14 November 2019
EMA/CHMP/690748/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Polivy

International non-proprietary name: polatuzumab vedotin

Procedure No. EMEA/H/C/004870/0000

Note

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

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List of abbreviations

ABC	activated B-cell-like
acMMAE	antibody-conjugated MMAE
ADA	anti-drug antibody
ADC	antibody-drug conjugate
ADR	adverse drug reaction
AE	adverse event
AEPI	adverse event of particular interest
AESI	adverse event of special interest
ALT	alanine aminotransferase
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCR	B-cell receptor
BG	bendamustine and obinutuzumab
BOR	best objective response
BR	bendamustine and rituximab
CAR	chimeric antigen receptor
CHMP	Committee for Medicinal Products for Human Use
CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, oral
CHP	cyclophosphamide, doxorubicin, prednisolone/prednisone
CLL	chronic lymphocytic leukemia
Cmax	maximum concentration ovserved
CR	complete response
CrCl	creatinine clearance
CRS	cytokine-release syndrome
CSR	clinical study report
CT	computed tomography
CTD	Common Technical Document
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interation
DEL	double-expressor lymphoma
DLBCL	diffuse large B-cell lymphoma
DOR	duration of response
DP	drug product
DS	drug substance
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
FL	follicular lymphoma
GCB	germinal center B-cell-like
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GGT	gamma-glutamyltransferase
IRR	infusion related reaction
ISS	Integrated Summary of Safety
lyo	lyophilized
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	monomethyl auristatin E
NALT	new anti-lymphoma treatment
NCA	non-compartmental analysis
NCI	CTCAE National Cancer Institute Common Tearminology Criteria for
NHL	non-Hodgkin’s lymphoma
NME	new molecular entity
OR	objective response
OS	overall survival
PBPK	physiologically based PK
PET	positron emission tomography
PFS	progression-free survival

pina	pinatuzumab vedotin
PJP	Pneumocystis jiroveci pneumonia
PK	pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency
PML	progressive multifocal leukencephalopathy
PN	peripheral neuropathy
pola	polatuzumab vedotin
PR	partial response
PRA	primary response assessment
PRIME	PRIority MEdicine
PS	performance score
PT	preferred term
Q3W	every 3 weeks
Q4W	every 4 weeks
R/R	relapse/refractory
RMP	Risk Management Plan
SAE	serious adverse event
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
TE	Transplant eligible
TNE	Transplant non eligible
ULN	upper limit of normal

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Roche Registration GmbH submitted on 20 December 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Polivy, through the centralised procedure falling within the Article 3(1) and point 1 of Annex I of Regulation (EC) No 726/2004.

Polivy was designated as an orphan medicinal product EU/3/18/2013 on 16 April 2018 in the following condition: diffuse large B-cell lymphoma.

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

Polivy was granted eligibility to PRIME on 22 June 2017 in the following indication: Treatment of relapsed and refractory patients with diffuse large B cell lymphoma (DLBCL).

Eligibility to PRIME was granted at the time in view of the following:

- Despite overall improvement in DLBCL outcomes after frontline therapy with R-CHOP, approximately 30-40% of patients will not respond to initial therapy or will eventually relapse and the unmet medical need in DLBCL was therefore agreed.
- Clinical results available at the time showed in a phase II study high ORR of 68% (CR=53%; PR=15%) with polatuzumab vedotin in combination with bendamustine and rituximab. PFS was greater than that reported with bendamustine + rituximab alone (6 months vs. 2.4 months respectively, with HR=0.33; 95% CI 0.18, 0.6) and the median OS was 10.4 months as compared to 4.5 months in the bendamustine + rituximab arm (HR=0.33; 95%CI 0.17-0.64).
- In view of the available evidence, it was considered that polatuzumab vedotin could have the potential to provide a major therapeutic advantage in the treatment of relapsed and refractory patients with DLBCL.

The applicant applied for the following indication "Polivy in combination with bendamustine and rituximab is indicated for the treatment of previously treated adult patients with diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant".

The legal basis for this application refers to:

Article 8(3) of Directive 2001/83/EC - complete and independent application

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

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0117/2018 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

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

Applicant's request(s) for consideration

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

New active Substance status

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

PRIME support

Upon granting of eligibility to PRIME, the Rapporteur was appointed by the CHMP.

A kick-off meeting was subsequently organised with the EMA, Rapporteur, assessors' team and experts from relevant scientific committees. The objective of the meeting was to discuss the development programme and regulatory strategy for the product. The applicant was recommended to address the following key issues through relevant regulatory procedures: quality development aspects, adequacy of clinical development progamme to support marketing authorisation, proposed combinations.

Scientific Advice

The applicant received Scientific Advice on the development relevant for the approved indication from the CHMP on 26 June 2014 (EMEA/H/SA/2809/1/2014/I), 18 December 2014 (EMEA/H/SA/2809/2/2014/II), 18 May 2017 (EMEA/H/SA/2809/4/2017/PR/II), 22 February 2018 (EMEA/H/SA/2809/5/2017/PR/HTA/II), and 26 July 2018 (EMEA/H/SA/2809/5/FU/1/2018/PA/PR/II, EMEA/H/SA/2809/4/FU/1/2018/PA/PR/II) The Scientific Advice pertained to the following quality, non-clinical and clinical aspects of the dossier:

- Approach for development of commercialised drug product; control system strategy to measure potency; process and equipment validation activities; adequacy of strategy for specification acceptance criteria; strategy to support drug product shelf life and storage specifications; control strategy and specification for linker-drug.
- Adequacy of the overall non-clinical programme: adequacy of the nonclinical pharmacology and pharmacokinetics programme; adequacy of repeat-dose toxicity studies; requirement for embryofoetal development and genotoxicity studies;
- A Phase 1b/II multicentre, open-label, randomised, active-controlled study: Adequacy of clinical package to support an application in the requested indication; Sufficiency of a single-arm cohort in the pivotal study to provide clinical data for the drug product intended for commercialisation; proposed registrational strategy and timing of submission of safety and efficacy data from the pivotal study to support the MAA in the proposed indication;

- Clinical pharmacology plan; clinical pharmacokinetics to characterize ADME and support dosing regimen; strategy to assess and monitor cardiac safety.
- Proposal for risk minimisation strategy in RMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Alexandre Moreau Co-Rapporteur: Jan Mueller-Berghaus

The application was received by the EMA on	20 December 2018
Accelerated Assessment procedure was agreed-upon by CHMP on	13 December 2018
The procedure started on	25 January 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	27 March 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	27 March 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	2 April 2019
In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 April 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	24 April 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	23 May 2019
The following GCP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product: – A routine GCP inspection at one investigator site in Korea and the sponsor site in the USA has been performed between 8/03/2019 and 29/03/2019. The outcome of the inspection carried out was issued on:	18 April 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	13 June 2019
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	25 June 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	2 July 2019

The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	11 July 2019
The CHMP agreed on a second list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	25 July 2019
The applicant submitted the responses to the second CHMP List of Outstanding Issues on	22 August 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the second List of Outstanding Issues to all CHMP members on	22 August 2019
SAG-Oncology experts were convened to address questions raised by the CHMP on The CHMP considered the views of the SAG-Oncology as presented in the minutes of this meeting.	13 September 2019
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	16 September 2019
The CHMP agreed on a third list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	19 September 2019
The applicant submitted the responses to the third CHMP List of Outstanding Issues on	15 October 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a conditional marketing authorisation to Polivy on	14 November 2019
The CHMP adopted a report on similarity of Polivy with Yescarta and Kymriah on (Appendix 1)	14 November 2019

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Polivy in combination with bendamustine and rituximab is indicated for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant.

2.1.2. Epidemiology

Diffuse large B cell lymphoma (DLBCL) is the most frequent non-Hodgkin lymphoma (NHL), with an incidence of 3.8/100000/year in Europe. This aggressive lymphoma is an adult/early elderly disease. About one-third of patients will develop relapsed/refractory (R/R) disease which remains a major cause of morbidity and mortality of this disease (Friedberg 2011) whereas approximately 60% of patients may be cured with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), the current standard of care (Vitolo et al. 2017).

2.1.3. Biologic features

DLBCL is a heterogeneous disease with distinctive prognostic profiles including cell of origin (activated B-cell-like [ABC], germinal center B-cell-like [GCB]) or elevated expression of MYC and BCL2 seen in double-expressor lymphoma [DEL]) which have been mostly characterized in the first-line (1L) setting (Schmitz et al. 2018; Scott et al. 2015; Lenz et al. 2008; Johnson et al. 2012; Johnson et al. 2009).

The human CD79b, - a signaling component of the B-cell receptor (BCR) -is located on the surface of B cells. As such, CD79b expression is restricted to normal cells within the B-cell lineage (with the exception of plasma cells) and malignant B cells; it is expressed in >95% of diffuse large B-cell lymphoma (DLBCL) (Koyama et al. 1997; Dornan et al. 2009; Zheng et al. 2009; Martin 2010; Rickert 2013; Pfeifer et al. 2015).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Outcomes for patients with relapsed/refractory DLBCL are poor.

After failure of front-line therapy, the main consideration for determining the treatment approach in the second-line setting is whether the patient is a haematopoietic stem cell transplant candidate. Most of R/R patients are ineligible for autologous stem cell transplant (ASCT) due to age, co-morbidities or chemotherapy-insensitive disease. The treatment approach for such patients in the second-line (2L) setting as well as for all patients beyond 2L is a palliative approach although there is still a goal of improving survival, albeit not necessarily with a curative intent. Outcomes of such transplant-ineligible patients (including patients who relapse after ASCT) remain poor, with median overall survival (OS) of approximately 6 months (Mounier et al. 2013; Crump et al. 2017; Czuczman et al. 2017).

While DLBCL is mostly frequently diagnosed between the ages of 65 and 74 years of age with median age at diagnosis of 65 years (SEER), it can also occur in the younger population including children and young adults.

2.1.5. Management

As per current guidelines, the first line treatment is mainly based on RCHOP therapeutic sequence.

Overall, 30% of DLBCL patients ultimately relapse.

In transplant non-eligible (TNE) patients, fewer therapeutic options are available in second line treatment, mainly with platinum- and/or gemcitabine-based regimens, and clinical trials with novel drugs. In 3rd or over treatment line, patients are driven to palliative care or clinical trials.

An unmet medical need remains for patients with R/R DLBCL who are ineligible for transplant or fail ASCT. Of patients eligible for transplant, less than half of patients who proceed to HSCT will be cured (Seyfarth et al. 2006; Gisselbrecht et al 2010). For those patients who are ineligible for transplant all together, the outcome is dismal with generally no chance of prolonged periods of disease control (Thieblemont and Coiffier 2007). Moreover, primary refractory patients who progress through front-line therapy do very poorly even after receipt of salvage treatment followed by autologous transplant with a 3–year progression-free survival (PFS) rate of 17% (Vardhana et al. 2017).

The CAR T-cell therapies represent a treatment option for R/R DLBCL patients that had two or more prior lines of systemic therapy, with sufficient disease control to await the manufacturing times, who are able to tolerate the conditioning regimen (usually fludarabine/cyclophosphamide), treatment emergent cytokine-release syndrome and sometimes severe neurotoxicities.

Yescarta (axicabtagene ciloleucel) is a CD19-directed genetically modified autologous T cell immunotherapy. Of 111 patients who underwent leukapheresis in the ZUMA-1 trial, 101 received Yescarta. Nine patients were not treated, primarily due to progressive disease or serious adverse events after enrolment and prior to cell delivery. One out of 111 patients did not receive the product due to manufacturing failure. The median time from leukapheresis to product delivery was 17 days (range: 14 to 51 days), and the median time from leukapheresis to infusion was 24 days (range: 16 to 73 days). The median dose was 2.0 x 106 anti-CD19 CAR T cells/kg. ITT was defined as all patients who underwent leukapheresis; mITT was defined as all patients who received Yescarta. The primary endpoint was objective response rate (ORR) was 66% at 12 months and CR was 47%.

Kymriah is an immunocellular therapy containing tisagenlecleucel, autologous T cells genetically modified ex vivo using a lentiviral vector encoding an anti-CD19 chimeric antigen receptor (CAR). The pivotal study (C2201) is a multicentre, single-arm phase II study in adult patients with relapsed or refractory DLBCL. Of 165 patients enrolled, 111 patients received infusion with Kymriah (4 infusions were pending at the time of analysis); for 12 patients (7%) Kymriah could not be manufactured. Approximately 30% of patients discontinued the study prior to Kymriah administration. Reasons for discontinuation prior to Kymriah infusion included death (n=16; 10%), physician decision/primary disease progression (n=16; 10%), patient decision (n=3; 2%) or adverse events (n=2; 1%) while awaiting Kymriah manufacturing in the clinical study. The complete response rate was 37%.

Pixuvri as single-agent was evaluated in a multicentre, randomised, active controlled trial against investigator chosen single-agent chemotherapy on the comparator arm in patients with relapsed or refractory aggressive NHL after receiving at least two prior therapies; 11.4% of patients treated with Pixuvri showed a complete response as compared to 0% in the comparator arm.

Table 1: Literature review on efficacy of selected regimens for Patients Who Are Ineligible for Transplant

Regimen	No. of Patients with Recurrent DLBCL	ORR		PFS and OS	Toxicity
		CR (%)	PR (%)		
Gemcitabine, dexamethasone, and cisplatin [a]	17	23	29	Median PFS, 3 months Median OS, 9 months	Neutropenia Grade 3–4: 33%; 31% Thrombocytopenia Grade 3–4: 26%; 4% Grade 2 ototoxicity: 25%; Grade 2 creatinine 6%
Gemcitabine + oxaliplatin [b]	17	47	12	Median FFS, 9 months	Neutropenia Grade 3, 35%; Grade 4, 16% Thrombocytopenia Grade 3–4, 26% Vomiting Grade 2–3, 34% Infection Grade 2–3, 14%
Gemcitabine + oxaliplatin + rituximab [b]	16	56	19	Median FFS, 18.5 months	Neutropenia Grade 3, 29%; Grade 4, 18% Thrombocytopenia Grade 3, 17% Vomiting Grade 2–3, 34% Infection Grade 2–3, 25%
Gemcitabine + vinorelbine [c]	22	14	35	Median TTP, 8 months Median OS, 13 months	Neutropenia Grade 3–4, 41% Thrombocytopenia Grade 3–4, 18%
Rituximab + gemcitabine + oxaliplatin [d]	49	44 [e]	17	Median PFS, 5 months 5-year PFS, 12% (Relapse <12 mo, median PFS 3 mo)	Neutropenia Grade 3 31%, Grade 4 42% Thrombocytopenia Grade 3 32%, Grade 4 21% Grade 3–4 infection, 22% of cycles
Bendamustine + rituximab [f]	59	37	25	Median PFS, 6.7 months (Relapse <12 mo, median PFS 3.4 mo)	Neutropenia Grade 3, 30%; Grade 4, 46% Thrombocytopenia Grade 3, 15%; Grade 4, 7% CD 4 lymphopenia Grade 3, 22%; Grade 4, 44% Infection Grade 3, 12%
Bendamustine + rituximab[g]	61	15[h]	31[h]	Median PFS 3.6 mo Median OS not reached[i]	Neutropenia Grade 3 29%; Grade 4 7% Thromboctyoepnia Grade 3 17%, Grade 4 5% Anemia Grade 3 12%; Febrile Neutropenia 7%

Regimen	No. of Patients with Recurrent DLBCL	ORR		PFS and OS	Toxicity
		CR (%)	PR (%)		
Investigator's choice[j]: Bendamustine + rituximab (BR) Gemcitabine + rituximab (GR)	172 BR = 137 RG = 35	BR: 21[k] GR: 0	BR: 28[l] GR: 26[m]	Median PFS, 3.5 mo Median OS 9.5 mo	Neutropenia Grade ≥ 3 40% Thrombocytopenia Grade ≥3 16% Lymphopenia Grade ≥ 3 22%
tisagenlecleucel[n]	165	24	10	Median OS 8.2 mo	Cytokine release syndrome ≥Grade 3 22% Neurological events ≥Grade 3 12% Infections ≥Grade 3 20% Febrile neutropenia 16%

1L = first-line; 2L = second-line; CD4 = cluster of differentiation 4; CEOP = cyclophosphamide, etoposide, vincristine, prednisone; CR = complete response; FFS = failure-free survival; NHL = non-Hodgkin's lymphoma; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; TTP = time-to-progression.

Note: Table source Crump et al. 2016.

* Table shows selected results from studies where ineligibility for stem cell transplant was an inclusion criteria

[a] Gemcitabine 1000 mg/m² on Days 1 and 8, dexamethasone 40 mg on Days 1 to 4, and cisplatin 75 mg/m² every 21 days (Crump et al. 2004). Prior treatment did not include rituximab.

[b] Gemcitabine 1200 mg/m² on Days 1 and 8, oxaliplatin 120 mg/m² on Day 2, rituximab 375 mg/m² on Day 1 every 3 weeks (gemcitabine + oxaliplatin), or 2 weeks (gemcitabine + oxaliplatin + rituximab; Corazzelli et al. 2009). Rituximab was a prior therapy for 66% of patients.

[c] Gemcitabine 1000 mg/m², vinorelbine 30 mg/m² on Days 1 and 8 every 21 days (Papageorgiou et al. 2005). All patients received 1L therapy with CEOP. Overall, 64% of patients received 1 prior line of therapy and 36% of patients were chemorefractory. No patients received prior rituximab.

[d] Rituximab 375 mg/m² on Day 1, gemcitabine 1000 mg/m² + oxaliplatin 100 mg/m² on Day 2 every 14 days (Mounier et al. 2013). Overall, 58% of patients had rituximab in 1L therapy, 8% patients had rituximab as part of 2L therapy.

[e] Response assessed after four cycles.

[f] Rituximab 375 mg/m² on Day 1, bendamustine 120 mg/m² on Days 2 and 3 every 21 days (Ohmachi et al. 2013). Refractory patients were excluded.

[g] First 2 study patients received rituximab 375 mg/m² on Day 1, bendamustine 90 mg/m² on Days 1 and 2 every 28 days. All other patients received rituximab 375 mg/m² on Day 1, bendamustine 120 mg/m² on Days 1 and 2 every 21 days (Vacirca et al. 2014).

[h] Treatment response percentages are reported out of treated patients (n = 59). Two patients had enrolled but did not receive treatment.

[i] Median OS was not reached due to high numbers of censored patients as patients withdrew from study follow-up.

[j] BR = rituximab 375 mg/m² on Day 1, bendamustine 120 mg/m² on Days 1 and 2 every 28 days. RG = rituximab 375 mg/m² on Days 1, 8, 15, and 22 of Cycle 1, and Day 1 of all other cycles + gemcitabine 1000 mg/m² on Days 1, 8, 15 every 28 days (Dang et al. 2017).

[k] 21% = 17% CR + 4% unconfirmed CR.

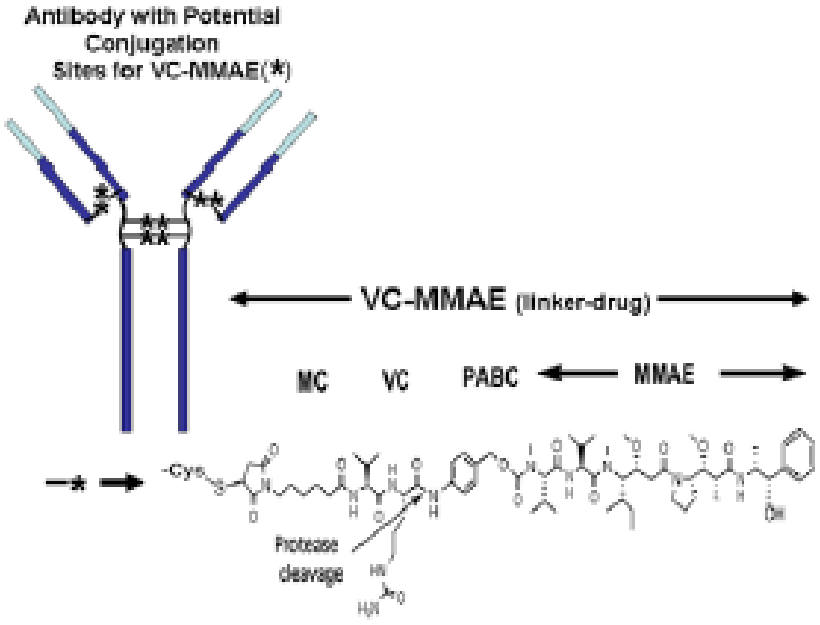
[l] 28% = 19% PR + 9% unconfirmed PR.

[m] 26% = 6% PR + 20% unconfirmed PR.

[n] Kymriah SmPC

About the product

Polatuzumab vedotin is a CD79b-targeted antibody-drug conjugate (ADC) that preferentially delivers a potent anti-mitotic agent (monomethyl auristatin E [MMAE]) to B cells, which results in anti-cancer activity against B-cell malignancies.



MC = maleimidocaproyl; MMAE = mono-methyl auristatin E; PABC = p-aminobenzyloxycarbonyl; VC = valine-citrulline.

Figure 1: chemical structure of polatuzumab vedotin

Polatuzumab vedotin specifically binds human CD79b, a signaling component of the B-cell receptor (BCR) located on the surface of B cells.

Therefore, targeted delivery of MMAE is expected to be restricted to these cells. Upon binding CD79b, polatuzumab vedotin is rapidly internalized (Polson et al. 2007, 2009; Pfeifer et al. 2015) and the linker is cleaved by lysosomal proteases, leading to intracellular release of MMAE (Sutherland et al. 2006). The released MMAE binds to microtubules and kills dividing cells by inhibiting cell division and inducing apoptosis (Bai et al. 1990; Doronina et al. 2003; Francisco et al. 2003).

The recommended dose of Polivy is 1.8 mg/kg, given as an intravenous infusion every 21 days in combination with bendamustine and rituximab for 6 cycles. Polivy, bendamustine and rituximab can be administered in any order on Day 1 of each cycle. When administered with Polivy, the recommended dose

of bendamustine is 90 mg/m2/day on Day 1 and Day 2 of each cycle and the recommended dose of rituximab is 375 mg/m2 on Day 1 of each cycle.

Polatuzumab vedotin was initially developed as a 100 mg liquid formulation, used in several studies including the pivotal study. The lyophilised formulation was developed, with 140mg strength intended for marketing.

Type of Application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on the expectation that the product fulfils an unmet medical need in the claimed indication as Polivy is intended for patients for whom no approved treatment exists (2nd line DLBCL) and newly authorized treatments such as car-T cells in 3rd line are associated with delay on treatment production from patients' blood- and preliminary results on efficacy and safety as of improved complete response rate over the comparator and improved outcomes in terms of secondary endpoints.

However, during the assessment the CHMP concluded that it was no longer appropriate to pursue accelerated assessment, as there were issues identified that could not be handled in an accelerated timetable and since the CHMP decided to consult the Scientific Advisory group on Oncology on some of these issues and for this purpose the assessment would exceed 150 days.

During the assessment the applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

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

  In response to a CHMP question, the applicant aknowledgeed that the evidence provided is based on a small exploratory trial in a very heterogeneous population in terms of prognosis. Available data are thus considered non-comprehensive and a conditional approval is therefore considered appropriate in order to confirm the size and duration of the effect in a larger population.

  The primary CSR for study GO29365 including the primary analysis of Arm H (n=64) as well as a pooled analysis of Arm G (n=42) and Arm H (n=64) was proposed to be provided as a specific obligation. Distinct histology subtypes will be analysed within Arm H which is considered necessary to confirm response in any relevant subtype at least on a descriptive level.

  The applicant also proposed to provide Study GO39942, a randomized, double-blind, placebo-controlled trial that evaluates polatuzumab vedotin in combination with R-CHP (rituximab, cyclophosphamide, doxorubicin, prednisone) versus R-CHOP in patients with previously untreated diffuse large B-cell lymphoma. The primary endpoint is progression-free survival. Key secondary endpoints include complete remission rate per independent review committee and overall survival.
- Unmet medical needs will be addressed, as

  The indication for Polivy includes patients in 2nd line of treatment for which no approved treatment exists, therefore Polivy will cover an unmet need in this population.

  Whilst in the 3rd and further lines of treatment Pixuvri (pixantrone) and the CAR-T therapies Yescarta and Kymriah are centrally approved Polivy still fulfils an unmet need in those areas as it provides improved efficacy compared to Pixuvri and a better safety profile comparing to CAR-T therapies. Also importantly, due to the complex manufacturing of CAR-Ts, their distribution and the

need for intense monitoring this treatment modality is currently limited to specialized tertiary centers and for patients who are well enough to withstand the delays in receiving an active treatment; Polivy will present a major contribution to patients' health as it will be a treatment for immediate administration to the patient.

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

  Since the benefit- risk of Polivy is positive in the claimed indication, with a manageable safety profile and an unmet need is fulfilled, the benefits to the patients from its immediate availability outweigh the risks associated with the fact that further efficacy and safety data in a larger population are expected.

2.2. Quality aspects

2.2.1. Introduction

The active substance (INN: Polatuzumab vedotin) is an antibody-drug conjugate (ADC) composed of a humanized immunoglobulin G1 (IgG1) anti-CD79b monoclonal antibody (polatuzumab antibody intermediate) and an antimitotic agent, monomethyl auristatin E (MMAE), linked through a protease-cleavable linker, maleimidocaproyl-valine-citrulline-paminobenzyloxycarbonyl (mc-vc-PAB). The antimitotic agent and linker are referred to as the linker-drug, vcMMAE.

The finished product is presented as a powder for concentrate for solution for infusion containing 140 mg of polatuzumab vedotin as active substance.

Other ingredients are: succinic acid, sodium hydroxide, sucrose, and polysorbate 20.

The product is available in 20 mL vial (Type 1 glass, colourless) with a stopper (fluororesin laminate), with an aluminium seal with plastic flip-off cap.

This report includes dedicated sections for the linker-drug intermediate and polatuzumab antibody intermediate, followed by the active substance and finished product sections.

2.2.2. Linker-drug intermediate

General Information (linker-drug intermediate)

The linker-drug intermediate vcMMAE is composed of a cytotoxic auristatin, a cleavable dipeptide linker and a maleimido group for conjugation to the terminal thiol of a cysteine. This same linker-drug structure was utilised in the centrally authorised product Adcetris (brentuximab vedotin).

Manufacture, process controls and characterisation (linker-drug intermediate)

The vcMMAE linker-drug intermediate is manufactured from six starting materials using a convergent, solution phase peptide synthesis, consisting of six separate stages and five isolated intermediates.

The manufacturing process is overall adequately described. The proposed starting materials are the same as already approved in brentuximab vedotin and are acceptable.

The overall control strategy contains elements of a traditional approach but includes extensive flexibility in the form of several PARs (Proven Acceptable Ranges) which go beyond what is normally expected as normal variability. The development section describes lab scale multivariate experiments conducted to support the proposed flexibility. The information is considered sufficient and it is considered that the proposed flexibility does not constitute a risk to the product quality across the manufacturing scale ranges.

The manufacturing process has been satisfactorily validated.

The impurity profile of vcMMAE is well established and the major impurities, either process-related or arising from degradation, were characterised and classified as conjugatable and non-conjugatable depending on the presence of the maleimido group.

Specification, analytical procedures, reference standards, batch analysis, and container closure (linker-drug intermediate)

The specification for vcMMAE linker-drug intermediate contains a suitable list of tests as per ICH Q6A. This includes tests for appearance/colour, identity, purity, assay, related substances, water content, specific rotation, residual solvents, and impurities.

The proposed specification acceptance criteria were adequately justified. Concerning other potential impurities such as residual solvents and heavy metals, it is to be noted that the post-conjugation step of diafiltration normally eliminate these effectively.

Analytical procedures were adequately described and validated. They were generally shown to be fit for use.

The batch analysis results confirm consistency and uniformity of the drug-linker quality attributes and indicate that the process is under control.

The vcMMAE linker-drug intermediate is stored either in a Type I amber glass vial, sealed with fluororesin-coated rubber serum stopper and an aluminum crimp seal or in a Type III amber glass jar, sealed with a polytetrafluoroethylene (PTFE)-lined cap and white electrical tape. An inert headspace with either argon or nitrogen is applied prior to sealing.

Stability (linker-drug intermediate)

The stability profile of vcMMAE is considered well established. Stability data on several batches have been generated to support the proposed retest period of 36 months from date of manufacture when stored at – 20°C/ambient RH. No significant changes have been observed in the appearance, identity, assay, purity, and impurity profile of the linker-drug.

The photostability study results demonstrate that the linker-drug is sensitive to light and is therefore stored in amber vials.

In conclusion, a retest period of 3 years at -20°C when stored in USP/PhEur Type I/III amber glass vials is considered acceptable.

2.2.3. Polatuzumab antibody intermediate

General Information (polatuzumab antibody intermediate)

Polatuzumab antibody intermediate is a humanized monoclonal antibody based on a human immunoglobulin G1 framework. The recombinant antibody is produced in Chinese hamster ovary (CHO) cells and consists of two heavy chains (447 amino acid residues each) and two light chains (218 amino acid residues each).

Polatuzumab antibody intermediate displays microheterogeneity in glycosylation and other post-translational modifications of amino acids. The CH2 domain of each heavy chain (HC) has a single conserved glycosylation site at Asn297. The N-linked oligosaccharides of the antibody intermediate are typical of those observed on other CHO-produced monoclonal antibodies. The C-terminal lysine residues of the HCs (Lys447) are partially cleaved by cellular carboxypeptidases during the cell culture process, resulting in charge heterogeneity.

The antibody has a molecular mass of 145,003 Da (peptide chains only, without heavy chain C-terminal lysine residues and with no glycosylation).

The Fourier transform infrared spectrum (FTIR) and differential scanning calorimetry confirm that the antibody intermediate is primarily a β-sheet structure, consistent with the structure of an IgG1 antibody.

Polatuzumab antibody intermediate binds to the extracellular domain of CD79b, which is a component of the B-cell receptor.

Manufacture, process controls and characterisation (polatuzumab antibody intermediate)

Description of manufacturing process and process controls

Confirmation of the GMP status for the antibody intermediate manufacturing and testing sites was provided.

The description of the manufacturing process and controls is appropriately detailed. Batch and scale definition is provided. The production consists of an expansion phase of WCB vials into stainless steel bioreactors, subsequently used to inoculate the main bioreactor. The production bioreactor operates in a fed-batch mode with non-selective medium and nutrient feeds during several days. Then, the harvest is collected and the secreted antibody intermediate is separated from cells and cell debris by centrifugation and filtration. The purification process includes three chromatography steps, two virus removal/inactivation steps, and one ultrafiltration/diafiltration (UFDF) step before final conditioning.

Control of materials

Information on the origin of the host cell line, on the development genetics (including origin of the gene and description of the gene construct) and on the establishment of the cell banks is provided. Master Cell Bank and Working Cell Bank were generated for commercial production. Both MCB and WCB are stored in liquid nitrogen at several independent sites. MCB and WCB were tested and characterized in accordance with ICH guideline requirements. The preparation and qualification procedures of future WCBs is described.

A list of raw materials used in the manufacturing process, including filter and chromatography gels, is provided. Raw materials are tested according to European pharmacopoeia (where available), or according to in-house monographs.

Control of critical steps and intermediates

Acceptable ranges are provided for each process parameter alongside the parameter's designation as critical or non-critical. These include acceptable ranges for lifetime, regeneration, sanitization, and storage of chromatographic columns and UFDF membrane used during the purification process. Justification of acceptable ranges is supported by a combination of process validation studies, manufacturing experience, and prior knowledge. IPCs were classified in two categories whether they are defined by action limits or acceptance criteria. Most of the proposed IPCs relate to safety/microbial parameters (e.g. bioburden, viruses). Cell culture is also monitored by IPCs that evaluate process consistency (e.g. viability).

Process validation

Process validation was performed following a two-tiered approach. Four consecutive process performance qualification (PPQ) batches were produced at full-scale using the commercial v1.0 process and six additional clinical batches produced according to the same v1.0 manufacturing process were compared to the four PPQ batches. Evaluation of CQAs, IPCs, and performance parameters demonstrated that the manufacturing process is consistent throughout the process. A shift in glycosylation profile (sum of afucosylation and G0F) was observed between v1.0 clinical and v1.0 PPQ batches. This shift was assigned

to increased levels of trace element manganese impurity. As a result, a manganese acceptance criterion was implemented and a verification batch was produced, showing glycosylation levels comparable to previous v1.0 clinical manufacturing runs.

Manufacturing process development

Three manufacturing processes have been used throughout the process development history of the antibody intermediate: toxicology, v0.1, and v1.0. Process v0.1 provided batches used in the pivotal clinical Study GO29365, while material from process v1.0 was used in supportive phase 2 and 3 clinical trials, as well as in the arm G of the pivotal study. Impact of the different processes on comparability is discussed at the active substance level.

An enhanced approach was used to establish acceptable ranges for the process parameters, as well as the assessment of their criticality. This approach was based on i) v1.0 clinical manufacturing experience, ii) risk ranking and filtering (RRF) assessment and iii), where appropriate, small-scale process parameter validation studies. The RRF assessment was based on prior knowledge, including product-specific process development data, scientific rationale, or validation data from similar processes. Small-scale process parameter validation studies consisted of a design of experiment study, single-factor studies, and transient excursion studies. Overall the CPPs and the process parameter acceptance ranges were thoroughly justified and, where appropriate, were supported by small-scale validation studies. The control strategy as proposed seems suitable to control the process and deliver a product with consistent quality.

Acceptable hold times and temperatures for in-process pools are provided and supported by appropriate biochemical stability studies.

Characterisation

The characterization of the antibody intermediate is adequate. The material used for characterisation is the primary reference standard. Polatuzumab was characterized for molecular mass, primary structure, size heterogeneity, charge heterogeneity, pH, extinction coefficient, distribution of N-linked glycans, and CD79b binding.

The expected primary structure of the antibody intermediate was confirmed by Electrospray ionization - mass spectrometry analysis using a time-of-flight mass spectrometer of intact, as well as analysis of reduced and reduced, deglycosylated antibody intermediate.

The primary structure was also confirmed by endoproteinase Lys-C (Lys-C) peptide mapping.

Analysis of isotope-labeled tryptic peptides by liquid chromatography – mass spectrometry was used to measure unformed disulfides as reactive unmodified sulfhydryl groups (or free thiol) at specific cysteine residues in polatuzumab antibody intermediate.

Polatuzumab antibody intermediate contains an N-linked glycan site at Asn297. The N-linked glycosylation profile of polatuzumab antibody intermediate was assessed. The glycans were typical of those observed in the Fc domain of CHO-derived IgG1 antibodies.

Size variants were determined using size exclusion high-performance liquid chromatography (SE-HPLC), analytical ultracentrifugation (AUC) and non-reduced capillary electrophoresis sodium dodecyl sulfate (CE-SDS).

Minor protein impurities, including host cell protein (HCP) of polatuzumab antibody intermediate reference standard, were evaluated with reversed-phase ultra-high-performance liquid chromatography coupled with tandem mass spectrometry.

Charge heterogeneity was evaluated using imaged capillary isoelectric focusing (iCIEF) with carboxypeptidase B (CpB)-treatment.

The mechanism of action (MOA) for B-cell depletion by polatuzumab vedotin requires direct binding of the antibody Fab domain to CD79b on the surface of B cells. An enzyme-linked immunosorbent assay (ELISA) that measures the ability of antibody intermediate to bind to CD79b was developed. The potency of samples is determined relative to the antibody intermediate reference standard.

Product-related impurities such as size and charge variants have been sufficiently characterized and are controlled at release. For process-related impurities such as HCP, residual DNA and leached protein A IPC testing is performed. Contaminants such as bioburden and endotoxins are controlled at release. Removal of other process-related impurities has been demonstrated during process validation.

Specification, analytical procedures, reference standards, batch analysis, and container closure (polatuzumab antibody intermediate)

The specification for the polatuzumab antibody intermediate include tests for appearance, pH, osmolality, identity, purity, protein concentration, potency, microbiology, polysorbate and glycosylation. The proposed acceptance criteria are considered acceptable.

The applicant commits to reevaluate the individual action limits and acceptance criteria for glycosylation variants once a sufficient number of antibody intermediate batches have been produced (See "Recommendations for future quality development").

Analytical methods

The analytical procedures have been briefly described.

Non-compendial analytical procedures have been validated according to ICH Q2 (R1). All results have passed the acceptance criteria specified in the method validation protocol. Compendial methods have been verified.

Batch analysis

Batch analysis results are provided for several batches produced by the v1.0 (commercial) process. Results confirm consistency and uniformity of the antibody intermediate, indicating that the process is under control.

Reference materials

The manufacturer established appropriately characterised in-house primary and secondary reference materials, prepared from lots representative of production and clinical materials (v1.0 process). The primary and secondary reference standards were qualified by release and extended characterization testing. All specifications were met. Aliquots of primary and secondary reference standards are stored at -70°C ± 20°C. The stability of the reference standards is confirmed annually. Preparation and qualification of future commercial reference standards are also described.

Container closure system

The antibody intermediate may be stored either in stainless steel tanks (120 L) for long-term storage or polyethylene bioprocess bags (20 L) for shipping to the active substance manufacturing site. The choice of the container closure systems was justified and both containers are in line with current pharmaceutical standards for biopharmaceutical manufacturing.

Stability (polatuzumab antibody intermediate)

A shelf-life of 18 months at -20°C for the antibody intermediate is claimed with allowable hold times of up to 10 days at 5°C and up to 3 days at 25°C. This claim is based on stability studies that were carried out in accordance with current ICH/CPMP guidelines.

Primary stability studies were performed on batches representative of the v1.0 commercial manufacturing process. The containers used (mini-tanks and/or bioprocess bags) are considered representative of the antibody intermediate manufacturing-scale storage containers. The ratio of surface-area-to-volume for the mini-tank and bioprocess bags is greater than that of the manufacturing-scale storage container and represents a worst case. Up to 60 month stability data are available at -20°C.

Accelerated (5°C) and stressed (25°C) stability studies were also conducted to confirm degradation products/pathways and support the proposed hold times of up to 10 days at 5 °C and up to 3 days at 25 °C. The results showed that the overall degradation behaviour is consistent with primary studies. The other parameters do not display any significant change.

2.2.4. Active Substance

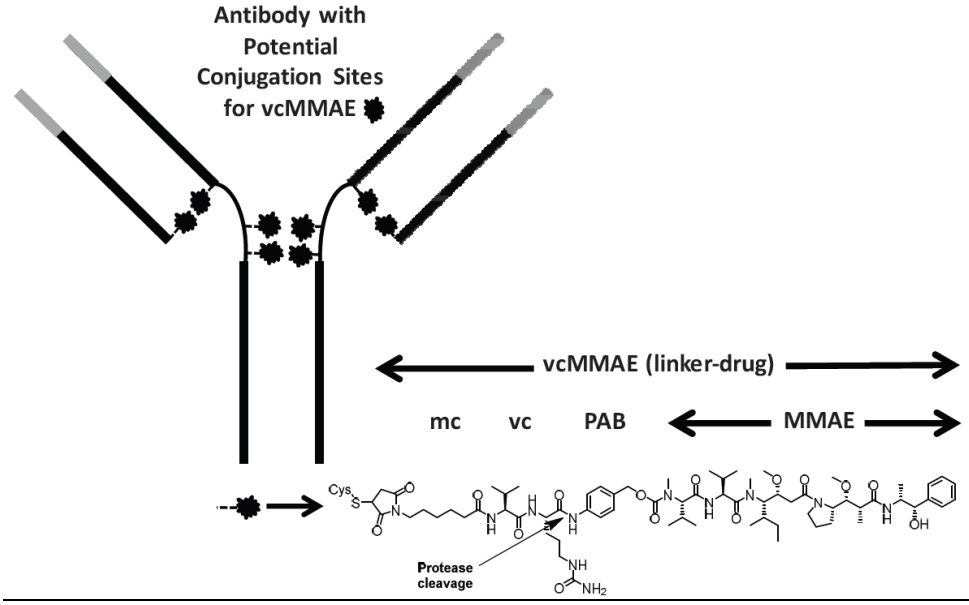
General Information

The active substance (INN: Polatuzumab vedotin) is an antibody-drug conjugate that contains the polatuzumab antibody intermediate and the linker-drug vcMMAE.

The linker-drug is bound to the reduced interchain cysteine residues of the antibody heavy and light chains through a thioether bond between the linker maleimide and the cysteine thiol group. The structure of polatuzumab vedotin is shown in Figure 2. Following cleavage of the linker by intracellular proteases at the indicated site, a spontaneous rearrangement results in the release of free MMAE, p-aminobenzyl alcohol, CO2, and the antibody containing a fragment of the linker. The released MMAE binds to microtubules and kills dividing cells by inhibiting cell division and inducing apoptosis.

Polatuzumab vedotin has an average of 3.5 linked MMAE moieties per antibody (drug-to-antibody ratio (DAR) = 3.5). The calculated molecular mass of polatuzumab vedotin, without C-terminal lysines and without N-linked glycosylation, is 149,613 Da.

Figure 2: Chemical Structure of Polatuzumab Vedotin



Manufacture, process controls and characterisation

Description of manufacturing process and process controls

The manufacturer of polatuzumab vedotin active substance is Lonza Ltd, Visp (Switzerland). Confirmation of the GMP status for the active substance manufacturing and testing sites was provided.

The active substance manufacturing process and process controls are appropriately described. The process consists of thawing of the polatuzumab antibody intermediate, followed by a pH adjustment and dilution step to prepare the subsequent reaction steps. The tris-(2-carboxyethyl) phosphine solution is added to partially reduce the interchain disulfide bonds of the antibody and then, the vcMMAE intermediate is added for conjugation. The antibody free thiols react with the maleimide functional group of the linker-drug intermediate to form the antibody-drug conjugate. An UF/DF step is applied to concentrate and buffer-exchange the product and removes small molecules (i.e. NAC). Finally, the recovered ultrafiltration and diafiltration pool is conditioned to the final concentration and composition of the active substance: 20 mg/mL polatuzumab vedotin in 10 mM sodium succinate, 120 mM sucrose, 1.2 mg/mL polysorbate 20, pH 5.3. The active substance is frozen in a freeze/thaw tank using a freeze/thaw skid.

For all steps adequate CPPs were defined. The CPPs are a subset of process parameters that have been determined to impact or may potentially impact CQAs of the active substance.

Control of materials

A list of raw materials used in the manufacture of polatuzumab vedotin active substance, as well as their quality grade, has been provided.

Process validation

Validation of the active substance manufacturing process was performed on three PPQ batches manufactured in 2018. In addition, clinical batches were compared with the three PPQ batches for consistency purpose. All batches were manufactured according to the commercial v1.0 manufacturing process. Overall, the data showed that the selected quality attributes, key performance indicators, and IPCs met their acceptance criteria when process parameters operated within their acceptable ranges. The manufacturing process demonstrated consistent results between clinical and PPQ batches.

Removal of raw materials was satisfactorily addressed. All results were below the limit of quantitation of the assay and below the toxicology-based limits.

Control of critical steps and intermediates

A process impact assessment was conducted for CQAs. The proposed process risk score for size-and charged-related variants, oxidation related variants and structural variants is considered acceptable. Of special interest are conjugation-related variants. The proposed active substance release acceptance criterion for DAR is considered sufficient. As the main MOA is mediated by the drug the absence of control of the free antibody is acceptable. To classify drug distribution and conjugation site distribution as low risk is accepted because of the tight DAR control. Free drug is monitored at release and the acceptance criterion was tightened.

Polatuzumab vedotin is an antibody-drug conjugate produced from two intermediates: the polatuzumab antibody intermediate and the linker-drug vcMMAE. Please refer to the respective sections for the two intermediates for further details.

Stability of in-process pools was validated and the hold times are defined.

Manufacturing process development

As stated for the polatuzumab intermediate, three different versions (toxicology, v0.1, and v1.0) of the active substance manufacturing process were used during development. Comparability assessment between materials from process v0.1 (liquid form) used in pivotal clinical Study GO29365 and materials intended for commercial process v1.0 (lyophilized form) used in phase 2 and phase 3 clinical trials, as well as in arm G of the pivotal clinical study, exhibited significant differences for glycosylation attributes (M5, sum of afucosylation, and G0F). Increased levels of M5 and sum of afucosylation were observed for v1.0 batches as compared to v0.1 batches, correlated with a decrease for G0F. According to the applicant, if the observed difference in total afucosylation (M5 and sum of afucosylation) results in a corresponding increase in ADCC-related activities for the v1.0-derived active substance batches, the impact on patient efficacy and safety is expected to be minimal taking into account that i) safety and efficacy are predominantly driven by MMAE-mediated effects and are not expected to be impacted by variations in effector function, ii) no detectable exposure difference was observed in the rat PK comparability study and iii) the finished product is co-administered with anti-CD20 therapeutic agents that displayed higher effector functionality. From a quality point of view, this justification is considered acceptable and no additional analytical data is required.

Characterisation

The structure of polatuzumab vedotin active substance was elucidated from a variety of biological, biochemical, and biophysical techniques to provide a comprehensive understanding of its structure and functional properties and assessment of critical quality attributes.

Two potency methods (binding and cell-based assays) were developed to monitor potency of the active substance/finished product and to characterize the biological activities of product variants. FcγR binding properties of the antibody intermediate and polatuzumab vedotin reference standards were also characterized using surface plasmon resonance methods. Both polatuzumab antibody intermediate and polatuzumab vedotin exhibit lower binding to FcγRs relevant to antibody-dependent cellular cytotoxicity (ADCC) (FcγRIIIa), antibody-dependent cellular phagocytosis (FcγRI, FcγRIIa), and inhibitory effects (FcγRIIb) compared to another IgG1 antibody, rituximab. Glycosylation, conjugation, and DAR demonstrated either enhancing (afucosylation) or inhibitory (conjugation, DAR) effects on in vitro ADCC activity. In addition, neither polatuzumab antibody intermediate nor polatuzumab vedotin shows detectable complement-dependent cytotoxicity activity.

Impurities include product-related impurities (charge and size variants), vcMMAE-related impurities, process-related impurities (MMAE, VC-MMAE and NAC-VC-MMAE) and residual solvents (DMA, glacial acetic acid).

Product-related impurities and free drug are controlled at release. vcMMAE-related impurities are not controlled at active substance level. However, even if not cleared by the UFDF step, these impurities would be present at low amounts only. Palladium is controlled upstream by the specification on vcMMAE prior to entering the conjugation process.

Product- and process-related impurities are sufficiently controlled at polatuzumab vedotin active substance level.

Specification, analytical procedures, reference standards, batch analysis, and container closure

An appropriate set of test methods to be routinely applied to active substance specifications was selected. Tests include appearance, pH, osmolality, identity, purity, protein concentration, free drug, residual solvents, DAR, potency, microbiology and polysorbate 20.

Residual N,N-dimethylacetamide (DMA), which is a Class 2 solvent used to solubilize vcMMAE in the reduced antibody solution, is monitored by RP-HPLC with an acceptance limit. This is acceptable. The content of the stabilizer polysorbate 20 is controlled at release. As mentioned before, the range of free drug observed was below LoQ and the release acceptance criterion was tightened. It is recommended to revise the proposed acceptance criteria for charge variants once sufficient data will be available (See "Recommendations for future quality development").

The acceptance criteria were established taking the following considerations into account: clinical experience, stability and process effects, product-specific knowledge, prior knowledge, current compendia or regulatory guidelines, and formulation development studies.

Analytical methods

Analytical procedures have been adequately described.

The potency of polatuzumab vedotin is controlled by an ELISA that measures the ability of antibody intermediate to bind to CD79b. The ELISA uses a peptide that corresponds to the anti-CD79b antibody epitope on the CD79b receptor's extracellular domain. Bound polatuzumab vedotin is detected with a mouse anti-auristatin antibody, goat anti-mouse IgG-HRP antibody, and a peroxidase substrate solution.

The cell-based bioassay measures the ability of polatuzumab vedotin to induce the killing of cells from a CD79b-expressing human B cell line.

Non-compendial analytical procedures have been validated according to ICH Q2 (R1). All results have passed the acceptance criteria specified in the method validation protocol. Compendial methods have been verified.

Batch analysis

Representative batch analysis data are provided for polatuzumab vedotin active substance batches manufactured for the purpose of clinical testing as well as process validation of the manufacturing process. For the current v1.0 manufacturing process batch analysis data for clinical batches and PPQ batches were presented. All batches were manufactured at Lonza located in Visp, Switzerland. For batches manufactured according to the previous v0.1 process multiple batches (including the v0.1 reference standard) have been presented. For all batches predefined acceptance criteria which were in effect at time of batch analysis and release were met and the results confirm consistency and uniformity of the product.

Reference materials

The same reference standard is used for the active substance as for the finished product. Reference is made to the finished product section.

Container closure system

120 L Hastelloy freeze/thaw tanks are used for polatuzumab vedotin active substance storage. The container closure system is in line with current pharmaceutical containers used for biotech product manufacturing. An adequate justification for not performing specific extractable and leachable studies is provided.

Stability

The Company claims an active substance shelf-life of 3 years when stored at -20°C (including hold times of up to 5 days at 5 °C and up to 3.5 days at 25 °C).

This claim is based on data obtained from PPQ batches, plus clinical batches produced using the commercial manufacturing process (v1.0) and stored in Hastelloy mini-tanks; up to 48 months of data are

available under long-term storage conditions (-20 °C) and 6-month stability data are available under accelerated conditions (6 months at 5 °C). All studies were carried out in accordance with current ICH/CPMP guidelines. In addition, stress stability studies (28 days at 25 °C/60% RH) were conducted on three batches to confirm degradation products/pathways and support the hold time of 3.5-day at 25 °C.

The long-term, real time, real-condition stability studies show minor increases in sum of HMW forms, with corresponding decrease in main peak. The same trends were observed for accelerated and stressed stability studies. In addition, batches under stress conditions exhibited an increase of the acidic region. Little or no change was observed for all other attributes tested. This suggests that methods used in stability studies are stability-indicating and are qualified for their intended use.

2.2.5. Finished Medicinal Product

Description of the product and pharmaceutical development

Polatuzumab vedotin finished product is provided in single-dose 20 mL vials as a sterile, white to grayish-white lyophilized cake and contains no preservatives. It is intended for intravenous infusion after reconstitution with sterile water for injections (SWFI, not supplied) and dilution in 0.9% sodium chloride solution, 0.45% sodium chloride solution, or 5% dextrose solution.

The composition of the finished product is shown in Table 2. Reconstitution of the finished product with 7.2 mL of SWFI yields approximately 7.52 mL of reconstituted solution containing 20 mg/mL polatuzumab vedotin in 10 mM succinate, 120 mM sucrose, 1.2 mg/mL polysorbate 20, pH 5.3. The reconstituted finished product solution is unchanged with regard to concentration and composition compared to the active substance solution. Each vial is designed to deliver 140 mg of polatuzumab vedotin.

Table 2: Composition of Polatuzumab Vedotin Finished Product

Ingredient	Function	Specification
Polatuzumab Vedotin	Active ingredient	Section S.4.1 Specification
Succinic Acid	Buffering agent	USP-NF/JPE
Sodium Hydroxide	pH-adjusting agent	USP-NF/Ph. Eur./JP
Sucrose	Stabilizer/ bulking agent	USP-NF/Ph. Eur./JP
Polysorbate 20	Surfactant	USP-NF/Ph. Eur./JPE

*Note: The finished product vials are backfilled with sterile nitrogen gas.

Formulation of the finished product (succinic acid, sodium hydroxide, sucrose, and polysorbate 20) does not include novel excipients and complies with the requirements and specifications of the relevant compendial monographs.

Pharmaceutical development

The finished product formulation evolved from a liquid formulation (v0.1 process) containing 10 mg/mL polatuzumab vedotin in histidine buffer to a lyophilized formulation (v1.0 process) containing 170 mg/vial (and thereafter 140 mg/vial) polatuzumab vedotin in succinate buffer. The lyophilized dosage form was

introduced to improve product stability. The dosage of 140 mg/vial is the one intended for commercialization.

A comparability assessment was conducted between the liquid formulation and the lyophilized finished product. The lyophilised finished product exhibited a better stability profile than the liquid form.

The primary container closure system consists of a type I glass vial with a rubber stopper. The rubber stopper is crimped with an aluminum seal fitted with a plastic flip-off cap. The seal and cap do not come into contact with the finished product. The choice of the container closure system is in line with pharmaceutical standards and the components comply with pharmacopeial requirements. Compatibility of the container closure system with the dosage form was assessed with respect to physico-chemical testing (i.e. extractables and leachables), stability testing, and container closure integrity testing. Polatuzumab vedotin was found to be compatible with the primary packaging components. Interaction between the finished product and the container closure is expected to be limited since the product is presented as a powder.

The potential presence of elemental impurities in the finished product has been assessed through a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities

The microbiological quality complies with European requirements for sterile products and is ensured by a combination of various measures: process validation, manufacturing controls, in-process testing and release and stability testing.

The finished product is intended to be administered at the dose of 1.8 mg/kg via intravenous infusion using infusion line equipped with a 0.2-0.22 µm filter. Physico-chemical stability of the reconstituted solution and the diluted infusions (with either 0.9% sodium chloride solution, 0.45% sodium chloride solution, or 5% dextrose solution) were demonstrated for the durations and conditions as listed in the product information. From a microbiological point of view, the prepared solution should be used immediately.

Manufacture of the product and process controls

Roche Pharma AG, Grenzach-Wyhlen, Germany, is responsible for EU batch certification. Confirmation of the GMP status for the finished product manufacturing and testing sites has been provided.

The finished product manufacturing process is standard and consists of thawing of the active substance (one or two batches) followed by a 0.2 µm filtration for bioburden reduction. The finished product solution is then sterilized through two membrane filters in series immediately prior to filling. The vials are partially stoppered and conveyed to lyophilizer. Upon completion of the lyophilization cycle, vials are fully stoppered and capped, and a 100% visual inspection is performed before shipping for labelling and packaging. The level of detail in the description of the manufacturing process is deemed sufficient.

Validation of the finished product manufacturing process is based on analysis of three consecutive PPQ batches. The validation studies included the control of all process parameters (CPPs and non-CPPs) and IPCs, as well as CQAs. The results met acceptance criteria, demonstrating the finished product manufacturing process is consistent throughout the different steps (thawing, filtration, pooling, filling, and lyophilisation).

The applicant applied Quality by Design (QbD) principles in the development of the finished product and to define the acceptable ranges of process parameters. However, no design spaces were claimed for the manufacturing process of the finished product. The in-process hold times are specified and validated through a combination of different studies (media fills, process design experiments, stability studies). Studies were also performed to provide assurance of transport of the polatuzumab vedotin finished product.

Product specification, analytical procedures, batch analysis

The commercial release and stability specification for polatuzumab vedotin finished product includes tests for appearance, particles, pH, osmolality, moisture, reconstitution time, identity, purity, protein concentration, free drug, DAR, potency, microbiology and container closure integrity.

The finished product specifications were established in line with ICH Q6B and monograph 2031 on monoclonal antibodies for human use.

Acceptance criteria setting is based on a combination of several factors: clinical experience, stability and process effects, product-specific knowledge, prior knowledge, current compendia or regulatory guidelines, and formulation development studies. Overall the proposed specifications are considered justified and sufficient to deliver product with consistent quality. It is recommended to revise the proposed acceptance criteria for charge variants once sufficient data will be available (See "Recommendations for future quality development").

Analytical methods

Characteristics of analytical procedures (e.g. accuracy, precision, specificity, linearity, range, quantitation limit) were validated as per ICH Q2 requirements.

The potency assays assays (binding and cell based) are the same as for the active substance.

Batch analysis

Analytical results of 140 mg/vial finished product batches derived from process validation and clinical trials are provided. All batches were manufactured at the commercial site using the intended v1.0 commercial process. All results comply with the defined acceptance criteria.

Reference materials

A two-tiered reference standard system, consisting of a primary and a secondary reference standard was established for polatuzumab vedotin active substance and finished product. The commercial primary reference standard will be used to qualify subsequent secondary reference standards. The secondary reference standard is used for testing the antibody intermediate in all assays requiring a reference standard.

For commercial release and stability testing, Batch 608784 is used as the primary reference standard, and Batch 608785 is used as the secondary reference standard. Aliquots of primary and secondary reference standards are stored at -70°C ± 20°C. The stability of the reference standards is confirmed annually.

The primary and secondary reference standards were qualified by release and extended characterization testing. All specifications were met. Preparation and qualification of future reference standards is also described.

Stability of the product

A 2-year shelf-life is claimed for the finished product, when stored at 2-8 °C and protected from light. The finished product should not be frozen or shaken.

This claim is based on the data obtained from i) primary batches (clinical and PPQ) manufactured using the commercial process (data available up to 18 months at 2-8°C), ii) technical batch manufactured using the same lyophilization cycle as clinical batches and using the same finished product configuration as the clinical and commercial batches (data available up to 36 months at 2-8°C), and iii) supportive batches at 170 mg/vial manufactured using the commercial process with the exception of an adjustment to the fill volume (data available up to 48 months at 2-8°C).

No primary batches have reached the proposed 2 year shelf-life yet. The proposed shelf life is mainly based on data obtained from the 140 mg/vial technical batch and three 170 mg/vial clinical batches. Although the 140 mg/vial technical batch and the 170 mg/vial clinical batches are not fully representative of the commercial material, they were manufactured using the same manufacturing and lyophilization process parameters as the commercial process, and using the same container closure system. The differences are not expected to significantly impact the stability behaviour of the finished product, as demonstrated by the available long-term, accelerated, and stress stability data which showed a consistent stability profile between the 140 mg/vial and 170 mg/vial.

