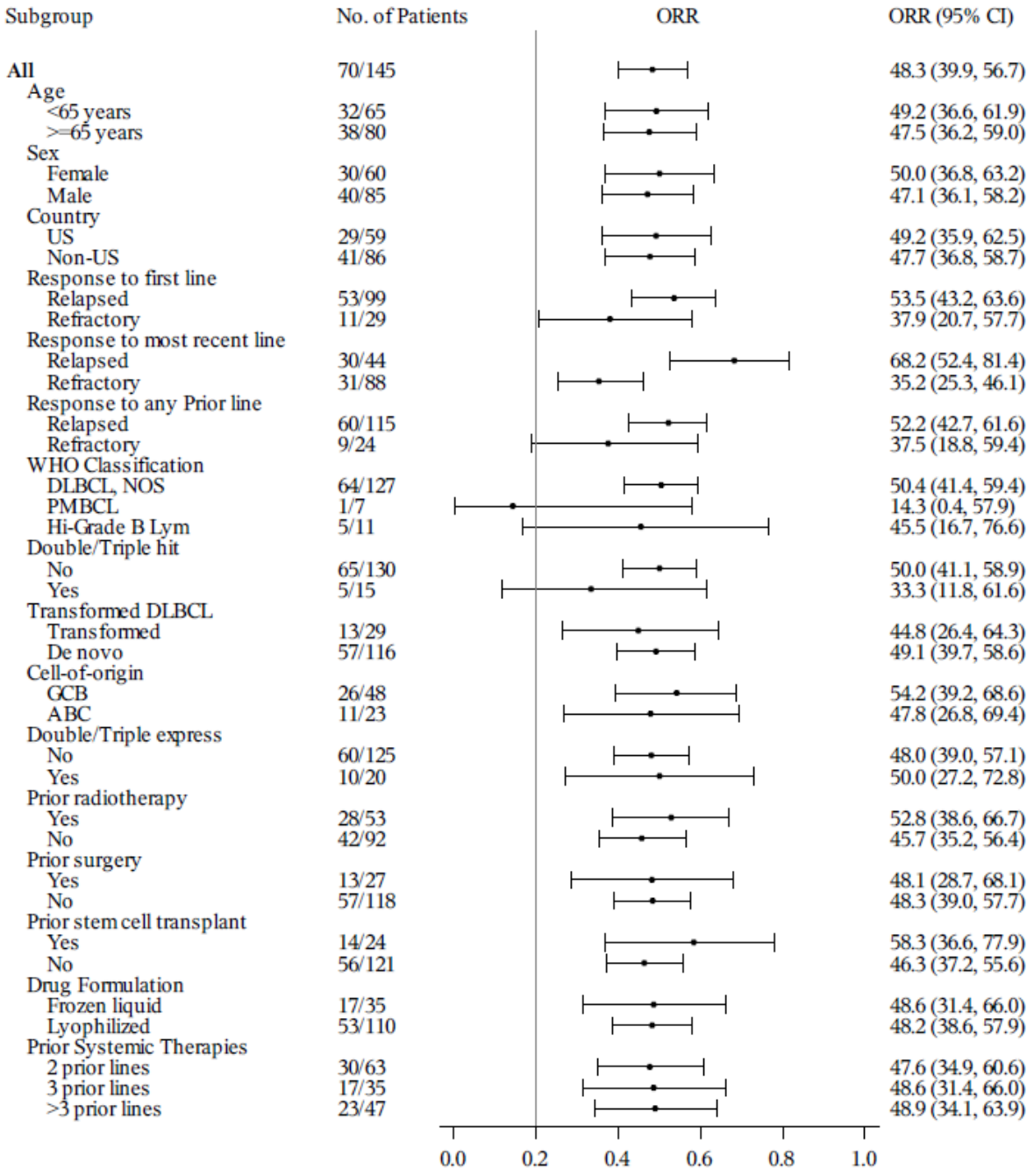
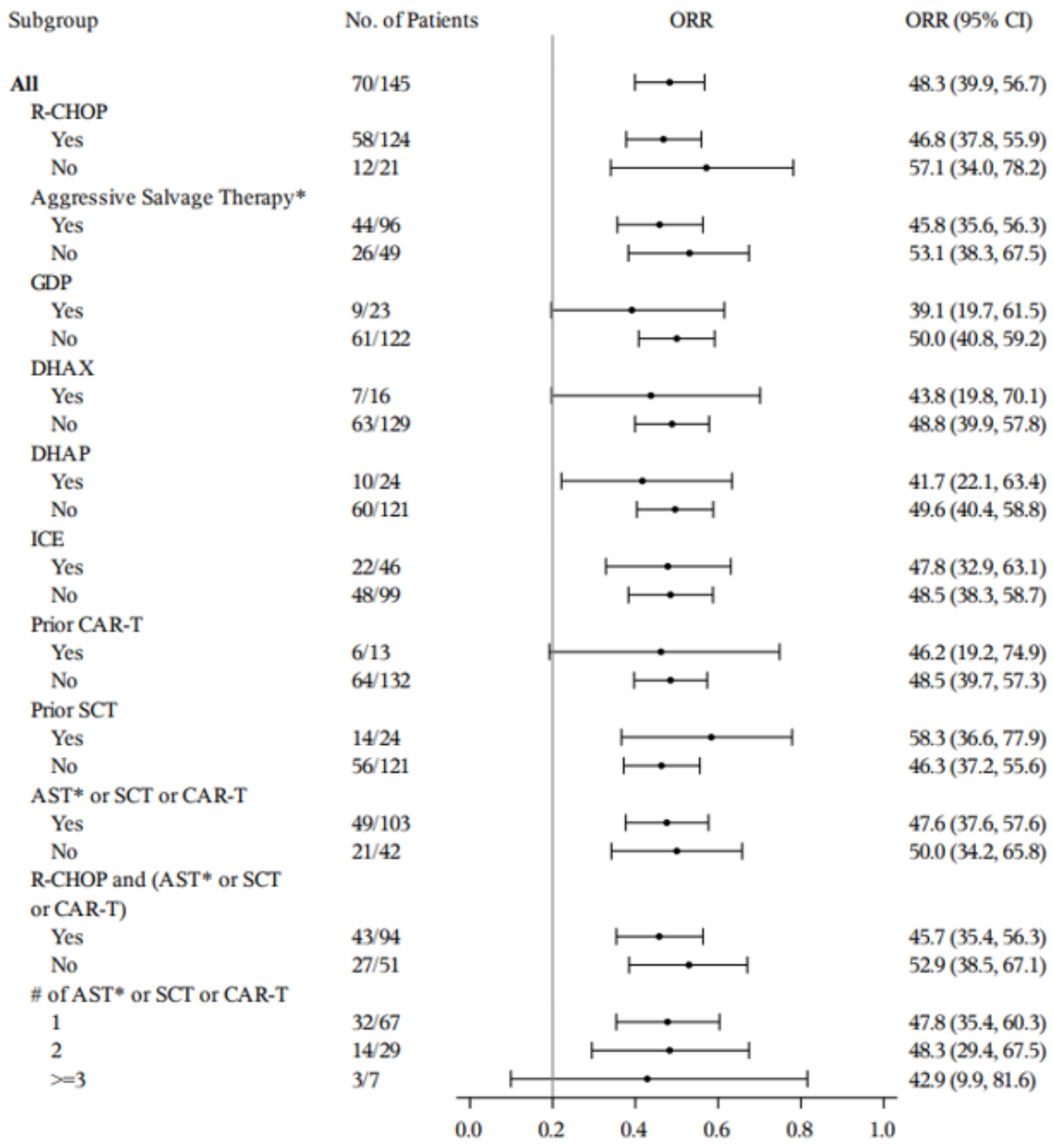


Figure 28. **Ad Hoc: ADCT-402-201 Forest Plot of Overall Response Rate by Prior Cancer Therapy (All-Treated Population)**



Source: Module 5, Section 5.3.5.2.2, Ad Hoc Figure 14.2.1.5.5
Note: * AST includes GDP, DHAX, DHAP and ICE.
AST = aggressive salvage therapy; CAR-T = chimeric antigen receptor T-cell; DHAP = cisplatin, cytarabine, dexamethasone; DHAX = dexamethasone, cytarabine, oxaliplatin; GDP = gemcitabine, dexamethasone, cisplatin; ICE = ifosfamide, carboplatin, etoposide; ORR = overall response rate; R-CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab; SCT = stem cell transplant

The ORR was 49.2% in the <65 years age group (n= 65), 45.8% in the ≥65 to <75 years age group (n= 59), and 52.4% in the ≥75 years age group (n=21). The subgroup analysis of ORR by Independent Reviewer showed no notable difference in ORR when analysed by sex, country or age, neither whether transformed disease or de novo, although small numbers of patients had transformed disease. The applicant also performed analysis of ORR in relation to prior treatment, for the 24 patients who had received prior SCT, the ORR was 58.3% and ORR was 46.2% for the 13 patients who had received prior CAR-T.

A total of 12 patients received stem cell transplantation (SCT) directly following loncastuximab tesirine therapy. Eleven patients received SCT as consolidation therapy after responding to loncastuximab tesirine These patients underwent SCT without intervening therapy. One patient went directly to allogeneic SCT after progression following loncastuximab tesirine therapy. Out of the 12 patients, 5 died at some time after transplant (2 of disease progression and 3 of other reasons).

Sixteen patients received chimeric antigen receptor T-cell (CAR-T) therapy at some time after progression following loncastuximab tesirine therapy. Out of these 16 patients, 10 died at some time after CAR-T therapy (9 of disease progression and 1 of other reasons).

In order to evaluate any potential centre effects, efficacy outcomes were compared for the largest sites vs all other sites: Overall, it is noted that efficacy data, in particular ORR, was similar between the largest sites versus all other sites.

Analysis of CD19 and efficacy

Immunophenotypic analysis of CD19 was not performed for the majority of the patients, (n=105, 72.4%). Retrospective central tumour CD19 expression data were available for the archival biopsies of 134 patients. Overall, the preliminary analyses conducted suggested no correlation between tumour CD19 expression in archival biopsies and clinical response or safety.

The 40 patients who had an assessment of CD19 were those for whom a local test was available but otherwise 135 patients had a retrospectively CD19 assessment by IHC (CD19 expression was required only for patients who previously received a CD-19-directed therapy). Regarding the 8 patients who were found to be negative for CD19, 6 showed responses (3 with PR and 3 with CR). However, 6 of these patients had a central assessment of CD19 that showed presence of CD19+ tumour cells. However, it was not possible to identify if these are the 6 patients with a response notably as the identification number for all but one patient was not found in the listings. It is acknowledged that these discrepancies may be due to several factors (difference in sensitivity of tests, tumour heterogeneity). Regarding the 135 with an archival biopsy, the expression of CD19 did not correlate with response to LT. Of these 135 patients only 59 had a biopsy obtained after the last treatment before administration of LT. Based on the results of the analysis provided by the applicant of these 59 patients whose CD-19 expression most likely represent the CD19 status at the time of LT treatment, the percentage of positive CD19 tumour cells and the H-score did not correlate with response to LT.

Overall, considering the apparent lack of correlation between CD19 level of expression and response to LT treatment based on the analysis of the 135 patients, it is acknowledged that a testing for CD19 expression is not required.

- **Summary of main efficacy results**

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

Table 26 Summary of Efficacy for Trial ADCT-402-201

Title: A Phase 2 Open-Label Single-Arm Study to Evaluate the Efficacy and Safety of Loncastuximab Tesirine in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL)			
Study identifier	Protocol Number: ADCT-402-201 EudraCT Number: 2017-004288-11		
Design	Multicentre, open-label, single-arm study		
	Duration of treatment phase: Duration of Run-in phase: Duration of Extension phase:		Up to 1 year; patients benefiting clinically at 1 year could continue treatment after a case by case review with the Sponsor not applicable not applicable
Hypothesis	Exploratory		
Treatments groups	Loncastuximab tesirine descriptor>		Patients (N=145) received 150 mcg/kg loncastuximab tesirine once every 3 weeks for 2 cycles, then 75 mcg/kg once every 3 weeks for subsequent cycles in a single arm trial.
	not applicable		not applicable
Endpoints and definitions	Primary endpoint	Overall response rate (ORR)	The proportion of patients with a best overall response (BOR) of complete response (CR) or partial response (PR)
	Secondary endpoint	Duration of response (DOR)	The time from first documentation of tumour response to disease progression or death.
	Secondary endpoint	Complete Response Rate (CRR)	The percentage of treated patients with a BOR or CR.
Database lock	6 April 2020 and 01 March 2021 (Data cut-off dates)		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	All-Treated Population: All patients who received at least 1 dose of loncastuximab tesirine		

Title: A Phase 2 Open-Label Single-Arm Study to Evaluate the Efficacy and Safety of Loncastuximab Tesirine in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL)			
Study identifier	Protocol Number: ADCT-402-201 EudraCT Number: 2017-004288-11		
Descriptive statistics and estimate variability	Treatment group	All treated population 6 April 2020	All treated population 01 March 2021
	Number of subjects	145	145
	ORR N (%) 95% CI	70 (48.3) (39.9, 56.7)	70 (48.3) (39.9, 56.7)
	DOR Median months (95% CI)	10.25 (6.87, NE)	13.37 (6.87, NE)
	CRR N (%) 95% CI	35 (24.1) (17.4, 31.9)	36 24.8 (18.0, 32.7)
	PFS Median months 95% CI	4.93 (2.89, 8.31)	4.93 (2.89, 8.31)
Effect estimates per comparison	Not applicable; uncontrolled		

2.6.5.3. Clinical studies in special populations

Table 27 **Study ADCT-402-201: Summary of Age Categories of Older Patients (All-Treated Population)**

	Number (%) of Patients Age ≥65 - <75 years (N=145)	Number (%) of Patients Age ≥75 - <85 years (N=145)	Number(%)of Patients Age ≥85 years (N=145)
Study ADCT-402-201	59 (40.7)	19 (13.1)	2 (1.4)

Source: Module 5.3.5.2, Study ADCT-402-201, Section 14 - Updated Tables and Figures, 2022, t3_q121_dm_age_saf

2.6.5.4. In vitro biomarker test for patient selection for efficacy

According to Protocol Amendment 1, 05 April 2018, the exposure relationship to blood biomarkers was removed because there was no plan to perform this against the pharmacogenetic measures.

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

Not applicable

2.6.5.6. Supportive study

The ADCT-402-101 study is a first in human, phase 1 open-label, dose-escalation study (Part 1) and expansion (Part 2). It is considered a supportive study, please refer to Section 3.2 and the pharmacokinetic part.

2.6.6. Discussion on clinical efficacy

Pivotal study ADCT-402-201: is a phase 2, open-label, multicentre, single-arm study of the efficacy and safety of loncastuximab tesirine (LT) (Zynlonta) as monotherapy in patients with relapsed or refractory DLBCL. A total of 145 patients were enrolled from the US and EU, the vast majority being white. Considering the rarity and prognosis of this clinical setting, the design of the pivotal study is endorsed and its open-label nature is acceptable. Although there is no standard of care for R/R DLBCL, an RCT would have been preferred with the physicians' best choice as comparator. However, the applicant has commenced a phase 3 study as confirmatory study for a CMA application.

Patients included had all received 2 or more lines of prior systemic anticancer therapy, with R-CHOP being the most common one as first line and the majority of the patients had advanced disease, 64.1% had stage IV, and 77.2% had Stage III/IV, indicating high grade disease. The majority of patients (n= 127, 87.6%) had DLBCL NOS (according to the 2016 WHO classification) of which 25 patients (17.2%) were transformed from follicular lymphoma.

The mean age of patients from the pivotal study was 62.7 years, the majority were <65 years of age (44.8%) or ≥65 to <75 (40.7%), and 14.5% were 75 years of age or more, this is reassuring, since DLBCL typically affects older individuals. The median number of prior systemic therapy was 3.0 (range 2-7). A total of 29 patients (20.0%) had primary refractory disease, 57.9% were refractory to their most recent line of prior systemic therapy and the majority of the patients, 68.3% had relapse after

their first line of prior systemic therapy. In conclusion the prognosis was unfavourable, and the enrolled patients were aligned to the in- and exclusion criteria.

The primary endpoint ORR according to the 2014 Lugano classification is considered acceptable and clinically meaningful considering the single-arm trial and the clinical setting. Secondary endpoints, such as DOR and PFS are also endorsed. The applicant presented sensitivity analyses implementing the following censoring rules: Progressive disease (PD)/death after new anticancer therapies other than transplant are counted as events and PD/death after stem cell transplant (SCT) are censored at the last valid assessment date before the transplant. The results were consistent with those reported in the CSR.

LT is a CD19-targeted antibody, and the CD19 analysis of the tumours is therefore of interest. The majority of sites reported that a local test for CD19 was not performed. Retrospective central tumour CD19 expression data were available for the archival biopsies of 134 patients. Overall, the preliminary analyses conducted suggested no correlation between tumour CD19 expression in archival biopsies and clinical response or safety.

The supportive study ADCT-402-101, was a first-in-human Phase 1 study of LT in patients with relapsed/refractory (R/R) B-NHL. The study design involved a dose escalation part (Part 1) followed by a dose expansion part (Part 2). A total of 183 patients received at least 1 infusion of LT, at initial doses of 15 to 150, or 200 µg/kg.

Efficacy data and additional analyses

The primary endpoint, ORR by IRC was 48.3% (70/145 patients; 95% CI: 39.9, 56.7), and CR of 24.1% (35/145 patients, 95% CI:17.4, 31.9). These results are encouraging and clinical meaningful in the R/R DLBCL setting. The ORR in the study ADCT-402-101 is supportive to the pivotal study, showing an ORR of 42.3% (95% CI: 33.9, 51.1).

The median time to response (CR or PR) in the pivotal study ADCT-402-201 was 41.0 days (range: 35 to 247 days), similarly 43.0 days (range 31-323) for the supportive study ADCT-402-101, indicating that most responders had a response after 2 doses of the study drug. The median duration of response (DOR) for the responding subjects was 13.37 months (95% CI: 6.87, NE) in the pivotal study, which is considered highly clinical meaningful. For the supportive study, ADCT-402-101, the median DOR was 4.47 months (95% CI: 3.94 to 9.46). Similarly, a difference was noted between the PFS results for the pivotal and the supportive study. In study ADCT-402-201, the median PFS was 4.93 months (95% CI: 2.89, 8.31) compared with 2.83 months (95% CI: 1.91, 3.75) in the Study ADCT-402-101. Although the Study ADCT-402-101 was a dose escalation study, the difference in DOR and PFS between the pivotal and the supportive study is not understood, especially since the ORR results are similar and the patients in the two studies seem to be comparable in most other aspects. The applicant states that the numerically higher DOR, PFS, and OS in diffuse large B-cell lymphoma (DLBCL) patients treated in Study ADCT-402-201 relative to patients treated in Study ADCT-402-101 likely reflects the fact that all patients treated in Study ADCT-402-201 received the optimal dosing regimen of loncastuximab tesirine with the planned reduction after Cycle 2, which provides consistent efficacious exposure. This could be correct. No difference was noted for OS, between the two studies, the median OS for the pivotal study was 9.53 months (95% CI: 6.93, 11.47) and 7.46 months (95% CI: 5.95 to 9.79 months) for the supportive study. This is considered reassuring and of clinical importance.

Subgroup analyses of ORR were performed and showed no notable difference in ORR when analysed by sex, country or age, neither whether transformed disease or de novo. The ORR seem to be negatively affected by known unfavourable prognostic factors, such as refractory disease to first line therapy and any line of prior systemic therapy, bulky disease and double-hit/triple-hit disease, this is as would be

expected. Although reassuring, the data should be interpreted with caution due to small subgroups and the single-arm design. A total of 12 patients received stem cell transplantation (SCT) directly following loncastuximab tesirine therapy. Out of the 12 patients, 5 died at some time after transplant (2 of disease progression and 3 of other reasons). It is encouraging that LT may also be used as bridging towards SCT.

In study 201 16 patients received chimeric antigen receptor T-cell (CAR-T) therapy at some time after progression following loncastuximab tesirine therapy. Out of these 16 patients, 10 died at some time after CAR-T therapy (9 of disease progression and 1 of other reasons). Although LT may facilitate bridging to CAR-T treatment, the efficacy and safety of this treatment after LT needs further exploration.

According to the inclusion criteria, three subtypes of DLBCL from the 2016 WHO classification of lymphoid neoplasms (Swerdlow et al, Blood 2016) were to be recruited in this single-arm trial: DLBCL-NOS, HGBL and PMBCL. Baseline characteristics of the recruited patients reflect this requirement, noting the currently adopted 5th edition of the WHO classification of lymphoid neoplasms (Alaggio et al, Leukemia 2022) outlines that DLBCL NOS, HGBL and PMBCL are all lymphoma entities within the LBCL group. However, evidence of efficacy of Zynlonta in the PMBCL subtype in the pivotal ADCT-402-201 (response in 1 out of 7 patients) is insufficient to guarantee its inclusion in the therapeutic indication. Furthermore, clarification that Zynlonta is to be given as monotherapy was required. These observations have resulted in the modification of the initially proposed indication as follows:

"Zynlonta as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy".

2.6.7. Conclusions on the clinical efficacy

The efficacy of loncastuximab tesirine in relapsed or refractory DLBCL patients having received ≥ 2 prior lines of systemic therapy is considered promising and clinical meaningful in a clinical setting with no standard of care therapy and a dismal prognosis.

In the context of a CMA, the applicant needs to conduct a confirmatory study within a reasonable timeframe to corroborate the efficacy and safety of Zynlonta. The applicant has initiated study ADCT-402-311, which is a phase 3, controlled, randomised study of loncastuximab tesirine combined with the CD-20-targeting monoclonal antibody rituximab (Lonca-R) versus standard immunochemotherapy (rituximab / gemcitabine / oxaliplatin) in patients with R/R DLBCL.

2.6.8. Clinical safety

The applicant has submitted safety data from 5 clinical studies with loncastuximab tesirine with the data cutoff date of 01 Mar 2021. The primary studies for safety of monotherapy with loncastuximab tesirine in patients with relapsed or refractory DLBCL are the pivotal Study ADCT-402-201 and the first-in-human Study ADCT-402-101, hence, safety data from these studies will be the main focus of the assessment of the safety profile of loncastuximab tesirine monotherapy.

ADCT-402-201 is an ongoing Phase 2, open-label, single-arm study of the efficacy and safety of loncastuximab tesirine in patients with relapsed or refractory DLBCL. The study has completed enrolment and 145 patients were enrolled at 16 centres in the US, 6 centres in the United Kingdom (UK), 5 centres in Italy and 1 centre in Switzerland. At the time of data cutoff for this submission, 145 patients had received at least 1 dose of loncastuximab tesirine, all patients had treatment withdrawn and 108 patients had discontinued from the study. There were 37 patients in follow-up. The

recommended dose of loncastuximab tesirine of 150 µg/kg every 3 weeks for the first two cycles followed by 75 µg/kg every 3 weeks for subsequent cycles was used in this study.

ADCT-402-101 was a completed Phase 1, open-label, dose-escalation (Part 1) and expansion (Part 2) study of the safety and tolerability of 183 patients with relapsed or refractory B-cell non-Hodgkin lymphoma (B-NHL) conducted at 8 centres in the US, 2 centres in the UK and 1 centre in Italy. The dosing in this study ranging from initial doses of 15 to 200 µg/kg was used to establish the recommended dosing regimen.

