EU RISK MANAGEMENT PLAN (RMP)

for

ADCETRIS® (Brentuximab vedotin)

RMP Version number: 20.0

Date: 28-March-2024

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EU Risk Management Plan for ADCETRIS® (Brentuximab vedotin)

Administrative Information

RMP version to be assessed as part of this application:

RMP Version number: 20.0

Data lock point (DLP) for this RMP: 18-February-2024

Date of final sign off: 28-March-2024

Rationale for submitting an updated RMP: Based on updates suggested from Pharmacovigilance risk assessment committee (PRAC), the below changes are being made in RMP:

- Propose to add a new indication "adult patients with previously untreated CD30+ Stage IIB with risk factors, Stage III or Stage IV HL in combination with etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone (BrECADD)" in RMP.
- Update to routine risk minimization measures for important potential risks of "severe hepatotoxicity" and "pulmonary toxicity" per PRAC recommendation during procedure EMEA/H/C/002455/II/0107.

Summary of significant changes in this RMP:

RMP Module:	Significant Changes:
Part I Product Overview	Proposed indication "adult patients with previously untreated CD30+ Stage IIB with risk factors, Stage III or Stage IV HL in combination with etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone (BrECADD)" added.
Part II Safety Specification	
• **Module SI Epidemiology of the indication(s) and target population(s)**	Not applicable
• **Module SII Nonclinical part of the safety specification**	Not applicable
• **Module SIII Clinical trial exposure**	Exposure updated as of DLP 18-February-2024.
• **Module SIV Populations not studied in clinical trials**	Not applicable
• **Module SV Post-authorisation experience**	Exposure updated as of DLP 18-February-2024.
• **Module SVI Additional EU requirements for the safety specification**	Not applicable
• **Module SVII Identified and potential risks**	Clinical trial and post marketing counts updated as of DLP 18-February-2024.
• **Module SVIII Summary of the safety concerns**	Not applicable
Part III Pharmacovigilance plan	Not applicable

[redacted]

RMP Module:	Significant Changes:
Part IV Plans for post-authorisation efficacy studies	Not applicable
Part V Risk minimisation measures	Update of routine risk minimization measures for important potential risks of "severe hepatotoxicity" and "pulmonary toxicity".
Part VI Summary of the risk management plan	Proposed new indication to include adult patients with previously untreated CD30+ Stage IIB with risk factors, Stage III or Stage IV HL in combination with etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone (BrECADD). Update of routine risk minimization measures for important potential risks of "severe hepatotoxicity" and "pulmonary toxicity".
Part VII Annexes	Not applicable

Other RMP versions under evaluation:

Not applicable.

Details of the currently approved RMP:

Version number: 18

Approved with procedure: EMEA/H/C/002455/II/0107

Date of approval (opinion date): 12-October-2023 (EC approval date)

QPPV name: Stéphane Brouckaert, MPharm

Please note that e-signature may also be performed by Deputy EU QPPV [redacted] on behalf of the EU and UK QPPV (i.e., 'per procurationem').

QPPV signature: Signatures are available on file.

[redacted]

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List of Abbreviations

Abbreviation	Definition/Description
ABVD	Adriamycin, bleomycin, vinblastine, dacarbazine
ADA	Anti-drug antibodies (formerly described as antitherapeutic antibodies)
ADC	Antibody-drug conjugate
AE	Adverse event
AHCT	Autologous hematopoietic cell transplantation
ALCL	Anaplastic large cell lymphoma
ALK	Anaplastic lymphoma kinase
ALL	Acute lymphoblastic leukaemia
ANLL	Acute nonlymphocytic leukaemia
ARDS	Acute respiratory distress syndrome
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical classification
AVD	Doxorubicin, vinblastine and dacarbazine
BEACOPP	Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone
BMI	Body mass index
BSC	Best supportive care
BV	Brentuximab vedotin
CD	Cluster of differentiation
CHMP	Committee for medicinal products for human use
CHOP	Cyclophosphamide, hydroxydaunorubicin, vincristine and prednisone
CHL	Classical Hodgkin Lymphoma
CHP	Cyclophosphamide, doxorubicin, prednisone

[redacted]

Abbreviation	Definition/Description
CLL	Chronic lymphocytic leukaemia
CR	Complete remission
CrCL	Creatinine clearance
CSR	Clinical study report
CTCL	Cutaneous T-cell lymphoma
CYP	Cytochrome P
DLP	Data lock point
EBV	Epstein-Barr virus
eCTD	Electronic common technical document
EEA	European economic area
EMA	European medicines agency
EPAR	European public assessment report
EU	European union
G-CSF	Granulocyte colony stimulating factor
GLP	Good laboratory practice
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HL	Hodgkin lymphoma
HNSTD	Highest non-severely toxic dose
IgG	Immunoglobulin G
ILD	Interstitial lung disease
INN	International non-proprietary name
IP	Investigational product
IRR	Infusion-related reactions
IV	Intravenous
LPLV	Last patient last visit

Abbreviation	Definition/Description
LTFU	Lost to follow-up
MA	Marketing authorisation
MC	Mixed cellularity
MedDRA	Medical dictionary for regulatory activities
MMAE	Monomethyl auristatin E
MR	Mole ratio
MTCL	Mature T-cell lymphomas
MTD	Maximum tolerated dose
NHL	Non-Hodgkin lymphoma
NOAEL	No-observed-adverse-effect level
NOS	Not otherwise specified
NS	Nodular sclerosis
ORR	Objective (overall) response rate
OS	Overall survival
PASS	Post-authorisation safety study
PBO	Placebo
PD-1	Programmed death receptor 1
PFS	Progression-free survival
PI	Product information
PIL	Patient information leaflet
PIP	Paediatric investigation plan
PK	Pharmacokinetics
PML	Progressive multifocal leukoencephalopathy
PN	Peripheral neuropathy
PRAC	Pharmacovigilance risk assessment committee

Abbreviation	Definition/Description
PSUR	Periodic safety update report
PTCL	Peripheral T-cell lymphoma
PUVA	Psoralen plus ultraviolet A
PV	Pharmacovigilance
QD	Once a day
RFI	Request for information
RMP	Risk management plan
r/r	Relapsed/refractory
SAE	Serious adverse event
sALCL	Systemic anaplastic large cell lymphoma
SOB	Specific obligation
SCT	Stem cell transplant
SEER	Surveillance, Epidemiology, and End Results
SJS	Stevens-Johnson Syndrome
SmPC	Summary of product characteristics
SMQ	Standardised MedDRA Query
SOC	System organ class
SS	Sézary syndrome
Tab	Total antibody
TEAE	Treatment emergent adverse event
TEN	Toxic epidermal necrolysis
ULN	Upper limit of normal
WBC	White blood cell count

[redacted]

Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	Brentuximab vedotin
Pharmacotherapeutic group(s) (ATC Code)	L01XC12
Marketing Authorisation Holder	Takeda Pharma A/S Delta Park 45 2665 Vallensbaek Strand, Denmark
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	ADCETRIS®
Marketing authorisation procedure	Centralised procedure
Brief description of the product	**Chemical class** Antineoplastic agents; other antineoplastic agents; monoclonal antibodies
	Summary of mode of action: Brentuximab vedotin is a CD30-directed ADC consisting of 3 components: 1) the monoclonal antibody cAC10, specific for human CD30; 2) the antimicrotubule agent monomethyl auristatin E (MMAE); and 3) a protease-cleavable linker that covalently attaches MMAE to cAC10. cAC10 has a structure typical of the chimeric immunoglobulin G1 (IgG1) subclass. The biological activity of brentuximab vedotin results from a multistep process. Binding of the ADC to CD30 on the cell surface initiates internalisation of the ADC-CD30 complex, which then traffics to the lysosomal compartment. Within the cell, a single defined active species, MMAE, is released via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, induces mitotic cell cycle arrest and results in apoptotic death of the CD30-expressing tumour cell. Brentuximab vedotin (powder for concentrate for solution for infusion) is formulated as a sterile, preservative-free, white to off-white cake for reconstitution and dilution for intravenous (IV) administration. Brentuximab vedotin for injection is supplied in single-use vials. The lyophilised product, after reconstitution with Sterile Water for injection, Eur. Ph., contains 5 mg/mL

	brentuximab vedotin, 63 mg/mL trehalose, 5.2 mg/mL sodium citrate.
	Important information about its composition: Brentuximab vedotin is produced by the conjugation of MMAE to cAC10. The points of attachment are cysteines produced by mild reduction of the interchain disulfides of the antibody, and the linker consists of a thiol reactive maleimide, a caproyl spacer, the dipeptide valine-citrulline, and p-amino-benzyloxycarbonyl, a self-immolative fragmenting group. The overall average drug-to-antibody mole ratio (MR) is approximately 4.
Hyperlink to the Product Information (PI)	Refer to eCTD Module 1.3.1 for proposed PI or latest approved PI.
Indication(s) in the EEA	Current (if applicable): ADCETRIS is indicated for adult patients with previously untreated CD30+ Stage III or Stage IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine (AVD). ADCETRIS is indicated for the treatment of adult patients with CD30+ HL at increased risk of relapse or progression following autologous stem cell transplant (ASCT). ADCETRIS is indicated for the treatment of adult patients with relapsed or refractory CD30+ HL: 1. following ASCT, or 2. following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option. ADCETRIS in combination with cyclophosphamide, doxorubicin, and prednisone (CHP) is indicated for adult patients with previously untreated systemic anaplastic large cell lymphoma(sALCL). ADCETRIS is indicated for the treatment of adult patients with relapsed or refractory sALCL. ADCETRIS is indicated for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy.
	Proposed (if applicable): ADCETRIS is indicated for adult patients with previously untreated CD30+ Stage IIB with risk factors, Stage III or Stage IV HL in combination with etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone (BrECADD)
Dosage in the EEA	Current (if applicable): The recommended dose as a monotherapy is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. The recommended starting dose for the retreatment of patients with relapsed or refractory HL or sALCL who have previously responded to treatment with ADCETRIS is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every

[redacted]

	3 weeks, up to 16 cycles. Alternatively, treatment may be started at the last tolerated dose. The recommended dose in combination with AVD is 1.2 mg/kg administered as an intravenous infusion over 30 minutes on days 1 and 15 of each 28-day cycle for 6 cycles. The recommended dose in combination with CHP is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks for 6 to 8 cycles. If the patient's weight is more than 100 kg, the dose calculation should use 100 kg.
	Proposed (if applicable): Not applicable
Pharmaceutical form(s) and strengths	Current (if applicable): Powder for concentrate for solution for infusion. White to off-white cake or powder. Each vial contains 50 mg of brentuximab vedotin. After reconstitution, each ml contains 5 mg of brentuximab vedotin.
	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

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

Hodgkin lymphoma (HL)

Incidence:

There are 4 different pathologic types of classical HL (CHL): nodular sclerosing (NS) subtype (accounts for approximately 70% of all newly diagnosed HL); mixed cellularity (MC) subtype (accounts for approximately 20%); lymphocyte-rich, and lymphocyte-depleted (LD) subtype (accounts for approximately 1%-5%). An additional type of HL, nodular lymphocyte-predominant HL, accounts for approximately 10% of HL cases, expresses CD20, and is currently not considered a form of classical HL. Approximately 46% of incident HL cases are stage III and IV[redacted].

Incidence of HL varies by region and sex, males have a higher incidence than females. Based on data reported by GLOBOCAN in 2020, the highest incidence rate in 2020 was in Italy followed by France[redacted]. In total, there were 83,087 cases of HL globally and 19,858 cases of HL in Europe in 2020[redacted]. The incidence rate of HL in Europe for 2020 was 2.8 per 100,000 in males and 2.1 per 100,000 in females[redacted].

Incidence rate per 100,000 person years for select countries is given in Table 1 below. These recent incidence rates are derived from various cancer registries.

Table 1: Incidence rate of Hodgkin's Lymphoma per 100,000 person years in select European Countries

Country	Incidence rate per 100,000 person years	Source Used
Austria	2.1	IARC [redacted]
Belgium	2.9	Belgian Cancer Registry [redacted]
Bulgaria	1.3	Bulgarian National Cancer Registry[redacted]
Croatia	2.6	Croatian National Cancer Registry [redacted]
Cyprus	3.7	IARC[redacted]
Czech Republic	2.7	Czech National Cancer Registry[redacted]
Denmark	2.9	NORDCAN [redacted]
Estonia	2.7	IARC[redacted]
Finland	3.1	NORDCAN[redacted]
France	3.2	Sante Publique France/FRANCIM [redacted]

[redacted]

Hodgkin lymphoma (HL)

Germany	3.0	Robert Koch Institute [redacted]
Iceland	2.5	NORDCAN [redacted]
Ireland	2.5	National Cancer Registry of Ireland [redacted]
Italy	3.6	IARC [redacted]
Latvia	2.7	IARC [redacted]
Lithuania	2.2	IARC [redacted]
Malta	3.3	IARC [redacted]
Netherlands	2.7	Netherlands Cancer Registry [redacted]
Norway	2.8	NORDCAN [redacted]
Poland	2.0	IARC [redacted]
Portugal	3.2	Regis to Oncológico Regional Sul [redacted]
Slovakia	2.8	IARC [redacted]
Slovenia	3.0	Cancer Registry of Slovenia [redacted]
Spain	2.9	IARC [redacted]
Sweden	2.2	NORDCAN [redacted]
UK	3.3	Cancer Registration Statistics, England [redacted]

Prevalence:	The 1-year, 3-year, and 5-year prevalence of HL in Europe for 2020 reported by GLOBOCAN was 2.1 per 100,000, 5.9 per 100,000, and 9.4 per 100,000, respectively. The 1-year, 3-year, and 5-year prevalence is higher in males than females [redacted].
Demographics of the target population in the indication:	Unlike other lymphomas, whose incidence increases with age, HL has a bimodal incidence curve; age-specific incidence rises during childhood and peaks in ages 20-24, rates then decrease until middle age and then rise again to reach a second peak at around 75-79 years [redacted]. The disease is slightly more frequent in men than in women and is less frequent in Blacks and Asians than in Whites [redacted].
Risk factors for the disease:	The aetiology of HL is largely unknown. However, higher risks have been reported in those with autoimmune diseases, males (except in adolescents and young adults), persons with higher socioeconomic status, smaller families, those with congenital and acquired immunodeficiency, those with family history of HL or other lymphoid neoplasms, and those with increased antibody titers against certain Epstein-Barr virus (EBV) antigens [redacted].

[redacted]

Hodgkin lymphoma (HL)	
The main existing treatment options:	The treatment of patients with HL is primarily guided by the clinical stage of disease as determined by the Lugano classification[redacted]. This staging system is important in determining not only prognosis and treatment but is also important for the comparison of results obtained with different types of treatment in different studies. Patients with early stage (stage I-II) CHL have a very favourable prognosis with various available treatments and concerns over late effects of treatment, particularly second malignancies, cardiac toxicities, and pulmonary damage, need to be considered when choosing optimal therapy. Standard treatment approaches for early stage CHL consist of abbreviated courses of chemotherapy followed by involved-field (or more recently involved site) radiotherapy. For advanced stage HL (stage III-IV), combination chemotherapy is the main treatment for patients, radiation therapy may be used for selected patients as consolidation. The three most widely used treatment regimens for advanced stage HL include: 1. ABVD[redacted]; 2. Brentuximab + doxorubicin, vinblastine, dacarbazine (AVD)[redacted]; 3. bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) [redacted]. Patients with relapsed/refractory (r/r) HL are generally treated with either conventional chemotherapy combined with radiation therapy, checkpoint inhibitors, monoclonal antibodies or enrolled in clinical trials; high-dose chemotherapy and ASCT given with or without radiation therapy. Advances in the use of combined chemotherapy and radiotherapy in HL over the past half century have resulted in a durable remission rate of approximately 70%[redacted]. However, these multiagent regimens are associated with significant morbidity, including second malignancies, cardiac disease, pulmonary disease, and infertility [redacted]. Approximately 10% to 20% of patients presenting with HL will become refractory to initial therapy or experience disease relapse. The therapeutic options for patients with refractory or relapsed disease are very limited and carry a high morbidity rate[redacted]. Patients presenting with advanced stage HL have an even less favourable prognosis than patients with early-stage disease and have a much higher relapse rate[redacted]. For patients who do not respond to standard chemotherapy or who relapse, the only potentially curative therapy is high-dose chemotherapy in combination with ASCT [redacted]. This treatment is associated with morbidity, mortality, and a 5-year survival rate of <50%[redacted]. In addition to brentuximab vedotin, there are 2 additional therapeutic agents currently approved in the EU for patients with refractory or relapsed classical HL, pembrolizumab (Keytruda®) and nivolumab (Opdivo®), both as programmed death receptor-1 (PD-1) blocking antibodies. Pembrolizumab has been approved by the European Medicines Agency (EMA) as monotherapy for the treatment of adult and paediatric patients aged 3 years and older with r/r classical HL who have failed ASCT and brentuximab vedotin, or who are transplant-ineligible and have failed brentuximab vedotin. The EMA approved nivolumab as

[redacted]

Hodgkin lymphoma (HL)	
	monotherapy for the treatment of adult patients with r/r classical HL after ASCT and treatment with brentuximab vedotin.
Natural history of the indicated condition in the population, including mortality and morbidity:	HL is one of the most curable paediatric and adult cancers, with long-term survival rates now exceeding 90% after treatment with chemotherapy alone or combined with radiotherapy[redacted]. However, at present approximately 2% of patients with classical HL are primarily refractory to conventional therapy of whom only 50% becoming long-term survivors. Another 13% of patients experience disease relapse, of whom only 60% being alive 10 years post recurrence[redacted]. The overall 5-year relative survival for HL is 85%, with higher rates reported in younger patients. In younger patients with low-risk HL, 5-year survival reaches 95%, whereas survival in high-risk HL patients is approximately 85%. This may be influenced by the age at diagnosis; it has been shown that adolescents (15-19 years old) fare worse than their younger (<15 years old) counterparts [redacted]. Additionally, patients whose disease relapse after stem cell transplantation (SCT) have an extremely poor prognosis [redacted]. Mortality in the first 15 years after diagnosis is related most often to the primary disease, followed by secondary cancers and cardiovascular disease[redacted].
Important co-morbidities:	Comorbidity is a major problem in the clinical management of older lymphoma patients. In one population-based Eindhoven Cancer Registry in the Netherlands, investigators found that the prevalence of serious comorbidity was 58% for patients with HL who were >60 years of age[redacted]. Some of the serious sequelae of radiation and alkylating chemotherapy are most pronounced in younger patients, in whom growth and development are particularly active when therapy is administered. In addition, cardiac toxicity appears to be age related, with younger patients at the highest risk. Second malignancies, including breast cancer in female patients and secondary myeloid neoplasms, represent the leading causes of mortality in survivors of paediatric HL[redacted]. **Peripheral Neuropathy** Patients with r/r HL or sALCL may have pre-existing neuropathy due to prior treatment with neurotoxic chemotherapy, such as vinblastine and vincristine in Adriamycin, bleomycin, vinblastine, dacarbazine (ABVD) and CHOP (cyclophosphamide, doxorubicin [hydroxydaunorubicin], vincristine [Oncovin®], prednisone), which are standard first-line regimens for HL and sALCL, respectively. In addition, demyelinating polyneuropathy, inflammatory neuropathy, and paraneoplastic neuropathy of unknown origin have been reported in HL and non-Hodgkin lymphoma (NHL). In a comprehensive evaluation of neuropathy in 150 patients with lymphoma that excluded patients with neuropathy due to chemotherapy or anti-myelin antibodies, 26 patients (17%) had non-drug-induced neuropathy. Half of the patients, all with indolent or aggressive NHL, had radiculopathy or axonal multiple mononeuropathy. The other half, all HL patients, had demyelinating polyneuropathy. Thus, demyelinating neuropathy is a recognised complication of HL, although the pathophysiology has not been characterised[redacted]. In addition to neuropathy possibly related to underlying lymphoma or prior history of exposure to chemotherapeutic agents that can contribute to neuropathy, hypothyroidism, a risk factor

