EU Risk Management Plan
for
Zynlonta®
(Loncastuximab tesirine)

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Table of Content

List of Tables

List of Abbreviations

Abbreviation/Term	Definition
ABC	Activated B-cell-like
ADA	Anti-drug antibodies
ADC	Antibody-drug conjugate
AE	Adverse event
ALT	Alanine aminotransferase
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
B-ALL	B-cell acute lymphoblastic leukaemia
BCRP	Breast cancer resistance protein
BLA	Biologics license application
B-NHL	B-cell non-Hodgkin lymphoma
BSEP	Bile salt export pump
CCI	Charlson comorbidity index
Cmax	Maximum concentration
CNS	Central nervous system
CR	Complete response
CrCL	Creatinine clearance
CTCAE	Common terminology criteria for adverse events
DLBCL	Diffuse large B-cell lymphoma
DNA	Deoxyribonucleic acid
DRF	Dose range finding
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End of treatment
E-R	Exposure-response
EU	European Union
GCB	Germinal centre B-cell-like
G-CSF	Granulocyte colony-stimulating factor
GemOx	Gemcitabine/oxaliplatin
GEP	Gene expression profiling

Abbreviation/Term	Definition
GGT	Gamma-glutamyl transferase
GLP	Good laboratory practice
HCV	Hepatitis C virus
HDC	High-dose chemotherapy
HGBL	High-grade B-cell lymphoma
HIV	Human immunodeficiency virus
HMRN	Haematological Malignancy Research Network
HNSTD	Highest non-severely toxic dose
ICH	International council for harmonisation of technical requirements for pharmaceuticals for human use
IgG1	Immunoglobulin G1
IV	Intravenous
Lonca-R	Loncastuximab tesirine + rituximab
MCL	Mantle cell lymphoma
MATE	Multi-antimicrobial extrusion protein
MedDRA	Medical dictionary for regulatory activities
MTD	Maximum tolerated dose
NHL	Non-Hodgkin's lymphoma
NOAEL	No observed adverse effect level
NOS	Not otherwise specified
OATP	Organic anion-transporting polypeptide
OCT	Organic cation transporter
OS	Overall survival
PABA	Para-aminobenzyl alcohol
PBD	Pyrrolobenzodiazepine
P-gp	P-glycoprotein
PL	Package leaflet
PR	Partial response
PSUR	Periodic safety update report
QTc	Corrected QT
QTcF	Corrected QT interval based on Fridericia's formula
R-CHOP	Rituximab - cyclophosphamide, vincristine, doxorubicin, and prednisone

Abbreviation/Term	Definition
R-GemOx	Rituximab - gemcitabine/oxaliplatin
RMP	Risk management plan
SCT	Stem cell transplant
SD	Standard deviation
SOC	System organ class
SmPC	Summary of product characteristics
SWFI	Sterile water for injection
TEAE	Treatment-emergent adverse event
UK	United Kingdom
ULN	Upper limit of normal
US	United States
UV	Ultraviolet
WHO	World Health Organisation

Part I: Product(s) Overview

Table 1: Product Overview

Active substance(s) (INN or common name)	Loncastuximab tesirine
Pharmacotherapeutic group(s) (ATC Code)	Antineoplastic agents; other antineoplastic agents; monoclonal antibodies (not yet assigned)
Marketing Authorisation Applicant	ADC Therapeutics (NL) B.V.
Medicinal products to which this RMP refers	One
Invented name(s) in the European Economic Area (EEA)	Zynlonta®
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Loncastuximab tesirine is a CD19-directed antibody conjugated to an alkylating agent.
	Summary of mode of action: Loncastuximab tesirine is an antibody-drug conjugate (ADC). Loncastuximab tesirine is composed of a humanised monoclonal antibody (RB4v1.2) to which the cytotoxin SG3199 has been conjugated through a cathepsin-cleavable linker. The toxin SG3199 attached to the linker is designated as SG3249, also known as tesirine. Once bound to CD19, loncastuximab tesirine is internalised and the cathepsin-cleavable linker is cleaved, releasing free pyrrolobenzodiazepine (PBD) dimers (SG3199) inside the target cell. The PBD dimers are highly efficient anticancer drugs that covalently bind in the minor groove of deoxyribonucleic acid (DNA) and form highly cytotoxic DNA interstrand cross-links. The cross-links formed by the PBD dimers are relatively non-distorting of the DNA structure, making them hidden to DNA repair mechanisms.
	Important information about its composition: Loncastuximab tesirine is composed of the following three components: • RB4v1.2: a humanised immunoglobulin G (IgG)1, kappa monoclonal antibody, specific for human CD19, generated by the variable domain resurfacing of the murine monoclonal anti-B4 (anti-CD19) antibody. • SG3199: a PBD dimer cytotoxin • A cathepsin-cleavable linker, including maleimide, 8-polyethylene glycol, a valine-alanine linker and a para-aminobenzyl alcohol (PABA) self-immolative group, which links SG3199 to the humanised monoclonal antibody. The drug product has an average of two SG3249 molecules covalently bound to the antibody and is supplied as a sterile, white to

	off-white lyophilised, preservative-free cake-like powder in a single-use vial for reconstitution and intended for refrigerated storage at 2 -8°C. Each vial is reconstituted with 2.2 mL Sterile Water for Injection (SWFI) to yield a single-use solution that contains 5 mg/mL of loncastuximab tesirine in 20 mM histidine hydrochloride, 175 mM sucrose, and 0.02% w/v (0.2 mg/mL) polysorbate 20 at pH 6.
Hyperlink to the Product Information	Zynlonta Product Information (Module 1.3)
Indication(s) in the EEA	Current: 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.
	Proposed: Not applicable
Dosage in the EEA	Current: The recommended dose is 0.15 mg/kg administered as an intravenous infusion over 30 minutes on Day 1 of each 3-week treatment cycle for two cycles, followed by 0.075 mg/kg for subsequent cycles.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Powder for concentrate for solution for infusion. Each vial of powder contains 10 mg loncastuximab tesirine.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication and target population

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.

Incidence and prevalence

Non-Hodgkin lymphoma (NHL) was the thirteenth most common cancer of 36 types of cancer reviewed worldwide, with 544,352 incident cases (2.8% of a total 19.3 million new cancer cases) in 2020 (Sung 2021). In the 27 European Union member states (EU-27) in 2020, NHL was the tenth most common cancer of 34 types of cancer, with 86,321 incident cases (3.2% of 2.7 million new cancer cases) (European Cancer Information System [ECIS, 2021]). The Global Cancer Observatory (https://gco.iarc.fr/today/home; accessed 15 March 2021) estimates world incidence of NHL as 5.8/100,000 (age-standardised to standard world population) and 7.0/100,000 (crude incidence). By comparison, the EU-27 incidence for 2020 is substantially higher and estimated at 9.4/100,000 (age-standardised to world standard population), 18.3/100,000 (age-standardised to new European standard population), and 19.4/100,000 (crude incidence) (ECIS, 2021).

DLBCL is the most common subtype of NHL, accounting for approximately 25% to 45% of NHL cases worldwide (Wild 2020). In the EU-27, DLBCL is estimated to represent a third of NHL cases, based on data from selected European registries over the period 2000 to 2019 (data submitted by Applicant for Orphan Medicinal Product Designation, June 2021). Based on these data, and as summarised below (Table 2), the DLBCL crude incidence rate in the EU-27/EEA is estimated to be 0.64 per 10,000, resulting in a prevalence of 4.3 per 10,000, below the threshold for orphan designation. Loncastuximab tesirine was granted orphan designation for the treatment of DLBCL on 20 August 2021 (EU/3/21/2481).

Table 2: Prevalence estimates for DLBCL in the EU and EEA

	A	B	C	I	P
Region/ Country	**Population in 2020**	**NHL incidence count for 2020 (ECIS)**	**DLBCL incidence count for 2020 (33% x B)**	**DLBCL incidence rate per 10k per year in 2020 ([C/A] x 10,000)**	**DLBCL prevalence per 10k in 2020 (I x 6.78 years)**
EU-27	**447,319,916**	**86,321**	**28,486**	**0.6368**	**4.318**
Norway	5,367,580	1,053	-	-	-
Iceland	364,134	54	-	-	-
Liechtenstein	38,747	8*	-	-	-
Total	**453,090,377**	**87,436**	**28,854**	**0.6368**	**4.318**

A: EEA population from Eurostat database (Eurostat, 2021)
B: NHL incident cases for EU-27, Norway, Iceland from ECIS database (ECIS, 2021); estimate identical to that from Globocan database (https://gco.iarc.fr)
C: DLBCL incidence was estimated using a DLBCL/NHL proportion of 33% (as submitted to and accepted by COMP for EU orphan designation for loncastuximab tesirine [EU/3/21/2481])
P: DLBCL prevalence was estimated using formula: Prevalence (P) = Incidence (I) x disease duration (D), where median disease duration (D) was estimated to be 6.78 years, using a 5-year survival of 60%, and assuming a constant hazard rate over the course of survival (as submitted to and accepted by COMP for EU orphan designation for loncastuximab tesirine [EU/3/21/2481])

*Estimated using incident rate of NHL for EU-27+NO+IS (19.3/100,000)

The incidence of DLBCL varies regionally within Europe. The age-standardised incidence rate of DLBCL was reported to be significantly lower in Eastern Europe (Czech Republic, Poland, Slovakia) at 1.79/100,000 and Northern Europe (Iceland, Norway, Sweden) at 0.79/100,000, with no remarkable differences between other European regions of UK/Ireland (3.67/100,000), Central Europe (4.68/100,000), and Southern Europe (4.15/100,000). Incidence increased with advancing age (Sant 2010).

Demographics of the population with the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease

DLBCL can occur at any age, but typically affects older individuals (median age at presentation is >65 years) and is slightly more frequent in males (Mounier 2015).

Although the aetiology of DLBCL is not well understood, a number of factors, including immunosuppression, infections and autoimmune disease, have been associated with a higher risk of DLBCL (Lodhi 2020, Swerdlow 2016, 2017; Tilly 2015, Chihara 2015, Morton 2014; Clarke 2013; Cerhan 2014):

- Chronic infections (e.g., hepatitis C virus [HCV], human immunodeficiency virus [HIV]) and autoimmune diseases, particularly B-cell activating diseases (e.g., Sjögren syndrome).
- Epstein-Barr-virus (EBV), in the setting of immunodeficiency, is strongly associated with specific lymphoma entities such as lymphomatoid granulomatosis, DLBCL associated with chronic inflammation, EBV-positive mucocutaneous ulcer, or primary effusion lymphoma. However, EBV has also been implicated in DLBCL patients with no

documented predisposing immunodeficiency (categorised as EBV-positive DLBCL, NOS when excluding specific disease entities) (Swerdlow 2017).

- Solid organ transplantation, possibly as a result of chronic immune activation in response to the donor organ, immunosuppression therapy, or both, resulting in chronic immune dysfunction.
- Family history of NHL.
- Exposure to certain chemicals (pesticides, hair dyes). An increased risk of lymphoid malignancies has been documented in farmers exposed to pesticides, in workers in industries using formaldehyde, and in those exposed to dioxins, where most workers in these sectors are male (Sant 2010), with employment as seamstress/embroiderer or hairdresser associated with higher risk for females (Chihara 2015).

The main existing treatment options

Treatment recommendations for DLBCL are provided in the European Society for Medical Oncology (ESMO) guidelines (Tilly 2015). The following recommendations are made for relapsed/refractory DLBCL:

- In patients aged <65–70 years with good performance status and no major organ dysfunction, salvage regimens with rituximab and chemotherapy followed, in responsive patients, by high-dose chemotherapy (HDC) and autologous stem cell transplantation (ASCT), are recommended.
- Salvage regimens such as R-DHAP (rituximab, cisplatin, cytarabine, dexamethasone) or R-ICE (rituximab, ifosfamide, carboplatin, etoposide) appear to have similar outcomes. R-GDP (rituximab, cisplatin, gemcitabine, dexamethasone) is also recommended as it has been shown to have similar efficacy but less toxicity than R-DHAP. BEAM (carmustine, etoposide, cytarabine and melphalan) is the most commonly used high-dose regimen.
- Maintenance with rituximab is not recommended.
- Allogeneic transplantation with a sibling or matched unrelated donor may be considered in patients with refractory disease, early relapse or relapse after ASCT.
- Patients not suitable for high-dose therapy may be treated with the same or other salvage regimens as R-GemOx (rituximab - gemcitabine/oxaliplatin). Pixantrone is discussed as an option in heavily treated patients, however the recommendation is to preferably enrol these patients in clinical trials testing the activity of other novel drugs.

The current ESMO guidelines do not reflect the introduction of newer treatments such as chimeric antigen receptor T-cell (CAR-T) therapies and antibody-drug conjugates (ADCs, e.g., Polivy). Certain anti-neoplastic agents are authorised (either centrally or nationally in several EU countries under different trade names) for the treatment of the broader condition of NHL, while others are authorised for non-NHL oncological indications.

Medicinal products authorised centrally in the EU for the treatment of DLBCL or B-cell NHL (see Table 3) are:

- Rituximab (several brands) is indicated for the treatment of patients with CD20 positive DLBCL in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy. Although not specifically authorised for relapsed/refractory

DLBCL, it is now included in combination with salvage chemotherapy for relapsed/refractory disease.

- Pixantrone (Pixuvri®), a cytotoxic aza-anthracenedione, is indicated as monotherapy for the treatment of adult patients with multiple relapsed or refractory aggressive B-cell NHL.
- Axicabtagene ciloleucel (Yescarta®) is indicated for the treatment of adult patients with relapsed/refractory DLBCL after two or more lines of systemic therapy.
- Tisagenlecleucel (Kymriah®) is indicated for the treatment of adult patients with relapsed/refractory DLBCL after two or more lines of systemic therapy.
- Lisocabtagene maraleucel (Breyanzi®) is indicated for the treatment of adult patients with relapsed or refractory DLBCL after two or more lines of systemic therapy.
- Polatuzumab vedotin (Polivy®) is an anti-CD79b antibody-drug conjugate that is authorised in combination with bendamustine and rituximab (BR) for the treatment of adult patients with relapsed/refractory DLBCL who are not candidates for haematopoietic stem cell transplant (SCT), and in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone for the treatment of adult patients with previously untreated DLBCL.
- Tafasitamab (Minjuvi®) is an anti-CD19 monoclonal antibody indicated in combination with lenalidomide followed by Minjuvi monotherapy for the treatment of adult patients with relapsed or refractory DLBCL who are not eligible for ASCT.

Table 3: Centrally authorised medicinal products in the EU for the treatment of DLBCL

Active Substance	Tradename (MAH)	Indication
Immunotherapeutic agents		
Rituximab	Mabthera (Roche) Truxima (Celltrion) Ritemvia (Celltrion) Blitzima (Celltrion) Riximyo (Sandoz) Rixathon (Sandoz)	Treatment of adult patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.
Pixantrone	Pixuvri (Servier)	Treatment of adult patients with multiply relapsed or refractory aggressive non-Hodgkin B-cell lymphoma.
Axicabtagene ciloleucel	Yescarta (Novartis)	Treatment of adult patients with R/R DLBCL after two or more lines of systemic therapy.
Tisagenlecleucel	Kymriah (Kite Pharma)	Treatment of adult patients with R/R DLBCL after two or more lines of systemic therapy.
Lisocabtagene maraleucel	Breyanzi (Bristol Myers Squibb)	Treatment of adult patients with R/R DLBCL after two or more lines of systemic therapy.
Polatuzumab vedotin	Polivy (Roche)	Treatment of adult patients with relapsed/refractory DLBCL, who are not candidates for haematopoietic SCT, in combination with bendamustine and rituximab.