The available stability data for samples stored at the recommended storage conditions (2-8°C) show good stability with no (significant) trends observed. Therefore, a 2-year shelf life can be granted for the finished product.

Supportive data from accelerated and stressed stability studies are available. Under the accelerated and stressed conditions a decrease in purity is observed as reflected by a decrease in the amount of main peak and an increase in the amount of HMW forms, as measured by SE-HPLC. Furthermore, the charge distribution on iCIEF has been affected, resulting in an increase in acidic variants with a consequent decrease in main peak.

To further support the shelf-life, a temperature cycling study has been initiated on one 140 mg/vial finished product PPQ batch to support potential temperature excursions/time out of recommended storage condition relevant for manufacturing, shipping, and handling of finished product vials. All current results are within specifications.

Stability of the finished product when exposed to light was investigated for one batch in the commercial container closure material. Samples were exposed to conditions consistent with ICH Q1B and the stability was determined by comparing the results for an unprotected exposed sample in the primary packaging (unlabeled vial) to the results for vials stored in the secondary packaging (in carton), relative to results obtained from vials wrapped in foil (control). Results showed that the finished product is light sensitive. The packaging configuration adequately protects the finished product vials from light and the product label contains a note to store the product in the outer carton to protect from light.

Adventitious agents

The overall viral safety of Polutuzumab vedotin relies on:

- The quality of starting materials (cell banks) and materials of biological origin

- The capacity of the production process to remove or inactivate viruses

- Virological control tests during the production process

The data provided by the applicant regarding material of biological origin used is deemed sufficient regarding TSE compliance and viral safety.

The data resulting from extensive experimental studies on the MCB, WCB, end of production cells (EPC)s and EPCs at the in vitro cell age do not reveal any viral contamination of these cell banks.

The virological control tests on unprocessed bulk strategy is conclusive and conforms to ICH Q5A (R1). The data resulting from virological controls of three unprocessed bulk lots are deemed acceptable.

The manufacturing process includes virus inactivation/removal and chromatography steps proven to clear adventitious viruses.

Global reduction factors reported are satisfactory regarding the virus removal/inactivation for enveloped viruses as well as for non-enveloped viruses.

2.2.6. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the intermediates (linker-drug and antibody), active substance and finished product have been presented in a satisfactory manner.

The linker-drug intermediate is the same as utilised in centrally authorised product Adcetris. The antibody intermediate, the active substance, and the finished product are appropriately described and the controls applied seem suitable to monitor the process and deliver a product with consistent quality.

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

The applicant has applied QbD principles in the development of the finished product and their manufacturing process. However, no design spaces were claimed.

2.2.7. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.8. Recommendation(s) for future quality development

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

The applicant commits to reevaluate the individual action limits and acceptance criteria for glycosylation variants once a sufficient number of antibody intermediate batches have been produced. The applicant is also recommended to include a revision of the acceptance criteria for charge variants for the antibody intermediate, active substance and finished product specifications.

2.3. Non-clinical aspects

2.3.1. Introduction

Non-clinical *in vivo* efficacy studies of polatuzumab vedotin were performed using in xenograft tumour models derived from human B cell lymphomas established in SCID mice. These studies evaluated the treatment with polatuzumab vedotin as monotherapy or in combination with CD20-targeting antibodies/chemotherapy.

The pivotal toxicity studies have been conducted under GLP regulations. Pharmacokinetic studies after single-dose administration were performed in SCID mice and *Cynomolgus* monkeys; TK analyses were performed after repeat-dose administration in rats and *Cynomolgus* monkeys. In these studies, test articles were administered IV, in accordance with the clinical route of administration. Tissue distribution studies with radiolabelled polatuzumab vedotin and MMAE were conducted in rats. Metabolism and excretion of polatuzumab vedotin and MMAE were assessed in rats and *in vitro* using animal and human hepatocytes /liver microsomes.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro pharmacodynamics

Binding of polatuzumab vedotin and the surrogate ADC to PBMC [study 10-2535]

The binding of polatuzumab vedotin and the surrogate ADC to PBMC from human, *Cynomolgus* monkey, rat, and mouse was assessed by flow cytometry. To identify B cells, PBMC were co-stained for B cell markers (CD20 in human and *Cynomolgus*, CD45RA in rat, and CD45R in mouse).

Polatuzumab vedotin bound to human peripheral B cells and not to *Cynomolgus* monkey, rat, or mouse peripheral B cells. The surrogate ADC bound to *Cynomolgus* monkey peripheral B cells and not to human, rat, or mouse peripheral B cells.

Sequence homology of human and rodent CD79b is low (approx. 68%). The overall sequence homology of human and *Cynomolgus* CD79b is higher, i.e. 85.3%. However, there are 3 amino acid differences in the epitope recognized by the anti-human CD79b antibody SN8 (parental Ab for polatuzumab) and the anti-*Cynomolgus* CD79b antibody (i.e. the first 21 N-terminal amino acids of CD79b (after removal of the signal sequence [Zheng et al., 2009]). This difference appears sufficient to prevent binding of polatuzumab to *Cynomolgus* CD79b.

Evaluation of binding affinity [study 10-2298]

Binding affinity of polatuzumab vedotin, polatuzumab Ab, surrogate ADC, and surrogate Ab to human and *Cynomolgus* monkey CD79b was determined by radiolabelled, equilibrium binding assays.

Table 3. Binding Affinity of Polatuzumab Vedotin, Surrogate ADC, Polatuzumab Antibody, and Surrogate Antibody (Study 10-2298)

Antibody	K_d (nM)
Polatuzumab Vedotin	1.83 ± 0.26
Polatuzumab Antibody	1.33 ± 0.14
Surrogate ADC	1.51 ± 0.25
Surrogate Antibody	1.21 ± 0.10

ADC = antibody–drug conjugate; K_d = equilibrium dissociation constant.
Note: Each value represents the average of three independent experiments ± the standard deviation of those measurements.

Evaluation of anti-proliferative activity of polatuzumab vedotin, polatuzumab Ab and MMAE [study 10-2308]

The anti-proliferative activities of polatuzumab vedotin, the polatuzumab Ab and MMAE were evaluated in a proliferation assay. To this end, the CD79b-positive Burkitt lymphoma cell line Ramos and the CD79b-negative T cell leukemia cell line Jurkat were incubated with increasing concentrations (0.5 pM to 10 nM) of polatuzumab vedotin, polatuzumab antibody, or MMAE. After 3 days of incubation cell proliferation was measured using Cell Titer Glo II reagent and IC50 values were calculated using a four-parameter sigmoidal fit.

Table 4. IC50 for Polatuzumab Vedotin in Ramos and Jurkat Cells [Study 10-2308]

IC_{50} (nM)	Ramos	Jurkat
Polatuzumab Vedotin	0.071 ± 0.014	No cell killing up to 10 nM [a]
Polatuzumab Antibody	No cell killing up to 10 nM [a]	No cell killing up to 10 nM [a]
MMAE	0.075 ± 0.024	0.13 ± 0.089

IC_{50} = half-maximal inhibitory concentration; MMAE = monomethyl auristatin E.

Note: Each value represents the average of three independent experiments ± the standard deviation of those measurements.

[a] 10 nM was the highest concentration tested.

Evaluation of cytokine-inducing potential of polatuzumab Ab and the surrogate Ab [study 10-2299]

Given that CD79b is a signalling component of the B-cell receptor (BCR), anti-CD79b antibodies have the potential to induce BCR signalling that may result in the production of cytokines. In particular, interleukin (IL)-1β, IL-6, IL-10, TGF-α, GM-CSF, MIP-1α, and MIP-1β have been shown to be produced by B cells upon stimulation of the BCR [Zheng et al. 2009].

Thus, the capacity of unconjugated polatuzumab and the unconjugated surrogate antibody to stimulate cytokine release by PBMCs from healthy human donors or *Cynomolgus* monkeys was evaluated *in vitro* and compared to the stimulatory activity of positive control antibodies (OKT-3, alemtuzumab) or the negative control antibody trastuzumab.

In human PBMCs exposed to polatuzumab only IL-1α and IP-10 were elevated above the negative-control level although at a level lower (IL-1α) or similar (IP-10) to that induced by OKT3. No other cytokine evaluated in the human PBMC experiments were elevated above the levels observed following exposure to trastuzumab.

In *Cynomolgus* PBMCs exposed to the surrogate Ab, none of the cytokines evaluated was elevated above the level of the negative-control antibody (trastuzumab). The level of IP-10 and IL-1α, two cytokines with increased level observed in human PBMCs, could not be evaluated in *Cynomolgus* monkey PBMCs due to the lack of assay reagents for these cytokines.

Binding to human FcγRs by polatuzumab vedotin and the surrogate ADC [study 10-2764]

The objectives of this study were to evaluate to what extent conjugation to MMAE has an impact on Ab binding to Fcγ receptors. Thus, the binding affinities of polatuzumab Ab, polatuzumab vedotin, the surrogate Ab and ADC to human Fcγ receptors were assessed by ELISA and compared to that of the control antibody rituximab.

Table 5. EC50 data of rituximab, polatuzumab vedotin, polatuzumab Ab, surrogate ADC, and surrogate antibody from with human FcγRs [study 10-2764]

	EC_{50}					
Test Article	FcγRIA (ng/mL)	FcγRIIA-H131 (µg/mL)	FcγRIIA-R131 (µg/mL)	FcγRIIB (µg/mL)	FcγRIIIA-F158 (µg/mL)	FcγRIIIA-V158 (µg/mL)
Rituximab	6.89 ± 2.01	0.457 ± 0.0739	1.42 ± 0.448	2.03 ± 0.144	2.72 ± 0.0404	0.618 ± 0.168
Polatuzumab Vedotin	9.46 ± 2.37	3.15 ± 0.204	5.13 ± 0.543	7.81 ± 0.728	7.39 ± 1.56	1.82 ± 0.272
Polatuzumab Antibody	12.4 ± 3.18	2.76 ± 0.466	8.11 ± 1.08	9.53 ± 0.110	6.52 ± 1.38	1.23 ± 0.247
Surrogate ADC	8.53 ± 2.17	1.49 ± 0.121	1.96 ± 0.276	2.98 ± 0.137	2.34 ± 0.289	0.714 ± 0.147
Surrogate Antibody	10.7 ± 3.02	1.24 ± 0.119	2.98 ± 0.690	3.77 ± 0.319	2.02 ± 0.244	0.547 ± 0.102

ADC = antibody–drug conjugate; EC_{50} = half-maximal effective concentration (the effective concentration of the antibody at which 50% of the maximum response from binding to the FcγR was detected); FcγR = Fc gamma receptor.

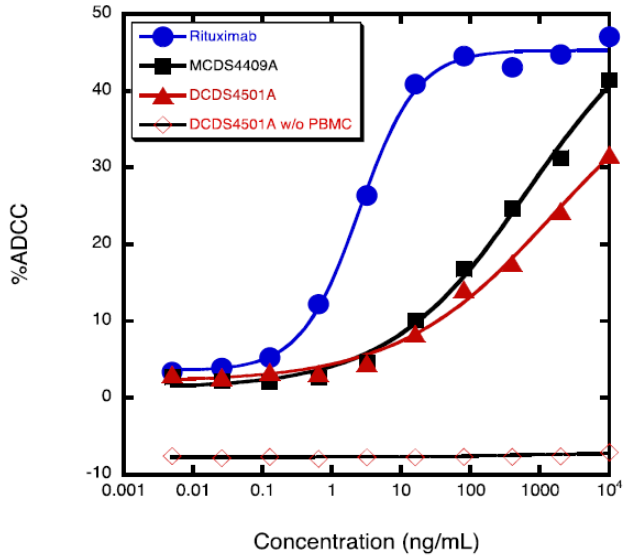
Notes: Each value represents the average of three independent experiments ± the standard deviation of those experiments.

Evaluation of ADCC and CDC induced by polatuzumab vedotin and polatuzumab Ab [study 10-2764]

As human IgG1 polatuzumab Ab and polatuzumab vedotin may induce antibody-dependent cytotoxicity (ADCC) or complement-dependent cytotoxicity against CD79+ target cells. Therefore, the capacity to mediate these effector functions was evaluated and compared to that of rituximab, an anti-CD20 mAb.

In the ADCC assay purified PBMCs from healthy donors were used as effector cells and the human B-lymphoma BJAB cell line was used as target. Rituximab was tested as a positive control for the assay, in addition to polatuzumab Ab and polatuzumab vedotin. To ensure that any observed ADCC activity from polatuzumab vedotin is not due to cytotoxicity of the MMAE, polatuzumab vedotin was also tested without the addition of PBMC effector cells.

Figure 3. ADCC activities of polatuzumab vedotin, the polatuzumab Ab, and rituximab in BJAB Cells [study 10-2764]



ADCC = antibody-dependent cell-mediated cytotoxicity; DCDS4501A = polatuzumab vedotin; MCDS4409A = polatuzumab antibody; PBMC = peripheral blood mononuclear cells; w/o = without.

In the CDC assay with rabbit complement the positive control mAb rituximab induced CDC in BJAB target cells, while polatuzumab Ab and polatuzumab vedotin were negative for detectable CDC activity at Ab concentrations up to 10 µg/ml.

Impact of co-treatment with anti-CD20 Ab on polatuzumab vedotin uptake and catabolism in vitro [study 15-0682]

Polatuzumab vedotin is in clinical development for the treatment of indolent B-cell lymphoma in combination with CD20-targeting mAbs rituximab or obinutuzumab. Thus, the impact of co-treatment of rituximab or obinutuzumab on the uptake and catabolism of polatuzumab vedotin in WSU-DLCL2 tumour cells that expresses both CD79b and CD20 receptors was assessed in vitro using radio-labelled polatuzumab vedotin (anti-CD79b-vc-[3H]-MMAE).

In this study, WSU-DLCL2 cell line (expressing both CD79b and CD20) and HT cell line (target negative) were either treated with [3H]-labelled tracer alone (polatuzumab vedotin-[3H]-MMAE at 0.0667 µCi/mL (equivalent to 1 µg/mL of ADC) or in combination with rituximab, obinutuzumab, unlabelled polatuzumab vedotin, or anti-gD at clinically relevant concentrations. Cells were harvested at 0, 3, 17, 24, and 48 hours following incubation at 37°C. Total cell numbers (dead and viable), viability, total radioactivity, and acetonitrile (ACN)-soluble and ACN-precipitable radioactivity were determined. In addition, the cell lysates were profiled for polatuzumab vedotin catabolites using RP-HPLC.

In WSU-DLCL2 cells, level of total radioactivity increased following treatment with polatuzumab vedotin tracer alone or co-treated with rituximab, obinutuzumab, or anti-gD antibody. In contrast, co-incubation of tracer with unlabelled polatuzumab vedotin significantly reduced the uptake of the tracer. These data indicate that the uptake of polatuzumab vedotin-[3H]-MMAE by WSU-DLCL2 cells is a target-specific-mediated process which is not impacted by co-treatment with anti-CD20 antibodies. There was little radioactivity detected in the target negative control HT cell line in any treatment group (data not shown).
ACN precipitation of WSU-DLCL2 cell lysates showed comparable catabolism between tracer alone and co-treatment with rituximab, obinutuzumab, or anti-gD antibody. Profiling of WSU-DLCL2 cell lysates using RP-HPLC revealed a similar catabolite profile between tracer alone and co-treatment with rituximab, obinutuzumab, or anti-gD antibody. MMAE was identified as the only detectable catabolite in all groups regardless of treatment.

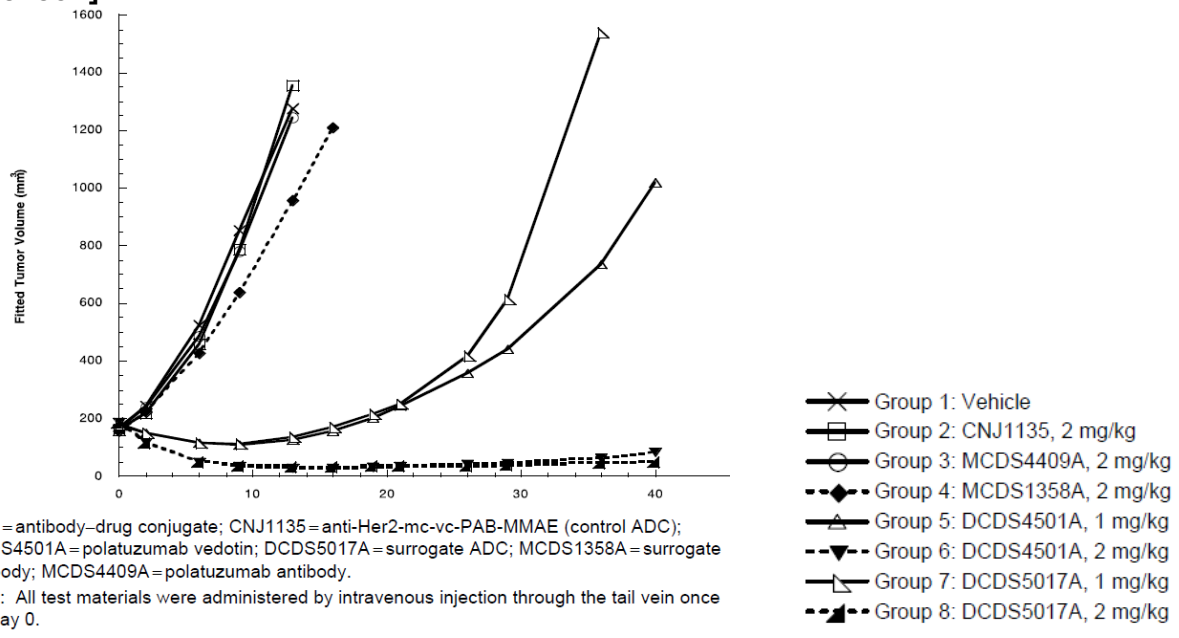
***In vivo* pharmacodynamics**

Comparison of polatuzumab vedotin and surrogate ADC against human Burkitt lymphoma xenograft [study 09-0406 B]

The anti-tumour activity of polatuzumab Ab, polatuzumab vedotin and of the surrogate Ab and ADC was compared in a murine xenograft model with the BJAB Burkitt lymphoma transfectant cell line which expresses comparable amounts of human CD79b and recombinant *Cynomolgus* CD79b. The anti-Her2 ADC was used as negative control ADC. Results are shown in Fig. 2-3 below.

Tumour growth inhibition was observed with polatuzumab vedotin and the surrogate ADC, but not with the Her2-targeting control ADC or polatuzumab and the surrogate Ab. The effects of polatuzumab vedotin and surrogate ADC were more pronounced at 2 mg/kg than at 1 mg/kg.

Figure 4 Growth inhibition of BJAB-PD.cyCD79b.E3 tumours in response to polatuzumab vedotin, polatuzumab Ab, surrogate ADC, surrogate Ab or control ADC in SCID mice [study 09-0406B]



ADC = antibody–drug conjugate; CNJ1135 = anti-Her2-mc-vc-PAB-MMAE (control ADC); DCDS4501A = polatuzumab vedotin; DCDS5017A = surrogate ADC; MCDS1358A = surrogate antibody; MCDS4409A = polatuzumab antibody.
Note: All test materials were administered by intravenous injection through the tail vein once on Day 0.

Effect of polatuzumab vedotin against human DLBCL xenograft [study 09-0406 D]

This study assessed the anti-tumour activity of polatuzumab Ab and the ADC polatuzumab vedotin against human diffuse large B-cell lymphoma WSU-DLCL2 xenograft tumours. Anti-Her2 ADC was used as control. A dose-dependent anti-tumour activity of polatuzumab vedotin at doses ≥ 3 mg/kg was

observed. No inhibition of tumour growth was observed in mice treated with high doses (12 mg/kg) of polatuzumab Ab or control ADC.

Effect of polatuzumab vedotin against human Burkitt lymphoma xenograft [study 09-0406 E]

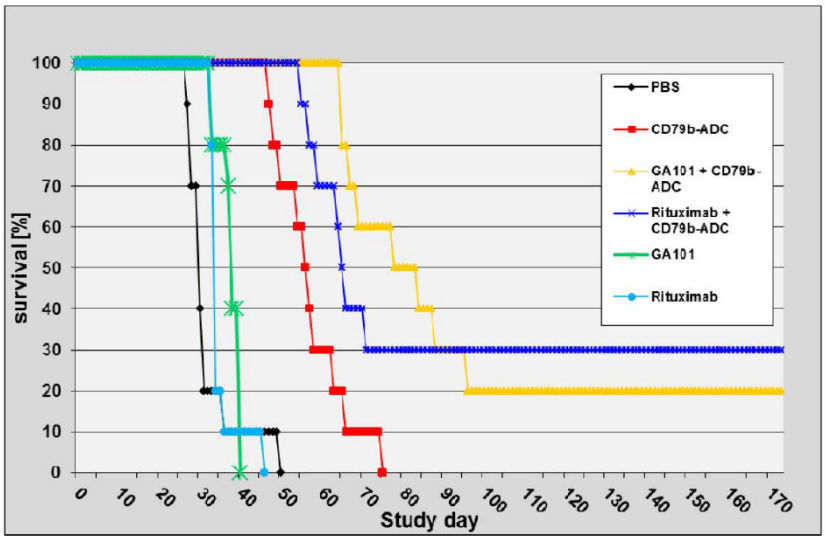
This study assessed the anti-tumour activity of polatuzumab Ab and its conjugate polatuzumab vedotin against human Burkitt's lymphoma BJAB-luc xenograft tumours. Anti-Her2 ADC was used as control. A dose-dependent anti-tumour activity of polatuzumab vedotin at doses ≥ 0.5 mg/kg was observed. No inhibition of tumour growth was observed in mice treated with high doses (4 mg/kg) of polatuzumab Ab and control ADC.

Xenograft studies with polatuzumab vedotin in combination with anti-CD20 and/or chemotherapy

Effect of polatuzumab vedotin in combination with anti-CD20 mAbs against Mantle cell lymphoma in a xenograft IV model [study 1048504]

The present study evaluated the anti-tumour activity of polatuzumab vedotin in combination with anti-CD20 mAbs (rituximab or obinutuzumab) in a xenograft model of human mantle cell lymphoma (Z138 cells, given IV to SCID beige mice). Twenty one days after tumour implantation treatment was initiated. All animals were monitored daily and were euthanized when they showed adverse clinical symptoms.

Figure 5 Survival of mice in /138 Mantle cell lymphoma model [study 1048504]



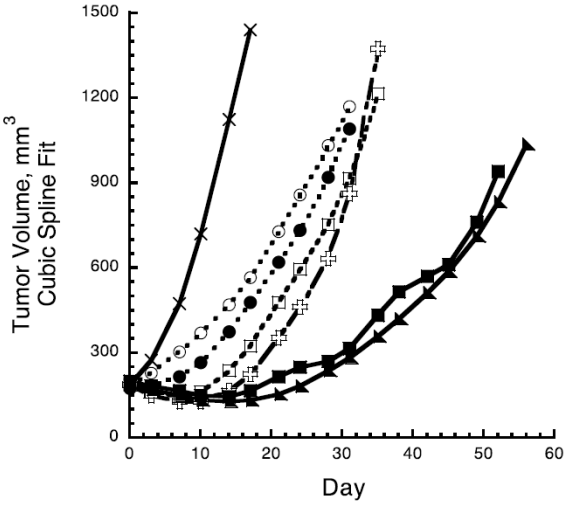
CD79b-ADC = polatuzumab vedotin; GA101 = obinutuzumab; PBS = phosphate-buffered saline.

Notes: All test materials were administered by intravenous injection through the tail vein. Polatuzumab vedotin (4 mg/kg) was given once on Day 21; vehicle (PBS), rituximab (30 mg/kg), and obinutuzumab (30 mg/kg) were given weekly on Days 21, 28, and 35.

Effect of polatuzumab vedotin in combination with rituximab plus chemotherapy in human DLBCL xenograft model [study 13-0599]

This study assessed the anti-tumour activity of polatuzumab vedotin in combination with rituximab plus chemotherapy (CHP or bendamustine) against human diffuse large B-cell lymphoma WSU-DLCL2 xenograft tumours in mice.

Figure 6 Growth inhibition of WSU-DLCL2 tumours in response to polatuzumab vedotin ± rituximab and chemotherapy [study 13-0599]



C = cyclophosphamide; H = doxorubicin (hydroxydaunorubicin); O = vincristine (oncovin); P = prednisone; IP = intraperitoneal; IV = intravenous; PO = oral.

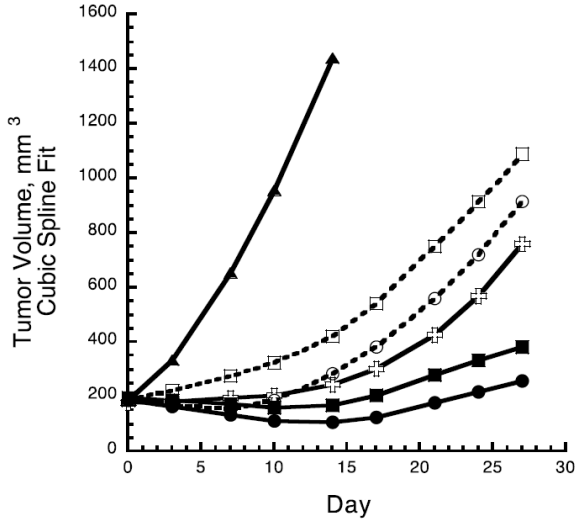
Notes: Cubic spline fitted tumor volumes are depicted for each group. Administration of test materials began on Day 0 in the following order, immediately after each other: (1) rituximab (30 mg/kg, IP, once); (2) bendamustine (30 mg/kg, IV, once), or CHO (30, 2.475, and 0.375 mg/kg, respectively, IV, once) + P (0.15 mg/kg, PO, daily × 5); and then (3) polatuzumab vedotin (2 mg/kg, IV, once).

01 - Vehicle
02 - Polatuzumab vedotin
03 - Rituximab + CHOP
04 - Rituximab + CHP
05 - Rituximab + Bendamustine
06 - Rituximab + CHP + Polatuzumab vedotin
07 - Rituximab + Bendamustine + Polatuzumab vedotin

Effect of polatuzumab vedotin in combination with obinutuzumab plus chemotherapy in human DLBCL xenograft model [study 14-3262 B]

This study assessed the anti-tumour activity of polatuzumab vedotin in combination with obinutuzumab plus chemotherapy (CHP or bendamustine) against human diffuse large B-cell lymphoma WSU-DLCL2 xenograft tumours in mice.

Figure 7 Growth inhibition of WSU-DLCL2 tumours in response to polatuzumab vedotin ± obinutuzumab and chemotherapy [study 14-3262 B]



C = cyclophosphamide; H = doxorubicin; IP = intraperitoneal; IV = intravenous; P = prednisone; PO = oral.

Notes: Cubic spline fitted tumor volumes are depicted for each group. Administration of test materials began on Day 0 in the following order, immediately after each other:
1) obinutuzumab (30 mg/kg, IP, once); 2) bendamustine (30 mg/kg, IV, once) or CH (30 and 2.475 mg/kg, respectively, IV, once) + P (0.15 mg/kg, PO, daily × 5); and then 3) polatuzumab vedotin (2 mg/kg, IV, once).

01 - Vehicle
02 - Polatuzumab vedotin
03 - Obinutuzumab + CHP
04 - Obinutuzumab + Bendamustine
05 - Obinutuzumab + CHP + Polatuzumab vedotin
06 - Obinutuzumab + Bendamustine + Polatuzumab vedotin

Pharmacodynamics of the surrogate ADC in Cynomolgus monkeys

The pharmacodynamic effects of the surrogate ADC (and the surrogate Ab) were evaluated in *Cynomolgus* monkeys after single or repeated administration.

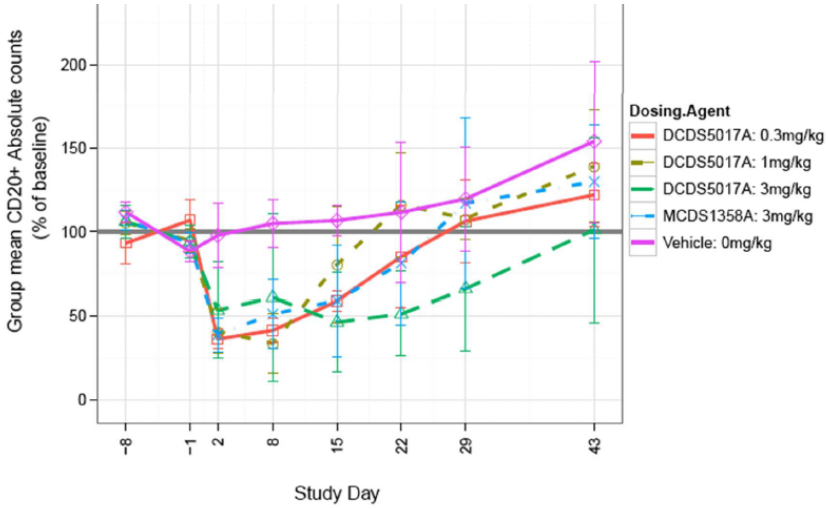
Single dose PK/PD study of the surrogate ADC and surrogate Ab in *Cynomolgus* [10-0899]

Male *Cynomolgus* monkeys were administered single IV bolus doses of vehicle, surrogate Ab MCDS1358A (3 mg/kg) or surrogate ADC DCDS5017A (0.3, 1, 3 mg/kg); samples for PK and PD assessment were obtained up to 43 days after treatment.

Partial depletion of peripheral blood CD20+ B cells was observed in all animals given the surrogate Ab or the ADC (see Fig. 2-9). The extent of B cell depletion was comparable in these groups; however, the duration of the effect was slightly longer in animals given 3 mg/kg surrogate ADC compared to those treated at lower doses of ADC or at 3 mg/kg surrogate Ab (see Fig. below). Furthermore, in animals given 3 mg/kg surrogate ADC, the % baseline of proliferating B cells (CD20+/Ki-67+) was lower than the % baseline of non-proliferating B cells (CD20+/KI-67-) on day 15. In animals given vehicle or surrogate Ab (3 mg/kg), the effect on proliferating and non-proliferating B cells was comparable on day 15.

No substantial differences were observed in levels of T cells or NK cells in animals given the surrogate Ab or ADC compared to animals given vehicle.

Figure 8 CD20+ counts (% of baseline) in cynomolgus peripheral blood [study 10-0899]



ADC = antibody–drug conjugate; DCDS5017A = surrogate ADC; MCDS1358A = surrogate antibody.
Note: Absolute count (% of baseline) is the percentage of gated lymphocytes expressed as a percentage of baseline (average of two predose values) for each individual animal.

Repeat-dose IV study of polatuzumab vedotin and the surrogate ADC in cynomolgus [10-0044]

PD effects of polatuzumab vedotin and the surrogate ADC were studied as part of the repeated-dose IV toxicity study in *Cynomolgus* monkeys. *Cynomolgus* were administered vehicle, polatuzumab vedotin at 1, 3 or 5 mg/kg or the surrogate ADC at 3 or 5 mg/kg (Q3W, 4 doses) and then followed in a 9-week treatment-free period. The effect on peripheral blood B cells was determined flow cytometry immunophenotyping.

Peripheral blood B cells decreased in a dose-independent manner on day 2 after administration of the surrogate ADC. Following multiple IV administrations of the surrogate ADC, the maximum decrease was observed on Day 50 (21% baseline) at the 3 mg/kg dose and on Day 71 (16% baseline) at the 5 mg/kg dose. After the end of treatment, B cell numbers recovered; estimated CD20+ lymphocyte recovery to >

40% of baseline levels in all remaining study animals was approximately achieved between Days 134 and 148 (see Fig. 2-10). As expected, treatment of *Cynomolgus* monkeys with the clinical candidate polatuzumab vedotin (non-binding ADC in *Cynomolgus* monkey) did not show any decrease in CD20+ lymphocyte numbers. Furthermore, there was no effect on T lymphocytes and NK cells in animals given surrogate ADC or polatuzumab vedotin as compared to vehicle.

Secondary pharmacodynamic studies

Secondary pharmacology studies have not been submitted (see discussion on non-clinical apsects).

Safety pharmacology programme

In vitro safety pharmacology

Effect of MMAE on cloned hERG channel current [study 07-0611]

The effect of MMAE on hERG potassium channel activity was examined in HEK 293 cells stably transfected with hERG cDNA. Cells were exposed to 10 and 100 µM MMAE, positive control (60 nM terfenadine) or vehicle negative control. Whole-cell patch clamp recordings were used to measure hERG tail current levels during agent application.

The positive control (60 nM terfenadine) inhibited hERG potassium current by 84.0 ± 0.4% (mean ± SD) vs. 0.3 ± 0.2% in the vehicle control. MMAE inhibited hERG potassium current by 1.8 ± 0.1% at 10 µM and by 13.6 ± 2.6% at 100 µM. Since hERG inhibition at the highest concentration tested (100 µM) was only 13.6%, the IC50 for the inhibitory effect of MMAE on hERG potassium current could not be determined and was estimated to be > 100 µM.

At a clinically relevant dose of 1.8 mg/kg polatuzumab vedotin, the mean Cmax of MMAE in plasma is approx. 7 ng/ml (10 nM) assuming no plasma protein binding. MMAE at 100 µM (approx. 10,000x greater than MMAE Cmax in patients) did not cause toxicologically relevant effects on the hERG channel.

In vivo safety pharmacology

Safety pharmacology and neurobehavioral assessments were incorporated into GLP repeat-dose toxicity studies in rats and *Cynomolgus* monkeys.

Repeat-dose IV study of polatuzumab vedotin in rats [10-0898, GLP]

Polatuzumab vedotin was administered QW to rats at IV doses of 2, 6, and 10 mg/kg for a total of 4 doses, followed by a 6-week recovery period.
Respiration rates were measured as part of the cage-side and hand-held evaluations. There were no test article-related respiratory observations noted in animals administered polatuzumab vedotin.
A functional observational battery, including motor activity, was performed on all animals. A slight increase of low arena locomotor activity was observed for males in the high-dose group and was attributed to the clinical decline of the animals rather than a specific neurobehavioral effect.

Repeat-dose IV study of polatuzumab vedotin and the surrogate ADC in *Cynomolgus* [10-0044, GLP]

In Cynomolgus monkeys, IV doses of 1, 3, and 5 mg/kg polatuzumab vedotin or 3 and 5 mg/kg of the surrogate ADC were administered Q3W for a total of 4 doses, followed by a 9-week recovery period. There were no test-article-related effects on heart rate, body temperature, ECG (including QT interval) or blood pressure in animals given polatuzumab vedotin or the surrogate ADC. There were no test article-related respiratory observations in animals administered polatuzumab vedotin or the surrogate ADC.

All animals in the study were subject to neurological evaluation, based on examination of behaviour, motor function, cranial nerves, and proprioception. No test-article-relate neurologic observations were noted.

Pharmacodynamic drug interactions

An *in vitro* study [15-0682] was conducted to evaluate the impact of co-treatment of polatuzumab vedotin with anti-CD20 antibodies (rituximab or obinutuzumab) on the activity, uptake and catabolism of polatuzumab vedotin in a cell line expressing both CD79b and CD20. This study is described under primary pharmacodynamics.

2.3.3. Pharmacokinetics

Absorption

All PK/TK studies were conducted using IV administration, since this is the intended route for administration of polatuzumab vedotin. The pharmacokinetics of polatuzumab vedotin was evaluated in mice, rats, and *Cynomolgus* monkeys. The PK of MMAE was characterized in *Cynomolgus* monkeys.

Single dose PK of polatuzumab vedotin, polatuzumab, surrogate ADC and surrogate Ab in C.B-17 SCID mice [10-1571]

The pharmacokinetics of polatuzumab vedotin, the surrogate ADC, and the respective non-conjugated Ab were determined in female SCID mice, the strain used in efficacy experiments. PK was assessed based on plasma concentrations of total antibody and acMMAE.

Following a single 5 mg/kg IV administration of polatuzumab vedotin or the surrogate ADC, both PK profiles were characterized by a short distribution phase and a long elimination phase, as expected for monoclonal antibody-based therapeutics. The plasma CL of polatuzumab vedotin total antibody was 5.09 mL/kg/day with a half-life of the beta phase (t1/2,β) of 11.8 days. The plasma CL of the surrogate ADC total antibody was 6.99 mL/kg/day with a t1/2,β of 10.5 days. The overall PK profiles of total antibody were similar between the two ADCs. Also, the acMMAE plasma concentration-time profiles were also comparable between the two ADCs. However plasma concentrations of acMMAE decreased faster than serum concentrations of total Ab.

Table 6 PK parameters estimates in mice based on total Ab measurements

PK Parameter	Group 1 5 mg/kg MCDS4409A [a] MCDS4409A	Group 2 5 mg/kg DCDS4501A [b] Total Antibody	Group 3 5 mg/kg MCDS1358A [c] MCDS1358A	Group 4 5 mg/kg DCDS5017A [d] Total Antibody
C_{max} (µg/mL)	112±3.40	114±3.99	100±2.97	96.5±2.26
AUC (day•µg/mL)	1800±113	983±44.8	1030±53.3	715±23.3
CL (mL/day/kg)	2.78±0.175	5.09±0.232	4.84±0.250	6.99±0.228
$t_{1/2, \alpha}$ (day)	0.115±0.0205	0.131±0.0276	0.220±0.0399	0.294±0.0470
$t_{1/2, \beta}$ (day)	22.4±1.82	11.8±0.753	15.4±1.13	10.5±0.533
V_1 (mL/kg)	44.6±1.35	44.0±1.54	50.0±1.48	51.8±1.21
V_{ss} (mL/kg)	89.5±2.58	85.8±3.02	106±3.71	102±3.11
C_{max}/D (kg•µg/mL/mg)	22.4	22.7	20.0	19.3
AUC/Dose (day•kg•µg/mL/mg)	360	197	207	143

ADC=antibody–drug conjugate; AUC=area under the plasma concentration–time curve (A/α+B/β); AUC/Dose=area under the plasma concentration–time curve normalized by dose; C_{max}=maximum observed concentration; C_{max}/Dose=maximum observed concentration normalized by dose; CL=clearance (Dose/AUC_{inf}); IV=intravenous; PK=pharmacokinetic; $t_{1/2, \alpha}$=half-life of the alpha phase (ln(2)/α); $t_{1/2, \beta}$=half-life of the beta phase (ln(2)/β); V_1=volume of distribution of the central compartment (Dose/(A+B)); V_{ss}=volume of distribution at steady state (MRT_{inf} • CL).

[a] Clinical candidate antibody.

[b] Clinical candidate ADC.

[c] Surrogate antibody.

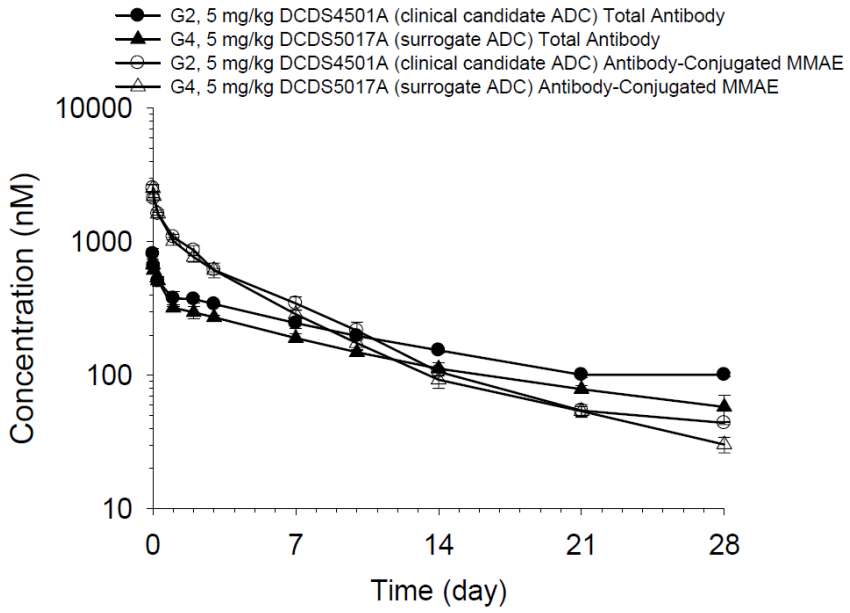
[d] Surrogate ADC.

Table 7 PK parameters estimates in mice based on acMMAE measurements

PK Parameter	Group 2 5 mg/kg DCDS4501A (127.44 nmol/kg MMAE) Antibody-Conjugated MMAE	Group 4 5 mg/kg DCDS5017A (120.47 nmol/kg MMAE) Antibody-Conjugated MMAE
C_{max} (nmol/L)	2530±92.6	2520±81.6
AUC_{last} (day • nmol/L)	7530±167	6900±97.1
AUC_{inf} (day • nmol/L)	8230	7280
CL (L/day/kg)	0.0155	0.0166
$t_{1/2, term}$ (day)	11.0	8.69
V_{ss} (L/kg)	0.141	0.122

AUC_{inf}=area under the plasma concentration–time curve extrapolated to infinity ($AUC_{last}+C_{last}/\lambda_z$); AUC_{last}=area under the plasma concentration–time curve from time=0 to time of the last measurable concentration; C_{max}=maximum observed concentration; CL=clearance (Dose/AUC_{inf}); PK=pharmacokinetic; $t_{1/2, term}$=terminal half-life (ln(2)/λ_z); V_{ss}=volume of distribution at steady state (MRT_{inf} • CL).

Figure 9 Serum total Ab and plasma AcMMAE concentration time profiles in SCID mice



IV = intravenous; LTS=less than standard (<0.1081 nM for Total Antibody of DCDS4501A or 0.1074 nM for Total Antibody of DCDS5017A); LLOQ=lower limit of quantitation (<0.195 nM for Antibody-Conjugated MMAE).

Single dose PK/PD study of the surrogate ADC and surrogate Ab in *Cynomolgus* [10-0899]

The objective of the study was to evaluate PK of the surrogate ADC and surrogate Ab when given as a single IV dose in *Cynomolgus* monkeys (relevant species). PD results of this study are discussed in the Primary Pharmacology section.

Male *Cynomolgus* monkeys were administered single IV bolus doses of vehicle, surrogate Ab (3 mg/kg) or surrogate ADC (0.3, 1, 3 mg/kg); samples for PK and PD assessment were obtained up to 43 days after treatment. Concentrations of total antibody, acMMAE and free MMAE were determined. PK parameters were estimated using a two-compartment model.

When measured as "total Ab", Cmax was maximal immediately after administration in all treatment groups. Subsequently, the serum concentrations declined in a bi-exponential manner. Cmax estimates for total Ab were dose-proportional within the dose range (0.3 – 3 mg/kg). Exposure (AUCinf) was non-proportional to dose, likely due to target-mediated drug disposition. At the same dose level (3 mg/kg), exposure (AUCinf) of the surrogate ADC was slightly lower than that of the ADC. Volume of distribution at steady state was comparable for the surrogate Ab and total antibody. When measured as "acMMAE", plasma concentrations were high immediately following administration of the surrogate but decreased faster than the "total Ab" concentrations of the ADC.

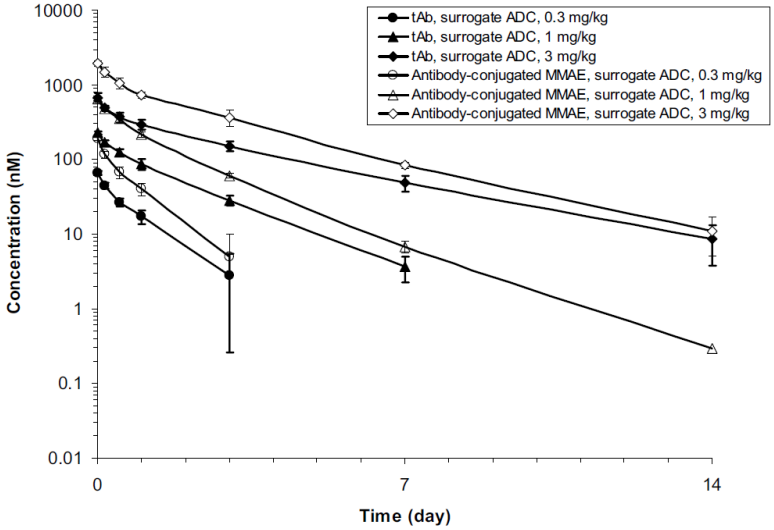
Free MMAE concentration increased with increasing doses of the surrogate ADC (1 and 3 mg/kg). Plasma concentration of free MMAE peaked on day 1-3 with a mean Cmax of 0.0575 ± 0.00425 ng/mL and 0.0930 ± 0.0178 ng/mL following a single IV administration of surrogate ADC at 1 and 3 mg/kg, respectively. Thus, free MMAE concentrations following administration of the surrogate ADC were low and could only be detected at limited time-points due to the assay sensitivity.

Table 8 PK parameters estimates for surrogate Ab and total Ab in cynomolgus

PK Parameter	Surrogate Antibody	Total Antibody		
	Surrogate Antibody 3 mg/kg IV (n=4)	Surrogate ADC 0.3 mg/kg IV (n=4)	Surrogate ADC 1 mg/kg IV (n=4)	Surrogate ADC 3 mg/kg IV (n=4)
C_{max} (μg/mL)	82.5±4.93	9.61±0.688	33.0±1.89	98.3±13.4
AUC_{inf} (day • μg/mL)	289±54.6	7.74±1.99	46.5±6.19	217±36.1
AUC_{0-3}(day • μg/mL)	125±7.23	7.31±1.51	36.2±4.23	124±16.1
C_{max}/D (kg • μg/mL/mg)	27.5±1.65	32.0±2.28	33.0±1.89	32.8 ±4.46
AUC_{inf}/D (day • kg • μg/mL/mg)	96.3±18.2	25.8±6.62	46.5 ± 6.19	72.1±12.0
AUC_{0-3}/D (day • kg • μg/mL/mg)	41.7±2.42	24.4±5.03	36.2±4.23	41.4±5.32
V_{ss} (mL/kg)	45.7±3.36	33.2±5.71	34.2±2.32	43.1±3.09

ADC = antibody–drug conjugate; AUC_{0-3} = area under the plasma concentration–time curve from Time 0 to Day 3; AUC_{0-3}/D = AUC_{0-3} normalized by dose; AUC_{inf} = area under the plasma concentration–time curve extrapolated to infinity ($AUC_{last} + C_{last}/\lambda_z$); AUC_{inf}/D = AUC_{inf} normalized by dose; C_{max} = maximum observed concentration; C_{max}/D = C_{max} normalized by dose; IV = intravenous; PK = pharmacokinetic; V_{ss} = volume of distribution at steady state.

Figure 10 Serum total Ab and plasma acMMAE concentrations in cynomolgus



Single-dose IV toxicity study of MMAE in cynomolgus [study 07-0609, GLP]

The objective of this study was to assess the toxicokinetics of MMAE when administered to *Cynomolgus* monkeys as a single IV injection at 0.030 or 0.063 mg/kg.

Overall, the MMAE plasma concentration-time profiles of both dose groups exhibited apparent biphasic disposition with a rapid initial distribution phase was followed by a slower elimination phase. The mean AUClast parameter estimates were dose proportional at 0.03 and 0.063 mg/kg. No sex-related differences in the toxicokinetic parameters were observed.

Table 9 MMAE compartmental TK parameters estimates in cynomolgus

PK Parameter	Group 2 MMAE; 0.030 mg/kg IV (n = 10)	Group 3 MMAE; 0.063 mg/kg IV (n = 10)
AUC_{0-inf} (min • ng/mL)	1350 ± 214	3930 ± 796
AUC_{last} (min • ng/mL)	1170 ± 160	2460 ± 342
C_{max} (ng/mL)	34.5 ± 14.2	65.9 ± 25.8
C_{max}/Dose (kg • ng/mL/mg)	1150 ± 471	1050 ± 408
AUC_{last}/Dose (min •ng/mL/mg/kg)	38900 ± 5330	39000 ± 5430

AUC_{last} = area under the plasma concentration versus time curve from time = 0 to time of the last measurable concentration; AUC_{0-inf} = area under the plasma concentration versus time curve from time = 0 to infinity; C_{max} = maximum observed concentration; C_{max}/Dose = C_{max} normalized by dose; AUC_{last} /Dose = AUC_{last} normalized by dose; IV = intravenous.

Repeat-dose toxicity study of polatuzumab vedotin in rats

In study 10-0898 after intravenous injection of polatuzumab vedotin, MMAE slowly appeared in plasma; Tmax was 1 day post-dose after the first and the last dose. Males generally had higher Cmax and AUC values than females but the differences were not greater than 2-fold. Cmax and AUC values after the last dose were slightly higher than after the first dose, indicating limited accumulation of MMAE after multiple dosing of polatuzumab vedotin in rats.

Repeat-dose toxicity study of polatuzumab vedotin and the surrogate ADC in *Cynomolgus*

In study 10-0044 the systemic exposure of total Ab was observed to increase dose-proportionally with the increase in polatuzumab vedotin dose from 1 to 5 mg/kg and in surrogate ADC dose from 3 to 5 mg/kg. No accumulation was observed after four doses of given Q3W and there were no observed sex-related differences in total antibody or unconjugated MMAE exposure. When comparing the two ADCs at the same dose levels, the systemic exposure of total antibody following IV administration of polatuzumab vedotin was about 1.2- to 1.4-fold higher than exposure of the surrogate ADC. Free MMAE exposure of polatuzumab vedotin was similar to that of the surrogate ADC in equivalent dose groups. Overall, free MMAE concentrations were low.

Table 10. TK parameters of free MMAE in cynomolgus after administration of polatuzumab vedotin or surrogate ADC

				Day 1			
Group No.	Dose Level mg/kg (μg/m^2)	Test Material		Tmax (day)	Cmax (ng/mL)	AUC(0-t) (ng•day/mL)	AUC(0-3) (ng•day/mL)
3	3 (~659) [a]	Clinical	Mean [c]	1	0.0726	0.380	0.171
			SD		0.0122	0.107	0.0226
4	5 (~1098) [a]	Clinical	Mean [c]	3	0.0968	0.496	0.233
			SD		0.0205	0.143	0.0459
5	3 (~622) [b]	Surrogate	Mean [c]	1	0.0832	0.313	0.204
			SD		0.0145	0.101	0.0298
6	5 (~1038) [b]	Surrogate	Mean [c]	2	0.115	0.618	0.291
			SD		0.0195	0.0957	0.0453

				Day 64			
Group No.	Dose Level mg/kg ($\mu g/m^2$)	Test Material		Tmax (day)	Cmax (ng/mL)	AUC(0-t) (ng•day/mL)	AUC(0-3) (ng•day/mL)
3	3 (~659) [a]	Clinical	Mean [c]	3	0.0726	0.394	0.181
			SD		0.00910	0.107	0.0174
4	5 (~1098) [a]	Clinical	Mean [c]	3	0.104	0.565	0.253
			SD		0.0213	0.0984	0.0484
5	3 (~622) [b]	Surrogate	Mean [c]	3	0.0729	0.381	0.178
			SD		0.00814	0.102	0.0264
6	5 (~1038) [b]	Surrogate	Mean [c]	3	0.107	0.583	0.263
			SD		0.0218	0.105	0.0518

a Dose expressed as mg total polatuzumab vedotin/kg of body weight (as dose of MMAE (µg/m2).
b Dose expressed as mg total surrogate ADC/kg of body weight (as dose of MMAE (µg/m2).
c Median value reported for Tmax.
** Dose level in µg/m2 was used in calculations.*

Distribution

Tissue distribution was assessed in rats using different radio-labelled test articles: polatuzumab Ab (labelled with iodine-125 or Dota-indium-111), polatuzumab vedotin (labelled with 125-I or 111-In on the Ab moiety or labelled with 3-H on the drug moiety) and MMAE (labelled with 3-H).

Tissue distribution of polatuzumab vedotin in rats using radiolabelled Ab moiety [14-0596]

The objective of this study was to determine the tissue distribution of polatuzumab vedotin compared to that of the polatuzumab Ab in SD rats following single IV administration of using non-residualized [125I]- and residualized DOTA-[111In]-labelled polatuzumab vedotin and polatuzumab Ab.
Blood and various tissues were collected at multiple intervals up to 14 days post-dose and analyzed using a gamma counter. The blood and tissue radioactivity data were calculated as percentage of injected dose (ID) normalized by blood volume (% ID/mL) or tissue weight (% ID/g).

Radioactivity was detected in multiple highly perfused tissues, including liver, lungs, heart, kidneys, spleen, adrenal gland, ovaries and bone marrow, within hours post-dose in all groups.

For [125I] probes, the radioactivity levels in tissues peaked at 2 hours post-dose and then decreased in parallel to the decrease of blood radioactivity over time without persistence in any tissue analysed in any group. The [125I] radioactivity levels in tissues were below that in the corresponding blood samples. Rats dosed with [111In]-polatuzumab vedotin had slightly higher uptake and longer retention of radioactivity in several tissues, particularly in the liver, than rats dosed with [111In]-polatuzumab Ab, either as tracer alone or tracer plus unlabelled materials.
The ratio of radioactivity from the residualized [111In] to the non-residualized [125I] increased over time in several highly perfused tissues such as liver, kidney, spleen, adrenal gland, lymph node, and ovaries in all groups, suggesting that polatuzumab vedotin and the polatuzumab antibody underwent catabolism in these tissues.

Tissue distribution of polatuzumab vedotin in rats using radiolabelled MMAE moiety [14-2852]

In this study, tissue distribution of polatuzumab vedotin was investigated following a single IV dose of 10 mg/kg (150 µCi/kg) polatuzumab vedotin-[3H]-MMAE in SD rats (15 F/group). Blood and various tissues were collected at multiple intervals up to 14 days post-dose.

Radioactivity was detected in various tissues, mostly in highly perfused tissues including liver, lungs, heart, kidneys, spleen, adrenal gland, ovaries, and bone marrow at levels lower than that in the corresponding blood samples. The radioactivity level was highest at 1 hour post-dose in highly perfused

tissues, while radioactivity levels in other tissues (such as eyes, skin, and muscle) peaked at 1 day post-dose. Radioactivity decreased in parallel to the decrease of blood radioactivity over time and no persistency was observed in any tissues examined. There was little radioactivity detected in the brain and nerves (sciatic nerve and dorsal root ganglia) over the entire study period.

Acetonitrile (ACN) extraction of tissue homogenates showed a time-dependent increase in the relative ACN-soluble fractions ranging from 6.11% - 60.5% at 1 hour post-dose to 12.3%-96.3% at 14 days post-dose across the different tissues. These data indicate that the ADC underwent various levels of catabolism in tissues.

Distribution of MMAE

Tissue distribution of MMAE in rats [12-2085]

Tissue distribution of MMAE was characterised in SD rats following a single IV injection of [3H]-MMAE at 80 µCi/kg (mixed with unlabelled MMAE resulting in 0.2 mg/kg). Various tissues were collected at multiple intervals and evaluated for radioactivity up to 6 days post-dose.

Following IV administration, radioactivity levels in whole blood decreased rapidly. After 2 minutes the level in whole blood was only 0.272% ± 0.0667% ID/ml (0.109 ± 0.0267 µg-Eq/mL). The level further decreased to 0.0668% ± 0.00605% ID/mL at 10 minutes post-dose. At the same time, [3H]-MMAE showed a rapid distribution to various tissues. By 10 minutes post-dose, MMAE radioactivity was markedly detected in highly perfused tissues such as liver, lungs, and kidneys (greater than 1% ID/g), and to a lesser extent in other tissues. No persistency was observed over the 6 day study period in any tissue examined.

Plasma protein binding of MMAE *in vitro* [14-0296]

Plasma protein binding of MMAE was determined in plasma from humans, rat and *Cynomolgus* monkeys. To this end, MMAE (1 – 1000 nM) or control (5 µM) was spiked into plasma and incubated at 37°C for 4 hrs in a rapid equilibrium dialysis device. After incubation, dialysate and plasma retentate were analysed by LC-MS/MS. The mean plasma protein binding of MMAE was 70.6%−76.7% in human plasma, 87.5%−90.8% in rat, and 61.4%−69.2% in *Cynomolgus* plasma. Protein-binding in plasma was independent of the MMAE concentration.

Red blood cell partitioning *in vitro* [14-0271]

The RBC partitioning potential of MMAE was assessed in human and animal blood using [3H]-MMAE at concentrations ranging from 2 to 5000 nM *in vitro*. The ratio of the amount of radioactivity in whole blood to the amount in plasma (B/P ratio) was calculated. The results show that MMAE does not significantly partition into human RBCs at all concentrations tested *in vitro* (B/P ratio 1.34 to 1.65). In contrast, MMAE showed significant RBC partitioning in non-clinical species. B/P ratios were approximately 20 in mice, approximately 4 in rats, and approximately 3 in cynomolgus monkeys at concentrations of 2, 20, and 200 nM. At higher concentrations (1000 and 5000 nM) MMAE showed less partitioning, likely due to saturation. Therefore, MMAE RBC partitioning is species-dependent, with strong partitioning in mice, rats, and *Cynomolgus* monkeys, but not in humans.

Metabolism

Catabolism of polatuzumab vedotin in vivo

Catabolite profile of polatuzumab vedotin-[^{3}H]-MMAE in rats [14-2852]

The *in vivo* catabolism of polatuzumab vedotin was investigated following a single IV dose of 10 mg/kg (150 µCi/kg) polatuzumab vedotin-[3H]-MMAE in SD rats (15 F/group). Plasma, various tissues, urine, and bile were collected between 1 hour and 14 days post-dose. Polatuzumab vedotin and its potential

catabolites were analysed using ACN-precipitation, which separates protein-bound (ACN-precipitable) species from low-molecular-weight [3H]-containing species (ACN-soluble radioactivity), followed by liquid scintillation counting.