Table 28. Overview of Studies and Patients Included in Integrated Analyses

Study and Treatment	Population and Numbers of Patients, N	Numbers of Patients			Loncastuximab Tesirine Monotherapy, 150 µg/kg DLBCL Population N
		Level 1	Level 2	Level 3	
		Loncastuximab Tesirine Monotherapy DLBCL Population N	Loncastuximab Tesirine Monotherapy Population N	Loncastuximab Tesirine All Treated Population N	
ADCT-402-201 loncastuximab tesirine alone	DLBCL, 145	145	145	145	145
ADCT-402-101 loncastuximab tesirine alone	All B-NHL, 183	139	183	183	70
ADCT-402-102 loncastuximab tesirine alone	All B-ALL, 35	NA	35	35	NA
ADCT-402-103 loncastuximab tesirine + ibrutinib	All B-NHL, 92[a]	NA	NA	92[a]	NA
ADCT-402-104 loncastuximab tesirine + durvalumab	All B-NHL, 13	NA	NA	13	NA
All studies combined	468	284	363	468	215

Source: Statistical Analysis Plan, Module 5, Section 5.3.5.3; ISS Table 3.2.1

[a] Still recruiting

B-ALL = B-cell acute lymphoblastic leukaemia; B-NHL = B-cell non-Hodgkin lymphoma; DLBCL = diffuse large B-cell lymphoma; NA = not applicable

2.6.8.1. Patient exposure

Table 29. Study Drug Administration and Extent of Exposure-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

			150µg/kg				
	≤90 µg/kg (N=10)	**120 µg/kg (N=32)**	**s101 (N=70)**	**s201 (N=145)**	**Subtotal (N=215)**	**200 µg/kg (N=27)**	**All Doses (N=284)**
Total number of cycles dose administered							
n	10	32	70	145	215	27	284
Mean	3.8	3.3	3.3	4.6	4.2	2.1	3.9
std	3.79	1.86	2.31	4.26	3.78	1.12	3.48
Median	2.0	3.0	3.0	3.0	3.0	2.0	3.0
Min, Max	1, 13	1, 9	1, 12	1, 26	1, 26	1, 5	1, 26
Duration of treatment (days)							
n	10	32	70	145	215	27	284
Mean	63.0	57.5	62.0	85.7	78.0	45.1	72.0
std	83.84	52.49	62.54	100.36	90.35	53.00	84.13
Median	22.0	42.0	44.0	45.0	45.0	22.0	43.0
Min, Max	1, 253	1, 238	1, 256	1, 569	1, 569	1, 177	1, 569
Total dose administered (µg*1000)							
n	10	32	70	145	215	27	284
Mean	15.66	30.88	32.68	34.81	34.12	30.70	32.78
std	17.510	18.488	18.552	21.871	20.829	15.985	20.280
Median	5.93	23.40	28.43	30.00	30.00	28.00	28.43
Min, Max	2.0, 45.5	5.8, 71.8	7.5, 88.5	7.5, 112.5	7.5, 112.5	9.7, 71.1	2.0, 112.5
Total weight adjusted dose (µg/kg)							
n	10	32	70	145	215	27	284
Mean	185.10	386.82	427.07	462.73	451.12	345.19	424.44
std	202.295	216.959	258.746	318.712	300.363	151.352	283.033
Median	89.27	293.95	361.37	375.68	375.51	317.42	371.40
Min, Max	29.2, 617.2	118.5, 1125.3	129.0, 1646.2	122.4, 2061.1	122.4, 2061.1	196.0, 600.0	29.2, 2061.1
Average dose per cycle (µg*1000)							
n	10	32	70	145	215	27	284
Mean	3.75	9.31	10.72	9.24	9.72	15.59	10.02
std	2.845	2.531	3.336	2.798	3.056	5.640	3.927
Median	3.25	9.00	10.50	9.08	9.40	15.75	9.50
Min, Max	1.0, 10.4	5.1, 16.4	5.1, 22.2	3.0, 17.4	3.0, 22.2	7.0, 32.1	1.0, 32.1
Average weight adjusted dose per cycle (µg/kg)							
n	10	32	70	145	215	27	284
Mean	46.56	117.73	136.06	119.95	125.20	175.42	126.36
std	27.076	7.690	19.791	26.517	25.627	34.229	33.138

			150µg/kg				
	≤90 µg/kg (N=10)	120 µg/kg (N=32)	s101 (N=70)	s201 (N=145)	Subtotal (N=215)	200 µg/kg (N=27)	All Doses (N=284)
Median	42.76	119.87	147.25	113.50	125.97	197.61	125.00
Min, Max	14.6, 94.9	95.7, 125.2	84.8, 156.5	49.2, 160.6	49.2, 160.6	105.8, 203.3	14.6, 203.3

Source: ISS Table 1.2.1

DLBCL = diffuse large B-cell lymphoma; max = maximum; min = minimum; std = standard deviation; s101 = Study ADCT-402-101; s201 = Study ADCT-402-201

At the DCO of 1 March 2021, among the 215 patients who received 150 µg/kg loncastuximab tesirine monotherapy, the median treatment duration was 45.0 days (range: 1 to 569) and the median number of treatment cycles administered was 3.0 cycles (range: 1 to 26). The median total weight-adjusted dose administered was 375.51 µg/kg (range: 122.4 to 2,061.1), while the median average weight-adjusted dose per cycle was 125.97 µg/kg (range: 49.2 to 160.6).

The applicant finds that the 215 patients with diffuse large B-cell lymphoma (DLBCL) treated with an initial loncastuximab tesirine dose of 150 µg/kg are the most relevant to determine the safety profile for the submitted indication, with the remainder of the patients in the safety database providing supportive information.

Table 30. Number (%) of Diffuse Large B-cell Lymphoma Patients Who Received Loncastuximab Tesirine Monotherapy Treatment for ≥6 months and ≥12 months on 150 µg/kg Dose Level

Treatment Duration, n (%)	150 µg/kg (N = 215)
Treatment ≥6 months	21 (9.8)
Treatment ≥12 months	4 (1.9)

DLBCL = diffuse large B-cell lymphoma.
Source: Module 5.3.5.3, Integrated Summary of Safety - Updated Tables and Figures, 2022 t8_q147_ex_ema_p1.rtf

The applicant has provided the requested fractions of patients treated for up to 6 months and up to 12 months and only 21 (9.8%) were treated for ≥6 months while 4 patients were treated for ≥12 months (Table above).

2.6.8.2. Adverse events

Table 31. Overall Summary of TEAEs-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

			150 µg/kg				
Treatment-emergent adverse event	≤90 µg/kg (N=10)	120 µg/kg (N=32)	s101 (N=70)	s201 (N=145)	Subtotal (N=215)	200 µg/kg (N=27)	All Doses (N=284)
Number of TEAEs	93	453	1061	1780	2841	458	3845
Patients with any TEAE	10 (100)	32 (100)	69 (98.6)	143 (98.6)	212 (98.6)	27 (100)	281 (98.9)

Patients with any Grade 3 or higher TEAE	4 (40.0)	23 (71.9)	53 (75.7)	107 (73.8)	160 (74.4)	23 (85.2)	210 (73.9)
Patients with any TEAE related to ADCT-402	7 (70.0)	29 (90.6)	58 (82.9)	118 (81.4)	176 (81.9)	23 (85.2)	235 (82.7)
Patients with any TEAE leading to ADCT-402 dose delay or reduction	1 (10.0)	14 (43.8)	27 (38.6)	75 (51.7)	102 (47.4)	7 (25.9)	124 (43.7)
Patients with any TEAE leading to ADCT-402 withdrawal	1 (10.0)	5 (15.6)	8 (11.4)	36 (24.8)	44 (20.5)	4 (14.8)	54 (19.0)
Patients with any serious TEAE	2 (20.0)	12 (37.5)	30 (42.9)	57 (39.3)	87 (40.5)	6 (22.2)	107 (37.7)
Patients with any TEAE with fatal outcome	0	3 (9.4)	11 (15.7)	8 (5.5)	19 (8.8)	0	22 (7.7)

Source: ISS Table 1.3.1
Related TEAEs include TEAEs that were considered by the Investigator to be possibly or probably related to the study drug or TEAEs with a missing relationship on the case report form. Adverse events were graded using CTCAE v4.0. For each category (except for Number of TEAEs), patients were included only once, even if they experienced multiple events in that category.
ADCT-402 = loncastuximab tesirine; CTCAE = Common Terminology Criteria for Adverse Events; DLBCL = diffuse large B-cell lymphoma; s101 = Study ADCT-402-101; s201 = Study ADCT-402-201; TEAE = treatment-emergent adverse event

Table 32. Most Common (≥10% of Patients in All Doses Combined) TEAEs by SOC-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

System Organ Class	≤90 µg/kg (N=10)	120 µg/kg (N=32)	150 µg/kg s101 (N=70)	150 µg/kg s201 (N=145)	150 µg/kg Subtotal (N=215)	200 µg/kg (N=27)	All Doses (N=284)
Patients with any TEAE	10 (100.0)	32 (100.0)	69 (98.6)	143 (98.6)	212 (98.6)	27 (100.0)	281 (98.9)
General disorders and administration site conditions	4 (40.0)	27 (84.4)	44 (62.9)	96 (66.2)	140 (65.1)	20 (74.1)	191 (67.3)
Gastrointestinal disorders	4 (40.0)	23 (71.9)	43 (61.4)	77 (53.1)	120 (55.8)	20 (74.1)	167 (58.8)
Investigations	3 (30.0)	20 (62.5)	34 (48.6)	83 (57.2)	117 (54.4)	21 (77.8)	161 (56.7)
Blood and lymphatic system disorders	3 (30.0)	12 (37.5)	30 (42.9)	83 (57.2)	113 (52.6)	17 (63.0)	145 (51.1)
Skin and subcutaneous tissue disorders	5 (50.0)	18 (56.3)	38 (54.3)	68 (46.9)	106 (49.3)	14 (51.9)	143 (50.4)
Metabolism and nutrition disorders	3 (30.0)	10 (31.3)	34 (48.6)	77 (53.1)	111 (51.6)	17 (63.0)	141 (49.6)
Respiratory, thoracic and mediastinal disorders	2 (20.0)	15 (46.9)	35 (50.0)	61 (42.1)	96 (44.7)	13 (48.1)	126 (44.4)
Musculoskeletal and connective tissue disorders	2 (20.0)	15 (46.9)	28 (40.0)	46 (31.7)	74 (34.4)	11 (40.7)	102 (35.9)
Infections and infestations	3 (30.0)	11 (34.4)	25 (35.7)	48 (33.1)	73 (34.0)	6 (22.2)	93 (32.7)
Nervous system disorders	3 (30.0)	16 (50.0)	23 (32.9)	41 (28.3)	64 (29.8)	6 (22.2)	89 (31.3)
Vascular disorders	2 (20.0)	8 (25.0)	12 (17.1)	28 (19.3)	40 (18.6)	6 (22.2)	56 (19.7)
Psychiatric disorders	1 (10.0)	3 (9.4)	10 (14.3)	28 (19.3)	38 (17.7)	6 (22.2)	48 (16.9)
Eye disorders	1 (10.0)	4 (12.5)	17 (24.3)	20 (13.8)	37 (17.2)	2 (7.4)	44 (15.5)
Injury, poisoning and procedural complications	2 (20.0)	4 (12.5)	14 (20.0)	17 (11.7)	31 (14.4)	2 (7.4)	39 (13.7)
Cardiac disorders	2 (20.0)	6 (18.8)	9 (12.9)	19 (13.1)	28 (13.0)	3 (11.1)	39 (13.7)

Source: ISS Table 1.3.6

Adverse events were coded using MedDRA version 22.0. For each SOC, patients were included only once.

DLBCL = diffuse large B-cell lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; s101 = Study ADCT-402-101; s201 = Study ADCT-402-201; SOC = system organ class; TEAE = treatment-emergent adverse event

Table 33. Most Common (≥10% of Patients in All Doses Combined) TEAEs by Preferred Term-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

Preferred Term	≤90 µg/kg (N=10)	120 µg/kg (N=32)	150 µg/kg s101 (N=70)	150 µg/kg s201 (N=145)	150 µg/kg Subtotal (N=215)	200 µg/kg (N=27)	All Doses (N=284)
Patients with any TEAE	10 (100.0)	32 (100.0)	69 (98.6)	143 (98.6)	212 (98.6)	27 (100.0)	281 (98.9)
Fatigue	4 (40.0)	19 (59.4)	25 (35.7)	40 (27.6)	65 (30.2)	11 (40.7)	99 (34.9)
Gamma-glutamyltransferase increased	2 (20.0)	10 (31.3)	16 (22.9)	61 (42.1)	77 (35.8)	10 (37.0)	99 (34.9)
Neutropenia	1 (10.0)	5 (15.6)	17 (24.3)	58 (40.0)	75 (34.9)	9 (33.3)	90 (31.7)
Anaemia	3 (30.0)	5 (15.6)	24 (34.3)	38 (26.2)	62 (28.8)	10 (37.0)	80 (28.2)
Nausea	2 (20.0)	7 (21.9)	23 (32.9)	34 (23.4)	57 (26.5)	11 (40.7)	77 (27.1)
Thrombocytopenia	1 (10.0)	8 (25.0)	13 (18.6)	48 (33.1)	61 (28.4)	7 (25.9)	77 (27.1)
Oedema peripheral	1 (10.0)	9 (28.1)	21 (30.0)	29 (20.0)	50 (23.3)	9 (33.3)	69 (24.3)
Cough	0	5 (15.6)	13 (18.6)	32 (22.1)	45 (20.9)	6 (22.2)	56 (19.7)
Rash	1 (10.0)	5 (15.6)	24 (34.3)	19 (13.1)	43 (20.0)	5 (18.5)	54 (19.0)
Blood alkaline phosphatase increased	1 (10.0)	4 (12.5)	12 (17.1)	29 (20.0)	41 (19.1)	6 (22.2)	52 (18.3)
Pyrexia	1 (10.0)	6 (18.8)	8 (11.4)	28 (19.3)	36 (16.7)	6 (22.2)	49 (17.3)
Constipation	0	10 (31.3)	18 (25.7)	17 (11.7)	35 (16.3)	2 (7.4)	47 (16.5)

Decreased appetite	2 (20.0)	5 (15.6)	9 (12.9)	22 (15.2)	31 (14.4)	9 (33.3)	47 (16.5)
Dyspnoea	0	7 (21.9)	17 (24.3)	17 (11.7)	34 (15.8)	6 (22.2)	47 (16.5)
Aspartate aminotransferase increased	0	3 (9.4)	11 (15.7)	23 (15.9)	34 (15.8)	9 (33.3)	46 (16.2)
Diarrhoea	2 (20.0)	2 (6.3)	13 (18.6)	25 (17.2)	38 (17.7)	4 (14.8)	46 (16.2)
Alanine aminotransferase increased	0	4 (12.5)	12 (17.1)	23 (15.9)	35 (16.3)	5 (18.5)	44 (15.5)
Vomiting	1 (10.0)	5 (15.6)	14 (20.0)	19 (13.1)	33 (15.3)	5 (18.5)	44 (15.5)
Pleural effusion	1 (10.0)	6 (18.8)	13 (18.6)	16 (11.1)	29 (13.5)	6 (22.2)	42 (14.8)
Hypokalaemia	1 (10.0)	2 (6.3)	14 (20.0)	22 (15.2))	36 (16.7)	2 (7.4)	41 (14.4)
Abdominal pain	1 (10.0)	7 (21.9)	8 (11.4)	17 (11.7)	25 (11.6)	6 (22.2)	39 (13.7)
Pruritus	1 (10.0)	4 (12.5)	6 (8.6)	19 (13.1)	25 (11.6)	4 (14.8)	34 (12.0)
Hypomagnesaemia	0	1 (3.1)	8 (11.4)	20 (13.8)	28 (13.0)	0	29 (10.2)
Hypophosphataemia	1 (10.0)	2 (6.3)	1 (1.4)	23 (15.9)	24 (11.2)	2 (7.4)	29 (10.2)

Source: ISS Table 1.3.3

The 10% cutoff was based on All Doses. Adverse events were coded using MedDRA version 22.0. For each preferred term, patients were included only once.

DLBCL = diffuse large B-cell lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; s101 = Study ADCT-402-101; s201 = Study ADCT-402-201; TEAE = treatment-emergent adverse event

Grade 3-4 adverse events

Table 34. Patients With Any TEAE Grade 3 or Higher and Any Treatment-related TEAE Grade 3 or Higher by Maximum CTCAE Grade-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

			150 µg/kg				
Maximum CTCAE Grade	≤90 µg/kg (N=10)	120 µg/kg (N=32)	s101 (N=70)	s201 (N=145)	Subtotal (N=215)	200 µg/kg (N=27)	All Doses (N=284)
Patients with any TEAE of Grade ≥ 3							
Grade 3	1 (10.0)	11 (34.4)	22 (31.4)	62 (42.8)	84 (39.1)	12 (44.4)	108 (38.0)
Grade 4	3 (30.0)	9 (28.1)	20 (28.6)	37 (25.5)	57 (26.5)	11 (40.7)	80 (28.2)
Grade 5	0	3 (9.4)	11 (15.7)	8 (5.5)	19 (8.8)	0	22 (7.7)
All Grades	4 (40.0)	23 (71.9)	53 (75.7)	107 (73.8)	160 (74.4)	23 (85.2)	210 (73.9)
Patients with any Related TEAE of Grade ≥ 3							
Grade 3	1 (10.0)	10 (31.3)	16 (22.9)	45 (31.0)	61 (28.4)	8 (29.6)	80 (28.2)
Grade 4	1 (10.0)	9 (28.1)	18 (25.7)	30 (20.7)	48 (22.3)	9 (33.3)	67 (23.6)
Grade 5	0	0	1 (1.4)	0	1 (0.5)	0	1 (0.4)
All Grades	2 (20.0)	19 (59.4)	35 (50.0)	75 (51.7)	110 (51.2)	17 (63.0)	148 (52.1)

Source: ISS Table 1.3.9 and Table 1.3.22

Adverse events were graded using CTCAE v4.0.
Related TEAEs include TEAEs that were considered by the Investigator to be possibly or probably related to the study drug or TEAEs with a missing relationship on the case report form.

CTCAE = Common Terminology Criteria for Adverse Events; DLBCL = diffuse large B-cell lymphoma; s101 = Study ADCT-402-101; s201 = Study ADCT-402-201; TEAE = treatment-emergent adverse event

Almost all of the patients in the relevant safety pool (n=215) had an AE (98.6%), and the most common were: GGT increased (35.8%), neutropenia (34.9%), fatigue (30.2%), anaemia (28.8%), thrombocytopenia (28.4%), nausea (26.5%), oedema peripheral (23.3%), cough (20.9%), rash (20.0%), blood alkaline phosphatase increased (19.1%), diarrhoea (17.7%), pyrexia and hypokalaemia (16.7% each), alanine aminotransferase (ALT) increased and constipation (16.3% each), dyspnoea and aspartate aminotransferase (AST) increased (15.8% each), vomiting (15.3%), decreased appetite (14.4%), pleural effusion (13.5%), hypomagnesaemia (13.0%), abdominal pain and pruritus (11.6% each), and hypophosphataemia (11.2%).

Grade 3 or higher AEs were also very common (74.4%), and those often reported were (grade 3 and >grade 3): neutropenia (24.2% and 20.0%), GGT increased (17.2% and 13.5%), thrombocytopenia (15.8% and 9.8%), anaemia (11.6% and 6.5%), and neutrophil count decreased (3.3% and 2.8%).

It is noted that haematological toxicities are common, also of high grade, and this is further assessed under Adverse events of special interest (AESI's).

Clinical GI toxicities such as nausea, diarrhea, constipation, vomiting, decreased appetite and abdominal pain were rather commonly observed and this is concerning, as they may affect the patient's general condition and lead to weight loss and/or other detrimental effects to the prognosis. However, of these only a fraction of the AEs of nausea (26.5%) were assessed to be treatment related (16.7%), so the remaining AEs could be considered to be due to the underlying disease of DLBCL, which is plausible. However, it is noted that symptoms that may be caused by infusion-related reactions were reported with LT, such as rash and nausea, although no infusion-related reactions were reported in the dossier or the SmPC for LT.

Treatment-related AEs (ADRs)

Table 35. Overall Summary of Treatment-related TEAEs-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

			150 µg/kg				
Related treatment-emergent adverse event	**≤90 µg/kg (N=10)**	**120 µg/kg (N=32)**	**s101 (N=70)**	**s201 (N=145)**	**Subtotal (N=215)**	**200 µg/kg (N=27)**	**All Doses (N=284)**
Number of related TEAEs	48	273	491	858	1349	229	1899
Patients with any related TEAE	7 (70.0)	29 (90.6)	58 (82.9)	118 (81.4)	176 (81.9)	23 (85.2)	235 (82.7)
Patients with any Grade 3 or higher related TEAE	2 (20.0)	19 (59.4)	35 (50.0)	75 (51.7)	110 (51.2)	17 (63.0)	148 (52.1)
Patients with any related TEAE leading to ADCT-402 dose delay or reduction	1 (10.0)	12 (37.5)	21 (30.0)	63 (43.4)	84 (39.1)	6 (22.2)	103 (36.3)
Patients with any related TEAE leading to ADCT-402 withdrawal	1 (10.0)	5 (15.6)	7 (10.0)	27 (18.6)	34 (15.8)	4 (14.8)	44 (15.5)
Patients with any related serious TEAE	1 (10.0)	3 (9.4)	8 (11.4)	22 (15.2)	30 (14.0)	1 (3.7)	35 (12.3)
Patients with any related TEAE with fatal outcome	0	0	1 (1.4)	0	1 (0.5)	0	1 (0.4)

Source: ISS Table 1.3.1.0

Related TEAEs include TEAEs that were considered by the Investigator to be possibly or probably related to the study drug or TEAEs with a missing relationship on the case report form. Adverse events were graded using CTCAE v4.0. For each category (except for Number of TEAEs), patients were included only once, even if they experienced multiple events in that category.

ADCT-402 = loncastuximab tesirine; CTCAE = Common Terminology Criteria for Adverse Events; DLBCL = diffuse large B-cell lymphoma; s101 = Study ADCT-402-101; s201 = Study ADCT-402-201; TEAE = treatment-emergent adverse event

Table 36. Most Common (≥10% of Patients in All Doses Combined) Treatment-related TEAEs by Preferred Term-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

Preferred Term	≤90 µg/kg (N=10)	120 µg/kg (N=32)	150 µg/kg s101 (N=70)	150 µg/kg s201 (N=145)	150 µg/kg Subtotal (N=215)	200 µg/kg (N=27)	All Doses (N=284)
Patients with any Related TEAE	7 (70.0)	29 (90.6)	58 (82.9)	118 (81.4)	176 (81.9)	23 (85.2)	235 (82.7)
Gamma-glutamyltransferase increased	2 (20.0)	10 (31.3)	10 (14.3)	52 (35.9)	62 (28.8)	9 (33.3)	83 (29.2)
Fatigue	3 (30.0)	15 (46.9)	17 (24.3)	28 (19.3)	45 (20.9)	10 (37.0)	73 (25.7)
Neutropenia	1 (10.0)	5 (15.6)	14 (20.0)	42 (29.0)	56 (26.0)	7 (25.9)	69 (24.3)
Rash	0	5 (15.6)	24 (34.3)	18 (12.4)	42 (19.5)	4 (14.8)	51 (18.0)
Oedema peripheral	1 (10.0)	9 (28.1)	16 (22.9)	20 (13.8)	36 (16.7)	4 (14.8)	50 (17.6)
Thrombocytopenia	1 (10.0)	7 (21.9)	9 (12.9)	26 (17.9)	35 (16.3)	5 (18.5)	48 (16.9)
Nausea	1 (10.0)	2 (6.3)	12 (17.1)	24 (16.6)	36 (16.7)	8 (29.6)	47 (16.5)
Blood alkaline phosphatase increased	1 (10.0)	4 (12.5)	5 (7.1)	27 (18.6)	32 (14.9)	5 (18.5)	42 (14.8)
Anaemia	2 (20.0)	4 (12.5)	10 (14.3)	19 (13.1)	29 (13.5)	6 (22.2)	41 (14.4)
Pleural effusion	1 (10.0)	6 (18.8)	11 (15.7)	13 (9.0)	24 (11.2)	6 (22.2)	37 (13.0)
Aspartate aminotransferase increased	0	3 (9.4)	6 (8.6)	19 (13.1)	25 (11.6)	7 (25.9)	35 (12.3)
Alanine aminotransferase increased	0	4 (12.5)	7 (10.0)	17 (11.7)	24 (11.2)	3 (11.1)	31 (10.9)

Source: ISS Table 1.3.17

Related TEAEs include TEAEs that were considered by the Investigator to be possibly or probably related to the study drug or TEAEs with a missing relationship on the case report form. Adverse events were coded using MedDRA version 22.0. For each preferred term, patients were included only once.