Active Substance	Tradename (MAH)	Indication
Immunotherapeutic agents		
		Treatment of adult patients with previously untreated DLBCL in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone.
Tafasitamab	Minjuvi (Incyte)	Treatment of adult patients with relapsed or refractory DLBCL, who are not eligible for ASCT, in combination with lenalidomide followed by Minjuvi monotherapy.

ASCT=autologous stem cell transplantation; DLBCL=diffuse large B-cell lymphoma; R/R=relapsed/refractory; SCT=stem cell transplant.

In previously untreated DLBCL, the combination of the anti-CD20 monoclonal antibody rituximab and CHOP chemotherapy (R-CHOP) remains the backbone of therapy, with the total number of cycles, and addition of radiation, dependent on stage at presentation and tumour bulk. This approach can achieve durable remissions in approximately 60% of patients. For those who develop disease that is refractory to up-front treatment, or who relapse after achieving remission, outcomes are particularly poor, with HDC and autologous stem cell transplant (ASCT) achieving long term remissions in only a minority of patients in the era of rituximab (Liu 2019).

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Diffuse large B-cell lymphoma is an aggressive B-cell lymphoma histologically characterised by dense proliferation of neoplastic medium or large B lymphoid cells with a nuclear size equal to or exceeding normal macrophage nuclei, or more than twice the size of a large lymphocyte (Swerdlow 2017). DLBCL can arise *de novo* (primary DLBCL) or transform from an existent, less aggressive lymphoma, such as follicular lymphoma or small lymphocytic lymphoma (secondary DLBCL) (Lodhi 2020).

DLBCL is considered the most common subtype of NHL. Patients usually present with a rapidly enlarging tumour mass at single or multiple nodal or extranodal sites. The majority of cases occur in the lymph nodes; approximately 40% of patients have extranodal involvement. The most common site of extranodal involvement is the gastrointestinal tract (stomach, ileocecal region), but DLBCL may occur in any organ/tissue including the bone, testes, spleen, skin, central nervous system (CNS), Waldeyer's ring, salivary gland, thyroid, liver, kidneys and adrenal glands. DLBCL involving the kidneys and adrenal glands is associated with an increased risk of spread to the CNS (Swerdlow 2017; Beham-Schmid 2017).

Many patients are asymptomatic, but symptoms may occur when tissues or organs are infiltrated. Pain in an enlarged lymph node or organ may be noted if the lymphomatous mass enlarges rapidly, and can be associated with B symptoms (fever, night sweats, weight loss). Other symptoms include pruritus, anorexia, fatigue, pedal oedema (caused by pelvic lymphadenopathy), chest discomfort (caused by mediastinal lymphadenopathy). Additional complications include end-organ damage from disease involvement and myelosuppression leading to infections, anaemia, and thrombocytopenia (Swerdlow 2017).

Since 1993, clinicians have used the International Prognostic Index (IPI) to characterise prognosis in aggressive NHL based on five clinical factors: age, stage, the number of extranodal

sites, performance status, and (LDH) lactate dehydrogenase (Liu 2019; Zhou 2014). However, the addition of rituximab to conventional CHOP or CHOP-like regimens for DLBCL has resulted in a major improvement in survival across all risk groups and, as a result, the capacity of the IPI to discriminate between risk groups has declined.

DLBCL can be divided into two histologically indistinguishable molecular subtypes using gene-expression profiling (GEP): germinal center B-cell-like (GCB-DLBCL; ~60%) and non-GCB-like; most of the latter have an activated B-cell-like phenotype (ABC-DLBCL; ~40%) (Lodhi 2020; Swerdlow 2016; Alizadeh 2000).The non-GCB group has a more aggressive clinical course than GCB, and is associated with substantially worse outcomes when treated with R-CHOP (Lodhi 2020). The World Health Organisation (WHO) 2016 classification separates 'double-hit' and 'triple-hit' lymphomas into a new category 'high-grade B-cell lymphomas with *MYC* and *BCL2* and/or *BCL6* rearrangements', representing 1-12% of DLBCL tumours that are also associated with poorer outcomes (Wild 2020; Liu 2019; Swerdlow 2016).

Survival of European DLBCL patients has been improving as a result of better disease management, although regional and age-dependent variations persist (Sant 2014; Mounier 2015; Monnereau 2016). The age-standardised 5-year relative survival for DLBCL patients from 30 European cancer registries (EUROCARE-5; 54,361 cases) increased from 42% for those under observation in 1997-1999 (and diagnosed in the preceding years) to 55.4% a decade later (observation period: 2006-2008) (Sant 2014). These estimates were also consistent when using modified methodology for a selected EUROCARE-5 dataset from 43 registries, revealing an increase in 5-year net survival ranging from 40%-47% (period of diagnosis: 1996-1998) to 46%-58% (period of diagnosis: 2002-2004) for 25,320 DLBCL patients with a median follow-up of 7 years (Mounier 2015). Similarly, survival data of DLBCL patients (diagnosed during 2000-2007) collected in 94 European registries (RARECARENet) was 52.6% at 5 years (Botta 2020). A recent study in metropolitan France for DLBCL patients diagnosed during 2005-2010 (22 registries), presented a 5-year survival rate of 60% (Cowppli-Bony 2019). This is also in line with the most recent Haematological Malignancy Research Network (HMRN) survival data for DLBCL, NOS (relative 5-year survival of 59.8%; www.hmrn.org [last accessed 23 Aug 2021]). For the orphan designation of loncastuximab tesirine (EU/3/21/2481), the median survival was estimated to be 6.78 years, using a 5-year survival of 60%, and assuming a constant hazard rate over the course of survival.

Important co-morbidities

DLBCL is mainly a disease of older individuals with the median age at diagnosis between 60 and 70 years and 30% of patients being older than 75 years of age (Sehn 2021). Hence many comorbidities reflect co-existent disease in this older age group. Comorbidities represent competing adverse risk factors and may influence treatment decision-making in patients since they can preclude the use of certain drugs or may require a dose reduction (Kocher 2020). The Charlson Comorbidity Index (CCI) was originally developed to elaborate the prognostic significance of comorbidities irrespectively of the underlying disease (Charlson 1987). This score has also been used to estimate the comorbidity burden in cancer patients, including DLBCL (Wieringa 2014; Morrison 2020).

An observational population-based cohort study performed in the Netherlands investigated the role of comorbidity on outcome and treatment-related toxicity in 154 patients (median age 69 years) with newly diagnosed advanced-stage DLBCL treated with R-CHOP. Thirty-seven percent (37%) patients had at least one coexistent disease. The planned R-CHOP schedule was completed by 84%, and 75% reached complete remission (CR). In those with CCI ≥2,

67% completed treatment with 46% CR. In patients with a CCI <2, overall survival (OS) after 1, 2 and 5 years was 84%, 79% and 65%, respectively, and it was 64%, 48% and 48% for those with CCI ≥2. Comorbidity was demonstrated to be an independent risk indicator for worse OS in patients with advanced DLBCL treated with R-CHOP, due to interference with intensive treatment schedules and more grade III/IV toxicity. The more common comorbidities included: diabetes (13.6%); peripheral vascular disease (7.8%); cerebrovascular disease (7.1%); chronic pulmonary disease (5.8%) (Wieringa 2014).

Another study in 181 Austrian patients evaluated the clinical impact of comorbidities at diagnosis (median age 60 years) (Kocher 2020). Although the majority (76.8%) of patients (n=139) did not reveal any comorbidities, 9.9% had a CCI ≥2 with the most prevalent comorbid conditions being chronic obstructive pulmonary disease, diabetes without complications and a second coincidental non-metastatic tumour. Advanced age was significantly associated with an increased burden of comorbidities. The complete remission rate was 77.3% in patients with CCI <2, whereas the CR rate was 50.0% in patients with CCI ≥2 (p=0.020). Comorbidity burden represented an adverse prognostic factor. Patients with a CCI score of 0–1 had a 3-year OS rate of 81.3%, whereas this percentage was significantly lower in patients with CCI ≥2: 38.9% (p<0.001). CCI ≥2 was associated with a 3.6-fold (95% CI 1.7–7.4) increased risk for death (Kocher 2020).

The Swedish Lymphoma Register was used to identify 3,905 adult patients diagnosed with DLBCL, 2007-2013, and comorbid disease history was assessed according to the CCI. Overall, 45% of the patients (n=1,737) had a history of at least one comorbidity at DLBCL diagnosis (cardiovascular disease, diabetes, and solid cancer were most frequent), and 997 (26%) had a CCI score of ≥2. Comorbidity was shown to be associated with inferior DLBCL outcome, mainly due to a lower likelihood of receiving treatment with curative intent (Wasterlid 2019).

Part II: Module SII - Non-clinical part of the safety specification

Loncastuximab tesirine (also referred to as ADCT-402) is an ADC composed of the humanised monoclonal immunoglobulin G1 (IgG1) antibody RB4v1.2, directed against human CD19, to which SG3199, a PBD dimer cytotoxic agent, has been conjugated via a protease cleavable valine-alanine linker. The SG3199 cytotoxic agent attached to the linker is designated SG3249 (also known as tesirine).

PBDs are a class of naturally occurring anti-tumour antibiotics found in *Streptomyces* spp. PBD monomers bind in the DNA minor groove and form a single covalent aminal linkage to the exocyclic N2 amino group of guanines within purine-guanine-purine sequences. 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 (Hartley 2011). The cross-links formed by PBD dimers are relatively non-distorting of the DNA structure, making them hidden to repair mechanisms (Adair 2012).

In a human tissue cross reactivity study, ADCT-402 selectively bound to tissues known to contain CD19-expressing cells, and no evidence of off-target binding was observed.

The nonclinical toxicity of ADCT-402 was evaluated in cynomolgus monkeys. ADCT-402 is not cross-reactive with cynomolgus monkey CD19, or CD19 from any other nonclinical species. Nevertheless, the cynomolgus monkey was selected for nonclinical safety assessment of ADCT-402 considering the general suitability of this species for nonclinical safety evaluation of ADCs, and the fact that the potential human pharmacokinetic (PK) parameters and the toxicities associated with the PBD cytotoxic agent of ADCT-402 are adequately predicted in this species to allow for prediction 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 monoclonal antibodies that alleviates potential on-target toxicity concerns (Kimby 2005; Blanc 2011; Chen 2012; Hammer 2012; Marshall 2017).

The nonclinical toxicity of the cytotoxic agent SG3199 was evaluated primarily in the rat, with a dose-range finding (DRF) study in the dog. In addition, *in vitro* toxicity evaluations were conducted with SG3199 to assess genotoxicity and photoreactivity.

Key safety findings from non-clinical studies and relevance to human usage are presented in Table 4.

Table 4: Key safety findings from non-clinical studies and relevance to human usage

Key safety findings (from non- clinical studies)	Relevance to human usage
Toxicity	
Acute or repeat-dose toxicity studies **Loncastuximab tesirine (ADCT-402)** In Good Laboratory Practice (GLP)-compliant repeat-dose toxicity studies of up to 3 months duration in cynomolgus monkeys, the toxicities observed upon IV administration included dose-dependent skin changes (epidermal hyperpigmentation with hyperplasia/hyperkeratosis), anaemia associated with bone marrow hypocellularity, nephropathy and testicular atrophy with reduced spermatogenesis. The toxicities observed were largely consistent with toxicity mediated by the SG3199 cytotoxic agent. In the pivotal GLP 13-week repeat-dose toxicity study, the observed minimal-to-moderate skin discoloration showed evidence of a trend towards reversibility, with reduced incidence and/or severity following a 12-week treatment-free phase, and these findings would be expected to reverse over time and were not considered adverse. The severe depletion/degeneration of germ cells that was observed in sexually mature cynomolgus monkeys in the pivotal study was considered adverse. Although an assessment of sperm production was not included in the study, given the severity of the changes (severe atrophy of the seminiferous tubules, reduced height of germinal epithelium, disorganised spermatogenesis, germ cell degeneration, tubules with Sertoli cells only, and reduced weight, sperm and lumen of the epididymis) it seems highly likely that sperm production, and therefore organ function, would be adversely affected. In the pivotal 13-week toxicity study these findings had not reversed by the end of the 12-week recovery period. Minimal-to-marked nephropathy, characterised by localised degeneration and hyperplasia/hypertrophy of distal tubules and collecting ducts, mainly in the corticomedullary junction, was noted at all dose levels in the pivotal 13-week toxicity study. These findings were not associated with glomerulopathy and showed some evidence of reduced severity by the end of the 12-week recovery phase. These changes were associated with evidence of fibrosis and modest increases in serum creatinine at 0.3 mg/kg high dose only, without evidence of any effects on urinalysis parameters. These findings were considered adverse, but with exception of the observed fibrosis would be expected to reverse without measurable impact on kidney function. Based on the totality of the findings, the 0.6 mg/kg dose was considered to represent a Highest Non-Severely Toxic Dose (HNSTD) in the GLP 4-week study, whilst the 0.3	The toxicity profile of ADCT-402 was characterised by dose-dependent skin changes (epidermal hyperpigmentation with hyperplasia/hyperkeratosis), anaemia associated with bone marrow hypocellularity, nephropathy and testicular atrophy with reduced spermatogenesis. These effects were generally found or considered to be reversible. The toxicity profile of SG3199 in both rats and dogs was characterised by dose-dependent myelosuppression, increased liver enzymes/liver toxicity, inflammation of the gastrointestinal tract, reduced body weight and poor clinical condition. The above observed effects in nonclinical studies with ADCT-402 and SG3199 are consistent with the safety profile of loncastuximab tesirine in clinical studies within the loncastuximab tesirine monotherapy (0.15 mg/kg) DLBCL population (n=215; 145 patients from pivotal study ADCT-402-201 and 70 DLBCL patients from study ADCT-402-101). Based on the results from animal studies, Zynlonta may impair human male fertility. The exposure multiple at the HNSTD in the pivotal GLP 13-week toxicity study in cynomolgus monkeys over the recommended human dose of 0.15 mg/kg was approximately 3.2- or 3.5-fold based on Cmax or AUC, respectively.

Key safety findings (from non- clinical studies)	Relevance to human usage
mg/kg dose was considered to represent an HNSTD in the pivotal GLP 13-week repeat-dose toxicity study. In both cases this was the highest dose level tested (2.4 Nonclinical Overview). **SG3199** The toxicity profile of SG3199 upon daily dosing was evaluated primarily in Sprague-Dawley rats, with a dose-range finding (DRF) study in Beagle dogs. In both rats and dogs, the toxicity profile of SG3199 was characterised by dose-dependent myelosuppression associated with bone marrow hypocellularity, increases in liver enzymes and bilirubin, associated with centrilobular hypertrophy, inflammation of the gastrointestinal tract associated with epithelial degeneration in the duodenum, ileum and jejunum, and reductions in body weight. These findings were largely consistent with those of a cytotoxic agent such as SG3199. In the GLP 4-week repeat-dose toxicity study in the rat, the NOAEL for SG3199 was the 0.1 µg/kg/day dose. In the DRF study in the dog (Study 525532), the MTD for SG3199 was 0.3 µg/kg/day, given as a 3-day cycle (2.4 Nonclinical Overview).	
<u>Reproductive/developmental toxicity</u> Based on the outcome of the genotoxicity studies (see below), and in line with ICH S9 guidance, no reproductive/developmental toxicity studies were conducted.	Zynlonta contains a genotoxic component, SG3199 (see Genotoxicity). In the clinical development programme, women who were pregnant or breastfeeding were excluded from participation because of the potential harm that loncastuximab tesirine could have on the foetus (Module SIV.1). There was no loncastuximab tesirine exposure during pregnancy in the clinical setting (Module SIV.3). However, based on its mechanism of action, Zynlonta can cause embryo-foetal toxicity and/or teratogenicity when administered to a pregnant woman. Women of reproductive potential and pregnant women must be advised of the potential risk to a foetus. Women of reproductive potential should use effective contraception during treatment with Zynlonta and for 10 months after the last dose. Because of the potential for genotoxicity, male patients with female partners of reproductive potential should use effective contraception during the treatment with Zynlonta and for 7 months after the last dose.
<u>Genotoxicity</u> Loncastuximab tesirine contains SG3199, which is an alkykating agent. In an *in vitro* micronucleus test and a chromosome aberration assay using human lymphocytes	Refer to reproductive/developmental toxicity section.