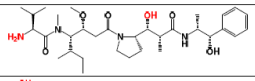
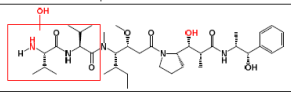
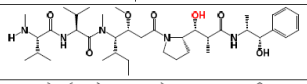
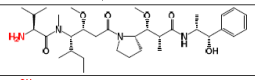
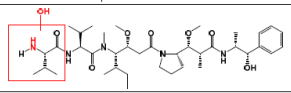
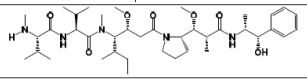
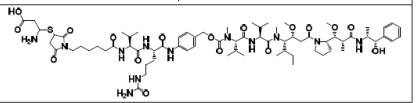
Radioactivity in blood was eliminated in a biphasic manner. The majority (72.7%-98.6%) of radioactivity in blood was associated with the plasma and a minor amount (1.03%-27.1%) was in the cell pellet. Nearly all radioactivity (> 99%) in the plasma was ACN-precipitable with a small amount in the ACN-soluble fraction, suggesting that polatuzumab vedotin was the major species in circulation. Radioactivity appeared in urine and feces within the first day post-dose. The level of radioactivity in feces (mostly ACN-soluble form) increased rapidly over the first 2-3 days and a smaller amount was eliminated daily until end of the study. In contrast, only a small amount of radioactivity (mostly ACN-soluble form) was detected in urine over the whole study period.

Plasma, bile (collected from bile duct-cannulated [BDC] rats in Study 14-2851), and urine samples were further analysed for catabolite profile and identification; the results are reported in Study 16-2563.

Catabolite profile of polatuzumab vedotin-[^{3}H]-MMAE in plasma, urine and bile [16-2563]

The catabolism of polatuzumab vedotin in SD rats was further characterised. Plasma, urine and bile samples were analysed by radio-profile and LC mass spectrometry to characterise the catabolite profile and to identify the catabolites. The major catabolites of polatuzumab vedotin identified in rats (see Table 3-17) were unconjugated MMAE (in all three matrices, representing 2.56% of dose in urine and 16.5% of dose in bile), O-demethylated MMAE (representing 13.5% of dose in bile), and metabolites resulting from amide hydrolysis and N-demethylation with hydroxylation (representing 12.2% of dose in bile).

Table 11. MMAE-related metabolites in rat urine and bile following a single IV dose of Polatuzumab Vedotin-[3H]-MMAE (Study 16-2563)

Catabolite	Mass (Da)	Retention Time (min)	% Dosed (Urine)	% Dosed (Bile)	% Dosed (Urine + Bile)	Matrix	Structure
C1	NA	5.3	2.26	NA	2.26	Urine	Unknown
C2: Amide hydrolysis + *O*-demethylation	590.40	14.9	NA	3.94	3.94	Bile	
C3: *O*-, *N*-demethylation + OH	705.47	16.8	NA	9.32	9.32	Bile	
C4: *O*-demethylation (-CH3)	703.48	18.5	NA	13.49	13.49	Bile	
C5: Amide hydrolysis	604.42	19.5 [a]	NA	12.16 [b]	12.16 [b]	Bile	
C6: *N*-demethylation + hydroxylation	719.48		NA			Bile	
C7: MMAE	717.50	21.6	2.56	16.48	19.04	Plasma, Urine, Bile	
C8: Cys-vc-MMAE	1436.79	34.3	NA	2.60	2.60	Bile	

MMAE = monomethyl auristatin E; NA = not applicable.

[a] Catabolites C5 and C6 share the same retention time.

[b] Combined total % dose of catabolites C5 and C6.

Metabolism of MMAE

In vivo metabolic profiles and identity of MMAE metabolites were determined in plasma and bile of SD rats after a single IV administration of [3H]-MMAE. The amount of MMAE in this study (0.2 mg/kg) equates approximately the amount of MMAE delivered with a polatuzumab vedotin dose of 10 mg/kg. MMAE was rapidly cleared from the plasma. Radioactivity was detected in bile within hours post-dose and cumulative

radioactivity increased steadily over the first 24 hours post-dose. The radio-chromatogram of the bile samples using RP-HPLC analysis showed a main peak corresponding to [3H]-MMAE which accounted for a large part of the radioactivity detected in bile samples (62.9% of the 74.2% total dosed radioactivity recovered in the bile up to 6 hours post-dose). This result suggested that MMAE is the main component excreted into the bile while other metabolites were minor in the bile sample.
Further analysis of the bile samples using LC-MS/MS detection showed six metabolites of MMAE corresponding to M1 to M6 generated in the bile, which were the same metabolites (except for M2 and M6 only seen *in vivo*) identified from in vitro Study 14-0733. Therefore, MMAE does not appear to undergo extensive metabolism *in vivo* in rats. More than 60% of the dose was identified as intact MMAE in rat bile.

The intrinsic clearance of MMAE (1 to 1000 nM) in human, rat, and monkey liver microsomes (LM) and hepatocytes was determined and the major human cytochrome P450 (CYP) isoforms responsible for the metabolism of MMAE were identified. MMAE is not extensively metabolised in vitro, based on low to moderate CLhep in LM and hepatocytes from all species tested (for human LM = 10.1 -17.2 ml/min/kg, hepatocytes = 1.2-3.5 mL/min/kg; rat LM= 30.2-35.6 ml/min/kg, hepatocytes = 12.5-20.3 mL/min/kg, and *Cynomolgus* LM= 28.1-39.0 ml/min/kg, hepatocytes = 8.8-12.3 mL/min/kg). Reaction phenotype studies, using recombinant CYP enzymes or human liver microsomes in the presence of specific CYP inhibitors suggest that CYP3A4/5 is responsible for MMAE metabolism.

The metabolic profile of MMAE in rats, *Cynomolgus* monkeys and humans was determined**.** To this end MMAE (1µM) was incubated with cryopreserved hepatocytes and liver microsomes from the different species. Metabolites were identified and characterised based on LC separation and MS/MS fragmentation patterns. Fifteen MMAE metabolites were identified and characterized in rat, monkey, and human liver microsomes and hepatocytes. In both test systems (hepatocytes and liver microsomes), no human-specific metabolites were detected. All 15 metabolites were Phase I metabolites formed as the result of oxidation and/or hydrolysis with several sequential metabolites.

Excretion

The excretion of MMAE and polatuzumab vedotin was studied in rats using radio-labelled polatuzumab vedotin-[3H]-MMAE or [3H]-MMAE to non-cannulated rats (for feces and urine collection) and bile duct-cannulated rats (for bile collection).

Elimination route and mass balance of polatuzumab vedotin were determined following a single IV injection of 10 mg/kg polatuzumab vedotin-[3H]-MMAE in bile duct cannulated or non-cannulated rats. Excretion was followed over a period of 14 days.

Radioactivity appeared in urine and feces within the first day post-dose. Only a small amount of radioactivity was detected in urine over whole study period. The level of radioactivity in feces increased steadily over the first 2−3 days and in smaller amounts until the end of the study. Cumulatively, about 103%± 11.8% injected dose was eliminated in feces and 5.21%± 1.03% injected dose in urine over the 14-day study. In bile, radioactivity was detected within 2 hours post-dose and increased steadily over the first 4 days (50% of injected dose). Cumulatively approx. 70% of the injected dose radioactivity was eliminated in bile over the 14-day study. ACN precipitation showed that the vast majority (> 95%) of radioactivity detected in the bile was in the soluble fraction, indicating that polatuzumab vedotin-[3H]-MMAE is eliminated as catabolites.

The excretion route of MMAE was assessed following a single IV injection of [3H]-MMAE in bile duct cannulated or non-cannulated rats. The amount of MMAE administered (0.2 mg/kg) equates approximately the amount of MMAE delivered in a polatuzumab vedotin dose of 10 mg/kg. Excretion was followed over a period of 6 days.
Radioactivity was detected in urine and feces within hours post-dose. Cumulatively, 98.3% ± 6.00% ID was detected in feces while only a small amount of dosed radioactivity was detected in urine (8.61% ±

3.16% ID) by the end of the study. In bile, radioactivity was detected within hours post-dosing and increased steadily over the first 24 hours. Cumulatively, about 50% ID was eliminated in the bile during the first 3 hours, about 95% ID over the first day. By the end of the 6-day study, 103% ± 8.07% ID was recovered in the bile.

Pharmacokinetic drug interactions

CYP induction potential by MMAE in human hepatocytes [14-0732]

CYP induction was assessed using preparations of cryopreserved human hepatocytes; both mRNA levels and CYP activity for CYP1A2, CYP2B6, and CYP3A4/5 were used as markers for CYP induction. At concentrations up to 1 µM, MMAE did not induce CYP1A2, CYP2B6, and CYP3A4/5 activity. Instead, concentration-dependent decreases in CYP1A2, CYP2B6, and CYP3A4 (mRNA level and functional activity) were observed. This was unlikely due to cytotoxicity.

CYP inhibition by MMAE using human liver microsomes [XT085021]

The ability of MMAE (0.1 to 100 µM) to inhibit the major CYP enzymes (i.e. CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 [using two different substrates]) was assessed in human liver microsomes.

These studies showed that MMAE is a direct inhibitor of CYP3A4/5 with an IC50 value of 10 µM. MMAE is a time-dependent inhibitor of CYP3A4/5; an increase in inhibition was observed with pre-incubation. The MMAE inhibition kinetics of testosterone 6β-hydroxylation had a k_{inact} value of 0.10 min-1 and a KI value of 1.12 µM. MMAE formed a quasi-irreversible inhibitory complex with CYP3A4/5 as an increase in absorption from 380 to 520 nm was observed with a HLM sample.

MMAE interaction with drug transporters

Interaction of MMAE with human efflux transporter MDR1 [XT108004]

The interactions (substrate and inhibitor) of MMAE with human efflux transporter multidrug resistance (MDR) 1 were tested in the vesicular transport assay and Caco-2 model. The studies showed that MMAE is actively transported by MDR1 in the Caco-2 monolayer, but is not an inhibitor of MDR1-mediated digoxin transport.

Interaction of MMAE with human OATP1B1, OATP1B3, OCT1,OCT2, OAT1, OAT3, BCRP, BSEP, MRP2 Transporters [PDM-0008, PDM-0009, PDM-0010, PDM-0011, PDM-0012, 15-3234]

The interactions of MMAE with SLC uptake transporters (OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3) and ABC efflux transporters (BCRP, BSEP, MRP2) were assessed in vitro.

Based on the results from these studies, MMAE did not appear to be a substrate of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MRP2, and BCRP. MMAE did not inhibit (defined as inhibition < 20%) BCRP, BSEP, MRP2, OAT1, OAT3, OATP1B1, and OATP3B. However, at the highest applied concentration of 5 µM MMAE slightly inhibited OCT1 (29%) and OCT2 (23%).

2.3.4. Toxicology

Single dose toxicity

Single dose toxicity studies were performed in rats and *Cynomolgus* for the toxin moiety MMAE, but not for the antibody-drug-conjugates. A tabulated summary is provided below.

Table 12 Overview single-dose toxicity studies with MMAE:

Study ID	Species/ Sex/ Number per group	Route / MMAE Dose (mg/kg)	Maximum tolerated dose (mg/kg)	Major findings
03-0202	SD rat / 6F	IV / 0, 0.206	0.206 mg/kg	- bone marrow toxicity, reversible - lymphoid organ toxicity, reversible
03-0315	SD rat / 6F	IV / 0, 0.516	Not determined	- Moribundity in all animals on study day 3 - Bone marrow toxicity, reversible - Liver toxicity, reversible - Lymphoid organ toxicity, reversible
SNBL-163.19	*Cynomolgus* / 1M / 1F	IV / 0.116	Not determined	- Mortality on Study 28 in 1 M due to bone marrow toxicity with localized opportunistic infection in the lung - Bone marrow toxicity, reversible in 1 F
07-0609 (GLP)	*Cynomolgus* / 5M/ 5F	IV / 0, 0.03, 0.063	0.030	- Mortality on Study Day 9 in 1 M given 0.063 mg/kg; attributed to bone marrow toxicity - Bone marrow toxicity, reversible - Lymphoid organ toxicity, reversible

For all studies: Bone marrow toxicity was characterized by contributions of decreased peripheral platelet, red and/or white blood cell parameters, and decreased bone marrow cellularity. Lymphoid organ toxicity was characterized by decreased lymphoid cellularity in the thymus and/or spleen.
In rats: Liver toxicity was characterized by elevated peripheral liver indices and hepatocellular apoptosis, necrosis, and increased mitosis.

Repeat dose toxicity

Repeat-dose toxicity studies with MMAE

Table 13: Overview repeated-dose toxicity studies with MMAE

Study ID	Species/ Sex/Number/ Group	Dose (mg/kg) /Route	Duration	NOAEL (mg/kg)	Major findings
7646-118 (GLP)	SD rat / M+F / 15 per sex main 10 per sex TK	IV / 0, 0.0097, 0.097 0.194	QW x4 (Day 1, 8, 15, 22)	NOAEL= 0.097 HNSTD = 0.194	- bone marrow toxicity, dose-dependent, reversible - liver toxicity, reversible - testes toxicity; dose dependent, **non**-reversible during 4-week recovery
SNBL-163.19	*cynomolgus* / 1M / 1F	IV / 0.058	Q3W x2 (Day 1, 22)		- bone marrow toxicity, reversible
SNBL-163.16 (GLP)	*cynomolgus* / M+F / 5 – 6 per sex1M /	IV / 0.058	Q3W x4 (Day 1, 22, 43, 64)		- bone marrow toxicity, reversible - lymphoid organ toxicity, reversible

For all studies: Bone marrow toxicity was characterized by contributions of decreased peripheral platelet, red and/or white blood cell parameters, and decreased bone marrow cellularity. Lymphoid organ toxicity was characterized by decreased lymphoid cellularity in the thymus and/or spleen.
In rats: Liver toxicity was characterized by elevated peripheral liver indices and hepatocellular apoptosis, necrosis, and increased mitosis. Testes toxicity was characterized by seminiferous tubule degeneration and decreased spermatogenesis.

4-week repeat-dose IV toxicity study of MMAE in rats [study 7646-118, GLP]

In this dose-range finding study rats were treated once weekly for 4 weeks with vehicle, MMAE (0.0097, 0.097, 0.194 mg/kg). Additional study arms included administration of brentuximab vedotin or brentuximab Ab, which are not discussed here. Animals were necropsied 4 and 29 days after the last dose. Morbidity and mortality, clinical signs, body weights, food consumption, ophthalmology, clinical pathology, TK, immunogenicity, organ weights, macroscopic and microscopic pathology were evaluated.

MMAE was tolerated at all doses without mortality. Test article-related findings were dose-dependent, toxicologically important effects occurred at the high dose level (0.194 mg/kg MMAE).

Once-weekly intravenous injection of MMAE for 4 weeks caused decreased body weights and food consumption. Clinical pathology findings were characterised by significantly reduced erythropoiesis resulting in non-regenerative anaemia and by hepatobiliary injury. These changes correlated with microscopic changes in bone marrow and liver. Effects on other parameters, such as leukocyte counts, platelet counts and serum proteins, were less severe.

Microscopic findings were seen in bone marrow (minimal – marked hypo-cellularity) and thymus (minimal to marked lymphoid depletion, correlating with reduced thymus weight) and testes (irreversible seminiferous tubule degeneration; Sertoli cell vacuolation; reduced spermatogenesis and epididymal aspermia, correlating with decreased weights of epididymides and testes). In addition, a slight increase in the incidence of foci of coagulative necrosis was observed in the liver of males in the high-dose group. After the 4-week recovery period, all test article-related findings had reversed/were reversing except for the testicular toxicity, which was non-reversible.

Based on these results, the no-observable-adverse-effect level (NOAEL) of MMAE was 0.097 mg/kg/dose.

Repeat-dose IV toxicity study of MMAE in *Cynomolgus* [study SNBL.163.19]

In the repeated-dose arm of this study *Cynomolgus* monkeys (1/sex/group) received MMAE at 0.058 mg/kg, Q3W x2. Animals were observed for a period of 28 after the second dose. Assessment of tolerability was based on mortality, clinical signs, body weight, clinical pathology and macroscopic pathology (for premature decedents only). There was no terminal necropsy.

Repeat administration MMAE at 0.058 mg/kg to two *Cynomolgus* monkeys was well tolerated, with mild clinical observations and changes in clinical pathology parameters (red and white blood cell parameters, albumin, and AST).

11-week repeat-dose IV study of MMAE in *Cynomolgus* monkeys [SNBL.163.16, GLP]

In this study, *Cynomolgus* monkeys (3-8/sex/group) were treated with MMAE at 0 or 0.058 mg/kg, Q3W x4 (or with brentuximab vedotin, not discussed here). Animals were necropsied 1 and 5 weeks after the last dose. Morbidity and mortality, clinical signs, food consumption, body weights, cardiovascular parameters, ophthalmology, haematology, immunophenotyping, coagulation, serum chemistry, urinalysis, macroscopic and microscopic pathology, organ weight, TK and immunogenicity were evaluated.

No mortality was observed in MMAE-treated animals. There were no MMAE-related effects on body weight, blood pressure, heart rate, respiration, body temperature, ophthalmology, electro-cardiology, coagulation and urinalysis. Also clinical chemistry test results were relatively unaffected.

The primary response to MMAE was moderate to marked myelotoxicity. Animals showed decreases in most haematopoietic cell components of the bone marrow and had leukopenia with severe neutropenia 1 and 2 weeks post-dose. The haematological changes correlated with reduced thymus weight and histopathology findings of bone marrow hypo-cellularity and lymphoid depletion in thymus and spleen. In addition, some responses considered secondary were manifested, included mild changes in serum chemistry parameters. All responses were completely reversible following the 5-week recovery period.

Repeat-dose toxicity with the polatuzumab vedotin or the surrogate ADC

Table 14: Overview of repeat-dose toxicity studies with ADC

Study ID	Species/ Sex/Number/ Group	Test article / Dose (mg/kg) /Route	Duration	SDT10 / HNSTD	Major findings
10-0898 (GLP)	SD rat / M+F / 15 per sex main 9-10 per sex TK	polatuzumab vedotin IV / 0, 2, 6, 10	QW x4 (Day 1, 8, 15, 22)	SDT10 = 10 mg/kg	- moribundity in 1 M @ 10 mg/kg on day 31, due to BM toxicity - bone marrow toxicity, dose-dependent, reversible - liver toxicity, dose-dependent, reversible - lymphoid organ toxicity dose-dependent, reversible - testes toxicity; dose dependent, **non**-reversible
10-0044 (GLP)	*Cynomolgus* / M+F / 5 per sex	polatuzumab vedotin IV / 0, 1, 3, 5 surrogate ADC IV / 0, 3, 5	Q3W x4 (Day 1, 22, 43, 64)	Surrogate ADC HNSTD = 3 mg/kg	polatuzumab vedotin - Bone marrow toxicity, dose-dependent, reversible surrogate ADC - moribundity in 1 M on day 53 due to BM toxicity with systemic opportunistic infection - Bone marrow toxicity, dose-dependent, reversible - B cell depletion in periphery and lymphoid tissue

For all studies: Bone marrow toxicity was characterized by contributions of decreased peripheral platelet, red and/or white blood cell parameters, and decreased bone marrow cellularity. Lymphoid organ toxicity was characterized by decreased lymphoid cellularity in the thymus and/or spleen.
In rats: Liver toxicity was characterized by elevated peripheral liver indices and hepatocellular apoptosis, necrosis, and increased mitosis. Testes toxicity was characterized by seminiferous tubule degeneration and decreased spermatogenesis.

Genotoxicity

The genotoxic potential of MMAE was evaluated in 2 in vitro assays (bacterial reverse mutation, and L5178Y TK+/- mouse lymphoma forward mutation assay) and *in vivo* in a rat bone marrow micronucleus assay.

Table 15: Overview of genotoxicity studies with MMAE

Type of test/ study ID/GLP	Test system	Concentration range/ Metabolising system	Results Positive/negative/equivocal
Gene mutations in bacteria / A66EH.503.BTL / GLP	*S. typhimurium* TA98, TA100, TA1453, TA1537 *E. coli* WP2 uvrA	0.25 – 5000 µg/plate +/- S9	no genotoxicity
Gene mutations in mammalian cells / 8204155 / GLP	Mouse lymphoma L5178Y $TK^{+/-}$	0.05 – 100 ng/ml +S9 0.005 – 15 ng/ml –S9	no genotoxicity, but cytotoxic activity
Chromosomal aberrations *in vivo* / 8204151 / GLP	rat, micronuclei in bone marrow	Single dose IV, 0.01, 0.1, 0.2 mg/kg	increase in micro-nucleated PCE at 0.1 and 0.2 mg/kg, predominantly centromere-positive micronuclei (aneugenic mode of action) bone marrow cytotoxicity at 0.2 mg/kg, 48 hrs

PCE = polychromatic erythrocytes

Carcinogenicity

No Carcinogenicity studies have been submitted (see discussion on non-clinical aspects).

Reproduction Toxicity

Dedicated reproductive and developmental toxicity studies with polatuzumab vedotin have not been performed. However, the embryo-fetal toxicity of MMAE was assessed in rats.

Table 16 Overview of embryofoetal-development studies

Study type/ Study ID / GLP	Species; Number	Test article	Dose (mg/kg)	Dosing period	Major findings	NOAEL (mg/kg)
EFD / 8204397 /GLP	SD rat, 25 F main + 9 TK / group	MMAE	0, 0.2	QW x2 (GD6 -13)	**for F0:** BW↓; haematological decrements; thymus lymphocytic depletion. abortion/resorption (1/24) for F1: live fetuses↓ low incidence of external variations and malformations	not determined

Dedicated fertility studies of polatuzumab vedotin have not been performed (see discussion on Non-clinical aspects).

Following treatment with MMAE external malformations were observed and consisted of protruding tongue, malrotated hindlimbs, gastroschisis, and agnathia. The observed skeletal variations and

malformations as well as soft tissue malformation were considered unrelated to treatment due to the low fetal and litter incidence of the findings. Maternal exposure of MMAE on GD13 was measured to be as follows: Cmax = 50.2 ng/ml, AUClast = 25.6 ng*day/ml. On GD 18, MMAE concentrations in maternal serum were below LoQ; however, MMAE was detected in amniotic fluid or foetal serum for some fetuses, indicating that MMAE crossed the placenta.

No dedicated pre- and postnatal development studies have been conducted (see discussion on Non-Clinical aspects).

Toxicokinetic data

See under PK section - Absorption

Local Tolerance

Dedicated local tolerance studies were not conducted. Injection sites were evaluated as part of the repeated-dose toxicity studies with polatuzumab vedotin, the surrogate ADC and MMAE. There were no test-article-related findings at the injection sites.

Other toxicity studies

Development of ADA against polatuzumab vedotin and the surrogate ADC was evaluated as part of the toxicity studies in *Cynomolgus* monkeys. ADA incidence was 67% after a single dose of the surrogate ADC, 20% in *Cynomolgus* given repeat doses of the surrogate ADC; and 43% in *Cynomolgus* given repeat-doses of polatuzumab vedotin. Importantly, ADA did not appear to impact the PK/TK of total antibody and unconjugated MMAE exposures.

Specific immunotoxicity studies have not been performed (See discussion on non-clinical aspects).

Studies on impurities have not been performed. A risk assessment addressing process-related impurities from the conjugation process of vcMMAE to the Ab moiety is discussed under the quality section.

Phototoxicity

Study TRN-2926-A evaluated the absorption spectra of MMAE and vc-MMAE. For vc-MMAE, the evaluated wavelength range was 290 and 700 nmM with maximal absorption at 290 nm; the molar extinction coefficient at 290 nm was 700 M-1cm-1 for vc-MMAE. MMAE was evaluated in a range of 190 to 900 nm, the wavelength of maximum absorption was 203 nm. However, MMAE did not have any measured absorbance at 290 nm, so the molar extinction coefficient at this wavelength is zero.

Considering the lack of absorption of light within range of natural sunlight (290 – 700 nm) by MMAE and vc-MMAE, dedicated phototoxicity studies were not performed

Tissue cross-reactivity of polatuzumab vedotin with human tissue [study 10-0711, GLP]

The aim of this study was to evaluate the cross-reactivity of polatuzumab vedotin with a panel of human tissues. To this end, cryosections of human tissues were stained with polatuzumab vedotin (at 2.5 µg/ml or 12.5 µg/ml) or control human IgG1 (without MMAE); binding was detected using a biotinylated anti-MMAE secondary antibody and avidin-peroxidase and the peroxidase substrate DAB.

Polatuzumab vedotin-specific staining was observed in multiple human tissues at both concentrations; in general the staining intensity was greater at the higher concentration. Polatuzumab vedotin specific staining consisted of cytoplasmic staining of lymphocytes, especially those in B-cell areas, in lymph nodes, spleen, tonsil, and the gastrointestinal-associated lymphoid tissue (GALT) in stomach, colon and

gastrointestinal tract. Scattered positively staining lymphocytes were present in some sections of other tissues such as urinary bladder, bone marrow, breast, fallopian tube, and prostate.

Specific, non-target staining was observed in the placenta and possibly the central nervous system. In the placental villus stroma, cytoplasmic staining was observed at both antibody concentrations in some elongated cells that may be Hofbauer cells. In the central nervous system, staining of the cytoplasmic processes of some glial cells was observed in the white matter of the spinal cord, cerebellum, cerebral cortex, and the pars nervosa of the pituitary at 12.5 µg/ml but not at 2.5 µg/ml. Staining with polatuzumab vedotin thought to represent non-specific background staining was present in epithelial cells in 1 adrenal and 1 parathyroid. Furthermore, in the bone marrow, colon, gastrointestinal tract, and lymph nodes, scattered inflammatory cells had cytoplasmic staining in all sections, including antibody controls.

2.3.5. Ecotoxicity/environmental risk assessment

Table 1. Summary of main study results

Substance (INN/Invented Name): Polatuzumab vedotin					
CAS-number (if available): 1313206-42-6					
PBT-screening: The active ingredient is composed of an antibody linked to on average 3.5 molecules of vcMMAE (consisting of a peptide linker and the substance monomethylauristatin E) and is due to its mostly protein nature not amenable to determination of log K_{ow}					
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.445	ng/L			> 0.01 threshold (N)
Other concerns (e.g. chemical class)					(N)
Existing environmentally relevant information: Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Ready Biodegradability Test	OECD 301 F	77% (d 28), 10d window met			readily biodegradable
Existing environmentally relevant information: Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Desmodesmus subspicatus*	OECD 201	NOEC	≥100000	µg/L	No analytical verification of test substance concentration
Daphnia magna. Acute Toxicity Test	OECD 202	NOEC	≥100000	µg/L	No analytical verification of test substance concentration
Substance (INN/Invented Name): vcMMAE					
CAS-number (if available): 646502-53-6					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD117	log Dow (pH 5) = 2.45 log Dow (pH 7) = 2.35 log Dow (pH 9) = 2.42			Potential PBT (N)
A PBT-assessment is not required					
Existing environmentally relevant information: Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**

Inherent Biodegradability Test	OECD 302 C	13% (d 28)			not inherently biodegradable, formation of at least 1 transformation product (TP) observed, TP not identified, TP potentially more toxic than vcMMAE
Existing environmentally relevant information: Effect studies					
Study type	**Test protocol**	**End-point**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Desmodesmus subspicatus*	OECD 201	NOEC	230	µg/L	
Daphnia sp. Reproduction Test	OECD 211	NOEC	10	µg/L	Toxicity of transformation product
Daphnia magna. Acute Toxicity Test	OECD 202	EC_{50}	4100	µg/L	Toxicity of transformation product
Acute Fisch Toxicity Test/*Danio rerio*	OECD 203	NOEC	≥43800	µg/L	Toxicity of transformation product
Substance (INN/Invented Name): MMAE					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD117	log Dow (pH 5) = -0.07 log Dow (pH 7) = 1.17 log Dow (pH 9) = 1.97			Potential PBT (N)
A PBT-assessment is not required					

The PEC surfacewater is below the action limit of 0.01 µg/L and neither polatuzumab vedotin nor vcMMAE nor MMAE are considered to be PBT substances as log Dow values are below 4.5. Considering the above data polatuzumab vedotin is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

The non-clinical development program for polatuzumab vedotin was designed in accordance with ICH S9 guideline, regarding the treatment of patients with advanced cancer and is considered sufficient to

support the application in the claimed indication. Evaluation of pharmacology, pharmacokinetics, and toxicology of polatuzumab vedotin has been conducted *in vitro* and i*n vivo*. Non-clinical aspects of the development programme were addressed in EMA scientific advices (June 2014, January 2018). The advice has been considered and followed as appropriate.

The pharmacological profile of polatuzumab vedotin was demonstrated in *in vitro* assays and *in vivo* DLBCL model xenografted in rodents. The proof of concept was successfully demonstrated, an anti tumor efficacy was shown both as monotherapy or combination with rituximab and bendamustine. Results from both *in vitro* and *in vivo* studies support the clinical efficacy of polatuzumab vedotin treatment in CD79b tumors.

The pharmacodynamics studies demonstrate anti-proliferative effects of polatuzumab as monotherapy or in combination with rituximab and bendamustine.

Absorption, distribution, metabolism and excretion of polatuzumab vedotin, surrogate ADC and unconjugated MMAE have been thoroughly evaluated following intravenous administration in mice, rats, and *Cynomolgus* monkeys, species used for pharmacology and toxicology studies. Studies were performed to characterise the distribution, metabolism and excretion of the different components of polatuzumab vedotin.

Following a single 5 mg/kg IV administration of polatuzumab vedotin or the surrogate ADC in SCID mice, both PK profiles were characterized by a short distribution phase and a long elimination phase, as expected for monoclonal antibody-based therapeutics. The plasma CL of polatuzumab vedotin total antibody was 5.09 mL/kg/day with a half-life of the beta phase (t1/2,β) of 11.8 days. The plasma CL of the surrogate ADC total antibody was 6.99 mL/kg/day with a t1/2,β of 10.5 days. The overall PK profiles of total antibody were similar between the two ADCs. Also, the acMMAE plasma concentration-time profiles were also comparable between the two ADCs. The PK study in SCID mice assessed kinetics of the Ab-drug conjugates (polatuzumab vedotin and surrogate ADC) in comparison to their respective non-conjugated Abs. Overall, the pharmacokinetics of polatuzumab Ab and ADC as well as surrogate Ab and ADC were consistent with that of a monoclonal antibody, with low clearance, low volume of distribution and a long elimination half-life. When comparing polatuzumab vedotin and the surrogate ADC, overall PK profiles measured as total antibody and as acMMAE were comparable between the two ADCs. However, plasma concentrations of acMMAE decreased faster than the serum concentrations of total Ab, indicating some deconjugation of the ADC, even in the absence of target binding.

Results from the PK study in cynomolgus after administration surrogate ADC and Ab are consistent with the findings in mice. Cmax was maximal immediately after administration in all treatment groups and was dose-proportional. Serum concentrations of total Ab declined bi-exponentially. Again, plasma concentrations of acMMAE declined faster than concentrations of total Ab, this correlated with an increase in free MMAE.

Upon repeated dosing of polatuzumab vedotin in rats and of polatuzumab vedotin and surrogate ADC in cynomolgus monkeys, exposure of total antibody and free MMAE was dose-dependent. After 4 once weekly dose administrations in rats, there was limited accumulation, while there was no accumulation after repeated administration (Q3W, x4) in cynomolgus monkeys. In monkeys, the total antibody exposure of polatuzumab vedotin was 1.2-1.4-fold higher than that of the surrogate ADC. This is likely due to the contribution of target-mediated clearance to the clearance of the surrogate ADC.

Upon administration of radio-labelled polatuzumab, radioactivity (irrespective of the label) was highest in blood and distributed slowly to tissues. In highly-perfused tissues (e.g. liver, lung, heart, kidneys, spleen), levels of radioactivity peaked around 1-2 hrs post dose; in other tissues at 1 day post-dose. Overall, tissue to blood ratio was lower in animals administered polatuzumab vedotin compared to animals administered free MMAE.

Plasma protein binding of MMAE in vitro was shown to be highest in rat, followed by human and cynomolgus plasma. Partitioning of MMAE to RBC was species-dependent, with strong partitioning in mice, moderate portioning in rats and cynomolgus, and low portioning in humans.

Non-clinical studies in rats revealed that the majority of MMAE is excreted in faeces, while only minimal elimination occurred through renal excretion. Based on mass balance, complete elimination was achieved in rats. In plasma, polatuzumab vedotin was the major species, and unconjugated MMAE was the only low molecular weight catabolite. Catabolites in urine were unconjugated MMAE and an unknown catabolite C1. In rat bile, the major catabolites of polatuzumab vedotin were unconjugated MMAE, O-demethylated MMAE and metabolites resulting from amide hydrolysis and N-demethylation with hydroxylation. Essentially the same metabolites were identified in bile of rats administered free MMAE. In vitro studies using hepatocytes and liver microsomes from rats, cynomolgus monkeys and humans identified 15 MMAE metabolites, none of them being human-specific. All metabolites were derived from phase I reactions. CYP3A4 and CYP3A5 were identified to be responsible for MMAE metabolism.

It is not known whether polatuzumab vedotin or its metabolites are excreted in human breast milk. A risk for breast-feeding infants cannot be excluded. Women should discontinue breast-feeding during treatment with Polivy.

Pharmacokinetic drug interactions were studied in vitro for different drug transporters and CYP isozymes. MMAE was shown to be a substrate for MDR1, but not a potent inhibitor. MMAE was not a CYP enzyme inducer or inhibitor, apart from CYP3A4/5. Irreversible, time-dependent CYP3A4/5 inhibition was shown. However, the observed inhibition constant is much greater than the mean MMAE Cmax observed in humans. Thus, MMAE is not expected to markedly alter the PK of medicines dependent on CYP3A4/5 metabolism.

The toxicological profile of polatuzumab vedotin has been evaluated during single and repeat-dose toxicity studies in rats and *Cynomolgus* monkeys using polatuzumab vedotin, surrogate ADC or unconjugated MMAE, genotoxicity studies, reproductive and developmental toxicity studies in rats and phototoxicity. No further non clinical studies are provided in accordance with ICH S9 guideline, which is endorsed.

In both rats and *Cynomolgus* monkeys, the predominant systemic toxicities associated with administration of MMAE and polatuzumab vedotin included reversible bone marrow toxicity and associated peripheral blood cell effects.

Toxicity of polatuzumab vedotin and MMAE observed in rats and *Cynomolgus* monkeys is consistent with the expected toxicity of a tubulin-binding agent, causing arrest of the cell cycle and apoptosis especially in rapidly dividing tissues. The main target organs are bone marrow, lymphoid organs, reproductive organs and liver with less severe effects on eye, skin and pancreas.

No dedicated mutagenicity studies have been performed with polatuzumab vedotin. MMAE was not mutagenic in the bacterial reverse mutation assay (Ames test) or the L5178Y mouse lymphoma forward mutation assay.

MMAE was genotoxic in the rat bone marrow micronucleus study probably through an aneugenic mechanism. This mechanism is consistent with the pharmacological effect of MMAE as a microtubule disrupting agent.

No dedicated carcinogenicity studies have been performed with polatuzumab vedotin and/or MMAE. Based on its mode of action as a microtubule inhibitor targeting rapidly dividing cells, polatuzumab vedotin is expected to be carcinogenic. In accordance with ICH S9, omission of carcinogenicity studies is acceptable.

No dedicated fertility studies in animals have been performed with polatuzumab vedotin. However, results of the 4-week rat toxicity study indicate the potential for polatuzumab vedotin to impair male reproductive function and fertility. Testicular seminiferous tubule degeneration did not reverse following a 6-week treatment-free period and correlated with decreased testes weight and gross findings at recovery necropsy of small and/or soft testes in males given ≥ 2 mg/kg.

No dedicated teratogenicity studies in animals have been performed with polatuzumab vedotin. However, treatment of pregnant rats with MMAE at 0.2 mg/kg caused embryolethality and foetal malformations (including protruding tongue, malrotated limbs, gastroschisis, and agnathia). Systemic exposure (AUC) in rats at a dose of 0.2 mg/kg MMAE is approximately 50% of the AUC in patients who received the recommended dose of 1.8 mg/kg Polivy every 21-days.

Treatment with polatuzumab vedotin is not compatible with pregnancy and possibly may bear a risk for infertility in males. Dedicated fertility studies of polatuzumab vedotin have not been performed. This is acceptable, in accordance with ICH S9. Furthermore, the repeat-dose toxicity study in rats indicates that polatuzumab vedotin may impair male reproductive function and fertility.

In nonclinical studies, polatuzumab vedotin has resulted in testicular toxicity, and may impair male reproductive function and fertility (see section 5.3).

Therefore, men being treated with this medicine are advised to have sperm samples preserved and stored before treatment. Men being treated with Polivy are advised not to father a child during treatment and for up to 6 months following the last dose. (See SmPC section 4.6 and 5.3 and RMP).

The ADME profiles of polatuzumab vedotin is well documented but some concerns regarding metabolism and excretion should be clarified. The toxicological program, designed in accordance with ICH S9 guideline, allowed to draw main target organs toxicities in rodent and non-rodent species dependent and independent of the antigen target.

The embryo-fetal toxicity of MMAE was assessed in rats. Based on its mode of action (microtubule inhibitor) MMAE is expected to be teratogenic and embryotoxic. Studies in animals have shown reproductive toxicity (see SmPC section 5.3).

Dedicated local tolerance studies were not conducted. Injection sites were evaluated as part of the repeated-dose toxicity studies with polatuzumab vedotin, the surrogate ADC and MMAE. There were no test-article-related findings at the injection sites.

Considering the ERA data polatuzumab vedotin is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical package available with polatuzumab vedotin, in line with ICH S9 guideline and is considered sufficient to support the marketing authorization for the proposed indication. The safety information is adequately reported in the SmPC and RMP.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 17 Clinical Studies Providing Data on the Efficacy of polatuzumab

Study ID	Endpoints	Design	Diagnosis	Posology	Subjs by arm entered/ compl. Number of Patients (Safety Analysis Population)	Duration Analysis / Data Cutoff	Gender M/F Median Age
Study Reports of Controlled Clinical Studies							
GO29365	PhIb: safety and tolerability PhII: Efficacy (IRC assessed PET CR by Lugano Classification for randomized cohort)	Open-label, multicenter, Phase Ib safety run-in; randomized Phase II (pola+BR vs. BR); Phase II single arm expansion (pola⍰BG), single-arm cohort (140 mg Lyo DP pola+BR)	R/R DLBCL (exclude transformed, CNS) ineligible for 2L or beyond SCT	Pola 1.8 mg/kg+BR q 21 days × 6 cycles Pola 1.8 mg/kg+BG q 21 days × 6 cycles BR q 21 days × 6 cycles	Safety run-in and Randomized: Pola+BR: N=45 Pola+BG: N=26 BR: N=39	Study ongoing Interim (pivotal) CSR based on CCOD from 30 April 2018 141 patients •67% (94/141) were treated from >3 months to ≤6 months •31% (43/141) were treated for ≤3 months	58% (82/141 patients) were male 55% (78/141) were ≥65.0 years of age
			R/R FL (grade 1+3a) -ineligible for autologous transplant	Pola 1.8 mg/kg+BR q 28 days x 6 cycles Pola 1.8 mg/kg+BG q 28 days x 6 cycles BR q 28 days x 6 cycles	Safety run-in and Expansion: Pola+BR: N=44 Pola+BG: N=26 BR: N=41		
GO29365 Arm G Lyo formulation	Primary PK, safety Secondary efficacy (CR, OR, BOR, DOR, PFS), ADA	Ph II, open-label, single arm	R/R DLBCL	pola (lyo 1.8 mg/kg, IV) + B (90 mg/m^2, IV) + R (375 mg/m^2, IV) q3w × 6 cycles	ca. 30 will be submitted within initial submission, planned 40	Study ongoing (Efficacy data not included in primary submission, 30 patients planned to be submitted during review)	
GO29365 Arm H Lyo formulation	Primary: PET-CR at PRA by IRC Secondary: Additional efficacy including OR at PRA, BOR and TTE endponts	Ph II, open-label, single arm	R/R DLBCL	pola (lyo 1.8 mg/kg, IV) + B (90 mg/m2, IV) + R (375 mg/m2, IV) q3w × 6 cycles	60 planned	(No data will be avalable within submission)	
Study Reports of Uncontrolled Clinical Studies							
GO27834	<u>Primary</u> Safety and tolerability, anti-tumor activity <u>Secondary</u> PK, efficacy, ATA, safety	Ph II, open-label, single arms, except for Arm A&B randomized (Pola + R or G)	R/R DLBCL, ineligible for auto-HSCT	Pola 1.8 mg/kg+G q 21 days × 8 cycles Pola 2.4 mg/kg+R q 21 days for up to 1 year or until PD or unacceptable toxicity	Pola 1.8 mg/kg+G: N=43 Pola 2.4 mg/kg+R: N=39	Study ongoing CSR based on primary analysis from 10 April 2017 104 patients Pola 1,8 mg/kg 54% (56/104) were treated from >3 months to ≤6 months 33% (34/104) were treated for ≤3 months 59 patients Pola 2,4 mg/kg 39% (23/59) were treated from >6 months to ≤12 months 31% (18/59) were treated for ≤3 months 25% (15/59) were treated from >3 months to ≤6 months	59% (61/104 patients) were male, 54% (56/104) were ≥65.0 years of age
			R/R FL (grades 1–3a)	Pola 1.8 mg/kg+R q 21 days for up to 1 year or until PD or unacceptable toxicity Pola 1.8 mg/kg+G q 21 days x 8 cycles Pola 2.4 mg/kg+R q 21 days for up to 1 year or until PD or unacceptable toxicity	Pola 1.8 mg/kg+R: N=20 Pola 1.8 mg/kg+G: N=41 Pola 2.4 mg/kg+G: N=20		

GO29044	Phase Ib: MTD of pola in combination with chemotherapy Phase II: Safety, efficacy	Open-label, multicenter, single arm Phase Ib/II (pola+R/G-CHP)	Dose escalation: newly diagnosed or R/R B-cell NHL (≤1 prior line of systemic therapy) Expansion: Previously untreated DLBCL with IPI 2–5	Pola 1.0–1.8 mg/kg+R CHP q 21 days × 6–8 cycles Pola 1.4-1.8 mg/kg+G CHP q 21 days x 6-8 cycles Pola 1.8 mg/kg+R-CHP q 21 days x 6-8 cycles Pola 1.8 mg/kg+G-CHP q 21 days x 6-8 cycles	Other B-cell NHL Pola 1.8 mg/kg+R CHP: N=1 Pola 1.8 mg/kg+G CHP: N=2 Pola 1.0 mg/kg+R CHP: N=1 Pola 1.4 mg/kg+G CHP: N=2 DLBCL Pola 1.8 mg/kg+R CHP: N=45 Pola 1.8 mg/kg+G CHP: N=21 Pola 1.0-1.4 mg/kg+R CHP: N=5 Pola 1.4 mg/kg+G CHP: N=4	Study ongoing CSR based on Primary analysis from 29 December 2017 69 patients pola 1,8 - 87% (60/69) were treated from >3 months to ≤6 months 12 Pts with Pola 1 – 1,4 mg/kg 92% (11/12) were treated from >3 months to ≤6 months	52% (42/81 patients) were male, 72% (58/81) were ≥65.0 years of age
DCS4968g	Safety, PK and tolerability, MTD, anti tumor activity	Open-label, multicenter, single arm Phase Ia/Ib dose escalation/ expansion (pola mono, pola+R)	B-cell NHL: iNHL (grade 1-3a FL, MZL, SLL), grade 3b FL, DLBCL, MCL, CLL with a clinical indication for treatment	Pola 0.1-2.4 mg/kg (monotherapy) until PD or unacceptable toxicity Pola 2.4 mg/kg+R until PD or unacceptable toxicity	Pola mono <1.8 mg/kg: N=30 Pola 1.8 mg/kg: N=11 (DLBCL: N=4) Pola 2.4 mg/kg: N=45 Pola 2.4 mg/kg+R: N=9	Study completed CSR based on final analysis from 26 February 2015 11 patients 1.8 mg/kg 46% (5/11) were treated for ≤3 months 36% (4/11) were treated from >3 months to ≤6 months 1.0-1.8 mg/kg 70% (21/30) were treated for ≤3 months 54 patients 2.4 mg/kg 39% (21/54) were treated for ≤3 months 30% (16/54) were treated from >3 months to ≤6 months 20% (11/54) were treated from >6 months to ≤12 months	71% (67/95 patients) were male, 63% (60/95) were ≥65.0 years of age

2.4.2. Pharmacokinetics

Absorption

Polatuzumab vedotin is intended to be solely administered via the IV route, therefore no data on absorption are available.

Distribution

Distribution of acMMAE appeared to be mainly restricted to the systemic circulation, since V_{ss} determined by NCA was similar to the physiological serum/plasma volume. Across the doses tested (from 0.1 to 2.4 mg/kg), mean V_{ss} values for acMMAE at cycle 1 ranged between 43.2 and 99.3 mL/kg. According to population PK analysis, the central volume V_1 and the peripheral volume V_2 of acMMAE were estimated to be 3.15 L and 3.98 L, respectively. The population estimate of central volume of distribution for acMMAE was 3.15 L, which approximated plasma volume. In vitro, MMAE is moderately bound (71% 77%) to human plasma proteins. MMAE does not significantly partition into human red blood cells in vitro; the blood to plasma ratio is 0.79 to 0.98.

Population PK estimates for the apparent distribution volumes of unconjugated MMAE gave: V_{MMAE} (apparent central volume) = 82.2 L and $V_{2,MMAE}$ = 200 L.

Elimination

With regard to elimination, PK of acMMAE was characterized by low CL and relatively long $T_{1/2}$. In the pivotal study GO29365, the average CL of acMMAE at cycle 1 ranged between 11.3-15.8 mL/day/kg and the average acMMAE terminal half-life at cycle 1 ranged between approximately 5-7 days. Population PK analysis using the integrated acMMAE-MMAE model 201 predicted that over the first cycle, 82.7% of the dose is eliminated by CL_{NS}. Over 6 cycles, 95.2% dose is eliminated by CL_{NS}. These results suggest the non-specific linear clearance (CL_{NS}) is the major clearance pathway after 1.8 mg/kg Q3W dosing, and that acMMAE PK is largely linear. CL_{NS} was estimated to be 1.01 Liter/day at time zero, 0.9 Liter/day at the end of Cycle 6, and 0.826 L/day at time of infinity. Over the first cycle, 15.2% of the dose is eliminated by CL_t, which becomes negligible at later cycles. The MM clearance pathway accounts for 2% of dose eliminated over Cycle 1 and over all 6 cycles, suggesting a minor role on the overall elimination. The median terminal half-life of acMMAE at Cycle 6 was estimated to be 12.2 days.

The average terminal half-life of unconjugated MMAE was 2.9 to 6.4 days. The delayed T_{max} (2 to 3 days after dosing) and the long $T_{1/2}$ suggest formation rate-limited kinetics of unconjugated MMAE due to ADC catabolism. In the population PK analysis, the apparent clearance for the linear pathway (CL_{MMAE}) of unconjugated MMAE, which is a ratio of systemic clearance to the actual fraction of formation, was estimated to be 1.89 Liter/hour.

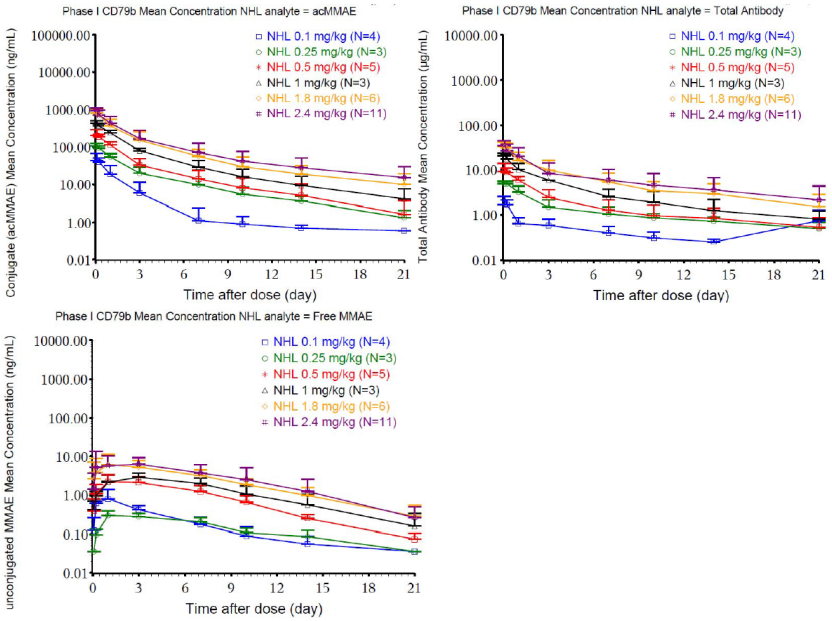
Classical monoclonal antibodies are not expected to be excreted by renal or hepatic pathways. As ADC, after uptake and lysosomal cleavage, polatuzumab vedotin however releases its payload MMAE, which is then eliminated via renal and hepatic pathways. Specific clinical excretion studies have not been conducted.

Dose proportionality and time dependencies

Study DCS4968g, a multicenter, open-label, dose-escalation Phase I study, mainly contributed to the dose proportionality assessment of polatuzumab vedotin. In this study, polatuzumab vedotin was administered as a single agent by IV infusion to patients with R/R haematologic malignancies on a 21-day cycle (Q3W) (0.1-2.4 mg/kg) dosing schedule.

After the first dose of polatuzumab vedotin, acMMAE, total antibody and unconjugated MMAE exposures (C_{max} and AUC_{inf}) increased approximately dose-proportionally over the 0.1 to 2.4 mg/kg polatuzumab vedotin dose range.

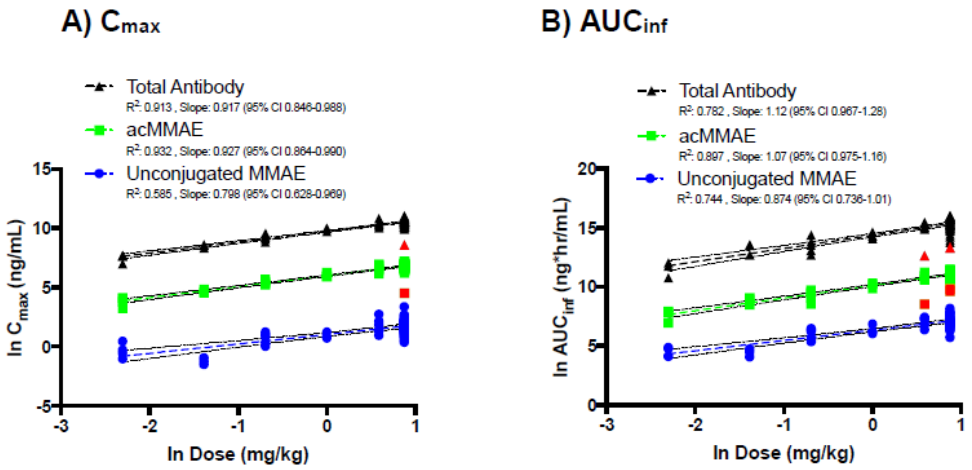
Mean (+ SD) Cycle 1Plasma Concentrations of acMMAE, TAb and unconjugated MMAE in NHL Patients - Dose Escalation Cohorts



Dose-proportionality was also suggested by the power coefficient of a power model of regression of Cycle 1 PK parameters by NCA (C_{max}, AUC_{inf}) versus Cycle 1 dose in patients with NHL. The power coefficient (95% CI) is 0.93 (0.86-0.99), 0.92 (0.85-0.99), and 0.80 (0.63-0.97) for C_{max} of acMMAE, total antibody, and unconjugated MMAE, 1.07 (0.98-1.2), 1.12 (0.97-1.3), and 0.87 (0.74-1.0) for AUC_{inf} of acMMAE, total antibody, and unconjugated MMAE. The 95% CI for these power coefficients were close to or including the value of 1.

Based on the same analysis, the correlation coefficient (R^2) of exposures with Cycle 1 dose suggested that the exposure of acMMAE and total antibody exposures (Cycle 1 C_{max} and AUC_{inf}) have an overall stronger correlation with dose compared to the correlation of unconjugated MMAE with dose, which is weaker. Across 0.1 to 2.4 mg/kg doses, the R^2 with dose for C_{max} and AUC_{inf} is 0.932 and 0.897 for acMMAE, 0.913 and 0.782 for total antibody, and 0.585 and 0.744 for unconjugated MMAE respectively. This is consistent with unconjugated MMAE as a catabolite of the conjugate.

Study DCS4968g: Dose Proportionality Assessment of Polatuzumab Vedotin in Patients with NHL Receiving a Single IV Administration of 0.1-2.4 mg/kg of Polatuzumab Vedotin within Cycle 1



ac= antibody-conjugated; AUC_{inf}=area under the concentration-time curve extrapolating to infinity; C_{max}=maximum concentration; IV=intravenous; MMAE=monomethyl auristatin E.

Note: Observations in red indicate statistical outliers. The y-axis is the natural log transformation of C_{max} and AUC_{inf} for each analyte.

Source: DCS4968g CSR t_pkpara_plasma_mmae, t_pkpara_serum_dcds4501a, t_pkpara_plasma_freemmae

Study DCS4968g: Dose Proportionality Assessment in Patients with NHL Receiving 0.1-2.4 mg/kg of Polatuzumab Vedotin

Analyte	No. of Patients	Parameter	Equation	R^2	Slope 95% CI
Total Antibody	65[a]	C_{max}	ln(y)= 9.743 + 0.9168ln(x)	0.913	0.846-0.988
	61[b]	AUC_{inf}	ln(y)= 14.36 + 1.122ln(x)	0.782	0.967-1.28
acMMAE	65[a]	C_{max}	ln(y)= 5.992 + 0.9271ln(x)	0.932	0.864 to 0.990
	61[c]	AUC_{inf}	ln(y)= 10.11 + 1.07ln(x)	0.897	0.975-1.16
Unconjugated MMAE	64	C_{max}	ln(y)= 1.031 +0.7983ln(x)	0.585	0.628-0.969
	57	AUC_{inf}	ln(y)= 6.323 +0.874ln(x)	0.744	0.736-1.01

In studies GO27834 and GO29044, dose proportional increases in exposure of acMMAE and unconjugated MMAE from 1.0 to 2.4 mg/kg were confirmed.

After the first 1.8 mg/kg polatuzumab vedotin dose, the acMMAE mean maximum concentration (C_{max}) was 803 (± 233) ng/mL and the area under the concentration-time curve from time zero to infinity (AUC_{inf}) was 1860 (±966) day•ng/mL. Based on the population PK analysis, Cycle 3 acMMAE AUC increased by approximately 30% over Cycle 1 AUC, and achieved more than 90% of the Cycle 6 AUC. The terminal half-life at Cycle 6 was approximately 12 days (95% CI of 8.1-19.5 days) for acMMAE. Based on population PK analysis, the predicted acMMAE concentration at the end of cycle 6 is approximately 80% of the theoretical steady-state value.

Exposures of unconjugated MMAE, the cytotoxic component of polatuzumab vedotin, increased dose proportionally over the 0.1 to 2.4 mg/kg polatuzumab vedotin dose range. MMAE plasma concentrations followed formation rate limited kinetics. After the first 1.8 mg/kg polatuzumab vedotin dose, the C_{max} was 6.82 (± 4.73) ng/mL, the time to maximum plasma concentration is approximately 2.5 days, and the terminal half-life is approximately 4 days. Plasma exposures of unconjugated MMAE are < 3% of acMMAE

exposures. Based on the population PK analysis there is a decrease of plasma unconjugated MMAE exposure (AUC) after repeated every-three-week dosing.

For unconjugated MMAE, similar findings of approximately dose-proportional behaviour were detected.

Time dependency

Mild increases of plasma acMMAE and serum total antibody pre-dose concentrations were observed with repeated Q3W dose. The average Cycle 4 day 1 pre-dose concentration was approximately 1.5 fold of the average concentration at Cycle 2 day 1 pre-dose for acMMAE and 2.4 fold for total antibody. No apparent increase of plasma trough concentrations of unconjugated MMAE after repeated Q3W dosing was identified.

In study GO29365, the average trough concentrations of acMMAE for DLBCL patients receiving Pola+BR or Pola+BG Q3W ranged between 13.6-17.0 ng/mL (Cycle 2 pre-dose) and increased to 20.4-26.7 ng/mL (Cycle 4 pre-dose).

Similar results with respect to time dependency were obtained through population PK analysis: The acMMAE AUC and C_{trough} increased with repeated Q3W dosing, potentially due to the decrease of acMMAE clearance with time after repeated dosing. The acMMAE Cycle 3 AUC and C_{trough} (i.e., Cycle 4 day 1 pre-dose) were approximately 1.3 and 1.8 fold of Cycle 1 AUC and C_{trough} (i.e., Cycle 2 day 1 pre-dose); the Cycle 6 values were approximately 1.4 and 2.2 fold of Cycle 1. There was no apparent increase in C_{max} values. In contrast, population PK analysis revealed a decrease of unconjugated MMAE AUC and C_{max} over repeated dosing, which was explained by a potential decrease of acMMAE clearance and decrease of fraction of formation of unconjugated MMAE from acMMAE with time.