[redacted]

Hodgkin lymphoma (HL)	
	itself, occurs frequently in HL patients treated with irradiation[redacted]. Because peripheral neuropathy can result from risk factors and pre-existing conditions, chemotherapy, and the underlying lymphoma, defining risk at an individual patient level or the course of resolution for a specific patient is not possible. **Cardiovascular Disease** The risk of cardiovascular disease is significantly increased among HL survivors at 5 to 10 years after treatment and appears to increase over time[redacted]. However, a significant proportion of this excess risk occurs among survivors who have other cardiac risk factors[redacted]. A recent study found a 3- to 5-fold increased risk of cardiovascular disease in 5-year HL survivors compared with the general population[redacted]. **Ventricular Dysfunction** Hodgkin's lymphoma survivors treated as children with anthracyclines or mediastinal radiation therapy are at an increased risk for delayed ventricular dysfunction. Krischer et al reviewed 25 studies and found subclinical cardiotoxicity in up to 57% of paediatric HL survivors [redacted]. **Coronary Artery Disease** Little information is known about coronary artery disease in HL survivors. In a recent prospective study of 294 HL survivors with no known cardiovascular disease and who had been previously treated with mediastinal radiation therapy, all subjects were asymptomatic. However, the prevalence of severe, 3-vessel, or main coronary artery disease detected by stress echocardiography and nuclear scintigraphy was 2.7%[redacted]. These findings suggest that even asymptomatic survivors with no known cardiovascular risk factors are at risk for coronary artery disease and should be monitored within 5 years of treatment completion. **Thyroid Hormone Abnormalities** Hypothyroidism is the most common form of thyroid dysfunction occurring in HL survivors. Within 20 years after completing radiation therapy, up to 50% of these patients may be affected, with approximately half of the incidences occurring within 5 years of treatment completion[redacted]. **Fertility** Women treated with alkylator-based chemotherapy may experience irregular menses or premature menopause, and males may have oligo- or azoospermia [redacted]. **Infections** Excess mortality from infectious causes has been reported among HL survivors, particularly among patients who received radiation therapy to the spleen[redacted]. Mycosis fungoides and Sézary syndrome (SS) patients with advanced disease develop severe immunodeficiency and often die of infections rather than complications from the tumour burden. **Fatigue** Fatigue is one of the most frequent patient-reported symptoms in HL patients. Patients with HL may have fatigue at the time of diagnosis, during treatment, and even years after treatment [redacted]. Recent reports

[redacted]

Hodgkin lymphoma (HL)	
	have shown that approximately one-third of HL survivors experience persistent fatigue after treatment [redacted]. Potential causes of fatigue in HL survivors are cardiac complications, depression, insomnia, anaemia, and hypothyroidism. **Secondary Cancers** Secondary cancers are the leading cause of morbidity and death among long-term HL survivors. The risk of secondary solid cancer is age related, and the predominant cancers are of the breast and lung. Risk factors for secondary breast cancer are female sex, young age at diagnosis/treatment (<30 years) and increasing exposure to radiation. Risk factors for lung cancer include chest irradiation (dose-dependent), alkylating chemotherapy (dose-dependent), and smoking. Cervical cancer is also increased in HL survivors. Lastly, there is a higher risk for colorectal cancer among HL survivors. A recent study demonstrated that the risk of colorectal cancer in HL survivors treated at ages 15 or 25 is equal to that of a 50-year old at approximately age 40[redacted]. A recent report by Hodgson et al found that the cumulative risk for secondary cancers for men and women were 18% and 26%, respectively, as compared to 7% and 9% in the general population, and that the risk of developing breast and colorectal cancers was elevated by 10 to 25 years before the age when routine screenings would be performed[redacted]. In addition to solid tumours, secondary cancers of the blood also occur. A study by Dores et al found that leukemias (e.g., acute lymphoblastic leukaemia [ALL], chronic lymphocytic leukaemia [CLL], acute nonlymphocytic leukaemia [ANLL], and chronic myeloid leukaemia) as well as NHL occurred subsequent to HL[redacted]. ANLL constituted approximately 80% of the leukemia cases. Excess leukemias may be attributable to treatment with alkylating agents or chemotherapy. It's been reported that patients with mycosis fungoides and SS are at a significantly increased risk of developing a second lymphoma, in particular HL and the CTCL subtype lymphomatoid papulosis, as well as nonhematologic malignancies[redacted].

Anaplastic large cell lymphoma (ALCL)	
Incidence:	ALCL is a rare form of NHL that is commonly classified as aggressive T-cell lymphoma. ALCL can present in either the systemic (sALCL) or cutaneous form. There is a third form described in recent years, that of Breast associated ALCL. ALCL is characterised as either anaplastic lymphoma kinase positive or negative (ALK+ or ALK-). Recent research in Europe indicates that sALCL represents approximately 1.13% of all NHL cases [redacted]. While incidence of sALCL is not readily available in the literature, it can be derived given the proportion of sALCL in NHL patients. Table 2 below provides incidence rates per 100,000 of NHL and sALCL, with the incidence rates of sALCL estimated as 1.13% of the incidence rates NHL. The incidence rates of NHL are based on recent information available in European cancer registries.

[redacted]

Anaplastic large cell lymphoma (ALCL)

Table 2 presents Incidence rate of non-Hodgkin's Lymphoma and ALCL per 100,000 person years in select European Countries.

Table 2: Incidence rate of non-Hodgkin's Lymphoma and sALCL per 100,000 person years in select European Countries

Country	NHL incidence rate per 100,000 person years	Source Used	Derived sALCL incidence rate per 100,000 person years*
Austria	14.3	IARC [redacted]	0.2
Belgium	17.8	Belgian Cancer Registry [redacted]	0.2
Bulgaria	5.3	Bulgarian National Cancer Registry [redacted]	0.1
Croatia	14.4	Croatian National Cancer Registry [redacted]	0.2
Cyprus	13.9	IARC [redacted]	0.2
Czech Republic	14.3	Czech National Cancer Registry [redacted]	0.2
Denmark	24.8	NORDCAN [redacted]	0.3
Estonia	12.6	IARC [redacted]	0.2
Finland	24.0	NORDCAN [redacted]	0.3
France	42.5	Sante Publique France/FRANCIM [redacted]	0.6
Germany	22.1	Robert Koch Institute [redacted]	0.3
Iceland	18.2	NORDCAN [redacted]	0.2
Ireland	17.9	National Cancer Registry of Ireland [redacted]	0.2
Italy	20.6	IARC [redacted]	0.3
Latvia	9.8	IARC [redacted]	0.1
Lithuania	11.2	IARC [redacted]	0.1
Malta	18.0	IARC [redacted]	0.2
Netherlands	21.3	Netherlands Cancer Registry [redacted]	0.3
Norway	18.5	NORDCAN [redacted]	0.2

[redacted]

Anaplastic large cell lymphoma (ALCL)

	Poland	7.5	IARC[redacted]	0.1
	Portugal	17.2	Registo Oncológico Regional Sul[redacted]	0.2
	Slovakia	9.9	IARC [redacted]	0.1
	Slovenia	9.5	Cancer Registry of Slovenia[redacted]	0.1
	Spain	15.1	IARC[redacted]	0.2
	Sweden	16.0	NORDCAN[redacted]	0.2
	UK	20.9	Cancer Registration Statistics, England [redacted]	0.3
	*Derived sALCL incidence rate is 1.13% of NHL incidence rate [redacted]			
Prevalence:	2/100,000 per Orphanet[redacted].			
Demographics of the target population in the indication:	sALCL affects both children and adults. Adolescents and children tend to have ALK+ tumours, while tumours in older patients over the age of 40 tend to be ALK-[redacted]			
Risk factors for the disease:	Aetiology is unknown. In the ALK+ subtype, the anaplastic lymphoma receptor tyrosine kinase *ALK* gene (2p23) is overexpressed due to a t(2;5) (p23;q35) translocation[redacted].			
The main existing treatment options:	Approximately 40% to 65% of patients with sALCL subsequently develop recurrent disease. Salvage therapy followed by ASCT in eligible patients is a standard approach in R/R ALCL. However, second complete remission (CR) with standard salvage chemotherapy such as EPOCH (e.g., etoposide, prednisone, vincristine [Oncovin], cyclophosphamide, doxorubicin [hydroxydaunorubicin], ESHAP (e.g., etoposide, methylprednisolone [Solu-Medrol], high-dose cytarabine [araC], cisplatin [Platinol AQ]), or ICE (e.g., ifosfamide-, carboplatin, etoposide), is achieved in only 25% to 30% of patients, who are able to proceed to AHCT[redacted].			
Natural history of the indicated condition in the population, including mortality and morbidity:	In absence of treatment, ALCL is a fatal disease with patients succumbing to a combination of progressive bulky lymphadenopathy that eventually compromised vital organ function and a wasting syndrome with steadily worsening constitutional symptoms, weight loss, cachexia, inanition, and death. Patients with ALK+ ALCL had better outcomes than ALK- ALCL[redacted]. With currently available chemotherapy and radiation treatments late manifestations of the disease have become uncommon. However, recurrence does affect a minority of patients. When disease relapses it typically recurs in sites of previous disease, if those sites were not treated with radiation, or novel sites if the original disease was irradiated. Even if novel sites are involved, they are usually in lymph node regions nearby original sites of disease or in the usual extranodal sites, lung, liver, bone, or bone marrow. At recurrence, the histologic subtype most often matches the original diagnosis. Eventually, involvement of vital organs, such as the lungs, liver, and bone marrow,			

[redacted]

Anaplastic large cell lymphoma (ALCL)	
	often complicated by systemic infections, marked nutritional compromise and generalised weakness leads to the patient's demise.
Important co-morbidities:	Patients with sALCL may have a wide range of important disease-related morbidities. A clinical review of clinical morbidities of patients with systemic ALCL found that 38% of patients had mediastinal involvement. Extranodal morbidities included bone marrow (15% of patients), liver (12%), spleen (18%), central nervous system (8%), skin (15%), lung (16%), gut (7%) and bone (8%) [redacted]. **Fertility** Women treated with alkylator-based chemotherapy may experience irregular menses or premature menopause, and males may have oligo- or azoospermia[redacted]. **Peripheral Neuropathy** Patients with sALCL may have pre-existing neuropathy due to prior treatment with neurotoxic chemotherapy, such as vinblastine and vincristine in ABVD and CHOP (cyclophosphamide, doxorubicin [hydroxydaunorubicin], vincristine [Oncovin®], prednisone), which are standard first-line regimens for sALCL, respectively. In addition, demyelinating polyneuropathy, inflammatory neuropathy, and paraneoplastic neuropathy of unknown origin have been reported in NHL. In a comprehensive evaluation of neuropathy in 150 patients with lymphoma that excluded patients with neuropathy due to chemotherapy or anti-myelin antibodies, 26 patients (17%) had non-drug-induced neuropathy. Half of the patients, all with indolent or aggressive NHL, had radiculopathy or axonal multiple mononeuropathy[redacted].

Cutaneous T-cell lymphoma (CTCL)	
Incidence:	Cutaneous T-cell lymphoma is a rare type of NHL with an incidence rate of 1/100,000 reported over 2005-2009[redacted]. Incidence rates have been gradually climbing over the last 20 years, although CTCL remains a rare malignancy[redacted]. Similar to ALCL, CTCL represents a proportion of NHL. Based on the Surveillance, Epidemiology, and End Results Program [redacted], 3.4% of NHL cases are CTCL. Therefore, we can derive the recent incidence of CTCL based on the incidence of NHL. Table 3 provides the incidence rates of NHL and CTCL per 100,000 person years, with the incidence of CTCL being 3.4% of the incidence of NHL. NHL incidence rates are based on recent information available in European cancer registries. **Table 3: Incidence rate of non-Hodgkin's Lymphoma and CTCL per 100,000 person years in select European Countries.**

Country	NHL incidence rate per 100,000 person years	Source Used	Derived CTCL incidence rate per 100,000 person years*
Austria	14.3	IARC[redacted]	0.5

[redacted]

Cutaneous T-cell lymphoma (CTCL)

Belgium	17.8	Belgian Cancer Registry [redacted]	0.6
Bulgaria	5.3	Bulgarian National Cancer Registry [redacted]	0.2
Croatia	14.4	Croatian National Cancer Registry [redacted]	0.5
Cyprus	13.9	IARC [redacted]	0.5
Czech Republic	14.3	Czech National Cancer Registry [redacted]	0.5
Denmark	24.8	NORDCAN [redacted]	0.8
Estonia	12.6	IARC [redacted]	0.4
Finland	24.0	NORDCAN [redacted]	0.8
France	42.5	Sante Publique France/FRANCIM [redacted]	1.4
Germany	22.1	Robert Koch Institute [redacted]	0.8
Iceland	18.2	NORDCAN [redacted]	0.6
Ireland	17.9	National Cancer Registry of Ireland [redacted]	0.6
Italy	20.6	IARC [redacted]	0.7
Latvia	9.8	IARC [redacted]	0.3
Lithuania	11.2	IARC [redacted]	0.4
Malta	18.0	IARC [redacted]	0.6
Netherlands	21.3	Netherlands Cancer Registry [redacted]	0.7
Norway	18.5	NORDCAN [redacted]	0.6
Poland	7.5	IARC [redacted]	0.3
Portugal	17.2	Registo Oncológico Regional Sul [redacted]	0.6
Slovakia	9.9	IARC [redacted]	0.3
Slovenia	9.5	Cancer Registry of Slovenia [redacted]	0.3
Spain	15.1	IARC [redacted]	0.5

[redacted]

Cutaneous T-cell lymphoma (CTCL)	
	<table><tr><td>**Sweden**</td><td>16.0</td><td>NORDCAN[redacted]</td><td>0.5</td></tr><tr><td>**UK**</td><td>20.9</td><td>Cancer Registration Statistics, England[redacted]</td><td>0.7</td></tr></table> *Derived CTCL incidence rate is 3.40% of NHL incidence rate
Prevalence:	24/100,000 per Orphanet[redacted]
Demographics of the target population in the indication:	CTCL is more common in men than women with a male: female ratio of 1.6:1, and disease onset is typically from age 55 onwards. While CTCL may occur in children and young adults, this is very uncommon[redacted]. Incidence rates are higher in blacks than whites (B:W ratio 1.3:1)[redacted].
Risk factors for the disease:	Aetiology is unknown. Environmental exposure, immunosuppression, as well as infections including HTLV1 and EBV are thought to play a role[redacted].
The main existing treatment options:	Skin-directed therapy for CTCL include steroid creams and ointments to control skin redness and itchiness, PUVA light therapy and topical chemotherapy or immunotherapy (bexarotene/tazarotene and imiquimod/resiquimod). Systemic therapies (single or in combination) include retinoids and interferons and chemotherapy agents (gemcitabine, liposomal doxorubicin etc); bexarotene and vorinostat to treat advanced or relapsed disease; romidepsin for patients who have received at least one prior chemotherapy drug; pralatrexate to treat advanced CTCL subtype transformed mycosis fungoides. Brentuximab vedotin is a biologic therapy targeted to patients with CD30 positive CTCL. For aggressive forms of CTCL, an allogeneic SCT may help the growth of new blood cells and boost the patient's defence against infection.
Natural history of the indicated condition in the population, including mortality and morbidity:	Cutaneous T-cell lymphoma is largely restricted to the skin and appears as a rash or scaly patches. The disease is treatable but not curable, and patients live with the disease lifelong. With available systemic medications, many patients achieve and remain in remission for long periods. As CTCL progresses, skin plaques and tumours develop, and the disease may occur in lymph nodes, viscera and blood. Survival is largely dependent on disease stage. Early stage disease has excellent survival (median overall survival 35 years), whereas advanced disease has a worse survival (median survival 5 years)[redacted].
Important co-morbidities:	**Drug-related toxicities** In early-stage disease, there are few co-morbidities. In later stages of disease, treatment-related co-morbidities may occur, with range and frequency dependent on combination of therapies being used. **Pruritus** Virtually all patients with CTCL have pruritus. Treatment of the underlying CTCL is likely to resolve any pruritus. However, for patients with relapsing or refractory disease, persistent pruritic may have significant negative impact on quality of life.

[redacted]

Part II: Module SII - Nonclinical part of the safety specification

The safety of brentuximab vedotin has been evaluated in Good Laboratory Practice (GLP) compliant nonclinical studies, including toxicology studies in the rat and monkey. The toxicities that have been noted include thymic lymphoid depletion, testicular atrophy and seminiferous tubular degeneration, minor liver toxicities, reproductive toxicities including embryofoetal lethality and maternal toxicity, peripheral neuropathy, and reductions of cytochrome P450 (CYP) activity. No additional nonclinical data are anticipated for the currently approved indications, including the use of brentuximab vedotin in special populations.

Key Safety Findings	**Relevance to human usage**
Toxicity:	

1. Thymic lymphoid depletion
• Repeated dose (rats and monkeys):
  • Rats given brentuximab vedotin intravenously (IV) at 0.5, 5, and 10 mg/kg q 1 week for 4 weeks experienced thymic lymphoid depletion, observed at the 5 and 10 mg/kg doses of brentuximab vedotin. This finding was reversed following drug cessation during the 4-week recovery period.
  • Cynomolgus monkeys given brentuximab vedotin IV at ≥3 mg/kg had reduced thymic weights and lymphoid depletion in the thymus. Effects were reversible.
	Toxicity was dose-dependent, being most pronounced at the high-dose levels of brentuximab vedotin in both rats and monkeys. Reversibility was observed in both rats and monkeys.
	In humans, as the thymus is the organ of T-cell development, defects in thymocyte development can lead to a profound T-cell immunodeficiency. This would be especially relevant to paediatric patients prior to puberty before involution of the thymus occurs. However, this is not observed among the paediatric patients.

2. Testicular toxicity • Repeated dose (rats): • Testicular atrophy and seminiferous tubular degeneration were observed in male rats who received 5 or 10 mg/kg of brentuximab vedotin IV once weekly for 4 weeks. Testicular findings were partially reversed following a 16-week recovery period.	Toxicity occurred at the middle and highest doses, which was only partially reversed by 16 weeks. In nonclinical studies, brentuximab vedotin has resulted in testicular toxicity, and may alter male fertility (SmPC Section 5.3, Preclinical safety data). Therefore, men being treated with brentuximab vedotin are advised to have sperm samples frozen and stored before treatment. Men being treated with brentuximab vedotin are advised not to father a child during treatment and for up to 6 months following the last dose. Women must use 2 methods of effective contraception during treatment with brentuximab vedotin and for 6 months after finishing their treatment with brentuximab vedotin. (SmPC Section 4.6, Fertility, pregnancy and lactation).
3. Minor liver toxicity • Single and repeated dose (rats and monkeys):	Toxicity was dose-dependent, being most pronounced at the high-dose levels of brentuximab vedotin in rats. Reversibility was observed.