Key safety findings (from non- clinical studies)	Relevance to human usage
SG3199 was determined to be clastogenic, consistent with its mode of action as a covalent DNA crosslinking/alkylating agent. Evaluation of mutagenicity of SG3199 in an Ames test was not possible due to the bactericidal activity of SG3199.	
Carcinogenicity In accordance with ICH S9 and ICH S1A no carcinogenicity studies were conducted with loncastuximab tesirine or SG3199 given the intended use in the treatment of patients with advanced cancer and the genotoxicity of SG3199.	Not applicable.
Safety pharmacology	
No stand-alone safety pharmacology studies were conducted with ADCT-402. In accordance with ICH S6(R1), safety pharmacology endpoints were included in the GLP-compliant repeat-dose toxicology studies in cynomolgus monkeys. Endpoints included were: • Neurological examinations: general sensory aspects, cerebral reflexes (pupillary, orbicularis oculi) and spinal reflexes (patellar, anal). • Neurobehavioral observations: vocalisation, grooming, posture, balance/coordination, locomotor activity, tremor, convulsion/twitches/jerks, muscle cramping, stereotypy, alertness, aggression, reaction to visual or acoustic stimuli, muscle tone and grip strength. • Respiratory rate assessment. • Cardiovascular investigations (8-lead electrocardiogram [ECG]; parameters determined included RR and PR intervals, QRS duration, QT interval, corrected QT [QTcF or QTcB] interval and heart rate). All the above endpoints were evaluated in the GLP 4-week study (Study 8303115) whilst in the GLP 13-week study (Study 8374716) only ECGs and blood pressure were evaluated. There were no ADCT-402-related findings on any of the endpoints studied (2.6.2 Pharmacology Written Summary).	In the clinical development programme, in Study ADCT-402-201, no large changes in mean QTc intervals (i.e., >20 msec) were detected following the treatment of loncastuximab tesirine by IV infusion at the maximum recommended therapeutic dose of 0.15 mg/kg dose (2.7.2 Summary of Clinical Pharmacology). No evidence of clinically significant toxicity for vital signs or depolarisation/repolarisation of myocardium as measured by ECG was observed and the magnitude of QTc prolongation change from baseline with loncastuximab tesirine peak exposure was not clinically relevant (2.7.4 Summary of Clinical Safety).

Key safety findings (from non- clinical studies)	Relevance to human usage
Mechanisms for drug interactions	
No pharmacodynamic drug interaction studies were conducted with ADCT-402 (2.6.2 Pharmacology Written Summary). *In vitro* studies have shown that SG3199 does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4/5 at clinically relevant unconjugated SG3199 concentrations. In addition, in human hepatocytes SG3199 did not induce CYP3A4 or CYP2B6 mRNA or enzyme activity, whilst it was found to induce CYP1A2 mRNA expression without concomitant increase in enzyme activity. SG3199 is a substrate of P-glycoprotein (P-gp), but not a substrate of breast cancer resistance protein (BCRP), organic anion-transporting polypeptide (OATP)1B1, OATP1B3, or organic cation transporter (OCT)1. SG3199 does not inhibit P-gp, BCRP, OATP1B1, OATP1B3, organic anion transporter (OAT)1, OAT3, OCT2, OCT1, multi-antimicrobial extrusion protein (MATE)1, MATE2-K, or bile salt export pump (BSEP) at clinically relevant unconjugated SG3199 concentrations (2.6.4 Pharmacokinetics Written Summary).	No drug-drug interaction studies have been performed in humans.
Other toxicity-related information or data	
Photoreactivity The potential effects of visible, ultraviolet (UV)A and UVB light on SG3199-mediated effects on the structural integrity of supercoiled plasmid DNA were investigated. These studies confirmed that SG3199 is photoreactive, and that exposure to visible light, UVA or UVB radiation enhance its ability to mediate DNA crosslinking and double-stranded breaks which may represent a contributory underlying mechanism to the epidermal hyperpigmentation and hyperkeratosis observed upon IV administration of ADCT-402 *in vivo* (2.4 Nonclinical Overview).	The UV-Vis absorption spectrum of SG3199 is indicative of a concern for photosensitivity reactions. Photosensitivity, manifesting as a skin reaction or rash, has been observed in patients treated with Zynlonta. In the 215 DLBCL patients treated with 0.15 mg/kg loncastuximab tesirine, TEAEs of photosensitivity reaction were observed in 17 (7.9%) patients; all except one were assessed as treatment-related with 3 (1.4%) of Grade 3 severity (2.7.4 Summary of Clinical Safety, Tables 1.3.2, 1.3.10, 1.3.17).

Part II: Module SIII - Clinical trial exposure

Two clinical studies contributed evidence for the safety of loncastuximab tesirine monotherapy in patients with relapsed or refractory DLBCL: one pivotal efficacy study (ADCT-402-201) in patients with DLBCL, and one supportive first-in-human study (ADCT-402-101) in patients with B-cell lineage non-Hodgkin lymphoma (B-NHL), including patients with DLBCL. Both studies were single-arm, open-label, and used loncastuximab tesirine as monotherapy.

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. The study has completed enrolment and 145 patients were enrolled at 16 centres in the United States (US), six centres in the United Kingdom (UK), five centres in Italy, and one centre in Switzerland.

ADCT-402-101 was a Phase 1, open-label, dose-escalation (Part 1) and expansion (Part 2) study to evaluate the safety and tolerability of loncastuximab tesirine in 183 patients with relapsed or refractory B-NHL. The study was conducted at eight centres in the US, two centres in the UK, and one centre in Italy, and was completed on 21 February 2019. There were 139 patients with DLBCL in this study.

Loncastuximab tesirine was supplied in two product presentations over the clinical development lifecycle: an initial frozen liquid product and later a lyophilised powder drug product. The frozen liquid formulation was used for study ADCT-402-101, and the lyophilised formulation was introduced into study ADCT-402-201.

In study ADCT-402-201, of the 145 patients who were enrolled and received loncastuximab tesirine, 35 patients received the frozen liquid formulation (for all dose cycles) and 110 patients received the lyophilised formulation (for all dose cycles).

The dosing regimens were different between studies ADCT-402-201 and ADCT-402-101. A single dose regimen was used in study ADCT-402-201 with all 145 patients enrolled at 0.15 mg/kg (150 µg/kg). Multiple dose levels/regimens were used in study ADCT-402-101, ranging from initial doses of 15 to 200 µg/kg and used to establish the recommended dosing used in the Phase 2 study. Among the 139 patients who were enrolled with a primary diagnosis of DLBCL, two patients were enrolled at 15 µg/kg, three patients were enrolled at 30 µg/kg, three patients were enrolled at 60 µg/kg, two patients were enrolled at 90 µg/kg (Part 1), 32 patients were enrolled at 120 µg/kg (Parts 1 and 2 combined), 70 patients were enrolled at 150 µg/kg (Parts 1 and 2 combined), and 27 patients were enrolled at 200 µg/kg (Part 1) (ADCT-402-101 CSR, Table 14.1.1.2).

In addition, there are three studies with loncastuximab tesirine in other indications or in combination with other therapies:

- ADCT-402-102 was a Phase 1 study of loncastuximab tesirine monotherapy in 35 patients with relapsed or refractory B cell acute lymphoblastic leukaemia (B-ALL); it was terminated early because of slow accrual.
- ADCT-402-103 is an ongoing Phase 1/2 study of loncastuximab tesirine in combination with ibrutinib in patients with relapsed or refractory DLBCL or mantle cell lymphoma (MCL).
- ADCT-402-104 was a Phase 1 study of loncastuximab tesirine in combination with durvalumab in patients with relapsed or refractory DLBCL, MCL, or follicular

lymphoma. Enrolment for ADCT-402-104 was closed early on 21 November 2019, after 13 patients had been enrolled and began treatment, as it was determined that there did not appear to be added benefit to the combination therapy as compared to loncastuximab tesirine alone.

The key data sets for safety evaluation in this RMP are the monotherapy DLBCL population (Level 1) and monotherapy B-NHL/B-ALL population (Level 2). Level 1 included 284 relapsed or refractory DLBCL patients treated with loncastuximab tesirine as monotherapy from the ADCT-402-201 and ADCT-402-101 studies, which consisted of 145 patients from pivotal study ADCT-402-201 and 139 DLBCL patients from study ADCT-402-101. The subset of 215 patients who received 0.15 mg/kg loncastuximab tesirine monotherapy was the primary group analysed for safety as it represents the population that will be exposed to risk with the commercial product. Level 2 included 363 patients, which consisted of 145 DLBCL patients from study ADCT-402-201, 183 B-NHL patients from study ADCT-402-101, and 35 B-ALL patients from study ADCT-402-102. This level provided supportive analyses and a relevant larger safety database that included 328 patients with relapsed or refractory B-NHL.

Level 3 is the loncastuximab tesirine all treated population, including all 468 relapsed or refractory B-NHL or B-ALL patients from the ADCT-402-201, ADCT-402-101, ADCT-402-102, ADCT-402-103, and ADCT-402-104 studies. However, Level 3 data are not further discussed as the number of patients treated with combination therapies was too small to make meaningful comparisons and the loncastuximab tesirine dosing in the combination therapies was limited to two doses for the majority of patients.

The number of subjects treated in all 5 studies is provided in Table 5.

Table 5: Overview of studies and patients included in integrated analyses

Study and Treatment	Population and Numbers of Patients, N	Numbers of Patients		
		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
ADCT-402-101 loncastuximab tesirine alone	All B-NHL, 183	139	183	183
ADCT-402-102 loncastuximab tesirine alone	All B-ALL, 35	NA	35	35
ADCT-402-103 loncastuximab tesirine + ibrutinib	All B-NHL, 92[a]	NA	NA	92[a]
ADCT-402-104 loncastuximab tesirine + durvalumab	All B-NHL, 13	NA	NA	13
All studies combined	468	284	363	468

B-ALL=B-cell acute lymphoblastic leukaemia; B-NHL=B-cell non-Hodgkin lymphoma; DLBCL= diffuse large B-cell lymphoma; NA=not applicable
[a] Still recruiting
Level 1: A total of 284 relapsed or refractory DLBCL patients who were treated with loncastuximab tesirine as monotherapy comprising 145 DLBCL patients from pivotal study ADCT-402-201 and 139 DLBCL patients from study ADCT-402-101; includes the subset of 215 DLBCL patients who received 0.15 mg/kg loncastuximab tesirine monotherapy.
Level 2: A total of 363 patients with relapsed or refractory disease who received loncastuximab tesirine monotherapy comprising 145 DLBCL patients from study ADCT-402-201, 183 B-NHL patients from study ADCT-402-101, and 35 B-ALL patients from study ADCT-402-102; includes 328 patients with relapsed or refractory B-NHL.
Level 3: All 468 relapsed or refractory B-NHL or B-ALL patients from the ADCT-402-201, ADCT-402-101, ADCT-402-102, ADCT-402-103, and ADCT-402-104 studies.

Source: 2.7.4 Summary of Clinical Safety

Among the 215 DLBCL patients who received 0.15 mg/kg loncastuximab tesirine monotherapy, 70 patients received initial doses of 0.15 mg/kg in Study ADCT-402-101 and 145 received initial doses of 0.15 mg/kg in Study ADCT-402-201. The median treatment duration among these 215 patients was 45.0 days (range: 1 to 569 days) (Table 6). The median number of treatment cycles administered was 3.0 cycles (range: 1 to 26 cycles) (Table 7). The median total dose administered was 30.0 mg (range: 7.5 to 112.5 mg), and the median total weight-adjusted dose administered was 0.376 mg/kg (range: 0.122 to 2.1 mg/kg) (Table 8). The median average weight-adjusted dose per cycle was 0.126 mg/kg (range: 0.049 to 0.16 mg/kg).

No notable differences in exposure were observed between the 215 DLBCL patients who received 0.15 mg/kg and the 284 DLBCL patients who received any dose of loncastuximab tesirine monotherapy.

Table 6: Exposure: Duration of treatment (DLBCL Population)

	Level 1 (all doses) (N = 284)	Level 1 (0.15 mg/kg) (N = 215)
Duration of Treatment (days)		
Mean (SD)	72.0 (84.13)	78.0 (90.35)
Median	43.0	45.0
Min, Max	1, 569	1, 569

Level 1: A total of 284 relapsed or refractory DLBCL patients who were treated with loncastuximab tesirine as monotherapy comprising 145 DLBCL patients from pivotal study ADCT-402-201 and 139 DLBCL patients from study ADCT-402-101; includes the subset of 215 DLBCL patients who received 0.15 mg/kg loncastuximab tesirine monotherapy.
Source: 2.7.4 Summary of Clinical Safety Table 4

Table 7: Exposure: Number of cycles (DLBCL Population)

	Level 1 (all doses) (N = 284)	Level 1 (0.15 mg/kg) (N = 215)
Number of cycles administered		
Mean (SD)	3.9 (3.48)	4.2 (3.78)
Median	3.0	3.0
Min, Max	1, 26	1, 26

Level 1: A total of 284 relapsed or refractory DLBCL patients who were treated with loncastuximab tesirine as monotherapy comprising 145 DLBCL patients from pivotal study ADCT-402-201 and 139 DLBCL patients from study ADCT-402-101; includes the subset of 215 DLBCL patients who received 0.15 mg/kg loncastuximab tesirine monotherapy.
Source: 2.7.4 Summary of Clinical Safety Table 4

Table 8: Exposure: Total dose administered (DLBCL Population)

	Level 1 (all doses) (N = 284)	Level 1 (0.15 mg/kg) (N = 215)
Total dose administered (mg)		
Mean (SD)	32.78 (20.28)	34.12 (20.83)
Median	28.43	30.00
Min, Max	2.0, 112.5	7.5, 112.5
Total weight adjusted dose (mg/kg)		
Mean (SD)	0.42 (0.28)	0.45 (0.30)
Median	0.37	0.38
Min, Max	0.03, 2.06	0.12, 2.06

Level 1: A total of 284 relapsed or refractory DLBCL patients who were treated with loncastuximab tesirine as monotherapy comprising 145 DLBCL patients from pivotal study ADCT-402-201 and 139 DLBCL patients from study ADCT-402-101; includes the subset of 215 DLBCL patients who received 0.15 mg/kg loncastuximab tesirine monotherapy.
Source: 2.7.4 Summary of Clinical Safety Table 4

Of the 328 B-NHL patients receiving loncastuximab tesirine monotherapy (Level 2 analysis of 145 DLBCL patients from study ADCT-402-201 and 183 B-NHL patients from study ADCT-402-101), 17 patients received initial doses of ≤0.090 mg/kg, 42 patients 0.120 mg/kg, 233 patients 0.15 mg/kg, and 36 patients 0.200 mg/kg. The median treatment duration of treatment in all doses combined was 43.0 days (range: 1 to 511 days). The median number of

treatment cycles administered was 3.0 cycles (range: 1 to 26). The median total dose administered was 28.4 mg (range: 2.0 to 136.8 mg), and the median total weight-adjusted dose administered was 0.366 mg/kg (range: 0.029 to 2.061 mg/kg). The median average weight-adjusted dose per cycle was 0.125 mg/kg (range: 0.015 to 0.204 mg/kg).