DLBCL = diffuse large B-cell lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; s101 = Study ADCT-402-101; s201 = Study ADCT-402-201; TEAE = treatment-emergent adverse event

Table 37. Patients with Any TEAE and Any Treatment-related TEAE by Maximum CTCAE Grade-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

			150 µg/kg				
Maximum CTCAE Grade	≤90 µg/kg (N=10)	120 µg/kg (N=32)	s101 (N=70)	s201 (N=145)	Subtotal (N=215)	200 µg/kg (N=27)	All Doses (N=284)
Patient with any TEAE							
Grade 1	5 (50.0)	5 (15.6)	4 (5.7)	7 (4.8)	11 (5.1)	1 (3.7)	22 (7.7)
Grade 2	1 (10.0)	4 (12.5)	12 (17.1)	29 (20.0)	41 (19.1)	3 (11.1)	49 (17.3)
Grade 3	1 (10.0)	11 (34.4)	22 (31.4)	62 (42.8)	84 (39.1)	12 (44.4)	108 (38.0)
Grade 4	3 (30.0)	9 (28.1)	20 (28.6)	37 (25.5)	57 (26.5)	11 (40.7)	80 (28.2)
Grade 5	0	3 (9.4)	11 (15.7)	8 (5.5)	19 (8.8)	0	22 (7.7)
Missing	0	0	0	0	0	0	0
All Grades	10 (100)	32 (100)	69 (98.6)	143 (98.6)	212 (98.6)	27 (100)	281 (98.9)
Patient with any Related TEAE							
Grade 1	5 (50.0)	5 (15.6)	5 (7.1)	16 (11.0)	21 (9.8)	0	31 (10.9)
Grade 2	0	5 (15.6)	18 (25.7)	27 (18.6)	45 (20.9)	6 (22.2)	56 (19.7)
Grade 3	1 (10.0)	10 (31.3)	16 (22.9)	45 (31.0)	61 (28.4)	8 (29.6)	80 (28.2)
Grade 4	1 (10.0)	9 (28.1)	18 (25.7)	30 (20.7)	48 (22.3)	9 (33.3)	67 (23.6)
Grade 5	0	0	1 (1.4)	0	1 (0.5)	0	1 (0.4)
Missing	0	0	0	0	0	0	0
All Grades	7 (70.0)	29 (90.6)	58 (82.9)	118 (81.4)	176 (81.9)	23 (85.2)	235 (82.7)

Source: ISS Tables 1.3.8 and 1.3.21

Adverse events were graded using CTCAE v4.0.

Related TEAEs include TEAEs that were considered by the Investigator to be possibly or probably related to the study drug or TEAEs with a missing relationship on the case report form.

CTCAE = Common Terminology Criteria for Adverse Events; DLBCL = diffuse large B-cell lymphoma; s101 = Study ADCT-402-101; s201 = Study ADCT-402-201; TEAE = treatment-emergent adverse event

Table 38. Most Common (≥5% of Patients in All Doses Combined) TEAEs Grade 3 and Higher by Preferred Term-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

			150 µg/kg				
Preferred Term	≤90 µg/kg (N=10)	120 µg/kg (N=32)	s101 (N=70)	s201 (N=145)	Subtotal (N=215)	200 µg/kg (N=27)	All Doses (N=284)
Patients with any TEAE of Grade ≥ 3	4 (40.0)	23 (71.9)	53 (75.7)	107 (73.8)	160 (74.4)	23 (85.2)	210 (73.9)
Neutropenia	1 (10.0)	4 (12.5)	14 (20.0)	38 (26.2)	52 (24.2)	6 (22.2)	63 (22.2)
Gamma-glutamyltransferase increased	1 (10.0)	6 (18.8)	12 (17.1)	25 (17.2)	37 (17.2)	6 (22.2)	50 (17.6)
Thrombocytopenia	1 (10.0)	5 (15.6)	8 (11.4)	26 (17.9)	34 (15.8)	4 (14.8)	44 (15.5)
Anaemia	2 (20.0)	2 (6.3)	10 (14.3)	15 (10.3)	25 (11.6)	2 (7.4)	31 (10.9)
Neutrophil count decreased	1 (10.0)	4 (12.5)	7 (10.0)	0	7 (3.3)	6 (22.2)	18 (6.3)

Source: ISS Table 1.3.5

The 5% cutoff was based on All Doses. Adverse events were coded using MedDRA version 22.0 and graded using CTCAE v4.0. For each preferred term, patients were included only once.

CTCAE = Common Terminology Criteria for Adverse Events; DLBCL = diffuse large B-cell lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; s101 = Study ADCT-402-101; s201 = Study ADCT-402-201; TEAE = treatment-emergent adverse event

The majority of patients had a treatment-related AE (ADR) i.e. 81.9%, of which 51.2% had a grade 3 or higher ADR. The most common ADRs of all grades were GGT increased (28.8%), neutropenia (26.0%), fatigue (20.9%), rash (19.5%), oedema peripheral and nausea (16.7% each),

thrombocytopenia (16.3%), blood alkaline phosphatase increased (14.9%), anaemia (13.5%), AST increased (11.6%) and pleural effusion and ALT increased (11.2% each).

The most frequently observed grade 3 or higher ADRs were neutropenia (24.2%), GGT increased (17.2%), thrombocytopenia (15.8%), anaemia (11.6%) and neutrophil count decreased (3.3%).

The safety profile is considered partly due to adverse drug effects, especially the increased GGT and peripheral oedema and pleural effusions. However, the haematological toxicity can also be related to late effects of prior treatments in this heavily pre-treated study population.

It is noted that neutropenia was very common (34.9%) and grade 3 or higher was observed in 24.2% of the patients, while only 3.3% had febrile neutropenia. The applicant has clarified that grade 3 and higher neutropenia was managed by holding loncastuximab tesirine therapy until the patient recovered to Grade 2 or lower. In the safety data base (n=215 patients), 33.5% of patients received at least 1 dose of a neutrophil growth factor (prophylactically to 15.3% of patients and as treatment to 26.0% of patients). Only 1 (0.5%) patient discontinued LT due to neutropenia.

Adverse events of special interest

The 5 AE groups of special interest were oedema or effusion, fatigue, LFT, pain, and skin reactions and nail disorders. Three AE groups of particular interest (oedema or effusion, LFT, and skin reactions and nail disorders) were identified based on the AE profiles of other PBD-based therapies reported in the literature and early clinical data.

Table 39. Most Common (≥10% of Patients in All Doses Combined) Selected TEAEs by Grouped AEs of Particular Interest and Preferred Term-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

			150 µg/kg				
AE Group Preferred Term	≤90 µg/kg (N=10)	120 µg/kg (N=32)	s101 (N=70)	s201 (N=145)	Subtotal (N=215)	200 µg/kg (N=27)	All Doses (N=284)
Edema or Effusion	2 (20.0)	16 (50.0)	33 (47.1)	45 (31.0)	78 (36.3)	13 (48.1)	109 (38.4)
Oedema peripheral	1 (10.0)	9 (28.1)	21 (30.0)	29 (20.0)	50 (23.3)	9 (33.3)	69 (24.3)
Pleural effusion	1 (10.0)	6 (18.8)	13 (18.6)	16 (11.0)	29 (13.5)	6 (22.2)	42 (14.8)
Liver Function Test	2 (20.0)	10 (31.3)	22 (31.4)	76 (52.4)	98 (45.6)	13 (48.1)	123 (43.3)
Gamma-glutamyltransferase increased	2 (20.0)	10 (31.3)	16 (22.9)	61 (42.1)	77 (35.8)	10 (37.0)	99 (34.9)
Blood alkaline phosphatase increased	1 (10.0)	4 (12.5)	12 (17.1)	29 (20.0)	41 (19.1)	6 (22.2)	52 (18.3)
Aspartate aminotransferase increased	0	3 (9.4)	11 (15.7)	23 (15.9)	34 (15.8)	9 (33.3)	46 (16.2)
Alanine aminotransferase increased	0	4 (12.5)	12 (17.1)	23 (15.9)	35 (16.3)	5 (18.5)	44 (15.5)
Skin Reactions and Nail Disorders	4 (40.0)	16 (50.0)	37 (52.9)	63 (43.4)	100 (46.5)	13 (48.1)	133 (46.8)
Rash	1 (10.0)	5 (15.6)	24 (34.3)	19 (13.1)	43 (20.0)	5 (18.5)	54 (19.0)
Pruritus	1 (10.0)	4 (12.5)	6 (8.6)	19 (13.1)	25 (11.6)	4 (14.8)	33 (12.0)

Source: ISS Table 1.3.10

Grouped AEs of particular interest included oedema or effusion, LFTs, and skin reactions and nail disorders.
The 10% cutoff was based on All Doses.
AEs were coded using MedDRA version 22.0.

AE = adverse event; DLBCL = diffuse large B-cell lymphoma; LFT = liver function test; MedDRA = Medical Dictionary for Regulatory Activities; s101 = Study ADCT-402-101; s201 = Study ADCT-402-201; TEAE = treatment-emergent adverse event

Table 1.3.11
Selected Treatment-emergent Adverse Events Grade 3 or Higher by Grouped AE, Preferred Term, and Maximum CTCAE Grade
Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

AE Group / Preferred Term / Maximum CTCAE Grade	<=90 µg/kg (N=10)	120 µg/kg (N=32)	150 µg/kg s101 (N=70)	150 µg/kg s201 (N=145)	150 µg/kg subtotal (N=215)	200 µg/kg (N=27)	All Doses (N=284)
Patient with any selected TEAE of grade ≥ 3							
Grade 3	1 (10.0)	10 (31.3)	17 (24.3)	42 (29.0)	59 (27.4)	11 (40.7)	81 (28.5)
Grade 4	1 (10.0)	2 (6.3)	2 (2.9)	3 (2.1)	5 (2.3)	0	8 (2.8)
Grade 5	0	0	0	0	0	0	0
All Grades	2 (20.0)	12 (37.5)	19 (27.1)	45 (31.0)	64 (29.8)	11 (40.7)	89 (31.3)
Edema or Effusion							
Grade 3	0	2 (6.3)	5 (7.1)	6 (4.1)	11 (5.1)	0	13 (4.6)
Grade 4	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
Grade 5	0	0	0	0	0	0	0
All Grades	0	2 (6.3)	5 (7.1)	7 (4.8)	12 (5.6)	0	14 (4.9)
Ascites							
Grade 3	0	0	0	3 (2.1)	3 (1.4)	0	3 (1.1)
Grade 4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
All Grades	0	0	0	3 (2.1)	3 (1.4)	0	3 (1.1)

AE Group / Preferred Term / Maximum CTCAE Grade	<=90 µg/kg (N=10)	120 µg/kg (N=32)	150 µg/kg s101 (N=70)	150 µg/kg s201 (N=145)	150 µg/kg subtotal (N=215)	200 µg/kg (N=27)	All Doses (N=284)
Lymphoedema							
Grade 3	0	0	1 (1.4)	0	1 (0.5)	0	1 (0.4)
Grade 4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
All Grades	0	0	1 (1.4)	0	1 (0.5)	0	1 (0.4)
Oedema peripheral							
Grade 3	0	0	1 (1.4)	2 (1.4)	3 (1.4)	0	3 (1.1)
Grade 4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
All Grades	0	0	1 (1.4)	2 (1.4)	3 (1.4)	0	3 (1.1)
Pericardial effusion							
Grade 3	0	1 (3.1)	0	2 (1.4)	2 (0.9)	0	3 (1.1)
Grade 4	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
Grade 5	0	0	0	0	0	0	0
All Grades	0	1 (3.1)	0	3 (2.1)	3 (1.4)	0	4 (1.4)

AE Group / Preferred Term / Maximum CTCAE Grade	<=90 µg/kg (N=10)	120 µg/kg (N=32)	150 µg/kg s101 (N=70)	150 µg/kg s201 (N=145)	150 µg/kg subtotal (N=215)	200 µg/kg (N=27)	All Doses (N=284)
Peripheral swelling							
Grade 3	0	0	1 (1.4)	0	1 (0.5)	0	1 (0.4)
Grade 4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
All Grades	0	0	1 (1.4)	0	1 (0.5)	0	1 (0.4)
Pleural effusion							
Grade 3	0	1 (3.1)	3 (4.3)	3 (2.1)	6 (2.8)	0	7 (2.5)
Grade 4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
All Grades	0	1 (3.1)	3 (4.3)	3 (2.1)	6 (2.8)	0	7 (2.5)
Fatigue							
Grade 3	0	2 (6.3)	2 (2.9)	3 (2.1)	5 (2.3)	3 (11.1)	10 (3.5)
Grade 4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
All Grades	0	2 (6.3)	2 (2.9)	3 (2.1)	5 (2.3)	3 (11.1)	10 (3.5)

AE Group			150 µg/kg				
Preferred Term Maximum CTCAE Grade	<=90 µg/kg (N=10)	120 µg/kg (N=32)	s101 (N=70)	s201 (N=145)	subtotal (N=215)	200 µg/kg (N=27)	All Doses (N=284)
Fatigue							
Grade 3	0	2 (6.3)	2 (2.9)	2 (1.4)	4 (1.9)	3 (11.1)	9 (3.2)
Grade 4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
All Grades	0	2 (6.3)	2 (2.9)	2 (1.4)	4 (1.9)	3 (11.1)	9 (3.2)
Malaise							
Grade 3	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
Grade 4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
All Grades	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
Liver Function Test							
Grade 3	1 (10.0)	5 (15.6)	10 (14.3)	28 (19.3)	38 (17.7)	7 (25.9)	51 (18.0)
Grade 4	0	2 (6.3)	2 (2.9)	2 (1.4)	4 (1.9)	0	6 (2.1)
Grade 5	0	0	0	0	0	0	0
All Grades	1 (10.0)	7 (21.9)	12 (17.1)	30 (20.7)	42 (19.5)	7 (25.9)	57 (20.1)

AE Group			150 µg/kg				
Preferred Term Maximum CTCAE Grade	<=90 µg/kg (N=10)	120 µg/kg (N=32)	s101 (N=70)	s201 (N=145)	subtotal (N=215)	200 µg/kg (N=27)	All Doses (N=284)
Alanine aminotransferase increased							
Grade 3	0	2 (6.3)	2 (2.9)	4 (2.8)	6 (2.8)	1 (3.7)	9 (3.2)
Grade 4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
All Grades	0	2 (6.3)	2 (2.9)	4 (2.8)	6 (2.8)	1 (3.7)	9 (3.2)
Ascites							
Grade 3	0	0	0	3 (2.1)	3 (1.4)	0	3 (1.1)
Grade 4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
All Grades	0	0	0	3 (2.1)	3 (1.4)	0	3 (1.1)
Aspartate aminotransferase increased							
Grade 3	0	1 (3.1)	1 (1.4)	1 (0.7)	2 (0.9)	1 (3.7)	4 (1.4)
Grade 4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
All Grades	0	1 (3.1)	1 (1.4)	1 (0.7)	2 (0.9)	1 (3.7)	4 (1.4)

AE Group			150 µg/kg				
Preferred Term Maximum CTCAE Grade	<=90 µg/kg (N=10)	120 µg/kg (N=32)	s101 (N=70)	s201 (N=145)	subtotal (N=215)	200 µg/kg (N=27)	All Doses (N=284)
Blood alkaline phosphatase increased							
Grade 3	1 (10.0)	3 (9.4)	2 (2.9)	1 (0.7)	3 (1.4)	1 (3.7)	8 (2.8)
Grade 4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
All Grades	1 (10.0)	3 (9.4)	2 (2.9)	1 (0.7)	3 (1.4)	1 (3.7)	8 (2.8)
Blood bilirubin increased							
Grade 3	0	0	1 (1.4)	2 (1.4)	3 (1.4)	0	3 (1.1)
Grade 4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
All Grades	0	0	1 (1.4)	2 (1.4)	3 (1.4)	0	3 (1.1)
Gamma-glutamyltransferase increased							
Grade 3	1 (10.0)	4 (12.5)	10 (14.3)	23 (15.9)	33 (15.3)	6 (22.2)	44 (15.5)
Grade 4	0	2 (6.3)	2 (2.9)	2 (1.4)	4 (1.9)	0	6 (2.1)
Grade 5	0	0	0	0	0	0	0
All Grades	1 (10.0)	6 (18.8)	12 (17.1)	25 (17.2)	37 (17.2)	6 (22.2)	50 (17.6)

AE Group			150 µg/kg				
Preferred Term Maximum CTCAE Grade	<=90 µg/kg (N=10)	120 µg/kg (N=32)	s101 (N=70)	s201 (N=145)	subtotal (N=215)	200 µg/kg (N=27)	All Doses (N=284)
Hypoalbuminaemia							
Grade 3	0	0	0	0	0	1 (3.7)	1 (0.4)
Grade 4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
All Grades	0	0	0	0	0	1 (3.7)	1 (0.4)
Pain							
Grade 3	0	1 (3.1)	2 (2.9)	4 (2.8)	6 (2.8)	1 (3.7)	8 (2.8)
Grade 4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
All Grades	0	1 (3.1)	2 (2.9)	4 (2.8)	6 (2.8)	1 (3.7)	8 (2.8)
Facial pain							
Grade 3	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
Grade 4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
All Grades	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)

AE Group			150 µg/kg				
Preferred Term Maximum CTCAE Grade	<=90 µg/kg (N=10)	120 µg/kg (N=32)	s101 (N=70)	s201 (N=145)	subtotal (N=215)	200 µg/kg (N=27)	All Doses (N=284)
Musculoskeletal chest pain							
Grade 3	0	0	1 (1.4)	0	1 (0.5)	0	1 (0.4)
Grade 4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
All Grades	0	0	1 (1.4)	0	1 (0.5)	0	1 (0.4)
Neck pain							
Grade 3	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
Grade 4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
All Grades	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
Non-cardiac chest pain							
Grade 3	0	1 (3.1)	0	1 (0.7)	1 (0.5)	1 (3.7)	3 (1.1)
Grade 4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
All Grades	0	1 (3.1)	0	1 (0.7)	1 (0.5)	1 (3.7)	3 (1.1)

AE Group			150 µg/kg				
Preferred Term Maximum CTCAE Grade	<=90 µg/kg (N=10)	120 µg/kg (N=32)	s101 (N=70)	s201 (N=145)	subtotal (N=215)	200 µg/kg (N=27)	All Doses (N=284)
Pain							
Grade 3	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
Grade 4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
All Grades	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
Procedural pain							
Grade 3	0	0	1 (1.4)	0	1 (0.5)	0	1 (0.4)
Grade 4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
All Grades	0	0	1 (1.4)	0	1 (0.5)	0	1 (0.4)
Skin Reactions and Nail Disorders							
Grade 3	0	1 (3.1)	2 (2.9)	6 (4.1)	8 (3.7)	0	9 (3.2)
Grade 4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
All Grades	0	1 (3.1)	2 (2.9)	6 (4.1)	8 (3.7)	0	9 (3.2)

AE Group			150 µg/kg				
Preferred Term Maximum CTCAE Grade	<=90 µg/kg (N=10)	120 µg/kg (N=32)	s101 (N=70)	s201 (N=145)	subtotal (N=215)	200 µg/kg (N=27)	All Doses (N=284)
Erythema							
Grade 3	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
Grade 4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
All Grades	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
Exfoliative rash							
Grade 3	0	0	1 (1.4)	0	1 (0.5)	0	1 (0.4)
Grade 4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
All Grades	0	0	1 (1.4)	0	1 (0.5)	0	1 (0.4)
Photosensitivity reaction							
Grade 3	0	1 (3.1)	0	3 (2.1)	3 (1.4)	0	4 (1.4)
Grade 4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
All Grades	0	1 (3.1)	0	3 (2.1)	3 (1.4)	0	4 (1.4)

AE Group			150 µg/kg				
Preferred Term Maximum CTCAE Grade	<=90 µg/kg (N=10)	120 µg/kg (N=32)	s101 (N=70)	s201 (N=145)	subtotal (N=215)	200 µg/kg (N=27)	All Doses (N=284)
Rash							
Grade 3	0	0	1 (1.4)	1 (0.7)	2 (0.9)	0	2 (0.7)
Grade 4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
All Grades	0	0	1 (1.4)	1 (0.7)	2 (0.9)	0	2 (0.7)
Rash maculo-papular							
Grade 3	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
Grade 4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
All Grades	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
Rash pustular							
Grade 3	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
Grade 4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
All Grades	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)

AE Group Preferred Term Maximum CTCAE Grade	<=90 µg/kg (N=10)	120 µg/kg (N=32)	150 µg/kg s101 (N=70)	150 µg/kg s201 (N=145)	150 µg/kg subtotal (N=215)	200 µg/kg (N=27)	All Doses (N=284)
Torsade de pointes/QT Prolongation/seizure							
Grade 3	0	1 (3.1)	0	2 (1.4)	2 (0.9)	0	3 (1.1)
Grade 4	1 (10.0)	0	0	0	0	0	1 (0.4)
Grade 5	0	0	0	0	0	0	0
All Grades	1 (10.0)	1 (3.1)	0	2 (1.4)	2 (0.9)	0	4 (1.4)
Cardiac arrest							
Grade 3	0	0	0	0	0	0	0
Grade 4	1 (10.0)	0	0	0	0	0	1 (0.4)
Grade 5	0	0	0	0	0	0	0
All Grades	1 (10.0)	0	0	0	0	0	1 (0.4)
Electrocardiogram QT prolonged							
Grade 3	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
Grade 4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
All Grades	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)

AE Group Preferred Term Maximum CTCAE Grade	<=90 µg/kg (N=10)	120 µg/kg (N=32)	150 µg/kg s101 (N=70)	150 µg/kg s201 (N=145)	150 µg/kg subtotal (N=215)	200 µg/kg (N=27)	All Doses (N=284)
Syncope							
Grade 3	0	1 (3.1)	0	1 (0.7)	1 (0.5)	0	2 (0.7)
Grade 4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
All Grades	0	1 (3.1)	0	1 (0.7)	1 (0.5)	0	2 (0.7)

Adverse events are coded using MedDRA version 22.0, and graded using CTCAE v4.0. For each AE group and preferred term, patients are included only once at the maximum severity.
Dataset: adae, adsl
Program: t-ae-grppt-maxgr1.sas, Output: t1_3_11_ae_grppt_maxgr3_p1.rtf, Generated on: 26APR2021 15:18

Among the 215 patients who received the proposed dosing, 36.3% of the patients had **oedema or effusions**, and 23.3% had peripheral oedema (grade 3: 1.4%), while pleural effusion was observed in 13.5% (grade 3: 0.4%). Grade 3 or higher events of ascites, pericardial effusion or peripheral oedema, in 3 patients each, while 1 patient each had lymphoedema grade 3 or peripheral swelling grade 3. Hence, low grade oedema and/or effusions were common with LT, but this was not a dose-limiting toxicity.