Key Safety Findings	Relevance to human usage
The data from individual nonclinical single- and repeat-dose toxicology studies demonstrate that the liver is a target organ of toxicity of brentuximab vedotin. Single cell hepatocellular necrosis and bile duct hyperplasia of the liver and elevations in hepatobiliary enzymes were observed in single-dose toxicity studies in rats with brentuximab vedotin. In sub-chronic (up to 1 month) repeat-dose toxicity studies of brentuximab vedotin in rats, at doses up to 15 mg/kg, focal coagulative necrosis of the liver was observed and was reversible during a 4-week recovery period. In rats, toxicity studies of greater than 1-month duration were not conducted. In sub-chronic toxicity studies (up to 3 months) of brentuximab vedotin in monkeys, at doses up to 6 mg/kg, focal coagulative necrosis was observed. In the chronic toxicity study (up to 6 months) of brentuximab vedotin conducted in monkeys at doses up to 3 mg/kg, hepatic toxicity was not observed.	Significant alterations in liver function tests were not frequently observed in the clinical studies conducted with brentuximab vedotin. Approximately 1% of patients treated with brentuximab vedotin in the clinical trial or commercial setting have had an AE within the Medical Dictionary for Regulatory Activities (MedDRA) hepatic disorders Standardised MedDRA Query (SMQ) (broad) that is suggestive of a hepatobiliary disorder.
4. Reproductive toxicity (rats) • Time-mated female rats were assigned to 6 groups that received either vehicle; brentuximab vedotin at 0.3, 1, 3, or 10 mg/kg; or SGD1010 (MMAE) at 0.2 mg/kg on gestation Days 6 and 13 as an IV bolus injection. • The administration of brentuximab vedotin at 3 and 10 mg/kg and SGD1010 at 0.2 mg/kg resulted in embryofoetal lethality. Embryofoetal developmental toxicity was characterised by an increase in total resorptions, post-implantation loss, and loss of viable foetuses. Dams experienced decreased maternal body weight and food consumption; decreased leukocyte and platelet counts; increased reticulocyte counts, haematocrit, and mean corpuscular volume; and decreased uterine weight, which correlated with lack of viable foetuses and complete fetal reabsorption with residual reimplantation sites.	The administration of brentuximab vedotin at 3 and 10 mg/kg resulted in embryofoetal lethality. There are no data from the use of brentuximab vedotin in pregnant women. Studies in animals have shown reproductive toxicity. Brentuximab vedotin should not be used during pregnancy unless the benefit to the mother outweighs the potential risks to the foetus. If a pregnant woman needs to be treated, she should be clearly advised on the potential risk to the foetus. Women of childbearing potential should use 2 methods of effective contraception during treatment with brentuximab vedotin and until 6 months after treatment. (SmPC Section 4.6, Fertility, pregnancy and lactation).
5. Peripheral neuropathy (method of detection in rats) • Eight to 12 male Sprague Dawley rats per group were administered paclitaxel	This non-GLP study evaluated the feasibility of using the von Frey assay to detect peripheral neuropathy in rats.

Key Safety Findings	Relevance to human usage
(2 mg/kg; positive control), vehicle (5% DMSO), or MMAE as an intraperitoneal injection once daily (QD) on 4 alternate days (Study Days 1, 3, 5, and 7). MMAE was given at 0.013, 0.025, or 0.05 mg/kg/dose (cumulative doses of 0.052, 0.1, or 0.2 mg/kg, respectively). MMAE dose levels were chosen based on multiples of the weekly highest non-severely toxic dose in rats (0.2 mg/kg) from IV toxicity studies. • Neuropathy was assessed using von Frey filaments beginning on Study Day 11 post-initial injection, and then twice weekly continuing through Study Day 35. • Repeat intraperitoneal (IP) bolus administration of either paclitaxel (2 mg/kg/dose) or MMAE (0.0130.05 mg/kg/dose) elicited neuropathy as assessed by paw withdrawal threshold as compared to vehicle controls.	Peripheral neuropathy is an identified risk of brentuximab vedotin. The incidence, severity, and reversibility of neuropathy observed with brentuximab vedotin is generally similar to that observed with other microtubule inhibitors such as the vinca alkaloids. SmPC Section 4.4, Special warnings and precautions for use, advises that patients should be monitored for symptoms of neuropathy. SmPC Section 4.2, Posology and method of administration offers specific recommendations for dose delay, reduction, or discontinuation in patients experiencing new or worsening peripheral neuropathy. Results of clinical trials will also serve to further define the incidence of neuropathy in patients.
6. Bone marrow hypocellularity (monkeys) Repeat-dose administration of MMAE caused qualitatively similar effects while no adverse effects were associated with the repeat-dose administration of cAC10. The no-observed-adverse-effect level (NOAEL) for repeat-dose administration of brentuximab vedotin was 0.5 and 1 mg/kg in rat and monkey, respectively. The highest non-severely toxic dose (HNSTD) for repeat-dose administration of brentuximab vedotin was 5 and 3 mg/kg in rat and monkey, respectively. In up to 6-month repeat-dose toxicity studies of brentuximab vedotin in monkeys at doses up to 6 mg/kg, the primary toxicity observed was bone marrow hypocellularity, characterised predominantly by decreases in circulating neutrophil numbers. In up to one-month repeat-dose toxicity studies of brentuximab vedotin in rats at doses up to 15 mg/kg, the following target organs were identified: bone marrow (hypocellularity), thymus (lymphoid depletion), spleen (lymphoid depletion), liver (focal coagulative necrosis), intestine (single cell necrosis), testis (seminiferous tubular degeneration), and lung (alveolar histiocytosis) in rat only.	The primary treatment-related effects of repeat-dose brentuximab vedotin administration to rats and monkeys (bone marrow hypocellularity and lymphoid depletion) and the associated decreases in peripheral blood cells are consistent with pharmacologic disruption of microtubules caused by MMAE.

Key Safety Findings	Relevance to human usage
Following a 4-week recovery period, all target organ toxicity was reversible except for testicular toxicity. Testicular toxicity in rat was partially resolved following a 16-week off-treatment recovery phase.	
Other toxicity-related information or data:	
7. Effect on CYP3A by MMAE in Cultured Human Hepatocytes in Vitro • Three preparations of cultured human hepatocytes from 3 separate livers were treated QD for 3 consecutive days with dimethyl sulfoxide (DMSO, 0.1% v/v, vehicle control), flumazenil (25 µM, negative control), 1 of 4 concentrations of MMAE (1, 10, 100, or 1,000 nM) or 1 of 3 known human CYP inducers, namely, omeprazole (50 µM), phenobarbital (750 µM,) and rifampin (10 µM). After treatment, CYP activity, CYP protein levels, and CYP mRNA levels were determined. • The study showed that there was no CYP1A2, CYP2B6, and CYP3A induction observed in human hepatocytes with up to 1000 nM of MMAE. However, there were reductions in CYP activity and expression levels of mRNA and protein at 100 and 1000 nM, with no such effect at 1 and 10 nM.	The in vitro human hepatocytes study results indicated that brentuximab vedotin is not expected to increase clearance of other drugs that are metabolised by CYP1A2, CYP2B6, and CYP3A. Consistent with the in vitro induction data and low plasma levels of MMAE (< 10 nM) observed in the clinic, brentuximab vedotin did not cause any drug-drug interaction with the CYP3A substrate midazolam in patients. Thus, brentuximab vedotin was neither an inducer nor an inhibitor of CYP3A activity in the clinic. Overall, potential of MMAE to cause CYP-based DDIs in the clinic is low.

Abbreviations: CYP = cytochrome P450; CYP3A = cytochrome P450 3A4;IV = intravenous(ly); SGD-1010 = MMAE (monomethyl auristatin E); QD = once daily; SmPC = Summary of Product Characteristics; SMQ = standardised MedDRA search query.

[redacted]

Part II: Module SIII - Clinical trial exposure[a]

Table SIII.1: Duration of exposure

Cumulative (months) for all indications (person time):		
Duration of exposure	**Patients**	**Person time**
<1 m	63	38.5
1 to <3 m	669	1,171.6
3 to <6 m	1,249	5,420.1
≥6 m	1,634	14,439.1
Total person time	3,615	21,069.4

Person time (months) per indication:		
Hodgkin Lymphoma		
Duration of exposure	**Patients**	**Person time**
<1 m	11	5.5
1 to <3 m	133	248
3 to <6 m	340	1,411.4
≥6 m	1,050	8,343.8
Total person time for indication	1,534	10,008.7
Anaplastic Large Cell Lymphoma		
Duration of exposure	**Patients**	**Person time**
<1 m	7	4.9
1 to <3 m	64	111.7
3 to <6 m	208	969.7
≥6 m	125	1,435.5
Total person time for indication	404	2,521.7

[a] Note: Patients from ongoing studies (including blinded studies) were included in the clinical trial exposure estimates

[redacted]

Cutaneous T-Cell Lymphoma		
Duration of exposure	**Patients**	**Person time**
<1 m	2	1.4
1 to <3 m	9	16.5
3 to <6 m	15	65.0
≥6 m	40	435.4
Total person time for indication	66	518.4
non-sALCL PTCL		
Duration of exposure	**Patients**	**Person time**
<1 m	4	1.8
1 to <3 m	50	92.6
3 to <6 m	126	591.9
≥6 m	35	351.0
Total person time for indication	215	1,037.3
Other		
Duration of exposure	**Patients**	**Person time**
<1 m	39	25.0
1 to <3 m	418	711.7
3 to <6 m	560	2,381.1
≥6 m	392	3,865.5
Total person time for indication	1,409	6,983.3

Table SIII.2: Age group and gender

Cumulative for all age/gender groups (person time):				
Age group	**Patients**		**Person time**	
	Male	Female	Male	Female
<18 years	64	45	416.8	279.0
18 to <55 years	1,122	1,000	6,507.7	6,310.2
55 to <65 years	303	211	1,694.6	1,063.0
65 to <75	301	228	1,632.5	1,329.9
≥75 years	200	141	1054.3	781.4
Total	**1,990**	**1,625**	**11,305.8**	**9,763.6**

Table SIII.3: Dose

The currently approved dose of brentuximab vedotin in r/r HL, sALCL and CTCL is 1.8 mg/kg administered intravenously every 3 weeks for up to 16 cycles. For frontline HL, in combination with AVD, brentuximab vedotin is administered at 1.2 mg/kg as an intravenous infusion over 30 minutes on day 1 and 15 of each 28-day cycle for 6 cycles. For frontline sALCL, in combination with CHP, brentuximab vedotin is administered at 1.8 mg/kg intravenously every 3 weeks for 6 to 8 cycles. Other than initial dose-escalation studies, and small studies in special populations, the vast majority of patients have received the 1.8 mg/kg dose. Therefore, only the total cumulative dose is reported.

Cumulative dose (All indications)				
	Patients	**Mean**	**Median**	**Range**
Total	3,377	888.7	800.0	1.8–7,200.6

Person time per dose of exposure:				
Indication	**Patients**	**Mean**	**Median**	**Range**
Hodgkin Lymphoma	1,534	971.5	896.0	3.6-6,804.0
Anaplastic Large Cell Lymphoma	404	925.4	799.5	3.6-6,914.0
Cutaneous T-Cell Lymphoma	66	1,305.3	1,381.0	100.0-2,880.0
non-sALCL PTCL	215	737.2	660.0	100.0-5,282.0
Other	1,171	762.0	652.0	1.8-4,424.4
Total	3,377	888.7	800.0	1.8–7,200.6

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

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

1. Patients with a known hypersensitivity to recombinant proteins, murine proteins, or any excipient contained in the drug formulation	
Reason for exclusion:	Contraindication
Is it considered to be included as missing information?	No
Rationale:	Not included as missing information since it is understood that a patient with a known hypersensitivity to recombinant proteins, murine proteins, or any excipient contained in the drug formulation would be at a high likelihood of having a hypersensitivity to brentuximab vedotin.

2. Patients with cardiovascular impairment	
Reason for exclusion:	To accurately understand any impact of brentuximab vedotin on cardiac function.
Is it considered to be included as missing information?	No
Rationale:	There is no rationale to expect that the use of brentuximab vedotin in this population will be associated with significant safety risk.

3. Patients with a history of another primary malignancy that has not been in remission for at least 3 years	
Reason for exclusion:	Recurrence/progression of another primary malignancy would interfere with the ability to assess the safety and efficacy endpoints of the clinical studies.
Is it considered to be included as missing information?	No
Rationale:	The safety and efficacy of brentuximab vedotin should not be affected by the presence of other primary malignancies, although patients with more than one primary malignancy may have decreased rates of OS unrelated the malignancy under study. Hence, progression of a second primary malignancy could interfere with the patient's ability to complete a clinical trial independent of brentuximab vedotin's

[redacted]

3. Patients with a history of another primary malignancy that has not been in remission for at least 3 years	
	activity against the malignancy under study, which in turn could lead to an inability to determine a therapeutic effect.

4. Patients with known cerebral/meningeal disease	
Reason for exclusion:	Pre-existing cerebral/meningeal disease may indicate a very poor prognosis, which may in turn lead to an inability to test the drug in a reasonable setting that would allow a therapeutic effect to be detected.
Is it considered to be included as missing information?	No
Rationale:	Cerebral and/or meningeal involvement are less common manifestations of the diseases under study and they are associated with very poor prognoses, which may in turn lead to an inability to test the drug in a reasonable setting that would allow a therapeutic effect to be detected. Although these patients are expected to have lower response rates given the more advanced stages of their underlying malignancies, as well as the general pharmacokinetic limitations of drug distribution across the blood-brain barrier, the target population represents an underserved population having limited treatment options. The treating physician is best able to evaluate the risk: benefit of the treatments available for an individual patient.

5. Patients with renal and/or hepatic impairment	
Reason for exclusion:	In the early course of clinical development, it was not known how patients with renal and/or hepatic impairment would tolerate brentuximab vedotin.
Is it considered to be included as missing information?	No
Rationale:	Given the potential for increased exposure at the full clinical dose, patients with renal and/or hepatic impairment were excluded from the phase 3 trials. However, patients with hepatic and/or renal impairment were included in Study SGN35 008 (Part B). Results from this study indicate that, compared to patients with normal hepatic or renal function, MMAE exposure is increased by approximately 2.3-fold in patients with hepatic impairment, and

[redacted]

	1.9-fold in patients with severe (CrCl <30 mL/min) renal impairment. A reduced starting dose is recommended for patients with hepatic impairment or severe renal impairment. Physicians are instructed to carefully monitor patients with renal impairment and those with hepatic impairment (SmPC Section 4.2, Posology and method of administration).

6. Patients having active systemic viral, bacterial, or fungal infection(s) requiring systemic antibiotics at baseline	
Reason for exclusion:	To ensure patient safety and to ensure that safety assessments are not confounded by pre-existing conditions and their treatments.
Is it considered to be included as missing information?	No
Rationale:	Patients with acute or unstable medical conditions were excluded from the development program since they may be less likely to complete the trial. Tumour response rates in patients with active infections are not expected to differ relative to non-infected patients. Brentuximab vedotin has been associated with serious and opportunistic infections. Patients should be carefully monitored during treatment for the exacerbation or emergence of possible serious and opportunistic infections. The treating physician is best able to evaluate the risk-benefit of the treatments available for an individual patient who has an active infection.

7. Patients using concurrent therapy with other antineoplastic or experimental agents	
Reason for exclusion:	Concurrent therapy with other antineoplastic or experimental agents would interfere with the ability to assess the safety and efficacy endpoints of the clinical studies.
Is it considered to be included as missing information?	No
Rationale:	ADCETRIS must not be used together with bleomycin as this combination is associated with lung toxicity (SmPC Section 4.3). Tumour response rates in patients who are receiving concurrent therapy are not expected to differ relative to other patients. These patients were excluded from the development program since it may be difficult to distinguish response to the study drug versus response to the

[redacted]

7. Patients using concurrent therapy with other antineoplastic or experimental agents	
	concurrent therapy. Multiagent chemotherapy is outside the labelled indication, but a general contraindication against multiagent therapy on safety grounds (except as noted for bleomycin) is not warranted with the currently available information. Multiagent chemotherapy regimens that include brentuximab vedotin are being investigated in ongoing and planned studies.

8. Patients with dementia or an altered mental status that would preclude the understanding and rendering of informed consent	
Reason for exclusion:	Standard exclusion study criteria based on ethical considerations.
Is it considered to be included as missing information?	No
Rationale:	Patients who have dementia/altered mental status were excluded based on ethical considerations. The safety and efficacy of brentuximab vedotin in these patients are not expected to differ relative to other patients. Based on standard medical practice, it is expected that treating physicians will obtain appropriate informed consent from a patient or his/her healthcare proxy.

9. Women who are pregnant and/or breastfeeding	
Reason for exclusion:	Standard exclusion study criteria based on ethical considerations.
Is it considered to be included as missing information?	No
Rationale:	Although there are some post-marketing data regarding the use of brentuximab vedotin in pregnant women, studies in animals have shown reproductive toxicity. Despite evidence from nonclinical studies of a possible risk to the developing foetus, the potential for lifesaving therapy to a pregnant or breastfeeding female may outweigh the risk of harm to the foetus. A decision regarding treatment should be based on a discussion between the patient and her physician regarding the potential benefits and risks of therapy (SmPC Section 4.6, Fertility, pregnancy and lactation). A decision should be made whether to discontinue breastfeeding or

[redacted]

9. Women who are pregnant and/or breastfeeding	
	to discontinue/abstain from this therapy, taking into account a potential risk of breastfeeding for the child and the benefit of therapy for the woman.

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

Limitations:

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

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

Table SIV.3 Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Paediatric	Five (3%) patients between 12 and 18 years of age were enrolled in the Pivotal phase 2 studies (SG035-0003 and SG035-0004). In C25002 study, 36 paediatric patients (age range 7 -18 years) with relapsed or refractory sALCL or classical HL were enrolled and received BV monotherapy. In C25004 study, 59 paediatric patients (age 6-17 years) with advanced stage newly diagnosed Hodgkin lymphoma were enrolled for the combination treatment of BV with AVD.
Elderly	Fifty-three patients (or 11%) >=65 years old were part of monotherapy studies (SG035-0003, SG035-0004, SGN35-005, SGN35-006 Part A, C25001 and C25007) One Hundred twenty-eight patients (or 15%) >=65 years old were part of combination studies (C25003 and SGN35-014).
Pregnant women	Not included in the clinical development program.
Breastfeeding women	
Patients with a disease severity different from inclusion criteria in clinical trials	Patients in the clinical trial program were considered to be generally representative of patients with relapsed or refractory HL or sALCL. The effect of brentuximab vedotin on patients with disease severity different from that studied in clinical trials is not known.

[redacted]

Type of special population	Exposure
Population with relevant different ethnic origin	Patients were not excluded from the clinical development based on ethnic origin. No clinical trials were planned to investigate the potential impact of different ethnic origins on the safety and/or efficacy of brentuximab vedotin. In the Pivotal phase 2 studies, the predominant race was white (137/160). Non-Caucasians represented approximately 15%. Twenty Japanese patients were part of the phase 1/2, dose-finding, pharmacokinetic (PK) bridging study (clinical study TB-BC010088) to identify interracial differences in the pharmacokinetics of ADCETRIS ADC or MMAE.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.

Part II: Module SV - Post-authorisation experience

SV.1. Post-authorisation exposure

SV.1.1. Method used to calculate exposure

For brentuximab vedotin, patient exposure to commercial product was estimated based on the following calculations:

The total number of vials shipped at the data cut-off date (as noted above) was divided by an average dose of 3 vials to derive the total number of doses shipped. The dosing cycle and continuation rate were both based on the duration of product availability. In this report, the dosing cycle is considered as 6 cycles/patient and the continuation rate was assumed to be 80%. To convert the total number of cycles administered over the entire period to unique patients treated, it was assumed that 20% of patients discontinued brentuximab vedotin therapy after any individual dose, so 80% would be a conservative estimate. The number of patients exposed was therefore obtained by dividing the number of cycles by 6 and multiplying by 0.80.

In the [redacted] and [redacted], the estimate of post-marketing exposure takes consideration of the Real-World data from the [redacted] claims database (from the vendor Symphony Health), using the following dynamic method:

> Patient Exposure Estimate (by indication) = Actual New Patient count (by indication, derived from the [redacted] claims database) x Projection Multiplier
>
> Projection Multiplier = Actual vials sales (finance data)/Actual vials sales (captured within the claims database)

SV.1.2. Exposure

Globally, the estimated cumulative patient exposure from marketing experience since the first approval of brentuximab vedotin is estimated to be approximately 144,112patients through 18-February-2024. [redacted]

[redacted]

[redacted]

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

Potential for misuse for illegal purposes

The pharmacological properties of brentuximab vedotin, along with its approved indications and the distribution of the product only for IV administration by a healthcare professional, minimise the potential for illegal use or misuse.