Among the 215 patients who received 0.15 mg/kg loncastuximab tesirine monotherapy, there were fewer females (43.7%) than males (56.3%). The median age was 64.0 years (range: 20 to 94 years). Age groups were about evenly divided with 51.2% of patients <65 years old and 48.8% ≥65 years old (Table 9). Most patients were white (91.6%), followed by black (3.3%) and all others (5.1%). A small percentage of patients were Hispanic or Latino (7.9%) (Table 10).

No notable differences in demographic and baseline characteristics were observed between the 215 DLBCL patients who received 0.15 mg/kg and the 284 DLBCL patients who received any dose of loncastuximab tesirine monotherapy.

Table 9: Exposure by age and gender (DLBCL Population)

	Level 1 (all doses) (N = 284)	**Level 1 (0.15 mg/kg) (N = 215)**
Age (years)		
Mean (SD)	62.1 (14.43)	61.1 (14.43)
Median	65.0	64.0
Min, Max	20, 94	20, 94
Age Group, n (%)		
<65 years	138 (48.6)	110 (51.2)
≥65 years	146 (51.4)	105 (48.8)
Gender, n (%)		
Male	165 (58.1)	121 (56.3)
Female	119 (41.9)	94 (43.7)

Level 1: A total of 284 relapsed or refractory DLBCL patients who were treated with loncastuximab tesirine as monotherapy comprising 145 DLBCL patients from pivotal study ADCT-402-201 and 139 DLBCL patients from study ADCT-402-101; includes the subset of 215 DLBCL patients who received 0.15 mg/kg loncastuximab tesirine monotherapy.
Source: 2.7.4 Summary of Clinical Safety Table 6

Table 10: Exposure by race and ethnicity

	Level 1 (all doses) (N = 284)	**Level 1 (0.15 mg/kg) (N = 215)**
Race, n (%)		
White	256 (90.1)	197 (91.6)
Black or African American	12 (4.2)	7 (3.3)
Asian	6 (2.1)	3 (1.4)
American Indian or Alaskan Native	1 (0.4)	1 (0.5)
Native Hawaiian or Pacific Islander	1 (0.4)	1 (0.5)
Other	7 (2.5)	5 (2.3)
Missing	1 (0.4)	1 (0.5)
Ethnicity, n (%)		
Hispanic or Latino	19 (6.7)	17 (7.9)
Not Hispanic or Latino	265 (93.3)	198 (92.1)

Level 1: A total of 284 relapsed or refractory DLBCL patients who were treated with loncastuximab tesirine as monotherapy comprising 145 DLBCL patients from pivotal study ADCT-402-201 and 139 DLBCL patients from study ADCT-402-101; includes the subset of 215 DLBCL patients who received 0.15 mg/kg loncastuximab tesirine monotherapy.
Source: 2.7.4 Summary of Clinical Safety Table 6

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Exclusion criteria from Study ADCT-402-201 are detailed below.

Exclusion criteria to ensure standardisation of the trial population that are common to most clinical trials are not further discussed, including:

- Patients aged <18 years
- Previous treatment with loncastuximab tesirine (i.e., the medicinal product under investigation)
- Use of any other experimental medication within 14 days prior to start of study drug (Cycle 1, Day 1)
- Known history of hypersensitivity or positive serum human anti-drug antibody to a CD19 antibody

Exclusion criteria related to ongoing or recent conditions or treatments that may interfere with the study results and impact the safety and efficacy assessment of loncastuximab tesirine are similarly not further discussed, including:

- Bulky disease, defined as any tumour 10 cm in longest dimension
- 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 documented should not lead to exclusion
- Autologous SCT within 30 days prior to start of study drug (Cycle 1, Day 1)
- Allogeneic SCT within 60 days prior to start of study drug (Cycle 1, Day 1)
- Active graft-versus-host disease
- Post-transplant lymphoproliferative disorders
- Active autoimmune disease, including motor neuropathy considered of autoimmune origin and other CNS autoimmune disease
- Known seropositive and requiring antiviral therapy for HIV, hepatitis B virus, or HCV
- Lymphoma with active CNS involvement at the time of screening, including leptomeningeal disease
- Significant medical comorbidities, including but not limited to uncontrolled hypertension (blood pressure ≥160/100 mmHg repeatedly), unstable angina, congestive heart failure (greater than New York Heart Association class II), electrocardiographic evidence of acute ischaemia, 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

- 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
- Planned live vaccine administration after starting study drug (Cycle 1, Day 1)
- Failure to recover to Grade ≤1 (Common Terminology Criteria for Adverse Events [CTCAE] version 4.0) from acute nonhematologic toxicity (Grade ≤2 neuropathy or alopecia) due to previous therapy prior to screening
- 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)
- History of Stevens-Johnson syndrome or toxic epidermal necrolysis
- 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

Pregnant or breastfeeding

Reason for exclusion:

Loncastuximab tesirine contains a genotoxic component, SG3199, which is a covalent DNA crosslinking/alkylating agent. Based on its mechanism of action, loncastuximab tesirine can cause embryo-foetal toxicity and/or teratogenicity when administered to a pregnant woman. There is no information regarding the presence of loncastuximab tesirine or SG3199 in human milk, the effects on the breastfed child, or milk production. For these reasons, and because of the potential for exposure of the infant, women who were pregnant or breastfeeding were excluded from the study.

Is it considered to be included as missing information? No

Rationale:

Although no reproductive and developmental toxicity studies were conducted with loncastuximab tesirine or SG3199, the demonstration that the SG3199 cytotoxic agent is a potent clastogen indicates a potential safety hazard to the foetus. Based on its mechanism of action, Zynlonta affects actively dividing cells and can cause embryo-foetal toxicity and/or teratogenicity when administered to a pregnant woman. The Zynlonta SmPC specifies that pregnant women must be advised of the potential risk to the foetus and women of reproductive potential should use effective contraception during treatment with Zynlonta and for at least 10 months after the last dose. Because of the potential for genotoxicity, male patients with female partners of reproductive potential should use effective contraception during the treatment with Zynlonta and for at least 7 months after the last dose. In addition, women should be advised not to breastfeed during treatment with Zynlonta and for at least 3 months after the last dose, because of the potential for exposure of the infant. Since the nonclinical findings suggest that use of Zynlonta in pregnant women may give rise to an undesirable clinical outcome, embryo-foetal toxicity is included as an important potential risk (Module SVII.1.2).

Absolute neutrophil count <1.0×10^3/µL (off growth factors at least 72 hours)

Platelet count <75×10^3/µL (without transfusion in the prior 7 days)

Reason for exclusion:

The toxicity profile of SG3199 is characterised by dose-dependent myelosuppression associated with bone marrow hypocellularity.

Is it considered to be included as missing information? No

Rationale:

Neutropenia, thrombocytopenia, and anaemia are very common adverse reactions, which can be managed by dose modifications or delay in dosing if Grade ≥3 neutropenia or thrombocytopenia occurs. Serious infections are not considered an important identified risk in this RMP but are described in Section 4.4 of the Zynlonta SmPC. Physicians are advised to monitor complete blood counts throughout treatment. Cytopenia may require more frequent lab monitoring and/or interruption, dose reduction, or discontinuation of Zynlonta. Prophylactic granulocyte colony-stimulating factor (G-CSF) administration may be considered as applicable.

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT) >2.5×the upper limit of normal (ULN).

Total bilirubin >1.5×ULN

Reason for exclusion:

Increases in liver enzymes and bilirubin, associated with centrilobular hypertrophy were observed in the toxicity studies with SG3199 (Part II Module SII). Loncastuximab tesirine has not been studied in patients with moderate or severe hepatic impairment (total bilirubin >1.5 x ULN and any AST).

Is it considered to be included as missing information? Yes

Blood creatinine >1.5×ULN or calculated creatinine clearance <60 mL/min by the Cockcroft and Gault equation

Reason for exclusion:

Minimal-to-marked nephropathy was noted at all dose levels in the pivotal 13-week toxicity study. With the exception of the observed fibrosis, these effects would be expected to reverse without measurable impact on kidney function (Part II Module SII). The effect of severe renal impairment (creatinine clearance [CrCL] 15 to 29 mL/min) and end-stage renal disease, with or without haemodialysis, on loncastuximab tesirine pharmacokinetics is unknown.

Is it considered to be included as missing information? Yes

Pathologic diagnosis of Burkitt lymphoma

Reason for exclusion:

Burkitt lymphoma is a very aggressive lymphoma. Accurate diagnosis of Burkitt lymphoma is critical because Burkitt lymphoma and DLBCL are treated differently. Thus, inclusion of these patients could confound both efficacy and safety assessments.

Is it considered to be included as missing information? No

Rationale: Loncastuximab tesirine as monotherapy is indicated for the treatment of adult patients with relapsed or refractory DLBCL and HGBL, after two or more lines of systemic therapy as specified in the Zynlonta SmPC. Burkitt lymphoma is a rare B-NHL and sometimes difficult to distinguish from the more common DLBCL but can be distinguished by flow cytometric immunophenotypic markers. Next generation sequencing studies have identified mutations associated with Burkitt lymphoma and helped in the 2016 WHO classification of Burkitt lymphoma facilitating distinction from DLBCL (Swerdlow 2016). Patients diagnosed with Burkitt lymphoma are not indicated for treatment with Zynlonta.

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

Reason for exclusion:

Studies with other antibody products that employed the same PBD dimer toxin as loncastuximab tesirine reported TEAEs of serosal infusions including pleural and pericardial effusions (Collins 2018, Hamadani 2018, Rudin 2017). Patients with pre-existing clinically significant fluid accumulation were excluded to avoid interference with the study results and impact on the safety and efficacy assessment.

Is it considered to be included as missing information? No

Rationale:

Oedema and effusion are classed as an important identified risk (Module SVII.1.2). The product labelling warns that oedema and effusion, which may be serious, have been reported in patients treated with Zynlonta, including pleural effusion, pericardial effusion, ascites, peripheral oedema, and general oedema. Patients should be monitored for new or worsening oedema or effusions and Zynlonta withheld for Grade ≥2 oedema or effusion until the toxicity resolves. Diagnostic imaging should be considered in patients who develop symptoms of pleural effusion or pericardial effusion, such as new or worsened dyspnoea, chest pain, and/or ascites such as swelling in the abdomen and bloating, and appropriate medical management for oedema or effusions initiated.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged exposure.

The primary safety evaluation data set comprised a total of 284 patients with relapsed/refractory DLBCL who received loncastuximab tesirine monotherapy (at doses of ≤ 0.09, 0.12, 0.15, 0.20 mg/kg; N=10; 32; 215; 27, respectively). Adverse reactions occurring with a true frequency greater than 1 in 95 could be quantified in a data set of this size if the background incidence for the event is assumed to be zero (i.e., “common” or “very common” events).

For Study ADCT-402-201, the median treatment duration in subjects treated with loncastuximab tesirine in the DLBCL pool (n=145) was 45.0 days (range 1, 351). The median number of treatment cycles that subjects received was 3.0 cycles (range 1, 15). Adverse reactions with a long latency or cumulative effects are not expected but patient exposure to loncastuximab tesirine in the clinical development programme is limited.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 11: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme
Breastfeeding women	
Patients with relevant comorbidities:	
• Patients with hepatic impairment	In the clinical development programme patients were included if they had adequate hepatic function at study entry (ALT, AST, GGT ≤2.5 x ULN; total bilirubin ≤1.5 x ULN) (Module SIV.1). No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin ≤ULN and AST >ULN, or total bilirubin >1 to 1.5 x ULN and any AST); from the exposure-response (E-R) analysis of efficacy and safety, the exposure in the mild hepatic impairment subgroup was not associated with an increased safety concern (2.7.2 Summary of Clinical Pharmacology Studies). The impact of hepatic impairment was evaluated in the population PK analysis (n=328; studies ADCT-402-201 and ADCT-402-101 only). The majority of patients had normal hepatic function (n=277) or mild hepatic impairment (n=49); 1 patient had moderate hepatic impairment (2.7.2 Summary of Clinical Pharmacology Studies). Due to the limited number of patients with moderate/severe hepatic impairment (n=1), no associations between loncastuximab tesirine exposure and moderate/severe hepatic impairment can be made and such patients are an area of missing information (Module SVII.1.2). A hepatic impairment study will be conducted to determine a safe and appropriate dosing regimen of loncastuximab tesirine in patients with moderate and severe hepatic impairment (Part III.2).

Type of special population	Exposure
• Patients with renal impairment	In the clinical development programme patients were included if they had adequate renal function at study entry (blood creatinine ≤1.5 × ULN or calculated CrCL ≥60 mL/min by the Cockcroft and Gault equation) (Module SIV.1). The impact of renal impairment was evaluated in the population PK analysis (n=328; studies ADCT-402-201 and ADCT-402-101 only) that included patients with normal renal function (n=159; CrCL ≥90 mL/min), mild renal impairment (n=118; CrCL ≥60-<90 mL/min), and moderate/severe renal impairment (n=51; CrCL ≥15-<60 mL/min). Creatinine clearance was not identified as a statistically significant covariate of loncastuximab tesirine PK, which is consistent with renal elimination not being a significant clearance pathway of loncastuximab tesirine. No clinically relevant differences in the exposure to PBD-conjugated antibody were observed between patients with differing baseline renal function (2.7.2 Summary of Clinical Pharmacology Studies). Overall, no dose adjustment is recommended for patients with mild or moderate renal impairment, based on the minimal magnitude of the effect of renal impairment on PK exposure, and that the renal elimination pathway is not expected to contribute significantly to the clearance of therapeutic antibodies or SG3199. Given that there was only 1 patient in the severe renal impairment subgroup, no definitive conclusion can be drawn for patients with severe renal impairment and such patients are an area of missing information (Module SVII.1.2). Study ADCT-402-311 will evaluate the use of loncastuximab tesirine in patients with moderate renal impairment (calculated CrCL ≥30 mL/min by the Cockcroft and Gault equation), but not those with severe renal impairment (Part IV)
• Patients with cardiovascular impairment	Patients with known history of uncontrolled hypertension (blood pressure ≥160/100 mmHg repeatedly), unstable angina, congestive heart failure (greater than New York Heart Association class II), electrocardiographic evidence of acute ischaemia, coronary angioplasty, myocardial infarction within 6 months prior to screening, or uncontrolled atrial or ventricular cardiac arrhythmias were excluded from participation (Module SIV.1). In the clinical development programme loncastuximab tesirine was not found to cause significant cardiac toxicity (Module SII).
• Immunocompromised patients	Seropositive patients requiring antiviral therapy for HIV were excluded from participation (Module SIV.1). However, other patients with underlying immunodeficiencies were not specifically excluded and it is likely that many patients would have some decrease in immune function related to their prior therapy.
Patients with a disease severity different from inclusion criteria in clinical trials	The proposed indication for loncastuximab tesirine as monotherapy is for the treatment of adult patients with relapsed or refractory DLBCL and HGBL, after two or more lines of systemic therapy. Study ADCT-402-101 recruited subjects with pathologically-confirmed relapsed or refractory B-NHL (per 2008 WHO classification) whereas patients were included in Study ADCT-402-201 if they had a pathologic diagnosis of DLBCL, as defined by the 2016 WHO classification, to

Type of special population	Exposure
	include: DLBCL NOS; primary mediastinal large B-cell lymphoma; and high-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements. Among the 215 patients who received 0.15 mg/kg loncastuximab tesirine monotherapy, the disease subtypes were most categorised as DLBCL NOS (92.1%), followed by high grade B-cell lymphoma (4.7%), and primary mediastinal B-cell lymphoma (3.3%). The most common stage was Stage IV disease at enrolment (65.1%). Subtypes included Subtype E (extranodal involvement; 56.7%), Subtype X (bulky disease; 7.9%), and Subtype S (spleen involved; 4.2%). Among disease subtypes and pretreatment disease characteristics, no notable differences were observed between the 215 patients who received 0.15 mg/kg and the 284 patients who received any dose of loncastuximab tesirine monotherapy (2.7.4 Summary of Clinical Safety).
Population with relevant different ethnic origin	In the 284 DLBCL patient pool, in all loncastuximab tesirine doses combined, most patients were white (90.1%), followed by all others (5.6%), and black (4.2%). A small percentage of patients were Hispanic or Latino (6.7%) (2.7.4 Summary of Clinical Safety).
Subpopulations carrying relevant genetic polymorphisms	Not applicable.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Loncastuximab tesirine was granted accelerated approval in the United States (US) on 23 April 2021 under Biologics License Application (BLA) 761196 with continued approval contingent upon verification and description of clinical benefit in a confirmatory trial. Loncastuximab tesirine has not been approved in any country or region outside of the US.