Table 40. Medical History for Patients with Oedema or Effusion by System Organ Class and Preferred Term: Loncastuximab Tesirine Monotherapy Treated Diffuse Large B-cell Lymphoma Patients on 150 µg/kg Dose Level

System Organ Class Preferred Term	Study ADCT-402-101 (N = 33)	Study ADCT-402-201 (N = 45)	Total (N = 78)
Patients with any medical history	33 (100)	44 (97.8)	77 (98.7)
Cardiac disorders	16 (48.5)	14 (31.1)	30 (38.5)
Atrial fibrillation	7 (21.2)	5 (11.1)	12 (15.4)
Coronary artery disease	6 (18.2)	3 (6.7)	9 (11.5)
Sinus tachycardia	3 (9.1)	2 (4.4)	5 (6.4)
Cardiac failure congestive	2 (6.1)	2 (4.4)	4 (5.1)
Cardiomyopathy	1 (3.0)	3 (6.7)	4 (5.1)
Bundle branch block right	2 (6.1)	1 (2.2)	3 (3.8)
Angina pectoris	2 (6.1)	0	2 (2.6)
Pericardial effusion	0	2 (4.4)	2 (2.6)
Tachycardia	1 (3.0)	1 (2.2)	2 (2.6)
Atrial flutter	1 (3.0)	0	1 (1.3)
Atrial tachycardia	1 (3.0)	0	1 (1.3)
Atrioventricular block complete	1 (3.0)	0	1 (1.3)
Ischaemic cardiomyopathy	1 (3.0)	0	1 (1.3)
Mitral valve incompetence	1 (3.0)	0	1 (1.3)
Myocardial infarction	0	1 (2.2)	1 (1.3)

System Organ Class Preferred Term	Study ADCT-402-101 (N = 33)	Study ADCT-402-201 (N = 45)	Total (N = 78)
Myocardial ischaemia	0	1 (2.2)	1 (1.3)
Sinus node dysfunction	0	1 (2.2)	1 (1.3)
Supraventricular extrasystoles	0	1 (2.2)	1 (1.3)
Ventricular extrasystoles	0	1 (2.2)	1 (1.3)
Ventricular tachycardia	1 (3.0)	0	1 (1.3)

Source: Module 5.3.5.3, Integrated Summary of Safety – Updated Tables and Figures, 2022, t9_1_q149_mh_socpt_p1.rtf

The applicant has clarified that among the patients who had oedema or effusions, 30 patients (38.5%) had cardiac conditions. The table above provides the medical history relating to cardiac disorders for patients with oedema or effusion by system organ class and preferred term among the population of diffuse large B-cell lymphoma patients treated with loncastuximab tesirine monotherapy at the 150 µg/kg dose level. The most common supportive measure was diuretic medication, with 50 patients (64.1%) receiving this therapy for oedema or effusion. Albumin administration was infrequent, with only 3 patients (3.8%) receiving this therapy for oedema or effusion.

The applicant has clarified that the events of effusions and oedema reported in patients receiving loncastuximab tesirine in clinical studies, including peripheral oedema, general oedema, ascites, pleural effusion, and pericardial effusion are probably related to LT treatment as it contains Pyrrolobenzodiazepine (PBD) dimers, which have been associated with events of effusion and oedema. Most of the events of effusions and oedema were non-serious, but serious events were reported for pleural effusion (1.9%) and pericardial effusion (0.9%). The underlying cause of these events is unknown but may include vascular leak syndrome.

In summary, 5 patients experienced 7 serious adverse events of pleural and/or pericardial effusion; 3 patients experienced pleural effusion; 1 patient experienced pericardial effusion; and 1 patient experienced both pleural and pericardial effusion. One patient experienced 2 serious TEAEs of pleural effusion, and another patient experienced 2 serious TEAEs of both pericardial and pleural effusion. One event of pleural effusion was assessed by the investigator as unlikely related to study treatment, while the remaining events were assessed as related to study treatment. After request, the applicant clarified that all SAEs of effusions and/or oedema were considered related to treatment with LT.

Fatigue was observed in ~30% of the patients, but grade 3 or higher events were rare (2.3%). This is to be expected, also considering the underlying disease.

LFT /liver function tests were increased overall in ~45% of the patients, including GGT (35.8%), blood alkaline phosphatase increased (19.1%), AST increased (15.8%) and ALT increased (16.3%). Grade 3 events were observed in 17.7% and grade 4 in 1.9% of the patients. Again, the high-grade events were rarely observed and no cases of hepatic failure were reported.

Pain was selected as an AESI, but only abdominal pain is reported as a common AE (11.6%) and 2.8% of the patients reported grade 3 events of pain. These grade 3 events consisted of facial pain, musculoskeletal pain, neck pain, and non-cardiac chest pain (1 patient each). Hence, this was rare events, that may also have been related to manifestations from the underlying disease.

Skin reactions and nail disorders were commonly observed (46.5%), but grade 3 events were rare (3.7%), and there were no grade 4 or 5 events. The events mainly consisted of: rash (20.0%) and pruritus (11.6%), while a few grade 3 events of erythema, exfoliative rash, rash maculopapular, and rash pustular (1 patient each) were observed. 3 patients had a grade 3 photosensitivity reaction, and 2 patients had grade 3 rash. Overall, most events were in the skin and were related to treatment with LT. The applicant has clarified that skin toxicity was handled at the discretion of the investigator. Oral steroid therapy was administered to 17 (7.9%) patients, topical steroid therapy was administered to 38 (17.7%) patients, other topical therapies were administered to 27 (12.6%) patients, and

anti-pruritic therapy was administered to 20 (9.3%) patients. The applicant reiterates that skin toxicity was an uncommon cause of treatment discontinuation (1.4%).

Other safety findings:

Cardiac events:

It is noted that Torsade de points, cardiac arrest, QT prolonged and syncope are also reported. The applicant has clarified that a medical review of the clinical events of Torsade de points, cardiac arrest, QT prolonged and syncope does not suggest a safety signal associated with these events. Moreover, pharmacologic exposure-response analysis for QTc prolongation demonstrated no clinically relevant effect apparent with loncastuximab tesirine. Hence, these events are not considered to be of special interest with loncastuximab tesirine, but will continue to be monitored by routine pharmacovigilance, which is acceptable.

Phototoxicity:

The applicant has provided the requested detailed discussion on the risk of **phototoxicity**; and the argumentation regarding plausible mechanisms and non-clinical observations raised from toxicology studies are acceptable. With current knowledge of this toxicity, the updated text in the SmPC is now considered clear and acceptable. Moreover, phototoxicity has been included as an Important Identified Risk in the Risk Management Plan.

2.6.8.3. Serious adverse event/deaths/other significant events

Table 41. Most Common (≥1% of Patients in All Doses Combined) Serious TEAEs by Preferred Term-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

Preferred Term	≤90 µg/kg (N=10)	120 µg/kg (N=32)	150 µg/kg s101 (N=70)	150 µg/kg s201 (N=145)	150 µg/kg Subtotal (N=215)	200 µg/kg (N=27)	All Doses (N=284)
Patients with any serious TEAE	2 (20.0)	12 (37.5)	30 (42.9)	57 (39.3)	87 (40.5)	6 (22.2)	107 (37.7)
Pyrexia	0	4 (12.5)	1 (1.4)	4 (2.8)	5 (2.3)	0	9 (3.2)
Febrile neutropenia	1 (10.0)	0	2 (2.9)	5 (3.4)	7 (3.3)	0	8 (2.8)
Abdominal pain	0	1 (3.1)	1 (1.4)	3 (2.1)	4 (1.9)	1 (3.7)	6 (2.1)
Hypercalcaemia	0	0	0	6 (4.1)	6 (2.8)	0	6 (2.1)
Disease progression	0	1 (3.1)	3 (4.3)	1 (0.7)	4 (1.9)	0	5 (1.8)
Dyspnoea	0	1 (3.1)	3 (4.3)	1 (0.7)	4 (1.9)	0	5 (1.8)
Pleural effusion	0	0	1 (1.4)	3 (2.1)	4 (1.9)	1 (3.7)	5 (1.8)
DLBCL	0	1 (3.1)	2 (2.9)	1 (0.7)	3 (1.4)	0	4 (1.4)
Acute kidney injury	0	0	1 (1.4)	2 (1.4)	3 (1.4)	0	3 (1.1)
Anaemia	0	1 (3.1)	0	2 (1.4)	2 (0.9)	0	3 (1.1)
Lung infection	0	1 (3.1)	1 (1.4)	1 (0.7)	2 (0.9)	0	3 (1.1)
Mental status changes	1 (10.0)	0	0	2 (1.4)	2 (0.9)	0	3 (1.1)
Noncardiac chest pain	0	1 (3.1)	0	2 (1.4)	2 (0.9)	0	3 (1.1)
Pericardial effusion	0	1 (3.1)	0	2 (1.4)	2 (0.9)	0	3 (1.1)
Sepsis	0	0	2 (2.9)	1 (0.7)	3 (1.4)	0	3 (1.1)

Source: ISS Table 1.3.15

Adverse events were coded using MedDRA version 22.0. For each preferred term, patients were included only once.

DLBCL = diffuse large B-cell lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; s101 = Study ADCT-402-101; s201 = Study ADCT-402-201; TEAE = treatment-emergent adverse event

SAEs grade 3 or higher

Among the 215 patients who received 150 µg/kg loncastuximab tesirine monotherapy, for the most common serious TEAEs, the incidence of grade 3 or higher events and those assessed as **treatment-related**, respectively, were: disease progression, grade 5 (1.9% and 0%); DLBCL, grade 5 (1.4% and 0%); sepsis, grade 5 (0.9% and 0%) and grade 3 (0.5% and 0%); lung infection, grade 5 (0.5% and 0.5%) and grade 3 (0.5% and 0.5%); acute kidney injury, grade 5 (0.5% and 0%) and grade 3 (0.9% and 0%); hypercalcaemia, grade 4 (0.9% and 0%) and grade 3 (1.9% and 0.5%); abdominal pain, grade 4 (0.5% and 0%) and grade 3 (0.9% and 0.5%); pericardial effusion, grade 4 (0.5% and 0.5%) and grade 3 (0.5% and 0.5%); febrile neutropenia, grade 3 (3.3% and 2.8%); pleural effusion, grade 3 (1.4% and 1.4%); dyspnoea and anaemia, grade 3 (0.9% and 0.9% each); noncardiac chest pain, grade 3 (0.5% and 0.5%); and pyrexia, grade 3 (0.5% and 0%). Mental status changes did not have any events grade 3 or higher.

Serious adverse events of all grades were observed in 40.5% of the 215 patients of interest. Most commonly observed were: febrile neutropenia (3.3%), hypercalcaemia (2.8%), and pyrexia (2.3%). The grade 3 or higher SAEs has been summarised in the text above and it is noted and agreed that not all of these are treatment-related. The observed level of SAEs and treatment-related SAEs are acceptable considering the treatment setting and the underlying disease.

Deaths

Table 42 (Updated). Number (%) of Patients Who Died during the Studies and Reasons for Death (Loncastuximab Tesirine Monotherapy Treated DLBCL Patients)

			150 µg/kg				
	≤90 µg/kg (N = 10)	120 µg/kg (N = 32)	s101 (N = 70)	s201 (N = 145)	subtotal (N = 215)	200 µg/kg (N = 27)	All doses (N = 284)
Death during study	6 (60.0)	22 (68.8)	49 (70.0)	96 (66.2)	145 (67.4)	15 (55.6)	188 (66.2)
Disease progression	4 (40.0)	20 (62.5)	37 (52.9)	75 (51.7)	112 (52.1)	11 (40.7)	147 (51.8)
Other	2 (20.0)	2 (6.3)	12 (17.1)	21 (14.5)	33 (15.3)	4 (14.8)	41 (14.4)

DLBCL = diffuse large B-cell lymphoma; s101 = Study ADCT-402-101; s201 = Study ADCT-402-201.
Source: Module 2.7.4, Table 18 and Module 5.3.5.3, Integrated Summary of Safety, Listing 1.5.7

Table 43. Number (%) of Patients Who Died within 30 Days after the Last Dose of Study Drug-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

			150 µg/kg				
	≤90 µg/kg (N=10)	120 µg/kg (N=32)	s101 (N=70)	s201 (N=145)	Subtotal (N=215)	200 µg/kg (N=27)	All doses (N=284)
Death within 30 days of last dose without taking new anticancer therapy	0	2 (6.3)	6 (8.6)	10 (6.9)	16 (7.4)	0	18 (6.3)
Disease progression	0	1 (3.1)	4 (5.7)	5 (3.4)	9 (4.2)	0	10 (3.5)
Other	0	1 (3.1)	2 (2.9)	5 (3.4)	7 (3.3)	0	8 (2.8)

Source: ISS Table 1.3.28 DLBCL = diffuse large B-cell lymphoma; s101 = Study ADCT-402-101; s201 = Study ADCT-402-201

Table 44. Fatal TEAEs by SOC and Preferred Term-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

			150 µg/kg				
System Organ Class Preferred Term	≤90 µg/kg (N=10)	120 µg/kg (N=32)	s101 (N=70)	s201 (N=145)	Subtotal (N=215)	200 µg/kg (N=27)	All Doses (N=284)
Patients with any Fatal TEAE	0	3 (9.4)	11 (15.7)	8 (5.5)	19 (8.8)	0	22 (7.7)
Gastrointestinal disorders	0	1 (3.1)	2 (2.9)	1 (0.7)	3 (1.4)	0	4 (1.4)
Gastrointestinal haemorrhage	0	1 (3.1)	1 (1.4)	0	1 (0.5)	0	2 (0.7)
Abdominal compartment syndrome	0	0	1 (1.4)	0	1 (0.5)	0	1 (0.4)
Small intestinal perforation	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
General disorders and administration site conditions	0	1 (3.1)	3 (4.3)	1 (0.7)	4 (1.9)	0	5 (1.8)
Disease progression	0	1 (3.1)	3 (4.3)	1 (0.7)	4 (1.9)	0	5 (1.8)
Infections and infestations	0	0	2 (2.9)	3 (2.1)	5 (2.3)	0	5 (1.8)
Sepsis	0	0	1 (1.4)	1 (0.7)	2 (0.9)	0	2 (0.7)
Lung infection	0	0	1 (1.4)	0	1 (0.5)	0	1 (0.4)
Pneumonia	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
Septic shock	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)

Injury, poisoning and procedural complications	0	0	1 (1.4)	0	1 (0.5)	0	1 (0.4)
Subdural haematoma	0	0	1 (1.4)	0	1 (0.5)	0	1 (0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (3.1)	3 (4.3)	1 (0.7)	4 (1.9)	0	5 (1.8)
DLBCL	0	1 (3.1)	2 (2.9)	1 (0.7)	3 (1.4)	0	4 (1.4)
Lymphoma	0	0	1 (1.4)	0	1 (0.5)	0	1 (0.4)
Renal and urinary disorders	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
Acute kidney injury	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
Respiratory, thoracic and mediastinal disorders	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
Haemoptysis	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)

Source: ISS Table 1.3.16. Adverse events were coded using MedDRA version 22.0. For each SOC and preferred term, patients were included only once.

DLBCL = diffuse large B-cell lymphoma; incl = including; MedDRA = Medical Dictionary for Regulatory Activities; s101 = Study ADCT-402-101; s201 = Study ADCT-402-201; SOC = system organ class; TEAE = treatment-emergent adverse event

Of the relevant 215 patients in the current safety database, 67.4% of the patients had died and 52.1% of disease progression. Table 42 has been updated to move the 4 patients who died from disease progression, which was reported as an adverse event from 'Other' category to 'Disease progression' category. They include 1 patient from Study ADCT-402-101 and 3 patients from Study ADCT-402-201.

It is noted that 5 patients died due to infections and/or sepsis and that one lung infection (0.5%) was assessed as treatment-related. This is acceptable.

The narratives for the patients, who received the proposed dosing of LT have been assessed and the conclusions on causes of death are overall agreed. Patients, who died from other causes, generally died after subsequent treatment, so it is agreed that these deaths were not related to treatment with LT.

2.6.8.4. Laboratory findings

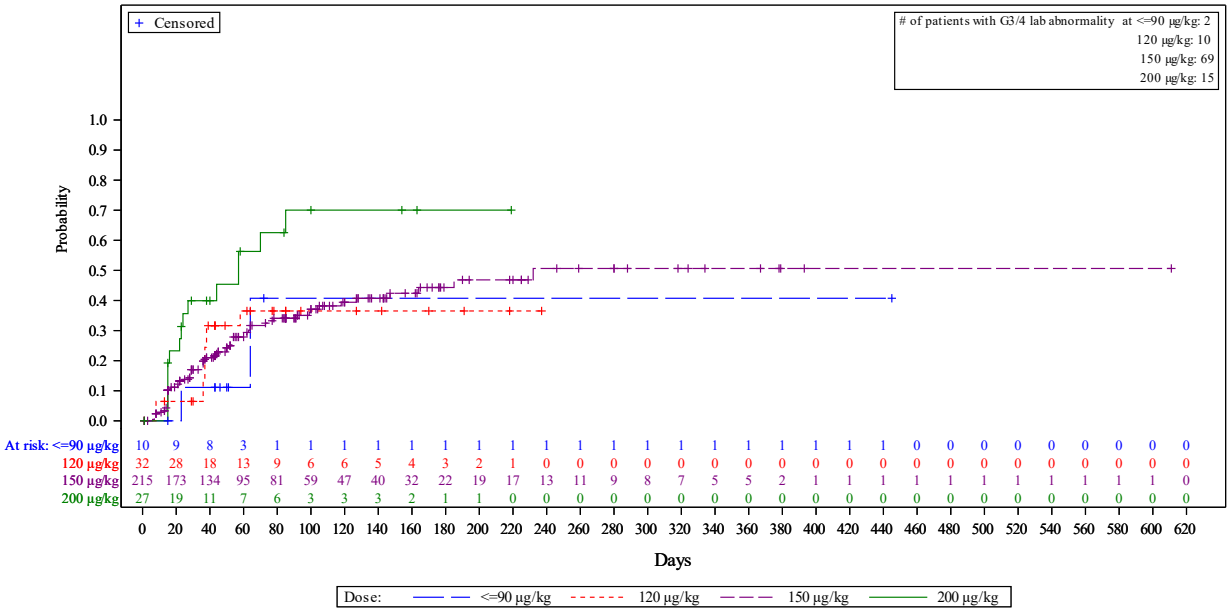
Table 45. Maximum Postbaseline CTCAE Grade for Haematology-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

Parameter Toxicity Grade	≤90 µg/kg (N=10)	120 µg/kg (N=32)	150 µg/kg s101 (N=70)	150 µg/kg s201 (N=145)	150 µg/kg Subtotal (N=215)	200 µg/kg (N=27)	All doses (N=284)
Haemoglobin (g/L) - DEC	10 (100.0)	31 (96.9)	69 (98.6)	145 (100.0)	214 (99.5)	26 (96.3)	281 (98.9)
Grade 0	0	1 (3.1)	2 (2.9)	9 (6.2)	11 (5.1)	0	12 (4.2)
Grade 1	5 (50.0)	18 (56.3)	25 (35.7)	75 (51.7)	100 (46.5)	11 (40.7)	134 (47.2)
Grade 2	4 (40.0)	9 (28.1)	31 (44.3)	45 (31.0)	76 (35.3)	13 (48.1)	102 (35.9)
Grade 3	1 (10.0)	3 (9.4)	11 (15.7)	16 (11.0)	27 (12.6)	2 (7.4)	33 (11.6)
Grade 4	0	0	0	0	0	0	0
Leukocytes (10^9/L) - DEC	10 (100.0)	31 (96.9)	69 (98.6)	145 (100.0)	214 (99.5)	26 (96.3)	281 (98.9)
Grade 0	4 (40.0)	7 (21.9)	22 (31.4)	45 (31.0)	67 (31.2)	1 (3.7)	79 (27.8)
Grade 1	2 (20.0)	7 (21.9)	7 (10.0)	29 (20.0)	36 (16.7)	9 (33.3)	54 (19.0)
Grade 2	2 (20.0)	11 (34.4)	16 (22.9)	34 (23.4)	50 (23.3)	5 (18.5)	68 (23.9)
Grade 3	2 (20.0)	6 (18.8)	17 (24.3)	27 (18.6)	44 (20.5)	7 (25.9)	59 (20.8)
Grade 4	0	0	7 (10.0)	10 (6.9)	17 (7.9)	4 (14.8)	21 (7.4)
Lymphocytes (10^9/L) - DEC	10 (100.0)	31 (96.9)	69 (98.6)	144 (99.3)	213 (99.1)	26 (96.3)	280 (98.6)
Grade 0	0	3 (9.4)	3 (4.3)	10 (6.9)	13 (6.0)	1 (3.7)	17 (6.0)
Grade 1	5 (50.0)	4 (12.5)	3 (4.3)	17 (11.7)	20 (9.3)	3 (11.1)	32 (11.3)
Grade 2	2 (20.0)	7 (21.9)	10 (14.3)	37 (25.5)	47 (21.9)	4 (14.8)	60 (21.1)
Grade 3	2 (20.0)	14 (43.8)	36 (51.4)	47 (32.4)	83 (38.6)	11 (40.7)	110 (38.7)
Grade 4	1 (10.0)	3 (9.4)	17 (24.3)	33 (22.8)	50 (23.3)	7 (25.9)	61 (21.5)
Neutrophils (10^9/L) - DEC	10 (100.0)	31 (96.9)	68 (97.1)	144 (99.3)	212 (98.6)	26 (96.3)	279 (98.2)
Grade 0	5 (50.0)	15 (46.9)	29 (41.4)	67 (46.2)	96 (44.7)	7 (25.9)	123 (43.3)
Grade 1	0	1 (3.1)	7 (10.0)	10 (6.9)	17 (7.9)	3 (11.1)	21 (7.4)
Grade 2	3 (30.0)	5 (15.6)	6 (8.6)	24 (16.6)	30 (14.0)	1 (3.7)	39 (13.7)
Grade 3	1 (10.0)	5 (15.6)	6 (8.6)	18 (12.4)	24 (11.2)	8 (29.6)	38 (13.4)
Grade 4	1 (10.0)	5 (15.6)	20 (28.6)	25 (17.2)	45 (20.9)	7 (25.9)	58 (20.4)
Platelets (10^9/L) - DEC	10 (100.0)	31 (96.9)	69 (98.6)	144 (99.3)	213 (99.1)	26 (96.3)	280 (98.6)
Grade 0	5 (50.0)	12 (37.5)	22 (31.4)	48 (33.1)	70 (32.6)	6 (22.2)	93 (32.7)
Grade 1	3 (30.0)	8 (25.0)	20 (28.6)	56 (38.6)	76 (35.3)	6 (22.2)	93 (32.7)
Grade 2	1 (10.0)	4 (12.5)	9 (12.9)	15 (10.3)	24 (11.2)	3 (11.1)	32 (11.3)
Grade 3	1 (10.0)	2 (6.3)	8 (11.4)	19 (13.1)	27 (12.6)	7 (25.9)	37 (13.0)
Grade 4	0	5 (15.6)	10 (14.3)	6 (4.1)	16 (7.4)	4 (14.8)	25 (8.8)

Source: ISS Table 1.4.3

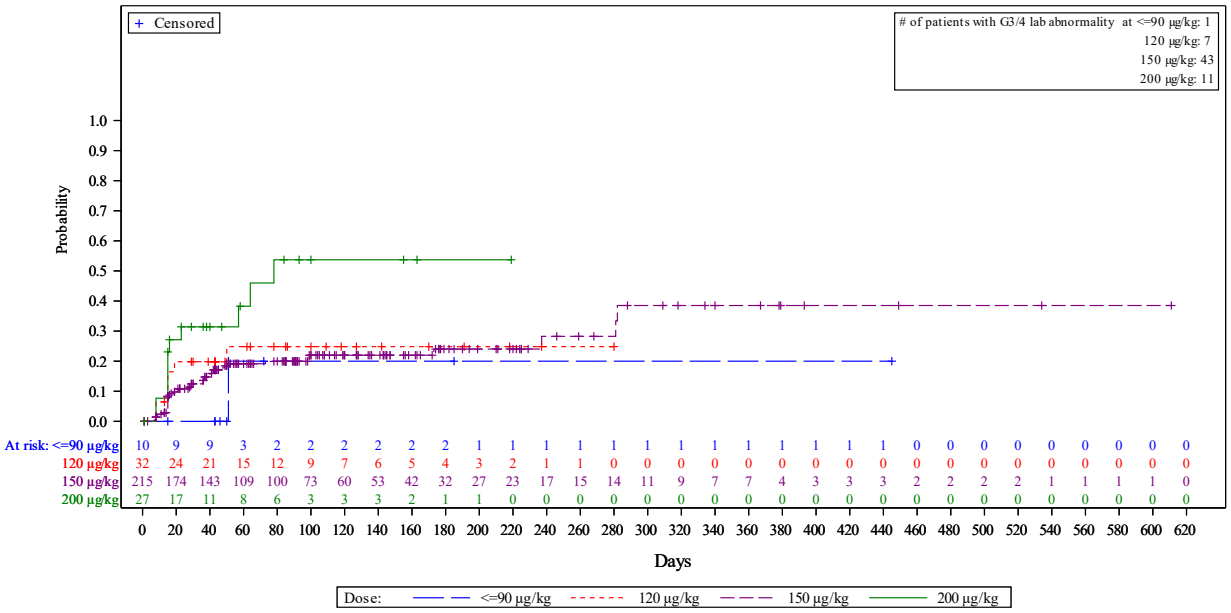
Baseline was defined as the last nonmissing value before the initial administration of loncastuximab tesirine. CTCAE v4.0 was used for grading. For each parameter, patients were included only once at the maximum severity.
CTCAE = Common Terminology Criteria for Adverse Events; DEC = decrease; DLBCL = diffuse large B-cell lymphoma; s101 = Study ADCT-402-101; s201 = Study ADCT-402-201

Figure 29. Time to the First Onset of Grade 3/4 Neutrophil Decrease-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients



Source: ISS Figure 1.4.103
DLBCL = diffuse large B-cell lymphoma

Figure 30. Time to the First Onset of Grade 3/4 Platelet Count Decrease-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients



Source: ISS Figure 1.4.105
DLBCL = diffuse large B-cell lymphoma

Haematological toxicity was common with LT. Decreases in **haemoglobin** was mostly of low grade (≤grade 2: 82%), while grade 3 decreases were observed in 12.6% of the patients.