Part II: Module SVII - Identified and potential risks

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

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

Progressive multifocal leukoencephalopathy (PML), pulmonary toxicity associated with combination use of bleomycin and brentuximab vedotin, Stevens-Johnson syndrome/toxic epidermal necrolysis (TEN), tumour lysis syndrome, gastrointestinal complications, reproductive toxicity and interactions with drugs modifying CYP3A4 activity are known risks that require no further characterisation and are followed up via routine pharmacovigilance (PV).

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

Important Identified Risks	Risk-benefit impact
1. Peripheral neuropathy (sensory and motor)	Peripheral neuropathy (sensory and motor) was frequently observed in the brentuximab vedotin clinical development program. The majority of neuropathy events reported have been Grade 1 to 2 in severity. The neuropathy was generally reversible by dose delay, dose reduction, or discontinuation. The median time from onset to resolution or improvement of PN symptoms was 16.1 weeks. SmPC Section 4.4, Special warnings and precautions for use, advises that patients should be monitored for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paraesthesia, discomfort, a burning sensation, neuropathic pain, or weakness. Patients experiencing new or worsening PN Grade 2 or Grade 3 in severity may require a dose delay followed by a dose reduction of brentuximab vedotin to 1.2 mg/kg; it is recommended that patients with Grade 4 PN discontinue brentuximab vedotin treatment (SmPC Section 4.2, Posology and method of administration).
2. Myelosuppression (including Neutropenia, Febrile neutropenia, Thrombocytopenia and Anaemia)	Myelosuppression, including neutropenia, febrile neutropenia, thrombocytopenia and anaemia, was observed in the brentuximab vedotin clinical studies. Microscopic effects in bone marrow correlated with anaemia and leukopenia (primarily neutropenia) and thrombocytopenia in repeat-dose toxicology studies in monkeys and rats dosed with brentuximab vedotin[redacted]. These effects were reversible upon cessation of dosing. Patients likely to develop myelosuppression following exposure to brentuximab vedotin cannot be identified. Grade 3 or 4 prolonged (≥1 week) myelosuppression can occur with brentuximab vedotin. Patients should be monitored with complete blood counts prior to administration of each dose (SmPC Section 4.4, Special warnings and precautions for use). Per SmPC Section 4.2, Posology and method of administration, in monotherapy

[redacted]

Important Identified Risks	Risk-benefit impact
	setting brentuximab vedotin should be held for Grade 3 or Grade 4 neutropenia until the values return to baseline or ≤Grade 2 in severity. Growth factor support (G-CSF or GM-CSF) should be considered in subsequent cycles for patients who develop Grade 3 or Grade 4 neutropenia. In combination therapy, primary prophylaxis with G-CSF is recommended for all patients beginning with the first dose. Patients should be monitored closely for fever and managed according to best medical practice if febrile neutropenia develops. In combination therapy with brentuximab vedotin, primary prophylaxis with G-CSF is recommended for all adult patients beginning with the first dose (SmPC Section 4.4, Warnings and precautions for use). Early institution of broad-spectrum antibiotic treatment reduces mortality in patients with febrile neutropenia[redacted].
3. Infections (including bacteraemia, sepsis, septic shock and opportunistic infections)	Infections (including bacteraemia, sepsis, septic shock and opportunistic infections) were observed in the brentuximab vedotin clinical studies. The majority of infections reported in patients treated with brentuximab vedotin have been non-serious. Patients likely to develop infections following exposure to brentuximab vedotin cannot be identified. Serious infection such as pneumonia, staphylococcal bacteraemia, sepsis/septic shock (including fatal outcomes), herpes zoster, Pneumocystis jirovecii pneumonia and oral candidiasis have been reported in patients treated with brentuximab vedotin. Patients should be carefully monitored during treatment for the emergence of possible serious infection and opportunistic infections (SmPC Section 4.4, Special warnings and precautions for use; SmPC Section 4.8, Undesirable effects). However, complications of infections can be minimised by vigilance for early signs/symptoms of infection, serum testing and use of antibiotic prophylaxis as per current practice guidelines and prompt treatment with anti-infective agent(s).
4. Infusion-related reactions	Brentuximab vedotin is administered via IV infusion. Infusion of proteins can result in hypersensitivity reactions that may be fatal if not rapidly and appropriately managed. Infusion-related reactions (IRRs) occur very commonly in patients treated with brentuximab vedotin. However, the majority of events have been non-serious. Patients who develop IRRs may experience a range of symptoms, ranging from mild

[redacted]

Important Identified Risks	Risk-benefit impact
	discomfort (such as itching, nausea, or chills) to anaphylaxis requiring immediate medical therapy. Patients should be carefully monitored during and after infusion. If anaphylaxis occurs, administration of brentuximab vedotin should be immediately and permanently discontinued and appropriate medical therapy should be administered. If an IRR occurs, the infusion should be interrupted, and appropriate medical management instituted. The infusion may be restarted at a slower rate after symptom resolution. Patients who have experienced a prior IRR should be premedicated for subsequent infusions. Premedication may include paracetamol, an antihistamine, and a corticosteroid. IRRs are more frequent and more severe in patients with antibodies to brentuximab vedotin.
5. Hyperglycaemia	Hyperglycaemia was observed in the brentuximab vedotin clinical development program. The majority of hyperglycaemia events reported in patients treated with brentuximab vedotin have been non-serious. In general, hyperglycaemia developed early during treatment with brentuximab vedotin (i.e., usually after 1 or 2 doses). All patients who developed new onset hyperglycaemia or diabetes had an elevated body mass index (BMI) at enrolment, and in several instances, the patients had elevated glucose values before initiating treatment with brentuximab vedotin. In all patients with new onset hyperglycaemia, glucose values were generally well controlled using conventional doses of insulin or oral hypoglycaemic agents.

Important Potential Risks	Risk-benefit impact
1. Severe hepatotoxicity	The liver was identified as a target organ in single and repeat-dose toxicity studies in animals. Cases of severe hepatotoxicity have been reported in patients receiving brentuximab vedotin. The majority of hepatic AEs have been reported as Grade 1-2 in intensity. Increased liver enzymes (MedDRA Investigations system organ class [SOC]) have constituted the majority of hepatic AEs. Most events have been reported as improved, recovered, or resolved, and no action was taken in response to the vast majority of events. Liver function should be tested before initiating treatment and routinely monitored in patients receiving brentuximab vedotin (SmPC Section 4.4,

[redacted]

Important Potential Risks	Risk-benefit impact
	Special warnings and precautions for use). Hepatobiliary disorders (aspartate aminotransferase [AST] /alanine aminotransferase [redacted] increased) are listed as adverse reactions in SmPC 4.8, Undesirable Effects. In the patient information leaflet (PIL), increased liver enzyme levels are listed as common side effects and patients are instructed to tell their physicians if they have trouble with their liver.
2. Pulmonary toxicity	Cases of pulmonary toxicity in patients receiving brentuximab vedotin without concomitant bleomycin have been reported. Cases include acute respiratory distress syndrome (ARDS), interstitial lung disease (ILD), and pneumonitis; some events were fatal. Based on available data, there is no clear evidence for a causal association between brentuximab vedotin and pulmonary toxicity in the context of co-morbidities and confounding conditions, as well as the baseline predisposition to pulmonary toxicity in the population being treated. Confounding factors include infection, other systemic disease (e.g., myocardial infarction), prior therapies, and pre-existing comorbid conditions. In the event of new or worsening pulmonary symptoms (e.g., cough, dyspnoea), a prompt diagnostic evaluation should be performed, and patients should be treated appropriately (SmPC Section 4.4, Special warnings and precautions for use).

Missing Information	Risk-benefit impact
1. Long term safety	Ongoing clinical trials and maintenance studies aim to provide additional information about the safety with long-term use of the product. There is no evidence to suggest a different safety profile with long-term use.

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

Not applicable.

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

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

[redacted]

Important Identified Risk: Peripheral Neuropathy (Sensory and Motor) (MedDRA preferred terms: Burning sensation, Demyelinating polyneuropathy, Gait disturbance, Hypoaesthesia, Muscular weakness, Nerve conduction studies abnormal, Neuralgia, Neuropathy peripheral, Paraesthesia, Peripheral motor neuropathy, Peripheral sensory neuropathy and Polyneuropathy)	
Potential mechanisms:	Peripheral neuropathy is a relatively common dose-limiting toxicity of anti-tubulin agents. The most commonly proposed mechanism is breakdown of microtubules in axons, compromising axoplasmic flow and leading to neurite injury[redacted].
Evidence source(s) and strength of evidence:	Nonclinical study data; adverse event reports from phase 1, 2, and 3 clinical trials; and spontaneous adverse event reports from the post-marketing setting. Labels of other anti-tubulin agents.
Characterisation of the risk:	In the Overall Clinical Study Population (n=3,615) as of DLP of the RMP (18-February-2024), a cumulative search of the clinical trial database found that PN occurred in 1,810 subjects (50%). Most subjects (1,562; 43%) experienced PN events ≤Grade 2. Thirty-nine subjects (1%) experienced treatment-emergent SAEs. No events with a fatal outcome have been reported in this population to date. Results from a search (MedDRA SSQ terms) conducted from other sources outside of the Overall Clinical Study Population for the identified risk of peripheral neuropathy revealed a total of 3,484 cumulative cases of PN (sensory and motor) involving 3,798 events. Of all reported events, 1,097 (28.86%) were considered stabilized, improved, recovered, resolved, recovered/resolved, recovered/resolved with sequel or recovering/resolving at the time of DLP.
Risk factors and risk groups:	Prior exposure to neurotoxic chemotherapy regimens with subclinical nerve injury; history of diabetes or alcohol use; hypothyroidism. Among lymphoma patients, disease-specific risk factors include paraneoplastic, vasculitic, or paraproteinemic neuropathies.
Preventability:	Patients (without known risk factors) likely to develop PN following exposure to BV cannot be identified. Patients should be monitored for symptoms of neuropathy (EU SmPC Section 4.4 "Special warnings and precautions for use"), such as hypoesthesia, hyperesthesia, paraesthesia, discomfort, a burning sensation, neuropathic pain, or weakness. There are no drugs proven to be effective for prophylaxis of chemotherapy-induced neuropathy. In general, brentuximab vedotin-induced PN is typically an effect

[redacted]

Important Identified Risk: Peripheral Neuropathy (Sensory and Motor) (MedDRA preferred terms: Burning sensation, Demyelinating polyneuropathy, Gait disturbance, Hypoaesthesia, Muscular weakness, Nerve conduction studies abnormal, Neuralgia, Neuropathy peripheral, Paraesthesia, Peripheral motor neuropathy, Peripheral sensory neuropathy and Polyneuropathy)	
	of cumulative exposure to this medicinal product. It is generally reversible and should be managed by dose delays and adjustment. EU SmPC Section 4.2 advises that for Grade 2 or Grade 3 PN, BV should be withheld until neuropathy resolves to ≤Grade 1 or baseline and then the dose reduced to 1.2 mg/kg. For patients with Grade 4 neuropathy, treatment with BV should be discontinued.
Impact on the risk-benefit balance of the product:	Available information regarding this risk has not caused it to impact the overall positive benefit-risk ratio. More data is being collected regarding this risk and any potential impact to the benefit-risk ratio will continue to be evaluated.
Public health impact:	Peripheral neuropathy occurs very commonly in patients treated with BV; however, the majority of events have been non-serious. Therefore, the public health impact is not considered to be high.

Overall Clinical Study Population data include active and control arm cohorts.
Number of Events: 1) Events having the same Preferred Term and overlapping start/stop dates were counted as 1 event; 2) Events having the same Preferred Term but not overlapping start/stop dates were counted as separate events.
(a) Unresolved Events: Includes events with outcome of Unknown, Not Recovered/Not Resolved, or Recovering/Resolving
(b) Incidence Density: Number of Events/Total Person Time in Years. Days for Person Time = (End of study date – first dose date of SGN-35 +1). For ongoing studies, End of Study Date=date of data cut-off.
(c) A subject is counted only once. if a subject has more than one events, then the one with highest grade is counted.
(d) Person Years is defined as (End of Treatment date - first dose date + 1)/365.25 For patients with End of Treatment date missing, impute the missing date as the earlier date of last dose date + 30 days or date of death. For ongoing studies, End of study Date = the date of data cut-off.

Important Identified Risk: Myelosuppression (including neutropenia, febrile neutropenia, thrombocytopenia and anaemia) (MedDRA preferred terms: Anaemia, Febrile neutropenia, Haematocrit decreased, Haemoglobin decreased, Neutropenia, Neutrophil count decreased, Platelet count decreased, Red blood cell count decreased, and Thrombocytopenia)	
Potential mechanisms:	Microscopic effects in bone marrow correlated with anaemia and leukopenia (primarily neutropenia) and thrombocytopenia in repeat-dose toxicology studies in monkeys and rats dosed with brentuximab vedotin[redacted]. These effects were reversible upon cessation of dosing.
Evidence source(s) and strength of evidence:	Nonclinical study data; adverse event reports from phase 1, 2, and 3 clinical trials; and spontaneous

[redacted]

Important Identified Risk: Myelosuppression (including neutropenia, febrile neutropenia, thrombocytopenia and anaemia) (MedDRA preferred terms: Anaemia, Febrile neutropenia, Haematocrit decreased, Haemoglobin decreased, Neutropenia, Neutrophil count decreased, Platelet count decreased, Red blood cell count decreased, and Thrombocytopenia)	
	adverse event reports from the post-marketing setting.
Characterisation of the risk:	Myelosuppression, including neutropenia, febrile neutropenia, thrombocytopenia and anemia, were observed in the clinical studies. In the Overall Clinical Study Population (n=3,615) as of DLP of the RMP (18-February-2024), 46% of patients (n=1,647) experienced a myelosuppression AE. A total of 1,360 (38%) reported Grade 3 or 4 events, however only 308 subjects (9%) reported a treatment-emergent SAE. Unresolved events were reported in 491 subjects (14%). Results from a search (MedDRA SSQ) conducted from other sources outside of the Overall Clinical Study Population for the identified risk of myelosuppression revealed 3,164 cumulative cases involving 4,055 events.
Risk factors and risk groups:	Prior ASCT, chemotherapy, underlying malignancy. Patients with neutropenia, decreased white blood cell (WBC) and/or platelet count, haemoglobin, haematocrit, or red blood cell counts at baseline. The risk of febrile neutropenia is increased for patients with lower absolute neutrophil counts. The risk of febrile neutropenia in oncology patients receiving chemotherapy increases with duration of neutropenia and with degree of mucosal damage [redacted]. Thus, the incidence is often higher in patients receiving multiagent chemotherapy[redacted], as the cumulative toxicities of multiple chemotherapeutics can increase both duration of neutropenia and mucosal damage. Other risk factors that may increase the likelihood of developing febrile neutropenia include advanced stage of underlying malignancy, older age, high body surface area, poor performance status, and poor nutritional status [redacted].
Preventability:	Patients likely to develop myelosuppression following exposure to brentuximab vedotin cannot be identified. Grade 3 or 4 prolonged (≥1 week) myelosuppression can occur with brentuximab vedotin. Patients should be monitored with complete blood counts prior to administration of each dose (EU SmPC Section 4.4 "Special warnings and precautions for use"). Per EU SmPC Section 4.2 "Posology and method of administration," brentuximab vedotin

[redacted]

Important Identified Risk: Myelosuppression (including neutropenia, febrile neutropenia, thrombocytopenia and anaemia) (MedDRA preferred terms: Anaemia, Febrile neutropenia, Haematocrit decreased, Haemoglobin decreased, Neutropenia, Neutrophil count decreased, Platelet count decreased, Red blood cell count decreased, and Thrombocytopenia)	
	should be held for Grade 3 or Grade 4 neutropenia until the values return to baseline or ≤Grade 2 in severity. Growth factor support (G-CSF or GM-CSF) should be considered in subsequent cycles for patients who develop Grade 3 or Grade 4 neutropenia. Patients should be monitored closely for fever and managed according to best medical practice if febrile neutropenia develops (EU SmPC Section 4.4 "Warnings and precautions for use"). Early institution of broad-spectrum antibiotic treatment reduces mortality in patients with febrile neutropenia[redacted].
Impact on the risk-benefit balance of the product:	Available information regarding this risk has not caused it to impact the overall positive benefit-risk ratio. More data is being collected regarding this risk and any potential impact to the benefit-risk ratio will continue to be evaluated.
Public health impact:	Neutropenia occurs very commonly in patients treated with brentuximab vedotin; however, the majority of events have been non-serious and completely resolved. Therefore, the public health impact is not considered to be high.

Overall Clinical Study Population data include active and control arm cohorts.
Number of Events: 1) Events having the same Preferred Term and overlapping start/stop dates were counted as 1 event; 2) Events having the same Preferred Term but not overlapping start/stop dates were counted as separate events.
(a) Unresolved Events: Includes events with outcome of Unknown, Not Recovered/Not Resolved, or Recovering/Resolving
(b) Incidence Density: Number of Events/Total Person Time in Years. Days for Person Time = (End of study date – first dose date of SGN-35 +1). For ongoing studies, End of Study Date=date of data cut-off.
(c) A subject is counted only once. if a subject has more than one events, then the one with highest grade is counted.
(d) Person Years is defined as (End of Treatment date - first dose date + 1)/365.25 For patients with End of Treatment date missing, impute the missing date as the earlier date of last dose date + 30 days or date of death. For ongoing studies, End of study Date = the date of data cut-off.

[redacted]

Important Identified Risk: Infections (including bacteraemia, sepsis, septic shock and opportunistic infections)	
(MedDRA preferred terms: Aspergillus infection, Bacteremia, Bronchitis, Bronchopulmonary aspergillosis, Candida infection, Cellulitis, Cystitis, Cytomegalovirus viraemia, Cytomegalovirus infection, Ear infection, Endocarditis staphylococcal, Folliculitis, Fungal infection, Fungal skin infection, Groin abscess, H1N1 influenza, Herpes simplex, Herpes virus infection, Herpes zoster, Herpes zoster infection neurological, Influenza, Klebsiella bacteremia, Nasopharyngitis, Oesophageal candidiasis, Opportunistic infection, Oral candidiasis, Oral herpes, Pneumocystis jirovecii pneumonia, pneumonia, Pyelonephritis, Rhinitis, Sepsis, Septic shock, Sinusitis, Soft tissue infection, Staphylococcal bacteremia, Superinfection bacterial, Upper respiratory tract infection, Urinary tract infection, Urinary tract infection staphylococcal, Viral upper respiratory tract infection)	
Potential mechanisms:	Brentuximab vedotin recognises the CD30 antigen on tumour cells and normal activated T-cells. In nonclinical toxicology studies, neutropenia, hypocellularity of the bone marrow and lymphoid depletion of the thymus were observed in rats and monkeys. It is possible that binding of brentuximab vedotin to normal CD30 positive T cells could render these cells ineffective thus leading to alterations in immune function with a potential for a higher risk of infection.
Evidence source(s) and strength of evidence:	Nonclinical study data; adverse event reports from phase 1, 2, and 3 clinical trials; and spontaneous adverse event reports from the post-marketing setting.
Characterisation of the risk:	In the Overall Clinical Study Population (n=3,615) as of DLP of the RMP (18-February-2024), infection occurred in 1,291 subjects (36%); 965 subjects (27%) experienced Grade 1 or 2 events and 306 subjects (8%) experienced Grade 3 or 4 events. Treatment emergent SAEs were reported in 303 subjects (8%), and 22 (<1%) patients died. Results from a search (MedDRA SSQ) conducted from other sources outside of the Overall Clinical Study Population for the identified risk of infections including bacteremia/sepsis/septic shock and opportunistic infections revealed 1,735 cases of infection cumulatively involving 1,947 events. Of these events, 277 (14.23%)were fatal. Approximately half of the reported events (811; 41.65%) were stabilized, improved, recovered with treatment, recovered/resolved, recovered/resolved with sequel, recovering/resolving, resolved and stabilized as of the DLP.
Risk factors and risk groups:	Patients with alterations in immune function, including patients with pre-existing neutropenia or leukopenia, or secondary to prior ASCT or chemotherapy.