Following launch in the US in 2021 until 30 June 2022, sales data indicate [redacted] vials of loncastuximab tesirine have been distributed. It is estimated [redacted] patients have been exposed to loncastuximab tesirine (if assuming an average of 5 vials used per patient).

Part II: Module SVI - Additional EU requirements for the safety specification

SVI.1 Potential for misuse for illegal purposes

No studies have been conducted to evaluate the abuse and dependence potential of loncastuximab tesirine. Based on its mechanism of action and safety profile in DLBCL, loncastuximab tesirine is not expected to be associated with the potential for abuse or dependence. As loncastuximab tesirine is administered as an intravenous infusion by medical personnel and administration by the patient will not occur, the potential for abuse is minimal.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

- **Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):**

None.

- **Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:**

None.

- **Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised):**

Myelosuppression

Among the 215 patients who received 0.15 mg/kg loncastuximab tesirine monotherapy, at least one TEAE occurred in 98.6% of patients. The 10 most common TEAEs included those of neutropenia (34.9%), anaemia (28.8%), and thrombocytopenia (28.4%) (Table 12). No notable differences were observed between the 215 patients who received 0.15 mg/kg and the 284 patients who received any dose of loncastuximab tesirine monotherapy. The 10 most common treatment-related TEAEs also included neutropenia (26.0%), thrombocytopenia (16.3%), and anaemia (13.5%). Again, no notable differences were observed between the 215 patients who received 0.15 mg/kg and the 284 patients who received any dose of loncastuximab tesirine monotherapy. Most frequent severe adverse reactions (≥Grade 3) in >5% of cases included neutropenia (24.2%), thrombocytopenia (15.8%), and anaemia (11.6%) with ≥Grade 3 treatment-related adverse reactions being 20.0%, 9.8%, and 6.5%, respectively (2.7.4 Summary of Clinical Safety).

Table 12: Myelosuppression (≥10% of patients in all doses combined) TEAEs by preferred term in 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)
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)
Thrombocytopenia	1 (10.0)	8 (25.0)	13 (18.6)	48 (33.1)	61 (28.4)	7 (25.9)	77 (27.1)

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 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.
Source: 2.7.4 Summary of Clinical Safety, Table 12

Myelosuppression is not an important risk of loncastuximab tesirine as it can be managed in clinical practice through healthcare professional awareness of the precautions to take with oncology therapeutic agents, patient monitoring, loncastuximab tesirine dose modification and G-CSF administration.

The product information for Zynlonta requires that it should only be administered under the supervision of a healthcare professional experienced in the diagnosis and treatment of cancer patients.

The Zynlonta SmPC instructs healthcare professionals to monitor patients for complete blood counts throughout treatment since cytopenia may require more frequent lab monitoring and/or interruption, dose reduction, or discontinuation of Zynlonta. Prophylactic G-CSF administration should be considered as applicable.

Infections

The most common TEAEs within the Infections and Infestations System Organ Class (SOC) occurred in 34.0% of the 215 patients receiving 0.15 mg/kg loncastuximab tesirine monotherapy with serious TEAEs accounting for 9.3% of patients. The most common serious TEAEs in this SOC included sepsis (Grade 3, 0.5%; Grade 5, 0.9%), lung infection (Grade 3, 0.5%; Grade 5, 0.5%), and pneumonia (Grade 3, 0.5%; Grade 5, 0.5%). Although 5 (2.3%) cases in the Infections and Infestations SOC were fatal (2 cases of sepsis, and 1 each of lung infection, pneumonia, septic shock; Table 13) only lung infection (0.5%) was assessed as treatment-related (2.7.4 Summary of Clinical Safety).

Table 13: Fatal infection TEAEs by SOC and preferred term for loncastuximab tesirine monotherapy treated DLBCL patients

System Organ Class 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 Fatal TEAE	0	3 (9.4)	11 (15.7)	8 (5.5)	19 (8.8)	0	22 (7.7)
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)

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
Adverse events were coded using MedDRA version 22.0. For each SOC and preferred term, patients were included only once.
Source: 2.7.4 Summary of Clinical Safety, Table 20

Infection is not an important risk of loncastuximab tesirine as it can be managed in clinical practice through healthcare professional awareness of the precautions to take with oncology therapeutic agents and will continue to be monitored via routine pharmacovigilance activities.

The product information for Zynlonta requires that it should only be administered under the supervision of a healthcare professional experienced in the diagnosis and treatment of cancer patients.

The Zynlonta SmPC instructs healthcare professionals to monitor patients for any new or worsening signs or symptoms consistent with infection. For Grade 3 or 4 infection, Zynlonta should be withheld until infection has resolved.

Serious cutaneous reactions (unrelated to exposure to sunlight)

The incidence of the most common (≥10% of patients in all doses combined) selected TEAEs in the skin reaction and nail disorder group of adverse events (AEs) of particular interest in the 215 DLBCL patients who received 0.15 mg/kg loncastuximab tesirine monotherapy was 46.5% with 44.2% assessed as treatment-related (Table 14) (2.7.4 Summary of Clinical Safety).

The most common specific events (≥10%) in this category included rash (20.0%), pruritus (11.6%), and erythema (10.2%), with treatment-related adverse reactions being 19.5%, 8.4%, and 9.8%, respectively. No notable differences were observed between the 215 patients who received 0.15 mg/kg and the 284 patients who received any dose of loncastuximab tesirine monotherapy (2.7.4 Summary of Clinical Safety).

Table 14: Most common (≥10% of patients in all doses combined) selected TEAEs by skin reaction and nail disorder group of AEs and preferred term for loncastuximab tesirine monotherapy treated DLBCL patients

AE Group 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)
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 (11.6)

AE=adverse event; 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 10% cutoff was based on All Doses. Adverse events were coded using MedDRA version 22.0.
Source: 2.7.4 Summary of Clinical Safety, Table 24

Serious cutaneous reactions have been reported in patients treated with loncastuximab tesirine. In clinical studies with Zynlonta oral and topical corticosteroids and anti-pruritic therapy were used to treat cutaneous reactions. The incidence of Grade 3 or higher events in the skin reaction and nail disorder AE group of particular interest in patients who received 0.15 mg/kg loncastuximab tesirine monotherapy was 3.7% and included photosensitivity reaction (see Module SVII.1.2), rash (including exfoliative, pustular, and maculo-papular), and erythema. All were assessed as treatment-related.

The following adverse drug reactions have been identified from post-marketing reports for Zynlonta in the US: telangiectasia, blister, rash vesicular (Skin and Subcutaneous Tissue Disorders SOC). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Serious cutaneous reactions (unrelated to exposure to sunlight) are a risk of loncastuximab tesirine not considered important for inclusion in the list of safety concerns in the RMP as these can be managed in clinical practice through healthcare professional awareness of the precautions to take with oncology therapeutic agents and will continue to be monitored via routine pharmacovigilance activities.

The product information for Zynlonta requires that it should only be administered under the supervision of a healthcare professional experienced in the diagnosis and treatment of cancer patients.

The Zynlonta SmPC instructs healthcare professionals to monitor patients for new or worsening cutaneous reactions and to withhold Zynlonta for severe (Grade 3) cutaneous reactions until resolution. If a skin reaction or rash develops, dermatologic consultation should be considered.

- **Known risks that do not impact the risk-benefit profile:**

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Anti-drug antibodies (ADA) towards loncastuximab tesirine from patients participating in the clinical studies ADCT-402-101, ADCT-402-201 and ADCT-402-102 have been evaluated (2.7.2 Summary of Clinical Pharmacology Studies). Screening, confirmation, and titration of anti-loncastuximab tesirine ADA were performed using a validated bridging electro-chemiluminescence immunoassay (ECLIA). From a total of 183 NHL patients and 145 DLBCL patients tested for ADA to loncastuximab tesirine, six (3.28%) patients in ADCT-402-101 and one patient (0.69%) in ADCT-402-201 exhibited confirmed positive ADA occurring at any time (Table 15). One patient exhibited a confirmed positive ADA which occurred at post-dose only, with a low $\log_2$ titre (<1). These data indicate that loncastuximab tesirine did not exert a clinically relevant ADA induction effect.

Table 15: Summary of anti-drug antibody response to loncastuximab tesirine

Study	Number of Patients Tested for ADA	Confirmed Positive ADA Predose N (%)	Confirmed Positive ADA Post-dose 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 (0.690%)	0 (0%)	1 (0.690%)	0 (0.0%)
Total	328	6 (1.83%)	1 (0.305%)	7 (2.13%)	2 (0.610%)

Footnote: ADA=anti-drug antibody; N=total number of patients
Source: 2.7.2 Summary of Clinical Pharmacology Studies, Table 3-16

The impact of immunogenicity on safety was further evaluated in patients from loncastuximab tesirine from ADCT-402-101 and ADCT-402-201. The relative frequency of safety signals was compared in the ADA-positive (n=7) and ADA-negative subgroups (n=321). In general, there was no increased safety signal in the ADA-positive subgroup. It is noted that AEs of GGT increased and neutrophil count decreased/neutropenia were observed with higher relative frequency in the ADA-positive subgroup, possibly due to some confounding factors and limited number of patients in the ADA-positive subgroup. However, in general safety signals detected in the ADA-positive subgroup were no worse than those in the ADA-negative subgroup (2.7.2 Summary of Clinical Pharmacology Studies).

Overall, the potential risk for ADA-mediated adverse effects upon administration of loncastuximab is low. Consistent with this, no ADA-linked AEs were observed in the clinical trials with loncastuximab tesirine. As such, immunogenicity is not an important risk in the post-marketing setting but will continue to be monitored via routine pharmacovigilance activities.

- **Other reasons for considering the risks not important:**

None.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk 1: Phototoxicity

Nonclinical studies have demonstrated that SG3199, the cytotoxic agent of loncastuximab tesirine, is photoreactive, and that exposure to visible light, UVA or UVB radiation enhances its ability to mediate DNA crosslinking and double-stranded breaks. This may represent an underlying mechanism for the observed dose-dependent skin changes (epidermal hyperpigmentation with hyperplasia/hyperkeratosis) in repeat-dose toxicity studies with ADCT-402 in cynomolgus monkeys (2.4 Nonclinical Overview). Among the 215 patients who received 0.15 mg/kg loncastuximab tesirine monotherapy, the TEAE of photosensitivity reaction was observed in 17 (7.9%) patients (16 [7.4%] treatment-related). Grade 3 photosensitivity reaction was observed in 3 (1.4%) patients, and all considered treatment-related. Dose delay occurred in 4 (1.9%) patients and treatment withdrawal in 1 (0.5%) patient as a result of photosensitivity reaction (2.7.4 Summary of Clinical Safety, ISS Tables 1.3.10, 1.3.25, 1.3.14.1 and 1.3.23)

Risk-benefit impact:

Grade 3 photosensitivity reactions have been reported in patients treated with loncastuximab tesirine. The benefit of loncastuximab tesirine as treatment for adult patients with relapsed or refractory DLBCL after two or more lines of systemic therapy outweighs this important identified risk of phototoxicity that can be managed in clinical practice through healthcare professional awareness and adherence to the guidance in the Zynlonta SmPC.

The Zynlonta SmPC advises healthcare professionals to monitor patients for new or worsening photosensitivity reactions and to withhold Zynlonta for severe (Grade 3) reactions until resolution. Healthcare professionals should advise patients to minimise or avoid exposure to direct natural or artificial sunlight including exposure through glass windows and instruct them to protect skin from exposure to sunlight by wearing sun-protective clothing and/or the use of sunscreen products. A patient alert card issued to patients by prescribing physicians addresses the important identified risk of phototoxicity (Part V.2) ensuring that special information regarding the patient's therapy with Zynlonta and its important risk of phototoxicity is always held by the patient.

Important Identified Risk 2: Oedema and effusion

The AE of oedema peripheral was one of the most common (≥10% of patients in all doses combined) TEAEs in DLBCL patients who received loncastuximab tesirine monotherapy occurring in 23.3% of the 215 patients who received 0.15 mg/kg loncastuximab tesirine monotherapy (24.3% for all doses combined [n=284]). Pleural effusion occurred in 13.5% of the 215 patients receiving 0.15 mg/kg loncastuximab tesirine and 14.8% of the 284 patients (all doses combined). Oedema peripheral and pleural effusion were two of the most common treatment-related TEAEs occurring in 16.7% and 11.2%, respectively, of the 215 patients receiving 0.15 mg/kg loncastuximab tesirine monotherapy (2.5 Clinical Overview).

Risk-benefit impact:

The benefit of loncastuximab tesirine as treatment for adult patients with relapsed or refractory DLBCL after two or more lines of systemic therapy outweighs this important identified risk of oedema and effusion that can be managed in clinical practice through healthcare professional awareness and adherence to the guidance in the Zynlonta SmPC.

The Zynlonta SmPC instructs healthcare professionals to monitor patients for new or worsening oedema or effusions and to withhold Zynlonta for Grade 2 or greater oedema or effusion until the toxicity resolves. Diagnostic imaging in patients is suggested for those who develop symptoms of pleural effusion or pericardial effusion, such as new or worsened dyspnoea, chest pain, and/or ascites such as swelling in the abdomen and bloating. Appropriate medical management for oedema or effusions should be implemented.

Important Potential Risk 1: Embryo-foetal toxicity

Loncastuximab tesirine contains the cytotoxic agent SG3199, which was demonstrated to be clastogenic in *in vitro* studies, consistent with its mode of action as a covalent DNA crosslinking/alkylating agent. Severe depletion/degeneration of germ cells was observed in sexually mature cynomolgus monkeys in the pivotal GLP 13-week repeat-dose toxicity study (Module SII). Based on nonclinical genotoxicity findings and the mechanism of action of loncastuximab tesirine there is a risk of embryo-foetal toxicity during pregnancy. However, there are no data on loncastuximab tesirine exposure in pregnant women since pregnant females and women of childbearing potential or fertile men with female partners of childbearing potential

unwilling to use highly effective contraception were excluded from clinical trial participation for safety reasons (Module SIV.1; Module SIV.3).