Inter-individual variability

Inter-individual variability of PK parameters was relatively low and could be further reduced by accounting for all statistically significant covariates in the final integrated acMMAE-MMAE model (IIV of acMMAE CL_{INF} = 19.5% and V_1 = 12.2%). Higher variability was seen for unconjugated MMAE, which is plausible due to the fact that MMAE is a catabolite of acMMAE with significant variability in its formation and elimination.

PK in target population

Noncompartmental analyses

For the proposed Q3W dosing regimen of 1.8 mg/kg polatuzumab vedotin, similar exposure (C_{max} and AUC) of acMMAE and unconjugated MMAE was observed throughout the clinical studies DCS4968g, GO27834, GO29365 and GO29044. In cycle 1 of the pivotal study GO29635, C_{max} and AUC_{inf} of acMMAE were determined to be 622-738 ng/mL and 2180 – 2850 ng*day/mL, respectively. After repeated administration, C_{max} of acMMAE was similar to C_{max} seen following the first dose, average post-infusion concentrations of acMMAE were 694 – 841 ng/mL on Cycle 2 Day 1, and 671 – 820 ng/mL on Cycle 4 Day 1.

Study GO29365: Summary of Cycle 1 PK Parameters of Polatuzumab Vedotin Analytes in Patients with DLBCL or FL (from Safety Run-in Cohorts)

Conjugate (evaluated as acMMAE)						
Dose, Treatment, Histology	No. of patients	C_{max} (ng/mL)	AUC_{inf} (ng/mL)*day	$t_{1/2}$ (day)	V_{ss} (mL/kg)	CL (mL/kg/day)
1.8 (combination with BR) FL	6	676 (176)	2850 (360) [a]	7.14 (0.641) [a]	74.3 (15.7) [a]	11.3 (1.38) [a]
1.8 (combination with BR) DLBCL	6	634 (158)	2180 (532)	5.85 (1.06)	86.3 (27.4)	15.8 (4.87)
1.8 (combination with BG) FL	6	738 (165)	2720 (857) [b]	7.27 (1.09) [b]	82.1 (35.9) [b]	12.9 (4.63) [b]
1.8 (combination with BG) DLBCL	6	725 (104)	2680 (439)	5.36 (0.901)	66.0 (13.5)	12.2 (2.06)

Unconjugated MMAE				
Dose, Treatment, Histology	No. of patients	C_{max} (ng/mL)	AUC_{last} (ng/mL)*day	T_{max} (day)
1.8 (combination with BR) FL	6	3.31 (4.00)	20.1 (12.1)[b]	5.93 (0.0778-6.11)
1.8 (combination with BR) DLBCL	6	2.21 (1.34)	19.2 (10.8)	5.92 (4.86-7.16)
1.8 (combination with BG) FL	6	2.17 (1.08)	22.4 (11.1)[b]	5.93 (5.01-6.97)
1.8 (combination with BG) DLBCL	6	2.39 (0.492)	20.0 (3.62)	5.86 (4.96-7.02)

ac= antibody-conjugated; AUC_{inf} = area under the concentration-time curve extrapolating to infinity; AUC_{last} = area under the concentration-time curve from time zero to time of last measureable concentration; CL = clearance; C_{max} = peak serum/plasma concentration; DLBCL= diffuse large B-cell lymphoma; FL= follicular lymphoma; MMAE=monomethyl auristatin E; NHL=non-Hodgkin's lymphoma; $t_{1/2}$ = terminal half-life; t_{max}= time to reach maximum concentration; V_{ss} = volume of distribution at steady state.

[a]n=4, [b]n=5

Note: Data represent mean (SD) of pharmacokinetic-evaluable patients apart from T_{max} which is reported as median (min-max)

Source: GO29365 CSR t_pkc_polaac;t_pkp_polaac; t_pkc_polafree;t_pkp_polafree.

Throughout the pivotal and supportive clinical studies, T_{max} of unconjugated MMAE was determined to be 3 – 6 days. C_{max} of unconjugated MMAE after the first polatuzumab vedotin dosing at 1.8 mg/kg was significantly lower as compared to acMMAE (< 1 – 2%) and ranged between 2 – 6.8 ng/mL.

Population PK analysis

The PK exposures (assuming 1.8 mg/kg Q3W) based on individual empirical Bayes estimates (EBE) of PK parameters were simulated and summarized by mean (SD) for 460 patients.

The Cycle 3 acMMAE exposures reached the majority (>80%) of the Cycle 6 exposures, and the Cycle 6 exposures (the theoretically maximum acMMAE exposures for the proposed dosing regimen of up to 6 cycles) reached the majority (>80%) of the steady state exposures. The Cycle 3 acMMAE AUC, C_{max} and C_{trough} (i.e., Cycle 4 day 1 pre-dose) values are 91%, 99%, and 81% of Cycle 6 AUC, C_{max}, and C_{trough} (i.e., Cycle 6 day 21) values. The Cycle 6 acMMAE AUC, C_{max}, and C_{trough} values are 90%, 99%, and 80% of the model predicted steady-state AUC, C_{max}, and C_{trough} values (represented by the simulated value for the exposure during hypothetical Cycle 30 after repeated Q3W dosing, at which time the CL_{NS} approximated the value of time of infinity [CL_{INF}]).

For unconjugated MMAE, AUC and C_{max} values were the highest in Cycle 1 after which they were estimated to decline to 72% and 60% of the values of Cycle 1 at Cycle 3, and 69% and 56% of the values of Cycle 1 at Cycle.

Pharmacokinetic interaction studies

Impact of rituximab on the PK of polatuzumab vedotin-related analytes

A population PK analysis approach was used to assess the impact of rituximab combination on acMMAE and unconjugated MMAE PK. Rituximab combination is a statistically significant covariate for acMMAE CL_{INF} and k_{des} (rate constant of decay of CL_T with time), and for FRAC of unconjugated MMAE.

Simulation of Cycle 6 exposures (AUC, C_{max} of Cycle 6 by 1.8 mg/kg q3w) comparing the PK exposures for patients who received single-agent of polatuzumab vedotin (N=68) and for patients who received pola in combination with rituximab were performed (N=229). The acMMAE exposures (AUC and C_{max}) in patients received R combination were moderately higher (24% for AUC) than patients received single-agent, while unconjugated MMAE exposures are moderately lower (37% for AUC and 40% for C_{max}).

Table 18: Comparison of Covariate-Corrected Cycle 6 Exposures of acMMAE and Unconjugated MMAE* with or without Rituximab Administration

Exposure	Statistics	Monotherapy	Rituximab combination
	N	68	229
acMMAE AUC (ng*day/mL)	GM (CV%)	2350 (34%)	2910 (18%)
	GMR (90% CI)		1.24 (1.15-1.33)
acMMAE C_{max} (ng/mL)	GM (CV%)	696 (17%)	729 (15%)
	GMR (90% CI)		1.05 (1.01-1.09)
Unconjugated MMAE AUC (ng*day/mL)	GM (CV%)	33.2 (58%)	20.8 (49%)
	GMR (90% CI)		0.627 (0.551-0.713)
Unconjugated MMAE C_{max} (ng/mL)	GM (CV%)	3.22 (59%)	1.92 (43%)
	GMR (90% CI)		0.597 (0.525-0.679)

Impact of polatuzumab vedotin on the PK of rituximab

The observed concentrations at Cycle 1 30 minutes post-infusion, Cycle 2 pre-dose and Cycle 4 pre-dose were summarized for each study and compared. The observed exposures of rituximab are largely similar across these polatuzumab vedotin clinical studies in different histologies and in treatment naïve or R/R patients (maximum difference across arms less than 25%). For the DLBCL or FL patients in the randomized Phase II portion of the pivotal study GO29365, the rituximab exposures in the BR arm were similar to the pola+BR arm (less than 10% differences across time points). This suggested a low risk for polatuzumab vedotin to impact the PK of rituximab when given in combination.

Table 19: Comparison of Rituximab Exposure across Single- and Multiple-cycles when Administered at 375 mg/m2 in Combination with other Study Treatments

Study No.	Treatment Combination	Histology	N	Cycle 1 Post-infusion (µg/mL)	Cycle 2 Pre-dose (µg/mL)	Cycle 4 Pre-dose (µg/mL)
DCS4968g	R+ 2.4 mg/kg Pola	B-NHL	9	169 (82.0)	29.6 (27.5)[a]	58.5 (41.6)[b]
GO27834	R+2.4 mg/kg Pola	DLBCL	38	225 (75.1)	58.4 (39.2)[c]	92.1 (30.3)[d]
	R+2.4 mg/kg Pola	FL	18	203 (106)	50.2 (33.6)	88.2 (46.6)
	R+1.8mg/kg Pola	FL	19	225 (31.9)	42.8 (18.2)	82.0 (29.4)[e]
GO29365	R+Benda	DLBCL	33	183 (33.6)	40.7 (21.7)[f]	91.3 (37.7)[g]
	R+Benda+1.8 mg/kg Pola	DLBCL	34	191 (35.9)	42.9 (24.8)[h]	82.2 (32.8)[i]
	R+Benda	FL*	38	207 (50.1)	27.6 (14.7)[j]	67.6 (28.3)[j]
	R+Benda+1.8 mg/kg Pola	FL*	36	188 (49.2)[k]	27.7 (15.3)	71.4 (30.7)[j]
GO29044	R+CHP+1.8mg/kg Pola	DLBCL	28	173 (46.3)[d]	NA	70.2 (23.5)

In addition, the rituximab PK in these studies were pooled and analyzed by a population PK approach. A historical rituximab population PK model based on rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) or cyclophosphamide, vincristine and prednisone (CVP) in previously untreated FL patients in the historical study BO22334/SABRINA was used as a starting model. The model was refined to describe the rituximab PK data in the four polatuzumab vedotin studies (DCS4968g, GO27834, GO29044 and GO29365) with or without co-administration of polatuzumab vedotin. The final refined model adequately described rituximab PK in these patients.

Based on the covariate assessment, the polatuzumab vedotin combination was not a statistically significant covariate of rituximab PK parameters. Furthermore, the rituximab Cycle 8 exposures (AUC, C_{max}) computed based on individual EBE parameters were similar with or without the combination of polatuzumab vedotin, as indicated by difference of less than 10%. These results again supported a low risk of polatuzumab vedotin impacting rituximab PK when given in combination in this R/R DLBCL patient population.

Table 20 Comparison of Cycle 8 Rituximab Exposures Based on Individual Empirical Bayes Estimates of PK Parameters for Patients with and without Polatuzumab Vedotin Combination in Clinical Studies

Exposure	Statistics	R/R NHL patients without Polatuzumab vedotin combination	R/R NHL patients With Polatuzumab vedotin Combination
		N=79	N=160
AUC (µg*day/mL)	GM (CV%)	4060 (21%)	3780 (32%)
	GMR (90% CI)		0.932 (0.881-0.987)
C_{max} (µg/mL)	GM (CV%)	297 (18%)	290 (22%)
	GMR (90% CI)		0.975 (0.933-1.02)

Impact of bendamustine on the PK of polatuzumab vedotin-related analytes

Population PK approach was used to assess whether bendamustine impacts the PK of acMMAE and unconjugated MMAE after polatuzumab vedotin dosing to patients.

Simulation of Cycle 6 exposures (AUC, C_{max} of Cycle 6 by 1.8 mg/kg q3w) comparing the PK of patients without bendamustine combination (N=321) and patients with bendamustine combination (N=139) were performed.

Table 21 Comparison of covariate-corrected Cycle 6 exposures of acMMAE and unconjugated MMAE with or without bendamustine administration

Exposure	Statistics	Without bendamustine	With bendamustine
		N=321	N=139
acMMAE AUC (ng*day/mL)	GM (CV%)	2870 (22%)	3010 (16%)
	GMR (90% CI)		1.05 (1.02-1.08)
acMMAE C_{max} (ng/mL)	GM (CV%)	737 (16%)	728 (14%)
	GMR (90% CI)		0.987 (0.964-1.01)
Unconjugated MMAE AUC(ng*day/mL)	GM (CV%)	22.2 (52%)	19.1 (42%)
	GMR (90% CI)		0.862 (0.799-0.929)
Unconjugated MMAE C_{max} (ng/mL)	GM (CV%)	2.05 (47%)	1.77 (36%)
	GMR (90% CI)		0.864 (0.808-0.923)

Impact of polatuzumab vedotin on the PK of bendamustine

Table 22: Cycle 1 Plasma Pharmacokinetic Parameters of Bendamustine following IV Administration of 90 mg/m^2 Dose in Patients with R/R DLBCL or R/R FL

Treatment Arm	N	C_{max} (µg/mL)	AUC_{INF} (µg*hr/mL)	V_{ss} (L)	CL (L/hr)	$t_{1/2\lambda z}$ (hr)
Arm A (Pola+BR) FL	34	3.57 (2.06)	3.96 (2.41)[a]	45.5 (29.6)[c]	55.6 (30.8)[b]	0.551 (0.166)[a]
Arm B (BR) FL	34	3.21 (2.09)	3.38 (2.01)[e]	54.5 (38.0)[a]	63.1 (35.6)[d]	0.527 (0.191)[e]
Arm C (Pola+BR) DLBCL	33	4.23 (2.26)	4.45 (2.92)[b]	39.2 (21.9)[c]	50.1 (29.1)[c]	0.538 (0.210)[b]
Arm D (BR) DLBCL	30	3.85 (2.91)	4.68 (3.90)[c]	38.7 (21.5)[f]	62.7 (52.3)[c]	0.554 (0.196)[c]

Drug Interaction Risk Assessment with CYP3A Substrates, Strong CYP3A Inhibitors or Inducers

A physiologically based pharmacokinetic (PBPK) model was developed using a Simcyp population-based ADME simulator (Version 12) to predict the DDI risk for unconjugated MMAE after polatuzumab vedotin dosing as a perpetrator or a victim with coadministered drugs that are CYP substrates, inhibitors or inducers (PBPK report 1090612 and Chen et al. 2015). No dedicated clinical DDI studies with inducers or inhibitors of CYP3A have been conducted.

Table 23 Predicted DDI (AUC and Cmax ratios) of Unconjugated MMAE or Midazolam given Polatuzumab Vedotin (1.8 mg/kg) as a Perpetrator or Victim Based on the PBPK Model Simulations

PK Parameter	Simulated GMR (90% CI)
Unconjugated MMAE exposures after polatuzumab vedotin dosing with / without ketoconazole	
AUC	1.48 (1.44–1.51)[a]
C_{max}	1.18 (1.17–1.19)
Unconjugated MMAE exposures after polatuzumab vedotin dosing with / without rifampicin	
AUC	0.51 (0.49–0.53)[b]
C_{max}	0.71 (0.69–0.72)
Midazolam exposures with / without polatuzumab vedotin	
AUC	1.00[c]
C_{max}	1.00

Exposure relevant for safety

For evaluation of safety, the following exposure of unconjugated MMAE at the proposed dosing regimen of 1.8 mg/kg polatuzumab vedotin should be considered: C_{max} ranged between 2 – 6.8 ng/mL (C_{max} (predicted by population PK analysis) = 2.27 – 4.08 ng/mL and C_{max}x (NCA analysis) = 2 – 6.8 ng/mL). AUC was predicted by population PK analysis and ranged from 25.1 to 36.5 ng*day/mL. After the first administration of polatuzumab vedotin, AUC_{inf} was calculated to 52.3 ng*day/mL.

2.4.3. Pharmacodynamics

Mechanism of action

Polatuzumab vedotin is an ADC that contains a humanized IgG1 anti-CD79b monoclonal antibody (MCDS4409A) and a potent anti-mitotic agent (MMAE) linked through a protease-labile linker (mc-vc-PAB). Upon binding CD79b, polatuzumab vedotin is rapidly internalized and the conjugate MMAE is released by cleavage by lysosomal enzymes. MMAE then binds to tubulin and disrupts the microtubule network, resulting in inhibition of cell division and cell growth and induction of apoptosis.

Throughout the clinical studies, no specific pharmacodynamic endpoints were investigated.

Immunogenicity

The potential for polatuzumab vedotin to induce an undesirable immune response was assessed in the available data from Study GO29365 and 6 supportive studies (DCS4968g, GO27834, GO29044, GO29833, GO29834, and BO29561). Anti-drug antibodies (ADA) were assessed at pre-infusion of Cycles 1, 2, and 4, at treatment completion/early termination, and at follow-up (3, 6, 12, 18, 24 months) visits.

GO29365 Immunogenicity Results

In study GO29365, ADAs were detected post-baseline in 8 of 134 (6.0%) ADA evaluable patients treated with polatuzumab vedotin. All 8 patients had treatment-induced ADA (i.e. ADA negative at baseline or missing a baseline sample for ADA analysis and at least one positive post-baseline ADA result). Out of the 8 patients with treatment-induced ADA, 6 patients had a transient response and 2 patients had persistent responses. Titers ranged from <1.7 (the minimum reportable titer) to 2.71.

Incidence of Anti-Drug Antibodies to Polatuzumab Vedotin in Study GO29365

Disease histology	DLBCL				FL				All
Study Phase	Phase Ib	Phase II	Phase Ib	Phase II	Phase Ib	Phase II	Phase Ib	Phase II	Phase Ib/II
Cohort/Arm	1a	C	1b	F	1a	A	1b	E	
Treatment	Pola+BR		Pola+BG		Pola+BR		Pola+BG		all pola
Sample size	N = 6	N = 40	N = 6	N = 21	N = 6	N = 39	N = 6	N = 20	N = 144
Baseline Prevalence of ADAs									
Baseline evaluable patients	6	36	6	18	6	37	6	19	134
Patients with a positive sample at baseline	2 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (3.7%)
Patients with no positive samples at baseline	4	36	6	18	3	37	6	19	129
Post-Baseline Incidence of ADAs									
Post-baseline evaluable patients	6	35	6	18	6	38	6	19	134
Patients positive for ADA	2 (33.3%)	1 (2.9%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	3 (7.9%)	0 (0.0%)	1 (5.3%)	8 (6.0%)
Treatment-induced ADA	2	1	0	1	0	3	0	1	8
Treatment-enhanced ADA	0	0	0	0	0	0	0	0	0
Patients negative for ADA	4	34	6	17	6	35	6	18	126
Treatment unaffected	2	0	0	0	3	0	0	0	5

In this study, a total of 8 patients (4 DLBCL, 4 FL) developed ADAs. ADA positive status did not appear to impact efficacy: Of the 4 DLBCL patients, one a pola+BR patient (2101) developed ADAs during Cycle 2 and was assessed with progressive disease during the Cycle 3 Day 15 (C3D15) interim assessment. The other two pola+BR patients responded to treatment (2102, 4018). The final DLBCL patient (6012, pola+BG) had ADAs detected during Cycle 2, completed 6 cycles, and has an ongoing DOR of 21.1 months. Of the four FL patients who developed ADAs against polatuzumab vedotin, one pola+BR patient (3053) had ADAs detected during Cycle 2, had a partial response at C3D15 interim assessment, and progressive disease at PRA. The other 3 patients had ADAs detected at later timepoints and after completing 6 cycles. All three of these patients (3043, 5020, 3080) have ongoing responses at time of analysis.

GO29365 and Supportive Studies Immunogenicity Results

For all patients treated with polatuzumab vedotin, the baseline prevalence of ADAs was 2.4% (13 of 545 ADA evaluable patients). Post baseline, ADAs were detected in 14 of 536 (2.6%) ADA evaluable patients treated with polatuzumab vedotin. Out of the 14 patients positive for ADA, 13 patients had treatment-induced ADA and 1 was treatment-enhanced. Out of the 13 patients with treatment-induced ADA, 8 patients had a transient response and 5 patients had persistent responses. Out of the 13 patients who tested positive for ADA at baseline, 12 were treatment unaffected.

Impact of ADA on PK by Population PK Analysis

Population PK analysis was performed to assess the impact of ADA on the PK of acMMAE and unconjugated MMAE. Only 12 (2.6%) of 460 patients of the analysis dataset were ADA positive.

Based on the final model, simulation of Cycle 6 exposures (AUC, C_{max} of Cycle 6 by 1.8 mg/kg q3w) revealed that for the PK of ADA positive patients (N=12), the acMMAE exposures are similar to the ADA negative patients (<10% difference). The unconjugated MMAE exposures are moderately higher in ADA positive patients (10% for AUC, 24% for C_{max}), but the difference is not statistically significant as indicated by the GMRs of including 1. The magnitude of difference is much smaller compared to CV% of unconjugated MMAE of 44-58%.

Table 24: Comparison of Covariate-Corrected Exposures in ADA Positive and ADA Negative Patients

Exposure	Statistics	ADA negative	ADA positive
		N=410	N=12
acMMAE AUC (ng*day/mL)	GM (CV%)	2920 (21%)	2710 (29%)
	GMR (90% CI)		0.928 (0.798-1.08)
acMMAE C_{max} (ng/mL)	GM (CV%)	732 (15%)	786 (14%)
	GMR (90% CI)		1.07 (1-1.15)
Unconjugated MMAE AUC (ng*day/mL)	GM (CV%)	21 (49%)	23.1 (46%)
	GMR (90% CI)		1.1 (0.863-1.4)
Unconjugated MMAE C_{max} (ng/mL)	GM (CV%)	1.94 (44%)	2.42 (58%)
	GMR (90% CI)		1.24 (0.918-1.68)

Primary and Secondary pharmacology

Exposure-response analysis

Exposure-efficacy and exposure-safety analysis was performed. Only the R/R DLBCL patients were included for this analysis. Two separate analyses were performed. The first analysis was based on the pooled data of supportive studies DCS4968g and GO27834. The second analysis was based on the pivotal study GO29365 alone.

Table 25: Studies, Patients, PK Exposure Parameters and Dosing Regimens included in the Exposure-Response Analyses in R/R DLBCL Patients

E-R analysis	Analysis	Analyte	Exposure Measures	Study included	Arm included (dose)	N total (N by arm)	Endpoints
Exposure-Safety	Analysis based on supportive studies	acMMAE	AUC [1] C_{max} [1]	DCS4968g GO27834 [2]	Pola single agent (0.1-2.4 mg/kg) [3] Pola + R (2.4 mg/kg) Pola + G (1.8 mg/kg up to 8 cycles)	119 (36/40/43)	Grade ≥ 3 neutropenia, Grade ≥ 2 peripheral neuropathy (PN), Grade ≥ 3 infection and infestation, Grade ≥ 3 anemia, Grade ≥ 3 thrombocytopenia, Grade ≥ 3 diarrhea, Grade ≥ 3 AST increase (by lab), Grade ≥ 3 ALT increase (by lab) and Grade ≥ 3 total bilirubin increase (by lab); probability of dose modification (reduction, delay, or early discontinuation) due to AE; time to the first dose modification (reduction, delay, or early discontinuation) due to AE, polatuzumab vedotin dose intensity, rituximab dose intensity and bendamustine dose intensity[4]
		Unconjugated MMAE	AUC C_{max}				
	Analysis based on pivotal study	acMMAE	AUC C_{max}	GO29365	Pola + BR (1.8 mg/kg up to 6 cycles) Pola + BG (1.8 mg/kg up to 6 cycles)	69 (44/25)	
		Unconjugated MMAE	AUC C_{max}				

E-R analysis	Analysis	Analyte	Exposure Measures	Study included	Arm included (dose)	N total (N by arm)	Endpoints
Exposure-Efficacy	Analysis based on supportive studies	acMMAE	AUC	DCS4968g GO27834 [2]	Pola single agent (0.1-2.4 mg/kg) [3] Pola + R (2.4 mg/kg)	75 (36/39)	Investigator (INV)-assessed best overall response (BOR) up to 8-cycle landmark by PET-CT or CT (INV- BOR); INV - assessed objective response (OR) rate at 8-cycle landmark by PET-CT or CT (INV- OR) [6]
	Analysis based on pivotal study	acMMAE	AUC	GO29365	Pola + BR (1.8 mg/kg up to 6 cycles) BR [5]	84 (44/40)	IRC-assessed BOR by PET-CT or CT (IRC-BOR); IRC-assessed CR at primary response assessment time by PET-CT (IRC-CR); IRC-assessed OR at primary response assessment time by PET-CT (IRC-OR); IRC-assessed duration of objective response (time to relapse) up to clinical cut-off date (IRC-DOR); IRC-assessed progression-free survival (PFS) and Overall Survival (OS) [7]

The exposures of acMMAE and unconjugated MMAE based on the integrated population PK model were used for the exposure-response analysis. The acMMAE exposures are highly correlated with the dose of

polatuzumab vedotin. It is considered the key analyte of interest driving efficacy and safety based on the MOA of the molecule. Unconjugated MMAE is a catabolite of the conjugate. Unconjugated MMAE exposures increase proportionally with dose and have a weaker correlation with dose. Unconjugated MMAE is not considered a major driver of efficacy based on the design of the molecule, but might be associated with some adverse events given its high potency. For exposure-safety analysis, the correlation of acMMAE or unconjugated MMAE exposures (AUC, C_{max}) with the incidence of clinically relevant adverse events and dose intensity related measurements were explored for the pivotal study and the supportive studies. For exposure-efficacy analysis, the correlation of acMMAE exposures (AUC) with key efficacy endpoints for the pivotal study and the supportive studies were performed.

Exposure-Safety Analysis

Analysis was not performed for AEs with incidence less than 5% or with number of events less than 5 due to limited data. For all other safety endpoints, the statistical significance as indicated by p-value based on the supportive studies (DCS4968g and GO27834) and the pivotal study (GO29365) were summarized.

Table 26: Summary of the Results for Exposure-Safety Analysis

Adverse Event	Analysis Type	N	N (%) with Event	p-value			
				acMMAE		unconjugated MMAE	
				AUC	C_{max}	AUC	C_{max}
Analysis based on the supportive studies							
Grade ≥3 Neutropenia	Logistic regression	119	39 (32.8%)	0.091	0.157	0.338	0.339
Grade ≥2 Peripheral Neuropathy		119	30 (25.2%)	0.003	0.011	0.571	0.755
Grade ≥3 Infections and Infestations		119	12 (10.1%)	0.615	0.631	0.066	0.101
Grade ≥3 Anemia		119	9 (7.6%)	0.866	0.964	0.010	0.015
Grade ≥3 Thrombocytopenia		119	6 (5.0%)	0.638	0.928	0.327	0.221
Dose Modification due to AE		119	32 (26.9%)	0.340	0.256	0.455	0.325
Time to the First Dose Modification due to AE	Cox PH model	119	32 (26.9%)	0.359	0.601	0.004	0.002
Polatuzumab vedotin Dose intensity	Linear regression	119	-	0.030	0.026	0.128	0.114
Rituximab Dose intensity		40	-	0.544	0.986	0.725	0.560
Analysis based on the pivotal study							
Grade ≥3 Neutropenia	Logistic regression	69	35 (50.7%)	0.649	0.269	0.810	0.993
Grade ≥2 Peripheral Neuropathy		69	10 (14.5%)	0.586	0.965	0.309	0.226
Grade ≥3 Infections and Infestations		69	20 (29.0%)	0.376	0.879	0.765	0.930
Grade ≥3 Anemia		69	13 (18.8%)	0.888	0.390	0.117	0.119
Grade ≥3 Thrombocytopenia		69	24 (34.8%)	0.781	0.780	0.253	0.253
Dose Modification due to AE		69	40 (58.0%)	0.100	0.062	0.448	0.465
Time to the First Dose Modification due to AE	Cox PH model	69	40 (58.0%)	0.145	0.009	0.639	0.541
Polatuzumab vedotin Dose intensity	Linear regression	69	-	0.099	0.555	0.984	0.953
Bendamustine Dose intensity		69	-	0.339	0.192	0.118	0.242
Rituximab Dose intensity		44	-	0.070	0.232	0.296	0.186

ac=antibody conjugate; AUC=area under the concentration-time curve; C_{max}=maximum concentration; MMAE=monomethyl auristatin E.
Shaded cell indicates p-value < 0.05; Source: ER report 1090634 Table 56

Grade ≥ 3 Neutropenia

Grade ≥ 3 neutropenia was the most common adverse event. Approximately 33% of patients in the supportive studies and 51% of patients in the pivotal study experienced treatment-emergent Grade ≥3 neutropenia.

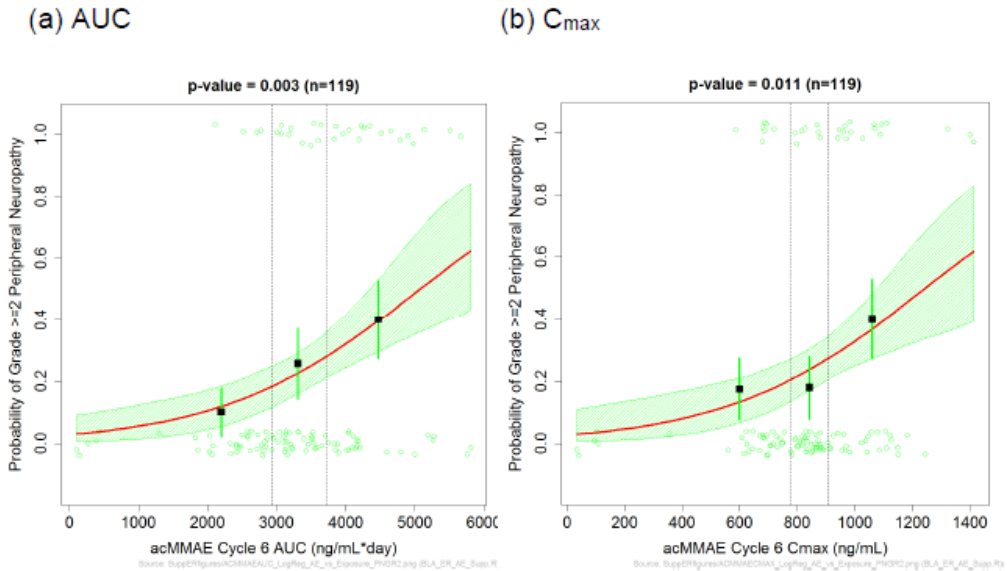
The logistic regression analyses indicate that there were no statistically significant correlations ($p > 0.05$) between exposures (AUC and C_{max}) of acMMAE or unconjugated MMAE and probability of Grade ≥ 3 neutropenia for both the supportive studies and the pivotal study. The higher incidence of Grade ≥ 3 Neutropenia in the pivotal study was experienced by 26.1% at 1.8 mg/kg and from supportive studies; 50.7% at 1.8 mg/kg from pivotal studies).

Grade ≥ 2 Peripheral Neuropathy

The incidence of Grade ≥ 2 peripheral neuropathy was 25.2% in the supportive studies based on data from 0.1-2.4 mg/kg and treatment duration of up to 8 cycles. The analyses based on supportive studies indicated that probability of Grade ≥ 2 peripheral neuropathy increased ($p < 0.05$) with increasing acMMAE exposures (AUC and C_{max}) but had no statistically significant correlation with unconjugated MMAE exposures.

In the pivotal Study GO29365 with polatuzumab vedotin given at 1.8 mg/kg up to 6 cycles, the frequency of Grade ≥ 2 peripheral neuropathy was 14.5%. The pivotal analysis did not identify statistically significant correlations between acMMAE or unconjugated MMAE exposures with the probability of Grade ≥ 2 peripheral neuropathy.

Figure 11 Logistic Regression for acMMAE Exposures and Grade ≥ 2 Peripheral Neuropathy Based on the Supportive Studies



ac=antibody conjugate; AUC=area under the concentration time curve; C_{max}=maximum concentration; MMAE=monomethyl auristatin E.

The red solid line and green shaded area represent the logistic regression model prediction and 90% confidence interval of predictions. Points show exposure of individual patients with events (p=1) and without events (p=0). Black squares and vertical green lines show observed fraction of subjects with events in each exposure group and 90% confidence interval for these fractions. Dashed vertical lines show bounds of exposure groups.

In addition, a time to event analysis (Lu et al. 2017) based on DCS4968g and GO27834 studies suggested that the incidence of Grade ≥ 2 peripheral neuropathy increased with increasing acMMAE exposures (i.e., dose of polatuzumab vedotin) and treatment duration, and a treatment duration of 6-8 cycles is desirable for mitigating the risk of Grade ≥ 2 peripheral neuropathy.

Grade ≥ 3 Infections and Infestations

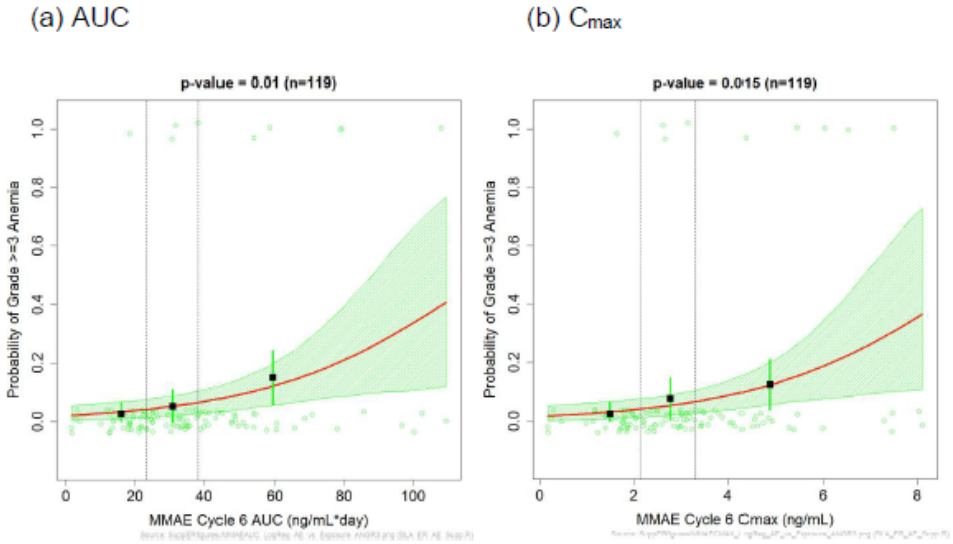
The incidences of treatment-emergent Grade ≥ 3 Infections and Infestations were 10.1% in the supportive studies and 29% in the pivotal study. The analysis based on the supportive studies and the pivotal study did not identify statistically significant correlations between acMMAE or unconjugated MMAE exposures with the probability of Grade ≥ 3 Infections and Infestations.

Grade ≥ 3 Anemia

The incidence of treatment-emergent Grade ≥ 3 anemia was 7.6% in the supportive studies and 18.8% in the pivotal study. The analysis based on the supportive studies indicated that probability of treatment-emergent Grade ≥ 3 anemia increased significantly ($p < 0.05$) with increasing unconjugated

MMAE exposures (AUC and C_{max}), but had no statistically significant correlation with acMMAE exposures. The analysis based on the pivotal study did not identify any statistically significant correlations with both acMMAE and unconjugated MMAE exposures, potentially due to a relatively narrow exposure range from a single dose level of 1.8 mg/kg. The higher incidence of Grade ≥ 3 Anemia in the pivotal study (6.5% at 1.8 mg/kg from supportive studies; 18.8% at 1.8 mg/kg from pivotal studies) was probably due to the bendamustine combination, which as a chemotherapy agent is associated with haematologic adverse events.

Figure 12 Logistic regression of Unconjugated MMAE Exposures and Grade ≥ 3 Anemia Based on the Supportive Studies



AUC=area under the concentration time curve; C_{max}=maximum concentration; MMAE=monomethyl auristatin E.

The red solid line and green shaded area represent the logistic regression model prediction and 90% confidence interval of predictions. Points show exposure of individual patients with events (p=1) and without events (p=0). Black squares and vertical green lines show observed fraction of subjects with events in each exposure group and 90% confidence interval for these fractions. Dashed vertical lines show bounds of exposure groups.

Grade ≥ 3 Thrombocytopenia

The incidence of treatment-emergent Grade ≥ 3 thrombocytopenia was 5% in the supportive studies and 34.8% in the pivotal study. There were no statistically significant correlations between acMMAE or unconjugated MMAE exposures and the incidence of Grade ≥ 3 thrombocytopenia in both the supportive studies and the pivotal study. The higher incidence of Grade ≥ 3 thrombocytopenia in the pivotal study was probably due to the bendamustine combination, which as a chemotherapy agent is associated with haematologic adverse events.

Probability of Dose Modification due to AE and Time to First Dose Modification due to AE for Polatuzumab Vedodin

Frequency of dose modification (including dose delay, dose reduction and early discontinuation) due to AE was 26.9% in the supportive analysis and 58% in the pivotal analysis. For the analysis based on the supportive studies and the pivotal study, the logistic regression models indicated that there were no statistically significant correlations between exposures (AUC and C_{max}) of acMMAE or unconjugated MMAE and probability of dose modification due to AE.

The analysis (cox proportional hazard model) based on the supportive studies indicated that time to the first dose modification due to AE decreased significantly ($p < 0.05$) (i.e., earlier time to first dose modification) with increasing unconjugated MMAE exposures (AUC, C_{max}). The analysis (cox proportional

hazard model) based on the pivotal study indicated that time to the first dose modification due to AE decreased significantly ($p < 0.05$) with the increase of acMMAE C_{max} However, the probability of dose modification due to AE was not significantly impacted by acMMAE or unconjugated MMAE.

Exposure-Efficacy Analysis

For the investigated efficacy endpoints, the statistical significance as indicated by p-value for the analysis based on supportive studies (DCS4968g and GO27834) and the pivotal study (GO29365) are summarized below.

Table 27: Summary of the results for exposure-efficacy analysis

Endpoint	Analysis Type	N Evaluable	N (%) with Event	p-value
Analysis based on the supportive studies				
INV-BOR	Logistic regression	76	31 (40.8%)	0.037
INV-OR at Cycle 8 landmark or earlier if less than 8 cycles		76	23 (30.3%)	0.014
Analysis based on the pivotal study				
IRC-BOR	Logistic regression	44	26 (59.1%)	0.852
IRC-CR at primary response assessment		44	19 (43.2%)	0.521
IRC-OR at primary response assessment		44	21 (47.7%)	0.956
IRC-DOR (i.e., time to relapse)	Cox PH model	26	11 (42.3%)	0.057
IRC-PFS		44	26 (59.1%)	0.102
OS		44	24 (54.5%)	0.048

BOR=best overall response; CR=complete response; INV=investigator; IRC=independent review committee; OS=overall survival; PFS=progression free survival.

Shaded cells show analyses with p-value ≤ 0.05; Source: ER report 1090634 Table 57

Analysis based on the supportive studies

A total of 31 (40.8%) out of 76 patients were responders (complete response or partial response) based on investigator assessed best overall response (INV-BOR) by treatment up to 8-cycle landmark, and a total of 23 (30.3%) out of 76 patients were responders (complete response or partial response) based on investigator assessed objective response (INV-OR) at the end of Cycle 8 landmark or earlier if less than 8 cycles. The logistic regression analysis indicated a statistically significant correlation between acMMAE AUC and the probability of INV-BOR and INV-OR. A higher acMMAE AUC is associated with a higher probability of response (p=0.037 and 0.014, respectively, by logistic regression).

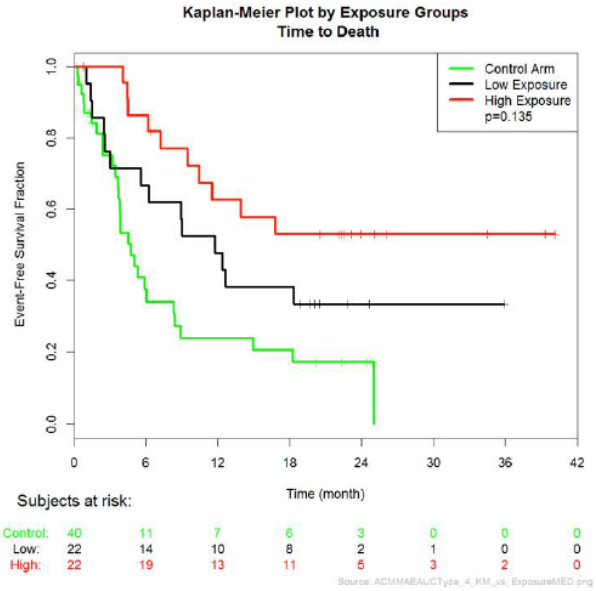
Analysis based on the pivotal study: Independent Review Committee (IRC) assessed CR at Primary Response Assessment (PRA) Time (IRC-CR), OR at PRA time (IRC-OR), and BOR by treatment up to 6 cycles (IRC-BOR)

Out of 44 patients, 19 (43.2%) patients achieved CR at PRA time by IRC assessment; 21 (47.7%) patients achieved objective response (OR, i.e., complete response or partial response) at PRA time by IRC assessment; and 26 (59.1%) patients were responders based on IRC-BOR data for treatment up to 6 cycles. There are no statistically significant correlations between acMMAE AUC and these endpoints by logistic regression within the exposure range in the pivotal study.

Analysis based on the pivotal study: IRC assessed duration of response (i.e., time to relapsed, IRC-DOR) for patients with response, PFS by IRC (IRC-PFS) and OS

Of 26 (out of 44) patients who achieved complete or partial response, 11 (42.3%) patients relapsed within the assessment duration and others were censored. Of 44 patients with available PFS and OS data, 26 (59.1%) and 24 (54.5%) had the respective events and others were censored.

Figure 13: Analysis Based on the Pivotal Study: Kaplan-Meier Plot of Time to Death (OS) by acMMAE AUC



ac = antibody conjugate; AUC=area under the concentration–time curve; MMAE=monomethyl auristatin E; OS=overall survival..

Note: Low exposure: ≤ median, High exposure > median. P-value: p-value of the log-rank test comparing patients with low and high exposure. Event-free survival: overall survival.

Source: ER report 1090634 Figure 74

Cardiac electrophysiology (ECG)

The effect of polatuzumab vedotin on the corrected QT (QTc) interval was evaluated based on triplicate ECG data from 2 clinical studies (DCS4968g and GO27834).

Based on the overall results from *in vitro* and preclinical assessments, the risk of polatuzumab vedotin on QT prolongation at therapeutic doses is low. To assess the QT prolongation risk of polatuzumab vedotin in patients, concentration-QT analysis was conducted based on the observed PK data and triplicate ECG data from the pooled dataset of DCS4968g and GO27834 studies. The QT data by Fridericia's correction (QTcF) (FDA and EMA) and the change of QTcF from the baseline (ΔQTcF) were derived at each visit. Theoretically, based on molecule size and properties, only unconjugated MMAE would be expected to be capable of entering cardiac cells and binding to the intracellular part of the rapidly activating delayed rectifier potassium channel (IKr). Regardless, all three analytes were assessed for this modeling.

First, categorical analyses of observed QTcF and ΔQTcF values were conducted. Selected QTc categories were > 500 ms, > 480 to ≤ 500 ms, and ≤ 450 ms. Selected ΔQTcF categories were > 60 ms, > 30 to ≤ 60 ms, and ≤ 30 ms. Second, concentration-ΔQTcF modeling was performed for each analyte separately, by linear mixed-effect modeling. In both analyses, a threshold of 20 ms was selected as ICH E14 guidance asserts that any drug causing mean ΔQTcF prolongation > 20 ms has a substantially increased likelihood of causing clinical arrhythmic events (FDA and EMA, Garnett et al. 2018).

At average C_{max} of each analyte at 1.8 mg/kg q3w dose level, the upper bound of two-sided 90% CI of model predicted ΔQTcF were all below 10ms for each analyte. ΔQTcF was estimated to be 3.64 ms [1.83, 5.45] at a Cycle 3 C_{max} of 859 ng/mL for acMMAE, 4.05 ms [2.22, 5.88] at a Cycle 3 C_{max} of 46.3 µg/mL for total antibody, and 1.95 ms [-2.21, 6.10] at a Cycle 1 Cmax of 6.82 ng/mL for unconjugated MMAE.

Table 28 Mean ΔQTcF Predictions at Average Cmax of Cycle 1 and Cycle 3 for 1.8 mg/kg Based on the Final Models of Each Analyte

Analyte/Cycle	*C_{max}*	*Estimate (ms)*	*90% CI* (ms)*
acMMAE, Cycle 1	803 ng/mL	3.37	(1.62, 5.13)
acMMAE, Cycle 3	859 ng/mL	3.64	(1.83, 5.45)
Total Antibody, Cycle 1	42.2 µg/mL	3.62	(1.87, 5.37)
Total Antibody, Cycle 3	46.3 µg/mL	4.05	(2.22, 5.88)
Unconjugated MMAE, Cycle 1**	6.82 ng/mL	1.95	(-2.21, 6.1)

ac=antibody-conjugate MMAE; estimate = mean ΔQTc. C_{max}=maximum concentration; MMAE=monomethyl auristatin E.

* The 90% CI is based on parameter uncertainty, and is calculated using the "contrast" function in R based on the one-degree of freedom Wald test.

**For unconjugated MMAE PK at Cycle 3, we do not have the PK sampling between Day 1 and Day 8 to capture the C_{max}, and the Cycle 3 exposure is lower than Cycle 1. Thus only the Cycle 1 observed C_{max} is listed.

Special populations

The PK of acMMAE and unconjugated MMAE were evaluated in special populations including the elderly (≥ 65 years old), race (Asian versus non-Asian), region (Asia region versus non-Asia region), and patients with hepatic or renal function impairment, by using the population PK approach. Formal covariate analysis was performed during the model building when appropriate. A simulation of Cycle 6 acMMAE and unconjugated MMAE exposures (AUC and C_{max}) was performed to compare the exposures in the different groups.

Impaired renal function

Based on the population PK analysis, CrCL is not identified as a statistically significant covariate of acMMAE or unconjugated MMAE PK parameters. Patients with mild renal impairment (N=161) and moderate renal impairment (N=109) have similar acMMAE and unconjugated MMAE exposures as normal patients (N=185) (<10% difference of AUC and Cmax).

Based on the similar PK exposures for patients with mild or moderate renal impairment (CrCL of 30-90 mL/min) to the normal patients (CrCL >90 mL/min), and the safety analysis which suggested a similar safety profile for patients with mild or moderate renal impairment to patients with normal renal functions, no starting dose adjustment is recommended. No conclusion can be drawn for patients with severe renal impairment (N=3) and end-stage renal disease (N=0) due to limited data.

Table 29 Comparison of covariate-corrected exposures for patients with normal renal function, mild or moderate renal impairment

Exposure	Statistics	Normal	Mild Impairment	Moderate Impairment
		N=185	N=161	N=109
acMMAE AUC (ng*day/mL)	GM (CV%)	2930 (19%)	2910 (21%)	2890 (22%)
	GMR (90% CI)		0.991 (0.956-1.03)	0.985 (0.944-1.03)
acMMAE C_{max} (ng/mL)	GM (CV%)	763 (15%)	736 (15%)	694 (13%)
	GMR (90% CI)		0.964 (0.939-0.99)	0.909 (0.884-0.935)
Unconjugated MMAE AUC (ng*day/mL)	GM (CV%)	20.4 (43%)	22 (54%)	21.7 (52%)
	GMR (90% CI)		1.08 (0.989-1.18)	1.06 (0.966-1.17)
Unconjugated MMAE C_{max} (ng/mL)	GM (CV%)	1.95 (39%)	2.01 (50%)	1.97 (45%)
	GMR (90% CI)		1.03 (0.952-1.12)	1.01 (0.926-1.1)

ac=antibody conjugate; AUC=area under concentration-time curve; C_{max}=maximum concentration
GM = geometric mean; GMR = geometric mean ratio; MMAE= monomethyl auristatin E.

Individual exposures were computed for patients with normal renal function, mild or moderate renal impairment following 1.8 mg/kg q3w dosing for 6 cycles using pCC procedure. CV was computed as standard deviation of a log-transformed variable.

Impaired hepatic function

Based on the final population PK model, hepatic impairment status based on NCI clasification was identified as a statistically significant covariate for unconjugated MMAE PK parameter ($FRAC_{NS}$), but it is not a covariate for acMMAE PK.

Simulation of Cycle 6 individual exposures (AUC, C_{max} of Cycle 6 by 1.8 mg/kg q3w) based on individual EBE of PK parameters using pCC procedure was performed. The PK in patients with mild hepatic impairment (N=54) versus patients with normal hepatic impairment (N=399) suggested that acMMAE exposures are similar (<5% difference), while unconjugated MMAE exposures are moderately higher in patients with mild hepatic impairment (40% for AUC, 34% for C_{max}). This magnitude of higher unconjugated MMAE exposures is not expected to have a clinically relevant impact on safety based on the exposure-safety results.

Thus, no starting dose adjustment is warranted for patients with AST or ALT of >1-2.5 ULN or total bilirubin of >1-1.5 ULN. No conclusions can be drawn for patients with moderate hepatic impairment (total bilirubin >1.5-3 ULN, and enzyme elevation is not due to Gilbert's syndrome or underlying disease) (N=2) or severe hepatic impairment (total bilirubin >3 ULN and enzyme elevation is not due to Gilbert's syndrome or underlying disease) (N=0) due to limited data.

Table 30: Comparison of Covariate-Corrected Exposures between Patients with Mild Hepatic Impairment and Normal Hepatic Function

Exposure	Statistics	Normal hepatic function	Mild hepatic Impairment
		N=399	N=54
acMMAE AUC (ng*day/mL)	GM (CV%)	2920 (20%)	2810 (24%)
	GMR (90% CI)		0.96 (0.906-1.02)
acMMAE C_{max} (ng/mL)	GM (CV%)	738 (15%)	710 (17%)
	GMR (90% CI)		0.962 (0.924-1)
Unconjugated MMAE AUC (ng*day/mL)	GM (CV%)	20.4 (47%)	28.5 (57%)
	GMR (90% CI)		1.40 (1.22-1.6)
Unconjugated MMAE C_{max} (ng/mL)	GM (CV%)	1.9 (43%)	2.55 (49%)
	GMR (90% CI)		1.34 (1.2-1.51)

Individual exposures were computed for patients with normal hepatic function and mild hepatic impairment following 1.8 mg/kg q3w dosing for 6 cycles using pCC procedure. CV was computed as standard deviation of a log-transformed variable.

Gender

Sex is a statistically significant covariate for acMMAE CL_{INF} and V_1, and for FRAC of unconjugated MMAE.

Simulation of Cycle 6 exposures (AUC, C_{max} of Cycle 6 by 1.8 mg/kg Q3W) demonstrated that the simulated PK exposures for male (N=272) were similar (<10% differences for AUC and C_{max}) for acMMAE and unconjugated MMAE compared to female (N=188).

Comparison of Covariate-Corrected Exposures by Sex

Exposure	Statistics	Females	Males
	N	188	272
acMMAE AUC (ng*day/mL)	GM (CV%)	2990 (21%)	2860 (20%)
	GMR (90% CI)		0.956 (0.926-0.988)
acMMAE C_{max} (ng/mL)	GM (CV%)	770 (15%)	711 (15%)
	GMR (90% CI)		0.923 (0.902-0.944)
Unconjugated MMAE AUC (ng*day/mL)	GM (CV%)	20.7 (45%)	21.5 (52%)
	GMR (90% CI)		1.04 (0.966-1.12)
Unconjugated MMAE C_{max} (ng/mL)	GM (CV%)	1.94 (41%)	1.98 (47%)
	GMR (90% CI)		1.02 (0.954-1.09)

ac=antibody conjugate; AUC=area under concentration-time curve; C_{max}=maximum concentration; GM = geometric mean; GMR = geometric mean ratio; MMAE= monomethyl auristatin E; Q3W=every 3 weeks.

Individual exposures were computed for all patients following 1.8 mg/kg Q3W dosing for 6 cycles using pCC procedure. CV was computed as standard deviation of a log-transformed variable.

Race and Region

Patients were grouped to Asian (N=18) and Non-Asian (N=422). Race was identified as a statistically significant covariate for acMMAE V_1.

Simulation of Cycle 6 exposures (AUC, Cmax of Cycle 6 by 1.8 mg/kg q3w) suggested nearly identical exposures of acMMAE (<1.2% differences) comparing the PK results of Asian (N=18) and Non-Asian (N=422) patients. For unconjugated MMAE, the exposure is mildly lower in Asian patients (18.6% for AUC, 16.9% for Cmax).

Table 31: Comparison of Covariate-Corrected Exposures by Race

Exposure	Statistics	Non-Asian	Asian
		N=442	N=18
acMMAE AUC (ng*day/mL)	GM (CV%)	2910 (21%)	2870 (12%)
	GMR (90% CI)		0.988 (0.94-1.04)
acMMAE C_{max} (ng/mL)	GM (CV%)	734 (15%)	733 (13%)
	GMR (90% CI)		0.998 (0.944-1.05)
Unconjugated MMAE AUC (ng*day/mL)	GM (CV%)	21.4 (49%)	17.4 (40%)
	GMR (90% CI)		0.814 (0.688-0.963)
Unconjugated MMAE C_{max} (ng/mL)	GM (CV%)	1.98 (45%)	1.64 (38%)
	GMR (90% CI)		0.831 (0.708-0.975)

ac=antibody conjugate; AUC=area under concentration-time curve; C_{max}=maximum concentration GM = geometric mean; GMR = geometric mean ratio; MMAE= monomethyl auristatin E.

Individual exposures were computed for all patients following 1.8 mg/kg q3w dosing for 6 cycles using pCC procedure. CV was computed as standard deviation of a log-transformed variable.

Similar results were found in the analysis of the impact of region (Asia region vs Non-Asia region).

Body Weight

Whether dose capping is needed for relatively heavy patients (defined as body weight ≥ 100 kg in this analysis) was assessed by simulating the Cycle 6 exposures (AUC, C_{max}) of the 1.8 mg/kg Q3W regimen for patients with body weight≥ 100 kg (N=59) compared to the others (< 100 kg, N=401). For patients with body weight ≥ 100 kg, acMMAE exposures are slightly higher than others (8% for AUC, 17% for

C_{max}); unconjugated MMAE exposures for these patients are moderately higher than others (27% for both AUC and C_{max}).

Comparison of Covariate-Corrected Exposures by Body Weight Categories

Exposure	Statistics	Body weight < 100 kg	Body weight ≥ 100 kg
	N	401	59
acMMAE AUC(ng*day/mL)	GM (CV%)	2880 (20%)	3110 (22%)
	GMR (90% CI)		1.08 (1.03-1.14)
acMMAE C_{max} (ng/mL)	GM (CV%)	720 (15%)	842 (13%)
	GMR (90% CI)		1.17 (1.14-1.21)
Unconjugated MMAE AUC (ng*day/mL)	GM (CV%)	20.6 (50%)	26 (39%)
	GMR (90% CI)		1.27 (1.15-1.39)
Unconjugated MMAE C_{max} (ng/mL)	GM (CV%)	1.91 (45%)	2.43 (38%)
	GMR (90% CI)		1.27 (1.16-1.39)

ac=antibody conjugate; AUC=area under concentration-time curve; C_{max}=maximum concentration; GM = geometric mean; GMR = geometric mean ratio; MMAE= monomethyl auristatin E; Q3W=every 3 weeks.
Individual exposures were computed for all patients following 1.8 mg/kg Q3W dosing for 6 cycles using pCC procedure. CV was computed as standard deviation of a log-transformed variable.

Elderly

Age (< 65 years old versus ≥ 65 years old) was not a statistically significant covariate of acMMAE or unconjugated MMAE PK parameters.

Simulation of Cycle 6 exposures (AUC, C_{max} of Cycle 6 by 1.8 mg/kg q3w for 6 cycles) indicated similar exposures for both acMMAE and unconjugated MMAE (<10% differences of AUC and C_{max}) in patients with age <65 years (N=187) and age ≥65 years (N=273).

Table 32: Comparison of Covariate-Corrected Exposures by Age Categories

Exposure	Statistics	Age < 65	Age ≥ 65
		N=187	N=273
acMMAE AUC (ng*day/mL)	GM (CV%)	2950 (19%)	2880 (22%)
	GMR (90% CI)		0.974 (0.944-1)
acMMAE C_{max} (ng/mL)	GM (CV%)	758 (15%)	718 (15%)
	GMR (90% CI)		0.947 (0.926-0.97)
Unconjugated MMAE AUC (ng*day/mL)	GM (CV%)	20.2 (47%)	21.9 (51%)
	GMR (90% CI)		1.08 (1-1.17)
Unconjugated MMAE C_{max} (ng/mL)	GM (CV%)	1.91 (43%)	2 (46%)
	GMR (90% CI)		1.05 (0.976-1.12)

ac=antibody conjugate; AUC=area under concentration-time curve; C_{max}=maximum concentration GM = geometric mean; GMR = geometric mean ratio; MMAE= monomethyl auristatin E.
Individual exposures were computed for all patients following 1.8 mg/kg q3w dosing for 6 cycles using pCC procedure. CV was computed as standard deviation of a log-transformed variable.

Table 33: Older population in PK trials

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials	187/460	76/460	10/460

Children

No studies have been conducted to investigate the pharmacokinetics of polatuzumab vedotin in the paediatric population (<18 years old).