[redacted]

Important Identified Risk: Infections (including bacteraemia, sepsis, septic shock and opportunistic infections)	
(MedDRA preferred terms: Aspergillus infection, Bacteremia, Bronchitis, Bronchopulmonary aspergillosis, Candida infection, Cellulitis, Cystitis, Cytomegalovirus viraemia, Cytomegalovirus infection, Ear infection, Endocarditis staphylococcal, Folliculitis, Fungal infection, Fungal skin infection, Groin abscess, H1N1 influenza, Herpes simplex, Herpes virus infection, Herpes zoster, Herpes zoster infection neurological, Influenza, Klebsiella bacteremia, Nasopharyngitis, Oesophageal candidiasis, Opportunistic infection, Oral candidiasis, Oral herpes, Pneumocystis jirovecii pneumonia, pneumonia, Pyelonephritis, Rhinitis, Sepsis, Septic shock, Sinusitis, Soft tissue infection, Staphylococcal bacteremia, Superinfection bacterial, Upper respiratory tract infection, Urinary tract infection, Urinary tract infection staphylococcal, Viral upper respiratory tract infection)	
Preventability:	Patients likely to develop infections following exposure to brentuximab vedotin cannot be identified. Serious infection such as pneumonia, staphylococcal bacteraemia, sepsis/septic shock (including fatal outcomes), herpes zoster, *Pneumocystis jirovecii* pneumonia and oral candidiasis have been reported in patients treated with brentuximab vedotin. Patients should be carefully monitored during treatment for the emergence of possible serious and opportunistic infections (EU SmPC Section 4.4 "Special warnings and precautions for use;" EU SmPC Section 4.8 "Undesirable effects"). However, complications of infections can be minimised by vigilance for early signs/symptoms of infection, serum testing and use of antibiotic prophylaxis as per current practice guidelines and prompt treatment with anti-infective agent(s).
Impact on the risk-benefit balance of the product:	Available information regarding this risk has not caused it to impact the overall positive benefit-risk ratio. More data is being collected regarding this risk and any potential impact to the benefit-risk ratio will continue to be evaluated.
Public health impact:	The majority of infections reported in patients treated with brentuximab vedotin have been non-serious. Therefore, the public health impact is not considered to be high.

Overall Clinical Study Population data include active and control arm cohorts.
Number of Events: 1) Events having the same Preferred Term and overlapping start/stop dates were counted as 1 event; 2) Events having the same Preferred Term but not overlapping start/stop dates were counted as separate events.
(a) Unresolved Events: Includes events with outcome of Unknown, Not Recovered/Not Resolved, or Recovering/Resolving
(b) Incidence Density: Number of Events/Total Person Time in Years. Days for Person Time = (End of study date – first dose date of SGN-35 +1). For ongoing studies, End of Study Date=date of data cut-off.
(c) A subject is counted only once. if a subject has more than one events, then the one with highest grade is counted.
(d) Person Years is defined as (End of Treatment date - first dose date + 1)/365.25 For patients with End of Treatment date missing, impute the missing date as the earlier date of last dose date + 30 days or date of death. For ongoing studies, End of study Date = the date of data cut-off.

[redacted]

Important Identified Risk: Infusion-Related Reactions (IRRs) (MedDRA preferred terms: Anaphylactic reaction, Anaphylactic shock, Angioedema, Back pain, Bronchospasm, Chills, Cough, Diarrhoea, Dizziness, Dyspepsia, Dysphagia, Dyspnoea, Erythema, Flushing, Infusion related reaction, Lip swelling, Swelling, Nausea, Oropharyngeal pain, Pharyngeal oedema, Pruritus, Pyrexia, Rash, Swelling face, Throat tightness, Urticaria and Vomiting)	
Potential mechanisms:	Infusion of proteins and chimeric antibody can result in hypersensitivity reactions and IRRs. Hypersensitivity reactions observed with brentuximab vedotin may also be due to the polysorbate 80 excipient, which in animal models has been shown to induce histamine release and cause hypersensitivity reactions. Polysorbate 80 has also been shown to be a causative agent of hypersensitivity reactions in humans.
Evidence source(s) and strength of evidence:	Nonclinical study data; adverse event reports from phase 1, 2, and 3 clinical trials; and spontaneous adverse event reports from the post-marketing setting.
Characterisation of the risk:	In the Overall Clinical Study Population (n=3,615) as of DLP of the RMP (18-February-2024), most subjects (2,748 [76%]) experienced an IRR AE regardless of temporal relationship or causality. Most of these subjects (2,354 [65%]) had an IRR AE of Grade 1 or 2. Treatment emergent SAEs were reported in 279 subjects (8%). There were no deaths or hospitalizations as a result of IRR AEs. Results from a search (MedDRA SSQ) conducted from other sources outside of the Overall Clinical Study Population for the identified risk of IRR (based on reported terms only and not considering the temporal relationship with the infusion) revealed 3,897 cumulative cases involving 5,586 events of IRR.
Risk factors and risk groups:	Patients with allergy to brentuximab vedotin or excipients.
Preventability:	Brentuximab vedotin is administered via IV infusion. Infusion of proteins can result in hypersensitivity reactions that may be fatal if not rapidly and appropriately managed. Immediate and delayed IRRs, as well as anaphylaxis, have been reported. Patients should be carefully monitored during and after infusion. If anaphylaxis occurs, administration of BV should be immediately, and permanently discontinued and appropriate medical therapy should be administered. If an IRR occurs, the infusion should be interrupted, and appropriate medical management instituted. The infusion may be restarted at a slower rate after symptom resolution. Patients who have

Important Identified Risk: Infusion-Related Reactions (IRRs) (MedDRA preferred terms: Anaphylactic reaction, Anaphylactic shock, Angioedema, Back pain, Bronchospasm, Chills, Cough, Diarrhoea, Dizziness, Dyspepsia, Dysphagia, Dyspnoea, Erythema, Flushing, Infusion related reaction, Lip swelling, Swelling, Nausea, Oropharyngeal pain, Pharyngeal oedema, Pruritus, Pyrexia, Rash, Swelling face, Throat tightness, Urticaria and Vomiting)	
	experienced a prior IRR should be premedicated for subsequent infusions. Pre-medication may include paracetamol, an antihistamine, and a corticosteroid. IRRs are more frequent and more severe in patients with antibodies to BV (EU SmPC Section 4.4 "Special warnings and precautions for use").
Impact on the risk-benefit balance of the product:	Available information regarding this risk has not caused it to impact the overall positive benefit-risk ratio. More data is being collected regarding this risk and any potential impact to the benefit-risk ratio will continue to be evaluated.
Public health impact:	IRRs occur very commonly in patients treated with brentuximab vedotin. However, the majority of events have been non-serious; therefore, the public health impact is not considered to be high.

Overall Clinical Study Population data include active and control arm cohorts.
Number of Events: 1) Events having the same Preferred Term and overlapping start/stop dates were counted as 1 event; 2) Events having the same Preferred Term but not overlapping start/stop dates were counted as separate events.
(a) Unresolved Events: Includes events with outcome of Unknown, Not Recovered/Not Resolved, or Recovering/Resolving
(b) Incidence Density: Number of Events/Total Person Time in Years. Days for Person Time = (End of study date – first dose date of SGN-35 +1). For ongoing studies, End of Study Date=date of data cut-off.
(c) A subject is counted only once. if a subject has more than one events, then the one with highest grade is counted.
(d) Person Years is defined as (End of Treatment date - first dose date + 1)/365.25 For patients with End of Treatment date missing, impute the missing date as the earlier date of last dose date + 30 days or date of death. For ongoing studies, End of study Date = the date of data cut-off.

Important Identified risk: Hyperglycaemia (MedDRA preferred terms: Blood glucose increased, Diabetes mellitus, Diabetes mellitus inadequate control, Hyperglycaemia, Increased insulin requirement, Insulin resistant diabetes, Insulin-requiring type 2 diabetes mellitus, Type 2 diabetes mellitus)	
Potential mechanisms:	Exact mechanism is not known.
Evidence source(s) and strength of evidence:	Nonclinical study data; adverse event reports from phase 1, 2, and 3 clinical trials; and spontaneous adverse event reports from the post-marketing setting.
Characterisation of the risk:	In the Overall Clinical Study Population (n=3,615) as of DLP of the RMP (18-February-2024), 161 (4%) subjects developed a treatment emergent event of hyperglycemia. Only 63 subjects (2%) developed

[redacted]

Important Identified risk: Hyperglycaemia (MedDRA preferred terms: Blood glucose increased, Diabetes mellitus, Diabetes mellitus inadequate control, Hyperglycaemia, Increased insulin requirement, Insulin resistant diabetes, Insulin-requiring type 2 diabetes mellitus, Type 2 diabetes mellitus)	
	Grade 3-4 events of hyperglycemia and 16 subjects (<1%) reported a treatment emergent SAE. No subjects died due to hyperglycemia. Results from a search (MedDRA SSQ) conducted from other sources outside of the Overall Clinical Study Population for the identified risk of hyperglycemia revealed 176 cumulative cases involving 183 events which met the search criteria for hyperglycemia
Risk factors and risk groups:	Potential factors that may be associated with an increased risk of developing hyperglycemia following the administration of brentuximab vedotin include a fasting glucose above the upper limit of normal (ULN), pre-existing diabetes mellitus, or concurrent steroid use.
Preventability:	Patients likely to develop hyperglycemia following exposure to brentuximab vedotin cannot be identified. Patients with known diabetes mellitus, pre-existing hyperglycemia, or who are being treated with concomitant steroid medications may be at increased risk of developing hyperglycemia following exposure to brentuximab vedotin. Hyperglycemia has been reported during clinical trials in patients with an elevated BMI with or without a history of diabetes mellitus. However, any patient who experiences an event of hyperglycemia should have their serum glucose closely monitored. Antidiabetic treatment should be administered as appropriate (EU SmPC Section 4.4 "Special warnings and precautions for use").
Impact on the risk-benefit balance of the product:	Available information regarding this risk has not caused it to impact the overall positive benefit-risk ratio. More data is being collected regarding this risk and any potential impact to the benefit-risk ratio will continue to be evaluated.
Public health impact:	The majority of hyperglycaemia events reported in patients treated with brentuximab vedotin have been non-serious; therefore, the public health impact is not considered to be high.

Overall Clinical Study Population data include active and control arm cohorts.
Number of Events: 1) Events having the same Preferred Term and overlapping start/stop dates were counted as 1 event; 2) Events having the same Preferred Term but not overlapping start/stop dates were counted as separate events.
(a) Unresolved Events: Includes events with outcome of Unknown, Not Recovered/Not Resolved, or Recovering/Resolving

[redacted]

(b) Incidence Density: Number of Events/Total Person Time in Years. Days for Person Time = (End of study date – first dose date of SGN-35 +1). For ongoing studies, End of Study Date=date of data cut-off.
(c) A subject is counted only once. if a subject has more than one events, then the one with highest grade is counted.
(d) Person Years is defined as (End of Treatment date - first dose date + 1)/365.25 For patients with End of Treatment date missing, impute the missing date as the earlier date of last dose date + 30 days or date of death. For ongoing studies, End of study Date = the date of data cut-off.

Important Potential Risk: Severe hepatotoxicity (MedDRA preferred terms: Cholestasis and jaundice of hepatic origin SMQ Broad, Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions SMQ Broad, Hepatitis, non-infectious SMQ Broad, Liver related investigations, signs and symptoms [SMQ] Broad)	
Potential mechanisms:	In animals, minor dose-dependent liver toxicity was observed and was most pronounced at the high-dose levels of brentuximab vedotin. Reversibility was observed. Significant alterations in liver function tests were not frequently observed in the clinical studies conducted with brentuximab vedotin.
Evidence source(s) and strength of evidence:	Nonclinical study data; adverse event reports from phase 1, 2, and 3 clinical trials; and spontaneous reports from the post-marketing setting.
Characterisation of the risk:	In the Overall Clinical Study Population (n=3,615) as of DLP of the RMP (18-February-2024), 29 subjects (<1%) reported a treatment emergent SAE consistent with severe hepatotoxicity. The incidence of TEAEs in all subjects was 486 subjects (13%) and 3 deaths (<1%) were reported as a result of hepatoxicity. Results from a search (MedDRA SMQs, broad [listed above]) conducted from other sources outside of the Overall Clinical Study Population for the potential risk of severe hepatotoxicity revealed 1,012 cases cumulatively involving 1,425 events.
Risk factors and risk groups:	Persons who consume high levels of alcohol are generally susceptible to drug toxicity because alcohol induces liver injury and cirrhotic changes that alter drug metabolism. Elderly persons are at increased risk of hepatic injury because of decreased clearance, drug-to drug interactions, reduced hepatic blood flow, variation in drug binding, and lower hepatic volume. Hepatic dysfunction may also arise from liver involvement by malignant lymphoma in a subgroup of patients. Prior or current treatments and medications administered to lymphoma patients may negatively impact the liver on a temporary or permanent basis. Genetic differences in the P-450 enzymes can result in abnormal reactions to drugs, including

Important Potential Risk: Severe hepatotoxicity (MedDRA preferred terms: Cholestasis and jaundice of hepatic origin SMQ Broad, Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions SMQ Broad, Hepatitis, non-infectious SMQ Broad, Liver related investigations, signs and symptoms [SMQ] Broad)	
	idiosyncratic reactions. In addition, poor diet, infections, and multiple hospitalizations are important contributing factors of drug-induced hepatotoxicity.
Preventability:	Liver function should be tested before initiating treatment and routinely monitored in patients receiving brentuximab vedotin (EU SmPC Section 4.4 "Special warnings and precautions for use"). Hepatobiliary disorders (AST/ALT increase) are listed as adverse reactions in EU SmPC section 4.8 "Undesirable Effects."
Impact on the risk-benefit balance of the product:	Available information regarding this risk has not caused it to impact the overall positive benefit-risk ratio. More data is being collected regarding this risk and any potential impact to the benefit-risk ratio will continue to be evaluated.
Public health impact:	The majority of hepatotoxicity events reported in patients treated with brentuximab vedotin have been non-serious, and the incidence of severe hepatotoxicity is uncommon; therefore, the public health impact is not considered to be high

Overall Clinical Study Population data include active and control arm cohorts.
Number of Events: 1) Events having the same Preferred Term and overlapping start/stop dates were counted as 1 event; 2) Events having the same Preferred Term but not overlapping start/stop dates were counted as separate events.
(a) Unresolved Events: Includes events with outcome of Unknown, Not Recovered/Not Resolved, or Recovering/Resolving
(b) Incidence Density: Number of Events/Total Person Time in Years. Days for Person Time = (End of study date – first dose date of SGN-35 +1). For ongoing studies, End of Study Date=date of data cut-off.
(c) A subject is counted only once. if a subject has more than one events, then the one with highest grade is counted.
(d) Person Years is defined as (End of Treatment date - first dose date + 1)/365.25 For patients with End of Treatment date missing, impute the missing date as the earlier date of last dose date + 30 days or date of death. For ongoing studies, End of study Date = the date of data cut-off.

Important Potential Risk: Pulmonary Toxicity (MedDRA preferred terms: Interstitial lung disease [SMQ] Broad)	
Potential mechanisms:	Exact mechanism with the drug is not known.
Evidence source(s) and strength of evidence:	Nonclinical study data; adverse event reports from phase 1, 2, and 3 clinical trials; and spontaneous reports from the post-marketing setting.
Characterisation of the risk:	Cases of pulmonary toxicity including acute respiratory distress syndrome (ARDS), ILD, and

[redacted]

Important Potential Risk: Pulmonary Toxicity (MedDRA preferred terms: Interstitial lung disease [SMQ] Broad)	
	pneumonitis, some with fatal outcomes, have been reported in patients receiving BV. In the Overall Clinical Study Population (n=3,615) as of DLP of the RMP (18-February-2024), 114 (3%) of patients experienced an AE from the ILD SMQ (broad). Grade 3 and 4 events have been observed in 47 (1%) of patients across this population. A total of 59 patients (2%) developed treatment-emergent SAE, and 9 (<1%) patients died. Results from a search (MedDRA Interstitial Lung disease [SMQ broad]) conducted from other sources outside of the Overall Clinical Study Population for the potential risk of pulmonary toxicity revealed 412 cases cumulatively involving 437 events consistent with pulmonary toxicity.
Risk factors and risk groups:	Exact risk factors with BV are not known. However, general risk factors for pulmonary toxicity include smoking history, underlying lung disease, radiation exposure, advanced age, and infectious complications. The identified risk of pulmonary toxicity associated with the combination of BV and bleomycin has been described earlier in this document.
Preventability:	Although a causal association with BV has not been established, the risk of pulmonary toxicity cannot be ruled out. In the event of new or worsening pulmonary symptoms (e.g., cough, dyspnea), a prompt diagnostic evaluation should be performed, and patients should be treated appropriately (EU SmPC Section 4.4 "Special warnings and precautions for use").
Impact on the risk-benefit balance of the product:	Available information regarding this risk has not caused it to impact the overall positive benefit-risk ratio. More data is being collected regarding this risk and any potential impact to the benefit-risk ratio will continue to be evaluated.
Public health impact:	Cases of pulmonary toxicity have been reported in patients treated with brentuximab vedotin; however, the public health impact is not considered to be high.

Overall Clinical Study Population data include active and control arm cohorts.
Number of Events: 1) Events having the same Preferred Term and overlapping start/stop dates were counted as 1 event; 2) Events having the same Preferred Term but not overlapping start/stop dates were counted as separate events.
(a) Unresolved Events: Includes events with outcome of Unknown, Not Recovered/Not Resolved, or Recovering/Resolving
(b) Incidence Density: Number of Events/Total Person Time in Years. Days for Person Time = (End of study date – first dose date of SGN-35 +1). For ongoing studies, End of Study Date=date of data cut-off.

[redacted]

(c) A subject is counted only once. if a subject has more than one events, then the one with highest grade is counted.
(d) Person Years is defined as (End of Treatment date - first dose date + 1)/365.25 For patients with End of Treatment date missing, impute the missing date as the earlier date of last dose date + 30 days or date of death. For ongoing studies, End of study Date = the date of data cut-off.

SVII.3.2. Presentation of the missing information

Long term safety	
Evidence source:	Population in need of further characterisation: Ongoing clinical trials and maintenance studies aim to provide additional information about the safety with long-term use of the product. There is no evidence to suggest a different safety profile with long-term use.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	1. Peripheral neuropathy (sensory and motor) 2. Myelosuppression (including Neutropenia, Febrile neutropenia, Thrombocytopenia and Anaemia) 3. Infections (including bacteraemia, sepsis, septic shock and opportunistic infections) 4. Infusion-related reactions 5. Hyperglycaemia
Important potential risks	1. Severe hepatotoxicity 2. Pulmonary toxicity
Missing information	1. Long term safety

[redacted]

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

III.1. Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

None.

III.2. Additional pharmacovigilance activities

None.

III.3. Summary Table of additional Pharmacovigilance activities

Table Part III.1: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

[redacted]

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

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Peripheral Neuropathy (Sensory and Motor)	**Routine risk communication:** SmPC Sections 4.2, 4.4 and 4.8 Package Leaflet section 2 and section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendations regarding monitoring patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paraesthesia, discomfort, burning sensation, neuropathic pain or weakness and the possibility of delaying or reducing the dose in patients who experience new or worsening neuropathy are included in SmPC Section 4.4 "Special warnings and precautions for use" and SmPC Section 4.2 "Posology and method of administration." **Other routine risk minimisation measures beyond the Product Information:** Legal Status: Brentuximab vedotin is available by prescription only and should be administered under the supervision of a physician experienced in the use of anticancer agents.
Myelosuppression (including neutropenia, febrile neutropenia, thrombocytopenia and anaemia)	**Routine risk communication:** SmPC Sections 4.2, 4.4 and 4.8 Package Leaflet section 2 and section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.2 "Posology and method of administration" and SmPC Section 4.4 "Special warnings and precautions for use" contain recommendations that patients should have a full blood count prior to administration of each dose of brentuximab vedotin and for close monitoring of patients who develop fever during treatment and for patients to be managed according to best medical practice if febrile neutropenia develops. Dose delays should be considered in patients who develop neutropenia and growth factor support (G-CSF or GM-CSF) should be considered in subsequent cycles for patients who develop Grade 3 or Grade 4 neutropenia in monotherapy with brentuximab vedotin. In combination therapy, primary prophylaxis with G-CSF is recommended for adult patients beginning with the first dose.