Risk-benefit impact:

Whilst there is a risk of embryo-foetal toxicity during pregnancy, the benefit of loncastuximab tesirine as treatment for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy may on a case-by-case assessment outweigh this important potential risk of embryo-foetal toxicity that can be managed in clinical practice through healthcare professional awareness and adherence to the guidance in the Zynlonta SmPC.

The Zynlonta SmPC informs healthcare professionals that Zynlonta, based on its mechanism of action, can cause embryo-foetal harm when administered to a pregnant woman because it contains a genotoxic compound (SG3199) and affects actively dividing cells. Healthcare professionals are advised to inform pregnant women of the potential risk to the foetus. Females of childbearing potential are advised to use effective contraception during treatment with Zynlonta and for 10 months after the last dose. Similarly, male patients with female partners of childbearing potential are advised to use effective contraception during treatment with Zynlonta, and for 7 months after the last dose. Zynlonta is not recommended during pregnancy unless the potential benefit for the woman outweighs the potential risk to the foetus. Zynlonta is not recommended in women of childbearing potential not using contraception. Pregnancy testing is advised prior to initiating Zynlonta.

Missing information 1: Use in patients with moderate or severe hepatic impairment

Use in patients with moderate or severe hepatic impairment is missing information based on the limited exposure in this population in the clinical development programme (Module SIV.3).

Risk-benefit impact:

The benefit of loncastuximab tesirine as treatment for adult patients with relapsed or refractory DLBCL after two or more lines of systemic therapy may outweigh the risk of use of loncastuximab tesirine in patients with moderate or severe hepatic impairment based on an individual risk-benefit assessment conducted by the prescriber. No dose adjustment of Zynlonta is recommended for patients with mild hepatic impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin >1 to 1.5 x ULN and any AST). However, the risk to patients with moderate or severe hepatic impairment is currently not known.

The Zynlonta SmPC informs healthcare professionals that Zynlonta has not been studied in patients with moderate or severe hepatic impairment (total bilirubin >1.5 × ULN and any AST). In patients with hepatic impairment, monitoring for adverse reactions is recommended.

Missing information 2: Use in patients with severe renal impairment

There are very limited data on use of loncastuximab tesirine in patients with severe renal impairment in the clinical development programme and such patients are an area of missing information.

Risk-benefit impact:

The benefit of loncastuximab tesirine as treatment for adult patients with relapsed or refractory DLBCL after two or more lines of systemic therapy may outweigh the risk of use of loncastuximab tesirine in patients with severe renal impairment based on an individual risk-benefit assessment conducted by the prescriber. No dose adjustment of Zynlonta is required for patients with mild to moderate renal impairment. The Zynlonta SmPC informs healthcare

professionals that Zynlonta has not been studied in patients with severe renal impairment (CrCL 15 to 29 mL/min). The effect of severe renal impairment, and end-stage renal disease, with or without haemodialysis, on loncastuximab tesirine pharmacokinetics is unknown. Additional monitoring for adverse reactions may be warranted in these patients when loncastuximab tesirine is administered.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risk 1: Phototoxicity

Potential mechanisms:

Phototoxicity is a chemically induced skin irritation, requiring exposure to light, that does not involve the immune system, whereby the skin response resembles an exaggerated sunburn. Loncastuximab tesirine contains a cytotoxic agent, SG3199, which has been shown to be photoreactive. Exposure to visible light, UVA or UVB radiation enhances the ability of SG3199 to mediate DNA crosslinking and double-stranded breaks, which may represent a contributory underlying mechanism to the epidermal hyperpigmentation and hyperkeratosis observed upon IV administration of loncastuximab tesirine to cynomolgus monkeys *in vivo* (Module SII).

Evidence source(s) and strength of evidence:

In clinical studies, of the 215 DLBCL patients treated with 0.15 mg/kg loncastuximab tesirine monotherapy, photosensitivity reaction was observed in 17 (7.9%) patients with 3 of these patients (1.4%) experiencing a severe reaction.

Minimal-to-moderate skin discoloration was observed in animal studies.

Characterisation of the risk:

The incidence of the most common (≥10% of patients in all doses combined) selected TEAEs in the skin reaction and nail disorder group of AEs of particular interest in the 215 DLBCL patients who received 0.15 mg/kg loncastuximab tesirine monotherapy was 46.5% with 44.2% assessed as treatment-related (2.7.4 Summary of Clinical Safety).

The most common specific events in this category (≥10%) included rash (20.0%), pruritus (11.6%), and erythema (10.2%). No notable differences were observed between the 215 patients who received 0.15 mg/kg and the 284 patients who received any dose of loncastuximab tesirine monotherapy. The incidence of Grade 3 or higher events in the skin reaction and nail disorder AE group of particular interest was 3.7% and all were assessed as treatment-related.

Specifically, the TEAE of photosensitivity reaction was observed in 17 (7.9%) patients with all but one (16 [7.4%]) assessed as treatment-related (Table 16). Of the patients experiencing treatment-related photosensitivity reactions 3 (1.4%) were Grade 3 severity; there were no Grade 4 photosensitivity events. No notable differences were observed between the 215 patients who received 0.15 mg/kg and the 284 patients who received any dose of loncastuximab tesirine monotherapy.

Table 16: TEAE of photosensitivity reaction in 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)
Patient with any TEAE	10 (100.0)	32 (100.0)	69 (98.6)	143 (98.6)	212 (98.6)	27 (100.0)	281 (98.9)
Skin Reaction and Nail Disorder group	4 (40.0)	16 (50.0)	37 (52.9)	63 (43.4)	100 (46.5)	13 (48.1)	133 (46.8)
Photosensitivity reaction	0	2 (6.3)	2 (2.9)	15 (10.3)	17 (7.9)	1 (3.7)	20 (7.0)
Patient 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)
Skin Reaction and Nail Disorder group	4 (40.0)	16 (50.0)	34 (48.6)	61 (42.1)	95 (44.2)	12 (44.4)	127 (44.7)
Photosensitivity reaction	0	2 (6.3)	1 (1.4)	15 (10.3)	16 (7.4)	1 (3.7)	19 (6.7)

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
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.
Source: 2.7.4 Summary of Clinical Safety, ISS Tables 1.3.10 and 1.3.25

Among the 215 patients who received 0.15 mg/kg loncastuximab tesirine monotherapy, 4 (1.9%) experienced a photosensitivity reaction leading to dose delay and all were assessed as treatment-related. Treatment withdrawal occurred in 1 (0.5%) patient as a result of photosensitivity reaction (2.7.4 Summary of Clinical Safety).

In non-clinical toxicity studies with loncastuximab tesirine in cynomolgus monkeys, minimal-to-moderate skin discoloration was observed, potentially related to phototoxicity, which correlated microscopically with epidermal hyperpigmentation and hyperkeratosis. These findings showed a trend towards reversibility, with reduced occurrence and/or severity following a 12-week treatment-free period (Module SII).

Risk factors and risk groups:

Risk factors for phototoxicity (sun allergy) caused by loncastuximab tesirine include exposure to natural or artificial sunlight. However, the occurrence of such drug-induced photoreaction can vary from person to person according to ethnic group and geographic area, probably due to different skin types, sun radiation intensity, and use of sunscreen products or sun-protective clothing (Lozzi 2020). Some medical disorders and some concomitant medications can also increase sensitivity to sunlight.

Preventability:

The Zynlonta SmPC advises healthcare professionals to monitor patients for new or worsening cutaneous reactions, including photosensitivity reactions and to withhold Zynlonta for severe (≥Grade 3) cutaneous reactions until resolution. In clinical studies with Zynlonta oral and topical corticosteroids and anti-pruritic therapy were used to treat cutaneous reactions. Patients should be advised to minimise or avoid exposure to direct natural or artificial sunlight including exposure through glass windows. Healthcare professionals should instruct patients to protect skin from exposure to sunlight by wearing sun-protective clothing and/or the use of sunscreen products. If a skin reaction or rash develops, dermatologic consultation should be considered. A patient alert card issued to patients by prescribing physicians addresses the important identified risk of phototoxicity (Part V.2) ensuring that special information regarding the patient's therapy with Zynlonta and its important risk of phototoxicity is always held by the patient.

Impact on the risk-benefit balance of the product:

Loncastuximab tesirine has been observed to cause photosensitivity reactions. However, relapsed or refractory DLBCL is a serious and life-threatening condition with limited effective therapeutic options (Module SI).

The benefit of loncastuximab tesirine as a treatment for adult patients with relapsed or refractory DLBCL, after two or more lines of systemic therapy, outweighs the important identified risk of photosensitivity that can be managed in clinical practice through healthcare professional awareness of this type of reaction due to the cytotoxic component (SG3199) of Zynlonta, and by adhering to the guidance in the Zynlonta SmPC that warns against exposure to direct natural or artificial sunlight including exposure through glass windows during use and recommends patient monitoring for new or worsening cutaneous reactions, including photosensitivity reactions. Zynlonta should be withheld for severe (Grade 3) cutaneous reactions until resolution.

Phototoxicity will be further characterised using a targeted questionnaire beyond adverse reactions reporting and signal detection of routine pharmacovigilance (Part III.1). Both the ongoing study, ADCT-402-201 (Part III.2), and the post-authorisation efficacy study, ADCT-402-311 (Part IV), will also provide additional safety information regarding phototoxicity.

Public health impact:

Nonclinical findings have suggested a potential risk of phototoxicity (Module SII), and photosensitivity reactions have been observed in humans. However, minimal impact on public health is anticipated since phototoxicity can be managed by preventative measures such as the wearing of sun-protective clothing, use of sunscreen products and avoidance of exposure to direct natural or artificial sunlight.

Important Identified Risk 2: Oedema and effusion

Potential mechanisms:

Adverse event profiles of PBD-based therapies reported in the literature and early clinical data have included oedema and effusion TEAEs (see SIV.1). Loncastuximab tesirine incorporates the same PBD dimer toxin and hence PDB-associated events of oedema and effusion are similarly anticipated although the exact mechanism by which PBD elicits such reactions is not fully understood.

Evidence source(s) and strength of evidence:

In clinical studies, of the 215 DLBCL patients treated with 0.15 mg/kg loncastuximab tesirine monotherapy, oedema and effusion reactions were observed in 78 (36.3%) patients. Oedema and effusion events were severe or potentially life-threatening in 5.1% and 0.5%, respectively, of the 215 patients.

Characterisation of the risk:

Overall, the incidence of TEAEs for the oedema and effusion group of AEs was 36.3% (Table 17) with 27.9% being treatment-related and 5.6% being Grade 3 or higher of which 4.6% were treatment-related. Specifically, oedema peripheral occurred in 23.3% patients (16.7% treatment-related) and pleural effusion in 13.5% patients (11.2% treatment related) (2.5 Clinical Overview).

Table 17: Most common (≥10% of patients in all doses combined) selected TEAEs by oedema or effusion group of AEs and preferred term for loncastuximab tesirine monotherapy treated DLBCL patients

AE Group 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)
Oedema 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)

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 10% cutoff was based on All Doses.
Adverse events were coded using MedDRA version 22.0.
Source: 2.7.4 Summary of Clinical Safety, Table 24

Grade 3 and Grade 4 oedema and effusion AEs were observed in 5.1% and 0.5%, respectively, of the 215 patients who received 0.15 mg/kg loncastuximab tesirine monotherapy. Of the most common serious TEAEs, pleural effusion occurred in 1.9% patients (1.4% Grade 3), pericardial effusion in 0.9% patients (0.5% Grade 3, 0.5% Grade 4), and oedema peripheral in 0.9% patients (all Grade 3) treated with 0.15 mg/kg loncastuximab tesirine monotherapy. Treatment withdrawal occurred as a result of peripheral oedema in 2.8% patients (all assessed as treatment-related), and as a result of localised oedema, pericardial effusion, and pleural effusion in 1.4% of patients each (assessed as 1.4%, 0.9%, and 0.9% treatment-related, respectively) (2.7.4 Summary of Clinical Safety).

Based on outcomes from the Phase 1 study ADCT-402-101, and to mitigate toxicities such as oedema and effusion, dexamethasone premedication was introduced for the Phase 2 study (ADCT-402-201). Dexamethasone was administered over a course of three days, beginning the day before treatment, and the dose of loncastuximab tesirine was reduced following the first two cycles. In addition, treatment was held for any patient that experienced Grade ≥2 oedema or effusion until the toxicity resolved to Grade ≤1. As a result, a notable decrease was seen in patients who experienced oedema and effusion reactions in clinical study ADCT-402-201 relative to ADCT-402-101 (Table 17).

Oedema and effusion were not evident as part of the toxicity profile of SG3199 in nonclinical studies in rats and dogs or of ADCT-402 in cynomolgus monkeys (Module SII).

Risk factors and risk groups:

DLBCL is mainly a disease of older individuals who may have other co-existing diseases. In general, risk factors for pleural effusion include congestive heart failure, cancer, pneumonia, and pulmonary embolism, whilst peripheral oedema may be caused by several different reasons including immobility, obesity, complications from heart, liver, or kidney disease, and pregnancy. Most of these conditions are associated with the older population and hence observed in patients with DLBCL.

Preventability:

Oedema and effusion can be managed in clinical practice through healthcare professional awareness of the precautions to take with oncology therapeutic agents and adhering to the guidance in the Zynlonta SmPC. The Zynlonta SmPC states that, unless contraindicated, dexamethasone 4 mg is to be administered orally or intravenously twice daily for 3 days, beginning the day before administering Zynlonta and advises healthcare professionals to monitor patients for new or worsening oedema or effusions. Treatment with Zynlonta should be withheld

for Grade 2 or greater oedema or effusion until the toxicity resolves to Grade 1 or less. For patients who develop symptoms of pleural effusion or pericardial effusion, such as new or worsened dyspnoea, chest pain, and/or ascites such as swelling in the abdomen and bloating. diagnostic imaging should be considered and appropriate medical management for oedema or effusions implemented. Patients are advised to seek urgent medical attention if they develop any signs or symptoms of fluid retention such as chest pain, difficulty breathing, or swelling in any part of their body.

The product information for Zynlonta requires that it should only be administered under the supervision of a healthcare professional experienced in the diagnosis and treatment of cancer patients.

Impact on the risk-benefit balance of the product:

Loncastuximab tesirine has been observed to cause oedema and effusions reactions. However, relapsed or refractory DLBCL is a serious and life-threatening condition with limited effective therapeutic options (Module SI). The benefit of loncastuximab tesirine as a treatment for adult patients with relapsed or refractory DLBCL, after two or more lines of systemic therapy, outweighs the important identified risk of oedema and effusion that can be managed in clinical practice through healthcare professional awareness of this type of reaction and by adhering to the guidance in the Zynlonta SmPC that warns of serious effusion and oedema and recommends premedication with dexamethasone. Both the ongoing study, ADCT-402-201 (Part III.2), and the ongoing post-authorisation efficacy study, ADCT-402-311 (Part IV), will also provide additional safety information regarding oedema and effusion.

Public health impact:

Oedema and effusion have been observed in humans. However, minimal impact on public health is anticipated since oedema and effusion can be managed by premedication with dexamethasone, monitoring of patients for new or worsening oedema or effusions, and withholding Zynlonta for Grade 2 or greater oedema or effusion until the toxicity resolves.