2.4.4. Discussion on clinical pharmacology

A total of 7 clinical studies contributed to the characterization of the clinical pharmacology of polatuzumab vedotin: Studies DCS4968g, GO29365, GO27834, GO29044 (conducted with the v0.1-derived liquid DP, arm G in study GO29365 with v1.0 lyophylized 140 mg/vial DP), and studies GO29833, GO29834, BO29561 (conducted with v1.0-derived lyophilized DP). In all studies, polatuzumab vedotin was administered by intravenous (IV) infusion over 30 to 90 minutes. Studies were intended to characterize single- and multiple-dose pharmacokinetics of the three major analytes of polatuzumab vedotin: conjugate (evaluated as antibody-conjugated MMAE [acMMAE]), total antibody, and unconjugated MMAE. PK characteristics of acMMAE, total antibody and unconjugated MMAE were analysed by noncompartmental analysis (NCA). In addition, a two-analyte (acMMAE-MMAE) integrated population pharmacokinetic analysis was used to further characterize the PK properties of acMMAE and unconjugated MMAE. The final proposed dosing regimen of polatuzumab vedotin in patients with R/R DLBCL is 1.8 mg/kg every 3 weeks (Q3W) for up to 6 cycles, in combination with rituximab and bendamustine.

Comparability of the v1.0-derived material to the v0.1-derived material of polatuzumab vedotin was demonstrated by population PK analysis. Clinically relevant differences in PK are not anticipated, considering that the 90% CI of the GMR of AUC and C_{max} of acMMAE and unconjugated MMAE comparing the v1.0-derived lyophilized DP with the v0.1-derived liquid DP were contained within the bioequivalence margin of 0.8 – 1.25. These results support the comparability of both the liquid and the lyo formulations.

Polivy is administered as an IV infusion. There have been no studies performed with other routes of administration.

Volume of distribution of MMAE could solely be estimated by population PK analyses as apparent values, since MMAE follows formation-rate limited kinetics. The population estimate of central volume of distribution for acMMAE was 3.15 L, which approximated plasma volume**.** *In vitro*, MMAE is moderately bound (71%-77%) to human plasma proteins. MMAE does not significantly partition into human red blood cells in vitro; the blood to plasma ratio is 0.79 to 0.98. Clearance of acMMAE declined with multiple dosing and was estimated to 1.01 L/day at time zero and 0.825 L/day at time of infinity.

In vitro data indicate that MMAE is a P-gp substrate but does not inhibit P-gp at clinically relevant concentrations.

MMAE has previously been shown to be predominantly excreted via the hepatic pathway. No clinical excretion studies with polatuzumab vedotin have been conducted. Polatuzumab vedotin is expected to undergo catabolism in patients, resulting in the production of small peptides, amino acids, unconjugated MMAE, and unconjugated MMAE related catabolites. The levels of MMAE metabolites have not been measured in human plasma.

In vitro studies indicate that MMAE is a substrate for CYP3A4/5 but does not induce major CYP enzymes. MMAE is a weak time-dependent inhibitor of CYP3A4/5 but does not competitively inhibit CYP3A4/5 at clinically relevant concentrations.

MMAE does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6.

Based on a population PK analysis, the conjugate (acMMAE) is primarily eliminated by non-specific linear clearance pathway with a value of 0.9 L/day. *In vivo* studies in rats dosed with polatuzumab vedotin (radiolabel on MMAE) demonstrate that the majority of radioactivity is excreted in faeces and the minority of radioactivity is excreted in urine.

Antibody-conjugated MMAE (acMMAE) plasma exposure increased dose-proportionally over the 0.1 to 2.4 mg/kg polatuzumab vedotin dose range. After the first 1.8 mg/kg polatuzumab vedotin dose, the acMMAE mean maximum concentration (C_{max}) was 803 (± 233) ng/mL and the area under the concentration-time curve from time zero to infinity (AUC_{inf}) was 1860 (±966) day•ng/mL. Based on the population PK analysis, Cycle 3 acMMAE AUC increased by approximately 30% over Cycle 1 AUC, and achieved more than 90% of the Cycle 6 AUC. The terminal half-life at Cycle 6 was approximately 12 days (95% CI of 8.1-19.5 days) for acMMAE. Based on population PK analysis, the predicted acMMAE concentration at the end of cycle 6 is approximately 80% of the theoretical steady-state value.

Exposures of unconjugated MMAE, the cytotoxic component of polatuzumab vedotin, increased dose proportionally over the 0.1 to 2.4 mg/kg polatuzumab vedotin dose range. MMAE plasma concentrations followed formation rate limited kinetics. After the first 1.8 mg/kg polatuzumab vedotin dose, the C_{max} was 6.82 (± 4.73) ng/mL, the time to maximum plasma concentration is approximately 2.5 days, and the terminal half-life is approximately 4 days. Plasma exposures of unconjugated MMAE are < 3% of acMMAE exposures. Based on the population PK analysis there is a decrease of plasma unconjugated MMAE exposure (AUC) after repeated every-three-week dosing.

Based on population pharmacokinetics simulations, a sensitivity analysis predicted exposure to unconjugated MMAE for patients with bodyweight over 100 kg to be increased by 27%.

Differences in PK of polatuzumab vedotin in special populations has been adequately investigated by population PK analysis. Body weight was identified as the most important statistically significant covariate for PK of acMMAE and unconjugated MMAE. Weight-based dosing of polatuzumab vedotin is considered justified. However, due to limited clinical experience in patients treated with 1.8 mg/kg Polivy at a total dose >240 mg, it is recommended not to exceed the dose 240mg/cycle. Age was not a statistically covariate for acMMAE and unconjugated MMAE PK parameters. No dose adjustments in Asian patients or among male / female patients was considered necessary.

In patients with mild (CrCL 60-89 mL/min, n = 161) or moderate (CrCL 30- 59 mL/min, n = 109) renal impairment, acMMAE and unconjugated MMAE exposures are similar to patients with normal renal function (CrCL ≥ 90 mL/min, n = 185), based on a population PK analysis. There are insufficient data to assess the impact of severe renal impairment (CrCL 15-29 mL/min, n = 3) on PK. No data are available in patients with end-stage renal disease and/or who are on dialysis (see SmPC section 5.2). No dose adjustment of Polivy is required in patients with creatinine clearance (CrCL) ≥ 30 mL/min. A recommended dose has not been determined for patients with CrCL < 30mL/min due to limited data (see SmPC section 4.2).

In patients with mild hepatic impairment [AST > 1.0-2.5×ULN or ALT > 1.0-2.5×ULN or total bilirubin > 1.0-1.5×ULN, n = 54], acMMAE exposures are similar whereas unconjugated MMAE AUC are 40% higher compared to patients with normal hepatic function (n = 399), based on a population PK analysis (see SmPC section 5.2). The administration of Polivy in patients with moderate or severe hepatic impairment (bilirubin greater than 1.5 × ULN) should be avoided. No adjustment in the starting dose is required when administering Polivy to patients with mild hepatic impairment (bilirubin greater than ULN to less than or equal to 1.5 × ULN or AST greater than ULN) (see SmPC section 4.2). There are insufficient data to assess the impact of moderate hepatic impairment (total bilirubin > 1.5-3×ULN, n = 2) on PK. No data are available in patients with severe hepatic impairment or liver transplantation.

The safety and efficacy in children and adolescents less than 18 years have not been established. No studies have been conducted to investigate the pharmacokinetics of polatuzumab vedotin in the paediatric population (<18 years old).

Age did not have an effect on the pharmacokinetics of acMMAE and unconjugated MMAE based on a population PK analysis with patients aged 20-89 years. No significant difference was observed in the

pharmacokinetics of acMMAE and unconjugated MMAE among patients < 65 years of age (n = 187) and patients ≥ 65 years of age (n = 273).

No dedicated clinical drug-drug interaction studies with polatuzumab vedotin in humans have been conducted.

The potential impact of polatuzumab vedotin on the PK of bendamustine was evaluated, based on the observed bendamustine PK data in R/R DLBCL and R/R FL patients who received rituximab + bendamustine + polatuzumab vedotin versus rituximab + bendamustine treatment (randomized arms of GO29365 study).

The plasma PK parameters of bendamustine including C_{max}, $AUC_{0-\infty}$, V_{ss}, CL, and $T_{1/2\lambda z}$ were similar in patients with R/R DLBCL and R/R FL receiving Pola+BR or BR respectively (less than 20% difference, which is well within the CV% of each parameter). These results supported a low risk for polatuzumab vedotin to impact bendamustine PK when given in combination.

Based on physiological-based pharmacokinetic (PBPK) model simulations of MMAE released from polatuzumab vedotin, strong CYP3A4 and P-gp inhibitors (e.g., ketoconazole) may increase the area under the concentration-time curve (AUC) of unconjugated MMAE by 48%. In the SmPC (see section 4.5) caution is advised in case of concomitant treatment with CYP3A4 inhibitor. Patients receiving concomitant strong CYP3A4 inhibitors should be monitored more closely for signs of toxicities.

Prior to polatuzumab DDI prediction, the model prediction of acMMAE and unconjugated MMAE predictions were compared to polatuzumab clinical PK data. It showed an overall trend to under-estimate the exposure. Additional simulations were performed by the applicant to ensure the predictive performance of the PBPK model in the updated 1090612v19 PBPK report. Data from phase 1 Study DCS4968g at 2.4 mg/kg in R/R NHL patients were used. The simulated exposures for acMMAE and MMAE with larger dataset (N=45) were acceptable and estimated to be within 20% of the observed exposure. Unconjugated MMAE is not predicted to alter the AUC of concomitant medicines that are CYP3A4 substrates (e.g., midazolam).

Caution is advised in case of concomitant treatment with CYP3A4 inhibitor. Patients receiving concomitant strong CYP3A4 inhibitors (e.g., boceprevir, clarithromycin, cobicistat, indinavir, itraconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) should be monitored more closely for signs of toxicities.

The pharmacokinetics (PK) of rituximab and bendamustine are not affected by co-administration with polatuzumab vedotin. Concomitant rituximab is associated with increased antibody conjugated MMAE (acMMAE) plasma AUC by 24% and decreased unconjugated MMAE plasma AUC by 37%, based on population PK analysis. No dose adjustment is required.

Bendamustine does not affect acMMAE and unconjugated MMAE plasma AUC.

DDI risk was determined to be low for the combination of rituximab and bendamustine with polatuzumab vedotin. Differences in respective PK parameters were either small or suggested to be not clinically relevant, referring to exposure-response modelling. The DDI risk for unconjugated MMAE as a perpetrator or a victim with co-administered drugs that are CYP substrates, inhibitors or inducers was analysed by a PBPK model. The exposure of unconjugated MMAE was suggested to be increased after concomitant treatment with strong CYP3A4 inhibitors, while exposure of unconjugated MMAE was reduced after concomitant treatment with strong CYP3A4 inducers. Changes in exposure of unconjugated MMAE were not considered to result in a clinically relevant impact on safety. Polatuzumab vedotin itself did neither inhibit nor induce CYP3A.

Strong CYP3A4 inducers (e.g., rifampicin) may decrease the exposure of unconjugated MMAE.

The potential interaction of MMAE with UGT was discussed. Given the clinical concentration at the intended dose (7ng/mL) and the in vitro Ki value for azatnavir inhibition of UGT1A1, it is concluded that there is minimal potential to cause any drug-drug interactions as a substrate or inhibitor of UGT enzymes at the clinically relevant concentrations following administration of polatuzumab vedotin is endorsed.

Throughout the clinical studies, no specific pharmacodynamic endpoints were investigated.

Overall, post-baseline ADA incidence across all studies (DCS4968g, GO27834, GO29044, GO29365a, BO29561, GO29833, and GO29834) was low (2.6%). In the pivotal study GO29365, the incidence of treatment-emergent ADA was 6%. Given the low numbers of ADA positive patients, no final conclusion of the impact of ADA positive status on efficacy can be drawn. Two patients with early ADA development in cycle 2 subsequently presented with PD. A causal relationship with ADA may not be excluded. The applicant provided immunogenicity data of remaining patients (Arm G) with the most recent cut-off. Population PK analysis predicted that ADA positivity did not have a statistically significant or clinically meaningful impact on the PK of acMMAE and unconjugated MMAE. In case of unconjugated MMAE, differences observed in exposure were generally much smaller than CV% of 44-58%.

Two separate analyses for the investigation of exposure-response relationship were conducted. The first analysis was based on supportive studies (DCS4968g and GO27834) and the second analysis was based on pivotal study GO29365. The analysis based on the pivotal study was performed to ultimately support the label proposed combination and dosing regimen; results should be interpreted with caution due to the small sample size of the exposure-response analysis.

No statistically significant correlations ($p > 0.05$) between exposures (AUC and C_{max}) of acMMAE or unconjugated MMAE were identified for neutropenia, infections and infestations, thrombocytopenia, and probability of dose modification due to an adverse event.

In the supportive studies, significant correlations were identified for the probability of Grade ≥ 2 peripheral neuropathy, which increased significantly with increasing acMMAE exposures, and for the probability of Grade ≥ 3 anemia, which increased significantly with increasing unconjugated MMAE exposures. However, these significant correlations were not confirmed in the pivotal study analysis.

Overall, exposure-safety analyses suggest that the proposed dosing regimen of polatuzumab vedotin is adequate, since no statistically significant correlations with safety endpoints were identified across the narrow exposure range in study GO29365 (except for time to first dose modification due to an AE), while supportive studies indicated that higher doses and longer treatment duration may be associated with higher incidence of peripheral neuropathy or anaemia. Exposure-efficacy analysis based on the supportive studies suggested that higher acMMAE exposure significantly correlated with higher tumour response rate (INV-BOR and INV-OR). However, this was not confirmed for IRC-BOR and IRC-OR in the exposure-efficacy analysis of the pivotal study. Again, it should be considered that patient numbers were quite low. Nevertheless, increasing acMMAE exposures significantly correlated with longer OS in the pivotal study, and at least trends of increasing time to event endpoints (IRC-DOR, IRC-PFS) with increased acMMAE were identified.

Exposure-safety analyses were performed using data collected from the pivotal and supportive studies. Overall, the exposure response analyses support the proposed dosing regimen of 1.8 mg/kg polatuzumab vedotin Q3W up to 6 cycles in combination with rituximab and bendamustine for treating R/R DLBCL patients.

No secondary pharmacodynamics studies were conducted. *In vitro* data raised that MMAE does not inhibit the hERG channel at clinically relevant concentrations, and no cardiac toxicity was observed in monkeys. In humans, triplicate ECG data retrieved low mean QTc prolongation at clinical concentration of 1.8mg/kg, not over 20 ms from baseline. After polatuzumab dosing, mean increase in ΔQTcF and the upper bound of the 90% CI was < 20 ms at each nominal time. Similarly, concentration-ΔQTcF modeling

did not show a clinically relevant ΔQTcF risk at the mean Cmax from 1.8 mg/kg dose groups in studies DCS4968g and GO27834, as the upper bounds of 90% CI were all below 10 ms for the three analytes (acMMAE, TAb, unconjugated MMAE). Polatuzumab vedotin did not prolong the mean QTc interval to any clinically relevant extent based on ECG data from two open-label studies in patients with previously treated B-cell malignancies at the recommended dosage (see SmPC section 5.1).

No dose adjustment of Polivy is required in patients ≥ 65 years of age (see SmPC sections 4.2 and 5.2).

No dose adjustment of Polivy is required in patients with creatinine clearance (CrCL) ≥ 30 mL/min. A recommended dose has not been determined for patients with CrCL < 30mL/min due to limited data.

The administration of Polivy in patients with moderate or severe hepatic impairment (bilirubin greater than 1.5 × ULN) should be avoided.

No adjustment in the starting dose is required when administering Polivy to patients with mild hepatic impairment (bilirubin greater than ULN to less than or equal to 1.5 × ULN or AST greater than ULN).

The safety and efficacy in children and adolescents less than 18 years have not been established. No data are available.

Exposure-safety and exposure-response analyses conducted further suggested that changes in acMMAE and/or unconjugated MMAE exposure, as observed e.g. in special populations or due to DDI, are not expected to have a clinically relevant impact on safety and/or efficacy.

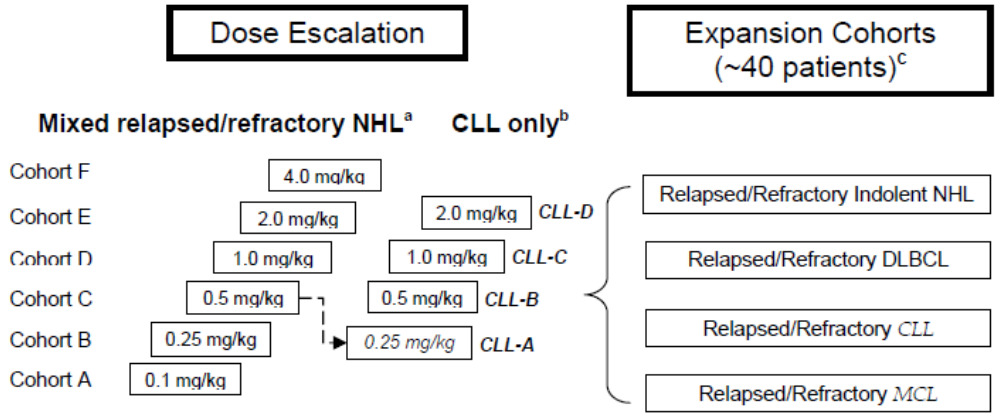
2.4.5. Conclusions on clinical pharmacology

Overall, it is concluded that the pharmacokinetics of polatuzumab vedotin has been sufficiently described by its three major analytes acMMAE, total antibody and unconjugated MMAE. The incidence of anti-polatuzumab vedotin antibodies in the clinical studies was rather low. Results suggested that polatuzumab vedotin at the proposed dose of 1.8 mg/kg Q3W regimen does not have a clinically meaningful effect on QT prolongation.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

- **Study DCS4968g:** An open-label, multicenter, phase I trial of the safety and pharmacokinetics of escalating doses of DCDS4501A (pola) in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma and chronic lymphocytic leukemia and DCDS4501A in combination with rituximab in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma



CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; MCL = mantle cell lymphoma; NHL = Non-Hodgkin lymphoma.

[a] Dose escalation in mixed B-cell NHL patients started at 0.1 mg/kg and could continue at the possible dose levels listed.

[b] After clearance of the 0.5 mg/kg Dose in NHL patients, CLL patients were enrolled in a separate dose escalation starting at 0.25 mg/kg. Note that doses listed in the figure are examples only; the actual doses tested depended on the doses tested and cleared in dose-escalation cohorts.

[c] In order to obtain additional safety, tolerability, and pharmacokinetic data, as well as preliminary evidence of clinical activity, patients could be enrolled at the RP2D in each of the following separate indication-specific expansion cohorts (to a maximum of approximately 40 patients in total): relapsed or refractory indolent/follicular NHL, DLBCL, and CLL (independent RP2D). Patients could subsequently be enrolled into the relapsed/refractory MCL cohort depending on the safety and anti-tumor activity observed in the other expansion (indolent NHL, DLBCL, and CLL) cohorts and at the discretion of the Sponsor.

Figure 14: Phase I Study Design (with an Example of the Dose Escalation)

The dose escalation cohorts were to enroll at least 3 patients (unless DLTs were observed in the first 2 patients prior to enrollment of a third patient) according to a standard 3 + 3 design.

Dose escalation was carried out with polatuzumab vedotin as a single agent, and in combination with rituximab. The inclusion/exclusion criteria properly represented the population of DLBCL patients with unmet medical need, transplant ineligible.

Results

95 patients were enrolled: 61 in dose-escalation cohorts and 34 in expansion cohorts. Among the DLBCL patients (n=40), median age was 67 years [20;81], with60% of patients ≥ 65 years; 25.0 presented with ECOG 2, and bulky disease in 30.0%.

The median number of treatment cycles received was 4.0 (n = 84). Dosing cycle adjustments to ≥28 day cycles were permitted per protocol.

DLT in dose-escalation, single – agent (SA): In the 2.4 mg/kg group, 2/11 patients experienced DLTs:

- Grade 4 neutropenia and Grade 4 pneumonia with neutropenic fever (1)
- Grade 3 hypoxia (1)

Polatuzumab vedotin at 2.4 mg/kg q3w was determined to be the recommended SA Phase II dose in DLBCL patients.

DLT in the combination group: A DLT of Grade 4 neutropenia occurred in 1 patient out of 9 DLT-evaluable patients. Based on the safety of the patients in this cohort, polatuzumab vedotin at 2.4 mg/kg q3w was deemed to be an acceptable RP2D in combination with rituximab.

Based on the 3+3 escalation study design, the dose of 2.4mg/kg was initially considered as the recommended Phase II dose, in single-agent treatment and in combination with rituximab (375mg/m2). Of note, the combination with rituximab was only tested with pola at 2.4mg/kg, not at lower doses.

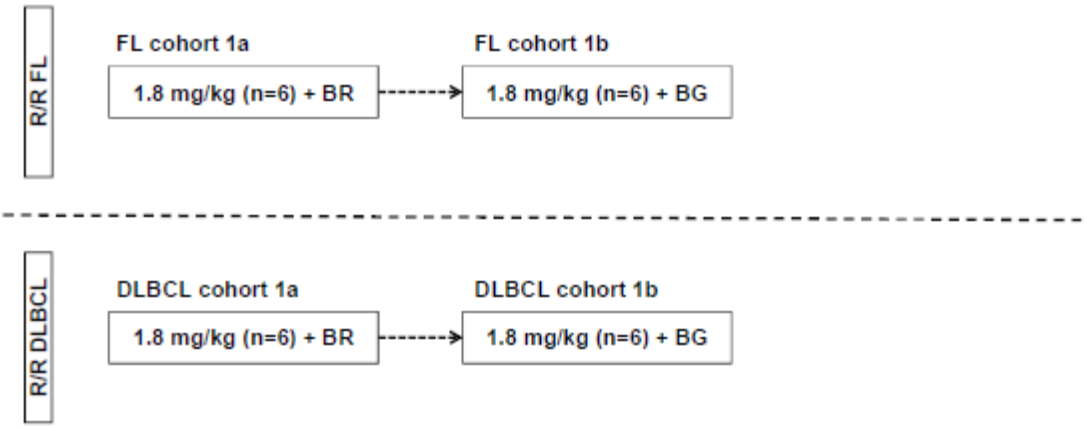
Among the 45 patients treated with pola 2.4 mg/kg SA, ORR was 51.1% (23/45, 7 CR and 16 PR), and 9 patients presented with stable disease (20.0%). The median duration of response (DoR) was 6.2 months (95% CI: 3.25, 19.32) and the median PFS was 5.7 months (95% CI: 2.99, 7.92).

Among the 11 patients treated with pola 1.8 mg/kg SA, 4 had PR (36.4%) and 3 (27.3%) had SD. The median PFS was 4.4 months (95% CI: 1.35, 7.36).

In the combination 2.4 mg/kg group (n=9), 2 CR and 5 PR was observed, with a median DoR of 12.3 months (95% CI: 4.27, NE) and a median PFS of 12.5 months (95% CI: 6.93, 17.35).

- **Study GO29365:** A Phase Ib/II study evaluating the safety, tolerability, and anti-tumor activity of polatuzumab vedotin (DCDS4501A) in combination with rituximab (R) or obinutuzumab (G) plus bendamustine (B) in relapsed or refractory follicular or diffuse large B-cell lymphoma.

Figure 15: Safety Run-in with separate FL (n = 12) and DLBCL (n = 12) cohorts in study GO29365



The phase Ib part of the pivotal study aimed at characterize the safety and tolerability of the combination of polatuzumab vedotin with BR or BG in R/R FL or R/R DLBCL patients, and define the R2PD.

The protocol was amended after FDA clinical hold at 2.4mg/kg, due to the frequency of deaths, serious adverse events and adverse events leading to study discontinuation at the 2.4 mg/kg dose of polatuzumab vedotin in studies DCS4968g (Phase I) and GO27834 (ROMULUS, Phase II). Thus, the phase Ib of the pivotal study was updated to a safety run-in, carried out in 6 patients per treatment arm (pola+BR / pola+BG), with pola at 1.8mg/kg.

In R/R DLBCL patients, 6 patients received pola +BR, and 6 received pola +BG. The median duration of treatment was 2.4 months in pola +BR arm, with a median of 4.5 cycles [2, 6]. Results were similar in pola+BG patients.

Safety criteria were observed in <33% of patients enrolled in safety run-in phase.

Two patients in each treatment arm died from PD. All patients presented with AEs, mainly grade 3-4 (5/6 in both treatment groups).

The dose of 1.8 mg/kg pola was defined as the RP2D in combination with BR or BG for the Phase II part of the study.

- Exposure response analysis

The exposure-response analysis, focused on R/R DLBCL patients, was based on supportive studies DCS4968g and GO27834, with pola SA and/or combined with rituximab or obinutuzumab, and the pivotal study GO29365 with pola +BR/BG.

The exposure-safety results included both analytes acMMAE and unconjugated MMAE, with AUC and Cmax measures. Exposure-efficacy results are focused on acMMAE AUC.

Based on supportive and pivotal studies, exposure-safety analysis did not identify significant correlation between acMMAE nor unconjugated MMAE exposure and the probability of the following AEs: Grade ≥3 Neutropenia, Grade ≥3 Infections and Infestations and Grade ≥3 Thrombocytopenia. It should be noted that a higher incidence of these AEs was observed in the pivotal study, possibly related to the addition of bendamustine and longer FU (refer to safety discussion).

Dose modification due to AEs was not significantly correlated to exposure in any of these analyses. However, based on cox PH regression, the TTO of dose modification was correlated to the exposure to unconjugated MMAE in supportive studies, and acMMAE in the pivotal study; thus the probability would not be increased with higher exposure, but it would be sooner.

Exposure-safety results showed a correlation between grade ≥2 peripheral neuropathy (PN) and acMMAE exposure in supportive studies, with both AUC (p=0.003) and Cmax (p=0.011). No similar correlation was observed in the pivotal study; this is expected since there was no dose escalation in the pivotal study. Moreover, a higher incidence of PN was observed in pooled supportive studies (25.2% vs 14.5%), possibly related to the wider dose range up to 2.4mg/kg and up to 8 cycles or more.

A correlation between grade ≥3 anemia and exposure to unconjugated MMAE was observed in the supportive studies (p=0.01 and 0.015 with AUC and Cmax respectively). This was not observed in the pivotal study, despite a higher incidence (18.8% vs 7.6%), possibly related to the addition of bendamustine.

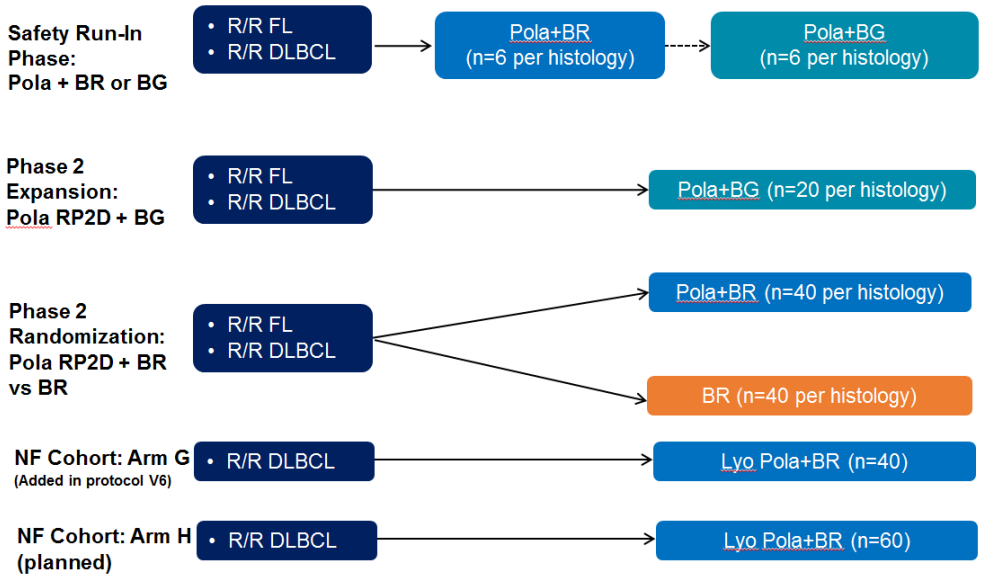
Exposure-efficacy results only showed significant correlation between acMMAE exposure and BOR/OR in the supportive studies (p=0.037 and 0.014 respectively). As expected in absence of dose increase, this was not observed in the pivotal study. However, the cox PH regression showed an increase in OS (p=0.048) with higher acMMAE exposure.

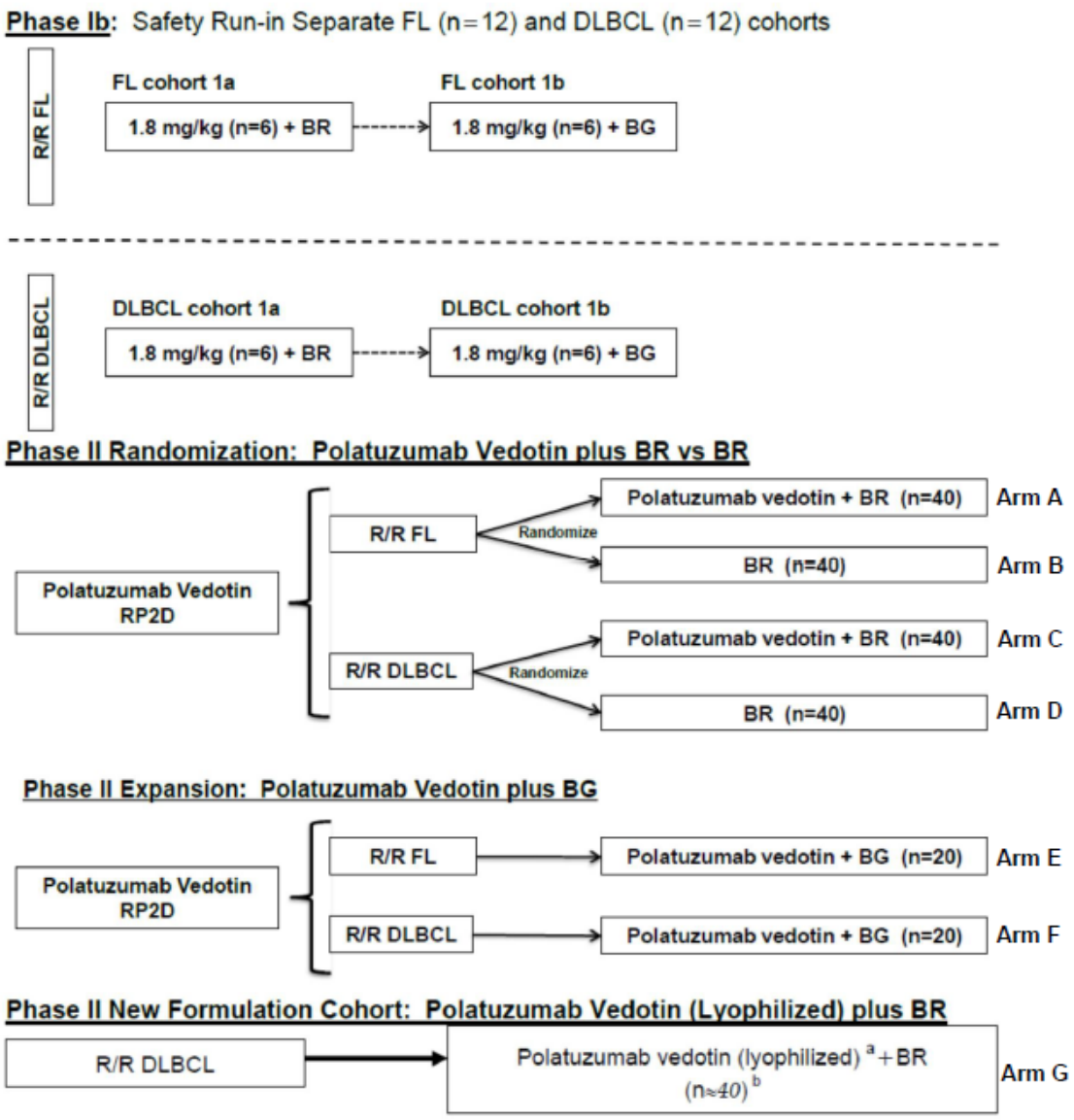
2.5.2. Main study(ies)

Study GO29365; **Phase Ib/II multicenter open-label study evaluating the safety, tolerability, and anti-tumor activity of polatuzumab vedotin (DCDS4501A) in combination with rituximab (R) or obinutuzumab (G) plus bendamustine (B) in relapsed or refractory follicular or diffuse large B-cell lymphoma**

Figure 16: Overview of GO29365 Study Design

Design





BR=bendamustine and rituximab; BG=bendamustine and obinutuzumab; DLBCL=diffuse large B-cell lymphoma; FL=follicular lymphoma; RP2D=recommended Phase II dose; R/R=relapsed or refractory. Rituximab (375 mg/m^2) D1 of each cycle, or obinutuzumab (1000 mg) D1, D8, D15 in Cycle 1, then D1 of each subsequent cycle plus bendamustine (90 mg/m^2) D2 and D3 in Cycle 1, then D1 and D2 in each subsequent cycle. Polatuzumab vedotin (1.8 mg/kg) D2 in C1 then D1 of each subsequent cycle.

FL: Treatment administered every 28 days x 6 cycles.

DLBCL: Treatment administered every 21 days x 6 cycles.

[a] Polatuzumab vedotin (lyophilized) dose 1.8 mg/kg.

Methods

Study Participants

Main inclusion criteria were:

- Age ≥ 18 years

- Histologically confirmed FL (Grade 1, 2, or 3a) or DLBCL
- Must have received at least one prior therapy for FL or DLBCL. Patients must have either relapsed or have become refractory to a prior regimen as defined below.

  R/R FL

  - Relapsed to prior regimen(s) after having a documented history of response (CR, CR unconfirmed [CRu], or PR) of ≥ 6 months in duration from completion of regimen(s)
  - Refractory to any prior regimen, defined as no response to the prior therapy, or progression within 6 months of completion of the last dose of therapy

  R/R DLBCL

  - Patients who are ineligible for second-line stem cell transplant (SCT), with progressive disease or no response (stable disease [SD]) < 6 months from start of initial therapy (2L refractory)
  - Patients who are ineligible for second-line SCT, with disease relapse after initial response ≥ 6 months from start of initial therapy (2L relapsed)
  - Patients who are ineligible for third-line (or beyond) SCT, with progressive disease or no response (SD) < 6 months from start of prior therapy (3L + refractory)
  - Patients who are ineligible for third-line (or beyond) SCT with disease relapse after initial response ≥ 6 months from start of prior therapy (3L + relapsed)

  In addition to the above defined responses to prior regimens, the Phase II, single-arm, NF Cohort (Arm G) includes the following diagnoses by 2016 WHO classification of lymphoid neoplasms:

  – DLBCL, not otherwise specified (NOS) (including both germinal center B-cell type and activated B-cell type)
  – T-cell/histiocyte-rich large B-cell lymphoma
  – High-grade B-cell lymphoma with MYC and BCL-2 and/or BCL-6 Rearrangements
  – High grade B-cell lymphoma, NOS
  – Primary mediastinal (thymic) large B-cell lymphoma
  – Epstein Barr virus positive DLBCL, NOS
  – HHV8-positive DLBCL, NOS

- If the patient has received prior bendamustine, response duration must have been > 1 year (for patients who have relapse disease after a prior regimen)

Main exclusion criteria were:

- History of severe allergic or anaphylactic reactions to humanized or murine MAbs (or recombinant antibody-related fusion proteins) or known sensitivity or allergy to murine products
- Ongoing corticosteroid use > 30 mg/day prednisone or equivalent, for purposes other than lymphoma symptom control
- Completion of autologous stem cell transplant within 100 days prior to Cycle 1 Day 1
- Prior allogeneic stem cell transplant
- Eligibility for autologous SCT

- Grade 3b follicular lymphoma
- History of transformation of indolent disease to DLBCL
- Primary or secondary CNS lymphoma
- Current Grade >1 peripheral neuropathy
- Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina) or significant pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment or any major episode of infection requiring treatment with intravenous (IV) antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 4 weeks prior to Cycle 1 Day 1
- Vaccination with a live vaccine within 28 days prior to treatment
- Any of the following abnormal laboratory values, unless abnormal laboratory values are due to underlying lymphoma per the investigator:
  - Creatinine $>1.5\times$ ULN or a measured creatinine clearance <40 mL/min
  - AST or ALT $>2.5\times$ ULN
  - Total bilirubin $\geq 1.5\times$ ULN

Treatments

Polatuzumab vedotin: 1.8 mg/kg administered by intravenous (IV) infusion on Day 2 of Cycle 1 and then Day 1 of subsequent Cycles 2–6

Bendamustine: 90 mg/m^2 administered by IV infusion on Days 2 and 3 of Cycle 1, then Days 1 and 2 of subsequent Cycles 2–6

Rituximab: 375 mg/m^2 administered by IV infusion on Day 1 of Cycles 1–6

Objectives

Primary efficacy objectives and endpoints

Phase Ib; To identify the recommended Phase II dose (RP2D) for polatuzumab vedotin

Phase II; To evaluate the efficacy of the combination of polatuzumab vedotin plus BR as measured by positron emission tomography (PET)- defined complete response (CR) rate using Modified Lugano 2014 Response Criteria (positron emission tomography– computed tomography [PET-CT] criteria) at the time of primary response assessment (6–8 weeks after Cycle 6 Day 1 or last dose of study medication) as defined by the Independent Review Committee (IRC)

Main Secondary Objectives

- Safety:
  - To assess the safety and tolerability of the combination of polatuzumab vedotin with BR or BG
  - To assess the immunogenicity of polatuzumab vedotin and obinutuzumab
- Patient-Reported Outcomes, evaluating peripheral neuropathy (PN).

- OS was studied as part of the exploratory objectives.

Outcomes/endpoints

Table 34: Efficacy Outcome Measures and Analysis Methodology for Study GO29365

Outcome Measure	Analysis Methodology
Primary Efficacy Endpoint	
CR rate as measured at the primary response assessment (6–8 weeks after Cycle 6 Day 1 or last dose of study medication) as measured by PET-CT scan and as determined by an IRC. (pola+BR vs. BR randomized arms).	CR rate, defined as the percentage of patients with CR, was estimated and the corresponding Clopper-Pearson exact 95% CI was constructed for each treatment arm. The difference in PET CR rates between pola+BR and BR arms was estimated along with the corresponding 95% CI on the basis of normal approximation to the binomial distribution. An exploratory comparison of CR rates for the pola+BR and BR regimens was conducted using the Cochran-Mantel-Haenszel χ^2-square test adjusted for randomization stratification factors (Agresti, 2002).
Secondary Efficacy Endpoint	
Response rates measured at the primary response assessment: • CR (INV-assessed) and OR (INV- and IRC-assessed CR or PR) based on PET alone • CR (IRC-assessed) based on PET (pola+BG cohorts) • CR and OR (INV- and IRC-assessed) based on CT alone • BOR (INV-assessed) at any assessment while on study based on PET alone or CT alone. • BOR (IRC-assessed) by PET-CT or CT alone Time-to -event outcome measures (DLBCL only): • DOR (IRC-assessed) by PET-CT or CT alone • PFS (IRC-assessed) by PET-CT or CT alone	Patients without a post–baseline tumor assessment were considered non-responders. Analyses of secondary efficacy response endpoints identical to those described above for the primary efficacy endpoint Analyses of time to event endpoints are described below
Exploratory Efficacy Endpoint	
Time-to-event outcome measures: • DOR (INV-assessed)	Definitions and the censoring rules applied are described in Section 6.4.3 of the protocol. Median DOR was estimated, along with the corresponding 95% CI using the method of Brookmeyer and Crowley (1982). No formal comparisons of DOR across treatment arms were conducted.
• PFS (INV-assessed) • EFS • OS	Distribution of durations for PFS, EFS and OS summarized descriptively using Kaplan-Meier methodology (Kaplan and Meier, 1958) to estimate median (if analytically possible), 1-year, and 2-year PFS and 95% CIs using Greenwood's formula. There was no pre-specified alpha control plan; p-values are provided for descriptive purpose only.

Sample size

Sample size calculation was based on the following assumptions:

- With 40 patients per arm, 95% exact Clopper-Pearson Confidence Intervals for estimation of the true CR rate for would have a margin of error not exceeding ± 17%.
- With 40 patients in each arm, assuming a 40% CR rate in the BR arm, and a 25% increase in CR rate when polatuzumab vedotin is added to BR, the 95% CI for the difference in CR rates is (3.8%, 46.2%).

Randomisation

DLBCL subjects were randomized in an 1:1 ratio to receive Polatuzumab + BR (Arm A, N=40) or BR alone (Arm B, N=40). A new formulation cohort (Polatuzumab Vedotin lyophilized) was included in Arm G (N=40 subjects, including 10 subjects with one prior line of therapy). Further 60 subjects are planned to be included in Arm H (N=60) receiving the new formulation based upon, whereof at least 30% had one prior line of therapy. Randomization was stratified by duration of response to prior therapy (≤12 months vs. >12 months).

Blinding (masking)

This is an open-label study.

Statistical methods

No proper statistical hypothesis was raised in this exploratory phase Ib/II study.

The applicant used 95% exact Clopper-Pearson confidence intervals (CIs). The applicant assumed a 40% CR rate in the BR arm, and a 25% increase in CR rate when polatuzumab vedotin is added to BR. Thus, with 40 patients per arm, the 95% CI for the difference in CR rates is 3.8%, 46.2%. The applicant estimated that with 40 patients in each of the BR arms, there is at least an 87% chance of observing at least one AE with true incidence of ≥5%.

The applicant assumed a margin of error of +/- 17% based on sample size of 40 patients per arm.

An exploratory comparison of CR rates for the BR-containing regimens was conducted using the Cochran Mantel Haenszel chi-square test adjusted for randomization stratification factors.

Response assessment was determined using the Modified Lugano 2014 Response Criteria. Analysis was performed on ITT population.

Sensitivity analysis:

To assess the robustness of the results of PFS by IRC in the randomized Phase II portion, the applicant provide sensitivity analysis with two additional censoring rules.

- For the patients who had missed one or more assessments before their recorded event of disease progression or death, the data were censored at the date of the last non-missing disease assessments prior to the events.
- For patients who started new antilymphoma therapies (NALT) prior to the disease progression, the data were censored at the date of the last non-missing disease assessments before the NALT.

The estimates of the PFS by IRC using additional censoring rules are consistent with previous IRC PFS results with the initial censoring rule.

Multiple Cox Regression, for PFS and OS

The prognostic factors included in the final models were selected based on the statistical threshold (p=0.2) and clinical consideration while controlling for the multi-colinearity among the factors. Two sets

of factors were used for PFS and OS: PFS: Ann Arbor Stage, Baseline ECOG and IPI; OS: Ann Arbor Stage, Baseline ECOG and bulky disease and IPI. The multiple cox-regression adjusted on these prognostic factors confirmed previous PFS and OS results, in favor of pola+BR arm (both INV and IRC assessed).

Recruitment

Between 15 October 2014 (first patient in) and 13 September 2016 (last patient in, Arms A-F), a total of 225 patients were enrolled in study Arms A to F at 54 investigator centres in the following countries: US (12 sites), France (6 sites), Spain (5 sites), Australia (4 sites), Canada (4 sites), Czech Republic (4 sites), Italy (4 sites), Turkey (4 sites), Great Britain (3 sites), Hungary (3 sites), Germany (2 sites), Korea (2 sites) and The Netherlands (1 site).

First Patient Entered: 15 October 2014

Last Patient Entered Arms A–F: 13 September 2016

Conduct of the study

The first version of the protocol for Study GO29365 was dated 23 May 2014. Protocol amendments for Study GO29365 - all implemented after the first patient had been dosed on 15 October 2014- are summarized below.

1st Amendment dated 27 April 2015, Protocol v2.0, This was implemented after the first 9 patients in Cohort 1A of the safety run-in (all 6 DLBCL and 3 FL) had been dosed with pola+BR. The key reasons for this amendment were as follows:

- Amendment to the Phase Ib portion to be a safety run-in at the 1.8 mg/kg polatuzumab vedotin dose for each lymphoma histology. The original design for a Phase Ib dose-escalation of polatuzumab vedotin to 2.4 mg/kg was modified following the issuance of a Partial Clinical Hold at the 2.4 mg/kg dose by the U.S. Food and Drug Administration in September 2014.
- Adoption of the new Lugano 2014 response criteria (Cheson et al. 2014) for NHL (which were published after finalization the first protocol), for evaluating CR by PET at the primary response assessment by IRC.

2nd Amendment dated 14 September 2015, Protocol v3.0 This was implemented after one patient in the BR arm of the randomized Phase II had been dosed, and included the following key changes:

- Modification of the Lugano 2014 response criteria to include the requirement for bone marrow examinations for all patients (DLBCL as well as FL) at screening for staging purposes. Response was assessed by the IRC and the investigator on the basis of physical examinations, CT scans, PET scans, and bone marrow examinations using the modified Lugano 2014 response criteria.
- Update to eligibility criteria to exclude patients with secondary, as well as primary and CNS lymphoma and exclude all patients (R/R FL as well as R/R DLBCL) eligible for autologous stem cell transplantation.
- Inclusion of gastrointestinal perforations as an identified risk associated with obinutuzumab treatment.
- Updates to the guidelines for monitoring of hepatitis B reactivation for patients with occult or prior hepatitis B virus infection (negative HBsAg and positive HBcAb), for pregnancy prevention for women of childbearing age and for men (extension of period of contraception) and for the pregnancy test for all women of childbearing age.

3rd Amendment dated 11 July 2017, Protocol v4.0 The primary purpose of this amendment was to include second malignancies as a AESI/non-serious expedited AE requiring expedited reporting, and to require indefinite reporting of second malignancies (even if the study has ended) for patients enrolled in the obinutuzumab containing cohorts (pola+BG).

4th Amendment dated 16 November 2017, Protocol v5.0. The primary purpose of this amendment was to add an additional cohort of 20–30 patients (Arm G) with R/R DLBCL who will receive a new lyophilized formulation of polatuzumab vedotin (140 mg/vial) in combination with BR, in order to gain clinical experience with this combination in R/R DLBCL in terms of PK and safety. Additionally, protocol v5 introduced the analysis of PFS and DOR by IRC for the DLBCL cohorts as requested by the U.S. FDA.

5th Amendment dated 31 May 2018, Protocol v6. The primary purpose of this amendment was the expansion of Arm G, adding 10 patients with R/R DLBCL with one prior line of therapy (i.e., second line [2L]) to evaluate the efficacy of polatuzumab vedotin (lyophilized) in combination with BR. Protocol v6 also added the analysis of IRC assessed best overall response for the DLBCL cohorts.

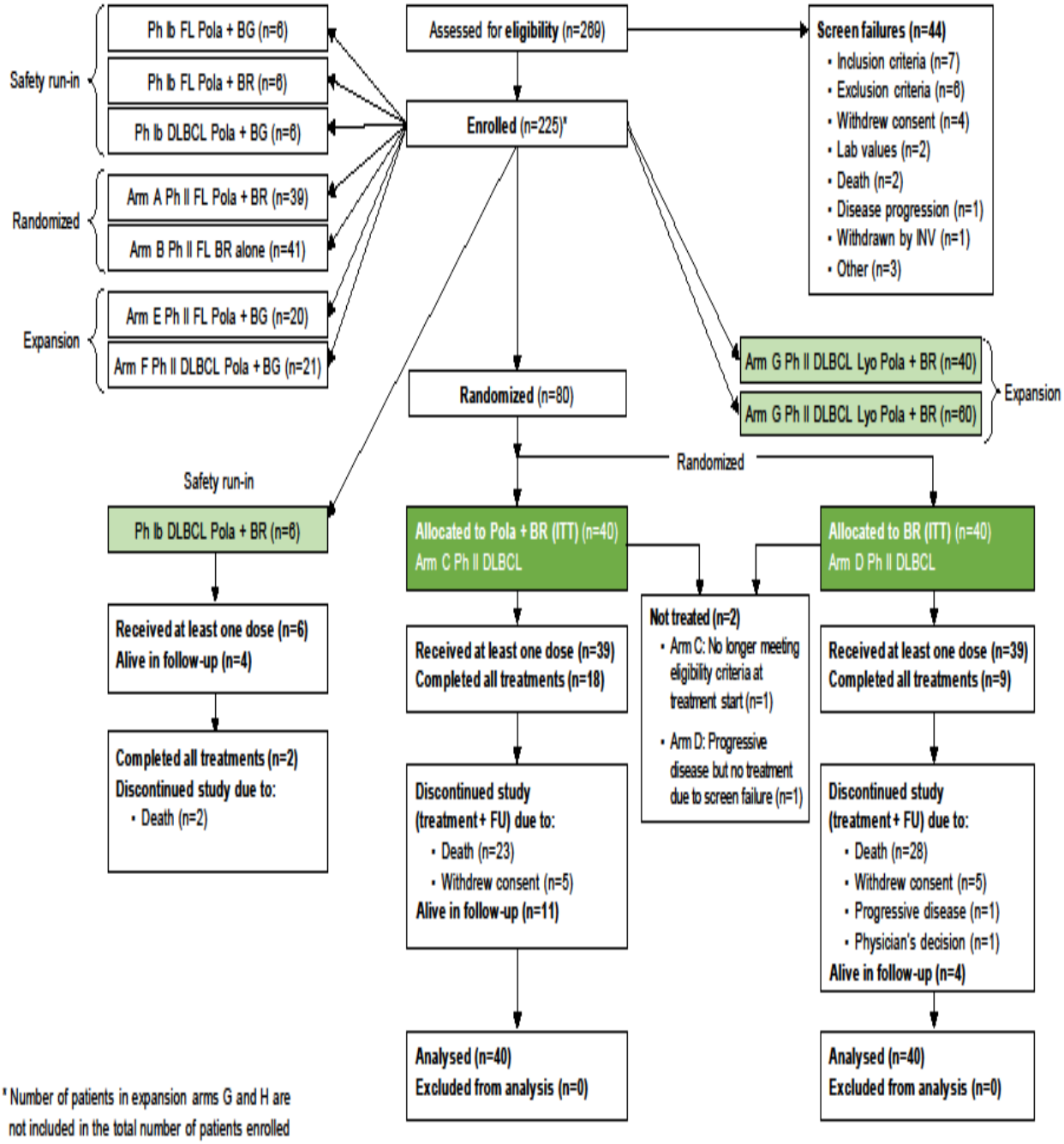
6th Amendment dated 02 October 2018, Protocol v7 The purpose was to add a new arm (Arm H) to the Phase II New Formulation (NF) Cohort that will enroll approximately 60 patients with relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL) who will receive the new 140-mg/vial lyophilized formulation in order to gain supportive clinical experience with the combination of polatuzumab vedotin (lyophilized formulation) with BR. Objectives, study description, exploratory biomarker assessments were updated for Arm H, inclusion criterion for HHV8-positive DLBCL, not otherwise specified was deleted. Pharmacokinetic Sampling and Anti-Drug Antibody Schedule for the NF Cohort (Arm H) for Patients Treated with Polatuzumab Vedotin (Lyophilized) plus BR was added. Additional important requirements were: Updated the Statistical Considerations and Analysis Plan for the NF Cohort, including the rationale for sample size and pooled efficacy analysis plan (Arms G and H); Updated the secondary objectives for Arm G of the NF Cohort to include investigator-assessed duration of response, progression-free survival, event-free survival, and overall survival.

Results

Primary analysis, with data cut-off date on 30 Apr 2018, was provided, allowing a 1-year FU after preliminary response assessment for all treated patients.

Participant flow

Figure 17 Participant flow



Baseline data

Table 35: Key Demographic, Baseline Disease Characteristics and Prognostic Factors for Patients with R/R DLBCL (ITT Population)

	Phase Ib	Phase II (randomized)		Phase Ib/II
	Pola+BR	BR	Pola+BR	Pola+BR (total)
	N = 6	N = 40	N = 40	N = 46
Demographics				
Age: median, range (years)	65.0 (58–79)	71.0 (30–84)	67.0 (33–86)	66.5 (33–86)
≥65 years	3 (50.0%)	26 (65.0%)	23 (57.5%)	26 (56.5%)
Sex, male	4 (66.7%)	25 (62.5%)	28 (70.0%)	32 (69.6%)
Race				
White	5 (83.3%)	31 (77.5%)	26 (65.0%)	31 (67.4%)
Asian	1 (16.7%)	4 (10.0%)	6 (15.0%)	7 (15.2%)
American Indian or Alaska Native	0	1 (2.5%)	0	0
Black or African American	0	0	3 (7.5%)	3 (6.5%)
Unknown	0	4 (10.0%)	5 (12.5%)	5 (10.9%)
Ethnicity				
Not Hispanic or Latino	6 (100.0%)	36 (90.0%)	35 (87.5%)	41 (89.1%)
Hispanic or Latino	0	1 (2.5%)	1 (2.5%)	1 (2.2%)
Unknown/not stated	0	3 (7.5%)	4 (10.0%)	4 (8.7%)

	Phase Ib	Phase II (randomized)		Phase Ib/II
	Pola+BR	BR	Pola+BR	Pola+BR (total)
ECOG PS at Baseline				
0 or 1	6 (100.0%)	31 (77.5%)	33 (82.5%)	39(84.7%)
2	0	8 (20.0%)	6 (15.0%)	6 (13.0%)
Unknown	0	1 (2.5%)	1 (2.5%)	1 (2.2%)
Primary Reason for Stem Cell Transplant Ineligibility				
Age	1 (16.7%)	19 (47.5%)	13 (32.5%)	14 (30.4)
Co-morbidities	0	1 (2.5%)	1 (2.5%)	1 (2.2%)
Failed prior transplant	0	6 (15.0%)	10 (25.0%)	10 (21.7%)
Insufficient cells collected	0	0	0	0
Insufficient response to salvage therapy	2 (33.3%)	9 (22.5%)	12 (30.0%)	14 (30.4%)
Other	1 (16.7%)	1 (2.5%)	2 (5.0%)	3 (6.5%)
Patient refused transplant	2 (33.3%)	2 (5.0%)	2 (5.0%)	4 (8.7%)
Performance status	0	2 (5.0%)	0	0
Baseline Disease Characteristics				
Time since diagnosis at study entry: median, range (months)	0.5 (0–1)	0.8 (0–15)	0.7 (0–20)	0.7 (0–20)
WHO 2016 DLBCL status[a]				
DLBCL, NOS: ABC	4 (66.7%)	19 (47.5%)	19 (47.5%)	23 (50.0%)
DLBCL, NOS: GCB	1 (16.7%)	17 (42.5%)	15 (37.5%)	16 (34.8%)

	Phase Ib	Phase II (randomized)		Phase Ib/II
	Pola+BR	BR	Pola+BR	Pola+BR (total)
DLBCL, NOS	1 (16.7%)	4 (10.0%)	4 (10.0%)	5 (10.9%)
FL	0	0	1 (2.5%)	1 (2.2%)
Burkitt lymphoma	0	0	1 (2.5%)	1 (2.2%)
Primary mediastinal (thymic) large B-cell lymphoma	-	-	-	-
Ann Arbor Stage III or IV at study entry	4 (66.7%)	36 (90.0%)	34 (85.0%)	38 (82.6%)
Bulky disease (≥7.5 cm)	1 (16.7%)	15 (37.5%)	10 (25.0%)	11 (23.9%)
Extranodal involvement	4 (66.6%)	29 (72.5%)	27 (67.5%)	31 (67.4%)
Prognostic Factors				
IPI score at enrollment				
0–1 (low)	1 (16.7%)	3 (7.5%)	9 (22.5%)	10 (21.7%)
2 (low–intermediate)	3 (50.0%)	8 (20.0%)	9 (22.5%)	12 (26.1%)
3 (high–intermediate)	2 (33.3%)	12 (30.0%)	13 (32.5%)	15 (32.6%)
4–5 (high)	0	17 (42.5%)	9 (22.5%)	9 (19.6%)

Table 36: Previous Anti-Lymphoma Treatment and Response in Patients with R/R DLBCL (ITT Population)

	Phase Ib	Phase II (randomized)*		Phase Ib/II	Phase Ib	Phase II (expansion)	Phase Ib/II
	Pola+BR	BR	Pola+BR	Pola+BR (total)	Pola+BG	Pola+BG	Pola+BG (total)
	N = 6	N = 40	N = 40	N = 46	N = 6	N = 21	N = 27
Prior anti-lymphoma chemotherapy:	6 (100.0%)	40 (100.0%)	40 (100.0%)	46 (100.0%)	6 (100.0%)	21 (100.0%)	27 (100.0%)
Median no. lines (range)	2.0 (1–2)	2.0 (1–5)	2.0 (1–7)	2.0 (1–7)	2.0 (1–5)	3.0 (1–5)	2.0 (1–5)
1 line	2 (33.3%)	12 (30.0%)	11 (27.5%)	13 (28.3%)	1 (16.7%)	5 (23.8%)	6 (22.2%)
2 lines	4 (66.7%)	9 (22.5%)	11 (27.5%)	15 (32.6%)	4 (66.7%)	5 (23.8%)	9 (33.3%)
≥3 lines	0	19 (47.5%)	18 (45.0%)	18 (39.1%)	1 (16.7%)	11 (52.4%)	12 (44.4%)
Prior treatments:							
Anti-CD20	6 (100.0%)	40 (100.0%)	39 (97.5%)	45 (97.8%)	6 (100.0%)	21 (100.0%)	27 (100.0%)
Bendamustine	0	0	1 (2.5%)	1 (2.2%)	0	2 (9.5%)	2 (7.4%)
Bone-marrow transplant	0	6 (15.0%)	10 (25.0%)	10 (21.7%)	1 (16.7%)	1 (4.8%)	2 (7.4%)
Cancer radiotherapy	1 (16.7%)	10 (25.0%)	11 (27.5%)	12 (26.1%)	2 (33.3%)	10 (47.6%)	12 (44.4%)
Refractory to last prior anti-CD20 agents[a]	4 (66.7%)	18 (45.0%)	18 (45.0%)	22 (47.8%)	4 (66.7%)	9 (42.9%)	13 (48.1%)
No	1 (16.7%)	6 (15.0%)	10 (25.0%)	11 (23.9%)	2 (33.3%)	2 (9.5%)	4 (14.8%)
Unknown	1 (16.7%)	16 (40.0%)	12 (30.0%)	13 (28.3%)	0	10 (47.6%)	10 (37.0%)
Refractory to last prior anti-lymphoma therapy[b]	5 (83.3%)	34 (85.0%)	30 (75.0%)	35 (76.1%)	4 (66.7%)	19 (90.5%)	23 (85.2%)
Time from last anti-lymphoma therapy: median, range (days)[c]	53.0 (43–1477)	82.0 (21–2948)	131.0 (17–11744)	114.0 (17–11744)	249.5 (48–1359)	107.0 (7–991)	115.0 (7–1359)
Duration of response to prior therapy:[d]							
≤12 months	5 (83.3%)	33 (82.5%)	32 (80.0%)	37 (80.4%)	4 (66.7%)	19 (90.5%)	23 (85.2%)

BG : bendamustine and obinutuzumab; BR : bendamustine and rituximab; CRF : case report form; DLBCL : diffuse large B-cell lymphoma; ITT : intent-to-treat; IxRS : interactive voice or Web-based response system; R/R : relapsed/refractory.
a Defined as no response or progression or relapse within 6 months of last anti-lymphoma therapy end date among patients whose last prior regimen contained anti−CD20.
b Defined as no response or progression or relapse within 6 months of last anti−lymphoma therapy end date.
c Defined as time from end date of last anti−lymphoma therapy to first dose date

d Duration of response to prior therapy was based on IxRS for randomized cohorts and CRF for non-randomized cohorts.