Safety concern	Routine risk minimisation activities
	Other routine risk minimisation measures beyond the Product Information: Legal Status: Brentuximab vedotin is available by prescription only and should be administered under the supervision of a physician experienced in the use of anticancer agents.
Infections (including bacteriemia, sepsis, septic shock and opportunistic infections)	**Routine risk communication:** SmPC Section 4.4 and 4.8 Package Leaflet section 2 and section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.4 "Special warnings and precautions for use" contain a recommendation that patients should be carefully monitored during treatment for the emergence of possible serious and opportunistic infections. **Other routine risk minimisation measures beyond the Product Information:** Legal Status: Brentuximab vedotin is available by prescription only and should be administered under the supervision of a physician experienced in the use of anticancer agents.
Infusion-Related Reactions (IRRs)	**Routine risk communication:** SmPC Section 4.4 and 4.8 Package Leaflet section 2 and section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk**: SmPC Section 4.4 "Special warnings and precautions for use" contains a warning about the possibility of patients developing immediate and delayed IRRs including anaphylactic reactions and recommend that administration of brentuximab vedotin should either be interrupted or immediately and permanently discontinued and appropriate medical therapy administered if an IRR or anaphylactic reaction occurs. The SmPC also recommends restarting the infusion at a slower rate after symptom resolution and pre-medicating patients who have experienced a prior IRR with medications such as paracetamol, an antihistamine, and a corticosteroid. **Other routine risk minimisation measures beyond the Product Information:** Legal Status: Brentuximab vedotin is available by prescription only and should be administered under the supervision of a physician experienced in the use of anticancer agents.
Hyperglycemia	**Routine risk communication:** SmPC Section 4.4 and 4.8 Package Leaflet section 2 and section 4

Safety concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.4 "Special warnings and precautions for use" contains a recommendation that any patient who experiences an event of hyperglycemia should have their blood glucose closely monitored and antidiabetic treatment should be administered as appropriate. **Other routine risk minimisation measures beyond the Product Information:** Legal Status: Brentuximab vedotin is available by prescription only and should be administered under the supervision of a physician experienced in the use of anticancer agents.
Severe hepatotoxicity	**Routine risk communication:** SmPC Section 4.4 and 4.8 Package Leaflet section 2 and section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.4 "Special warnings and precautions for use" contains a recommendation that patients receiving brentuximab vedotin therapy should have a liver function test before initiating treatment and routinely monitored during treatment with brentuximab vedotin. Patients who experience hepatotoxicity may require a dose delay, change in dose, or discontinuation of brentuximab vedotin. **Other routine risk minimisation measures beyond the Product Information:** Legal Status: Brentuximab vedotin is available by prescription only and should be administered under the supervision of a physician experienced in the use of anticancer agents.
Pulmonary Toxicity	**Routine risk communication:** SmPC Sections 4.3, 4.4, 4.5 and 4.8 Package Leaflet section 2 and section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.3 "Contraindications" prohibits the combined use of brentuximab vedotin and bleomycin as it causes pulmonary toxicity. SmPC. Section 4.4 "Special warnings and precautions for use" contains a recommendation that if new or worsening pulmonary symptoms are observed, a prompt diagnostic evaluation should be performed, and patients should be treated appropriately. Brentuximab vedotin therapy should be stopped during evaluation and until symptomatic improvement. **Other routine risk minimisation measures beyond the Product Information:** Legal Status: Brentuximab vedotin is available by prescription only and should be administered under the supervision of a physician experienced in the use of anticancer agents.

[redacted]

Safety concern	Routine risk minimisation activities
Long term Safety	**Routine risk communication** None **Routine risk minimisation activities recommending specific clinical measures to address the risk**: None **Other routine risk minimisation measures beyond the Product Information:** Legal Status: Brentuximab vedotin is available by prescription only and should be administered under the supervision of a physician experienced in the use of anticancer agents.

V.2. Additional Risk Minimisation Measures

Not applicable.

V.3. Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Peripheral Neuropathy (Sensory and Motor)	**Routine risk minimisation measures:** SmPC Section 4.8 SmPC sections 4.2 and 4.4 where there are recommendations regarding monitoring patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paraesthesia, discomfort, burning sensation, neuropathic pain or weakness) and the possibility of delaying or reducing the dose in patients who experience new or worsening neuropathy. Package Leaflet Section 2 and Section 4 Legal status **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Myelosuppression (including Neutropenia, Febrile neutropenia, Thrombocytopenia and Anaemia)	**Routine risk minimisation measures:** SmPC Section 4.8 SmPC Sections 4.2 and 4.4 where there are recommendations for patients to have a full blood count prior to administration of each dose of brentuximab vedotin and for close monitoring of patients	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

[redacted]

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	who develop neutropenia. If patients develop febrile neutropenia, they should be managed according to best medical practice. Dose delays should be considered in patients who develop neutropenia and growth factor support (G-CSF or GM-CSF) should be considered in subsequent cycles for patients who develop Grade 3 or Grade 4 neutropenia in monotherapy with brentuximab vedotin. In combination therapy for the frontline treatment of HL, primary prophylaxis with G-CSF is recommended for adult patients beginning with the first dose Package Leaflet Section 2 and Section 4 Legal status **Additional risk minimisation measures:** None	
Infections (including bacteriemia, sepsis, septic shock and opportunistic infections)	**Routine risk minimisation measures:** SmPC Section 4.8 SmPC Section 4.4 where there is a recommendation for patients to be carefully monitored during treatment for the emergence of possible serious and opportunistic infections. Package Leaflet Section 2 and Section 4 Legal status **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Infusion-Related Reactions (IRRs)	**Routine risk minimisation measures:** SmPC Section 4.8 SmPC Section 4.4 where there is information about the possibility of patients developing immediate and delayed IRRs including anaphylactic reactions and a recommendation that administration of brentuximab vedotin should either be interrupted or immediately and	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	permanently discontinued and appropriate medical therapy administered if an IRR or anaphylactic reaction occurs. The SmPC also recommends restarting the infusion at a slower rate after symptom resolution and pre-medicating patients who have experienced a prior IRR with pre-medications such as paracetamol, an antihistamine, and a corticosteroid. Package Leaflet Section 2 and Section 4 Legal status **Additional risk minimisation measures:** None	
Hyperglycemia	**Routine risk minimisation measures:** SmPC Section 4.8 SmPC Section 4.4 where there is a recommendation that any patient who experiences hyperglycemia should have their serum glucose closely monitored and antidiabetic treatment should be administered as appropriate. Package Leaflet Section 2 and Section 4 Legal status **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Severe hepatotoxicity	**Routine risk minimisation measures:** SmPC Section 4.8 SmPC Section 4.4 where there is a recommendation that patients receiving brentuximab vedotin therapy should have a liver function test before initiating treatment and routinely monitored during treatment with brentuximab vedotin. Patients who experience hepatotoxicity may require a dose delay, change in dose, or discontinuation of brentuximab vedotin. Package Leaflet Section 2 and Section 4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Legal status **Additional risk minimisation measures:** None	
Pulmonary toxicity	**Routine risk minimisation measures:** SmPC Sections 4.5 and 4.8 SmPC Section 4.3 prohibits the combined use of brentuximab vedotin and bleomycin as it causes pulmonary toxicity. SmPC Section 4.4 contain a recommendation that if new or worsening pulmonary symptoms are observed, a prompt diagnostic evaluation should be performed, and patients should be treated appropriately. Brentuximab vedotin therapy should be stopped during evaluation and until symptomatic improvement. Package Leaflet Sections 2 and Section 4 Legal status **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Long term safety	**Routine risk minimisation measures:** None Legal status **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Part VI: Summary of the risk management plan

Summary of risk management plan for ADCETRIS (brentuximab vedotin)

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

ADCETRIS's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how ADCETRIS should be used.

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

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

I. The medicine and what it is used for

ADCETRIS is indicated for the treatment of adult patients with previously untreated CD30+ Stage III or IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine (AVD), relapsed or refractory CD30+ HL following autologous stem cell transplant (ASCT), or following at least 2 prior therapies when ASCT or multiagent chemotherapy is not a treatment option; treatment of adult patients with CD30+ HL at increased risk of relapse or progression following ASCT; treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL), treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy, and other CD30-expressing peripheral T-cell lymphoma (PTCL) in combination with chemotherapy (see SmPC for the full indication).

ADCETRIS is also indicated in combination with cyclophosphamide, doxorubicin, and prednisone (CHP) for adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL). It contains brentuximab vedotin as the active substance and it is given by intravenous infusion.

ADCETRIS is indicated for adult patients with previously untreated CD30+ Stage IIB with risk factors, Stage III or Stage IV HL in combination with etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone (BrECADD).

Further information about the evaluation of ADCETRIS’s benefits can be found in the ADCETRIS’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002455/WC500135004.pdf

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

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

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

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

Together, these measures constitute routine risk minimisation measures.

[redacted]

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

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

II.A List of important risks and missing information

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

List of important risks and missing information	
Important identified risks	1. Peripheral neuropathy (sensory and motor) 2. Myelosuppression (including neutropenia, febrile neutropenia, thrombocytopenia and anaemia) 3. Infections (including Bacteriemia, Sepsis, Septic shock and Opportunistic infections) 4. Infusion-related reactions 5. Hyperglycaemia
Important potential risks	1. Severe hepatotoxicity 2. Pulmonary toxicity
Missing information	1. Long term safety

II.B Summary of important risks

Important identified risk: Peripheral neuropathy (sensory and motor)	
Evidence for linking the risk to the medicine	Nonclinical study data; adverse event reports from phase 1, 2, and 3 clinical trials; and spontaneous adverse event reports from the post-marketing setting.
Risk factors and risk groups	Prior exposure to neurotoxic chemotherapy regimens with subclinical nerve injury; history of diabetes or alcohol use; hypothyroidism. Among lymphoma patients, disease-specific risk factors include paraneoplastic, vasculitic, or paraproteinemic neuropathies.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.8 SmPC sections 4.2 and 4.4 where there are recommendations regarding monitoring patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paraesthesia, discomfort, burning sensation, neuropathic pain or weakness) and the possibility of delaying or reducing the dose in patients who experience new or

Important identified risk: Peripheral neuropathy (sensory and motor)	
	worsening neuropathy. Package Leaflet section 2 and section 4 Legal status **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk: Myelosuppression (including neutropenia, febrile neutropenia, thrombocytopenia and anaemia)	
Evidence for linking the risk to the medicine	Nonclinical study data; adverse event reports from phase 1, 2, and 3 clinical trials; and spontaneous adverse event reports from the post-marketing setting.
Risk factors and risk groups	Prior ASCT, chemotherapy, patients with neutropenia, decreased WBC and/or platelet count, haemoglobin, haematocrit, or red blood cell counts at baseline. The risk of febrile neutropenia is increased for patients with lower absolute neutrophil counts. The risk of febrile neutropenia in cancer patients receiving chemotherapy increases with duration of neutropenia and with degree of mucosal damage. Thus, the incidence is often higher in patients receiving multiagent chemotherapy as the cumulative toxicities of multiple chemotherapeutics can increase both duration of neutropenia and mucosal damage. Other risk factors that may increase the likelihood of developing febrile neutropenia include advanced stage of underlying malignancy, older age, high body surface area, poor performance status, and poor nutritional status.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.8 SmPC Sections 4.2 and 4.4 where there are recommendations for patients to have a full blood count prior to administration of each dose of brentuximab vedotin and for close monitoring of patients who develop fever. If patients develop febrile neutropenia, they should be managed according to best medical practice. Dose delays should be considered in patients who develop neutropenia and growth factor support (G-CSF or GM-CSF) should be considered in subsequent cycles for patients who develop Grade 3 or Grade 4 neutropenia in monotherapy with brentuximab vedotin. In combination therapy for the frontline treatment of HL, primary prophylaxis with G-CSF is recommended for adult patients beginning with the first dose. Package Leaflet section 2 and section 4 Legal status

[redacted]

Important identified risk: Myelosuppression (including neutropenia, febrile neutropenia, thrombocytopenia and anaemia)	
	Additional risk minimisation measures: None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk: Infections (including bacteriemia, sepsis, septic shock and opportunistic infections)	
Evidence for linking the risk to the medicine	Nonclinical study data; adverse event reports from phase 1, 2, and 3 clinical trials; and spontaneous adverse event reports from the post-marketing setting.
Risk factors and risk groups	Patients with alterations in immune function, including patients with pre-existing neutropenia or leukopenia, or secondary to prior ASCT or chemotherapy.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.8 SmPC Section 4.4 where there is a recommendation for patients to be carefully monitored during treatment for the emergence of possible serious and opportunistic infections. Package Leaflet section 2 and section 4 Legal status **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk: Infusion-related reactions	
Evidence for linking the risk to the medicine	Nonclinical study data; adverse event reports from phase 1, 2, and 3 clinical trials; and spontaneous adverse event reports from the post-marketing setting.
Risk factors and risk groups	Patients with allergy to brentuximab vedotin or excipients.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.8 SmPC Section 4.2 and Section 4.4 where there is information about the possibility of patients developing immediate and delayed IRRs including anaphylactic reactions and a recommendation that administration of brentuximab vedotin should either be interrupted or immediately and permanently discontinued and appropriate

[redacted]

Important identified risk: Infusion-related reactions	
	medical therapy administered if an IRR or anaphylactic reaction occurs. The SmPC also recommend restarting the infusion at a slower rate after symptom resolution and pre-medicating patients who have experienced a prior IRR with medications such as paracetamol, an antihistamine, and a corticosteroid. Package Leaflet section 2 and section 4 Legal status **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk: Hyperglycemia	
Evidence for linking the risk to the medicine	Nonclinical study data; adverse event reports from phase 1, 2, and 3 clinical trials; and spontaneous adverse event reports from the post-marketing setting.
Risk factors and risk groups	Potential factors that may be associated with an increased risk of developing hyperglycemia following the administration of brentuximab vedotin include a fasting glucose above the ULN, pre-existing diabetes mellitus, or concurrent steroid use.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2 and 4.8 SmPC Section 4.4 where there is a recommendation that any patient who experiences hyperglycemia should have their serum glucose closely monitored and antidiabetic treatment should be administered as appropriate. Package Leaflet section 2 and section 4 Legal status **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important potential risk: Severe hepatotoxicity	
Evidence for linking the risk to the medicine	Nonclinical study data; adverse event reports from phase 1, 2, and 3 clinical trials; and spontaneous reports from the post-marketing setting.

[redacted]

Important potential risk: Severe hepatotoxicity	
Risk factors and risk groups	Persons who consume high levels of alcohol are generally susceptible to drug toxicity because alcohol induces liver injury and cirrhotic changes that alter drug metabolism. Elderly persons are at increased risk of hepatic injury because of decreased clearance, drug-to drug interactions, reduced hepatic blood flow, variation in drug binding, and lower hepatic volume. Hepatic dysfunction may also arise from liver involvement by malignant lymphoma in a subgroup of patients. Prior or current treatments and medications administered to lymphoma patients may negatively impact the liver on a temporary or permanent basis. Genetic differences in the P-450 enzymes can result in abnormal reactions to drugs, including idiosyncratic reactions. In addition, poor diet, infections, and multiple hospitalisations are important contributing factors of drug-induced hepatotoxicity.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.8 SmPC Section 4.4 where there is a recommendation that patients receiving brentuximab vedotin therapy should have a liver function test before initiating treatment and routinely monitored during treatment with brentuximab vedotin. Patients who experience hepatotoxicity may require a dose delay, change in dose, or discontinuation of brentuximab vedotin. Package Leaflet section 2 and section 4 Legal status **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important potential risk: Pulmonary toxicity	
Evidence for linking the risk to the medicine	Nonclinical study data; adverse event reports from phase 1, 2, and 3 clinical trials; and spontaneous reports from the post-marketing setting.
Risk factors and risk groups	Exact risk factors with brentuximab vedotin are not known. However, general risk factors for pulmonary toxicity include smoking history, underlying lung disease, radiation exposure, advanced age, and infectious complications.

[redacted]

Important potential risk: Pulmonary toxicity	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.5 and 4.8 SmPC Section 4.3: co-administration of ADCETRIS with bleomycin is contraindicated due to increased pulmonary toxicity. SmPC Section 4.4: contains a recommendation that if new or worsening pulmonary symptoms are observed, a prompt diagnostic evaluation should be performed, and patients should be treated appropriately. Brentuximab vedotin therapy should be stopped during evaluation and until symptomatic improvement. Package Leaflet section 2 and section 4 Legal status **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: None

Missing information: Long term safety	
Evidence for linking the risk to the medicine	It is not known whether it is safe to use brentuximab vedotin for longer than 1 year.
Risk minimisation measures	**Routine risk minimisation measures:** None Legal status **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

II.C. Post-authorisation development plan

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

None.

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

None.

[redacted]

Part VII: Annexes

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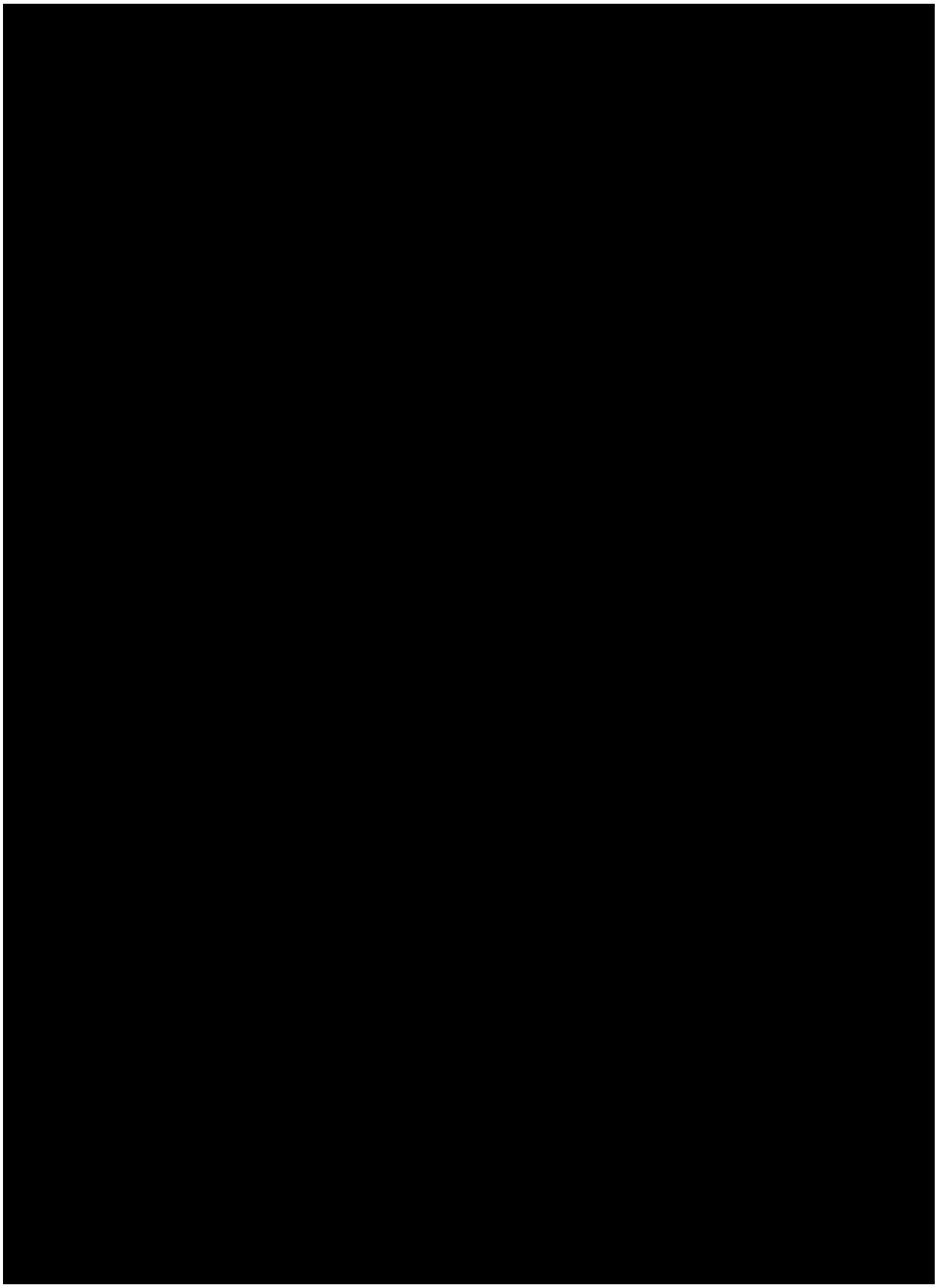

Annex 4: Specific adverse drug reaction follow-up forms

Not applicable.