Important Potential Risk 1: Embryo-foetal toxicity

Potential mechanisms:

Loncastuximab tesirine contains the cytotoxic agent, SG3199, which is a synthetic PBD dimer, where two PBD monomers are linked through their aromatic A-ring phenolic C8-positions via a flexible propyldioxy tether, creating a highly efficient DNA minor groove cross-linking agent with potent cytotoxicity (Hartley 2018). Although no reproductive and developmental toxicity studies were conducted, the nonclinical genotoxicity observations for SG3199 are consistent with its mode of action as a covalent DNA crosslinking/alkylating agent and indicate that exposure to loncastuximab tesirine during pregnancy may interfere with normal growth, homeostasis, development, and differentiation of the foetus (Module SII).

Evidence source(s) and strength of evidence:

Use of loncastuximab tesirine during pregnancy has not been evaluated in the clinical studies (Module SIV.1) and there are no data available for loncastuximab tesirine exposure in pregnant women. However, loncastuximab tesirine contains a component that is toxic to actively dividing cells. Based on its mechanism of action, loncastuximab tesirine can cause foetal malformations or foetal death when administered to a pregnant woman.

Findings from *in vitro* toxicity studies conducted with the cytotoxic component to assess genotoxicity may be relevant for humans and in the absence of data in humans suggest a potential safety concern.

Characterisation of the risk:

Women who were pregnant or breastfeeding were excluded from clinical trial participation because of the potential harm that loncastuximab could cause to the foetus (Module SIV.1). There are no data on loncastuximab tesirine exposure in pregnant women (Module SIV.3).

The cytotoxic component of loncastuximab tesirine, SG3199, was demonstrated to be clastogenic in an *in vitro* micronucleus test and a chromosome aberration assay, consistent with its mode of action as a covalent DNA crosslinking/alkylating agent (Module SII). Severe depletion/degeneration of germ cells was observed in sexually mature cynomolgus monkeys in the pivotal GLP 13-week repeat-dose toxicity study (Module SII).

Risk factors and risk groups:

Women of childbearing age and men with female partners of childbearing age who are not using an effective method of contraception during treatment with loncastuximab tesirine and for 10 months and 7 months, respectively, after the last dose are at risk of toxicity to the unborn child.

Preventability:

Embryo-foetal toxicity can be prevented by adhering to the guidance in the product information. The Zynlonta SmPC informs healthcare professionals that Zynlonta, based on its mechanism of action, can cause embryo-foetal harm when administered to a pregnant woman because it contains a genotoxic compound (SG3199) and affects actively dividing cells. Healthcare professionals are advised to inform pregnant women of the potential risk to the foetus. Zynlonta is not recommended during pregnancy unless the potential benefit for the woman outweighs the potential risk to the foetus. Pregnancy testing is advised prior to initiating Zynlonta. Females of childbearing potential are advised to use effective contraception during treatment with Zynlonta and for 10 months after the last dose. Similarly, male patients with partners of childbearing potential are advised to use effective contraception during treatment with Zynlonta, and for 7 months after the last dose. Zynlonta is not recommended in women of childbearing potential not using contraception.

Impact on the risk-benefit balance of the product:

Loncastuximab tesirine has been demonstrated to be clastogenic in *in vitro* studies. Based on nonclinical genotoxicity findings and the mechanism of action of loncastuximab tesirine there is a potential risk of embryo-foetal toxicity during pregnancy. However, relapsed or refractory DLBCL is a serious and life-threatening condition with limited effective therapeutic options (Module SI). The benefit of loncastuximab tesirine as a treatment for adult patients with relapsed or refractory DLBCL, after two or more lines of systemic therapy, may on a case-by-case assessment outweigh the important potential risk of embryo-foetal toxicity that can be managed in clinical practice through healthcare professional awareness of embryo-foetal toxicity due to the cytotoxic component (SG3199) of Zynlonta, and by advising patients to adhere to the guidance in the Zynlonta SmPC of effective contraception during treatment with Zynlonta, and for 10 months after the last dose for women or 7 months after the last dose for men.

Public health impact:

Nonclinical findings demonstrate a potential risk of embryo-foetal toxicity. However, minimal impact on public health is anticipated since embryo-foetal toxicity can be managed by preventative measures such as the use of effective contraception during treatment with Zynlonta, and for 7-10 months after the last dose. In addition, Zynlonta is not recommended during pregnancy unless the potential benefit for the woman outweighs the potential risk to the foetus.

SVII.3.2. Presentation of the missing information

Missing information 1: Use in patients with moderate or severe hepatic impairment

Evidence source:

In the clinical development programme, patients were excluded unless they had adequate hepatic function at study entry (ALT, AST, GGT ≤2.5 x ULN; total bilirubin ≤1.5 x ULN) (Module SIV.1). No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin ≤ULN and AST>ULN or total bilirubin >1 to 1.5 x ULN and any AST). Due to the limited number of patients with moderate/severe hepatic impairment (n=1), no conclusions can be drawn about either loncastuximab tesirine exposure or AEs in patients with moderate/severe hepatic impairment. Hence, use in patients with moderate or severe hepatic impairment is an area of missing information.

Anticipated risk/consequence of the missing information:

Hepatic impairment may increase the exposure of unconjugated SG3199, however there was no clinically significant effect on loncastuximab tesirine pharmacokinetics observed in humans with mild hepatic impairment. The monoclonal antibody portion of loncastuximab tesirine is expected to be metabolised into small peptides by catabolic pathways. The small molecule cytotoxin, SG3199, is metabolised by CYP3A4/5 *in vitro*.

Patients with mild/moderate hepatic impairment were associated with greater risk of death compared to patients with normal hepatic function. However, it is not clear whether this was attributable solely or partially to the trend of lower exposure to loncastuximab tesirine for patients with mild/moderate hepatic impairment determined from the population PK analysis, on the lower levels of albumin (and commensurate lower drug exposure) associated with their disease, on a more fragile overall health state, or a composite of these effects. It follows that maintaining the same dose level for patients with mild/moderate hepatic impairment as for patients with normal hepatic status is appropriate (2.7.2 Summary of Clinical Pharmacology Studies).

Use in patients with moderate/severe hepatic impairment will be monitored using routine pharmacovigilance as well as being further characterised through conduct of a hepatic impairment study (Part III.2).

Missing information 2: Use in patients with severe renal impairment

Evidence source:

In the clinical development programme, patients were excluded unless they had adequate renal function at study entry (blood creatinine ≤1.5xULN or calculated CrCL ≥60 mL/min by the Cockcroft and Gault equation) (Module SIV.1). Overall, no dose adjustment is recommended for patients with mild or moderate renal impairment, based on the minimal magnitude of the effect of renal impairment on PK exposure, and that the renal elimination pathway is not expected to contribute significantly to the clearance of therapeutic antibodies or SG3199. Given that there

was only 1 patient in the severe renal impairment subgroup use in such patients is an area of missing information.

Population in need of further characterisation:

Although Study ADCT-402-311 will include patients with calculated CrCL ≥30 mL/min (by the Cockcroft and Gault equation) to evaluate the use of loncastuximab tesirine in patients with moderate renal impairment (Part IV) patients with severe renal impairment (CrCL <30 mL/min) are excluded. Use in patients with renal impairment will be monitored using routine pharmacovigilance.

Part II: Module SVIII - Summary of the safety concerns

Table 18: 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

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific follow-up forms for the following safety concerns:

- A photosensitivity-targeted questionnaire will be available to collect and evaluate specific data related to phototoxicity in the post-marketing period (Annex 4).

Other forms of routine pharmacovigilance activities for the safety concerns:

- None

III.2 Additional pharmacovigilance activities

ADCT-402-201 Summary

Study short name and title:

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)

Rationale and study objectives:

Primary Objectives

- To evaluate the efficacy of single-agent loncastuximab tesirine in patients with relapsed or refractory DLBCL

Secondary Objectives

- 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

Study design:

This is an ongoing Phase 2, multicentre, open-label, single-arm study of the efficacy and safety of loncastuximab tesirine used as monotherapy in patients with relapsed or refractory DLBCL. To enhance patient safety, a 2-stage design was used, with an interim analysis for futility on the first 52 patients. The duration of study participation for each patient was defined as the time from the date of signed written informed consent to the completion of the follow-up period, withdrawal of consent, lost to follow-up, or death, whichever occurred first. The study included a screening period (up to 28 days), a treatment period (cycles of 3 weeks), and a follow-up period (visits approximately every 12 weeks for up to 3 years after treatment discontinuation, regardless of disease status). Loncastuximab tesirine was administered as an IV infusion over 30 minutes on

Day 1 of each cycle. Patients received 0.15 mg/kg every 3 weeks for 2 cycles, then 0.075 mg/kg every 3 weeks for subsequent cycles. Patients could continue treatment for up to one year or until disease progression, unacceptable toxicity, or other discontinuation criteria, whichever occurred first. Additionally, patients benefiting clinically at one year could have continued treatment following a case-by-case review.

Safety is being assessed based on AEs, serious AEs, treatment discontinuations due to AEs, periodic 12-lead ECG recordings, physical examinations, vital signs measurements, Eastern Cooperative Oncology Group (ECOG) performance status, laboratory values, and pregnancy testing (for women of childbearing potential). AEs are being graded according to CTCAE version 4.0.

Study population:

This study has enrolled 145 patients (male or female), aged 18 years and older, with relapsed or refractory DLBCL (following two or more multi-agent systemic treatment regimens) with adequate organ function and an ECOG performance status of 0 to 2. Patients had a pathologic diagnosis of DLBCL, as defined by the 2016 WHO classification, to include: DLBCL not otherwise specified (NOS); primary mediastinal large B-cell lymphoma; and high-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements.

Milestones:

Protocol finalised: Mar 2018

Trial completion: Aug 2022

CSR filing: Dec 2023

Hepatic Impairment Study Summary

Study short name and title:

Hepatic Impairment Study

An Open-Label, Non-Randomised, Dose-Escalation Trial in Patients with Moderate and Severe Hepatic Impairment and Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Rationale and study objectives:

An open-label study will be conducted with loncastuximab tesirine in patients with moderate and severe hepatic impairment, according to the National Cancer Institute Organ Dysfunction Working Group criteria. Safety and pharmacokinetic information for loncastuximab tesirine and SG3199 will be collected to determine the appropriate starting dose and dosing regimen of loncastuximab tesirine for this population.

Study design:

To be confirmed

Study population:

Patients with relapsed or refractory diffuse large B-cell lymphoma and with moderate or severe hepatic impairment.

Milestones:

Protocol finalised: Sep 2022

Trial completion: Dec 2026

CSR filing: Jun 2027

III.3 Summary Table of additional Pharmacovigilance activities

Table 19: 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

Part IV: Plans for post-authorisation efficacy studies

Table 20: Planned and ongoing post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Study **Status**	**Summary of objectives**	**Efficacy uncertainties addressed**	**Milestones**	**Due Date**
Efficacy studies which are conditions of the marketing authorisation				
None				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances*				
Study ADCT-402-311 A Phase 3 Randomised Study of Loncastuximab Tesirine Combined with Rituximab Versus Immunochemotherapy in Patients with Relapsed or Refractory Diffuse Large B Cell Lymphoma (DLBCL) Ongoing	To evaluate the efficacy of loncastuximab tesirine combined with rituximab compared to standard immunochemotherapy. To characterise the safety profile of loncastuximab tesirine combined with rituximab (including addressing the specific safety concerns of phototoxicity and oedema and effusion). To characterise the pharmacokinetic profile of loncastuximab tesirine combined with rituximab. To evaluate the immunogenicity of loncastuximab tesirine combined with rituximab. To evaluate the impact of loncastuximab tesirine combined with rituximab treatment on treatment-related and disease-related symptoms, patient-reported functions, and overall health status.	Efficacy (primary endpoint of progression free survival)	Protocol finalised	10 Mar 2020
			Trial completion (i.e., final data collection for primary outcome measure)	Jun 2025
			CSR filing	Dec 2025

*Routine pharmacovigilance activities during the post-authorisation efficacy study, ADCT-402-311, listed in Table 20 above, will support further characterisation of the two important identified risks of phototoxicity and oedema and effusion.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table 21: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Phototoxicity (Important identified risk)	Routine risk communication: • Adverse reaction in SmPC section 4.8 • Side effect in package leaflet (PL) section 4 • Warning of serious/severe cutaneous reactions (Grade 3), including photosensitivity reactions, in SmPC sections 4.4 and 4.8 • Warning that black skin spots potentially related to phototoxicity were observed in cynomolgus monkeys and were still present after a 12-week treatment-free period in SmPC section 5.3 • Warning that patients may burn more easily or get severe sunburns in PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance to monitor patients for new or worsening cutaneous reactions, including photosensitivity reactions, and to consider dermatologic consultation if a skin reaction or rash develops, in SmPC section 4.4 • Guidance to withhold Zynlonta for adverse reactions of ≥Grade 3 until the toxicity resolves to ≤Grade 1 in SmPC sections 4.2 and 4.4 • Guidance to advise patients to minimise or avoid exposure to direct natural or artificial sunlight including exposure through glass windows and to protect their skin from exposure to sunlight by wearing sun-protective clothing and/or the use of sunscreen products in SmPC section 4.4 • Warning for the patient to inform their doctor or nurse if they experience new or worsening skin reactions, including sensitivity to sunlight, skin rash, peeling, redness or irritation in PL section 2 • Warning that it is important for the patient to wear sunscreen and appropriate clothing to ensure they do not burn in PL section 2 Other routine risk minimisation measures beyond the Product Information: • Specialist prescribing only

Safety concern	Routine risk minimisation activities
Oedema and effusion (Important identified risk)	Routine risk communication: • Adverse reaction in SmPC section 4.8 • Side effect in PL section 4 • Warning of serious oedema and effusion in SmPC section 4.4 • Warning of fluid retention in PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance to monitor patients for new and worsening oedema or effusions in SmPC section 4.4 • Guidance to withhold Zynlonta for Grade 2 or greater oedema or effusion until the toxicity resolves in SmPC sections 4.2 and 4.4 • Instruction for patients to inform their doctor if they develop any symptoms of fluid retention in PL section 2 Other routine risk minimisation measures beyond the Product Information: • Specialist prescribing only
Embryo-foetal toxicity (Important potential risk)	Routine risk communication: • Warning of embryo-foetal harm in pregnant women in SmPC section 4.4 and 4.6 • Warning that Zynlonta can harm an unborn baby in PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance to not recommend treatment with Zynlonta during pregnancy unless the potential benefit for the woman outweighs the potential risk to the foetus in SmPC section 4.6 • Advice to test for pregnancy prior to initiating Zynlonta in SmPC section 4.6 • Guidance to advise women of the risk to the foetus and to use effective contraception in SmPC section 4.4 and 4.6 • Guidance to advise men with partners of childbearing potential to use effective contraception in SmPC section 4.4 and 4.6 • Warning for women to speak to doctor or nurse if pregnant or planning to become pregnant in PL section 2 • Warning for women of child-bearing potential and men with female partners to use effective contraception during and after treatment in PL section 2 • Warning for women not to get pregnant if taking Zynlonta and to speak to their doctor immediately if they become pregnant in PL section 2 Other routine risk minimisation measures beyond the Product Information: • Specialist prescribing only

Safety concern	Routine risk minimisation activities
Use in patients with moderate or severe hepatic impairment (Missing information)	Routine risk communication: • Information that Zynlonta has not been studied in patients with moderate or severe hepatic impairment (total bilirubin >1.5 x ULN and any AST) in SmPC section 4.2 • Information that mild hepatic impairment (total bilirubin ≤ULN and AST >ULN, or total bilirubin >1 to1.5 x ULN and any AST) may increase the exposure of unconjugated SG3199, but there was no clinically significant effect on loncastuximab tesirine pharmacokinetics in SmPC section 5.2 • Warning for the patient to speak to their doctor or nurse before being given Zynlonta if having liver problems in PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation to monitor for adverse reactions in patients with hepatic impairment in section 4.2 Other routine risk minimisation measures beyond the Product Information: • Specialist prescribing only
Use in patients with severe renal impairment (Missing information)	Routine risk communication: • Information that Zynlonta has not been studied in patients with severe renal impairment (CrCL 15 to 29 mL/min), and the effect of severe renal impairment, and end-stage renal disease, with or without haemodialysis, on loncastuximab tesirine pharmacokinetics is unknown in SmPC section 4.2 • Information that the clearance of loncastuximab tesirine in patients with mild to moderate renal impairment (CrCL 30 to <90 mL/min using the Cockcroft-Gault equation) was not significantly different from patients with normal renal function in SmPC section 5.2 • Warning that intravenous administration of loncastuximab tesirine in repeat-dose toxicity studies in cynomolgus monkeys was associated with renal toxicity including increased kidney weights and nephropathy with variable reversible inflammation and fibrosis in SmPC section 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation for additional monitoring for adverse reactions in patients with severe renal impairment in SmPC section 4.2 Other routine risk minimisation measures beyond the Product Information: • Specialist prescribing only

V.2. Additional Risk Minimisation Measures

Patient alert card

Objectives:

To address the important identified risk of phototoxicity by ensuring that special information regarding the patient's therapy with Zynlonta and its important risk of phototoxicity is always held by the patient and reaches the relevant healthcare professional as appropriate.