Decreases in **leucocytes** were also common of low grade (≤grade 2: 40%), but were rather commonly observed of grade 3 (20.5%) and grade 4 (7.9%) as well.

Decreases in **lymphocytes** were observed in ~31% of grade 1 and 2, while 62% had grade 3-4 events.

Decreases of **neutrophils** were observed for grade 1-2 in 22% and 32% had grade 3-4 events. From figure 29, the risk of grade 3-4 events increases over time and number of doses, which makes clinically sense, since slower and slower bone marrow recovery may occur with added number of cycles. The bone marrow's capacity to recover may also be affected by previous treatments and the study population was heavily pretreated. For the 150 µg/kg dose level (n=69), the patients started to develop Grade 3 or 4 neutrophil count decrease after the first dose and most of the events happened within the first 4 months. Moreover, the probability of developing grade 3 or 4 neutrophil decrease at Months 2 and 6 was 28% and 44%, respectively.

Decreases of **platelets** were most often grade 1-2 (47%) and in 20% of the cases of grade 3-4.

Overall, the level of haematological toxicity seems manageable; however, an OC has been posed earlier on the handling of neutropenia with LT.

Table 46. Maximum Postbaseline CTCAE Grade for LFTs-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

			150 µg/kg				
Parameter Toxicity Grade	**≤90 µg/kg (N=10)**	**120 µg/kg (N=32)**	**s101 (N=70)**	**s201 (N=145)**	**Subtotal (N=215)**	**200 µg/kg (N=27)**	**All doses (N=284)**
Alanine Aminotransferase (U/L) - INC	10 (100.0)	31 (96.9)	69 (98.6)	145 (100.0)	214 (99.5)	26 (96.3)	281 (98.9)
Grade 0	8 (80.0)	21 (65.6)	35 (50.0)	89 (61.4)	124 (57.7)	16 (59.3)	169 (59.5)
Grade 1	2 (20.0)	5 (15.6)	23 (32.9)	41 (28.3)	64 (29.8)	7 (25.9)	78 (27.5)
Grade 2	0	2 (6.3)	7 (10.0)	10 (6.9)	17 (7.9)	2 (7.4)	21 (7.4)
Grade 3	0	3 (9.4)	4 (5.7)	4 (2.8)	8 (3.7)	1 (3.7)	12 (4.2)
Grade 4	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
Albumin (g/L) - DEC	10 (100.0)	31 (96.9)	68 (97.1)	144 (99.3)	212 (98.6)	26 (96.3)	279 (98.2)
Grade 0	6 (60.0)	12 (37.5)	28 (40.0)	79 (54.5)	107 (49.8)	8 (29.6)	133 (46.8)
Grade 1	3 (30.0)	16 (50.0)	22 (31.4)	40 (27.6)	62 (28.8)	13 (48.1)	94 (33.1)
Grade 2	1 (10.0)	3 (9.4)	18 (25.7)	23 (15.9)	41 (19.1)	5 (18.5)	50 (17.6)
Grade 3	0	0	0	2 (1.4)	2 (0.9)	0	2 (0.7)
Grade 4	0	0	0	0	0	0	0
Alkaline Phosphatase (U/L) - INC	10 (100.0)	31 (96.9)	68 (97.1)	145 (100.0)	213 (99.1)	26 (96.3)	280 (98.6)
Grade 0	8 (80.0)	17 (53.1)	27 (38.6)	65 (44.8)	92 (42.8)	15 (55.6)	132 (46.5)
Grade 1	1 (10.0)	9 (28.1)	32 (45.7)	62 (42.8)	94 (43.7)	4 (14.8)	108 (38.0)
Grade 2	0	1 (3.1)	6 (8.6)	15 (10.3)	21 (9.8)	7 (25.9)	29 (10.2)
Grade 3	1 (10.0)	4 (12.5)	3 (4.3)	3 (2.1)	6 (2.8)	0	11 (3.9)
Grade 4	0	0	0	0	0	0	0
Aspartate Aminotransferase (U/L) - INC	10 (100.0)	31 (96.9)	69 (98.6)	145 (100.0)	214 (99.5)	26 (96.3)	281 (98.9)
Grade 0	5 (50.0)	16 (50.0)	21 (30.0)	69 (47.6)	90 (41.9)	8 (29.6)	119 (41.9)

Grade 1	5 (50.0)	11 (34.4)	37 (52.9)	65 (44.8)	102 (47.4)	15 (55.6)	133 (46.8)
Grade 2	0	2 (6.3)	8 (11.4)	10 (6.9)	18 (8.4)	1 (3.7)	21 (7.4)
Grade 3	0	2 (6.3)	3 (4.3)	1 (0.7)	4 (1.9)	2 (7.4)	8 (2.8)
Grade 4	0	0	0	0	0	0	0
Bilirubin (umol/L) - INC	10 (100.0)	31 (96.9)	68 (97.1)	145 (100.0)	213 (99.1)	26 (96.3)	280 (98.6)
Grade 0	10 (100.0)	29 (90.6)	59 (84.3)	132 (91.0)	191 (88.8)	22 (81.5)	252 (88.7)
Grade 1	0	2 (6.3)	4 (5.7)	6 (4.1)	10 (4.7)	1 (3.7)	13 (4.6)
Grade 2	0	0	1 (1.4)	5 (3.4)	6 (2.8)	2 (7.4)	8 (2.8)
Grade 3	0	0	3 (4.3)	2 (1.4)	5 (2.3)	1 (3.7)	6 (2.1)
Grade 4	0	0	1 (1.4)	0	1 (0.5)	0	1 (0.4)
Gamma-Glutamyl Transferase (U/L) - INC	10 (100.0)	31 (96.9)	69 (98.6)	143 (98.6)	212 (98.6)	26 (96.3)	279 (98.2)
Grade 0	4 (40.0)	12 (37.5)	18 (25.7)	38 (26.2)	56 (26.0)	4 (14.8)	76 (26.8)
Grade 1	4 (40.0)	8 (25.0)	16 (22.9)	48 (33.1)	64 (29.8)	11 (40.7)	87 (30.6)
Grade 2	1 (10.0)	2 (6.3)	14 (20.0)	24 (16.6)	38 (17.7)	3 (11.1)	44 (15.5)
Grade 3	1 (10.0)	8 (25.0)	19 (27.1)	31 (21.4)	50 (23.3)	8 (29.6)	67 (23.6)
Grade 4	0	1 (3.1)	2 (2.9)	2 (1.4)	4 (1.9)	0	5 (1.8)

Source: ISS Table 1.4.4

Baseline was defined as the last nonmissing value before the initial administration of loncastuximab tesirine. CTCAE v4.0 was used for grading. For each parameter, patients were included only once at the maximum severity.
CTCAE = Common Terminology Criteria for Adverse Events; DEC = decrease; DLBCL = diffuse large B-cell lymphoma; INC = increase; LFT = liver function test; s101 = Study ADCT-402-101; s201 = Study ADCT-402-201

Table 47. Maximum Postbaseline CTCAE Grade or Renal Function Tests-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

			150 µg/kg				
Parameter Toxicity Grade	**≤90 µg/kg (N=10)**	**120 µg/kg (N=32)**	**s101 (N=70)**	**s201 (N=145)**	**Subtotal (N=215)**	**200 µg/kg (N=27)**	**All doses (N=284)**
Creatinine (umol/L) - INC	10 (100.0)	31 (96.9)	69 (98.6)	145 (100.0)	214 (99.5)	26 (96.3)	281 (98.9)
Grade 0	3 (30.0)	7 (21.9)	14 (20.0)	19 (13.1)	33 (15.3)	1 (3.7)	44 (15.5)
Grade 1	7 (70.0)	22 (68.8)	50 (71.4)	106 (73.1)	156 (72.6)	23 (85.2)	208 (73.2)
Grade 2	0	2 (6.3)	5 (7.1)	16 (11.0)	21 (9.8)	2 (7.4)	25 (8.8)
Grade 3	0	0	0	4 (2.8)	4 (1.9)	0	4 (1.4)
Grade 4	0	0	0	0	0	0	0
Creatinine Clearance (mL/min) - DEC	6 (60.0)	20 (62.5)	28 (40.0)	0	28 (13.0)	14 (51.9)	68 (23.9)
Grade 0	1 (10.0)	5 (15.6)	13 (18.6)	0	13 (6.0)	5 (18.5)	24 (8.5)
Grade 1	1 (10.0)	1 (3.1)	1 (1.4)	0	1 (0.5)	1 (3.7)	4 (1.4)
Grade 2	4 (40.0)	14 (43.8)	14 (20.0)	0	14 (6.5)	6 (22.2)	38 (13.4)
Grade 3	0	0	0	0	0	2 (7.4)	2 (0.7)
Grade 4	0	0	0	0	0	0	0

Source: ISS Table 1.4. Baseline was defined as the last nonmissing value before the initial administration of loncastuximab tesirine. CTCAE v4.0 was used for grading. For each parameter, patients were included only once at the maximum severity.
CTCAE = Common Terminology Criteria for Adverse Events; DEC = decrease; DLBCL = diffuse large B-cell lymphoma; INC = increase; s101 = Study ADCT-402-101; s201 = Study ADCT-402-201

Table 48. Maximum Postbaseline CTCAE Grade for Glucose and Electrolytes-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

Parameter Toxicity Grade	≤90 µg/kg (N=10)	120 µg/kg (N=32)	150 µg/kg s101 (N=70)	150 µg/kg s201 (N=145)	150 µg/kg Subtotal (N=215)	200 µg/kg (N=27)	All doses (N=284)
Calcium (mmol/L) - DEC	10 (100.0)	31 (96.9)	69 (98.6)	145 (100.0)	214 (99.5)	26 (96.3)	281 (98.9)
Grade 0	7 (70.0)	22 (68.8)	37 (52.9)	98 (67.6)	135 (62.8)	16 (59.3)	180 (63.4)
Grade 1	2 (20.0)	8 (25.0)	25 (35.7)	39 (26.9)	64 (29.8)	8 (29.6)	82 (28.9)
Grade 2	0	1 (3.1)	6 (8.6)	6 (4.1)	12 (5.6)	2 (7.4)	15 (5.3)
Grade 3	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
Grade 4	1 (10.0)	0	1 (1.4)	1 (0.7)	2 (0.9)	0	3 (1.1)
Calcium (mmol/L) - INC	10 (100.0)	31 (96.9)	69 (98.6)	145 (100.0)	214 (99.5)	26 (96.3)	281 (98.9)
Grade 0	9 (90.0)	26 (81.3)	61 (87.1)	122 (84.1)	183 (85.1)	25 (92.6)	243 (85.6)
Grade 1	1 (10.0)	5 (15.6)	8 (11.4)	14 (9.7)	22 (10.2)	1 (3.7)	29 (10.2)
Grade 2	0	0	0	3 (2.1)	3 (1.4)	0	3 (1.1)
Grade 3	0	0	0	3 (2.1)	3 (1.4)	0	3 (1.1)
Grade 4	0	0	0	3 (2.1)	3 (1.4)	0	3 (1.1)
Glucose (mmol/L) - DEC	10 (100.0)	31 (96.9)	68 (97.1)	143 (98.6)	211 (98.1)	26 (96.3)	278 (97.9)
Grade 0	8 (80.0)	28 (87.5)	57 (81.4)	130 (89.7)	187 (87.0)	26 (96.3)	249 (87.7)
Grade 1	2 (20.0)	2 (6.3)	11 (15.7)	13 (9.0)	24 (11.2)	0	28 (9.9)
Grade 2	0	1 (3.1)	0	0	0	0	1 (0.4)
Grade 3	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0
Glucose (mmol/L) - INC	10 (100.0)	31 (96.9)	68 (97.1)	143 (98.6)	211 (98.1)	26 (96.3)	278 (97.9)
Grade 0	4 (40.0)	10 (31.3)	19 (27.1)	37 (25.5)	56 (26.0)	8 (29.6)	78 (27.5)
Grade 1	5 (50.0)	12 (37.5)	26 (37.1)	50 (34.5)	76 (35.3)	8 (29.6)	101 (35.6)
Grade 2	1 (10.0)	7 (21.9)	12 (17.1)	41 (28.3)	53 (24.7)	7 (25.9)	68 (23.9)
Grade 3	0	2 (6.3)	10 (14.3)	14 (9.7)	24 (11.2)	3 (11.1)	29 (10.2)
Grade 4	0	0	1 (1.4)	1 (0.7)	2 (0.9)	0	2 (0.7)
Magnesium (mmol/L) - DEC	10 (100.0)	31 (96.9)	69 (98.6)	145 (100.0)	214 (99.5)	26 (96.3)	281 (98.9)
Grade 0	8 (80.0)	26 (81.3)	48 (68.6)	88 (60.7)	136 (63.3)	21 (77.8)	191 (67.3)
Grade 1	1 (10.0)	4 (12.5)	19 (27.1)	51 (35.2)	70 (32.6)	5 (18.5)	80 (28.2)
Grade 2	1 (10.0)	1 (3.1)	2 (2.9)	5 (3.4)	7 (3.3)	0	9 (3.2)
Grade 3	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
Grade 4	0	0	0	0	0	0	0
Magnesium (mmol/L) - INC	10 (100.0)	31 (96.9)	69 (98.6)	145 (100.0)	214 (99.5)	26 (96.3)	281 (98.9)
Grade 0	10 (100.0)	30 (93.8)	65 (92.9)	138 (95.2)	203 (94.4)	24 (88.9)	267 (94.0)
Grade 1	0	0	4 (5.7)	5 (3.4)	9 (4.2)	2 (7.4)	11 (3.9)
Grade 2	0	0	0	0	0	0	0
Grade 3	0	1 (3.1)	0	2 (1.4)	2 (0.9)	0	3 (1.1)
Grade 4	0	0	0	0	0	0	0
Phosphate (mmol/L) - DEC	10 (100.0)	31 (96.9)	68 (97.1)	144 (99.3)	212 (98.6)	26 (96.3)	279 (98.2)
Grade 0	8 (80.0)	20 (62.5)	40 (57.1)	81 (55.9)	121 (56.3)	16 (59.3)	165 (58.1)
Grade 1	0	0	1 (1.4)	0	1 (0.5)	0	1 (0.4)
Grade 2	2 (20.0)	9 (28.1)	25 (35.7)	47 (32.4)	72 (33.5)	7 (25.9)	90 (31.7)
Grade 3	0	2 (6.3)	2 (2.9)	15 (10.3)	17 (7.9)	3 (11.1)	22 (7.7)
Grade 4	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
Potassium (mmol/L) - DEC	10 (100.0)	31 (96.9)	69 (98.6)	145 (100.0)	214 (99.5)	26 (96.3)	281 (98.9)

Grade 0	7 (70.0)	24 (75.0)	45 (64.3)	107 (73.8)	152 (70.7)	22 (81.5)	205 (72.2)
Grade 1	2 (20.0)	6 (18.8)	19 (27.1)	29 (20.0)	48 (22.3)	3 (11.1)	59 (20.8)
Grade 2	0	0	0	0	0	0	0
Grade 3	0	1 (3.1)	4 (5.7)	9 (6.2)	13 (6.0)	1 (3.7)	15 (5.3)
Grade 4	1 (10.0)	0	1 (1.4)	0	1 (0.5)	0	2 (0.7)
Potassium (mmol/L) - INC	10 (100.0)	31 (96.9)	69 (98.6)	145 (100.0)	214 (99.5)	26 (96.3)	281 (98.9)
Grade 0	10 (100.0)	31 (96.9)	65 (92.9)	128 (88.3)	193 (89.8)	23 (85.2)	257 (90.5)
Grade 1	0	0	2 (2.9)	12 (8.3)	14 (6.5)	3 (11.1)	17 (6.0)
Grade 2	0	0	2 (2.9)	2 (1.4)	4 (1.9)	0	4 (1.4)
Grade 3	0	0	0	2 (1.4)	2 (0.9)	0	2 (0.7)
Grade 4	0	0	0	1 (0.7)	1 (0.5)	0	1 (0.4)
Sodium (mmol/L) - DEC	10 (100.0)	31 (96.9)	69 (98.6)	145 (100.0)	214 (99.5)	26 (96.3)	281 (98.9)
Grade 0	9 (90.0)	21 (65.6)	43 (61.4)	92 (63.4)	135 (62.8)	20 (74.1)	185 (65.1)
Grade 1	1 (10.0)	9 (28.1)	19 (27.1)	42 (29.0)	61 (28.4)	6 (22.2)	77 (27.1)
Grade 2	0	0	0	0	0	0	0
Grade 3	0	1 (3.1)	7 (10.0)	11 (7.6)	18 (8.4)	0	19 (6.7)
Grade 4	0	0	0	0	0	0	0
Sodium (mmol/L) - INC	10 (100.0)	31 (96.9)	69 (98.6)	145 (100.0)	214 (99.5)	26 (96.3)	281 (98.9)
Grade 0	8 (80.0)	31 (96.9)	67 (95.7)	142 (97.9)	209 (97.2)	26 (96.3)	274 (96.5)
Grade 1	2 (20.0)	0	1 (1.4)	3 (2.1)	4 (1.9)	0	6 (2.1)
Grade 2	0	0	1 (1.4)	0	1 (0.5)	0	1 (0.4)
Grade 3	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0

Source: ISS Table 1.4.4

Baseline was defined as the last nonmissing value before the initial administration of loncastuximab tesirine. CTCAE v4.0 was used for grading. For each parameter, patients were included only once at the maximum severity.
CTCAE = Common Terminology Criteria for Adverse Events; DEC = decrease; DLBCL = diffuse large B-cell lymphoma; INC = increase; s101 = Study ADCT-402-101; s201 = Study ADCT-402-201

Table 49. Maximum Postbaseline CTCAE Grade for Other Biochemistry Parameters (Amylase, Lipase and Lipids)-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

			150 µg/kg				
Parameter Toxicity Grade	**≤90 µg/kg (N=10)**	**120 µg/kg (N=32)**	**s101 (N=70)**	**s201 (N=145)**	**Subtotal (N=215)**	**200 µg/kg (N=27)**	**All doses (N=284)**
Amylase (U/L) - INC	10 (100.0)	31 (96.9)	69 (98.6)	142 (97.9)	211 (98.1)	26 (96.3)	278 (97.9)
Grade 0	8 (80.0)	23 (71.9)	61 (87.1)	120 (82.8)	181 (84.2)	20 (74.1)	232 (81.7)
Grade 1	1 (10.0)	7 (21.9)	6 (8.6)	18 (12.4)	24 (11.2)	6 (22.2)	38 (13.4)
Grade 2	0	1 (3.1)	1 (1.4)	2 (1.4)	3 (1.4)	0	4 (1.4)
Grade 3	1 (10.0)	0	1 (1.4)	2 (1.4)	3 (1.4)	0	4 (1.4)
Grade 4	0	0	0	0	0	0	0
Lipase (U/L) - INC	10 (100.0)	31 (96.9)	69 (98.6)	142 (97.9)	211 (98.1)	26 (96.3)	278 (97.9)
Grade 0	9 (90.0)	26 (81.3)	48 (68.6)	115 (79.3)	163 (75.8)	18 (66.7)	216 (76.1)
Grade 1	0	3 (9.4)	13 (18.6)	15 (10.3)	28 (13.0)	3 (11.1)	34 (12.0)
Grade 2	0	1 (3.1)	6 (8.6)	5 (3.4)	11 (5.1)	2 (7.4)	14 (4.9)
Grade 3	0	1 (3.1)	1 (1.4)	6 (4.1)	7 (3.3)	2 (7.4)	10 (3.5)
Grade 4	1 (10.0)	0	1 (1.4)	1 (0.7)	2 (0.9)	1 (3.7)	4 (1.4)
Cholesterol (mmol/L) - INC	10 (100.0)	31 (96.9)	68 (97.1)	0	68 (31.6)	26 (96.3)	135 (47.5)

Grade 0	6 (60.0)	12 (37.5)	26 (37.1)	0	26 (12.1)	11 (40.7)	55 (19.4)
Grade 1	4 (40.0)	15 (46.9)	39 (55.7)	0	39 (18.1)	14 (51.9)	72 (25.4)
Grade 2	0	3 (9.4)	2 (2.9)	0	2 (0.9)	1 (3.7)	6 (2.1)
Grade 3	0	1 (3.1)	1 (1.4)	0	1 (0.5)	0	2 (0.7)
Grade 4	0	0	0	0	0	0	0
Triglycerides (mmol/L) - INC	10 (100.0)	31 (96.9)	68 (97.1)	0	68 (31.6)	26 (96.3)	135 (47.5)
Grade 0	6 (60.0)	7 (21.9)	20 (28.6)	0	20 (9.3)	4 (14.8)	37 (13.0)
Grade 1	4 (40.0)	18 (56.3)	31 (44.3)	0	31 (14.4)	14 (51.9)	67 (23.6)
Grade 2	0	5 (15.6)	16 (22.9)	0	16 (7.4)	6 (22.2)	27 (9.5)
Grade 3	0	1 (3.1)	1 (1.4)	0	1 (0.5)	2 (7.4)	4 (1.4)
Grade 4	0	0	0	0	0	0	0

Source: ISS Table 1.4.4

Baseline was defined as the last nonmissing value before the initial administration of loncastuximab tesirine. CTCAE v4.0 was used for grading. For each parameter, patients were included only once at the maximum severity.
CTCAE = Common Terminology Criteria for Adverse Events; DEC = decrease; DLBCL = diffuse large B-cell lymphoma; INC = increase; s101 = Study ADCT-402-101; s201 = Study ADCT-402-201

Alkaline phosphatase (AP) increased from a mean of 100.2 U/L at baseline to a mean of 110.1 U/L at Cycle 1, Day 15 and decreased to a mean of 101.4 U/L at Cycle 2, Day 1. AP was increased similarly at Cycle 2, Day 15 to a mean of 111.4 U/L and decreased at Cycle 3, Day 1 to a mean of 102.8 U/L. Grade 3 increases were rarely observed (2.8%).