Numbers analysed

Table 37: Summary of Analysis Populations

	Phase Ib	Phase II	Phase II	Phase Ib	Phase II
	Pola+BR	BR	Pola+BR	Pola+BG	Pola+BG
DLBCL					
No. included in ITT Population	6	40	40	6	21
No. included in Safety Population	6	39	39	6	20
FL					
No. included in ITT Population	6	41	39	6	20
No. included in Safety Population	6	41	38	6	20

BG = bendamustine and obinutuzumab; BR = bendamustine and rituximab; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; ITT = intent-to-treat.

Outcomes and estimation

The median duration of follow-up for all cohorts was between 20.7 and 37.6 months, as summarized in the table below.

Table 38: Duration of Follow-Up (ITT Population)*

Study Phase	Phase Ib	Phase II (randomized)		Phase Ib	Phase II (expansion)
Treatment	Pola+BR	BR	Pola+BR	Pola+BG	Pola+BG
R/R DLBCL					
Cohort/Arm	1a	D	C	1b	F
Sample size	n=6	n=40	n=40	n=6	n=21
median TTE, mo (95% CI)	37.6 (34.5, 40.1)	22.3 (20.1, 24.9)	22.3 (20.5, 23.1)	32.2 (32.2, NE)	26.9 (25.4, 28.0)
R/R FL					
Cohort/Arm	1a	B	A	1b	E
Sample size	n=6	n=41	n=39	n=6	n=20
median TTE, mo (95% CI)	35.0 (33.2, 37.8)	20.7 (20.3, 22.6)	21.5 (20.4, 23.0)	31.6 (13.4, 31.8)	23.8 (22.9, 24.6)

BG = bendamustine and obinutuzumab; BR = bendamustine and rituximab; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; ITT = intent-to-treat; NE = not estimable; TTE = time to event.

* Survival follow-up calculated by reverse K-M method.

Table 39: Overview of Efficacy in Patients with Relapsed/Refractory DLBCL (Phase II GO29365; ITT Population)

Study Phase	Randomized Phase		Expansion Phase
Treatment	BR Phase II	Pola+BR Phase II	Pola+BG Phase II
Sample size	n=40	n=40	n=21
Primary Efficacy Endpoint			
CR at PRA by PET (IRC assessed)			
n (%)	7 (17.5%)	16 (40.0%)	6 (28.6%)
95% CI for response rate (Clopper-Pearson)	(7.3, 32.8)	(24.9, 56.7)	(11.3, 52.2)
Δ (95% CI) (Wilson); p-value (CMH chi-square*)	22.5 (2.6, 40.2); p=0.0261		–
Secondary Efficacy Endpoints			
Response rates with PET			
OR (CR/PR) at PRA by PET (IRC assessed)			
n (%)	7 (17.5%)	18 (45.0%)	5 (23.8%)
95% CI for response rate (Clopper-Pearson)	(7.3, 32.8)	(29.3, 61.5)	(8.2, 47.2)
Δ (95% CI) (Wilson); p-value (CMH chi-square*)	27.5 (7.2, 45.0); p=0.0069		–
CR at PRA by PET (INV assessed)			
n (%)	6 (15.0%)	17 (42.5%)	7 (33.3%)
95% CI for response rate (Clopper-Pearson)	(5.7, 29.8)	(27.0, 59.1)	(14.6, 57.0)
Δ (95% CI) (Wilson); p-value (CMH chi-square*)	27.5 (7.7, 44.7); p=0.0061		–
OR (CR/PR) at PRA by PET (INV assessed)			
n (%)	7 (17.5%)	19 (47.5%)	7 (33.3%)
95% CI for response rate (Clopper-Pearson)	(7.3, 32.8)	(31.5, 63.9)	(14.6, 57.0)
Δ (95% CI) (Wilson); p-value (CMH chi-square*)	30.0 (9.5, 47.4); p=0.0036		–
Response rates without PET (CT alone)			
CR at PRA by CT (IRC assessed)			
n (%)	1 (2.5%)	9 (22.5%)	5 (23.8%)
95% CI for response rate (Clopper-Pearson)	(0.1, 13.2)	(10.8, 38.5)	(8.2, 47.2)
Δ (95% CI) (Wilson); p-value (CMH chi-square*)	20.0 (5.5, 35.1); p=0.0078		–
OR (CR/PR) at PRA by CT (IRC assessed)			
n (%)	6 (15.0%)	17 (42.5%)	8 (38.1%)
95% CI for response rate (Clopper-Pearson)	(5.7, 29.8)	(27.0, 59.1)	(18.1, 61.6)
Δ (95% CI) (Wilson); p-value (CMH chi-square*)	27.5 (7.7, 44.7); p=0.0051		–
CR at PRA by CT (INV assessed)			
n (%)	2 (5.0%)	8 (20.0%)	3 (14.3%)
95% CI for response rate (Clopper-Pearson)	(0.6, 16.9)	(9.1, 35.7)	(3.1, 36.3)
Δ (95% CI) (Wilson); p-value (CMH chi-square*)	15.0 (0.1, 30.2); p=0.0454		–

Study Phase	Randomized Phase		Expansion Phase
Treatment	**BR Phase II**	**Pola+BR Phase II**	**Pola+BG Phase II**
OR (CR/PR) at PRA by CT (INV assessed)			
n (%)	6 (15.0%)	18 (45.0%)	7 (33.3%)
95% CI for response rate (Clopper-Pearson)	(5.7, 29.8)	(29.3, 61.5)	(14.6, 57.0)
Δ (95% CI) (Wilson); p-value (CMH chi-square*)	30.0 (9.9, 47.1); p = 0.0032		–
BOR by PET-CT or CT (CR/PR) (INV assessed)			
n (%)	13 (32.5%)	28 (70.0%)	11 (52.4%)
95% CI for response rate (Clopper-Pearson)	(18.6, 49.1)	(53.5, 83.4)	(29.8, 74.3)
Δ (95% CI) (Wilson); p-value (CMH chi-square*)	37.5 (15.6, 54.7); p = 0.0006		–
BOR by PET-CT or CT (CR/PR) (IRC assessed)			
n (%)	10 (25.0%)	25 (62.5%)	9 (42.9%)
95% CI for response rate (Clopper-Pearson)	(12.7, 41.2)	(45.8, 72.3)	(21.8, 66.0)
Δ (95% CI) (Wilson); p-value (CMH chi-square*)	37.5 (15.8, 54.6); p = 0.0005		
DOR (IRC assessed)			
Patients with event, n (%)	8/10 (80.0%)	13/25 (52.0%)	4 (44.4%)
median DOR (95% CI)	7.7 (4.0, 18.9)	12.6 (7.2, NE)	NE (9.7, NE)
HR (95% CI); stratified p-value (log-rank)	0.47 (0.19, 1.14); p = 0.0889		–
PFS (IRC assessed)			
Patients with event, n (%)	32 (80.0%)	25 (62.5%)	15 (71.4%)
median PFS (95% CI)	3.7 (2.1, 4.5)	9.5 (6.2, 13.9)	5.8 (3.2, 11.9)
HR (95% CI); stratified p-value (log-rank)	0.36 (0.21, 0.63); p = 0.0002		–
Exploratory Efficacy Endpoints			
DOR (INV assessed)			
Patients with event, n (%)	11/13 (84.6%)	17/28 (60.7%)	6 (54.5%)
median DOR (95% CI)	4.1 (2.6, 12.7)	10.3 (5.6, NE)	16.1 (2.8, NE)
HR (95% CI); stratified p-value (log-rank)	0.44 (0.20, 0.95); p = 0.0321		–
PFS (INV assessed)			
Patients with event, n (%)	35 (87.5%)	27 (67.5%)	15 (71.4%)
median PFS (95% CI)	2.0 (1.5, 3.7)	7.6 (6.0, 17.0)	5.1 (2.1, 18.2)
HR (95% CI); stratified p-value (log-rank)	0.34 (0.20, 0.57); p < 0.0001		–
EFS (INV assessed)			
Patients with event, n (%)	38 (95.0%)	29 (72.5%)	16 (76.2%)
median EFS (95% CI)	2.0 (1.5, 3.1)	6.4 (4.0, 11.1)	4.5 (2.1, 11.6)
HR (95% CI); stratified p-value (log-rank)	0.30 (0.18, 0.50); p<0.0001		–
OS			
Patients with event, n (%)	28 (70.0%)	23 (57.5%)	13 (61.9%)
median OS (95% CI)	4.7 (3.7, 8.3)	12.4 (9.0, NE)	9.3 (4.4, NE)
HR (95% CI); stratified p-value (log-rank)	0.42 (0.24, 0.75); p = 0.0023		–

BG = bendamustine and obinutuzumab; BOR = best objective response; BR = bendamustine and rituximab; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CR = complete response; CT = computed tomography; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; EFS = event-free survival; INV = investigator; IRC = Independent Review Committee; ITT = intent to treat; K-M = Kaplan-Meier; NE = not estimable; OR = objective response; OS = overall survival; PD = progressive disease; PET = positron emission tomography; PFS = progression-free survival; PR = partial response; PRA = primary response assessment (6–8 weeks after Cycle 6 Day 1 or last dose of study medication); R/R = relapsed/refractory.

* Cochran-Mantel-Haenszel χ^2 test adjusted for randomization stratification factors: DOR to prior therapy (≤12 months vs. >12 months); see Section 3.6.3).

† Includes patients who achieved objective response (CR/PR) during the study.

Time to PFS event

Figure 18: Swim-Lane Plots of Time-to-PFS Event and Durability of Response with PET in Patients with R/R DLBCL _ Pola+BR arm _ (Randomized Phase II; ITT Population; INV-Assessed)

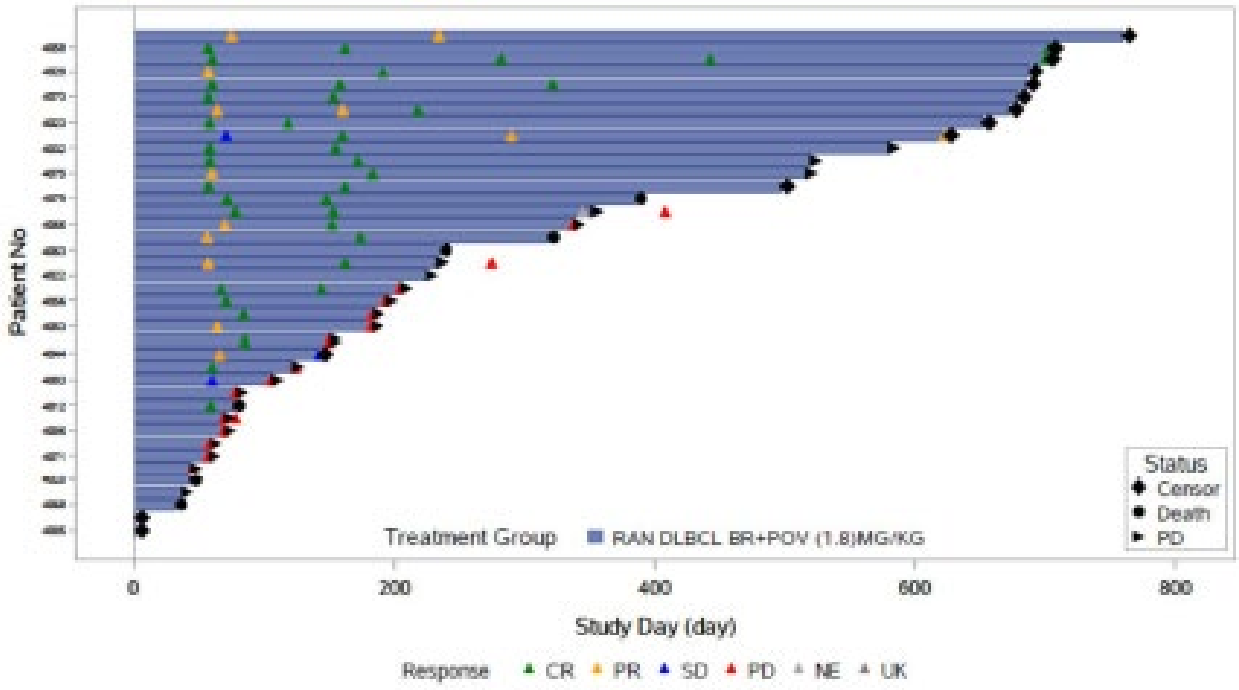
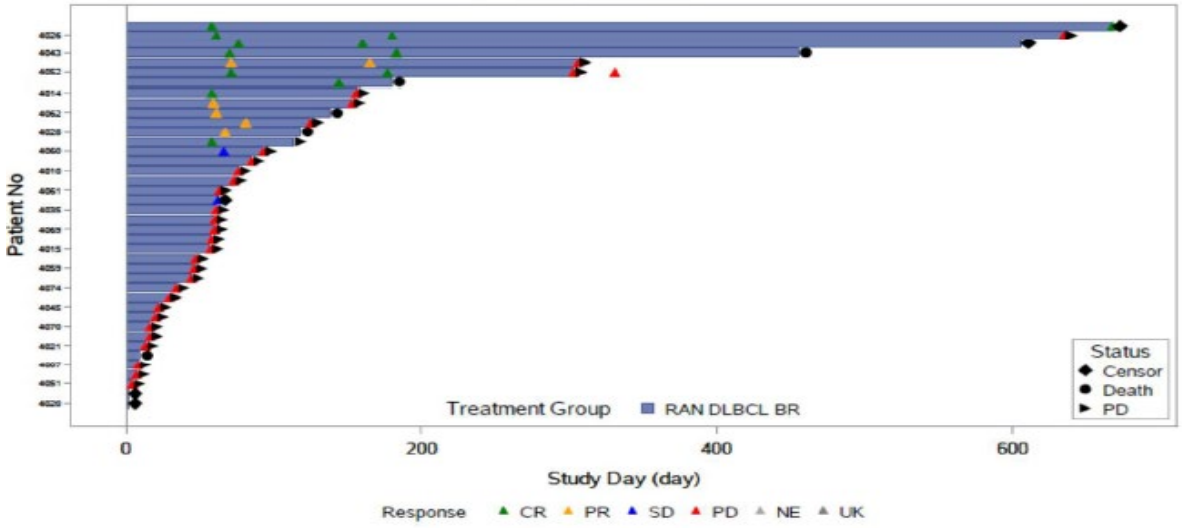
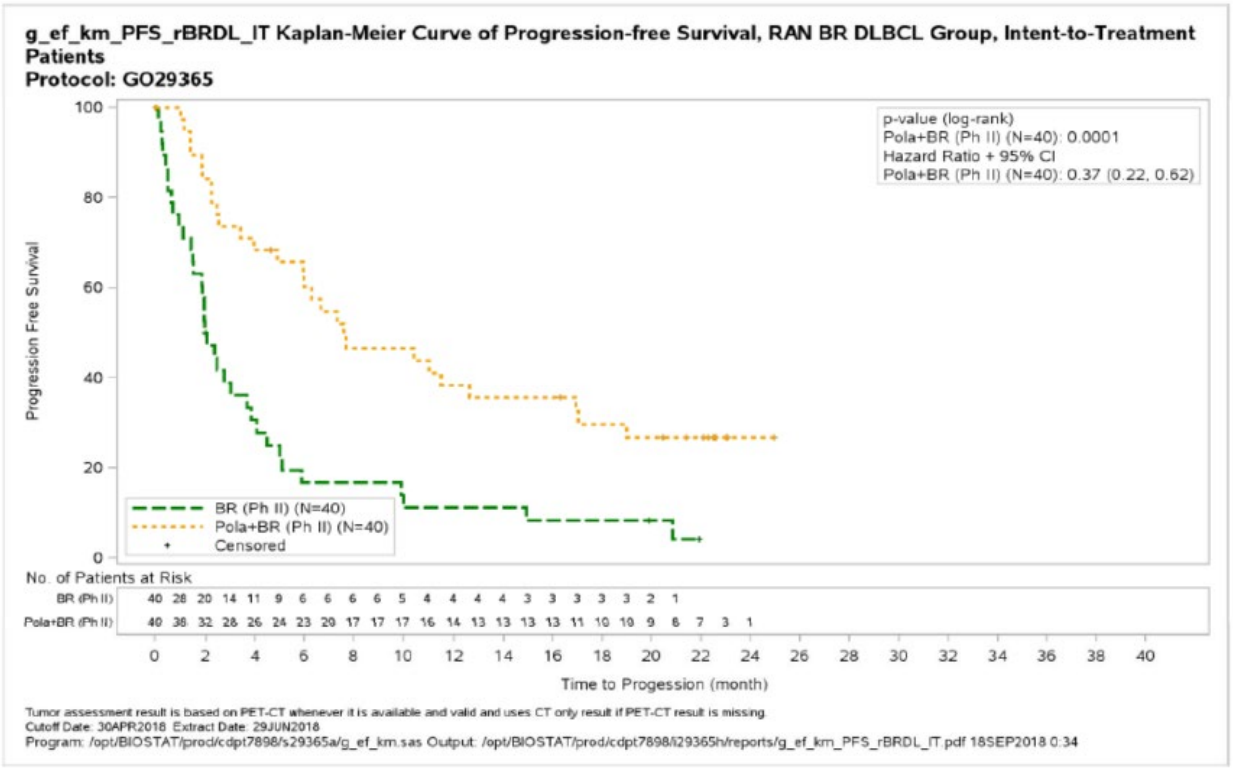


Figure 19: Swim-Lane Plots of Time-to-PFS Event and Durability of Response with PET in Patients with R/R DLBCL _ BR arm _ (Randomized Phase II; ITT Population; INV-Assessed)



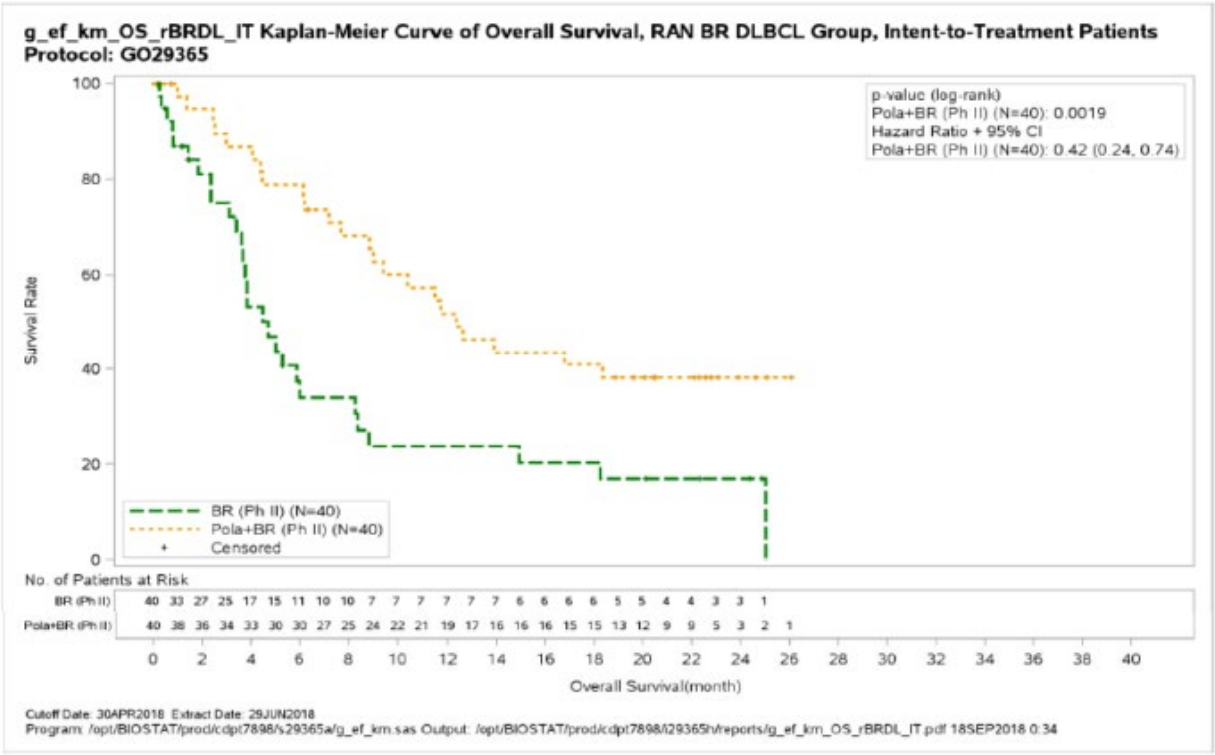
Kaplan-Meier Plot of Progression-Free Survival

Figure 20: Kaplan-Meier Plot of Progression-Free Survival (by Investigator) in Patients with R/R DLBCL Treated with Pola+BR or BR (Randomized Phase II; ITT Population)



Overall survival

Figure 21 : Kaplan-Meier Plot of Overall Survival in Patients with R/R DLBCL Treated with Pola+BR or BR (Randomized Phase II; ITT Population)



Patient-Reported Outcome (PRO)

Patient reports outcome (PRO) for peripheral neuropathy (PN) was evaluated based on TINAS scores.

Missing baseline information was 20.8% in phase Ib and 29.4% in phase II.

Less than 50% of patients filled the questionnaire; participation decreased further over time and less than 25% of the few compliant patients continued this assessment after week 29 in the pola+BR, DLBCL arm.

No significant change from baseline was identified from pooled pola+BR/BG data in the weekly tables. However, once presented in linear plots, mean TINAS scores appear higher in pola containing arms in DLBCL, vs BR arm whereas comparatively, BR scores remain flat in the linear slots.

Immunogenicity

Anti-drug antibodies (ADAs) were measured to assess the immunogenicity of polatuzumab vedotin and obinutuzumab. For all patients treated with polatuzumab vedotin, the baseline prevalence of ADAs was 3.7% (5/134 evaluable patients).

Table 40: Incidence of Anti-Drug Antibodies to Polatuzumab Vedotin in Study GO29365

Disease Histology	DLBCL				FL				All
Study Phase	Phase Ib	Phase II	Phase Ib	Phase II	Phase Ib	Phase II	Phase Ib	Phase II	Phase Ib/II
Cohort/Arm	1a	C	1b	F	1a	A	1b	E	
Treatment	Pola+BR		Pola+BG		Pola+BR		Pola+BG		all Pola
Sample Size	N=6	N=40	N=6	N=21	N=6	N=39	N=6	N=20	N=144
Baseline Prevalence of ADAs									
Baseline evaluable patients	6	36	6	18	6	37	6	19	134
Patients with a positive sample at baseline	2 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (3.7%)
Patients with no positive samples at baseline	4	36	6	18	3	37	6	19	129
Post-Baseline Incidence of ADAs									
Post–baseline evaluable patients	6	35	6	18	6	38	6	19	134
Patients positive for ADA	2 (33.3%)	1 (2.9%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	3 (7.9%)	0 (0.0%)	1 (5.3%)	8 (6.0%)
Treatment-induced ADA	2	1	0	1	0	3	0	1	8
Treatment-enhanced ADA	0	0	0	0	0	0	0	0	0
Patients negative for ADA	4	34	6	17	6	35	6	18	126
Treatment unaffected	2	0	0	0	3	0	0	0	5

ADA = anti-drug antibodies; BG = bendamustine and obinutuzumab; BR = bendamustine and rituximab; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; pola = polatuzumab vedotin.
Baseline evaluable patient = a patient with an ADA assay result from a baseline sample.
Post-baseline evaluable patient = a patient with an ADA assay result from at least one post–baseline sample.
Number of patients positive for ADAs = the number (and percentage) of post–baseline evaluable patients determined to have treatment-induced ADAs or treatment-enhanced ADAs during the study period.
Treatment-induced ADAs = a patient with negative or missing baseline ADA result(s) and at least one positive post-baseline ADA result.
Treatment-enhanced ADAs = a patient with positive ADA result at baseline who has one or more post-baseline titer results that are at least 0.60 t.u. greater than the baseline titer result.
Number of patients negative for ADAs = number of post-baseline evaluable patients with negative or missing baseline ADA result(s) and all negative post-baseline results, or a patient who is treatment unaffected.
Treatment unaffected = a post-baseline evaluable patient with a positive ADA result at baseline and (a) where all post-baseline titer results are less than 0.60 t.u. greater than the baseline titer result, OR (b) where all post-baseline results are negative or missing.
For any positive sample with titer result less than the minimum reportable titer or any positive sample where a titer cannot be obtained, titer value is imputed as equal to the minimum reportable titer.

Among all patients treated with pola in GO29365 study (all arms and all indications included), a total of 8 patients developed ADA: against the antibody (2) and against the linker, drug, or neo-epitopes (5; NE in 1 patient).

Among the 4 DLBCL patients presenting with ADA, impact on efficacy was not evidenced, considering that 3 of them completed 5 to 6 cycles of treatment and DOR from 21 to 38 months. However, the last patient presented with ADA at C2 and was diagnosed with PD at C3.

Similarly, among the 4 FL patients presenting with ADA, 3 had ADA detected after having completed the 6 cycles of treatment, with DOR from 15 to 21 months. The last patient had early ADA at C2 and was diagnosed with PR at C3 and PD at PRA.

In the pola+BG cohort, no ADAs were detected.

Subgroup analyses

Exploratory subgroup analysis of PFS in patients with R/R DLBCL evaluated the potential impact of demographic and baseline disease characteristics, and other prognostic factors on the treatment effect.

Subgroup analyses for the primary end point of PET-CR at PRA by IRC were presented showing consistent benefit of pola+BR versus BR in all subgroups defined by various baseline characteristics. For the patients having bulky disease in the BR arm, 2 patients had complete responses (13.3%, 95% CI: 1.7, 40.5) as compared to 4 in the pola+BR arm (40%, 95% CI: 12.2, 73.8).

Subgroup Analyses by Number of Lines of Prior Treatment

Table 41 Study GO29365–Summary of PET-CT Complete Response at PRA by Prior Line of Therapy (1, 2, 3 or more)

	INV Assessment		IRC Assessment	
	BR (N=40)	**Pola+BR (N=40)**	**BR (N=40)**	**Pola+BR (N=40)**
All lines, n Complete Response (CR) (95% CI for CR Rate)	40 6 (15.0%) (5.7, 29.8)	40 17 (42.5%) (27.0, 59.1)	40 7 (17.5%) (7.3, 32.8)	40 16 (40.0%) (24.9, 56.7)
1 prior line, n Complete Response (CR) (95% CI for CR Rate)	12 1 (8.3%) (0.2, 38.5)	11 7 (63.6%) (30.8, 89.1)	12 2 (16.7%) (2.1, 48.4)	11 7 (63.6%) (30.8, 89.1)
2 prior lines, n Complete Response (CR) (95% CI for CR Rate)	9 2 (22.2%) (2.8, 60.0)	11 5 (45.5%) (16.8, 76.6)	9 2 (22.2%) (2.8, 60.0)	11 4 (36.4%) (10.9, 69.2)
3 or more prior lines, n Complete Response (CR) (95% CI for CR Rate)	19 3 (15.8%) (3.4, 39.6)	18 5 (27.8%) (9.7, 53.5)	19 3 (15.8%) (3.4, 39.6)	18 5 (27.8%) (9.7, 53.5)

95% CI for rates were constructed using Clopper-Pearson method.
Cut-off date: 30 April 2018.
Extract date: 29 June 2018.

Table 42 Study GO29365–Summary of PFS by Prior Line of Therapy (1, 2, 3 or more)

	INV Assessment		IRC Assessment	
	BR (N=40)	**Pola+BR (N=40)**	**BR (N=40)**	**Pola+BR (N=40)**
All lines, n	40	40	40	40
Median PFS, mo (95% CI)	2.0 (1.5, 3.7)	7.6 (6.0, 17.0)	3.7 (2.4, 4.5)	11.1 (6.2, 13.9)
1 prior line, n	12	11	12	11
Median PFS, mo (95% CI)	3.9 (1.4, 5.1)	NE (10.4, NE)	4.7 (1.9, 5.8)	13.6 (10.4, NE)
HR (95% CI)	0.18 (0.04, 0.93)		0.22 (0.04, 1.18)	
9 month event-free rate	10.4%	80.0%	10.4%	80.0%
12 month event-free rate	NE	60.0%	10.4%	60.0%
18 month event-free rate	NE	50.0%	10.4%	40.0%
2 prior lines, n	9	11	9	11
Median PFS, mo (95% CI)	1.9 (0.5, 2.8)	6.7 (1.4, 19.0)	3.8 (0.4, 10.0)	6.2 (1.5, NE)
HR (95% CI)	0.40 (0.14, 1.11)		0.38 (0.12, 1.19)	
9 month event-free rate	22.2%	36.4%	25.0%	36.4%
12 month event-free rate	11.1%	36.4%	12.5%	36.4%
18 month event-free rate	11.1%	27.3%	12.5%	36.4%
3 or more prior lines, n	19	18	19	18
Median PFS, mo (95% CI)	2.0 (1.5, 3.1)	6.3 (2.6, 11.5)	3.2 (0.9, 4.1)	9.0 (2.6, 13.9)
HR (95% CI)	0.32 (0.15, 0.70)		0.36 (0.16, 0.80)	
9 month event-free rate	16.7%	32.7%	14.4%	50.3%
12 month event-free rate	16.7%	26.1%	14.4%	36.0%
18 month event-free rate	11.1%	19.6%	7.2%	21.6%

NE=not estimable.

95% CI for rates were constructed using Clopper-Pearson method.

Tumor assessment result is based on PET-CT whenever it is available and valid and uses CT only result if PET-CT result is missing.

Cut-off date: 30 April 2018.

Extract date: 29 June 2018.

Table 43 Study GO29365–Summary of OS by Prior Line of Therapy (1, 2, 3 or more)

	BR (N=40)	Pola+BR (N=40)
All lines, n	40	40
Median OS, mo (95% CI)	4.7 (3.7, 8.3)	12.4 (9.0, NE)
1 prior line, n	12	11
Median OS, mo (95% CI)	5.9 (4.7, 8.4)	NE (10.5, NE)
HR (95% CI)	0.29 (0.05, 1.64)	
9 month OS rate	13.9%	80.0%
12 month OS rate	13.9%	70.0%
18 month OS rate	13.9%	60.0%
2 prior lines, n	9	11
Median OS, mo (95% CI)	6.0 (3.7, 18.3)	8.9 (6.2, NE)
HR (95% CI)	0.46 (0.14, 1.47)	
9 month OS rate	25.9%	45.5%
12 month OS rate	25.9%	36.4%
18 month OS rate	25.9%	36.4%
3 or more prior lines, n	19	18
Median OS, mo (95% CI)	3.7 (2.4, 5.3)	12.4 (6.2, NE)
HR (95% CI)	0.37 (0.16, 0.85)	
9 month rate	26.6%	70.6%
12 month OS rate	26.6%	51.3%
18 month OS rate	19.9%	32.1%

NE=not estimable.

95% CI for rates were constructed using Clopper-Pearson method.

Tumor assessment result is based on PET-CT whenever it is available and valid and uses CT only result if PET-CT result is missing.

Cut-off date: 30 April 2018.

Extract date: 29 June 2018.

Efficacy by Lines of Therapy and Refractory Status

Table 44 Study GO29365–Summary of PET-CT CR at PRA by R/R Status and Prior Line of Therapy

	BR N=40			Pola+BR N=40		
	Relapsed	**Refractory**	**Total**	**Relapsed**	**Refractory**	**Total**
INV Assessment						
1 prior line, n	2	10	12	8	3	11
Complete Response (CR)	0	1 (10.0%)	1 (8.3%)	6 (75.0%)	1 (33.3%)	7 (63.6%)
2 or more prior lines, n	4	24	28	2	27	29
Complete Response (CR)	2 (50.0%)	3 (12.5%)	5 (17.9%)	2 (100.0%)	8 (29.6%)	10 (34.5%)
Total, n	6	34	40	10	30	40
Complete Response (CR)	2 (33.3%)	4 (11.8%)	6 (15.0%)	8 (80.0%)	9 (30.0%)	17 (42.5%)
IRC Assessment						
1 prior line, n	2	10	12	8	3	11
Complete Response (CR)	0	2 (20.0%)	2 (16.7%)	6 (75.0%)	1 (33.3%)	7 (63.6%)
2 or more prior lines, n	4	24	28	2	27	29
Complete Response (CR)	2 (50.0%)	3 (12.5%)	5 (17.9%)	2 (100.0%)	7 (25.9%)	9 (31.0%)
Total, n	6	34	40	10	30	40
Complete Response (CR)	2 (33.3%)	5 (14.7%)	7 (17.5%)	9 (90.0%)	8 (26.7%)	17 (42.5%)

95% CI for rates were constructed using Clopper-Pearson method.

Cut-off date: 30 April 2018.

Extract date: 29 June 2018.

Table 45: Study GO29365–Summary of PFS by Relapsed/Refractory Status and Prior Line of Therapy

	Relapsed		Refractory	
	BR N=6	**Pola+BR N=10**	**BR N=34**	**Pola+BR N=30**
INV Assessment				
1 prior line, n	2	8	10	3
Median PFS, mo (95% CI)	5.1 (5.0, 5.1)	NE (10.5, NE)	3.7 (1.4, 5.9)	NE (1.0, NE)
HR (95% CI)	<0.01 (0.00, NE)		0.40 (0.05, 3.33)	
2 or more prior lines, n	4	2	24	27
Median PFS, mo (95% CI)	6.2 (2.0, NE)	NE (19.0, NE)	1.9 (0.7, 2.4)	6.0 (3.5, 7.7)
HR (95% CI)	<0.01 (0.00, NE)		0.37 (0.20, 0.69)	
IRC Assessment				
1 prior line, n	2	8	10	3
Median PFS, mo (95% CI)	5.5 (5.1, 5.8)	13.6 (10.4, NE)	3.9 (1.9, 5.9)	NE (1.0, NE)
HR (95% CI)	<0.01 (0.00, NE)		0.58 (0.07, 4.80)	
2 or more prior lines, n	4	2	24	27
Median PFS, mo (95% CI)	7.3 (4.6, 10.0)	NE (NE)	2.8 (0.9, 3.8)	6.7 (4.5, 9.5)
HR (95% CI)	NE (NE)		0.39 (0.21, 0.75)	

NE=not estimable.

95% CI for rates were constructed using Clopper-Pearson method

Tumor assessment result is based on PET-CT whenever it is available and valid and uses CT only result if PET-CT result is missing.

Cut-off date: 30 April 2018.

Extract date: 29 June 2018.

Table 46 Study GO29365–Summary of OS by Relapsed/Refractory Status and Prior Line of Therapy

	Relapsed		Refractory	
	BR N=6	Pola+BR N=10	BR N=34	Pola+BR N=30
1 prior line, n	2	8	10	3
Median OS, mo (95% CI)	6.7 (5.1, 8.3)	NE (10.4, NE)	5.9 (3.9, 25.0)	NE (1.0, NE)
HR (95% CI)	<0.01 (0.00, NE)		0.81 (0.09, 7.14)	
2 or more prior lines, n	4	2	24	27
Median OS, mo (95% CI)	18.3 (6.0, NE)	NE (NE)	3.7 (2.4, 4.5)	9.5 (7.2, 16.8)
HR (95% CI)	NE (NE)		0.41 (0.21, 0.80)	

NE=not estimable.

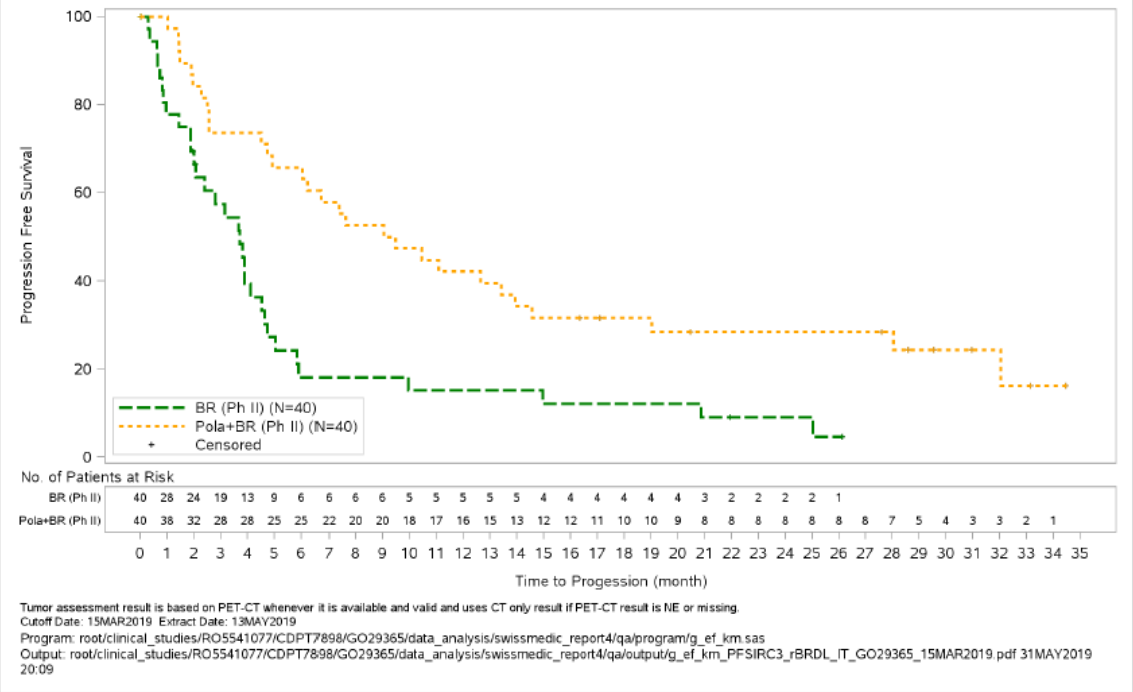
95% CI for rates were constructed using Clopper-Pearson method.

Tumor assessment result is based on PET-CT whenever it is available and valid and uses CT only result if PET-CT result is missing.

Cut-off date: 30 April 2018.

Extract date: 29 June 2018.

Figure 22 Updated Kaplan-Meier Curve for PFS by IRC



Updated PFS by Investigator

Figure 23 Updated Kaplan-Meier Curve for PFS by Investigator

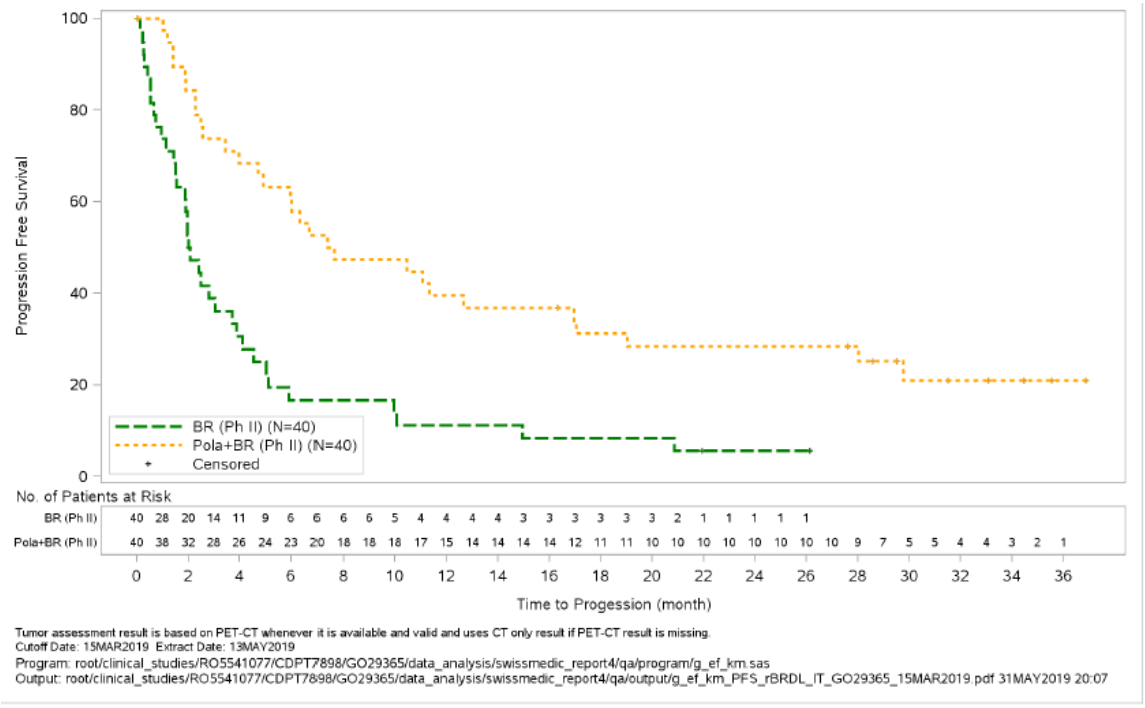
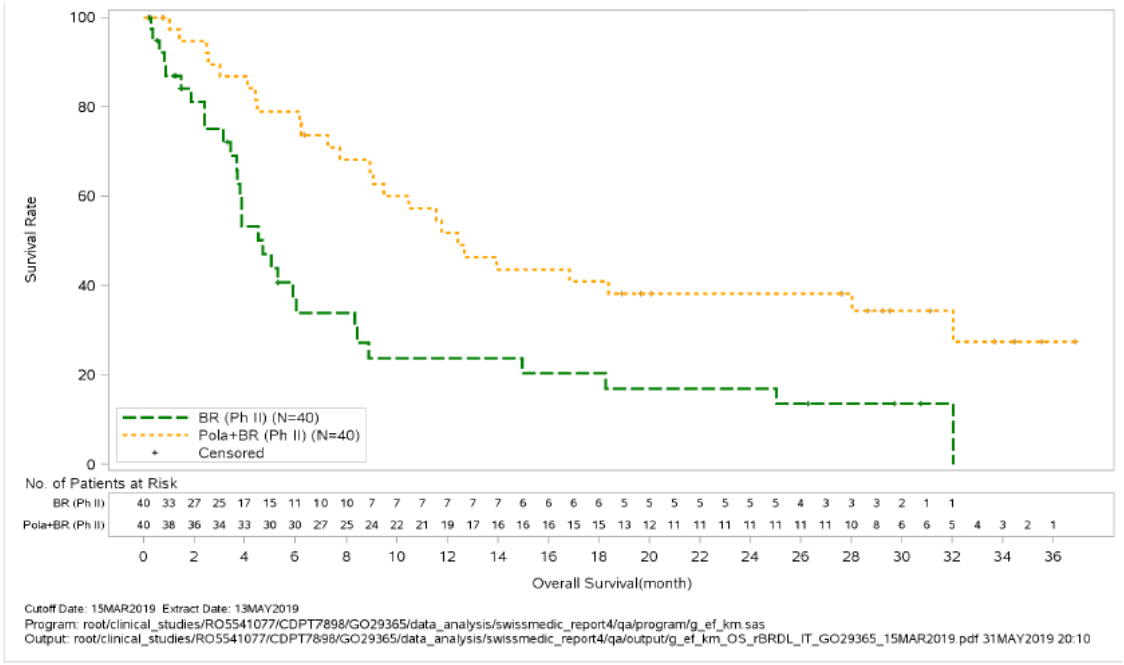


Figure 24 Updated Kaplan-Meier Curve for OS



Ancillary analyses

Table 47: Stratified Multiple Cox Regression Analyses for Time-To-Event Endpoints Adjusted for Potential Prognostic Factors

Adjusting for	Endpoint	Pola+BR vs BR HR (95% CI)	p value
Bulky disease	OS	0.45 (0.25, 0.80)	0.0062
	PFSINV	0.36 (0.21, 0.61)	0.0001
	PFSIRC	0.38 (0.22, 0.67)	0.0007
Refractory to last anti- lymphoma therapy	OS	0.44 (0.25, 0.78)	0.0053
	PFSINV	0.36 (0.21, 0.61)	0.0001
	PFSIRC	0.39 (0.22, 0.68)	0.0010
Previous Bone Marrow Transplant	OS	0.44 (0.25, 0.77)	0.0045
	PFSINV	0.35 (0.20, 0.58)	<0.0001
	PFSIRC	0.37 (0.21, 0.64)	0.0004
Age (<65yrs, ≥65yrs)	OS	0.42 (0.24, 0.74)	0.0028
	PFSINV	0.34 (0.20, 0.57)	<0.0001
	PFSIRC	0.36 (0.21, 0.61)	0.0002
IPI High (IPI=4 or 5)	OS	0.54 (0.30, 0.97)	0.0405
	PFSINV	0.41 (0.24, 0.71)	0.0013
	PFSIRC	0.45 (0.25, 0.79)	0.0055

Stratification factor: DoR to last therapy of ≤12 months versus >12 months.

Table 48: Stratified Multiple Logistic Regression for Response Endpoints Adjusted for Potential Prognostic Factors

Adjusting for	End point	Pola+BR vs. BR Odds Ratio (95% CI)	p value
Adjusting for bulky disease	CRIRC PET-CT	3.28 (1.09, 9.84)	0.0339
	BORIRC	5.69 (1.93, 16.79)	0.0016
	BORINV	5.33 (1.88, 15.11)	0.0016
Adjusting for refractory to last anti-lymphoma therapy	CRIRC PET-CT	3.11 (1.02, 9.48)	0.0458
	BORIRC	5.69 (1.89, 17.11)	0.0020
	BORINV	5.25 (1.86, 14.84)	0.0018
Adjusting for Previous Bone Marrow Transplant	CRIRC PET-CT	3.40 (1.14, 10.18)	0.0285
	BORIRC	5.93 (2.02, 17.39)	0.0012
	BORINV	5.38 (1.91, 15.15)	0.0015
Adjusting for Age (<65yrs, ≥65yrs)	CRIRC PET-CT	3.37 (1.13, 10.09)	0.0295
	BORIRC	6.63 (2.21, 19.94)	0.0008
	BORINV	6.43 (2.19, 18.83)	0.0007
Adjusting for IPI High (IPI=4 or 5)	CRIRC PET-CT	2.98 (0.97, 9.18)	0.0577
	BORIRC	5.39 (1.83, 15.88)	0.0022
	BORINV	4.88 (1.72, 13.91)	0.0030

Stratification factor: DoR to last therapy of ≤12 months versus >12 months.

Multiple Cox Regressions were performed for the time-to-event endpoints including PFS by investigator and IRC, and OS and included in the initial MAA dossier. All potential imbalanced baseline and prognostic factors (age, ECOG, refractory status, stage, bulky disease, IPI) were first examined individually, and those with a p-value <0.2 were put into the multiple regression model as candidates for the final model selection. Only factors that had a p-value <0.2 from the final model remained, and some factors were not included in the final multiple Cox-regression model due to multi-collinearity. For PFS by investigator, after adjusting for Ann Arbor stage and performance status, the HR was 0.34 (95%CI: 0.20, 0.58) and for PFS by IRC, the HR was 0.37 (95%CI: 0.21, 0.66). Similarly, for OS, after adjusting for the same factors and bulky disease, the HR was 0.43 (95%CI: 0.24, 0.78).

Sensitivity analyses

Two sensitivity analyses of PFS with two additional censoring rules were provided, for missing assessments and for NALT received prior to disease progression.

The stratified HR for PFS by IRC censoring for NALT was 0.28 (95% CI: 0.15, 0.53). The stratified HR for PFS by IRC censoring for one or more missed assessments was 0.33 (95% CI: 0.18, 0.59).

Multivariate regression models and propensity score analyses

Further two types of analyses were conducted, multivariable regression models and propensity score weighted regression models, on the following four key efficacy endpoints:

- IRC assessed complete response (CR) at the end of treatment (EoT)
- IRC assessed best overall response (BOR)
- IRC assessed progression free survival (PFS)
- Overall survival (OS)

The analysis population used in the modeling:

- Randomized cohorts pola+BR (n=40) versus BR (n=40)

Results were obtained from the snapshot with clinical cutoff date of 15 March 2019.

A comprehensive list of 12 baseline covariates that could potentially impact prognosis were included in both the multivariable regression model and propensity score model:

- Sex (M vs. F)
- Age (<65 vs. ≥65 years)
- Baseline ECOG PS (0/1 vs. 2)
- Duration of response to prior therapy (≤12 vs. >12 months)
- IPI (0-3 vs. 4-5)
- Extranodal involvement at study entry (Y vs. N)
- Bulky disease (Y vs. N)
- Ann Arbor stage (I/II vs. III/IV)
- Prior lines of lymphoma therapy (1 vs. 2+)
- Refractory to last prior anti-lymphoma therapy (Y vs. N)
- Primary refractory status (Y vs. N)
- Primary bone marrow transplant (Y vs. N)

Table 49: propensity score weighted baseline demographics

Table 3 Propensity Score Weighted Baseline Demographics

	BR (n=40)	Pola+BR (n=40)
Sex (%) Male Female	 71.4% 28.6%	 70.8% 29.2%
Age (%) <65 years ≥65 years	 44.6% 55.4%	 39.8% 60.2%
Baseline ECOG PS (%) 0 or 1 2	 84.5% 15.5%	 82.8% 17.2%
Primary refractory status (%) Y N	 53.2% 46.8%	 55.7% 44.3%
Refractory to last prior anti-lymphoma therapy (%) Y N	 71.5% 28.5%	 75.6% 24.4%
Prior lines of lymphoma therapy (%) 1 ≥2	 26.6% 73.4%	 28.8% 71.2%
Ann Arbor stage (%) I or II III or IV	 10.0% 90.0%	 12.4% 87.6%
Bulky disease (%) Y N	 27.5% 72.5%	 29.2% 70.8%
Extranodal involvement at study entry (%) Y N	 75.5% 24.5%	 70.0% 30.0%
IPI (%) 1–3 4–5	 72.8% 27.2%	 73.7% 26.3%
Duration of Response to Prior Therapy (%) ≤12months >12 months	 81.5% 18.5%	 77.8% 22.2%
Primary bone marrow transplant (%) Y N	 27.5% 72.5%	 21.9% 78.1%

Source: t_prop_base_rBRDL_IT

Table 50: Full multivariate model, backward selection model and propensity score weighted model results in Pola + BR (n=39)* vs BR (n=39)*

	Unadjusted model	Full multivariable model	Backward selection model	Propensity score weighted model
Odds ratio for CR at EoT 95% CI p-value	3.2 (1.1, 9.0) 0.0288	4.0 (0.9, 17.3) 0.0645	3.1 (0.9, 11.1) 0.0847	3.0 (1.1, 8.7) 0.0392
Odds ratio for BOR 95% CI p-value	4.2 (1.6, 10.9) 0.0036	8.2 (1.7, 39.0) 0.0087	5.9 (1.7, 21.3) 0.0064	3.6 (1.4, 9.3) 0.0092
PFS HR 95% CI p-value	0.39 (0.23, 0.66) 0.0006	0.43 (0.23, 0.80) 0.0072	0.40 (0.22, 0.73) 0.0026	0.48 (0.32, 0.70) 0.0001
OS HR 95% CI p-value	0.42 (0.24, 0.73) 0.0020	0.56 (0.31, 1.04) 0.0656	0.59 (0.33, 1.04) 0.0699	0.54 (0.37, 0.78) 0.0013

*Two patients (one from each arm) without ECOG at baseline were excluded from the analysis population; both of them are non-responders.

Summary of main study

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

Table 51: Summary of efficacy for study GO29365

Title: A Phase Ib/II study evaluating the safety, tolerability, and anti-tumor activity of polatuzumab vedotin (DCDS4501A) in combination with rituximab (R) or obinutuzumab (G) plus bendamustine (B) in relapsed or refractory follicular or diffuse large B-cell lymphoma		
Study identifier	GO29365 Eudra CT: 2014-001361-28	
Design	Phase Ib/II, multicenter, open-label study of polatuzumab vedotin in combination with BR or bendamustine plus obinutuzumab (BG) in patients with R/R FL or DLBCL. Randomized phase II study in DLCBL patients	
	First Patient Entered Last Patient Entered (A-F) Data Cut-off	15 October 2014 13 September 2016 30 April 2018
Hypothesis	Exploratory: An exploratory comparison of CR rates for the BR-containing regimens was conducted using the Cochran Mantel Haenszel chi-square test adjusted for randomization stratification factors.	

Treatments groups In Phase II randomized part of the study, in R/R DLBCL patients	Arm C Polatuzumab vedotin (POLA) + bendamustine and rituximab (BR)		N=40 *POLA:* 1.8 mg/kg administered by intravenous (IV) infusion on Day 2 of Cycle 1 and then Day 1 of subsequent Cycles 2-6 in combination with either BR *Bendamustine*: 90 mg/m2 administered by IV infusion on Days 2 and 3 of Cycle 1, then Days 1 and 2 of subsequent Cycles 2-6 *Rituximab*: 375 mg/m2 administered by IV infusion on Day 1 of Cycles 1-6
	Arm D bendamustine and rituximab (BR)		N=40 *Bendamustine*: 90 mg/m2 administered by IV infusion on Days 2 and 3 of Cycle 1, then Days 1 and 2 of subsequent Cycles 2-6 *Rituximab*: 375 mg/m2 administered by IV infusion on Day 1 of Cycles 1-6
Endpoints and definitions	Primary endpoint	Complete Response (CR), PET-CT scan, IRC assessed	CR at primary response assessment (PRA) (6–8 weeks after Cycle 6 Day 1 or last dose of study medication) as measured by PET-CT scan and as determined by an IRC using Modified Lugano 2014 Response Criteria
	Secondary endpoints	CR at PRA, based on PET CT, as determined by investigator (INV) Objective response (OR: CR or partial response [PR]) at PAR, based on PET-CT, as determined by INV and IRC CR at PRA based on CT only, as determined by INV and IRC OR at PRA based on CT only, as determined by INV and IRC Best objective response (BOR: CR or PR) while on study either by PET-CT or CT only, as determined by INV BOR, duration of response (DOR), and PFS (PFS) based on PET-CT or CT, as determined by IRC	
	Secondary endpoints: safety assessment	Assess the safety and tolerability of POLA+ BR Assess the potential relationships of ADA formation with other outcome measures (e.g., pharmacokinetic [PK], efficacy, safety)	
	Patient-Reported Outcomes	Evaluate peripheral neuropathy (PN) symptom severity and interference on daily functioning and better understand treatment impact, tolerability, and reversibility, as measured by the Therapy-Induced Neuropathy Assessment Scale (TINAS) v1.0.	
	Exploratory	Preliminary assessment of biomarkers related to the drug targets and mechanism of action and/or of biomarkers related to disease biology and/or assessments that inform the improvement of diagnostic tools, and that might predict disease response or resistance to treatment Evaluate the prognostic significance of interim PET-CT assessment Evaluate longer-term outcomes for patients using the Modified Lugano 2014 response criteria, as measured by: - DOR based on PET-CT or CT only, as determined by INV - PFS based on PET-CT or CT only, as determined by INV - Event-free survival (EFS) based on PET-CT or CT only, as determined by INV - Overall survival (OS)	
Database lock	Primary Analysis/ Data cut-off date: 30 April 2018		
Results and Analysis			

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (ITT) At PRA: 6–8 weeks after Cycle 6 Day 1 or last dose of study medication		
CR, at PRA (PET-CT IRC assessed)	Treatment group	POLA + BR	BR
	Number of subject	40	40
	N (%)	16 (40.0%)	7 (17.5%)
	95 % IC (Clopper-Pearson)	24.9, 56.7	7.3, 32.8
	Δ (95% CI) (Wilson); p-value (CMH chi-square)	22.5 (2.6, 40.2); p = 0.0261	
Analysis description	**Secondary Analysis**		
Analysis population and time point description	ITT PRA		
OR (CR/PR) at PRA by PET (IRC assessed)	Treatment group	POLA + BR	BR
	Number of subject	40	40
	N (%)	18 (45.0%)	7 (17.5%)
	95 % IC (Clopper-Pearson)	29.3, 61.5	7.3, 32.8
	Δ (95% CI) (Wilson); p-value (CMH chi-square)	27.5 (7.2, 45.0); p = 0.0069	
Analysis description	**Secondary Analysis**		
Analysis population and time point description	ITT Cut-off date		
DOR (IRC assessed, among patients with Best Objective	Treatment group	POLA + BR	BR
	Number of subject with BOR (IRC assessed)	23	10
	N (%)	11/23 (47.8%)	8/10 (80.0%)
	median DOR (95% CI)	NE (8.8, NE)	7.7 (3.2, 18.9)
	HR (95% CI); stratified p-value (log-rank)	0.40 (0.16, 1.01); p = 0.0462	
Analysis description	**Secondary Analysis**		
Analysis population and time point description	ITT Cut-off date PFS events: death, PD		
PFS (IRC assessed)	Treatment group	POLA + BR	BR
	Patients with event, n (%)	25 (62.5%)	31 (77.5%)

	median PFS (95% CI)	9.5 (6.2, 13.9)	3.7 (2.4, 4.5)
	HR (95% CI); stratified p-value (log-rank)	0.36 (0.21, 0.63); p = 0.0002	
Analysis description	**Exploratory Analysis**		
Analysis population and time point description	ITT Cut-off date		
Overall survival	Treatment group	POLA + BR	BR
	Patients with event, n (%)	23 (57.5%)	28 (70.0%)
	median OS (95% CI)	12.4 (9.0, NE)	4.7 (3.7, 8.3)
	HR (95% CI); stratified p-value (log-rank)	0.42 (0.24, 0.75); p = 0.0023	

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

Table 52: Historical comparisons in CR, PFS and OS in commonly used regimens, in studies with BR and Pola+BR

	BOR% (CR%)	Median PFS, months (95% CI, if reported)	Median OS, months (95% CI, if reported)
Pola+BR (RAN) INV IRC	 70 (58) 63 (50)	 7.6 (6.0, 17.0) 9.5 (6.2, 13.9)	12.4 (9.0, NE)
R-GemOx (Mounier et al. 2013) [a]	61 (44)	5 [b]	11
R-GemOx (Corazelli et al. 2009)	78 (50)	NR	NR
Pixantrone (PIX301) [c]	37 (20) [d]	5.3 (2.3, 6.2)	10.2 (6.4, 15.7) [e]
BR (Vacirca et al. 2014) [f]	46 (15)	3.6 (2.7, 7.2)	Not reached [g]
BR (Ohmachi et al. 2013) [h]	63 (37)	6.7	Not reported
BR (Hong et al. 2018) [i]	55 (31)	3.9 (2.4, 5.4)	6.7 (4.7, 8.7)
Yescarta INV Central	 79 (51) 64 (46)	 6.0 (3.9, 8.1) 7.3 (5.2, 12.4)	15.4 (11.1, NE) [j]
Kymriah	34 (24)	4.4 (3.6, 5.1)	8.2 (5.8, 11.7)

Clinical studies in special populations

No clinical studies were performed in special populations.