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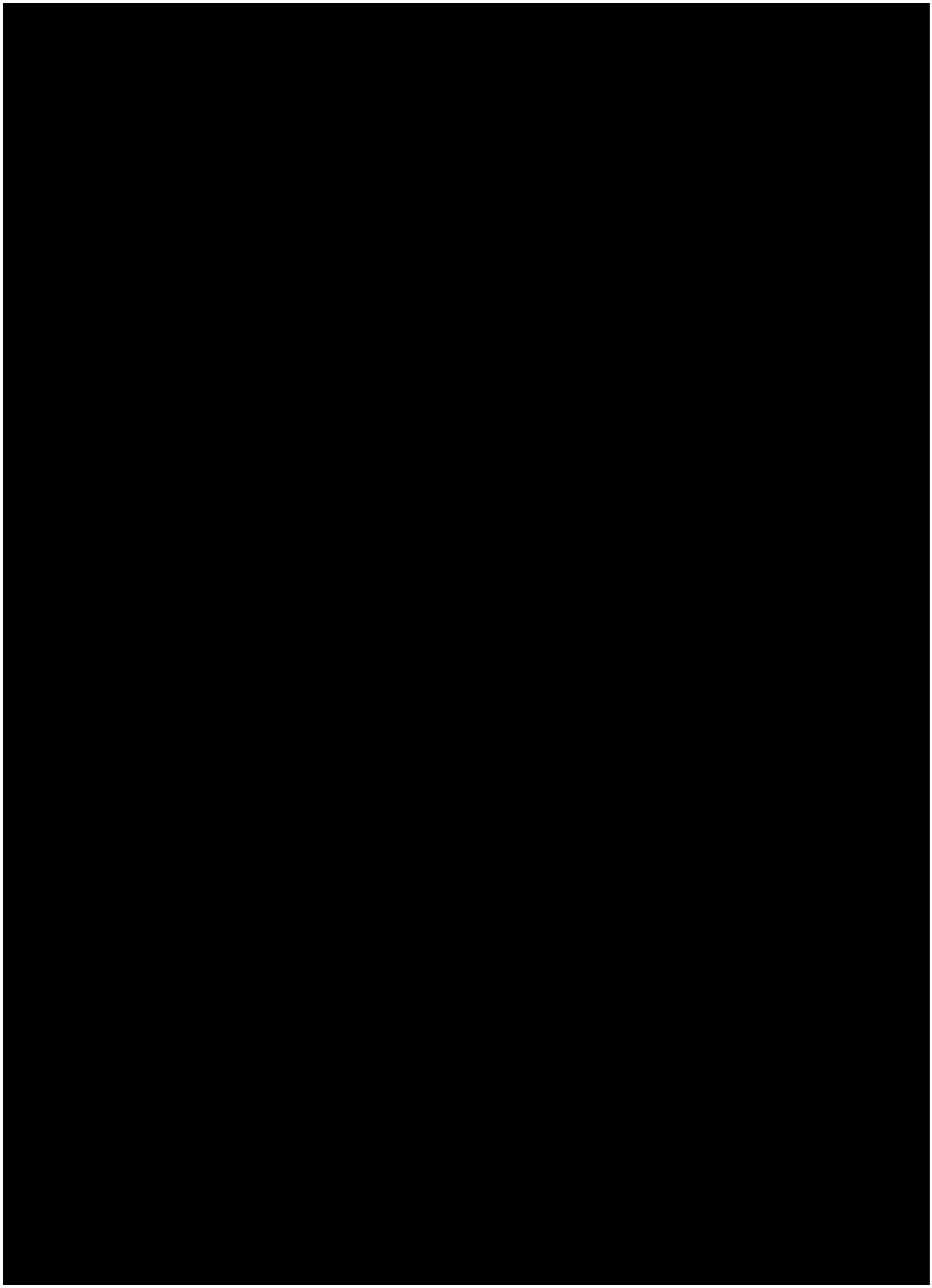
Annex 6: Details of proposed additional risk minimisation activities (if applicable)

Not applicable.



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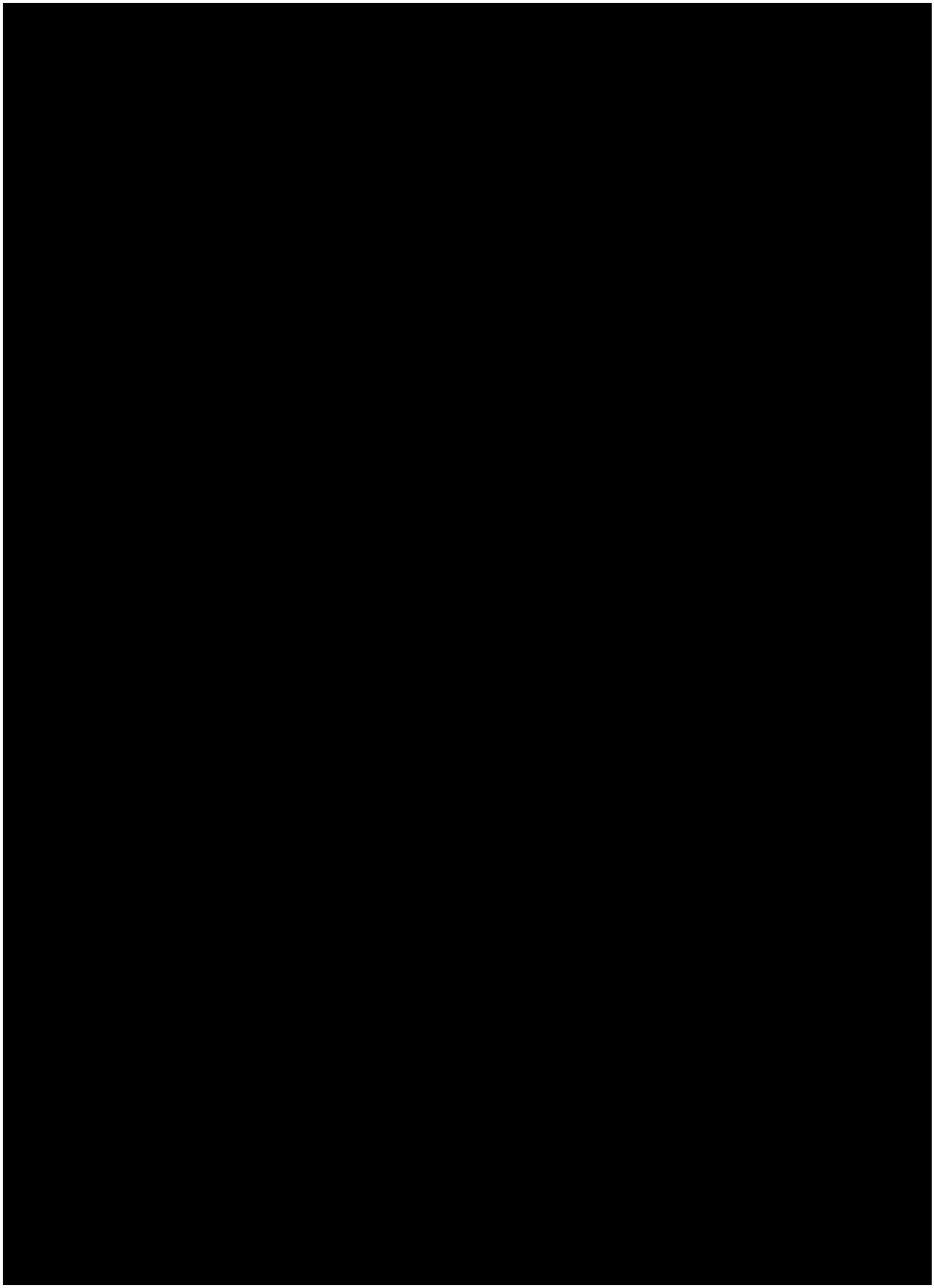

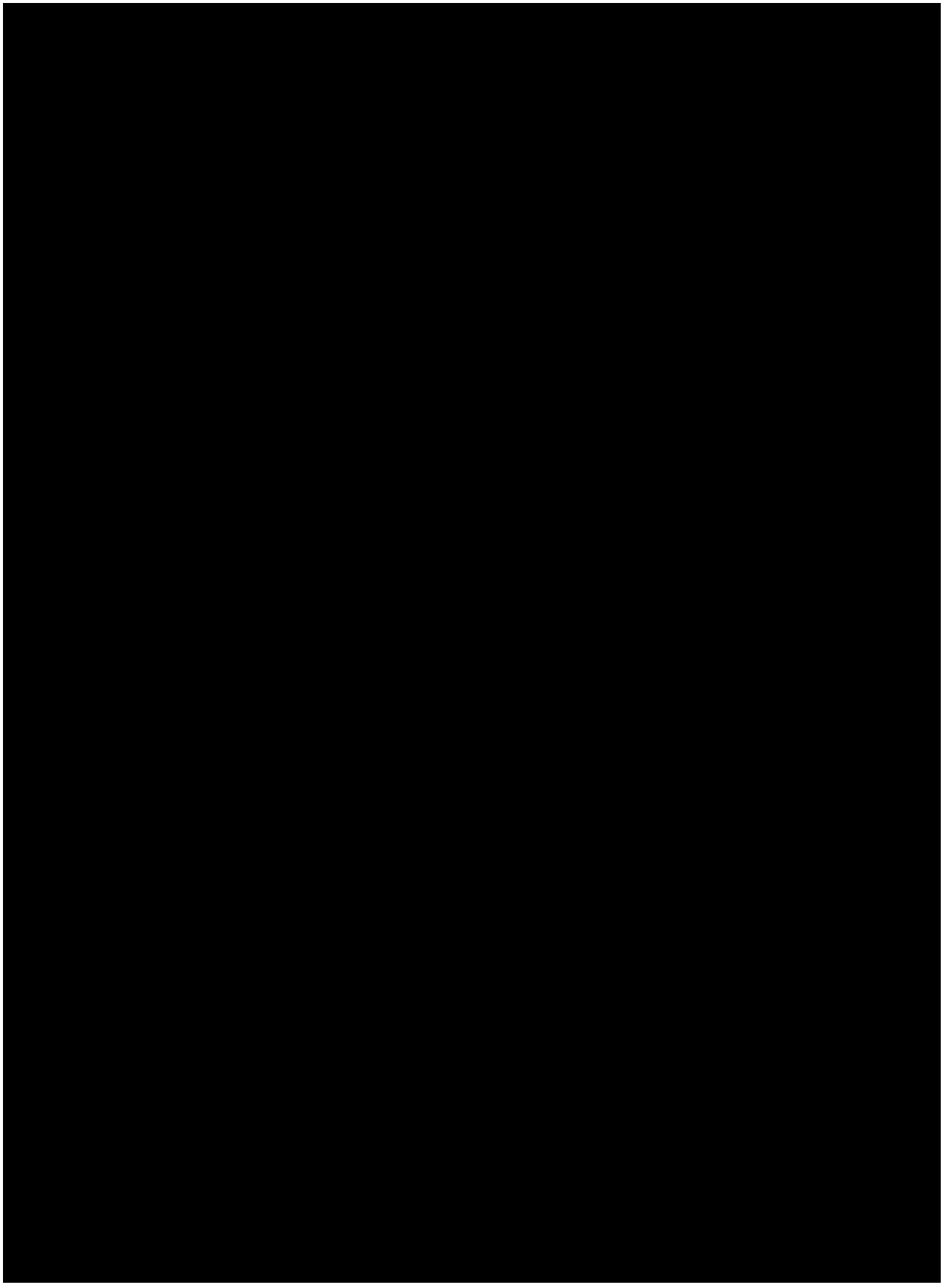

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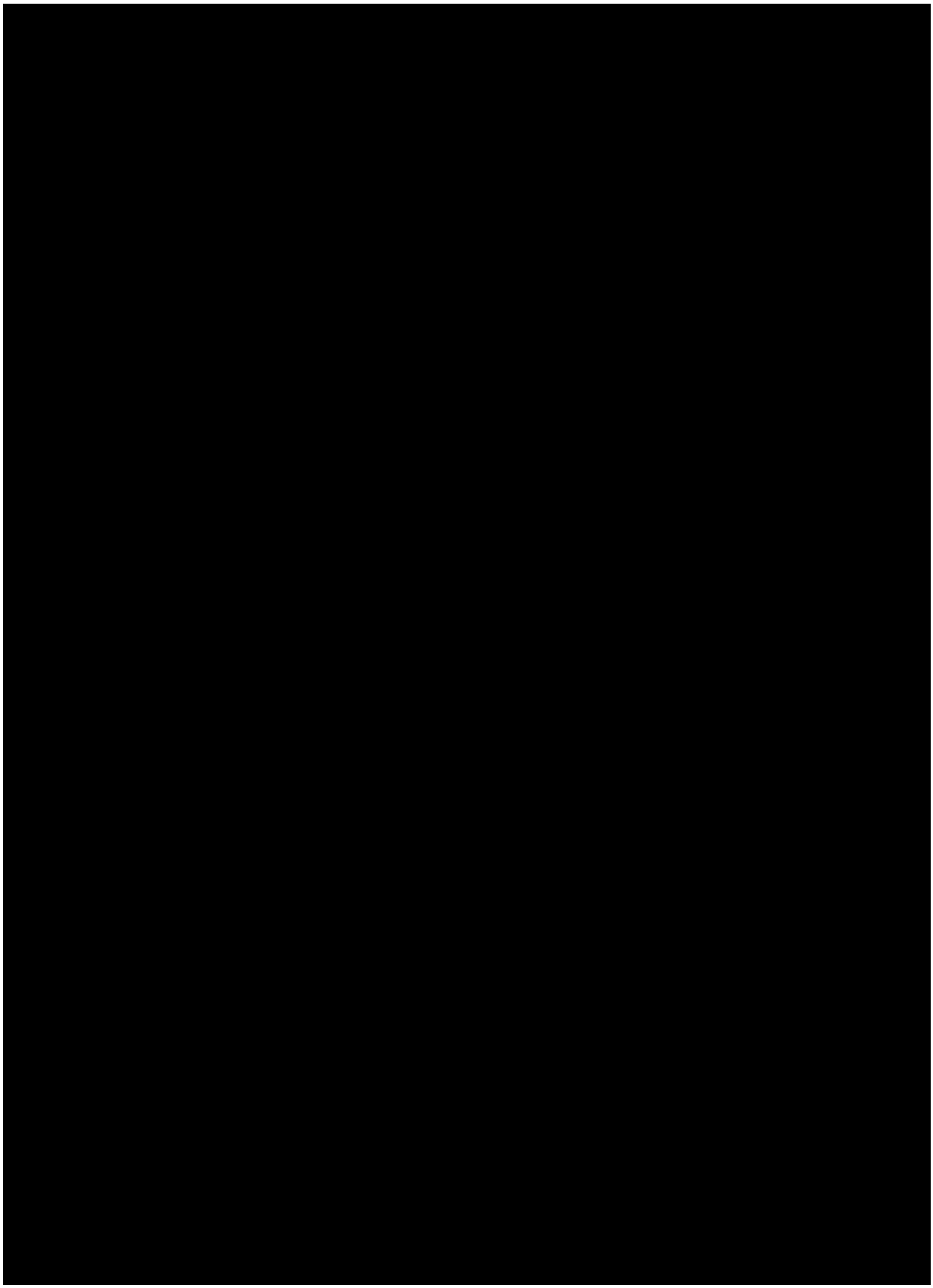