ALT increased from a mean of 24.3 U/L at baseline to a mean of 29.6 U/L at Cycle 1, Day 15. ALT values tended to decrease between cycles and increase again after treatment. There was 3.7% grade 3 events and 0.5% grade 4 events observed in the relevant safety population (n=215).

AST increased from a mean of 25.8 U/L at baseline to a mean of 34.5 U/L at Cycle 1, Day 15 and a mean of 35.0 U/L at Cycle 2, Day 15. AST values tended to decrease between cycles and increase again after treatment. Grade 3 increases were rarely observed (1.9%).

Amylase increased from a mean of 50.1 U/L at baseline to a mean of 58.7 U/L at Cycle 1, Day 15 and decreased to a mean of 55.8 U/L at Cycle 2, Day 1. Amylase values fluctuated across cycles. Grade 3 increases were rarely observed (1.4%).

Bilirubin increased from a mean of 8.51 µmol/L at baseline to a mean of 10.05 µmol/L at Cycle 1, Day 8 and decreased to a mean of 7.74 µmol/L at Cycle 2, Day 1. Bilirubin increased again to a mean of 8.55 µmol/L at Cycle 2, Day 15, but decreased to baseline level (mean of 8.05 µmol/L) by Cycle 3, Day 1. Grade 3/4 increases were rarely observed (2.3%/0.5%).

Creatine kinase (CK) decreased from a mean of 53.6 U/L at baseline to a mean of 42.1 U/L at Cycle 1, Day 8, increasing to a mean of 55.6 U/L by Cycle 1, Day 15. Creatine kinase decreased again after the next treatment with a mean of 41.8 U/L at Cycle 2, Day 8 and increased to a mean of 57.7 U/L at Cycle 3, Day 1.

Creatinine increased slightly from a mean of 79.28 µmol/L at baseline to a mean of 81.74 µmol/L at Cycle 1, Day 15 and decreased to baseline level (76.94 µmol/L) at Cycle 2, Day 1. Creatinine increased again after the next treatment to a mean of 84.51 µmol/L at Cycle 2, Day 15, decreasing to 76.60 µmol/L at Cycle 3, Day 1. Grade 3 increases were rarely observed (1.9%).

GGT increased from a mean of 55.0 U/L at baseline to 62.1 U/L at Cycle 1, Day 15. GGT decreased slightly at Cycle 2, Day 1 with a mean of 52.5 U/L and increased to a mean of 68.9 U/L at Cycle 2, Day 15. GGT values tended to decrease between cycles and increase following treatment. After Cycle 5, the mean GGT values tended to increase: Cycle 5, Day 1: 75.3 U/L, Cycle 6, Day 1: 91.0 U/L, Cycle 7, Day 1: 106.1 U/L and Cycle 8, Day 1: 105.5 U/L, suggesting a possible cumulative increase over cycles. Grade 3 increases were commonly observed (23.3%), while grade 4 events were rare

(1.9%). Hence, GGT increased often to a severe degree and the pattern observed suggest cumulative toxicity. Hence, TEAEs of GGT increased resulted in dose delay, dose reduction, and treatment withdrawal in 17.7%, 3.3%, and 8.8% of patients. The applicant has not added information neither to section 4.4 of the SmPC, and this is acceptable.

Glucose decreased from a mean of 7.45 mmol/L at baseline to 6.00 mmol/L at Cycle 1, Day 15 and increased by Cycle 2, Day 1 to a mean of 7.61 mmol/L. Mean glucose decreased again after Cycle 2 treatment, but was increased by Cycle 3, Day 1.

Lactate dehydrogenase decreased from a mean of 425.9 U/L at baseline to 386.4 U/L at Cycle 1, Day 15. Mean values continued to decrease over time: 315.2 U/L at Cycle 3, Day 1, 287.3 U/L at Cycle 4, Day 1, 263.8 U/L at Cycle 5, Day 1 and 247.8 U/L at Cycle 6, Day 1. Decrease in mean and median lactate dehydrogenase over time could be considered associated with an antitumor effect of LT and not a toxicity as such.

Lipase increased from a mean of 27.5 U/L at baseline to 35.8 U/L at Cycle 1, Day 15 and decreased to 27.3 U/L at Cycle 2, Day 1. Median values increased again following Cycle 2 treatment and were decreased again by Cycle 3. Grade 3/4 increases were rarely observed (3.3%/0.9%).

Potassium decreased from a mean of 4.20 mmol/L at baseline to a mean of 4.04 mmol/L at Cycle 1, Day 15, with increase at Cycle 2, Day 1 with a mean of 4.15 mmol/L. Mean potassium values decreased again during Cycle 2, but were increased by Cycle 3. Median and mean potassium values varied across cycles, and there was no evidence of a cumulative effect.

Sodium decreased from a mean of 138.6 mmol/L at baseline to a mean of 138.0 mmol/L at Cycle 1, Day 8 and increased to a mean of 139.3 mmol/L at Cycle 1, Day 15. A similar trend was found for Cycle 2, Day 1 with a mean value of 139.4 mmol/L a mean value of 138.2 mmol/L at Cycle 2, Day 8 and increase to a mean of 139.4 mmol/L at Cycle 2, Day 15. The changes observed are not considered clinically significant.

There were no clear changes over time in: albumin, BUN, calcium, chloride, magnesium, phosphate, protein and urea.

Overall, the laboratory values seem affected to a low degree except for GGT, which were increased often to a severe degree and the pattern observed suggest cumulative toxicity.

2.6.8.5. In vitro biomarker test for patient selection for safety

There was no biomarker test evaluated for patient safety.

2.6.8.6. Safety in special populations

Intrinsic factors

Age

Table 50. Overall Summary of Treatment-emergent Adverse Events by Age Group
Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

Age Group: < 65 years

Treatment-emergent adverse event	<=90 µg/kg (N=4)	120 µg/kg (N=11)	150 µg/kg s101 (N=45)	150 µg/kg s201 (N=65)	150 µg/kg subtotal (N=110)	200 µg/kg (N=13)	All Doses (N=138)
Number of TEAEs	31	196	579	914	1493	229	1949
Patients with any TEAE	4 (100)	11 (100)	45 (100)	65 (100)	110 (100)	13 (100)	138 (100)
Patients with any grade 3 or higher TEAE	1 (25.0)	7 (63.6)	35 (77.8)	51 (78.5)	86 (78.2)	10 (76.9)	104 (75.4)
Patients with any TEAE related to ADCT-402	2 (50.0)	10 (90.9)	37 (82.2)	53 (81.5)	90 (81.8)	11 (84.6)	113 (81.9)
Patients with any TEAE leading to ADCT-402 dose delay or reduction	0	6 (54.5)	18 (40.0)	36 (55.4)	54 (49.1)	3 (23.1)	63 (45.7)
Patients with any TEAE leading to ADCT-402 withdrawal	0	2 (18.2)	4 (8.9)	16 (24.6)	20 (18.2)	2 (15.4)	24 (17.4)
Patients with any serious TEAE	0	5 (45.5)	15 (33.3)	26 (40.0)	41 (37.3)	3 (23.1)	49 (35.5)
Patients with any TEAE with fatal outcome	0	1 (9.1)	5 (11.1)	4 (6.2)	9 (8.2)	0	10 (7.2)

Age Group: ≥ 65 years

Treatment-emergent adverse event	<=90 µg/kg (N=6)	120 µg/kg (N=21)	150 µg/kg s101 (N=25)	150 µg/kg s201 (N=80)	150 µg/kg subtotal (N=105)	200 µg/kg (N=14)	All Doses (N=146)
Number of TEAEs	62	257	482	866	1348	229	1896
Patients with any TEAE	6 (100)	21 (100)	24 (96.0)	78 (97.5)	102 (97.1)	14 (100)	143 (97.9)
Patients with any grade 3 or higher TEAE	3 (50.0)	16 (76.2)	18 (72.0)	56 (70.0)	74 (70.5)	13 (92.9)	106 (72.6)
Patients with any TEAE related to ADCT-402	5 (83.3)	19 (90.5)	21 (84.0)	65 (81.3)	86 (81.9)	12 (85.7)	122 (83.6)
Patients with any TEAE leading to ADCT-402 dose delay or reduction	1 (16.7)	8 (38.1)	9 (36.0)	39 (48.8)	48 (45.7)	4 (28.6)	61 (41.8)
Patients with any TEAE leading to ADCT-402 withdrawal	1 (16.7)	3 (14.3)	4 (16.0)	20 (25.0)	24 (22.9)	2 (14.3)	30 (20.5)
Patients with any serious TEAE	2 (33.3)	7 (33.3)	15 (60.0)	31 (38.8)	46 (43.8)	3 (21.4)	58 (39.7)
Patients with any TEAE with fatal outcome	0	2 (9.5)	6 (24.0)	4 (5.0)	10 (9.5)	0	12 (8.2)

Related TEAEs include TEAEs that were considered by the Investigator to be possibly or probably related to the study drug, or TEAEs with a missing relationship on the case report form.
ADCT-402=Loncastuximab tesirine; adverse events are graded using CTCAE v4.0. For each category (except for Number of TEAEs), patients are included only once, even if they experienced multiple events in that category.
Dataset: adsl, adae
Program: t-ae-overall.sas, Output: t1_3_1_1_ae_overall_age_p1.rtf, Generated on: 23APR2021 11:11

Adverse events according to age (<65 years vs ≥65 years) were significantly different regarding AEs leading to withdrawal (18.2 vs 22.9%) and SAEs (37.3% vs 43.5%), but this is an expected finding and within an acceptable level, considering the pre-treated study population.

Sex

Table 51. Overall Summary of Treatment-emergent Adverse Events by Sex
Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

Sex: Female

Treatment-emergent adverse event	<=90 µg/kg (N=7)	120 µg/kg (N=9)	150 µg/kg s101 (N=34)	150 µg/kg s201 (N=60)	150 µg/kg subtotal (N=94)	200 µg/kg (N=9)	All Doses (N=119)
Number of TEAEs	85	136	572	770	1342	149	1712
Patients with any TEAE	7 (100)	9 (100)	34 (100)	58 (96.7)	92 (97.9)	9 (100)	117 (98.3)
Patients with any grade 3 or higher TEAE	3 (42.9)	7 (77.8)	26 (76.5)	40 (66.7)	66 (70.2)	7 (77.8)	83 (69.7)
Patients with any TEAE related to ADCT-402	5 (71.4)	9 (100)	27 (79.4)	51 (85.0)	78 (83.0)	7 (77.8)	99 (83.2)
Patients with any TEAE leading to ADCT-402 dose delay or reduction	1 (14.3)	4 (44.4)	13 (38.2)	34 (56.7)	47 (50.0)	3 (33.3)	55 (46.2)
Patients with any TEAE leading to ADCT-402 withdrawal	1 (14.3)	1 (11.1)	3 (8.8)	14 (23.3)	17 (18.1)	2 (22.2)	21 (17.6)
Patients with any serious TEAE	1 (14.3)	6 (66.7)	18 (52.9)	18 (30.0)	36 (38.3)	2 (22.2)	45 (37.8)
Patients with any TEAE with fatal outcome	0	1 (11.1)	7 (20.6)	2 (3.3)	9 (9.6)	0	10 (8.4)

Sex: Male

Treatment-emergent adverse event	<=90 µg/kg (N=3)	120 µg/kg (N=23)	150 µg/kg s101 (N=36)	150 µg/kg s201 (N=85)	150 µg/kg subtotal (N=121)	200 µg/kg (N=18)	All Doses (N=165)
Number of TEAEs	8	317	489	1010	1499	309	2133
Patients with any TEAE	3 (100)	23 (100)	35 (97.2)	85 (100)	120 (99.2)	18 (100)	164 (99.4)
Patients with any grade 3 or higher TEAE	1 (33.3)	16 (69.6)	27 (75.0)	67 (78.8)	94 (77.7)	16 (88.9)	127 (77.0)
Patients with any TEAE related to ADCT-402	2 (66.7)	20 (87.0)	31 (86.1)	67 (78.8)	98 (81.0)	16 (88.9)	136 (82.4)
Patients with any TEAE leading to ADCT-402 dose delay or reduction	0	10 (43.5)	14 (38.9)	41 (48.2)	55 (45.5)	4 (22.2)	69 (41.8)
Patients with any TEAE leading to ADCT-402 withdrawal	0	4 (17.4)	5 (13.9)	22 (25.9)	27 (22.3)	2 (11.1)	33 (20.0)
Patients with any serious TEAE	1 (33.3)	6 (26.1)	12 (33.3)	39 (45.9)	51 (42.1)	4 (22.2)	62 (37.6)
Patients with any TEAE with fatal outcome	0	2 (8.7)	4 (11.1)	6 (7.1)	10 (8.3)	0	12 (7.3)

Related TEAEs include TEAEs that were considered by the Investigator to be possibly or probably related to the study drug, or TEAEs with a missing relationship on the case report form.
ADCT-402=Loncastuximab tesirine; adverse events are graded using CTCAE v4.0. For each category (except for Number of TEAEs), patients are included only once, even if they experienced multiple events in that category.
Dataset: adsl, adae
Program: t-ae-overall.sas, Output: t1_3_1_2_ae_overall_sex_p1.rtf, Generated on: 23APR2021 11:11

The adverse events according to sex are not considered clinically significantly different.

Race

Table 52. Overall Summary of Treatment-emergent Adverse Events by Race Group
Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

Race Group: White

Treatment-emergent adverse event	<=90 µg/kg (N=9)	120 µg/kg (N=24)	150 µg/kg s101 (N=67)	150 µg/kg s201 (N=130)	150 µg/kg subtotal (N=197)	200 µg/kg (N=26)	All Doses (N=256)
Number of TEAEs	86	329	1025	1608	2633	436	3484
Patients with any TEAE	9 (100)	24 (100)	66 (98.5)	130 (100)	196 (99.5)	26 (100)	255 (99.6)
Patients with any grade 3 or higher TEAE	3 (33.3)	18 (75.0)	50 (74.6)	94 (72.3)	144 (73.1)	22 (84.6)	187 (73.0)
Patients with any TEAE related to ADCT-402	6 (66.7)	21 (87.5)	56 (83.6)	106 (81.5)	162 (82.2)	22 (84.6)	211 (82.4)
Patients with any TEAE leading to ADCT-402 dose delay or reduction	1 (11.1)	10 (41.7)	26 (38.8)	67 (51.5)	93 (47.2)	7 (26.9)	111 (43.4)
Patients with any TEAE leading to ADCT-402 withdrawal	0	4 (16.7)	7 (10.4)	34 (26.2)	41 (20.8)	4 (15.4)	49 (19.1)
Patients with any serious TEAE	2 (22.2)	8 (33.3)	29 (43.3)	52 (40.0)	81 (41.1)	5 (19.2)	96 (37.5)
Patients with any TEAE with fatal outcome	0	1 (4.2)	11 (16.4)	8 (6.2)	19 (9.6)	0	20 (7.8)

Race Group: Black

Treatment-emergent adverse event	<=90 µg/kg (N=1)	120 µg/kg (N=4)	150 µg/kg s101 (N=2)	150 µg/kg s201 (N=5)	150 µg/kg subtotal (N=7)	200 µg/kg (N=0)	All Doses (N=12)
Number of TEAEs	7	71	19	45	64	-	142
Patients with any TEAE	1 (100)	4 (100)	2 (100)	4 (80.0)	6 (85.7)	-	11 (91.7)
Patients with any grade 3 or higher TEAE	1 (100)	1 (25.0)	2 (100)	4 (80.0)	6 (85.7)	-	8 (66.7)
Patients with any TEAE related to ADCT-402	1 (100)	4 (100)	1 (50.0)	4 (80.0)	5 (71.4)	-	10 (83.3)
Patients with any TEAE leading to ADCT-402 dose delay or reduction	0	2 (50.0)	0	4 (80.0)	4 (57.1)	-	6 (50.0)
Patients with any TEAE leading to ADCT-402 withdrawal	1 (100)	1 (25.0)	1 (50.0)	1 (20.0)	2 (28.6)	-	4 (33.3)
Patients with any serious TEAE	0	1 (25.0)	1 (50.0)	1 (20.0)	2 (28.6)	-	3 (25.0)
Patients with any TEAE with fatal outcome	0	0	0	0	0	-	0

Race Group: All Others

Treatment-emergent adverse event	<=90 µg/kg (N=0)	120 µg/kg (N=4)	150 µg/kg s101 (N=1)	150 µg/kg s201 (N=10)	150 µg/kg subtotal (N=11)	200 µg/kg (N=1)	All Doses (N=16)
Number of TEAEs	-	53	17	127	144	22	219
Patients with any TEAE	-	4 (100)	1 (100)	9 (90.0)	10 (90.9)	1 (100)	15 (93.8)
Patients with any grade 3 or higher TEAE	-	4 (100)	1 (100)	9 (90.0)	10 (90.9)	1 (100)	15 (93.8)
Patients with any TEAE related to ADCT-402	-	4 (100)	1 (100)	8 (80.0)	9 (81.8)	1 (100)	14 (87.5)
Patients with any TEAE leading to ADCT-402 dose delay or reduction	-	2 (50.0)	1 (100)	4 (40.0)	5 (45.5)	0	7 (43.8)
Patients with any TEAE leading to ADCT-402 withdrawal	-	0	0	1 (10.0)	1 (9.1)	0	1 (6.3)
Patients with any serious TEAE	-	3 (75.0)	0	4 (40.0)	4 (36.4)	1 (100)	8 (50.0)
Patients with any TEAE with fatal outcome	-	2 (50.0)	0	0	0	0	2 (12.5)

Related TEAEs include TEAEs that were considered by the Investigator to be possibly or probably related to the study drug, or TEAEs with a missing relationship on the case report form.
ADCT-402=Loncastuximab tesirine; Adverse events are graded using CTCAE v4.0. Only treatment-emergent adverse events are summarized. For each category (except for Number of TEAEs), patients are included only once, even if they experienced multiple events in that category.
Dataset: adsl, adae
Program: t-ae-overall.sas, Output: t1_3_1_3_ae_overall_race_p1.rtf, Generated on: 23APR2021 11:11

The assessment of adverse events according to race are hampered by low numbers of patients recruited from all races other than Caucasian.

Extrinsic factors

Region

Table 53. Overall Summary of Treatment-emergent Adverse Events by Region
Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

Region: USA

Treatment-emergent adverse event	<=90 µg/kg (N=10)	120 µg/kg (N=25)	150 µg/kg s101 (N=31)	150 µg/kg s201 (N=59)	150 µg/kg subtotal (N=90)	200 µg/kg (N=20)	All Doses (N=145)
Number of TEAEs	93	383	447	801	1248	324	2048
Patients with any TEAE	10 (100)	25 (100)	30 (96.8)	58 (98.3)	88 (97.8)	20 (100)	143 (98.6)
Patients with any grade 3 or higher TEAE	4 (40.0)	17 (68.0)	22 (71.0)	46 (78.0)	68 (75.6)	17 (85.0)	106 (73.1)
Patients with any TEAE related to ADCT-402	7 (70.0)	23 (92.0)	25 (80.6)	50 (84.7)	75 (83.3)	17 (85.0)	122 (84.1)
Patients with any TEAE leading to ADCT-402 dose delay or reduction	1 (10.0)	12 (48.0)	9 (29.0)	27 (45.8)	36 (40.0)	5 (25.0)	54 (37.2)
Patients with any TEAE leading to ADCT-402 withdrawal	1 (10.0)	3 (12.0)	3 (9.7)	13 (22.0)	16 (17.8)	2 (10.0)	22 (15.2)
Patients with any serious TEAE	2 (20.0)	8 (32.0)	11 (35.5)	27 (45.8)	38 (42.2)	5 (25.0)	53 (36.6)
Patients with any TEAE with fatal outcome	0	1 (4.0)	3 (9.7)	3 (5.1)	6 (6.7)	0	7 (4.8)

Region: Europe

Treatment-emergent adverse event	<=90 µg/kg (N=0)	120 µg/kg (N=7)	150 µg/kg s101 (N=39)	150 µg/kg s201 (N=86)	150 µg/kg subtotal (N=125)	200 µg/kg (N=7)	All Doses (N=139)
Number of TEAEs	-	70	614	979	1593	134	1797
Patients with any TEAE	-	7 (100)	39 (100)	85 (98.8)	124 (99.2)	7 (100)	138 (99.3)
Patients with any grade 3 or higher TEAE	-	6 (85.7)	31 (79.5)	61 (70.9)	92 (73.6)	6 (85.7)	104 (74.8)
Patients with any TEAE related to ADCT-402	-	6 (85.7)	33 (84.6)	68 (79.1)	101 (80.8)	6 (85.7)	113 (81.3)
Patients with any TEAE leading to ADCT-402 dose delay or reduction	-	2 (28.6)	18 (46.2)	48 (55.8)	66 (52.8)	2 (28.6)	70 (50.4)
Patients with any TEAE leading to ADCT-402 withdrawal	-	2 (28.6)	5 (12.8)	23 (26.7)	28 (22.4)	2 (28.6)	32 (23.0)
Patients with any serious TEAE	-	4 (57.1)	19 (48.7)	30 (34.9)	49 (39.2)	1 (14.3)	54 (38.8)
Patients with any TEAE with fatal outcome	-	2 (28.6)	8 (20.5)	5 (5.8)	13 (10.4)	0	15 (10.8)

Related TEAEs include TEAEs that were considered by the Investigator to be possibly or probably related to the study drug, or TEAEs with a missing relationship on the case report form.
ADCT-402=Loncastuximab tesirine; adverse events are graded using CTCAE v4.0. For each category (except for Number of TEAEs), patients are included only once, even if they experienced multiple events in that category.
Dataset: adsl, adae
Program: t-ae-overall.sas, Output: t1_3_1_4_ae_overall_regn_p1.rtf, Generated on: 23APR2021 11:11

Adverse events according to region (US vs Europe) show that overall there might be a tendency towards more toxicity observed in Europe; however, the differences are not clinically significant and the incidences are overall acceptable.