Supportive study(ies)

Supplemental Results – Arm G

Arm G was added to the pivotal study, as per CHMP advice during PRIME meetings, to gather clinical data with the 140 lyo DP, intended for marketing.

At time of initial submission, 25 patients were included in the safety population of arm G. The demographic in arm G is comparable to arm C (pola+BR, liquid formulation). It should be noted that a lower proportion of patients present with ECOG 2 (4.0% vs 15.0% in arm C).

For PK and safety results for arm G, refer to dedicated sections.

At time of response to LoQ, the applicant provided preliminary results from arm G. Arm H remains with ongoing recruitment, with results expected not before Q2 2020.

Based on results in 32 patients in arm G (CCOD 12 Nov 2018), CR rate was 34.3% (18.6, 53.2). However, median PFS and OS are sharply lower than in arm C:

- PFS: 6.0 months (3.5, 6.6) in arm G vs 11.1 months (6.2, 13.9) in arm C;
- OS: 6.1 months (4.4, NE) in arm G vs 12.4 (9.0, NE).

Of note, the median FU in arm G, at time of CCOD, was 6 months, vs 22.3 months in arm C.

Additional efficacy results in 42 patients, up to 15 March 2019, remain similar in terms of CR, lower than in arm C (33.3%; [19.6, 49.6]). However, OS increased up to 9.1 months [6.0, NE]. Subgroups analysis suggest that the difference in CR rates would mainly be due to the lower proportion of 2L refractory patients in arm G, which present with the higher CR rate in arm C.

PK analysis supports the comparability of both liquid and lyo formulations.

Regarding the safety profile, no new safety signal nor unexpected trend was retrieved from these updated safety results. The safety profile, including the important potential risk of carcinogenicity, remain closely monitored in this ongoing study.

Study DCS4968g, phase I study

An open-label, multicenter, Phase I trial of the safety and pharmacokinetics of escalating doses of DCDS4501A (pola) in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma and chronic lymphocytic leukemia and DCDS4501A in combination with rituximab in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma

The primary objective included the evaluation of the safety and tolerability of polatuzumab vedotin and the determination of the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) when administered Q3W in patients with NHL and CLL. Refer to the previous section dedicated to dose-response studies for further details regarding the determination of the dose.

The secondary objectives included efficacy assessment in RR NHL, with a preliminary assessment of the anti-tumor activity of pola (SA or combined with rituximab) in patients with RR NHL

This study was carried out with the liquid formulation of pola.

The inclusion/exclusion criteria are representative for the population of RR DLBCL patients with unmet medical need, transplant ineligible, and coherent with the population recruited in the pivotal study.

A total of 40 DLBCL patients were recruited, including 39 treated with polatuzumab vedotin alone, up to 2.4mg/kg, and 1 patient treated with pola 2.4mg/kg in combination with rituximab 375mg/m2.

Among patients with the selected dose of 1.8 mg/kg (n=4, SA), no CR was raised, but 2 PR, 1 SD and 1 PD. The patient treated with pola +R (2.4mg/kg) presented with PR.

The median DOR was 6.8 months (2.27, 11.40) in SA 1.8 mg/kg patients.

In the SA 1.8 mg/kg group, all patients had PFS events, with median PFS of 4.6 months (95% CI: 1.35, 13.90); the single patient in the combination 2.4 mg/kg group had a PFS of 17.3 months.

Study GO27834 (ROMULUS)

A Randomized, Open-Label, Multicenter, Phase II Trial Evaluating the Safety and Activity of Pinatuzumab Vedotin (DCDT2980S) in Combination with Rituximab or Polatuzumab Vedotin (DCDS4501A) in Combination with Rituximab and a Non-Randomized Phase IB/II Evaluation of Polatuzumab Vedotin in Combination with Obinutuzumab in Patients with Relapsed or Refractory B-Cell Non- Hodgkin's Lymphoma.

This study was carried out with the liquid formulation of polatuzumab.

The inclusion/exclusion criteria are representative for the population of RR DLBCL patients with high unmet need, transplant ineligible, and coherent with the population recruited in the pivotal study.

A total of 81 DLBCL patients were recruited in the rituximab containing arms (A and B), including 42 in arm A pinatuzumab + polatuzumab vedotin alone and 39 in arm B, pola + rituximab. Patients with PD in Arm A or B could cross over to the other treatment arm.

In arm B, patients received polatuzumab at 2.4mg/kg and rituximab at 375 mg/m2 by IV infusion in 21-day cycles.

Anti-tumor activity was observed in this study with pola+rituximab. ORR was observed in 53.8% of patients in the RTX+Pola arm, with median PFS of 5.6 months and median OS of 20.5 months.

Regarding results obtained in arms with pola+G, anti-tumor activity was observed but lower than in the pivotal study. No CR was obtained as IRC reviewed. The IRC-assessed OR rate by PET/CT was 19.4%, up to 25.8% by CT alone. IRC assessed CR rate by CT alone was 6.5%. A similar trend was observed while investigator-assessed. While OS was similar to the pivotal study results (10.7 months vs 9.3 months in pivotal study), median PFS was almost twice shorter (2.8 months vs 5.1).

Study GO29044, Phase Ib/II with R-CHP-pola in ND or R/R B-NHL

Study GO29044: A Phase Ib/II Study Evaluating the Safety, Tolerability and Anti-Tumor Activity of Polatuzumab Vedotin (DCDS4501A) in Combination with Rituximab or Obinutuzumab, Cyclophosphamide, Doxorubicin, and Prednisone in Patients with B-Cell Non-Hodgkin's Lymphoma.

The study included adult patients with confirmed B-cell NHL in the dose-escalation portion of the study (newly diagnosed or R/R) and previously untreated patients with DLBCL in the dose-expansion portion of the study.

This study was carried out with the liquid formulation of pola, from 1.0 to 1.8 mg/kg doses. It was associated with:

- CHP regimen: Cyclophosphamide 750 mg/m2 administered IV on Day 1, Doxorubicin 50 mg/m2 administered IV on Day 1 and Prednisone 100 mg/day by mouth (PO) on Days 1-5 (or prednisolone (100 mg/day) if not available)

- and Rituximab: Six to eight cycles of rituximab at 375 mg/m2, administered IV every 21 days (or over 28 days for those patients who experienced toxicity that necessitated an extended cycle duration).

- or Obinutuzumab: IV infusion as an absolute (flat) dose of 1000 mg on Days 1, 8, and 15 of Cycle 1 and on Day 1 of Cycles 2-6 or 2-8.

A total of 51 DLBCL patients (ITT population) were recruited in the rituximab containing arm (R-CHP-pola), in both dose escalation and expansion cohorts.

Globally, R-CHP-pola showed anti-tumor activity, with CR rate by CT/MRI with PET scan at 76.0% (38/50; 90% CI: 64.03, 85.53). The 12-month PFS was 90.0% (95% CI: 81.68, 98.32), 12-month EFS was 80.0% (95% CI: 68.91, 91.09), and 12-month OS was 94.0% (95% CI: 87.42, 100.00). The median PFS, EFS and OS were not reached, and most of patients remain in follow-up in this ongoing study.

When focused on results in the expansion cohort in DLBCL patients (n=40, 1.8mg/kg, untreated DLBCL), a similar trend was observed, with 72.5% of CR (58.61, 83.75). The 12-month PFS was 87.50% (95% CI: 77.25, 97.75), 12-month EFS was 75.0% (95% CI: 61.58, 88.42), and 12-month OS was 92.50% (95% CI: 84.34, 100.00). These results highlight anti-tumor activity of this combination R-CHP-pola in untreated DLBCL, more markedly than in the pivotal study and confirming the positive trend observed in the pivotal study in RR TNE DLBCL patients, with pola+BR treatment.

Regarding results obtained with pola+G-CHP in DLBCL patients, 25 patients were included, with 17 patients in the dose expansion cohort (1.8mg/kg, untreated DLBCL). Results obtained were broadly similar to the arm R-CHP-pola. Efficacy was also observed untreated DLBCL patients (expansion cohort), with 76.5% of CR (53.95, 91.54). The 12-month PFS was 94.12% (95% CI: 82.93, 100.00), 12-month EFS was 88.240% (95% CI: 72.92, 100.00), and 12-month OS was 94.12% (95% CI: 82.93, 100.00).

2.5.3. Discussion on clinical efficacy

Efficacy data have mainly been collected in one pivotal Phase IB/II evaluating the efficacy and safety of polatuzumab vedotin plus bendamustine and rituximab (BR) versus BR, in the treatment of R/R DLBCL in adults ineligible for HSCT (Study GO29365). The supportive studies GO27834 (ROMULUS) and DCS4968g provide additional data in patients with R/R DLBCL.

Design and conduct of clinical studies

The pivotal study GO29365 is a Phase Ib/II, multicenter, open-label study of polatuzumab vedotin in combination with BR or bendamustine plus obinutuzumab (BG) in patients with R/R FL or DLBCL. Study GO29365 originally used the liquid formulation of polatuzumab vedotin, while the lyophilized drug is intended for commercialization. The protocol was amended to add a new formulation cohort (Arm G).

The dose of 2.4mg/kg of polatuzumab vedotin was initially considered as the recommended Phase II dose. However, following the issuance of a Partial Clinical Hold at the 2.4 mg/kg dose by the U.S. FDA in September 2014 due to safety concerns, the dose of polatuzumab vedotin was reduced to 1.8 mg/kg. Thus, the 1.8 mg dose was tested in the safety run-in phase of the pivotal study GO29365, and confirmed as the RP2D for the phase II part of the study, in combination with bendamustine and rituximab or obinutuzumab.

The phase II part of the study, in RR DLBCL TNE patients, was randomized (1:1 randomization) between pola+BR and BR treatments, open-label, with a stratification per duration of response to the prior treatment (≤ 12 months versus > 12 months). As there is a 98% prevalence of positive CD79b staining in DLBCL, similar to what has been reported in the literature (92–100%) (Dornan et al. 2009; Pfeifer et al. 2015) and similar CD79b expression pattern seems to be detectable also across biologically distinct DLBCL subtypes, no requirement for CD79b subtyping as prerequisite for treatment in clinical practice was considered necessary.

According to the ESMO guideline for DLBCL treatment (September 2015), recommendations for transplant –non-eligible patients in first relapse mainly include Platinum- and/or gemcitabine-based regimens, or clinical trials with novel drugs. After 2 or more relapses, clinical trials or palliative care are

recommended. However, bendamustine +rituximab is listed among second line and subsequent therapies in the NCCN guidelines (version 1.2019) and was accepted by the CHMP / SAWP.

Patients received up to 6 cycles of treatment (21 days per cycle) of polatuzumab vedotin (pola) 1,8 mg/kg, associated with bendamustine at 90 mg/m2 and rituximab 375 mg/m2.

The primary endpoint is the CR at time of primary response assessment (6 to 8 weeks after D1C6 or last treatment received), with PET-SCAN as assessed by IRC. CR is completed by PFS, EFS and OS assessment as secondary endpoint.

Efficacy data and additional analyses

Between 15 October 2014 (first patient in) and 13 September 2016 (last patient in, Arms A-F), 40 patients were enrolled in each of the DLBCL arms.

No major protocol deviation led to patient withdrawal. However, the high frequency of major deviation in RR DLBCL patients was noted, with 12.5 % in BR patients and 19.6% in BR+pola patients (phase Ib and II). In the pola+BR, DLBCL arm, 3 (6.5%) patients had preliminary response assessment (PRA) not performed in due time, but with limited impact on primary endpoint assessment.

No patient was lost to follow up in pola+ BR nor BR DLBCL arms. AEs were the most common reason for patients discontinuing study treatment in pola+BR arm (30.8% stopped treatment).

The median age was 69 years (range: 30 86 years). Sixty-four out of 80 patients (80%) had ECOG performance score (PS) of 0 1 and 14 out of 80 patients (18%) had ECOG PS of 2. The majority of patients (98%) had DLBCL not otherwise specified (NOS). Overall, 48% of patients had activated B-cell (ABC) DLBCL and 40% had germinal center B-cell like (GCB) DLBCL. Primary reasons patients were not candidates for HSCT included age (40%), insufficient response to salvage therapy (26%) and prior transplant failure (20%). The median number of prior therapies was 2 (range: 1 7), with 29% (n = 23) receiving one prior therapy, 25% (n = 20) receiving 2 prior therapies, and 46% (n = 37) receiving 3 or more prior therapies. All except one patient in the pola+BR arm of the randomized Phase II were naïve to bendamustine treatment. 80% of patients had refractory disease.

The median age was slightly higher in the BR arm (71.0 years [30-84] vs 67.1 years [33-86] in POLA +BR arm). Patients in the comparator BR arm present with more severe condition at baseline, including tumour size (bulky) and IPI score, not balanced and favour the polatuzumab arm. A limited impact of these imbalances observed in terms of IPI and bulky disease was demonstrated via a multiple Cox Regression analysis.

WHO 2016 DLBCL status was heterogeneous, but balanced in both arms. Efficacy data per WHO status were provided in arms C and D. Only WHO NOS patients, ABC and GCB, were enrolled in arms C and D, and all but 3 were ABC/GCB in arm G (the 3 remaining were 1 EBV and 2 MYC/BCL2/BCL6 patients). Regarding PFS and OS results, in ABC patients, median PFS (10.76 months; [6.34, NE]) and OS (15.38 months; [10.45, NE]) were significantly higher in pola+BR arm vs BR arm (HR=0.21; [0.09, 0.51]). No such difference with pola+BR treatment was observed on PFS results in GCB patients, with median PFS of 2.5 months (1.91, NE) vs 1.87 months (0.95, 4.53) in BR arm. However, HR showed a favourable trend with pola+BR treatment in these patients (0.49; [0.23, 1.05]), and OS was almost twice longer in pola+BR arm vs BR in these patients (7.23 months [4.11, NE] vs 3.81 [1.87, NE], HR=0.57 [0.25, 1.31]). Further, distinct subtypes will be analysed within Arm H and it is considered necessary to confirm response in any relevant subtype at least on a descriptive level. Data from study Arm H will be presented as a condition to the CMA (see Annex II, RMP). This should include analyses by subtype.

In both randomized arms, only one third of patients were treated in 2nd (2L) line treatment; most patients had received at least 2 prior treatments. To be noted, 47.5% and 45% of patients had received at least

3 prior treatments in BR and POLA+BR arms respectively. In both arms, CR globally decreased with increasing number of prior treatments, in both IRC and INV assessed results. This trend was less marked in BR arm, since CR rate increased up to 22.2% in 3L patients. However, it should be interpreted with caution, considering the limited sample size for this subgroup. Despite crossing CIs, CR rate remained higher in pola+BR vs BR arm in each subgroup, mainly in 2L patients: 63.6% (30.8, 89.1) vs 16.7% (2.1, 48.4), despite limited sample size (11 and 12 patients respectively). Median PFS and OS were higher in pola+BR arm in each subgroup of treatment line, and with both IRC and INV assessments, with a positive trend despite CI of HR crossing 1. Results were significant in 4L+ patients (IRC assessed).

In order to assess the performance of the comparator arm, the applicant provided an updated literature review regarding the comparator arm, including Ohmachi et al. 2013; Hong et al. 2018; and Dang et al. 2018. Despite limited comparability, similar trends in BR efficacy are seen, with differences mainly based on the variable proportion of patients with refractory status between these publications and the pivotal study G029365 (pivotal GO29365 enrolled 85% refractory, Dang 2018 30%, Hong 2018 10% and Ohmachi 2013 0%), and on the number of prior treatments. A comparison of efficacy included only the relapsed patients from the pivotal trial. Despite the very small number of patients (N=6) results for the BR arm are overall comparable to those of the historical trials. Overall, the observed efficacy results in the BR arm are not considered to deviate substantially from those of the historical trials and any difference is likely to be attributed to the differences in study population and study design.

CR rate at PRA (based on PET-CT, IRC assessed), was higher in the pola+BR arm: 40.0% (16/40 patients; 95% CI: [24.9%, 56.7%]) vs 17.5% in the BR arm (7/40 patients; 95% CI: [7.3%, 32.8%]). The difference in CR rates between arms was 22.5%, significant and in favour of pola+BR (95% CI: 2.6%, 40.2%; p =0.0261, Cochran Mantel-Haenszel [CMH] chi-square). It has been discussed whether Wilson test was the appropriate one, but Wilson method was eventually considered acceptable as it appeared more conservative [22.5% (2.6%, 40.2%)] than if standard normal approximation method [22.5% (3.3%, 41.7%)] was used.

However, considering the 17% margin error applied in the statistical model, it should be noted that the lower real CI value for CR in pola+BR could get down to: 24.9 -17= 7.9%. The statistical model used in this phase II study does not allow to further adjust the CI.

As determined by the INV, CR described a trend similar to IRC results: 42.5% (27.0, 59.1) in pola+BR vs. 15.0% (5.7, 29.8), with a Δ 27.5% (7.7, 44.7) p=0.0061.

Secondary efficacy endpoints (CR and OR [CR or PR]), assessed by the INV or IRC per PET-CT and CT only, remained consistent with the primary efficacy results (POLA+BR vs BR).

The median DOR was not estimable (NE) (95% CI: 8.8, NE) for pola+BR vs 7.7 months (95% CI: 3.2, 18.9) for BR (stratified HR =0.40; 95% CI: 0.16, 1.01).

The favourable results observed in the response rates (CR and OR) are reflected in the secondary endpoints of PFS, EFS and OS. The PFS as determined by IRC was almost thrice increased in patients treated with pola+ BR compared to BR (stratified HR =0.36; 95% CI: 0.21, 0.63; p =0.0002), with median PFS of 9.5 months [6.2, 13.9] vs 3.7 months [2.4, 4.5]. Investigator-assessed progression free survival (PFS) was an exploratory endpoint which was not type 1 error controlled. The median PFS in the Polivy+BR arm was 7.6 months (95% CI: 6.0, 17.0) vs 2.0 months (95% CI: 1.5, 3.7) in the control arm. The unadjusted estimate for PFS HR was 0.34.

OS was an exploratory endpoint which was not type 1 error controlled. The unadjusted estimate for OS HR was 0.42. When accounting for the influence of baseline covariates the OS HR was adjusted to 0.59. Covariates included primary refractory status, number of prior lines of therapy, IPI, and prior stem cell transplant.

The median OS was 12.4 months (95% CI: 9.0, NE) in the pola+BR arm, and 4.7 months (95% CI: 3.7, 8.3) in the BR arm. At 6 months, 30/40 patients (event free rate of 78.95%; [65.99, 91.91]) remained alive in the pola+BR arm, vs 11/40 patients (event free rate of 37.38%; [20.68, 54.07]) in the BR arm. This difference remained persistent over time, at 9 months (24/40 vs 7/40) and at 12 months (19/40 vs 7/40).

Although relapsed patients were in minority compared to refractory ones, the clinical benefit for both of them seems numerically be shown.

Although - according to NCCN Guidelines- rituximab should not be used in patients with early relapse (<6 months) after Rituximab-based treatment it has been clearly shown, that also rituximab pretreated patients show benefit from Pola+BR and no indication restriction based on this is necessary.

All transplant ineligibile subgroups of patients derived clinical benefit from Pola+BR independently of the reasons for their ineligibility.

Based on the subgroups analysis on primary endpoint, PFS and OS the effect remains stable across subgroups, independently of baseline imbalances between arms in RR TNE DLBCL patients supporting the internal consistency of the study.

When combined with obinutuzumab in the expansion cohort (n=21 in the pola+BG arm) the primary endpoint raised 28.6% of CR (11.3, 52.2). Despite the fact that this expansion cohort was not designed for comparison, these results show anti-tumor activity, which remains lower than 40.0% (24.9, 56.7) of CR obtained in the pola+BR arm**.**

Patient reports outcome (PRO) for peripheral neuropathy was evaluated based on TINAS scores. Due to programming issues quality of these data was limited.

Among all patients treated with pola in GO29365 study, a total of 8 patients developed ADA: against the antibody (2) and against the linker, drug, or neo-epitopes (5; NE in 1 patient). Among the 4 DLBCL patients presenting with ADA, impact on efficacy was not evidenced, considering that 3 of them completed 5 to 6 cycles of treatment and DOR from 21 to 38 months. However, the last patient presented with ADA at C2 and was diagnosed with progressive disease at C3**.**

Ancillary analysis and sensitivity analysis confirmed the favorable trends in PFS and OS across subgroups in the overall R/R DLBCL population, in favor of the pola+BR arm. Further analysis was provided on primary endpoint and additional prognostic factors, raising a similar favorable trend.

Few patients became as consequence of treatment with Pola+BR transplant-eligible, have been transplanted and are in remission. This makes the regimen useful in introduction of potential curative treatment in otherwise incurable patients.

Despite different schemes in administration and combinations compared with the pivotal study, the efficacy results raised from the three main supportive studies are supportive for the positive efficacy results observed in the pivotal study.

As a conclusion, the positive effect of the addition of POLA to BR regimen in RR DLBCL, TNE patients, was observed in the primary endpoint, with a significant increase in CR rate (PET-scan, IRC assessed, at PRA) from 17.5% to 40.0%. This favourable effect was reinforced by secondary endpoints, showing similar trends in CR and OR, with or without PET-scan, and INV or IRC assessed.

This impact in CR was clinically relevant on PFS, EFS and OS, with a 7.7 months improvement in OS at time of cut-off date (from 4.7 to 12.4 months). The cut-off date for all results was initially April 30th 2018 (after all patients completed one year after primary response assessment). Median duration of follow-up for all cohorts in the study was then between 20.7 and 37.6 months. There was initially a sign of a possible PFS plateau in the Pola+BR, but in updated analyses from 11 October 2018 this was not shown. Therefore

it seems that despite of CR achievement, Pola+BR will still remain in most cases only a life-prolonging treatment.

These efficacy data were completed with preliminary results from arm G, carried out with the lyo fomulation. Based on results in 32 patients in arm G (CCOD 12 Nov 2018), trend in efficacy, observed in arm C, would be confirmed, with CR rate of 34.3% (18.6, 53.2); median PFS and OS are sharply lower, despite not designed for comparison to arm C: PFS: 6.0 months (3.5, 6.6) in arm G vs 11.1 months (6.2, 13.9) in arm C; OS: 6.1 months (4.4, NE) in arm G vs 12.4 (9.0, NE). However, the median FU in arm G, at time of CCOD, was 6 months, vs 22.3 months in arm C. Additional efficacy results in 42 patients, up to 15 March 2019, remain similar in terms of CR, lower than in arm C (33.3%; [19.6, 49.6]). However, OS increased up to 9.1 months [6.0, NE]. Subgroups analysis suggest that the difference in CR rates would mainly be due to the lower proportion of 2L relapsed patients in arm G, which present with the higher CR rate in arm C.

Furthermore, PK analysis supports the comparability of both liquid and lyo formulations (see Clinical Pharmacology). Considering interim results provided and additional efficacy data up to 15 March 2019, and also potential differences in the populations in arms C and G, results from arm G with the final formulation remain coherent with previous results.

Consultation with expert groups

The CHMP consulted the SAG-O on the following questions:

1. To what extent has it been demonstrated that polatuzumab vedotin as an add-on to bendamustine and rituximab confers additional clinical benefit?

The evidence provided is based on a small exploratory trial in a very heterogeneous population in terms of prognosis, and where there is an imbalance in important prognostic factors favouring the Polivy+BR group. This questions the robustness of any observed difference.

According to one group of SAG experts, the data were insufficient to establish the benefit of Polivy+BR compared to BR, which furthermore is a suboptimal comparator. Adequate evidence should be submitted (pre-approval) to establish a benefit in the claimed indication.

According to another group of SAG experts, at least a slight increase in terms of complete response rate compared to BR could be concluded, especially in patients with better prognosis. However, it is essential to confirm the size and duration of the effect in a larger population (post-approval).

2. How do you view the safety profile of polatuzumab in the proposed indication?

Given the unknown or assumed low contribution to efficacy of BR in the Polivy+BR combination, the unknown optimal treatment duration for any of the components, and the toxicity associated with the Polivy+BR combination, the safety profile is far from optimised. However, the toxicity is considered managable and does not exceed the toxicity of other regimens in this indication. It is also acknowledged that efficacy is the main objective in this situation and some patients may be willing to accept this level of toxicity, if efficacy was established.

One concern with the long treatment duration with B is that it will likely decrease the possibility of successful apheresis in case CAR T cells became a possible option. This is important for the currently claimed indication that includes 2nd line (i.e., hampering possible later CAR T-cell use).

3. What, if any, are the specific advantages in terms of efficacy, safety or convenience that polatuzumab vedotin would offer over available medicinal products indicated for the same or overlapping indications (Kymriah, Yescarta, Pixuvri, chemo-immunotherapy options)?

There are no data to establish any specific advantages over available treatment options. It is acknowledged that CAR T cells, although they may not always be available due to health care systems' or

other decisions, have nevertheless longer follow-up (24 months and beyond, showing durable response, "plateau"), which is not available for Polivy+BR.

There are no data to compare activity of Polivy+BR to other chemo-immunotherapy options directly. However, according to some SAG experts it can be assumed to be at best of a similar magnitude. Despite the lack of data, this group of experts agreed that in a population of transplant-ineligible, relapsed/refractory patients, if CAR T are not an option for whatever reason, and chemotherapy with platinum compounds are not indicated, e.g., due to neurotoxicity or other comorbidities, that there exists a "niche" of patients for whom there are no available treatment options and where the combination Polivy+BR could be a possible option.

Other SAG experts disagreed, based on the fact that the benefit of the combination is currently unknown due to the fundamental methodological pitfalls (see answer to question No. 1), and that the efficacy or activity of Polivy in such "niche" population is unknown.

4. For which patients might polatuzumab vedotin in combination with bendamustine and rituximab be the preferred therapy?

The SAG agreed that preference is particularly difficult to predict based on the lack of robust data to speculate on indirect comparisons among the available options.

Nevertheless, some SAG experts believed that some patients could benefit of treatment with the combination if there CAR T-cells or high-dose chemotherapy with aSCT or other schedules are not available or suitable options, e.g., because of frailty or neuropathy or in immunocompromised patients, although the lack of evidence of efficacy and safety in such population for whom all available options are unsuitable was acknowledged. However, Pola-BR might offer an additional therapy options for this patient population.

Others disagreed and could not identify a suitable population due to the many deficiencies of the "pivotal" study and the uncertainties about the possible benefit (see above).

The claim that Polivy+BR might be beneficial in case of rapidly progressive disease that is not amenable to CAR T-cell therapy because of the time lag between apheresis and CAR T-cell administration was not supported by the SAG. It is common practice that this can be managed using suitable conventional salvage "bridging" chemotherapy if needed, compatible with subsequent CAR T-cell treatment. Furthermore, the activity of Polivy+BR looked particularly weak in patients with poorer prognosis.

5. What further data, if any, would be relevant, and might feasibly be generated in a pre- or post-marketing setting, to further characterise the efficacy and safety of polatuzumab-vedotin to support the proposed use?

The SAG considered that the available evidence is extremely deficient as the main evidence comes from a small exploratory trial in a very heterogeneous population. As such, the results presented are far from robust or convincing.

According to some SAG members, further data are needed to establish efficacy, ideally, with a randomised controlled trial in the claimed population. Such a study would need to be conducted in the pre-marketing setting. However, the situation is more complex because given the uncertainties about the contributions of BR in the combination, early clinical trials to study rational choices of backbone and treatment duration would also be needed before embarking in a confirmatory trial. The ongoing trial in first-line, using a different combination, is not informative for the applied indication.

According to other SAG members, the proposed single-arm study is useful, especially if coupled with real-world data. The objective would be to confirm the response rate and response duration in a larger population and to determine the utilisation of the combination as well as to build a database to better explore any factors associated with a greater treatment effect and duration.

Further to issues raised at the SAG-O and per CHMP request, the applicant performed multivariate analysis for key efficacy endpoints including complete response (CR) at end of treatment (EoT) by IRC, best overall response (BOR) by IRC, progression free survival (PFS) by IRC and overall survival (OS). Such models, however suffer from limited degree of freedom in the parameter estimates when adjusting a large number of covariates simultaneously with relatively small size of each arm; the applicant performed also propensity score modelling, which preserves the power of detecting treatment effect while still balancing the baseline.

The different analyses (adjusted or not) provided by the applicant to exploring the impact of imbalances of baseline prognostic covariates on the four endpoints: (CR at EoT, BOR, PFS and OS) lead to consistent point estimates across statistical models for a given endpoint and across endpoints in terms of clinical benefit. It has to be noticed that regarding CR and OS analyses, the full and backward multivariate adjustments on pronostic factors gives statistically non-significant results. However, the confidence intervals of point estimates provided by these models are asymetric around 1, in favor of a clear clinical benefit over a detrimental clinical effect, which is consistent with the study main outcomes. The CHMP considered that analyses provided to justify the absence of impact of imbalances of baseline prognostic covariates on the efficacy endpoints is sufficient taking into account the limitations of this study.

Further, in order to understand the results in the context of the existing CAR-T therapies, a comparison of the populations investigated in the CAR-T pivotal studies and Study GO29365 was presented. Despite potential bias, the comparison of patients' characteristics between studies ZUMA-1, JULIET and GO29365 highlighted that patients included in CAR-T cells studies were younger (median 58, 56 and 67 years respectively), without ECOG 2 patients and stronger selection on baseline organ functions. Despite not quantified, the overlap between indications concerns TNE patients from 3L treatment. However, this overlap remains partial since CAR-T therapies may not be suitable for patients in an urgent medical need, frailer patients not able to complete leukapheresis and conditioning and patients at higher risks of CSR. In addition, access to polatuzumab treatment would be immediate, while CAR-T therapies require non-negligible time span for treatment preparation, leading to failure in treatment access for a non-negligible proportion of patients in pivotal studies for CAR-T cells. It was also clarified that, despite limited data in 5 patients from the pivotal study GO29365, pola+BR treatment would not preclude for subsequent CAR-T therapy.

Additional efficacy data needed in the context of a conditional MA

The evidence provided is based on a small exploratory trial in a limited size (82 patients in total received Polivy in trial GO29365; 40 patients from the randomized part arm C and 42 patients from arm G using the lyophilised formulation) and heterogeneous population in terms of prognosis. Available data are thus considered non-comprehensive and additional data are needed in order to confirm the size and duration of the effect in a larger population and render the data set comprehensive. For this reason, the CHMP considered that a full marketing authorisation could not be granted, but in light of the promising results, the CHMP was of the view that a conditional marketing authorisation (CMA) should be considered.

In order to confirm the benefit/risk, the primary CSR for study GO29365 including the primary analysis of Arm H (n=64) as well as a pooled analysis of Arm G (n=42) and Arm H (n=64) will be provided. Distinct histology subtypes will be analysed within Arm H which is considered necessary to confirm response in any relevant subtype at least on a descriptive level.

Furthermore, the results of Study GO39942, a randomized, double-blind, placebo-controlled trial that evaluates polatuzumab vedotin in combination with R-CHP (rituximab, cyclophosphamide, doxorubicin, prednisone) versus R-CHOP in patients with previously untreated diffuse large B-cell lymphoma should be provided. The primary endpoint is progression-free survival. Key secondary endpoints include complete remission rate per independent review committee and overall survival. Although this study is an earlier

line of treatment the CHMP considered that data from this randomized trial with a different backbone combination will be important to confirm the efficacy and safety of Polivy.

2.5.4. Conclusions on the clinical efficacy

Based on the results of GO29365 study, it is concluded that Pola+BR is significantly more effective as the chosen standard of care BR regimen in the treatment of R/R DLBCL patients. An improvement in CRs (40% for pola+BR vs 17.5% for BR), a clinically meaningful improvement in PFS (7.6 months vs. 2.0 months) and a survival benefit (12.4 months for pola+BR vs 4.7 months for BR) have been observed. However the evidence provided is based on a small exploratory trial in a very heterogeneous population in terms of prognosis. Available data are thus considered non-comprehensive and a full marketing authorisation is therefore not considered appropriate. Additional data are needed in order to confirm the size and duration of the effect in a larger population.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

- In order to further confirm the safety and efficacy of polatuzumab vedotin in combination with BR the MAH will provide the primary CSR for study GO29365 including the primary analysis of Arm H (n=64) as well as a pooled analysis of Arm G (n=42) and Arm H (n=64).
- In order to further confirm the safety and efficacy of polatuzumab vedotin in DLBCL the MAH will also provide Study GO39942, a randomized, double-blind, placebocontrolled trial that evaluates polatuzumab vedotin in combination with R-CHP (rituximab, cyclophosphamide, doxorubicin, prednisone) versus R-CHOP in patients with previously untreated diffuse large B-cell lymphoma.

2.6. Clinical safety

Clinical safety data for polatuzumab vedotin 1.8 mg/kg and other dose levels as a single agent or in combination treatment were collected from the pivotal Study GO29365 in R/R DLBCL and R/R FL, and three key supportive studies.

Pivotal Study GO29365 and the three key supportive Studies GO27834, GO29044, and DCS4968g were conducted with 100 mg liquid drug product (DP). Three additional ongoing supportive studies (GO29833, GO29834, and BO29561) are conducted using 170 mg lyophilized (lyo) DP filled from v1.0 DS (polatuzumab vedotin Phase III material that will be used for commercialization). An additional cohort (Arm G) in Study GO29365 is using 140 mg lyo DP filled from v1.0 DS. Safety data from these additional studies and cohort, with lyo DP, were also provided.

This overview provides detailed data mainly from the pivotal study GO29365 including updated data from arm G. With the responses to the D90 LoQ updated data from arm G have been provided (cut-off date March 2019).

Patient exposure

Overall, 588 patients received at least one dose of polatuzumab vedotin as single agent or in combination regimen. Among these patients, 383 patients received polatuzumab vedotin 1.8 mg/kg dose.

The period for AEs collection was shorter in supportive studies GO27834 and DCS4968g (up to 30 days after last administration) than in the pivotal study and the supportive study GO29044 (up to 90 days after the last administration)

Treatment duration in the pivotal study was limited to 6 cycles, as per to the study protocol, while exposure was longer in most of the supportive studies. Consequently, the median total cumulative dose

was higher in supportive studies. Of note, it was 724 mg in study GO29365, all arms included, vs 1015.6 mg in study GO27834 in pooled pola 1.8 mg/kg arms (R/G combined, all histologies).

In the ongoing arm G of the pivotal study (with lyo form), patients received 6x21-day cycles, during which a total of 6 doses of polatuzumab vedotin (1.8 mg/kg), 12 doses of bendamustine (90 mg/m2), and 6 doses of rituximab (375 mg/m2). At time of interim report, the 25 patients included in the safety analysis had completed a median of 3 cycles.

The 3 additional supportive studies (with 170mg lyo DP) are ongoing, with alternative combinations. The median number of doses received was lower, with lower cumulative dose consequently.

In the pivotal study, comparing DLBCL patients treated with pola 1.8 mg/kg +BR (n=45 in phase Ib+ phase II) vs BR (n=39 in phase II), AEs reported in ≥ 20% of patients in any group were anaemia (46.7% vs. 25.6%), neutropenia (46.7% vs. 38.5%), thrombocytopenia (46.7% vs. 28.2%), fatigue (40.0% vs. 35.9%), diarrhoea (37.8% vs. 28.2%), nausea (33.3% vs. 41.0%), pyrexia (33.3% vs. 23.1%), decreased appetite (26.7% vs. 20.5%), neuropathy peripheral (20.0% vs. 2.6%), constipation (17.8% vs. 20.5%), and cough (15.6% vs. 20.5%).

Moreover, lymphopenia was observed in 11.1% in pola+BR, and pancytopenia in 6.7%, vs none in the BR group. A higher frequency of PN events is observed in the pola+BR group (> 10% increase), mainly with peripheral sensory neuropathy (13.3% vs 0) and PN (20.0% vs 2.6%).

When compared to the FL group in the pivotal study, the safety profile of the pola +BR is broadly comparable. When associated with BG in the pivotal study, all histologies, the safety profile remains stable, despite a higher frequency of the following AEs: fatigue (42.7% vs 57.7% in pola+BG), diarrhoea (39.3 vs 57.7%), nausea (44.9 vs 57.7%) constipation (23.6 vs 42.3%), vomiting (19.1 vs 42.3%), dyspnoea (10.1 vs 32.7%) and back pain (5.6 vs 15.4%).

A similar profile was observed in safety population of arm G in study GO29365, with 140 lyo DP pola +BR. The updated data provided with the responses to the D90 LoQ confirmed these results.

Considering AEs in the supportive study GO27834, the safety profile is similar. Between doses of 1.8 mg/kg and 2.4 mg/kg of pola, in comparable groups (pola +R in FL patients), similar AEs were reported, expect for a higher frequency in the 2.4 +R group (≥20%) in diarrhoea (30.0 vs 55.0%), PN (30.0 vs 65.0%), asthenia (0 vs 35.0%), and oedema peripheral (15.0 vs 35.0%).

When pola 1.8 is combined to R/G-CHP in the supportive frontline study GO29044, similar AEs are reported. It should be noted that febrile neutropenia was reported in 17.4% of the patients (pola 1.8 +R/G –CHP, all histologies).

In study DCS4968g, in patients treated with SA pola 1.8 mg/kg (n=11) and 2.4 mg/kg (n=45), no unexpected AE nor increased AE frequency was observed in the 2.4 mg/kg group.

Adverse events

Table 53: Overview of Safety Profile for Patients Treated with Polatuzumab Vedotin 1.8 mg/kg (Pooled by Histologies) in Pivotal Study GO29365 and Key Supportive Studies GO27834, GO29044, and DCS4968g

	GO29365			GO27834		GO29044		DCS4968g
	Pola+BR All Histologies (N=89)	Pola+BG All Histologies (N=52)	All (N=141)	Pola+R All Histologies (Only FL) (N=20)	Pola+G All Histologies (N=84)	Pola+R-CHP All Histologies (N=46)	Pola+G-CHP All Histologies (N=23)	All (N=11)
	No. of Patients (%)							
Any AE	89 (100.0%)	52 (100.0%)	141 (100.0%)	20 (100.0%)	81 (96.4%)	46 (100.0%)	23 (100.0%)	11 (100.0%)
Grade 3-4 AEs	74 (83.1%)	44 (84.6%)	118 (83.7%)	11 (55.0%)	45 (53.6%)	29 (63.0%)	16 (69.6%)	8 (72.7%)
SAEs	55 (61.8%)	30 (57.7%)	85 (60.3%)	7 (35.0%)	25 (29.8%)	19 (41.3%)	9 (39.1%)	6 (54.5%)
Grade 5 AEs	12 (13.5%)	7 (13.5%)	19 (13.5%)	0	2 (2.4%)	1 (2.2%)	1 (4.3%)	1 (9.1%)
Deaths	31 (34.8%)	22 (42.3%)	53 (37.6%)	4 (20.0%)	26 (31.0%)	4 (8.7%)	1 (4.3%)	1 (9.1%)
AEs leading to pola discontinuation	18 (20.2%)	11 (21.2%)	29 (20.6%)	10 (50.0%)	10 (11.9%)	4 (8.7%)	4 (17.4%)	4 (36.4%)
AEs leading to pola dose delay or interruption	38 (42.7%)	23 (44.2%)	61 (43.3%)	10 (50.0%)	21 (25.0%)	7 (15.2%)	3 (13.0%)	5 (45.5%)
AEs leading to pola dose reduction	3 (3.4%)	4 (7.7%)	7 (5.0%)	3 (15.0%)	13 (15.5%)	5 (10.9%)	0	3 (27.3%)
AEPIs								
Neutropenia	53 (59.6%)	23 (44.2%)	76 (53.9%)	8 (40.0%)	23 (27.4%)	26 (56.5%)	16 (69.6%)	5 (45.5%)
Peripheral neuropathy	37 (41.6%)	25 (48.1%)	62 (44.0%)	17 (85.0%)	35 (41.7%)	18 (39.1%)	11 (47.8%)	5 (45.5%)
Infections	59 (66.3%)	34 (65.4%)	93 (66.0%)	10 (50.0%)	30 (35.7%)	26 (56.5%)	11 (47.8%)	6 (54.5%)
Hepatic toxicity	17 (19.1%)	8 (15.4%)	25 (17.7%)	0	9 (10.7%)	4 (8.7%)	2 (8.7%)	0
Anemia	28 (31.5%)	9 (17.3%)	37 (26.2%)	1 (5.0%)	10 (11.9%)	13 (28.3%)	5 (21.7%)	2 (18.2%)
Thrombocytopenia	31 (34.8%)	14 (26.9%)	45 (31.9%)	0	11 (13.1%)	22 (47.8%)	14 (60.9%)	3 (27.3%)

AE=adverse event; AEPI=adverse event of particular interest; BG=bendamustine+obinutuzumab; BR=bendamustine+rituximab; CHP= cyclophosphamide, doxorubicin, and oral prednisone; FL=follicular lymphoma; G=obinutuzumab; pola=polatuzumab vedotin; R=rituximab; SAE=serious adverse event.

Table 54: Overview of Safety Profile in Study GO29365 (Safety Analysis Population)

Protocol: GO29365

	Pola 1.8 +BR DLBCL (N=45)	BR DLBCL (N=39)	Pola 1.8 +BR FL (N=44)	BR FL (N=41)	Pola 1.8 +BR All Histologies (N=89)	Pola 1.8 +BG DLBCL (N=26)	Pola 1.8 +BG FL (N=26)	Pola 1.8 +BG All Histologies (N=52)	Pola 1.8 +BR/BG All Histologies (N=141)
Total number of patients with at least one adverse event	45 (100.0%)	38 (97.4%)	44 (100.0%)	41 (100.0%)	89 (100.0%)	26 (100.0%)	26 (100.0%)	52 (100.0%)	141 (100.0%)
Total number of events	711	446	773	395	1484	415	529	944	2428
Total number of patients with at least one AE	45 (100.0%)	38 (97.4%)	44 (100.0%)	41 (100.0%)	89 (100.0%)	26 (100.0%)	26 (100.0%)	52 (100.0%)	141 (100.0%)
Grade 5 AE	9 (20.0%)	11 (28.2%)	3 (6.8%)	2 (4.9%)	12 (13.5%)	5 (19.2%)	2 (7.7%)	7 (13.5%)	19 (13.5%)
Grade 3-4 AE	38 (84.4%)	28 (71.8%)	36 (81.8%)	25 (61.0%)	74 (83.1%)	23 (88.5%)	21 (80.8%)	44 (84.6%)	118 (83.7%)
Serious AE	29 (64.4%)	24 (61.5%)	26 (59.1%)	10 (24.4%)	55 (61.8%)	18 (69.2%)	12 (46.2%)	30 (57.7%)	85 (60.3%)
AE leading to study withdrawal	15 (33.3%)	9 (23.1%)	8 (18.2%)	5 (12.2%)	23 (25.8%)	4 (15.4%)	5 (19.2%)	9 (17.3%)	32 (22.7%)
AE leading to Polatuzumab Vedotin discontinuation	12 (26.7%)	0	6 (13.6%)	0	18 (20.2%)	6 (23.1%)	5 (19.2%)	11 (21.2%)	29 (20.6%)
AE leading to Polatuzumab Vedotin dose delay/interruption	22 (48.9%)	0	16 (36.4%)	0	38 (42.7%)	11 (42.3%)	12 (46.2%)	23 (44.2%)	61 (43.3%)
AE leading to Polatuzumab Vedotin dose reduction	2 (4.4%)	0	1 (2.3%)	0	3 (3.4%)	0	4 (15.4%)	4 (7.7%)	7 (5.0%)
AE leading to any treatment discontinuation	14 (31.1%)	6 (15.4%)	10 (22.7%)	5 (12.2%)	24 (27.0%)	6 (23.1%)	6 (23.1%)	12 (23.1%)	36 (25.5%)
AE leading to any treatment dose delay/interruption	23 (51.1%)	15 (38.5%)	19 (43.2%)	12 (29.3%)	42 (47.2%)	11 (42.3%)	13 (50.0%)	24 (46.2%)	66 (46.8%)
AE leading to any treatment dose reduction	8 (17.8%)	4 (10.3%)	9 (20.5%)	3 (7.3%)	17 (19.1%)	5 (19.2%)	6 (23.1%)	11 (21.2%)	28 (19.9%)
Any Grade AEPI for Neutropenia by SMQ	27 (60.0%)	21 (53.8%)	26 (59.1%)	17 (41.5%)	53 (59.6%)	11 (42.3%)	12 (46.2%)	23 (44.2%)	76 (53.9%)
Any Grade AEPI for Peripheral Neuropathy by SMQ	18 (40.0%)	3 (7.7%)	19 (43.2%)	11 (26.8%)	37 (41.6%)	10 (38.5%)	15 (57.7%)	25 (48.1%)	62 (44.0%)
Any Grade AEPI for Infection by SOC	24 (53.3%)	20 (51.3%)	35 (79.5%)	20 (48.8%)	59 (66.3%)	15 (57.7%)	19 (73.1%)	34 (65.4%)	93 (66.0%)
Any Grade AEPI for Hepatic Toxicity by SMQ	9 (20.0%)	5 (12.8%)	8 (18.2%)	4 (9.8%)	17 (19.1%)	3 (11.5%)	5 (19.2%)	8 (15.4%)	25 (17.7%)
Any Grade AEPI for Thrombocytopenia by SMQ	22 (48.9%)	13 (33.3%)	9 (20.5%)	7 (17.1%)	31 (34.8%)	8 (30.8%)	6 (23.1%)	14 (26.9%)	45 (31.9%)
Any Grade AEPI Anemia by SMQ	21 (46.7%)	11 (28.2%)	7 (15.9%)	5 (12.2%)	28 (31.5%)	5 (19.2%)	4 (15.4%)	9 (17.3%)	37 (26.2%)

Investigator text for AEs encoded using MedDRA version 21.0. Percentages are based on N in the column headings. Includes all treatment emergent adverse events.
Cutoff Date: 30APR2018
Extract Date: 29JUN2018

Table 55: Comparison of adverse events in arm G (cut-off date of May 2018 versus March 2019) (Safety Population)

Study Phase	Phase II
Cohort/Arm	G
Treatment	Pola+BR
Sample size	N = 25
	No. of subjects (%)
Total no. of deaths	3 (12)
Patients with at least one:	
Any AE	24 (96.0)
Grade 3–4 AE	18 (72.0)
Grade 5 AE	1 (4.0)
Serious AE	10 (40.0)
AE leading to discontinuation of:	
polatuzumab vedotin	2 (8.0)
any study drug	3 (12.0)
AE leading to delay/interruption of	
polatuzumab vedotin	6 (24.0)
any study drug	6 (24.0)
AE leading to dose reduction of	
polatuzumab vedotin	1 (4.0)
any study drug	2 (8.0)
Selected AEs/AEs to monitor	
Grade ≥2 Peripheral neuropathy	0
Grade ≥3 Neutropenia	10 (40.0)
Grade ≥3 Hepatotoxicity	2 (8.0)
Grade 3-4 Infections	3 (12.0)
Grade 5 Infections	1 (4.0)
Grade ≥3 Anemia	3 (12.0)
Grade ≥3 Thrombocytopenia	3 (12.0)
Grade ≥3 Diarrhea	2 (8.0)

Study Phase	Phase II
Cohort/Arm	G
Treatment	Pola+BR
Sample size	N = 42
	No. of subjects (%)
Total number of deaths	20 (47.6%)
Patients with at least one:	
Any AE	42 (100%)
Grade 3–4 AE	33 (78.6%)
Grade 5 AE	2 (4.8%)*
Serious AE	26 (61.9%)
AE leading to discontinuation of:	
Polatuzumab vedotin	7 (16.7%)
Any study drug	7 (16.7%)
AE leading to delay/interruption of	
Polatuzumab vedotin	14 (33.3%)
Any study drug	19 (45.2%)
AE leading to dose reduction of	
Polatuzumab vedotin	0
Any study drug	5 (11.9%)
Selected AEs/AEs to monitor	
Grade ≥3 peripheral neuropathy	2 (4.8%)
Grade ≥3 neutropenia	21 (50.0%)
Grade ≥3 hepatic toxicity	2 (4.8%)
Grade 3–4 infections [a]	11 (26.2%)
Grade 5 infections	2 (4.8%)
Grade ≥3 anemia	3 (7.1%)
Grade ≥3 thrombocytopenia	8 (19.0%)
Grade ≥3 diarrhoea	3 (7.1%)

Investigator text for AEs encoded using MedDRA version 21.0.

Includes all treatment emergent adverse events.

Adverse Events of Grade ≥3

In the pivotal study, while comparing DLBCL patients treated with pola 1.8 mg/kg +BR (n=45) vs BR (n=39 in phase II), the frequency of grade 3-4 events was higher in the pola+BR arm (84.4% vs 71.8%).

The most frequently reported SOCs (occurring in ≥ 20% of patients in any group) for the pola+BR and BR groups were Blood and Lymphatic System Disorders (64.4% vs. 56.4%), Infection and Infestations (24.4% vs. 20.5%), and Gastrointestinal Disorders (22.2% vs. 12.8%).

The most frequently reported Grade 3 or 4 events (occurring in ≥10% of patients in any group) for the pola+BR and BR groups were neutropenia (40.0% vs. 33.3%), thrombocytopenia (37.8% vs. 23.1%), anemia (24.4% vs. 17.9%), febrile neutropenia (11.1% vs. 12.8%), and lymphopenia (11.1% vs. 0), which were all under SOC Blood and Lymphatic System Disorders.

At SOC level, grade 3-4 AEs were more frequent (>10% higher) in pola +BR arms in SOC vascular disorders (11.1% vs 0). At PT level, the following grade 3/ 4 AEs were more frequent in pola+BR arm (> 5% higher): neutropenia (40.0 vs 33.3%), thrombocytopenia (37.8 vs 23.1%) anemia (24.4 vs 17.9%) lymphopenia (11.1% vs 0) and pneumonia (6.7% vs 0).

A similar trend was observed in FL patients treated with pola+BR vs BR in the pivotal study. However, in FL patients, the SOC infections and infestations was more frequently reported in the pola+BR arm (31.8 vs 7.3%).

A similar safety profile was observed in the 25 patients included in arm G of the pivotal study, treated with the 140 lyo DP.

In the supportive study GO27834, similar trends in the reporting of grade 3-4 AEs was observed between pola 1.8 and 2.4 mg/kg groups (+R/G, all histologies). However, it should be noted that grade 3-4 frequency was higher in 2.4 mg/kg +R DLBCL patients: 76.9% vs 53.8% in the 1.8 mg/kg pooled groups. This higher reporting of grade 3/ 4 AEs in the 2.4 mg/kg DLBCL patients was driven by the following SOCs: investigations (5.8 vs 15.4%), general disorders (2.9 vs 15.4%) and nervous system disorders (2.9 vs 15.4%).

A similar trend was observed in the supportive study GO29044, with 63.0% of incidence of Grade 3 or 4 AEs in Pola+R-CHP in 1L DLBCL or mixed (1L or R/R) other B-cell NHL (N=46), and 65.2% in Pola+R/G-CHP all histologies (N=69).

In the supportive study DCS4968g, despite differences in population size, similar trends in the reporting of grade 3-4 AEs were observed between both doses in SA arms (all histologies pooled), pola 1.8mg/kg and 2.4mg/kg.

AEs of special interest

Table 56: Adverse Events of Particular Interest and Search Definitions Used

AEPI	Definition (single/grouped PTs used)
Neutropenia including febrile neutropenia	SMQ "Haematopoietic leukopenia [narrow]" (SMQ20000030n)
Peripheral neuropathy	SMQ "Peripheral neuropathy [wide]" (SMQ20000034w)
Infections	SOC "Infections and Infestations"
Hepatic toxicity (hyperbilirubinemia, transaminase elevation)	SMQ "Drug-related hepatic disorders [wide]" (SMQ20000006w).
Anemia	SMQ "Haematopoietic erythropenia" [wide] (SMQ20000029)
Thrombocytopenia	SMQ "Haematopoietic thrombocytopenia [narrow]"(SMQ20000031n)

PT=preferred term; SOC=System Organ Class; SMQ=Standardized MedDRA Query.

Neutropenia

Neutropenia events observed in pola+BR vs BR DLBCL arms were: all grades (60.0 vs 53.8%) and grade 3/ 4 (55.6 vs 46.2%). The incidence of febrile neutropenia was also comparable (11.1% vs. 12.8%). Almost all neutropenia events were grade 3/ 4 in both arms. Neutropenia AEs led to study withdrawal and pola discontinuation (8.9% of patients each). All neutropenia AE resolved in the pola+BR arm.

Peripheral Neuropathy (PN)

In the pivotal study, PN events were more frequent in pola+BR arm (40.0% vs 7.7% in BR arm). None was fatal, serious nor led to study withdrawal. All events were Grade 1 or 2 in both arms. In pola+BR arm, the main reported PTs were neuropathy peripheral (9 patients) and peripheral sensory neuropathy (6 patients). Most events (11/18) resolved in the pola+BR group, despite 7 unresolved events, mainly grade 1**.** The median TTO was 1.4 months for the pola+BR group.

In the supportive study GO27834, the longer median treatment exposure (up to 13.5 cycles in pola 1.8 mg/kg+R group) correlated with the higher incidence and severity of PN events. In study DCS4968g, the frequency increased with higher dose of pola (up to 2.4 mg/kg) and longer treatment (over 8 cycles).

Infections

Infections, including pneumonia and other types of infections, were reported in 53.3% of patients in the Polivy plus BR arm and 51.3% of patients in the BR arm. In the Polivy plus BR arm, serious infections were reported in 28.9% of patients and fatal infections were reported in 8.9% of patients. In the BR arm, serious infections were reported in 30.8% of patients and fatal infections were reported in 10.3% of patients. One patient (2.2%) in the Polivy plus BR arm discontinued treatment due to infection compared to 5.1% of patients in the BR arm.

The incidence of infectious events was similar in pola+BR and BR DLBCL arms (53.3 vs 51.3%), and most events were Grade ≥ 3 in both groups in the pivotal study. The incidence of serious infections events was also comparable between both arms (28.9% vs. 30.8%). In the pola+BR group, 4 patients (8.9%) experienced fatal events, including pneumonia (2), meningoencephalitis herpetic (1), and sepsis (1). In the BR group, 4 patients (10.3%) experienced fatal events, including sepsis (2), pneumonia (1), and septic shock (1).

Six (6) opportunistic infections were reported in 4 patients (8.9%) in pola+BR arm: herpetic encephalitis (1 patient), cerebral toxoplasmosis, cytomegalovirus (CMV), and pneumonia (in the same patient), CMV infection (reported twice in the same patient), and pneumocystis jiroveci pneumonia (PJP) (1 patient).

Three of these patients died due to opportunistic infection. In the BR group, opportunistic infections were reported in 2 patients: CMV infection and pulmonary mycosis.