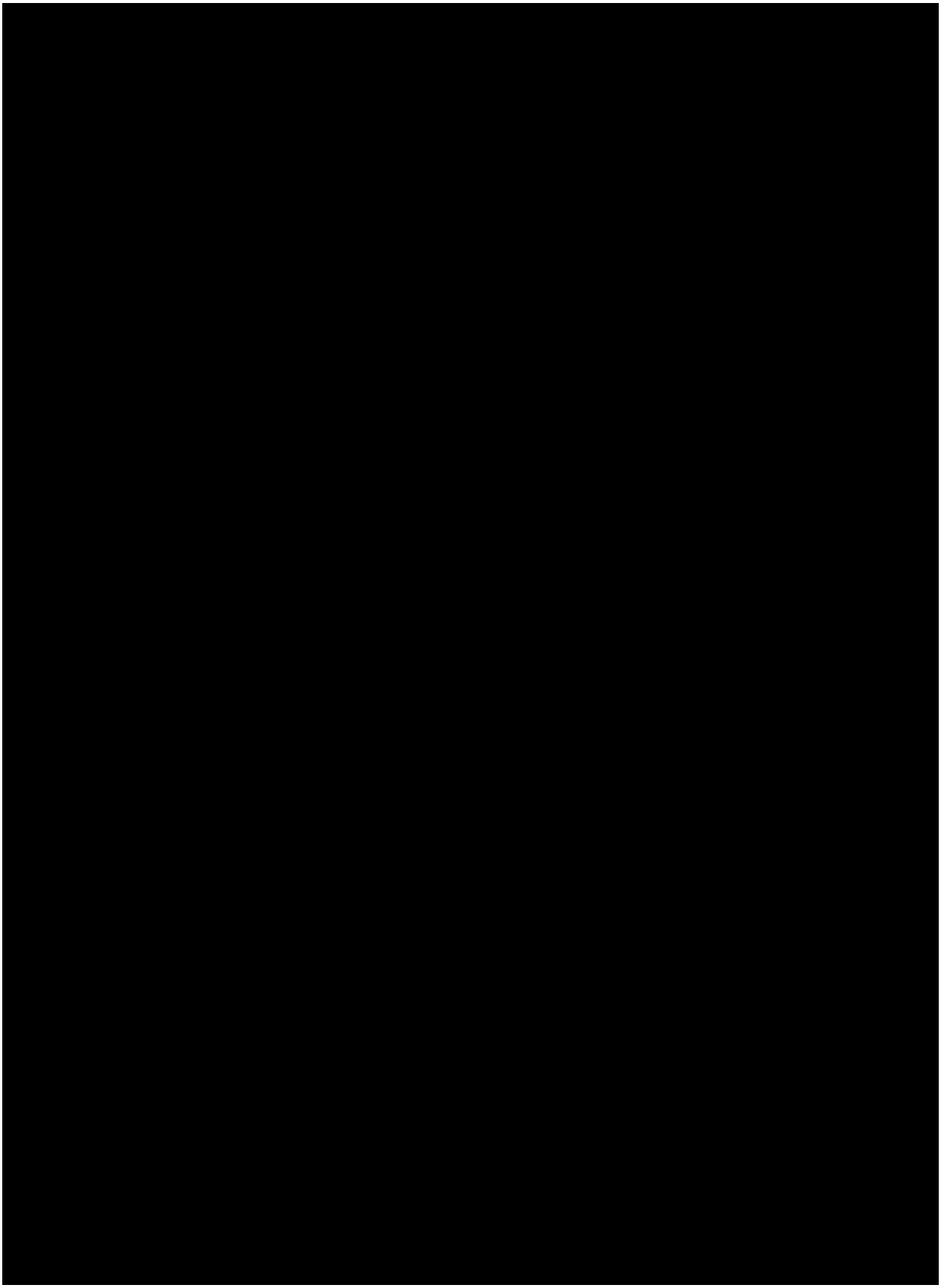

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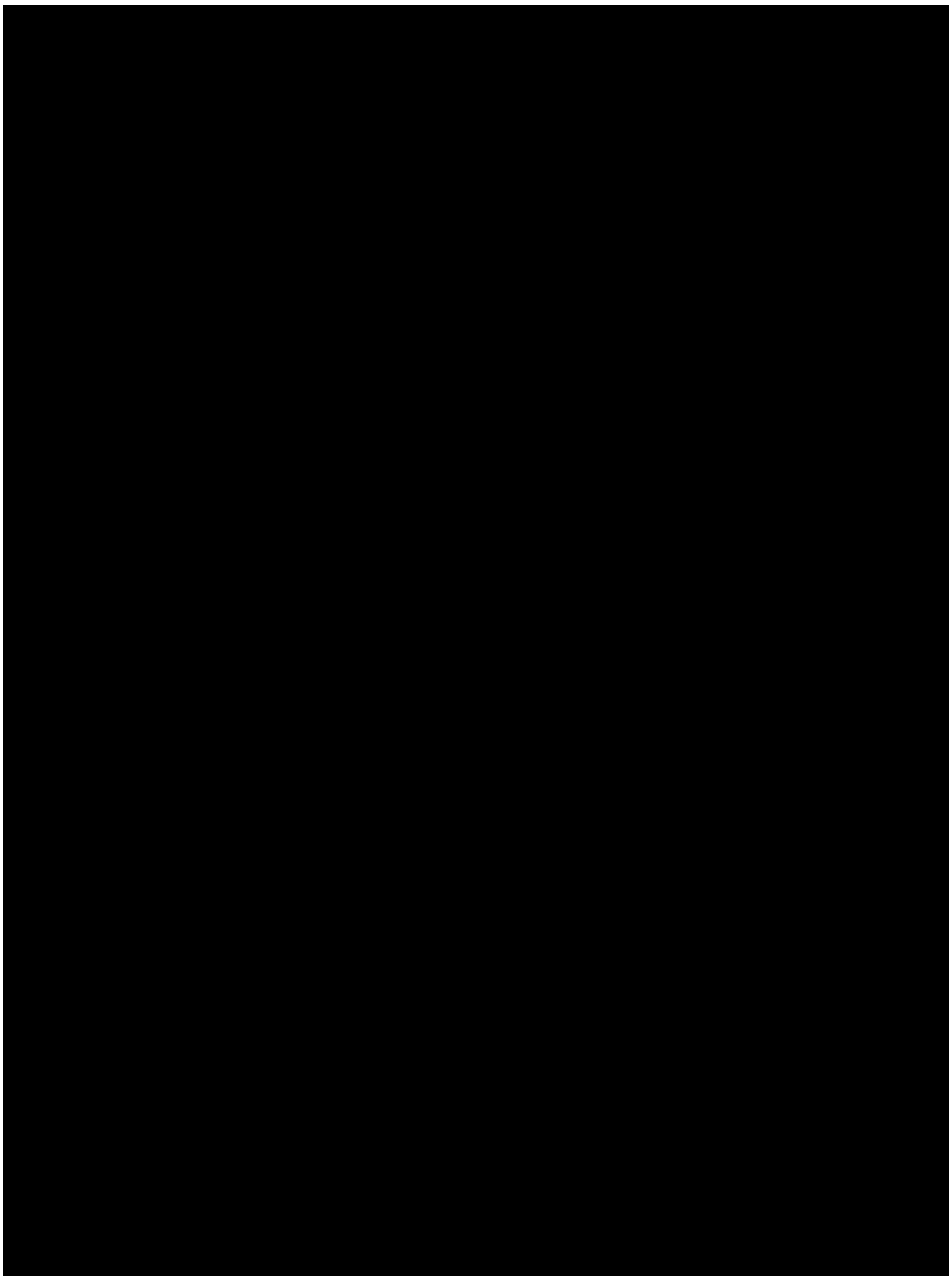

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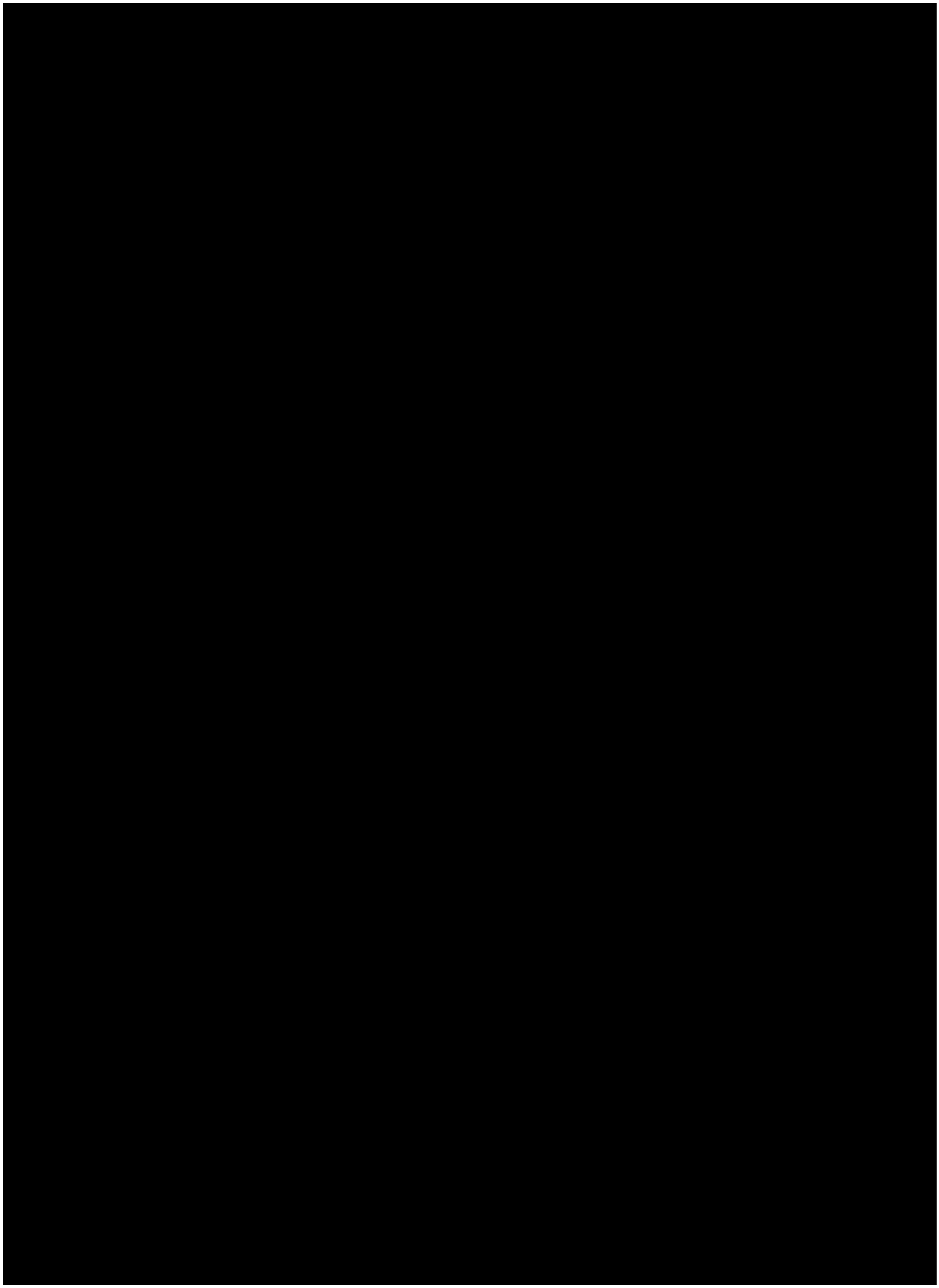

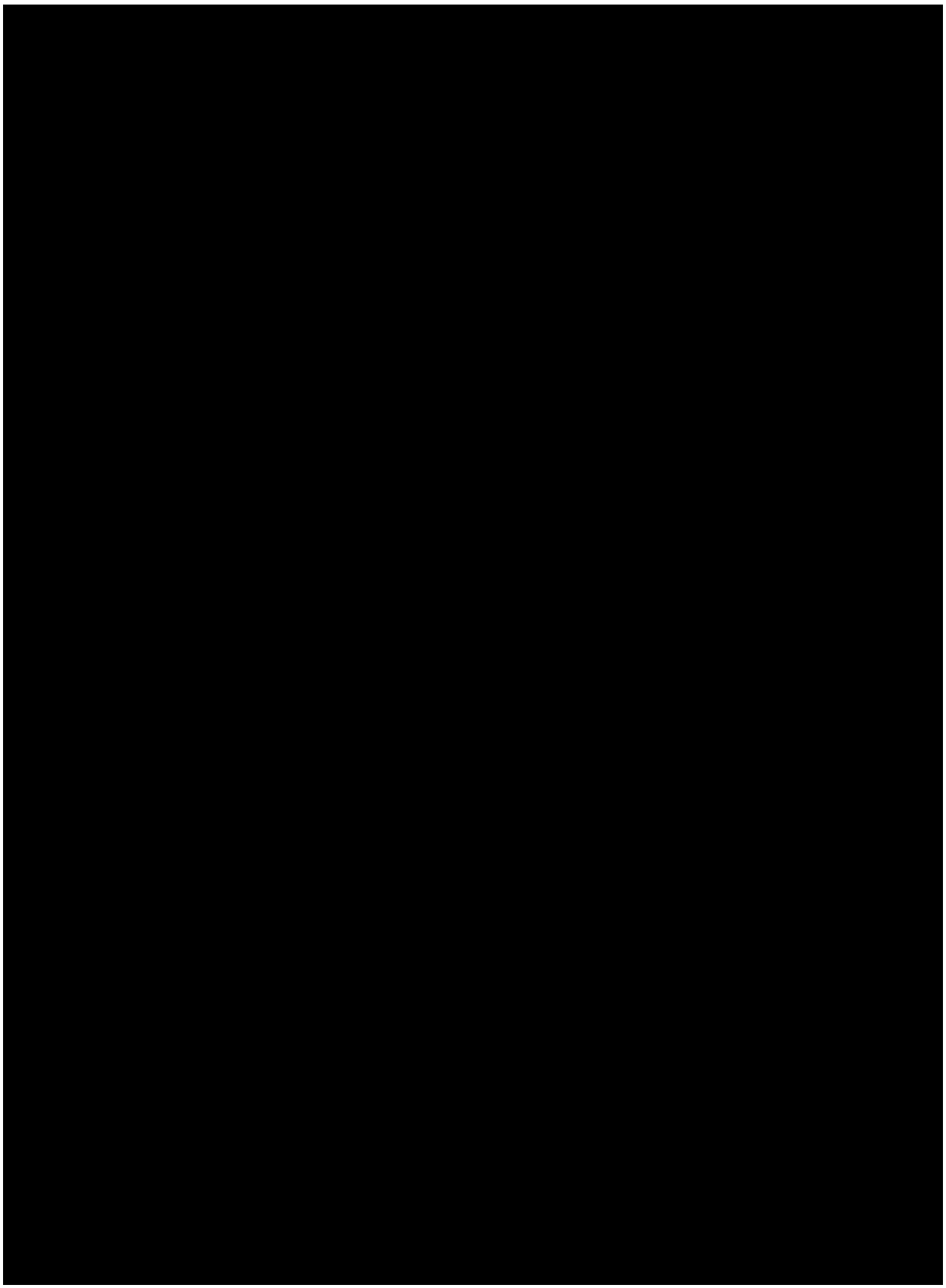

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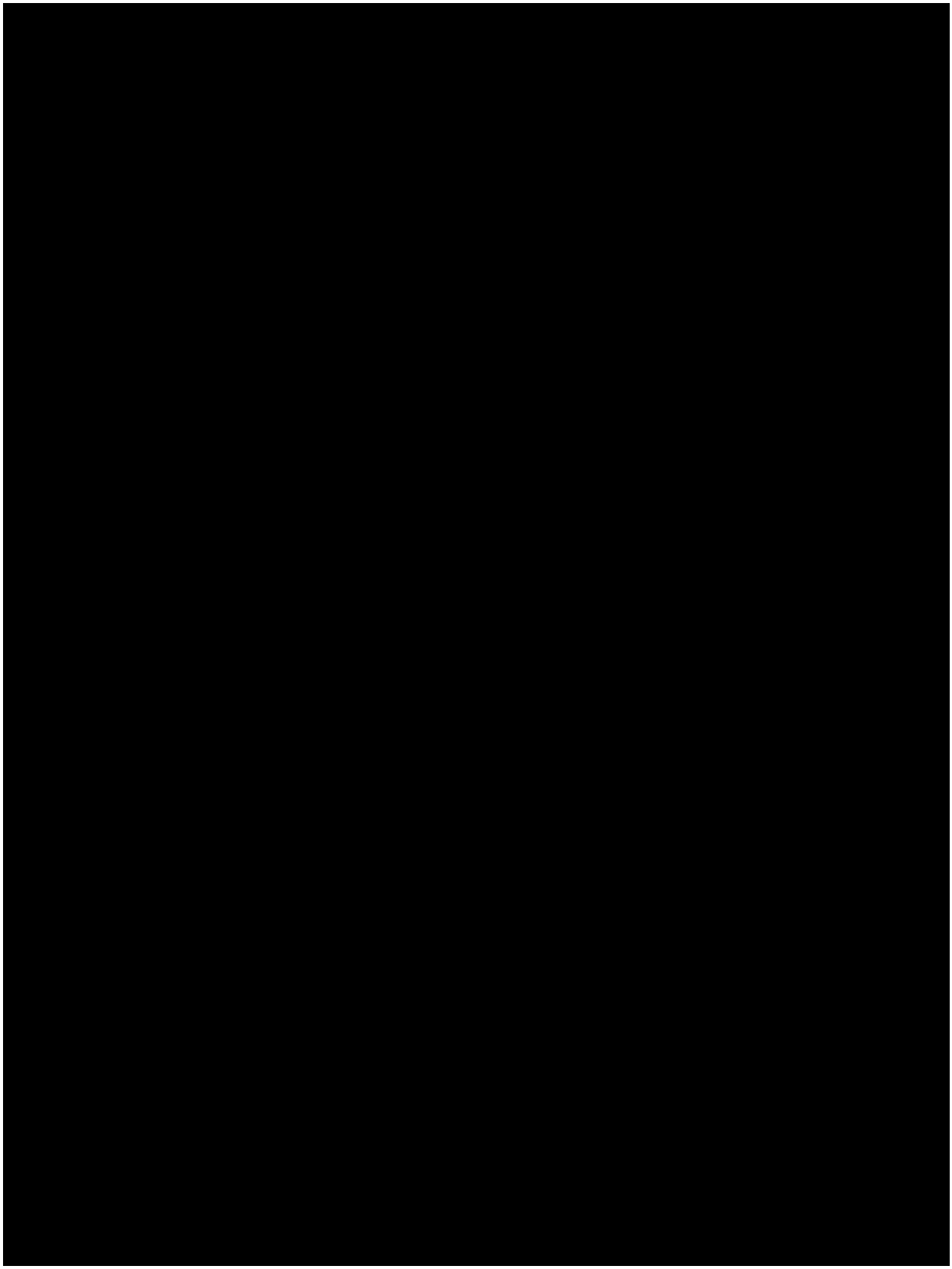

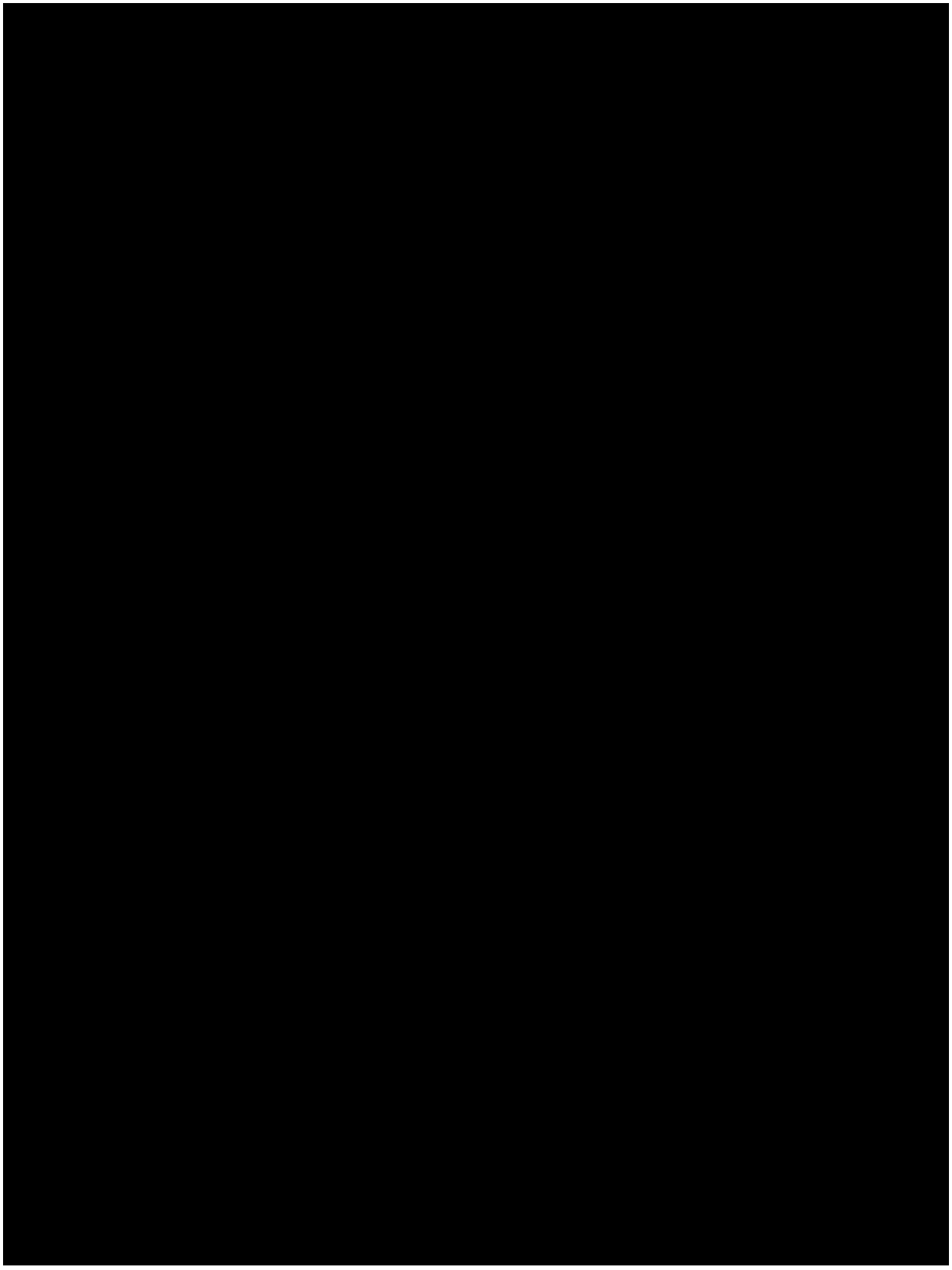

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