Table 54. Summary of Selected Treatment-Emergent Adverse Events by Age Group

MedDRA Terms	Age <65 (N = 110)	Age 65-74 (N = 77)	Age 75-84 (N = 24)	Age ≥85 (N= 4)	Total (N = 215)
Patients with any TEAE	110 (100)	75 (97.4)	23 (95.8)	4 (100)	212 (98.6)
Patients with any serious TEAE	41 (37.3)	35 (45.5)	9 (37.5)	2 (50.0)	87 (40.5)
- Fatal	9 (8.2)	10 (13.0)	0	0	19 (8.8)
- Hospitalisation/prolong existing hospitalisation	38 (34.5)	34 (44.2)	9 (37.5)	2 (50.0)	83 (38.6)
- Life-threatening	3 (2.7)	2 (2.6)	0	0	5 (2.3)
- Disability/incapacity	0	0	0	0	0
- Other (medically significant)	4 (3.6)	1 (1.3)	1 (4.2)	0	6 (2.8)
TEAE leading to drop-out	20 (18.2)	15 (19.5)	8 (33.3)	1 (25.0)	44 (20.5)
Psychiatric disorders	20 (18.2)	14 (18.2)	4 (16.7)	0	38 (17.7)
Nervous system disorders	32 (29.1)	21 (27.3)	10 (41.7)	1 (25.0)	64 (29.8)
Accidents and injuries	7 (6.4)	16 (20.8)	3 (12.5)	1 (25.0)	27 (12.6)
Cardiac disorders	12 (10.9)	13 (16.9)	3 (12.5)	0	28 (13.0)
Vascular disorders	17 (15.5)	18 (23.4)	4 (16.7)	1 (25.0)	40 (18.6)
Cerebrovascular disorders	2 (1.8)	2 (2.6)	0	0	4 (1.9)
Infections and infestations	29 (26.4)	32 (41.6)	8 (33.3)	4 (100)	73 (34.0)
Anticholinergic syndrome	41 (37.3)	27 (35.1)	10 (41.7)	2 (50.0)	80 (37.2)
Quality of life decreased	0	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	3 (2.7)	10 (13.0)	1 (4.2)	1 (25.0)	15 (7.0)
Other AE appearing more frequently in older patients (oedema peripheral)	21 (19.1)	19 (24.7)	8 (33.3)	2 (50.0)	50 (23.3)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
Source: Module 5.3.5.3, Integrated Summary of Safety - Updated Tables and Figures, 2022, t10_q155_ae_age_p1 and Module 5.3.5.3, Integrated Summary of Safety - Updated Tables and Figures, 2022, MedDRA search strategies

The applicant has provided the requested table of MedDRA terms and age groups. It is noted that more patients had peripheral oedema with increasing age, but this is within an acceptable range and are probably due to age-related comorbidities and not treatment with LT.

2.6.8.7. Immunological events

Table 55 **Summary of treated subjects, treatment regimen and ADA screening and confirmation figures by study and overall**

		Clinical trials				Overall
		[1]ADCT-402-101	[2]ADCT-402-102		[3]ADCT-402-201^	
Patient number information						
part 1+2/ pivotal	# of patients treated	183	35		145	**363**
	# of patients evaluated for ADA	183	36[$]		145	**364[$]**
	# of samples evaluated for ADA	925	112[$]		687[&]	**1724[$&]**
	# of samples screened positive (% of total samples screened)	177 (19.1%)	11 (9.82%)		99 (14.4%)	**287 (16.6%)**
	# of patients screened positive	82	8		54	**144**
	# of samples confirmed positive (% of samples screened positive)	26 (14.7%)	1 (9.09%)		1 (1.01%)	**28 (9.76%)**
	# of patients confirmed positive	6	1		1	**8**
	# patients confirmed positive pre-dose (% of patients treated)	5[#] (2.73%)	1 (2.86%)		1 (0.689%)	**7**
	#patients confirmed positive and negative pre-dose (% of patients treated)	1 (0.545%)	0 (0%)		0 (0%)	**1 (0.275%)**
Administration						
Part 1 dose-escalation	Route of administration	IV	IV	**pivotal**	IV	
	dose	dose-escalation including 15 (n=4), 30 (n=4), 60 (n=4), 90 (n=5), 120 (n=16), 150 (n=19) and 200 (n=36) µg/kg	dose-escalation including 15 (n=5), 30 (n=7), 60 (n=3), 90 (n=4), 120 (n=5), 150 and (n=6) µg/kg		150 µg/kg Q3W x 2 then 75 µg/kg thereafter (n=145) 06Apr2020	
	frequency	Q3W	Q3W		Q3W	
Part 2 expansion	Route of administration	IV	IV			
	dose	120 µg/kg (26), 150 µg/kg (n=69)	50 µg/kg (n=5)			
	frequency	a. For 120 µg/kg, Q3W; for 150 µg/kg, Q3W or Q3Wx3 then 75 µg/kg Q3W thereafter.	QW			

Sources:
[1] Table 12-32 CSR ADCT-402-101 and ADCT402_A_006_R
[2] Table 8 CSR ADCT-402-102 and ADCT402_A_005_R
[3] Separate PK/ADA report and ADCT402_A_0_019_R

$ 111 samples of 35 patients for clinical trial ADCT-402-102; one sample relate to patient 03-004 who was a screen failure was tested for ADA and 112 samples and 36 patients reported in bioanalytical report, Appendix Table 4, section 12 link.
& one sample collected after cut-off date 9th March20 measured and reported in bioanalytical report, Appendix Table 5, section 12 link
# 2 patients, with higher background values in samples, with very low titers after dosing, and indicative of low matrix influence
Abbreviations:
Q3W: Patients were given loncastuximab tesirine on day 1 of each 3-week (21-day) treatment cycle.
QW: Patients were given loncastuximab tesirine on day 1, 8, and 15
Patients with a BMI ≥35 kg/m^2 had their dose calculated based on an adjusted body weight as follows:
Adjusted body weight (ABW) in kg = 35 kg/m^2 * (height in meters)^2
Dose to administer (mg) = dosage (µg/kg) * ABW / 1000

In clinical studies, loncastuximab tesirine did not induce ADAs. Of 328 patients tested, only 1 patient (0.305%) exhibited a positive ADA response, which occurred at post-dose only, with very low log_2 titre (<1).

The applicant claims that only one patient tested positive for ADAs in the clinical studies. This is acceptable information at this time. Please refer also to the clinical pharmacology and efficacy sections.

2.6.8.8. Safety related to drug-drug interactions and other interactions

Clinical drug interaction studies have not been performed. *In vitro* assessments indicate that SG3199 is not a potent inhibitor of cytochrome P450 enzymes but is potentially metabolised via CYP3A4/5. SG3199 is a P-glycoprotein substrate, but not an inhibitor of P-glycoprotein. Given the short apparent half-life of SG3199 in circulation and exceedingly low exposure relative to half maximal inhibitory concentration (IC_{50}) for inhibition of the various human transporter proteins, loncastuximab tesirine has a minimal potential for drug-drug interactions.

No clinically important interactions are expected with LT. The provided information is acceptable; however, please refer also to the clinical pharmacology section.

2.6.8.9. Discontinuation due to adverse events

Table 56. Overall Summary of TEAEs-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

Treatment-emergent adverse event	≤90 µg/kg (N=10)	120 µg/kg (N=32)	150 µg/kg s101 (N=70)	150 µg/kg s201 (N=145)	150 µg/kg Subtotal (N=215)	200 µg/kg (N=27)	All Doses (N=284)
Number of TEAEs	93	453	1061	1780	2841	458	3845
Patients with any TEAE	10 (100)	32 (100)	69 (98.6)	143 (98.6)	212 (98.6)	27 (100)	281 (98.9)
Patients with any Grade 3 or higher TEAE	4 (40.0)	23 (71.9)	53 (75.7)	107 (73.8)	160 (74.4)	23 (85.2)	210 (73.9)
Patients with any TEAE related to ADCT-402	7 (70.0)	29 (90.6)	58 (82.9)	118 (81.4)	176 (81.9)	23 (85.2)	235 (82.7)
Patients with any TEAE leading to ADCT-402 dose delay or reduction	1 (10.0)	14 (43.8)	27 (38.6)	75 (51.7)	102 (47.4)	7 (25.9)	124 (43.7)
Patients with any TEAE leading to ADCT-402 withdrawal	1 (10.0)	5 (15.6)	8 (11.4)	36 (24.8)	44 (20.5)	4 (14.8)	54 (19.0)
Patients with any serious TEAE	2 (20.0)	12 (37.5)	30 (42.9)	57 (39.3)	87 (40.5)	6 (22.2)	107 (37.7)
Patients with any TEAE with fatal outcome	0	3 (9.4)	11 (15.7)	8 (5.5)	19 (8.8)	0	22 (7.7)

Source: ISS Table 1.3.1
Related TEAEs include TEAEs that were considered by the Investigator to be possibly or probably related to the study drug or TEAEs with a missing relationship on the case report form. Adverse events were graded using CTCAE v4.0. For each category (except for Number of TEAEs), patients were included only once, even if they experienced multiple events in that category.
ADCT-402 = loncastuximab tesirine; CTCAE = Common Terminology Criteria for Adverse Events; DLBCL = diffuse large B-cell lymphoma; s101 = Study ADCT-402-101; s201 = Study ADCT-402-201; TEAE = treatment-emergent adverse event

The most common TEAE leading to treatment withdrawal was GGT increased (8.8%), followed by oedema peripheral (2.8%) and thrombocytopenia (1.9%). TEAEs required dose reduction in 7.0% of patients, with 6.0% assessed as treatment-related. The most common TEAE leading to dose delay was GGT increased (17.7%), followed by neutropenia (11.2%) and thrombocytopenia (7.9%). The most common TEAE leading to dose reduction was GGT increased (3.3%).

Dose delay

Table 57. Most Common (≥1% of Patients in All Doses Combined) TEAEs Leading to Dose Delay by Preferred Term-Loncastuximab Tesirine Monotherapy Treated DLBCL Patients

			150 µg/kg				
Preferred Term	≤90 µg/kg (N=10)	120 µg/kg (N=32)	s101 (N=70)	s201 (N=145)	Subtotal (N=215)	200 µg/kg (N=27)	All Doses (N=284)
Patient with any dose delayed TEAE	1 (10.0)	14 (43.8)	26 (37.1)	74 (51.0)	100 (46.5)	7 (25.9)	122 (43.0)
Gamma-glutamyltransferase increased	0	3 (9.4)	7 (10.0)	31 (21.4)	38 (17.7)	3 (11.1)	44 (15.5)
Neutropenia	1 (10.0)	0	6 (8.6)	18 (12.4)	24 (11.2)	2 (7.4)	27 (9.5)
Thrombocytopenia	0	0	4 (5.7)	13 (9.0)	17 (7.9)	0	17 (6.0)
Oedema peripheral	0	2 (6.3)	2 (2.9)	4 (2.8)	6 (2.8)	0	8 (2.8)
Blood alkaline phosphatase increased	0	0	2 (2.9)	6 (4.1)	8 (3.7)	0	8 (2.8)
Alanine aminotransferase increased	0	0	2 (2.9)	5 (3.4)	7 (3.3)	0	7 (2.5)
Anaemia	0	1 (3.1)	1 (1.4)	4 (2.8)	5 (2.3)	0	6 (2.1)
Leukopenia	0	0	0	6 (4.1)	6 (2.8)	0	6 (2.1)
Fatigue	1 (10.0)	2 (6.3)	3 (4.3)	0	3 (1.4)	0	6 (2.1)
Pleural effusion	0	1 (3.1)	2 (2.9)	2 (1.4)	4 (1.9)	1 (3.7)	6 (2.1)
Pyrexia	0	1 (3.1)	1 (1.4)	3 (2.1)	4 (1.9)	0	5 (1.8)
Aspartate aminotransferase increased	0	0	2 (2.9)	3 (2.1)	5 (2.3)	0	5 (1.8)
Platelet count decreased	0	0	3 (4.3)	0	3 (1.4)	2 (7.4)	5 (1.8)
Rash	0	1 (3.1)	1 (1.4)	2 (1.4)	3 (1.4)	1 (3.7)	5 (1.8)
Abdominal pain	0	0	1 (1.4)	3 (2.1)	4 (1.9)	0	4 (1.4)
Blood bilirubin increased	0	0	2 (2.9)	2 (1.4)	4 (1.9)	0	4 (1.4)
Photosensitivity reaction	0	0	0	4 (2.8)	4 (1.9)	0	4 (1.4)
Hypophosphataemia	0	0	0	3 (2.1)	3 (1.4)	0	3 (1.1)
Erythema	0	0	0	3 (2.1)	3 (1.4)	0	3 (1.1)
Face oedema	0	2 (6.3)	0	1 (0.7)	1 (0.5)	0	3 (1.1)

Source: ISS Table 1.3.12

Adverse events were coded using MedDRA version 22.0. For each preferred term, patients were included only once at the maximum severity.
DLBCL = diffuse large B-cell lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; s101 = Study ADCT-402-101; s201 = Study ADCT-402-201; TEAE = treatment-emergent adverse event

A fifth of the patients (20.5%) had any TEAE leading to withdrawal of LT and this is considered a high number. The most common AEs leading to treatment withdrawal was GGT increased (8.8%), followed by oedema peripheral (2.8%) and thrombocytopenia (1.9%). The most common AEs leading to dose delay was GGT increased (17.7%), followed by neutropenia (11.2%) and thrombocytopenia (7.9%). The most common TEAE leading to dose reduction was GGT increased (3.3%). The high start dose for the first two cycles have probably increased these rates of withdrawal and dose delays, but considering the heavily pretreated study population and late-line treatment setting, this is acceptable.

It is not recommended to reduce the dose of LT in case of high-grade AEs, but rather to postpone the next dose by e.g. a week or two. he SmPC states that if the treatment is delayed more than 3 weeks, the dose of LT should be reduced by 50%. The applicant has provided the clarification requested regarding dose-reductions. In the pivotal study ADCT-402-201, which used the proposed dosing regimen exclusively, 61 (42.1%) patients had a dose delay. Out of these 9 (14.8%) patients had dose reduction.

Table 58. Overall Response Rate by Independent Reviewer by Dose Modification (All-Treated Population)

	Dose Delay with Reduction (N = 9)	Dose Delay without Reduction (N = 52)	Total (N = 145)
BOR, n (%)			
CR	4 (44.4)	24 (46.2)	36 (24.8)
PR	1 (11.1)	13 (25.0)	34 (23.4)
SD	1 (11.1)	6 (11.5)	22 (15.2)
NE	1 (11.1)	2 (3.8)	23 (15.9)
PD	2 (22.2)	7 (13.5)	30 (20.7)
ORR (CR + PR), n (%)	5 (55.6)	37 (71.2)	70 (48.3)
95% CI for ORR	(21.2, 86.3)	(56.9, 82.9)	(39.9, 56.7)
95% CI for CR	(13.7, 78.8)	(32.2, 60.5)	(18.0, 32.7)

BOR = best overall response; CI = confidence interval; CR = complete response; NE = not evaluable; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease.
Source: Module 5.3.5.2, Study ADCT-402-201, Section 14 - Updated Tables and Figures, 2022, t4_q141_orr_dosedly_eff

The table above provides the overall response rate for patients who had a dose reduction subsequently to dose delay at 50% of the initial dose, and for patients with a dose delay which did not require a dose reduction. The table shows that considerably fewer patients had a PR, while the same fraction in both groups obtained a CR or SD as best response. Considering the small sample size (n=9) of those who were dose-reduced, this difference could be due to chance and the proposed approach and update to the SmPC section 4.2 is acceptable. Especially since section 4.2 also states that: '*Note: If toxicity requires dose reduction following the second dose of 0.15 mg/kg (Cycle 2), the patient should receive the dose of 0.075 mg/kg for Cycle 3.'*

2.6.8.10. Post marketing experience

As of the data cut-off of 01 Mar 2021, loncastuximab tesirine was not marketed in any region. No post marketing data are available.

2.6.9. Discussion on clinical safety

The safety population of main focus is the 215 patients, who received the proposed dosing regimen i.e 150 µg/kg loncastuximab tesirine monotherapy (LT) every 3 weeks for 2 cycles followed by 75 µg/kg Q3W for the subsequent cycles. Although other safety populations are reported in the dossier, the assessment of the safety profile of loncastuximab tesirine is primarily based on these data. Hence, the frequencies of adverse reactions in the SmPC section 4.8 are based on these 215 patients. Although the safety database is limited in sample size, this is acceptable in the context of a CMA. However, a planned confirmatory study will report safety of loncastuximab tesirine in combination with rituximab versus rituximab/gemcitabine/oxaliplatin, so the applicant was asked to justify how the safety profile of loncastuximab tesirine monotherapy can be confirmed by safety results from this study. The applicant argues that the toxicity profile of LT can be confirmed by the planned confirmatory RCT, although rituximab is added to LT, because the toxicity profile of rituximab is well-characterised with minimal overlap with the toxicity profile of loncastuximab tesirine and this is agreed.

Considering that the median treatment duration among these 215 patients was 45.0 days (range: 1 to 569 days) and the median number of treatment cycles administered was 3.0 cycles (range: 1 to 26 cycles), the applicant has committed to provide the final CSR for the pivotal study ADCT-402-201 as a specific obligation post-authorisation**.**

Almost all of the patients in the studies 101 and 201 experienced at least one **adverse event (AE)** from the relevant safety data base (n=215). The most frequently observed events were GGT increased (35.8%), neutropenia (34.9%), fatigue (30.2%), anaemia (28.8%), thrombocytopenia (28.4%), nausea (26.5%), oedema peripheral (23.3%), cough (20.9%), rash (20.0%), blood alkaline phosphatase increased (19.1%), diarrhoea (17.7%), pyrexia and hypokalaemia (16.7% each), alanine aminotransferase (ALT) increased and constipation (16.3% each), dyspnoea and aspartate aminotransferase (AST) increased (15.8% each), vomiting (15.3%), decreased appetite (14.4%), pleural effusion (13.5%), hypomagnesaemia (13.0%), abdominal pain and pruritus (11.6% each), and hypophosphataemia (11.2%).

Grade 3 or higher adverse events were also very common (74.4%), and those often reported were (grade 3 and >grade 3): neutropenia (24.2% and 20.0%), GGT increased (17.2% and 13.5%), thrombocytopenia (15.8% and 9.8%), anaemia (11.6% and 6.5%) and neutrophil count decreased (3.3% and 2.8%).

Treatment-related adverse events (ADRs) were observed in the majority of patients i.e. 81.9%, of which 51.2% had a grade 3 or higher ADR. The most common ADRs of all grades were GGT increased (28.8%), neutropenia (26.0%), fatigue (20.9%), rash (19.5%), oedema peripheral and nausea (16.7% each), thrombocytopenia (16.3%), blood alkaline phosphatase increased (14.9%), anaemia (13.5%), AST increased (11.6%) and pleural effusion and ALT increased (11.2% each). The most frequently observed **grade 3 or higher ADRs** were neutropenia (24.2%), GGT increased (17.2%), thrombocytopenia (15.8%), anaemia (11.6%), and neutrophil count decreased (3.3%). It is noted that neutropenia was observed in a third of the patients (34.9%) and of grade 3 or higher in 24.2% of the patients, but only 3.3% had febrile neutropenia. The risk of neutropenia with LT is considered adequately reflected in the SmPC.

Regarding the laboratory data, the observed increase in GGT was further discussed by the applicant. However, it is concluded that increased GGT resulted in dose delay, dose reduction, and treatment withdrawal in 17.7%, 3.3%, and 8.8% of patients.

Adverse events of special interest included oedema or effusion, fatigue, increased liver function tests (LFT), pain, skin reactions and nail disorders. Of main interest in the assessment of the safety profile is the high rate of **oedema or effusions** (36.3%) and the 23.3% of the patients, who had peripheral oedema (grade 3: 1.4%) and/or pleural effusions (all grades: 13.5% / grade 3: 0.4%). The applicant has clarified that the events of effusions and oedema reported in patients receiving loncastuximab tesirine in clinical studies are probably related to LT treatment as it contains Pyrrolobenzodiazepine (PBD) dimers, which have been associated with events of effusion and oedema. Most of the events of effusions and oedema were non-serious, but serious events were reported for pleural effusion (1.9%) and pericardial effusion (0.9%). The underlying cause of these events is unknown but may include vascular leak syndrome. In summary, 5 patients experienced 7 serious adverse events of pleural and/or pericardial effusion; 3 patients experienced pleural effusion; 1 patient experienced pericardial effusion; and 1 patient experienced both pleural and pericardial effusion. All events of pleural effusion were assessed by the investigator as related to study treatment**.** The proposed text in Sections 4.4 and 4.8 was agreed. Events of oedema and effusion will continue to be closely monitored in the ongoing clinical trials and post-marketing surveillance and these ADRs have been classified as an important identified risk in the Risk Management Plan.

Additionally, **skin reactions and nail disorders** were commonly observed (46.5%), but grade 3 events were rare (3.7%) and there were no grade 4 or 5 events. The events mainly consisted of: rash (20.0%) and pruritus (11.6%) and most events were in the skin and were related to treatment with LT.

The applicant has provided the requested detailed discussion on the risk of **phototoxicity**; and the argumentation regarding plausible mechanisms and non-clinical observations raised from toxicology studies are acceptable. With current knowledge of this toxicity, the updated text in the SmPC is considered clear and acceptable. Moreover, phototoxicity has been included as an Important Identified Risk in the Risk Management Plan.

Serious adverse events (SAEs) were observed in 40.5%, most commonly febrile neutropenia (3.3%), hypercalcaemia (2.8%), and pyrexia (2.3%). Not all of the SAEs are considered treatment-related and the observed incidences are acceptable considering the treatment setting and the underlying disease.

Deaths in the safety database were mostly due to disease progression (52.1%). Five patients died due to treatment-related AEs, such as infections and/or sepsis and one died of lung infection. The narratives for the patients, who received the proposed dosing of LT have been assessed and the conclusions on causes of death are overall agreed. Patients, who died from other causes, generally died after subsequent treatment and it is agreed that these deaths were not related to treatment with LT.

The overall **discontinuation rate due to AEs** was 20.5%, most often due to GGT increased (8.8%), followed by oedema peripheral (2.8%) and thrombocytopenia (1.9%). This is a rather high rate, and may be due to the policy not to reduce the dose, but rather to delay the next dose in case of unacceptable toxicity. This approach has been clarified in section 4.2 of the SmPC. However, the rate of discontinuations is considered acceptable for the proposed indication and targeted patient population.

Since the start dose in the first 2 cycles is double (150 µg/kg iv) the dose for the subsequent cycles (75 µg/kg iv) according to the recommended dosing regimen, the safety profile of the individual dose is considered difficult to assess, although there is considered to be a dose-toxicity relationship. Therefore, it is not possible to differentiate between what toxicities are from the size of the dose or from cumulative toxicity from the continued use of LT.

Since it is expected that at least some infusion-related reactions are observed with an ADC such as LT after longer exposure, this will be a focus in the assessment of the final CSR. Overall, the pattern of toxicity with LT is considered acceptable and in line with other antibody-drug conjugates (ADCs).

Overall, the pattern of toxicity with LT seems acceptable and in line with the toxicity profile of other antibody-drug conjugates (ADCs). Currently, the safety profile observed with LT is considered partly due to adverse drug effects, especially the increased GGT and peripheral oedema and pleural effusions. However, the gastrointestinal and haematological toxicity can also be related to either the underlying disease or late effects of prior treatments in this heavily pre-treated population. Relevant information on clinical safety has been appropriately reflected in the SmPC.

2.6.10. Conclusions on the clinical safety

In conclusion, the safety profile of LT seems in line with other antibody-drug conjugates (ADCs) and the most common adverse reactions are oedema/effusions, gastrointestinal and haematological toxicity. The current safety database is acceptable for a CMA.