In pola+BR arms, one out of the 4 fatal infectious related to pola: meningoencephalitis herpetic, occurred in the follow up period. The incidence of infections was similar between the treatment arms (or even slightly higher in the BR arm). The review of potential cases of viral reactivation under SOC Infections and Infestations in the pola+BR arm of the DLBCL patient population retrieved 9 AEs, including 4 assessed as related to pola+BR regimen: Herpes infection and fatal meningoencephalitis in one patient, (previously discussed), one non-serious case of CMV infection, at D43, and one non-serious case of herpes virus infection, at D 48.

Hepatic toxicity:

The incidence of hepatic toxicity was higher in pola+BR vs BR DLBCL arm (20.0 vs 12.8%). The majority of events were grade 1-2 severity in both arms, and most events resolved (6/9) in the pola+BR arm. The median TTO was 1.4 month in the pola+BR arm.

In the pola+BR arm, the most frequently reported PT was hypoalbuminaemia (13.3%; 6 patients), followed by AST increased (4.4%; 2 patients). There were no cases of drug-induced liver injury as defined by Hy's Law.

Across supportive studies, grade 3/ 4 hepatic toxicities were reported in two patients in study GO27834 with pola 2.4 mg/kg, including one grade 4 hepatocellular injury and one grade 4 hepatic steatosis and hepatomegaly, assessed as treatment related and serious, leading to treatment discontinuation and resolved.

Anaemia

In the pivotal study, the incidence of anemia was higher in pola+BR vs BR DLBCL arm (46.7 vs 28.2%). The majority of events were non serious in both arms. However, RBC transfusion was comparable between both arms (20.0% vs. 17.9%). Limited impact on treatment was reported. The median TTO was 2.3 and 0.1 month for the pola+BR and BR groups.

A similar safety profile was observed in arm G regarding anemia, as well as in supportive studies.

Thrombocytopenia

In the pivotal study, the incidence of thrombocytopenia was higher in pola+BR vs BR DLBCL arm (48.9 vs 33.3%). The majority of events were grade 3/ 4 events, none fatal. Two patients (4.4%) in pola+BR group and 1 patient (2.6%) in BR group experienced serious thrombocytopenia. Platelet transfusion were comparable between the pola+BR and BR groups (8.9% vs. 12.8%).

In the pola+BR group, 1 patient presented a bleeding event (Grade 5 hemoptysis), in the context of anticoagulation therapy due to thromboembolic event (pulmonary embolism and deep vein thrombosis). The patient presented with an extranodal lesion in lung at baseline

Thrombocytopenia events led to pola discontinuation in 5 patients (11.1%), and dose delay or interruption of polatuzumab vedotin in 6 patients (13.3%).

The median TTO was 1.4 and 0.7 months for the pola+BR and BR groups. Most patients (81.8%; 18/22 vs. 46.2%; 6/13) had the thrombocytopenia events resolved in both groups, with median time to resolution of 0.5 and 0.3 month for the pola+BR and BR groups, respectively.

No further safety signal regarding thrombocytopenia was identified in arm G and in supportive studies.

Myelosuppression

8.9% of patients in the Polivy plus BR arm discontinued Polivy due to neutropenia compared to 2.6% of patients in the BR arm who discontinued treatment due to neutropenia. Thrombocytopenia events led to discontinuation of treatment in 11.1% of patients in the Polivy plus BR arm and 5.1% of patients in the BR arm. No patients discontinued treatment due to anaemia in either the Polivy plus BR arm or BR arm.

Progressive multifocal leukoencephalopathy (PML)

One case of PML, which was fatal, occurred in one FL patient treated with Polivy plus bendamustine and obinutuzumab. This patient had three prior lines of therapy that included anti-CD20 antibodies.

Gastrointestinal toxicity

Gastrointestinal toxicity events were reported in 80.0% of patients in the Polivy plus BR arm compared to 64.1% of patients in the BR arm. Most events were Grade 1-2, and Grade 3-4 events were reported in 22.2% of patients in the Polivy plus BR arm compared to 12.8% of patients in the BR arm. The most common gastrointestinal toxicity events were diarrhoea and nausea.

Adverse drug reactions (ADRs)

Adverse drug reactions (ADRs) from the polatuzumab vedotin, bendamustine, and rituximab combination treatment were identified based on the interim data analyses from Study GO29365 (the AEs by PTs reported in ≥ 10% of patients) in the pola+BR arm

Table 57: Summary of Adverse Drug Reactions Reported in ⩾10% of Patients Treated with Pola+BR Compared with Patients Treated with BR

	Pola+BR (N=45)		BR (N=39)	
ADR (MedDRA)	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Blood and Lymphatic System Disorders				
Anemia	46.7	24.4	25.6	17.9
Neutropenia	46.7	40.0	38.5	33.3
Thrombocytopenia	46.7	37.8	28.2	23.1
Lymphopenia	11.1	11.1	0	0
Leukopenia	11.1	6.7	12.8	7.7
Febrile Neutropenia	11.1	11.1	12.8	12.8
Gastrointestinal Disorders				
Diarrhea	37.8	4.4	28.2	5.1
Nausea	33.3	0	41.0	0
Constipation	17.8	0	20.5	2.6
Vomiting	17.8	2.2	12.8	0
Abdominal Pain Upper	11.1	2.2	5.1	0
Abdominal Pain	11.1	4.4	10.3	2.6
General Disorders and Administration Site Conditions				
Fatigue	40.0	4.4	35.9	2.6
Pyrexia	33.3	2.2	23.1	0
Asthenia	11.1	0	15.4	0
Chills	11.1	0	7.7	0
Infections and Infestations				
Penumonia	15.6	6.7	10.3	0
Metabolism and Nutrition Disorders				
Decreased appetite	26.7	2.2	20.5	0
Hypoalbuminemia	13.3	2.2	5.1	0
Hypokalemia	15.6	6.7	7.7	2.6
Hypocalcemia	11.1	2.2	2.6	0

Nervous System Disorders				
Neutropathy Peripheral	20.0	0	2.6	0
Periperal Sensory Neuropathy	13.3	0	0	0
Dizziness	13.3	0	7.7	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	15.6	0	20.5	0
Investigations				
Weight Decreased	15.6	2.6	7.7	2.6
Skin and Subcutaneous Tissue Disorders				
Pruritis	13.3	0	10.3	2.6
Injury, Poisoning, and Procedural				
Infusion Related Reactions[a]	33.3	6.7	23.1	10.3

ADR=adverse drug reaction; BR=bendamustine + rituximab; MedDRA=Medical Dictionary for Regulatory Activities; pola+BR=polatuzumab vedotin + bendamustine + rituximab.

a Infusion related reactions were defined as any AE occurring with 24 hours of treatment infusion and considered by the investigator as causally related to treatment.

Serious adverse event/deaths/other significant events

Serious AEs

Table 58 Serious Adverse Events Reported in More than One Patient with R/R DLBCL in Either Pola+BR, BR or Pola+BG Treatment Groups (Safety Population)

Study Phase	Phase I	Phase II (randomized)		Phase Ib/II	Phase Ib	Phase II (expansion)	Phase Ib/II
Cohort/Arm	1a	D	C	1a+C	1b	F	1b+F
Treatment	Pola+BR	BR	Pola+BR	Pola+BR (total)	Pola+BG	Pola+BG	Pola+BG (total)
Sample size	N = 6	N = 39	N = 39	N = 45	N = 6	N = 20	N = 26
MedDRA SOC							
preferred term							
Total number of patients with at least one AE							
Infections & Infestations							
Pneumonia	1 (16.7%)	3 (7.7%)	3 (7.7%)	4 (8.9%)	2 (33.3%)	0	2 (7.7%)
Sepsis	0	2 (5.1%)	2 (5.1%)	2 (4.4%)	0	1 (5.0%)	1 (3.8%)
Blood & Lymphatic System Disorders							
Febrile Neutropenia	1 (16.7%)	4 (10.3%)	4 (10.3%)	5 (11.1%)	1 (16.7%)	2 (10.0%)	3 (11.5%)
Anemia	0	1 (2.6%)	2 (5.1%)	2 (4.4%)	0	0	0
Thrombocytopenia	0	1 (2.6%)	2 (5.1%)	2 (4.4%)	0	0	0
Neutropenia	0	2 (5.1%)	1 (2.6%)	1 (2.2%)	0	0	0
General Disorders & Administrative Site Conditions							
Pyrexia	0	0	4 (10.3%)	4 (8.9%)	1 (16.7%)	2 (10.0%)	3 (11.5%)

Arm G

Table 59: Serious Adverse Events Reported in More than One Patient (Safety Population)

Study Phase	**Phase II**
Cohort/Arm	**G**
Treatment	**Pola+BR**
Sample size	**N = 25**
Total number of patients with at least one AE	10 (40.0%)
MedDRA SOC	
preferred term	
Blood & Lymphatic System Disorders	
Febrile Neutropenia	3 (12.0%)
Infections & Infestations	
Sepsis	2 (8.0%)
Urinary Tract Infection	2 (8.0%)
Gastrointestinal Disorders	
Diarrhea	2 (8.0%)

In study GO27834, 35.9% of patients presented with at least 1 SAE in DLBCL pola 2.4+R group. In this study, AE reporting period was twice shorter than in the pivotal study. SAEs frequencies were similar between treatment groups and coherent with SAEs reported in the pivotal study.

In study GO29044, the frequency of SAEs remains lower than in the pivotal study, reported in 40.6% of patients in the pola 8mg/kg +R/G–CHP group, all histologies. This study includes untreated DLBCL patients, while the pivotal study included heavily pre-treated R/R patients. The main reported SOCs remain unchanged. However, it should be noted that 2 SAEs of atrial fibrillation were reported in pola 1.8 +R-CHP arm, all histologies.

In study DCS4968g, no significant difference in SAEs reporting or safety signal was observed across all histologies groups. No signal was identified while increasing dose of pola SA in DLBCL arms (<1.8 mg/kg, 1.8 mg/kg and 2.4 mg/kg). The majority of related SAEs was Grade 3 (38.8% vs 66.6%) followed by Grade 4 (27.7% vs 20.0%) and Grade 5 (16.6% vs 13.3%). The most common SAEs by SOC were Infections and infestations and Blood and lymphatic system disorders for both treatment arms.

Deaths

In the pivotal study, 9 fatal AEs were reported in pola+BR patients (n=39), including two assessed as related to pola +BR: One case of meningoencephalitis herpetic, in a 72 years old female patient who completed 6 cycles of study treatment; 1 case of pulmonary oedema, in a 56 years old male patient; One of the 11 fatal AEs reported in the comparative BR arm was assessed as related to study drug, with a fatal septic shock at D114 during treatment period. Among pola +BG R/R DLBCL patients (N=26 in phase Ib + II), 5 fatal AEs were reported, including 1 MDS in a 67 years male patient - assessed as related to pola and bendamustine.

Among FL patients (n=99), 7 fatal AEs were reported, including 2 in BR patients (n=41), 3 in pola+BR patients (n=38) and 2 in pola+BG (n=20). None was assessed as related to study drug in BR arm, 1 AE of death of related to pola+BR, and 1 AE of questionable PML was assessed as related to pola+BG.

In arm G (pola 140 lyo DP +BR) of the pivotal study, 3 patients died due to AEs. The three patient deaths reported due to AEs included 2 patients with Grade 5 AEs of sepsis, and 1 patient with an unspecified Grade 5 AE that was amended to progressive disease after the CCOD.

Laboratory findings

In DLBCL pola+BR group in the pivotal study (n=45), the most frequent grade 3/ 4 shifts from baseline concerned decrease in lymphocytes (95.6%), neutrophils (51.1%) and platelets (31.1%). Based on previous discussion on AEPIs and MOA, this is not unexpected.

Increase in uric acid was observed in 26.7% of the patients in DLBCL pola+BR group. Grade 3-4 decrease inpotassium was also reported in 5 patients (11.1%, vs 5.1% in BR arm). Of note, 1 patient presented with grade 1 atrial fibrillation in DLBCL pola+BR arm. There were 5 patients in the BR arm who reported arrhythmias. No further event in cardiac arrhythmia SMQ was reported.

Similar trends were observed in supportive studies, without new safety signal identified from laboratory findings.

In the pivotal study GO29365, there was no clinical meaningful change from baseline throughout the course of treatment for diastolic or systolic blood pressure, heart rate, respiratory rate, or patient weight in any treatment groups. Vital signs data were not summarized in the three main supportive studies, but captured by AEs.

No new safety signal was identified on ECG abnormalities and vital signs.

Further discussion on the risk of hypogammaglobulinemia was provided.

Laboratory findings were similar in arm G.

Safety in special populations

Safety profile was similar between male and female across groups, as well as between younger and older patients (< 65 and ≥65 years).

No significant difference was identified across subgroups with baseline hepatic function normal, mild 1, 2 or moderate. Regarding baseline renal function, the global safety profile remained comparable between baseline normal, mild or moderate function. However, in pola +BR DLBCL arm, the frequency of grade 3-4 events increase from 78.9% in patients with normal renal function, to 87.5% in mild impairment and 90.0% in moderate impairment patients. A similar trend is observed in thrombocytopenia events, from 42.1% to 62.5 % in patients with mild renal function impairment.

Similar observations were raised from the three main supportive studies, mainly regarding gender and age groups. No meaningful difference in the safety profile was identified between groups with normal hepatic function, mild or moderate impairment. However, across the pivotal and supportive studies, despite small populations and differences in baseline, renal impairment is associated with a higher incidence of AEs leading to treatment discontinuation, delay or dose reduction in the pivotal study and supportive studies GO27834 and GO29044.

No significant difference was observed across studies between regions.

No studies of polatuzumab vedotin have been conducted in pregnant women, and to date no pregnancies were reported in the studies included in this summary document.

Table 60: Summary of Overall Adverse events profile by age group

MedDRA Terms	**Total (N=141)**	**Age <65 (N=63)**	**Age 65-74 (N=60)**	**Age 75-84 (N= 13)**	**Age 85+ (N=5)**
Total No of pts with at least 1 event	141 (100%)	63 (100%)	60 (100%)	13 (100%)	5 (100%)
Total AEs	2428	1177	962	204	85

MedDRA Terms	Total (N=141)	Age <65 (N=63)	Age 65-74 (N=60)	Age 75-84 (N= 13)	Age 85+ (N=5)
Serious AEs – Total	85 (60.3%)	35 (55.6%)	39 (65.0%)	8 (61.5%)	3 (60.0%)
- Fatal	19 (13.5%)	5 (7.9%)	7 (11.7%)	4 (30.8%)	3 (60.0%)
- Hospitalization/prolong existing hospitalization	76 (53.9%)	34 (54.0%)	32 (53.3%)	7 (53.8%)	3 (60.0%)
- Life-threatening	15 (10.6%)	6 (9.5%)	6 (10.0%)	1 (7.7%)	2 (40.0%)
- Disability/incapacity	0	0	0	0	0
- Other (medically significant)	4 (2.8%)	0	4 (6.7%)	0	0
AE leading to drop-out	32 (22.7%)	11 (17.5%)	16 (26.7%)	4 (30.8%)	1 (20.0%)
Psychiatric disorders	34 (24.1%)	13 (20.6%)	15 (25.0%)	4 (30.8%)	2 (40.0%)
Nervous system disorders	85 (60.3%)	41 (65.1%)	33 (55.0%)	9 (69.2%)	2 (40.0%)
Accidents and injuries	11 (7.8%)	5 (7.9%)	4 (6.7%)	1 (7.7%)	1 (20.0%)
Cardiac disorders	20 (14.2%)	6 (9.5%)	12 (20.0%)	1 (7.7%)	1 (20.0%)
Vascular disorders	31 (22.0%)	12 (19.0%)	14 (23.3%)	2 (15.4%)	3 (60.0%)
Cerebrovascular disorders	2 (1.4%)	0	2 (3.3%)	0	0
Infections and infestations	93 (66.0%)	37 (58.7%)	46 (76.7%)	9 (69.2%)	1 (20.0%)
Anticholinergic syndrome	0	0	0	0	0
Quality of life decreased					
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	26 (18.4%)	12 (19.0%)	10 (16.7%)	2 (15.4%)	2 (40.0%)
other AE appearing more frequently in older patients	N/A				

Immunological events

In Study GO29365, the incidence of treatment-emergent (sum of treatment-induced and treatment-enhanced) anti-drug antibody (ADA) was 6.0% (8 of 134 ADA evaluable patients). Baseline prevalence of ADAs was 3.7% (5 of 134 ADA evaluable patients). All 5 patients with a positive ADA result at baseline were treatment unaffected (a post-baseline evaluable patient with a positive ADA result at baseline and [a] where all post baseline titre results are less than 0.60 t.u. greater than the baseline titre result, OR [b] where all post-baseline results are negative or missing).

There were no events of immunogenicity reported in arm G at the data cut-off date.

To date, across all patients including Study GO29365 and six supportive studies (three main supportive studies GO27834, GO29044, DCS4968g, and additional GO29833, GO29834, and BO29561 studies), the post-baseline ADA incidence was 2.6% (14 of 536 ADA evaluable patients). Baseline prevalence of ADAs was 2.4% (13 of 545 ADA evaluable patients), of which, 11 baseline ADA-positive patients were treatment unaffected.

No identifiable relationship between an ADA response and reported AEs was observed. However, due to the limited number of anti-polatuzumab vedotin antibody positive patients to date, no conclusions can be drawn concerning a potential effect of immunogenicity on safety at this time.

Safety related to drug-drug interactions and other interactions

No clinical data on DDI are included in the submission (see discussion on Clinical Safety).

Discontinuation due to adverse events

In the pivotal study, 26.7% of patients in the pola+BR DLBCL arm had an AE leading to pola discontinuation, driven by thrombocytopenia (8.9%) and neutropenia (6.7%). Overall, the profile of AEs that led to treatment discontinuation of pola was similar between the pola+BR and pola+BG groups, despite a higher frequency of infections AEs leading to pola discontinuation in pola+BG groups.

In the supportive study GO27834, AEs leading to pola discontinuation concerned 19.2% of patients in the pola 1.8 +R/G all histologies group (n=104), driven by different AEs than in the pivotal study: peripheral sensory neuropathy (5.8%) and neutropenia (4.8%). A similar trend was observed in the pola 2.4 +R DLBCL group, despite a higher frequency of AEs leading to pola discontinuation (30.7%).

In the supportive study GO29044, in Pola-R-CHP arm, the incidence of AEs that led to discontinuation of pola was 8.7%, driven by the Nervous System Disorders SOC (6.5%; 3 patients). All events were each reported in a single patient (2.2%). No AEs led to pola discontinuation in groups at lower doses (n=6 in each group).

In the supportive study DCS4968g, a progressive increase in AEs leading to pola discontinuation was observed with increased dose across all histologies groups, with 23.3%, 36.4% and 51.1% with pola SA <1.8 mg/kg, 1.8 mg/kg and 2.4 mg/kg respectively.

Post marketing experience

Not applicable

2.6.1. Discussion on clinical safety

Clinical safety data were collected from the pivotal study and three key supportive studies, all conducted with the 100 mg liquid drug product (DP). Moreover, updated safety data from arm G of the pivotal study, using 140 mg lyophilized DP, were provided, as well as safety data from three additional supportive studies conducted with the 170 mg lyo DP.

In DLBCL patients in the pivotal study, comparing pola 1.8 mg/kg (safety analysis population, n=45 in phase Ib+phase II) vs BR (n=39 in phase II), almost all patients presented with AEs (100.0% vs 97.4%). A higher proportion of patients in the pola+BR arm presented with grade 3/4 AEs (84.4% vs 71.8%) and AEs leading to study withdrawal (33.3% vs 23.1%).

Most of AEs of particular interest (AEPIs) were more frequent in the in pola+BR arm, including neutropenia (60.0% vs 53.8%), PN (40.0 vs 7.7%), thrombocytopenia (48.9 vs 33.3%) and anaemia (46.7 vs 28.2%).

Across all studies, in pola 1.8 groups, and arm G of the pivotal study the safety profile was similar despite differences in exposure, combination, histologies and AEs reporting periods.

In the pivotal study, AEs reported in ≥ 20% of patients in any group (pola +BR vs BR) were anaemia (46.7% vs. 25.6%), neutropenia (46.7% vs. 38.5%), thrombocytopenia (46.7% vs. 28.2%), fatigue (40.0% vs. 35.9%), diarrhoea (37.8% vs. 28.2%), nausea (33.3% vs. 41.0%), pyrexia (33.3% vs. 23.1%), decreased appetite (26.7% vs. 20.5%), neuropathy peripheral (20.0% vs. 2.6%), constipation (17.8% vs. 20.5%), and cough (15.6% vs. 20.5%). A similar profile was observed in safety population of arm G in study GO29365, with 140 lyo DP +BR. The most frequently reported Grade 3 or 4 events

(occurring in ≥10% of patients in any group) for the pola+BR and BR groups were neutropenia (40.0% vs. 33.3%), thrombocytopenia (37.8% vs. 23.1%), anaemia (24.4% vs. 17.9%), febrile neutropenia (11.1% vs. 12.8%), and lymphopenia (11.1% vs. 0).

The most frequently reported (≥ 30%) ADRs in patients treated with Polivy in combination with BR were anaemia (46.7%), thrombocytopenia (46.7%), neutropenia (46.7%), fatigue (40.0%), diarrhoea (37.8%), nausea (33.3%), and pyrexia (33.3%). Serious adverse reactions were reported in 27% of Polivy plus BR treated patients, which includes febrile neutropenia (6.7%), pyrexia (4.4%), and pneumonia (4.4%).

ADRs leading to treatment regimen discontinuation in >5% of patients were thrombocytopenia (8.9%) and neutropenia (6.7%).

In the supportive study GO27834, a higher frequency of the following AEs was observed in the 2.4 mg/kg +R group (≥20%), vs 1.8 mg/kg group: diarrhoea (30.0 vs 55.0%), PN (30.0 vs 65.0%), asthenia (0 vs 35.0%), and oedema peripheral (15.0 vs 35.0%).

When focussed on very common (≥10%) and common related AEs in the pivotal study, the safety profile in ADR is similar to previously discussed AEs. ADRs of lower frequencies were not detectable, due to limited sample size.

In the pivotal study, while comparing pola+BR vs BR in DLBCL, no significant increase in SAEs frequency was observed (64.4% vs 61.5%), driven by Infections and Infestations SOC, blood and lymphatic system disorders and gastrointestinal disorders. SAEs profile was similar in arm G of the pivotal study, with 140 lyo DP+BR. Across main studies, no unexpected safety signal was observed in SAEs with pola. No new safety signal was identified across updated safety results from arm G.

No new safety signal was identified on ECG abnormalities and vital signs.

Related fatal AEs in polatuzumab containing arms were only reported in the pivotal study. No difference in safety profile was evidenced between liquid and lyophilized forms (arm G). It should be noted that 4 out of 5 fatal AEs were infectious, including 3 occurred early during treatment. Infectious risk is expected with polatuzumab vedotin, considering its MOA and the haematologic toxicity. The respective information has been included in section 4.4 and 4.8 of the SmPC. In pola+BR arms, one out of the 4 fatal infectious was assessed as related to pola: meningoencephalitis herpetic, occurred in the follow up period. The incidence of infections was similar between the treatment arms (or even slightly higher in the BR arm). The review of potential cases of viral reactivation under SOC Infections and Infestations in the pola+BR arm of the DLBCL patient population retrieved 9 AEs, including 4 assessed as related to pola+BR regimen: Herpes infection and fatal meningoencephalitis in one patient, (previously discussed), one non-serious case of CMV infection, at D43, and one non-serious case of herpes virus infection, at D 48. No unexpected safety signal was raised from these infectious cases. The SmPC reflects the relevant information.

In the pivotal study, the incidence of infectious events was similar in both arms (53.3 vs 51.3%), as well as serious infections (28.9% vs. 30.8%). In the pola+BR group, 4 patients (8.9%) experienced fatal events, including pneumonia (2), meningoencephalitis herpetic (1), and sepsis (1). In the BR group, 4 patients (10.3%) experienced fatal events, including sepsis (2), pneumonia (1), and septic shock (1). Six (6) opportunistic infections were reported in 4 patients (8.9%) in pola+BR arm: herpetic encephalitis (1 patient), cerebral toxoplasmosis, cytomegalovirus (CMV), and pneumonia (in the same patient), CMV infection (reported twice in the same patient), and pneumocystis jiroveci pneumonia (PJP) (1 patient).

The fatal case of MDS occurred 2 years after study start, in a heavily pre-treated patient; however, this case of second primary malignancy is of concern and the risk of carcinogenicity remains closely monitored, as part of the important potential risks for pola.

Despite questionable based on Mentzer criteria, the case of PML is of concern. A warning has been added in section 4.4 of the SmPC that patients should be monitored closely for new or worsening neurological, cognitive, or behavioural changes suggestive of PML. Polivy and any concomitant chemotherapy should be withheld if PML is suspected and permanently discontinued if the diagnosis is confirmed.

In the pivotal study, a higher frequency of neutropenia events was observed in pola+BR vs BR DLBCL arms, all grades (60.0 vs 53.8%). Almost all neutropenia events were grade 3/ 4 in both arms. Neutropenia AEs had a non-negligible impact on the polatuzumab treatment, leading to study withdrawal and pola discontinuation (8.9% of patients each). All neutropenia AE resolved in the pola+BR arm. A warning has been added in section 4.4 of the SmPC that complete blood counts should be monitored prior to each dose of Polivy. More frequent lab monitoring and/or Polivy delays or discontinuation should be considered for patients with Grade 3 or Grade 4 neutropenia and thrombocytopenia (see section 4.2).

In the pivotal study, PN events were more frequent in pola+BR arm (40.0% vs 7.7% in BR arm). None was fatal, serious nor led to study withdrawal. All events were Grade 1 or 2 in both arms. In pola+BR arm, PN events were mainly neuropathy peripheral (9 patients) and peripheral sensory neuropathy (6 patients). In the supportive study GO27834, TTO for grade ≥2 PN events was longer, up to 4.21 months. Overall, the longer median treatment exposure in this study (up to 13.5 cycles in pola 1.8 mg/kg+R group) correlated with the higher incidence and severity of PN events. In study DCS4968g, the frequency increased with higher dose of pola (up to 2.4 mg/kg) and longer treatment (over 8 cycles). This observation strengthens the limitation of pola treatment to 6 cycles, at 1.8 mg/kg. A warning has been added in section 4.4 of the SmPC that patients should be monitored for symptoms of PN such as hypoesthesia, hyperesthesia, paraesthesia, dysesthesia, neuropathic pain, burning sensation, muscle weakness, or gait disturbance. Patients experiencing new or worsening PN may require a delay, dose reduction, or discontinuation of Polivy (see section 4.2).

In the pivotal study, the incidence of hepatic toxicity was higher in pola+BR vs BR DLBCL arm (20.0 vs 12.8%). The majority of events were grade 1-2 severity in both arms, and most events resolved (6/9) in the pola+BR arm. In the pola+BR arm, the most frequently reported PT was hypoalbuminaemia (13.3%; 6 patients), followed by AST increased (4.4%; 2 patients). There were no cases of drug-induced liver injury as defined by Hy's Law. No hepatic event led to discontinuation or modification of pola treatment.

The hepatic safety profile was similar across R/G and DLBCL/FL groups, and also in arm G of the study, despite a higher reporting in blood alkaline phosphatase increased (3/7 concerned patients) in arm G.

Across supportive studies, grade 3/ 4 hepatic toxicities were reported in study GO27834 with pola a 2.4 mg/kg, including one grade 4 hepatocellular injury and one grade 4 hepatic steatosis and hepatomegaly, assessed as treatment related, leading to treatment discontinuation and resolved.

No significant difference was identified across subgroups with baseline hepatic function normal, mild 1, 2 or moderate. The administration of Polivy in patients with moderate or severe hepatic impairment (bilirubin greater than 1.5 × ULN) should be avoided. No adjustment in the starting dose is required when administering Polivy to patients with mild hepatic impairment (bilirubin greater than ULN to less than or equal to 1.5 × ULN or AST greater than ULN).

In the pivotal study, the incidence of anaemia was higher in pola+BR vs BR DLBCL arm (46.7 vs 28.2%). The majority of events were non serious in both arms.

In the pivotal study, the incidence of thrombocytopenia was higher in pola+BR vs BR DLBCL arm (48.9 vs 33.3%). The majority of events were grade 3/ 4 events, none fatal. Thrombocytopenia events had an impact on treatment course in the pola+BR group, with pola discontinuation in 5 patients (11.1%), and dose delay or interruption of polatuzumab vedotin in 6 patients (13.3%). No further safety signal regarding thrombocytopenia was identified in arm G and in supportive studies.

In the pola+BR group, 1 patient presented a bleeding event (Grade 5 hemoptysis), in the context of anticoagulation therapy due to thromboembolic event (pulmonary embolism and deep vein thrombosis).

Three additional supportive studies provided preliminary safety data with lyophilized form of pola (170 mg form, dosage not intended for marketing). To date, these ongoing studies provide data in limited population, in R/R DLBCL and R/R FL patients with combinations different from the target indication. Moreover, due to dose-escalation designs, few patients in each study were treated with pola at 1.8mg/kg.

Based on these data, the safety profile of pola 170mg lyo DP was coherent with the safety profile for the liquid formulation. Except for immune-mediated toxicities while associating pola +R/G+atezo, which led to enrollment halt in study BO29561, no further new safety signal was identified. It should anyway be noted that a higher incidence of IRR was reported in these studies, mainly considered related to obinutuzumab treatment. A relevant warning on IRR has been included in the SmPC as well as instructions for dose modifications (see SmPC section 4.4.).

Globally, the safety profile was similar between male and female across studies, as well as between younger and older patients (< 65 and ≥65 years).

Women of childbearing potential should be advised to use effective contraception during treatment with polatuzumab vedotin and for at least 9 months after the last dose.

Male patients with female partners of childbearing potential should be advised to use effective contraception during treatment with polatuzumab vedotin and for at least 6 months after the last dose.

There are no data in pregnant women using Polivy. Studies in animals have shown reproductive toxicity (see non – clinical section). Based on the mechanism of action and nonclinical studies, polatuzumab vedotin can be harmful to the foetus when administered to a pregnant woman. In women of childbearing potential, the pregnancy status shall be checked prior to treatment. Polivy is not recommended during pregnancy and in women of childbearing potential not using contraception unless the potential benefit for the mother outweighs the potential risk to the foetus.

A warning has been added in section 4.4 of the SmPC that live or live-attenuated vaccines should not be given concurrently with the treatment. Studies have not been conducted in patients who recently received live vaccines.

Regarding baseline renal function, the global safety profile remained comparable between baseline normal, mild or moderate function. However, it should be noted that the frequency of grade 3/ 4 events tented to increase with severity of renal impairment, as well thrombocytopenia events, and AEs leading to treatment modification.

No dose adjustment of Polivy is required in patients with creatinine clearance (CrCL) ≥ 30 mL/min. A recommended dose has not been determined for patients with CrCL < 30mL/min due to limited data.

A similar safety profile was observed across histologies and R or G combination, and in arm G in the pivotal study. The reporting was similar in the supportive studies, despite lower frequency.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Additional safety data needed in the context of a conditional MA

Overall, the safety data presented cannot be considered comprehensive evidence. The CHMP therefore concluded that additional safety data in a larger population and long-term safety - including second primary malignancies- will need to be generated in the context of a conditional marketing authorisation.

Safety data from the ongoing GO29365 study - Arm H (n=64) and the pooled analysis of Arm G (n=42) and Arm H (n=64) will be provided. Further safety data will be provided within the randomised Study GO39942, that evaluates polatuzumab vedotin in combination with R-CHP (rituximab, cyclophosphamide, doxorubicin, prednisone) versus R-CHOP, planning to enrol 875 patients with previously untreated diffuse large B-cell lymphoma at an estimated follow up of up to 65 months.

2.6.2. Conclusions on the clinical safety

Overall, the available data suggest that the safety profile of polatuzumab vedotin is not negligible (potential life-threatening AEs like myelosupression and infections were identified, and PN events impacting the treatment course), yet still manageable in the context of a severe condition like R/R TNE DLBCL.

The CHMP considers the following measures in the context of a conditional MA:

- In order to further confirm the safety and efficacy of polatuzumab vedotin in combination with BR the MAH will provide the primary CSR for study GO29365 including the primary analysis of Arm H (n=64) as well as a pooled analysis of Arm G (n=42) and Arm H (n=64).
- In order to further confirm the safety and efficacy of polatuzumab vedotin in DLBCL the MAH will also provide Study GO39942, a randomized, double-blind, placebo-controlled trial that evaluates polatuzumab vedotin in combination with R-CHP (rituximab, cyclophosphamide, doxorubicin, prednisone) versus R-CHOP in patients with previously untreated diffuse large B-cell lymphoma.

Further, at the recommendation of the CHMP the applicant will submit results from the evaluation of safety and tolerability in Study MO40598 - a phase III, open-label, multicenter randomized clinical trial that evaluates polatuzumab vedotin in combination with rituximab plus gemcitabine plus oxaliplatin (R-GemOx) versus R-GemOx alone in patients with relapsed or refractory diffuse large B-cell lymphoma. Note: Study MO40598 will have a 10-patient safety run-in period to assess peripheral neuropathy risk due to use of polatuzumab vedotin in combination with the R-GemOx regimen; based on the afore-mentioned safety assessment, study might continue or not in the randomized clinical trial stage.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Not applicable
Important potential risks	Carcinogenicity
Missing information	Long term safety Use in Severe Hepatic Impairment Use in Severe Renal Impairment Use in Pregnancy and Lactation

Pharmacovigilance plan

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 2—Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances.				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Study GO29365 A Phase Ib/II, multicenter, open-label study evaluating the safety, tolerability, and anti-tumor activity of polatuzumab vedotin (DCDS4501A) in combination with rituximab or obinutuzumab plus bendamustine in patients with R/R follicular lymphoma or R/R diffuse large B-cell lymphoma. (Ongoing)	To evaluate the risk of carcinogenicity in polatuzumab vedotin treated patients.	Carcinogenicity	Primary CSR Final CSR	Q3 2020 Q3 2022
Study GO39942 A Phase III, multicenter, randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of polatuzumab vedotin in combination with rituximab and CHP (R-CHP) versus rituximab and CHOP (R-CHOP) in previously untreated patients with diffuse large b-cell lymphoma. (Ongoing)	To evaluate safety of polatuzumab vedotin in combination with rituximab and CHP	Long term safety	Final CSR	Q4 2021

Risk minimisation measures

There are no additional risk minimisation measures.

Safety Concern	Routine Risk-Minimization Measures
Important potential risk: Carcinogenicity	*Proposed risk communication is described in* *SmPC:* • Section 5.3 Preclinical safety data
Missing Information	
Long-Term Safety	*Proposed risk communication is described in* *SmPC:* • None *Package Leaflet:* • None
Use in Patients with Severe	*Proposed risk communication is described in*

Safety Concern	Routine Risk-Minimization Measures
Hepatic Impairment	*SmPC:* • Section 4.2 Posology and method of administration: Special populations — Hepatic impairment • Section 5.2 Pharmacokinetic properties: Hepatic impairment
Use in Patients with Severe Renal Impairment	*Proposed risk communication is described in* *SmPC:* • Section 4.2 Posology and method of administration: Special populations — Renal impairment • Section 5.2 Pharmacokinetic properties: Renal impairment
Use in Pregnancy and Lactation	*Proposed risk communication is described in* *SmPC:* • Section 4.6 Fertility, pregnancy and lactation *Package Leaflet:* • Section 2 What you need to know before you use Polivy
SmPC=summary of product characteristics.	

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.3 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

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

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 10.06.2019. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

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

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

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the

applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.1. Labelling exemptions

A request to omit certain particulars from the vial label as per Article 63(3) of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group with the following comments: 1) it must be clear that this is a powder for concentrate and it needs to be diluted after reconstitution and before use, so this needs to be prominently displayed on the vial labelling; and 2) the inclusion of 'cytotoxic' should be considered, and "Do not shake" may also be important to state.

It was also noted that for the trilingual mock-up, some improvements could be made to simplify/increase the readability: 1) the route of administration could be mentioned as "*IV na reconstitutie en verdunning / après reconstitution et dilution / nach Rekonstitution und Verdünnung*"; and 2) as only the capital letter differs between FR/NL and DE, the active substance does not need to be repeated.

The particulars to be omitted as per the QRD Group decision described above will however be included in the Annexes published with the EPAR on EMA website and translated in all languages but will appear in grey-shaded to show that they will not be included on the printed materials.

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Polivy (polatuzumab vedotin) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU. Moreover, it is proposed to be approved under a conditional marketing authorisation.

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Polatuzumab vedotin, is intended in combination with bendamustine and rituximab, for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant.

3.1.2. Available therapies and unmet medical need

After failure of front-line therapy, the main consideration for determining the treatment approach in the second-line setting is whether the patient is a haematopoietic stem cell transplant candidate. The treatment approach for RR DLBCL, TNE patients, is mainly based on platinum- and/or gemcitabine-based regimens, and clinical trials with novel drugs. There is no specifically approved treatment in 2nd line of therapy whereas, the recent approval of CAR-T cell therapies offers an additional therapeutic option in patients after at least two previous lines of treatment. However, an unmet medical need still remains for patients with R/R DLBCL who are ineligible for transplant or fail ASCT and in these RR TNE DLBCL patients, as not all patients would be able to receive CAR-T therapies due to performance status and considering toxicities and delay in manufacturing times for these treatments.

3.1.3. Main clinical studies

The main efficacy data submitted come from a single pivotal phase IB/II, multicenter, open-label, randomized study of polatuzumab vedotin in combination with BR or bendamustine plus obinutuzumab (BG) in patients with R/R FL or DLBCL. In the randomized phase II part of the pivotal study, 40 RR DLBCL patients received pola+BR and BR each.

3.2. Favourable effects

The primary endpoint (CR rate at primary response assessment (6-8 weeks after Cycle 6 Day 1 or last dose of study medication, based on PET-CT, IRC assessed) was increased in the pola+BR arm: 40.0% (16/40 patients; 95% CI: [24.9%, 56.7%]) vs 17.5% in the BR arm (7/40 patients; 95% CI: [7.3%, 32.8%]). The Δ was 22.5%, statistically significant and in favour of pola+BR (95% CI: 2.6%, 40.2%; p =0.0261, Cochran Mantel-Haenszel [CMH] chi-square).

Secondary efficacy endpoints (CR and OR [CR or PR]), assessed by the INV or IRC per PET-CT and CT only, were consistent with this primary efficacy result (POLA+BR vs BR).

The PFS (secondary endpoint) as determined by IRC was almost thrice increased in patients treated with pola+ BR compared to BR (stratified HR =0.36; 95% CI: 0.21, 0.63; p =0.0002), with median PFS of 9.5 months [6.2, 13.9] vs 3.7 months [2.4, 4.5]. At 6 months, event free rate for PFS was 65.59% (CI: 50.42, 80.76) in the pola+BR arm, vs 15.82%; (CI: 3.16, 28.47) in the BR arm. This difference remained stable over time, at 9 and 12 months. A similar trend was observed in EFS.

The risk of death was reduced by 58% in patients treated with pola+BR compared to BR (stratified HR=0.42; 95% CI: 0.24, 0.75; p =0.0023).

The median OS was 12.4 months (95% CI: 9.0, NE) in the pola+BR arm, and 4.7 months (95% CI: 3.7, 8.3) in the BR arm. At 6 months, 30/40 patients remained alive in the pola+BR arm, vs 11/40 patients in the BR arm. This difference remained persistent over time, at 9 months (24/40 vs 7/40) and at 12 months (19/40 vs 7/40).

Ancillary analysis and sensitivity analysis confirmed the favorable trends in PFS and OS across subgroups in the overall R/R DLBCL population, in favor of the pola+BR arm.

In both randomized arms, only one third of patients were treated in 2L treatment. CR globally decreased with increasing number of prior treatments. This trend was less marked in BR arm, since CR rate increased up to 22.2% in 3L patients. CR rate remained higher in pola+BR vs BR arm in each subgroup, mainly in 2L patients: 63.6% (30.8, 89.1) vs 16.7% (2.1, 48.4), despite limited sample size (11 and 12 patients respectively). In both arms, CR was lower in refractory patients, independently from the treatment line.

Preliminary efficacy results obtained in arm G show a favourable trend in efficacy, with CR rate of 34.3% (18.6, 53.2), but lower than in arm C. Median PFS and OS are sharply lower, with shorter FU: PFS: 6.0 months (3.5, 6.6) in arm G vs 11.1 months (6.2, 13.9) in arm C; OS: 6.1 months (4.4, NE) in arm G vs 12.4 (9.0, NE). Additional efficacy results in 42 patients, up to 15 March 2019, remain similar in terms of CR, lower than in arm C (33.3%; [19.6, 49.6]). However, OS increased up to 9.1 months [6.0, NE].

3.3. Uncertainties and limitations about favourable effects

Randomized efficacy results in the target indication are available in a limited and heterogeneous population (n=40 in each arm), with the liquid formulation. Arm G, conducted with the lyo formulation in the pivotal study, is ongoing. Preliminary results in 32 patients were provided at time of response to LoQ, with additional top line results in 42 patients. However, the conduct of a larger (>100 patients) single arm

study, using the new formulation, was considered warranted by the CHMP to reach reassurance regarding findings in the pivotal study; arm H (n=60) was subsequently added to the study, with results expected Q3 2020 date as a specific obligation to the CMA (see RMP and Annex II).

In the pivotal trial the WHO 2016 DLBCL status was heterogeneous, however balanced between arms. Efficacy data per WHO status in ongoing arms G and H are expected (see RMP).

Among all patients treated with pola in GO29365 study, a total of 8 patients developed ADA, including 4 DLBCL patients. Impact on efficacy was not evidenced, considering that 3 of them completed 5 to 6 cycles of treatment and DOR from 21 to 38 months. However, the last patient presented with ADA at C2 and was diagnosed with PD at C3. Further data on ADA and potential impact on efficacy will be provided in the context of the additional data generated in arms G and H, which is an SOB (see RMP and Annex II).

3.4. Unfavourable effects

Myelosupression was reported across all studies. Neutropenia, including febrile neutropenia, anemia and thrombocytopenia were all included in the AEs of particular interest. In the pivotal study, neutropenia was more frequently observed in pola+BR (60.0 vs 53.8%). The incidence of febrile neutropenia was comparable between both arms (11.1% vs. 12.8%in BR arm), and almost all neutropenia events were grade 3/ 4 in both arms. The incidence of anemia was higher in pola+BR vs BR DLBCL arm (46.7 vs 28.2%). Limited impact on treatment was reported. Incidence of thrombocytopenia was higher in pola+BR vs BR DLBCL arm (48.9 vs 33.3%). The majority of events were grade 3/ 4 events. These events have an impact on treatment course, considering that neutropenia led to study withdrawal and pola discontinuation (8.9% of patients each). A warning has been added in section 4.4 of the SmPC to monitor complete blood counts prior to each dose of Polivy.

The incidence of infectious events was similar in pola+BR and BR DLBCL arms (53.3 vs 51.3%), and most events were Grade ≥ 3 in both groups. The incidence of serious infections events was also comparable between both arms (28.9% vs. 30.8%). In the pola+BR group, 4 patients (8.9%) experienced fatal events. Six (6) opportunistic infections were reported in 4 patients (8.9%) in pola+BR arm: 3 of these patients died due to opportunistic infection. A warning has been added in section 4.4 of the SmPC that patients should be closely monitored during treatment for signs of bacterial, fungal, or viral infections.

Peripheral neuropathy was reported across all studies. In the pivotal study, PN events were more frequent in pola+BR arm (40.0% vs 7.7% in BR arm). None was fatal, serious nor led to study withdrawal. All events were Grade 1 or 2 in both arms. In pola+BR arm, the main reported PTs were neuropathy peripheral (9 patients) and peripheral sensory neuropathy (6 patients). The median TTO was 1.4 months for the pola+BR group. In the supportive studies, longer median treatment exposure and higher cumulative dose correlated with the higher incidence and severity of PN events. A warning has been added in section 4.4 of the SmPC that patients should be monitored for symptoms of PN such as hypoesthesia, hyperesthesia, paraesthesia, dysesthesia, neuropathic pain, burning sensation, muscle weakness, or gait disturbance. Patients experiencing new or worsening PN may require a delay, dose reduction, or discontinuation of Polivy (see section 4.2).

Serious cases of hepatic toxicity that were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin, have occurred in patients treated with Polivy (see section 4.4 and 4.8). Pre-existing liver disease, elevated baseline liver enzymes, and concomitant medicinal products may increase the risk. Liver enzymes and bilirubin level should be monitored.

3.5. Uncertainties and limitations about unfavourable effects

At time of submission, the interim CSR for the pivotal study covered up to 1 year FU after primary response assessment for all enrolled patients. To date, limited long term safety data is available. Despite

available data on PN events, further investigation is needed also in terms of the impact of PN on PROs. Final results are expected, as part of the SOB to the CMA (see RMP and Annex II). The applicant accepted a recommendation of the CHMP to submit the results of a study (including a safety run-in) that evaluates polatuzumab in combination with rituximab, gemcitabine, and oxaliplatin (R-GemOx) versus R-GemOx alone.

A fatal case of MDS occurred 2 years after study start, in a heavily pre-treated patient; however, this case of second primary malignancy is of concern and the risk of carcinogenicity remains closely monitored, as part of the important potential risks for polatuzumab. Further evaluation of the risk of carcinogenicity in polatuzumab vedotin treated patients will be provided through post-authorisation long term data (see RMP). Further to a case of suspected PML a warning has been added in section 4.4 of the SmPC that patients should be monitored closely for new or worsening neurological, cognitive, or behavioural changes suggestive of PML. This issue will be further monitored through the agreed post authorisation studies.

3.6. Effects Table

Table 61. Effects Table for polatuzumab vedotin, in combination with bendamustine and rituximab, in the treatment of RR DLBCL in patients non-candidate for haematopoietic stem cells transplantation (data cut-off 30 April 2018)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Complete response	CR, at PRA (6–8 weeks after Cycle 6 Day 1 or last dose of study medication, PET-CT, IRC assessed	Rate	Pola +BR: 40.0% (24.9, 56.7)	BR: 17.5% (7.3, 32.8)	Limited population Δ 22.5 % (2.6, 40.2); p= 0.0261	Study GO29365
Objective response	OR (CR/PR) at PRA by PET, IRC assessed	Rate	Pola +BR: 45.0% (29.3, 61.5)	BR: 17.5% (7.3, 32.8)	Limited population Δ 27.5 (7.2, 45.0); p = 0.0069	
Progression free survival	Median PFS, IRC assessed	months	9.5 (6.2, 13.9)	3.7 (2.4, 4.5)	Secondary objective HR= 0.36 (0.21, 0.63); p = 0.0002	
Overall survival	Median OS	months	12.4 (9.0, NE)	4.7 (3.7, 8.3)	Exploratory objective HR= 0.42 (0.24, 0.75); p = 0.0023	

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Unfavourable Effects						
Deaths/fatal AE			9, including 2 related fatal AE	11, including 1 related fatal AE	In pola + BR arm: 1 case of fatal meningoencephalitis herpetic and 1 case of fatal pulmonary edema	
Peripheral neuropathy events	All grades	Incidence in %	40.0%	7.7%	In pola + BR arm: 7 unresolved events In the supportive studies, longer median treatment exposure and higher cumulative dose correlated with the higher incidence and severity of PN events.	
Infections	Serious	Incidence in %	28.9%	30.8%	Impact on treatment course in pola+BR arm Six (6) opportunistic infections were reported in 4 patients (8.9%) in pola+BR arm	
Neutropenia	Grade ⩾3	Incidence in %	55.6%	46.2%	febrile neutropenia: 11.1% vs. 12.8% in pola+BR and BR groups respectively	
PML	Serious	No of patients	1 case		Relation to Polivy unconfirmed / heavily pre-treated patient;	
MDS	Serious		1 case			
Hepatic toxicity	All grades	Incidence in %	20.0%	12.8%		

Abbreviations: CR: complete response, OR: objective response, PRA: preliminary response assessment, BR: bendamustine + rituximab, pola: polatuzumab vedotin, AE: adverse event, PN: peripheral neuropathy, OS: overall survival, HR; hazard ratio, IRC: independent review committee, PFS: progression free survival, PET-CT: positron emission tomography– computed tomography

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Treatment with polatuzumab vedotin at target doses of 1.8mg/kg, given as an intravenous infusion every 21 days in combination with bendamustine and rituximab (BR) for 6 cycles, shows a significant increase in CR and OR compared to the comparative BR treatment in patients with RR DLBCL, non-candidates for haematopoietic stem cell transplant. These results are further supported by a significant increase of PFS and OS, despite secondary and exploratory endpoints respectively. WHO 2016 DLBCL status was heterogeneous, but balanced in both arms.

Despite the limitations of the pivotal study GO29365 being conducted in a small number of patients the comparative design is valuable.

Ancillary analysis and sensitivity analysis confirmed the positive trends in PFS and OS across subgroups of the R/R DLBCL population, in favour of the pola+BR arm.

Despite different populations and combinations, the three key supportive studies confirm the favourable effect observed in the pivotal study while adding polatuzumab vedotin for RR DLBCL treatment.

Despite manageable, the safety profile includes myelosupression, infections, peripheral neuropathy and hepatic toxicity with a non-negligible impact on treatment course. One fatal case of MDS, added to the potential genotoxic effect of this product, highlight the need for longer follow up safety data.

3.7.2. Balance of benefits and risks

The benefit risk balance of Polivy in combination with bendamustine and rituximab in the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant, is positive.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

The submission is based on data from one pivotal study GO29365, performed in a small number of patients, with possible suboptimal comparative treatment. As comprehensive data on the product in the proposed indication are not available, the CHMP was of the view that a full marketing authorissaation could not be granted. Instead, a conditional marketing authorisation was proposed by the CHMP during the assessment, after having consulted the applicant.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease and is designated as an orphan medicinal product.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

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

  The evidence provided is based on a small exploratory trial in a limited (82 patients in total received Polivy in trial GO29365; 40 patients from the randomized part arm C and 42 patients from arm G using the lyophilised formulation) and heterogeneous population in terms of prognosis Long-term safety data are not available. Submitted data are thus considered non-comprehensive.

  The primary CSR for study GO29365 including the primary analysis of Arm H (n=64) as well as a pooled analysis of Arm G (n=42) and Arm H (n=64) will be provided. Distinct histology subtypes will be analysed within Arm H which is considered necessary to confirm response in any relevant subtype at least on a descriptive level. The study is ongoing and the required data are expected to be provide in Q3 2020.

  The MAH will also provide Study GO39942, by end 2021. This is a randomized, double-blind, placebocontrolled trial that evaluates polatuzumab vedotin in combination with R-CHP (rituximab, cyclophosphamide, doxorubicin, prednisone) versus R-CHOP in patients with previously untreated diffuse large B-cell lymphoma. The primary endpoint is progression-free survival. Key secondary endpoints include complete remission rate per independent review committee and overall survival. Thus, even though this trial is in an earlier line of treatment it is expected that efficacy and safety results will be confirmative in DLBCL.
- Unmet medical needs will be addressed, as:

No medicinal products have been approved for second line treatment of R/R DLBCL. Polivy in combination with bendamustine and rituximab (BR) provides a therapeutic option for patients in this setting where there is a clear unmet need.

Pola+BR also provides an important contribution to patient care in third line (3+) treatment of R/R DLBCL. In this setting, available treatment options include Pixuvri (pixantrone) and recently approved CAR-T cell therapies (Kymriah and Yescarta).

With regards to Pixuvri, it can be accepted that the activity of this compound is limited and a major therapeutic advantage of Polivy over pixantrone in terms of efficacy may be inferred. While clinically relevant activity has been shown for Polivy as well as for the CAR-T cell products approved in 3L+, comparing the relative impact of these medicinal products on time-dependent endpoints is fraught with uncertainty due to cross-study comparisons of relatively small studies, as well as the fact that the CAR-T cell products were approved based on single arm trials that do not isolate the impact of these drugs on PFS and OS.

Compared to the approved CAR-T therapies, Pola+BR presented with a manageable toxicity profile. Specifically, the CHMP noted that CAR-T cell treatment is associated with the risk of life-threatening or fatal cytokine-release syndrome (CRS) and CNS neurologic toxicities including seizures, cerebral edema, and encephalopathies requiring close monitoring of patients ideally in a hospital setting. In comparison, there have been no reports of CRS with Polivy +BR and neurologic toxicities, while observed with pola+BR, have been limited to peripheral neuropathy, were mostly low grade and non-serious. Pola+BR therefore compared favourable to CAR-T cells in these relevant safety aspects.

Polivy+BR also offers the additional benefits of an immediate treatment option whereas with CAR-T cells, patient may need to wait for a potentially significant interval prior to the actual administration of therapy, while the cells are being manufactured. This time span from diagnosis and leukapheresis to infusion of the finished product is of relevance for patients with an advanced disease, expected to progress rapidly and in need of urgent medical attention.

Taken together, the CHMP was of the view that Polivy when used in combination with BR addresses the unmet medical need of TNE patients with R/R DLBCL in 2nd and 3rd line treatment.

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

  In view of the promising efficacy results available with Polivy up to dat, its manageable safety profile and as unmet medical needs still exist as discussed above the benefits to public health of the immediate availability of Polivy outweigh the uncertainties inherent to the fact that long term safety date and more comprehensive efficacy data have been requested.

3.8. Conclusions

The overall B/R of Polivy in combination with bendamustine and rituximab in the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant, is positive.

Divergent positions are appended to this report.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Polivy is not similar to Yescarta and Kymriah within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the benefit-risk balance of Polivy is favourable in the following indication:

"Polivy in combination with bendamustine and rituximab is indicated for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant."

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

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to further confirm the safety and efficacy of polatuzumab vedotin in combination with BR the MAH will provide the primary CSR for study GO29365 including the primary analysis of Arm H (n=64) as well as a pooled analysis of Arm G (n=42) and Arm H (n=64).	Q3 2020
In order to further confirm the safety and efficacy of polatuzumab vedotin in DLBCL the MAH will provide Study GO39942, a randomized, double-blind, placebocontrolled trial that evaluates polatuzumab vedotin in combination with R-CHP (rituximab, cyclophosphamide, doxorubicin, prednisone) versus R-CHOP in patients with previously untreated diffuse large B-cell lymphoma.	Q4 2021

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

Not applicable.

New Active Substance Status

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

Appendix

Divergent positions to the majority recommendation

DIVERGENT POSITION DATED 14 November 2019

Polivy EMEA/H/C/004870/0000

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the conditional marketing authorisation of Polivy 140 mg powder for concentrate for solution for infusion in combination with bendamustine and rituximab for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant.

The reason for divergent opinion was the following:

Divergent position:

In line with the requirements for a conditional marketing authorisation, the applicant must ensure that the conditions for a conditional marketing authorisation have been shown for the product applied for. In the view of the divergent CHMP members, these requirements have not been fulfilled for the following reasons:

In the guideline on the implementation of conditional marketing authorization regulation (EMA/CHMP/509951/2006, Rev 1) is described that major therapeutic advantage (MTA) would normally be based on meaningful improvement of efficacy or clinical safety. In exceptional cases, also major improvements to patient care could provide a MTA. Current policy dictates that in case MTA is based on improved safety/patient care, no important reduction in benefit should be seen which would make the overall benefit risk balance less favourable. This is also in alignment with e.g. Guidance on elements required to support significant clinical benefit in comparison with existing therapies of a new therapeutic indication (2007).

In this context and as it is uncertain that Polivy has a similar or greater efficacy than what is understood for available therapies for the same target population, the differential safety profile or/and improvement in patient care is not considered to constitute a MTA per se.

CHMP Members expressing a divergent opinion:

Johann Lodewijk Hillege

Selma Arapovic Dzakula

Natalja Karpova

Concepcion Prieto Yerro

Sol Ruiz

DIVERGENT POSITION DATED 14 November 2019

Polivy EMEA/H/C/004870/0000

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the conditional marketing authorisation of Polivy indicated in combination with bendamustine and rituximab for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant:

The reason for divergent opinion was the following:

This application is based on a very small single pivotal RCT of exploratory character, which was nested in an umbrella trial where the activity of polatuzumab vedotin in both DLBCL and follicular lymphoma (FL) was studied. As would be anticipated in such a setting, there was no overarching type 1 error control, and the overall approach to data was exploratory.

The study in DLBCL unexpectedly demonstrated an OS gain of nominal statistical significance. However, the FL sub-study of similar design did not indicate any meaningful additive effect of Polivy to the same background regimen as in the DLBCL study. It appears that the reason for this inconsistency needs to be constructed post hoc.

Moreover, it has been positively demonstrated that measurable baseline factors in the small pivotal study favoured the experimental arm. With two different statistical approaches, it was shown that adjusting for known confounders inflated the HR from 0.42 to 0.54-0.59. While this analysis provides evidence that, due to the small study size, randomisation was not effective in producing treatment groups with similar prognosis, it obviously can only take measured confounders into account. The extent of impact of unmeasured confounders in this study, with treatment arms shown not to be balanced at baseline, remains unknown.

Adding to the uncertainty, activity was lower when Polivy was given with obinituzumab instead of rituximab in DLBCL, despite the former co-medication being considered more active than the latter. Furthermore, the CR rate in the reference arm of the pivotal trial appears lower than that reported in the literature. Thus, the true benefit of adding Polivy to BR in terms of incremental CR is also uncertain.

For these reasons, it not considered that the efficacy of Polivy has been adequately established. Consequently B/R has not been shown to be positive.

CHMP Members expressing a divergent opinion:

Kristina Dunder

Daniela Melchiorri