Rationale for the additional risk minimisation activity:

Zynlonta has been observed to cause photosensitivity reactions. A patient alert card will be employed as an additional risk minimisation measure to prevent the risk of photosensitivity, by emphasizing the need for patients to minimise or avoid exposure to direct natural or artificial sunlight including exposure through glass windows and to protect skin from exposure to sunlight by wearing sun-protective clothing and/or the use of sunscreen products.

Target audience and planned distribution path:

Patients are the target audience to receive the patient alert card, as provided by the prescribing physician prior to the initiation of therapy. The draft key messages for this additional risk minimisation measure are provided in Annex 6.

Plans to evaluate the effectiveness of the interventions and criteria for success:

The dissemination of the alert cards to medical institutions where they will be distributed to patients, will be tracked to ensure the Marketing Authorisation Holder has oversight of the implementation and management of additional risk minimisation measures.

Spontaneous AE cases, including information regarding actions taken by prescribers and concomitant medications used by patients, provided through targeted questionnaires will be evaluated. Cumulative reviews will be submitted with each periodic safety update report (PSUR), and assessment will be made if there is any specific cause of concern that requires further mitigation.

V.3 Summary of risk minimisation measures

Table 22: 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*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *Phototoxicity Questionnaire* Additional pharmacovigilance activities: • *Study ADCT-402-201*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• *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*	
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* • *Warning 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: • *Hepatic Impairment Study*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
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*

Part VI: Summary of the risk management plan

Summary of risk management plan for Zynlonta (loncastuximab tesirine)

This is a summary of the risk management plan (RMP) for Zynlonta. The RMP details important risks of Zynlonta, how these risks can be minimised, and how more information will be obtained about Zynlonta's risks and uncertainties (missing information).

Zynlonta's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Zynlonta should be used.

This summary of the RMP for Zynlonta should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Zynlonta's RMP.

I. The medicine and what it is used for

Zynlonta is authorised 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 (see SmPC for the full indication). It contains loncastuximab tesirine as the active substance and it is given by intravenous infusion.

Further information about the evaluation of Zynlonta's benefits can be found in Zynlonta's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page>.

II. Risks associated with the medicine and activities to minimise or further characterise these risks

Important risks of Zynlonta, together with measures to minimise such risks and the proposed studies for learning more about Zynlonta's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status - the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Zynlonta, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Zynlonta is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Zynlonta are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Zynlonta. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
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

II.B Summary of important risks

Important identified risk 1: Phototoxicity	
Evidence for linking the risk to the medicine	In clinical studies, of the 215 DLBCL patients treated with 0.15 mg/kg loncastuximab tesirine monotherapy, photosensitivity reaction was observed in 17 (7.9%) patients with 3 of these patients (1.4%) experiencing a severe reaction. Minimal-to-moderate skin discoloration was observed in animal studies.
Risk factors and risk groups	Risk factors for phototoxicity (sun allergy) caused by loncastuximab tesirine include exposure to sunlight or artificial light. However, the occurrence of such drug-induced photoreaction can vary from person to person according to ethnic group and geographic area, probably due to different skin types, sun radiation intensity, and use of sunscreen products or sun-protective clothing. Some medical disorders and some concomitant medications can also increase sensitivity to sunlight.

Important identified risk 1: Phototoxicity	
Risk minimisation measures	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 package leaflet section 2* • *Side effect in package leaflet section 4* • *Specialist prescribing only* Additional risk minimisation measures: • *Patient Alert Card*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study ADCT-402-201 See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk 2: Oedema and effusion	
Evidence for linking the risk to the medicine	In clinical studies, of the 215 DLBCL patients treated with 0.15 mg/kg loncastuximab tesirine monotherapy, oedema and effusion reactions were observed in 78 (36.3%) patients. Oedema and effusion events were severe or potentially life-threatening in 5.1% and 0.5%, respectively, of the 215 patients.
Risk factors and risk groups	DLBCL is mainly a disease of older individuals who may have other co-existing diseases. In general risk factors for pleural effusion include congestive heart failure, cancer, pneumonia, and pulmonary embolism, whilst peripheral oedema may be caused by several different reasons including immobility, obesity, complications from heart, liver, or kidney disease, and pregnancy. Most of these conditions are associated with the older population and hence observed in patients with DLBCL.

Important identified risk 2: Oedema and effusion	
Risk minimisation measures	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 package leaflet section 2* • *Side effect in package leaflet section 4* • *Specialist prescribing only* Additional risk minimisation measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study ADCT-402-201 See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk 1: Embryo-foetal toxicity	
Evidence for linking the risk to the medicine	Use of loncastuximab tesirine during pregnancy has not been evaluated in the clinical studies and there are no data available for loncastuximab tesirine exposure in pregnant women. However, loncastuximab tesirine contains a component that is toxic to actively dividing cells. Based on its mechanism of action, loncastuximab tesirine can cause foetal malformations or foetal death when administered to a pregnant woman. Findings from *in vitro* toxicity studies conducted with the cytotoxic component to assess genotoxicity may be relevant for humans and in the absence of data in humans suggest a potential safety concern.
Risk factors and risk groups	Women of childbearing age and men with female partners of childbearing age who are not using an effective method of contraception during treatment with loncastuximab tesirine and for 10 months and 7 months, respectively, after the last dose are at risk of toxicity to the unborn child.
Risk minimisation measures	Routine risk minimisation measures: • *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 package leaflet section 2* • *Specialist prescribing only* Additional risk minimisation measures: • *None*

Missing information 1: Use in patients with moderate or severe hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures: • *Warning/information in SmPC sections 4.2 and 5.2* • *Recommendation to monitor for adverse reactions in SmPC section 4.2* • *Warning in package leaflet section 2* • *Specialist prescribing only* Additional risk minimisation measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Hepatic Impairment Study: An Open-Label, Non-Randomised, Dose-Escalation Trial in Patients with Moderate and Severe Hepatic Impairment See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information 2: Use in patients with severe renal impairment	
Risk minimisation measures	Routine risk minimisation measures: • *Warning/information in SmPC sections 4.2, 5.2 and 5.3* • *Recommendation to monitor patients for adverse reactions in SmPC section 4.2* • *Specialist prescribing only* Additional risk minimisation measures: • *None*

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies are a condition of the marketing authorisation:

Study ADCT-402-201

Purpose of the study:

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.

Study ADCT-402-311

Purpose of the study:

To evaluate the efficacy of loncastuximab tesirine combined with rituximab compared to standard immunochemotherapy.

To characterise the safety profile of loncastuximab tesirine combined with rituximab.

To characterise the pharmacokinetic profile of loncastuximab tesirine combined with rituximab.

To evaluate the immunogenicity of loncastuximab tesirine combined with rituximab.

To evaluate the impact of loncastuximab tesirine combined with rituximab treatment on treatment-related and disease-related symptoms, patient-reported functions, and overall health status.

II.C.2 Other studies in post-authorisation development plan

Hepatic Impairment Study

Purpose of the study:

To determine a safe and appropriate starting dose and dosing regimen of loncastuximab tesirine for patients with moderate and severe hepatic impairment.

Part VII: Annexes

Table of contents

List of Annex Tables

Annex 4: Specific adverse drug reaction follow-up forms

Table of contents

Photosensitivity Questionnaire

Photosensitivity Reaction Questionnaire

Please return completed forms to:
drugsafety@adctherapeutics.com

ADCT Case ID No.: _____ Drug Trade Name (generic): _____ Report Date: _____

A. GENERAL INFORMATION	
Health Care Professional (HCP) Name and Specialty:	
HCP Address: (address, city, state, zip code, country) Phone Number Email	Address: Phone Number: Email:
Reporter Information: Name Relationship to the patient (provide details if not the patient)	Name: Relationship to patient: ☐ patient ☐ other

B. PATIENT DETAILS

Sex	Year of birth	Age	Race		Weight: ☐ kg ☐ lb Height: ☐ cm ☐ in
☐ Male ☐ Female	YYYY	Years	☐ White/Caucasian ☐ Asian ☐ Native Hawaiian/Other Pacific Islander	☐ Black/African American ☐ American Indian/Alaska Native ☐ Other:	

C. SUSPECT DRUG INFORMATION: ☐ Not Available

Initial Treatment Dosage and Date:

Recent Treatment Date:	Indication for use:	Batch/Lot Number:	Dose (Unit):	Route:	Cycle Number:

ACTION TAKEN DRUG AS A RESULT OF THE PHOTOSENSITIVITY REACTION

☐ No action taken
☐ Treatment Delayed; if delayed and restarted, resume date:
☐ Treatment Discontinued; if discontinued, date of discontinuation:
☐ Dose Reduced; if dose reduced, Prior Dose: New Dose:
☐ Unknown
☐ Not applicable (please clarify):

D. Relevant Medical History: ☐ Not Available ☐ See Attached

Medical History	Start Date (DD-MMM-YYYY)	Stop Date (DD-MMM-YYYY)	Ongoing
			☐
			☐
			☐
			☐
			☐
			☐

Version: V1.0 02Sep2021
Page **1** of **3**

Photosensitivity Reaction Questionnaire

E. EVENT DETAILS	
1. Onset Date (dd-mmm-yyyy)	
2. Did the patient wear sunscreen? If yes, please provide SPF	☐ Yes, SPF ☐ No ☐ Unknown
3. Does the patient apply sunscreen every day or only when going outside?	☐ Every day ☐ Only when going outside ☐ None ☐ Unknown ☐ Other: _____
4. How long was the affected area exposed to the sunlight?	
5. How long after sun exposure did the event begin?	
6. Did the event start after substances (such as lotions) were applied to the sun exposed area? If yes, please provide product name (see section F)	☐ Yes, Product Name(s): ☐ No ☐ Unknown
7. Was the patient seen by a physician / dermatologist? If yes, please provide evaluation details. (☐ See Attached)	☐ Yes ☐ No ☐ Unknown
8. Has the patient previously experienced photosensitivity reaction to any other product? If yes, please provide product name.	☐ Yes, Product Name(s): ☐ No ☐ Unknown
9. Please provide details related to the presentation of the reaction (ie, scaling, blisters, rash etc) and the approximate body surface area below (☐ See Attached) :	
10. Did the patient experience other non-rash like symptoms such as headaches, wheezing, nausea, weakness or dizziness? If yes, please provide details below:	
11. Did the patient receive treatment? If Yes, please provide details.	☐ Yes ☐ No ☐ Unknown
12. Has the event resolved?	☐ Yes w/treatment ☐ Yes w/o treatment ☐ No ☐ Unknown
13. Did the patient undergo any diagnostic testing to rule out other possible cause (such as systemic lupus erythematosus)? If so, please attach or provide details below:	

Version: V1.0 02Sep2021
Page **2** of **3**

Photosensitivity Reaction Questionnaire

E. EVENT DETAILS (cont'd)

14. Was the patient taking any medications or using any treatments that were applied directly to the skin and known to cause sensitivity to sunlight (including those listed below) **within 30 days** of the reaction?
Please select all that apply, and provide details in Section F below, as applicable: ☐No ☐Unknown

☐Alprazolam	☐Fluorouracil	☐omalizumab	☐Sulfonylureas
☐Amiodarone	☐Griseofulvin	☐Phenothiazines	☐Tetracyclines
☐Analgesics	☐hydroxychloroquine	☐piroxicam	☐Thiazides
☐Chlordiazepoxide	☐Isotretinoin	☐Quinidine	☐Tricyclic antidepressants
☐Chloroquine	☐Ketoprofen	☐Quinine	☐Trimethoprim
☐Dacarbazine	☐Methotrexate	☐Quinolones	☐Vinblastine
☐Furosemide	☐NSAIDs (ie piroxicam, ketoprofen)	☐Sulfonamides	☐Other:_____

☐Treatments applied directly to the skin: Antibacterial (such as chlorhexidine and hexachlorophene), Coal tar, Fragrances, Furocoumarin containing ingredients (such as limes, celery, and parsley)

F. CO-SUSPECT / CONCOMITANT MEDICATIONS ☐See Attached

Drug Name	Dose/Unit	Freq.	Route	Indication	Start Date (DD-MMM-YYYY)	Stop Date (DD-MMM-YYYY)	Ongoing
							☐
							☐
							☐
							☐

G. ADDITIONAL INFORMATION / DETAILS

Please use this area for any additional information or details related to this event.
(☐See Attached)

H. SIGNATURE

Individual completing this form:

☐Treating Physician (include specialty)_____
☐Other HCP (include details)_____
☐Other non-HCP (include details)_____

Name of individual completing the form:

Print name:_____

Signature:_____ Date:_____

Please return completed forms to:
drugsafety@adctherapeutics.com

Version: V1.0 02Sep2021
Page 3 of 3

Annex 6: Details of proposed additional risk minimisation activities

Draft key messages of the 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.

The phototoxicity risk minimisation material is aimed at addressing the important identified risk of phototoxicity by ensuring that special information regarding the patient's therapy with Zynlonta and the risk of photosensitivity reactions is held by the patient at all times and reaches the relevant healthcare professional as appropriate.

The MAH shall ensure that in each Member State where Zynlonta is marketed, all healthcare professionals and patients/carers who are expected to prescribe or use Zynlonta, respectively, have access to/are provided with the following:

- The Summary of Product Characteristics
- Package Leaflet
- Patient alert card

- **Patient alert card:**
  - A warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using Zynlonta (loncastuximab tesirine) for relapsed or refractory diffuse large B-cell lymphoma (DLBCL) or high-grade B-cell lymphoma (HGBL)
  - That Zynlonta treatment may increase the risk of photosensitivity reactions including through exposure to indirect sunlight (such as in vehicles and public transportation)
  - Measures that can be taken to prevent photosensitivity reactions
  - Signs and symptoms of photosensitivity reactions
  - To seek attention from a healthcare professional and contact the patient's treating physician when any skin eruption occurs
  - Contact details of the Zynlonta prescribing physician and patient