The following measures are necessary to address the missing safety data in the context of a conditional MA: The final CSR for the pivotal study ADCT-402-201 and the final CSR from the Phase 3 study ADCT-402-311, n=330 will be submitted.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 59. Summary of safety concerns

Summary of safety concerns	
Important identified risks	*Phototoxicity* *Oedema and effusion*
Important potential risks	*Embryo-foetal toxicity*
Missing information	*Use in patients with moderate or severe hepatic impairment* *Use in patients with severe renal impairment*

2.7.2. Pharmacovigilance plan

Table 60. Ongoing and planned additional pharmacovigilance activities

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
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				
Study ADCT-402-201 A Phase 2 Open-Label Single-Arm Study to Evaluate the Efficacy and Safety of Loncastuximab Tesirine in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL) Ongoing	To evaluate the efficacy of single-agent loncastuximab tesirine in patients with relapsed or refractory DLBCL To further evaluate the efficacy of loncastuximab tesirine To characterise the safety profile of loncastuximab tesirine To characterise the pharmacokinetic (PK) profile of loncastuximab tesirine To evaluate the immunogenicity of loncastuximab tesirine To evaluate the impact of loncastuximab tesirine treatment on health-related quality of life	The overall safety profile (including phototoxicity and oedema and effusion) of loncastuximab tesirine as presented in the final CSR	Protocol finalised	Mar 2018
			Trial completion	Aug 2022
			CSR filing	Dec 2023
Category 3 - Required additional pharmacovigilance activities				
Hepatic Impairment Study An Open-Label, Non-Randomised, Dose-Escalation Trial in Patients with Moderate and Severe Hepatic Impairment Planned	To determine a safe and appropriate dosing regimen of loncastuximab tesirine in patients with moderate and severe hepatic impairment	Use in patients with moderate or severe hepatic impairment	Protocol finalised	Sep 2022
			Protocol submission	1 month after EC decision
			Trial completion	Dec 2026
			CSR filing	Jun 2027

2.7.3. Risk minimisation measures

Table 61. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Phototoxicity	Routine risk minimisation measures: • *Dose modifications based on severity of occurrence in SmPC sections 4.2 and 4.4* • *Warning of serious/severe photosensitivity reactions in SmPC sections 4.4 and 4.8* • *Guidance to monitor patients for photosensitivity reactions in SmPC section 4.4* • *Guidance on preventative advice for patients in SmPC section 4.4* • *Adverse reaction in SmPC section 4.8* • *Information on animal phototoxicity in SmPC section 5.3* • *Warning and guidance in PL section 2* • *Side effect in PL section 4* • *Specialist prescribing only* Additional risk minimisation measures: • *Patient alert card*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *Phototoxicity Questionnaire* Additional pharmacovigilance activities: • *Study ADCT-402-201*
Oedema and effusion	Routine risk minimisation measures: • *Dose modifications based on severity of occurrence in SmPC sections 4.2 and 4.4* • *Warning and guidance to monitor patients in SmPC section 4.4* • *Adverse reaction in SmPC section 4.8* • *Warning and guidance in PL section 2* • *Side effect in PL section 4* • *Specialist prescribing only* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *Study ADCT-402-201*
Embryo-foetal toxicity	Routine risk minimisation methods: • *Warning and guidance on embryo-foetal harm and contraceptive use in SmPC section 4.4* • *Guidance on preventative advice in SmPC section 4.6* • *Warning and guidance in PL section 2* • *Specialist prescribing only* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *None*
Use in patients with moderate or severe hepatic impairment	Routine risk minimisation measures: • *Warning/information in SmPC sections 4.2 and 5.2* • *Recommendation to monitor for AEs in SmPC section 4.2*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• *Warning in PL section 2* • *Specialist prescribing only* Additional risk minimisation measures: • *None*	• *None* Additional pharmacovigilance activities: • *Hepatic Impairment Study*
Use in patients with severe renal impairment	Routine risk minimisation measures: • *Warning/information in SmPC sections 4.2, 5.2 and 5.3* • *Recommendation to monitor patients for AEs in SmPC section 4.2* • *Specialist prescribing only* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *None*

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

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

2.8.2. 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 request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 23 April 2021. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

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

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Zynlonta (loncastuximab tesirine) 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;
- It is approved under a conditional marketing authorisation [REG Art 14-a]

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indication is *as monotherapy for the treatment* of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy.

The definitions of relapsed and refractory are those of the International Working Group (IWG) response criteria (Cheson et al., 2007).

The aim of the therapy with Zynlonta is to improve overall response rate (ORR) in patients with relapsed or refractory DLBCL who have received at least 2 prior systemic lines of therapy, although complete response rate (CRR) is considered more clinically relevant in this non-curative setting. The targeted disease is the most common subtype of non-Hodgkin lymphoma (NHL), and accounts for 25% to 45% of all NHL cases worldwide.

3.1.2. Available therapies and unmet medical need

DLBCL is an aggressive disease with short life expectancy if left untreated. With currently available treatments, around 50% of newly diagnosed patients can be cured. The prognosis of patients whose disease is refractory to initial chemotherapy and therefore not eligible for high-dose therapy and autologous stem cell transplant (HD-ASCT), or who relapse early after HD-ASCT, is extremely poor. Few patients exhibit responses to salvage therapy, with an ORR of 26% (CR rate 7%) to the next line of therapy and a median survival of approximately 6 months (Crump, 2017).

Possible treatment options include a second HD-ASCT, allogeneic stem cell transplant (SCT), participation in clinical trials with novel drugs, or palliative care (ESMO, NCCN guidelines). Despite recently approved new treatment modalities (such as Polatuzumab vedotin (Polivy) and Tafasitamab (Minjuvi), no treatment is considered standard of care. Thus, there remains an unmet medical need for patients with relapsed or refractory DLBCL.

3.1.3. Main clinical studies

The main evidence of efficacy submitted on loncastuximab tesirine is the pivotal phase 2 study ADCT-402-201 (Study 201, also named LOTIS-2 n=145), a multicentre, open-label, single-arm study that evaluated its efficacy and safety in patients with relapsed or refractory DLBCL. The primary endpoint of the trial was ORR as assessed by an Independent Review Committee (IRC) using Lugano 2014 criteria. Secondary endpoints were IRC-DOR, IRC-PFS and OS.

Results from the phase 1 study ADCT-402-101 (Study 101, n=137) that assessed dose escalation and expansion are considered supportive.

3.2. Favourable effects

Study ADCT-402-201:

- The primary endpoint of the pivotal study, IRC-assessed ORR was 48.3% (70/145 patients; 95% CI: 39.9, 56.7), and complete response (CR) was 24.1% (35/145 patients, 95% CI:17.4, 31.9). The median duration of response (DOR) for the responding subjects was 13.37 months (95% CI: 6.87, NE). Median time-to-response (TTR) was 41 days (range 35-247 days).
- Median PFS in the overall population was 4.93 months (95% CI: 2.89, 8.31) and median OS was 9.53 months (95% CI: 6.93, 11.47).
- The applicant presented sensitivity analyses implementing the following censoring rules: Progressive disease (PD)/death after new anticancer therapies other than transplant are counted as events and PD/death after stem cell transplant (SCT) are censored at the last valid assessment date before the transplant. The results were consistent with those reported in the CSR.
- A total of 12 patients received SCT directly following loncastuximab tesirine therapy. Eleven patients received SCT as consolidation therapy after responding to loncastuximab tesirine. These patients underwent SCT without intervening therapy. One patient went directly to allogeneic SCT after progression following loncastuximab tesirine therapy. Out of the 12 patients, 5 died at some point after transplant (2 of disease progression and 3 of other reasons). It is rather encouraging that LT may also constitute a bridge towards SCT at this late-line stage.

Study ADCT-402-101:

In the supportive dose- escalation phase I study 402-101, ORR was 42.3%, and median DOR in responders was 4.5 months. Median PFS was 2.8 months and median OS 7.46 months. Median TTR was 43 days.

3.3. Uncertainties and limitations about favourable effects

- Notwithstanding that efficacy results from the pivotal trial are encouraging, the uncontrolled nature and limited duration of follow-up of the pivotal trial limits interpretation and extrapolation of data.
- Although Study 101 was a dose escalation study, the considerable difference between the pivotal and the supportive study in terms of median DOR (13.4 vs. 4.5 months, respectively) and median PFS (4.9 vs. 2.8 months) is not understood, especially since the ORR results are similar and the patients in the two studies seem to be comparable in their baseline characteristics. It was acknowledged that the numerically higher DOR, PFS, and OS in diffuse large B-cell lymphoma (DLBCL) patients treated in Study 201 as compared to those treated in Study 101 likely reflect the fact that all patients treated in Study 201 received the optimal dosing regimen of loncastuximab tesirine with the planned reduction after Cycle 2, which provides consistent efficacious exposure.
- In study 201 16 patients received chimeric antigen receptor T-cell (CAR-T) therapy at some time after progression following loncastuximab tesirine therapy. Out of these 16 patients, 10 died at some time after CAR-T therapy (9 of disease progression and 1 of other reasons). Although LT may facilitate bridging to CAR-T treatment, the efficacy of this treatment after LT needs further exploration.

In the context of a CMA, the applicant needs to submit the results from a confirmatory study within a reasonable timeframe to corroborate the efficacy and safety of Zynlonta. The applicant has initiated study ADCT-402-311, which is a phase 3, controlled, randomised study of loncastuximab

tesirine combined with the CD-20-targeting monoclonal antibody rituximab (Lonca-R) versus standard immunochemotherapy (rituximab / gemcitabine / oxaliplatin) in patients with R/R DLBCL.

3.4. Unfavourable effects

Almost all of the patients in the studies 101 and 201 experienced at least one AE from the relevant safety data base (n=215). The most frequently observed events were GGT increased (35.8%), neutropenia (34.9%), fatigue (30.2%), anaemia (28.8%), thrombocytopenia (28.4%), nausea (26.5%), oedema peripheral (23.3%), cough (20.9%), rash (20.0%), blood alkaline phosphatase increased (19.1%), diarrhoea (17.7%), pyrexia and hypokalaemia (16.7% each), alanine aminotransferase (ALT) increased and constipation (16.3% each), dyspnoea and aspartate aminotransferase (AST) increased (15.8% each), vomiting (15.3%), decreased appetite (14.4%), pleural effusion (13.5%), hypomagnesaemia (13.0%), abdominal pain and pruritus (11.6% each), and hypophosphataemia (11.2%).

Grade 3 or higher adverse events were also very common (74.4%), and those often reported were (grade 3 and >grade 3): neutropenia (24.2% and 20.0%), GGT increased (17.2% and 13.5%), thrombocytopenia (15.8% and 9.8%), anaemia (11.6% and 6.5%) and neutrophil count decreased (3.3% and 2.8%).

Treatment-related adverse events (ADRs) were observed in the majority of patients i.e. 81.9%, of which 51.2% had a grade 3 or higher ADR. The most common ADRs of all grades were GGT increased (28.8%), neutropenia (26.0%), fatigue (20.9%), rash (19.5%), oedema peripheral and nausea (16.7% each), thrombocytopenia (16.3%), blood alkaline phosphatase increased (14.9%), anaemia (13.5%), AST increased (11.6%) and pleural effusion and ALT increased (11.2% each).

Adverse events of special interest included oedema or effusion, fatigue, increased liver function tests (LFT), pain, skin reactions and nail disorders. Of particular interest in the assessment of the safety profile is the high rate of **oedema or effusions** (36.3%): peripheral oedema (23.3% of which grade 3: 1.4%) and/or pleural effusions (all grades: 13.5% of which grade 3: 0.4%).

Serious adverse events (SAEs) were observed in 40.5%, most commonly febrile neutropenia (3.3%), hypercalcaemia (2.8%), and pyrexia (2.3%). Not all of the SAEs are considered treatment-related and the observed incidences are acceptable considering the treatment setting and the underlying disease.

Deaths in the safety database were mostly due to disease progression (50.2%). Five patients died due to treatment-related AEs, such as infections and/or sepsis and one died of lung infection.

The overall **discontinuation rate due to AEs** was 20.5%, most often due to GGT increased (8.8%), followed by oedema peripheral (2.8%) and thrombocytopenia (1.9%).

3.5. Uncertainties and limitations about unfavourable effects

The median treatment duration among the 215 patients in the safety data base was 45.0 days (range: 1 to 569 days) and the median number of treatment cycles administered was 3.0 cycles (range: 1 to 26 cycles), which was considered limited. Therefore the applicant has committed to provide the final CSR for the pivotal study ADCT-402-201 as a specific obligation post-authorisation.

3.6. Effects Table

Table 62. Effects table for Loncastuximab Tesirine (Zynlonta) Monotherapy for the treatment of DLBCL after two prior systemic therapies (data cut-off: 01 March 2021).

Effect	Short Description	Unit	Treatment Loncastuximab Tesirine	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
ORR*	Overall response rate	% 95% CI	48.3 39.9, 56.7	NA	Single-arm trial	
CRR*	Complete response rate	% 95% CI	24.8 18.0, 32.7	NA		
mDOR*	Median duration of response	Months 95% CI	13.37 6.87, NE	NA		
mPFS*	Median progression free survival	Months 95% CI	4.93 2.89, 8.31	NA		
Unfavourable Effects (LT monotherapy, n=215)						
Any AEs		%	98.6	NA		
Any ADRs		%	81.4	NA		
Grade ≥ 3 AEs		%	74.4	NA		
SAEs		%	40.5	NA		
AEs leading to discontinuation		%	20.5	NA		
AEs leading to death		%	8.8	NA		

Abbreviations: AE – Adverse Event; ADR – Adverse Drug Reaction (treatment-related AE); SAE – Serious Adverse Event
*by IRC

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Despite several recent approvals for patients with R/R DLBCL, no standard treatment exists and the prognosis remains poor. For these patients, the European Society of Medical Oncology (ESMO) treatment guidelines recommend stem cell transplant, participation in clinical studies, or palliative care.

The efficacy results of Zylonta in a group of patients with relapse of refractory high-grade DLBCL are considered relevant and indicate a clinically meaningful favourable effect. Most responses occurred after 2 doses of LT and were durable. Response rates from the phase I dose escalation trial were supportive, although the median DOR in this group was considerably lower.

The main uncertainties regarding the benefit-risk assessment relate to the short duration of follow-up, the limitations associated with the single arm trial design and the difference in DOR and PFS between the pivotal study and the supportive study. Specific obligations are in place (see Annex II) to resolve these uncertainties.

The applicant has compared LT to approved and recommended therapies in R/R DLBCL utilizing a matching-adjusted indirect comparison (MAIC) with historical data. Considering the limitations of these cross-study comparisons, it is considered that LT monotherapy fulfills an unmet need based on the efficacy results.

The most important safety concerns are related to bone marrow toxicity. Febrile neutropenia was also noted and it should be clarified if B-cell depletion was observed and could have an impact on number of infections. Adverse events of special interest included oedema or effusion which have been further characterised, and the risk of oedema and effusions are now listed as an important identified risk in the RMP. For completeness regarding the assessment of safety, the applicant has committed to provide the final CSR for the pivotal study ADCT-402-201 as a specific obligation post-authorisation. Overall, the safety profile of LT is in line with other antibody-drug conjugates (ADCs) and seems generally manageable.

3.7.2. Balance of benefits and risks

The B/R of treatment with Loncastuximab Tesirine is positive.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

As comprehensive data on the product are not available a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease. In addition, the product is designated as an orphan medicinal product.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.
- It is likely that the applicant will be able to provide comprehensive data.

  The applicant will conduct a randomised Phase 3 study ADCT-402-311 of loncastuximab tesirine and the CD-20-targeting monoclonal antibody rituximab (Lonca-R) versus standard immunochemotherapy (rituximab / gemcitabine / oxaliplatin) in patients with R/R DLBCL to provide comprehensive and confirmatory clinical data following a CMA.

According to the protocol of confirmatory Phase 3 trial LOTIS-5, target enrolment for Part 2 is 330 subjects, aiming for final PFS analysis at 263 events, estimated at approximately 6 months after completing enrolment.

The applicant has reported that initial data from the safety run-in did not reveal new signals relative to the safety profile of LT + rituximab and Part 2 is ongoing: Up to August 2022, a total of 50 patients have been recruited, out of which 20 belonged to the safety run-in (Part 1, took place in 4 countries only), and the rest to the actual randomised phase (Part 2). Overall, considering the confirmatory trial timeline (due date for provision of efficacy and safety results is Q4 2025), its feasibility seems endorsed by the fact that current enrolment is taking place at 63 study sites in 12 countries, and more sites are expected to open across other countries in the EU and Latin America.

Additionally, the applicant has committed to providing the final CSR for pivotal study ADCT-402-201 as a specific obligation (see Annex II).

- Unmet medical need will be addressed, as:

Currently, many patients with R/R DLBCL will receive treatment with chemotherapy regimens which are composed of one or more chemotherapy agents not specifically approved for use in DLBCL. In the European Society for Medical Oncology (ESMO) guidelines treatment options for 3rd line therapy is limited to allogenic transplant (if eligible), clinical trials with novel drugs, or palliative care. Similarly, the NCCN (National Comprehensive Cancer Network) guidelines for the treatment of B-cell lymphoma lists several combinations that can be used in R/R DLBCL (NCCN 2021). However, the response to many of these regimens is low and short-lived. A recent analysis of patients requiring treatment for R/R DLBCL revealed that patients receiving 3rd line treatment had a response rate of 27%, and the ORR for patients who were refractory of last treatment at 21.2%. Response rates were even poorer in patients who received ≥4th line, with <10% of patients responding to therapy (Radford 2019). In addition, the overall survival for these patients is quite short, with a median of approximately 6 months (Radford 2019, Halwani et al 2019).

Several treatments for R/R B-NHL and R/R DLBCL, respectively, have been approved in the European Union in recent years:

Pixantrone ([Pixuvri] as monotherapy) received the indication: Monotherapy for the treatment of adult patients with multiply R/R aggressive non-Hodgkin B-cell Lymphomas (NHL). The benefit of pixantrone treatment has not been established in patients when used as 5th line or greater chemotherapy in patients who are refractory to last therapy. ORR in NHL reaches 40%, with ORR in patients previously receiving rituximab even lower at 32% (https://www.ema.europa.eu/en/documents/product-information/pixuvri-epar-product-information_en.pdf-). Clinically relevant adverse reactions include myelosuppression, cardiotoxicity and infections.

Two CAR-T therapies, Yescarta and Kymriah, have been approved in patients with R/R DLBCL after two or more lines of systemic therapy. The ORR for these therapies ranged from 53.5% to 72%, with a CR rate ranging from 40% to 51%. Median DOR was not estimable (Yescarta) and not reached (Kymriah) (Yescarta SmPC 2021, Kymriah SmPC 2021). They both show substantial toxicity, with 57% to 93% of patients having adverse drug reactions of cytokine release syndrome (11% to 23% Grade 3 or higher), and 20% to 58% having encephalopathy (11% to 31% Grade 3 or higher) (Yescarta SmPC 2021, Kymriah SmPC 2021). Further CAR-T therapies are only available at specialised centres and up to 30% of eligible patients may not be able to receive the planned therapy, either due to manufacturing problems or rapid disease progression.

Polatuzumab vedotin (Polivy) in combination with bendamustine + rituximab has been approved for the treatment of R/R DLBCL patients who are not candidates for haematopoietic stem cell transplant. The primary endpoint (CR rate at primary response assessment (6-8 weeks after Cycle 6 Day 1 or last dose of study medication, based on PET-CT, IRC assessed) was increased in the pola+BR arm: 40.0% (16/40 patients; 95% CI: [24.9%, 56.7%]) vs 17.5% in the BR arm (7/40 patients; 95% CI: [7.3%, 32.8%]). The Δ was 22.5%, statistically significant and in favour of pola+BR (95% CI: 2.6%, 40.2%; p =0.0261, Cochran Mantel-Haenszel [CMH] chi-square). The most frequently reported (≥ 30%) ADRs (all grades) in patients treated with Polivy plus BR in previously treated DLBCL were neutropenia (45.7%), diarrhoea (35.8%), nausea (33.1%), thrombocytopenia (32.5%), anaemia (31.8%) and neuropathy peripheral (30.5%)

Tafasitamab ([Minjuvi] in combination with lenalidomide) followed by Minjuvi monotherapy recently received a CMA for the treatment of adult patients with R/R DLBCL who are not eligible for ASCT. In a single-arm study in 81 adults with R/R DLBCL ORR of 56.8%, with a CRR of 39.5%, and a median overall DOR of 34.6 months. Toxicity was substantial, and Grade 3 or 4 adverse drug reactions included neutropenia (49%), thrombocytopenia (17%), and febrile neutropenia (12%). Grade 3 or 4 infections were seen in 28% of patients (Minjuvi) SmPC 2021).

In conclusion, available treatments show substantial toxicities, and response rates ranging from 40% to 70%, meaning that up to 60% of patients will not respond. Also, more than 50% of patients will not have a durable response. In addition, R/R DLBCL patients with high-risk characteristics such as primary refractory disease and double-hit / triple-hit disease have not been studied throughout. Thus, therapeutic alternatives in R/R DLBCL, especially with a different mechanism of action, to fulfil the unmet medical need are still required. With an IRC-assessed ORR of 48.3% and CR of 24.1% and a DOR for the responding subjects of 13.37 months loncastuximab tesirine, with its new mechanism of action (in the treatment of DLBCL) as well as its immediate availability, is considered to fulfil this unmet medical need. Therefore, Loncastuximab tesirine can be considered a major therapeutic advantage in the proposed target population for whom there are very limited and often no other treatment options available, in particular when available options are unlikely to be efficacious, or when it is the preferred option in view of its efficacy and safety profiles.

The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required: given the positive benefit risk, the poor prognosis in R/R DLBCL patients having received at least two prior systemic therapies and the fact that the different MOA leads to a favourable safety profile.

3.8. Conclusions

The overall benefit/risk balance of Zynlonta is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Zynlonta is not similar to Kymriah, Yescarta, Polivy, Minjuvi within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Zynlonta is favourable in the following indication:

Zynlonta as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy.

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

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

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

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

- **Risk Management Plan (RMP)**

The marketing authorisation holder (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.

- **Additional risk minimisation measures**

Prior to the launch of Zynlonta in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the phototoxicity risk minimisation material, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

An additional risk minimisation material is aimed at reducing the risk of photosensitivity reactions.

The MAH shall ensure that in each Member State where Zynlonta is marketed, all healthcare professionals who are expected to prescribe Zynlonta and all patients who are expected to use Zynlonta are provided with the following risk minimisation material:

- Patient Alert Card

- Patient Alert Cards are provided to Zynlonta prescribing physicians for distribution to patients receiving Zynlonta (loncastuximab tesirine) for relapsed or refractory diffuse large B-cell lymphoma (DLBCL) or high-grade B-cell lymphoma (HGBL)
- This card should be carried by patients at all times and provides the following key important safety information to patients:
    - Zynlonta treatment may increase the risk of photosensitivity reactions in patients
    - Signs and symptoms of photosensitivity reactions
    - Instructions to avoid exposure to direct and indirect sunlight and to contact a healthcare professional when any skin eruption occurs
    - A warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using Zynlonta

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
Hepatic Impairment Study: An Open-Label, Non-Randomised, Dose-Escalation Trial in Patients with Moderate and Severe Hepatic Impairment. To determine a safe and appropriate dosing regimen of loncastuximab tesirine in patients with moderate and severe hepatic impairment. (Category 3 study)	Protocol submission 1 month after EC decision Trial completion Dec 2026 CSR filing Jun 2027

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy and safety of loncastuximab tesirine in the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy, the MAH should submit the final results of study ADCT-402-311 (LOTIS 5), a Phase 3 study comparing loncastuximab tesirine combined with rituximab (Lonca R) versus immunochemotherapy in patients with relapsed or refractory DLBCL.	Q4/2025
In order to confirm the safety of loncastuximab tesirine in the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy, the MAH should submit the final results from study ADCT-402-201 a Phase 2, single-arm study investigating the efficacy and safety of loncastuximab tesirine in patients with relapsed or refractory DLBCL.	Q4/2023

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 loncastuximab tesirine is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.