

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

ADCETRIS 50 mg powder for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 50 mg of brentuximab vedotin.

After reconstitution (see section 6.6), each mL contains 5 mg of brentuximab vedotin.

ADCETRIS is an antibody-drug conjugate composed of a CD30-directed monoclonal antibody (recombinant chimeric immunoglobulin G1 [IgG1], produced by recombinant DNA technology in Chinese Hamster ovary cells) that is covalently linked to the antimicrotubule agent monomethyl auristatin E (MMAE).

Excipient with known effect

Each vial contains approximately 13.2 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White to off-white cake or powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ADCETRIS is indicated for adult patients with previously untreated CD30+ Stage IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine (AVD)(see sections 4.2 and 5.1).

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) (see section 5.1).

ADCETRIS is indicated for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL):

1. following ASCT, or
2. following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.

ADCETRIS is indicated for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).

ADCETRIS is indicated for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy (see section 5.1).

4.2 Posology and method of administration

ADCETRIS should be administered under the supervision of a physician experienced in the use of anti-cancer agents.

Posology

Previously Untreated HL

The recommended dose in combination with chemotherapy (doxorubicin [A], vinblastine [V] and dacarbazine [D] [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 (see section 5.1).

Primary prophylaxis with growth factor support (G-CSF) is recommended for all patients with previously untreated HL receiving combination therapy beginning with the first dose (see section 4.4).

Refer to the summary of product characteristics (SmPC) of chemotherapy agents given in combination with ADCETRIS for patients with previously untreated HL.

HL at increased risk of relapse or progression

The recommended dose is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks.

ADCETRIS treatment should start following recovery from ASCT based on clinical judgment. These patients should receive up to 16 cycles (see section 5.1).

Relapsed or refractory HL

The recommended dose 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 who have previously responded to treatment with ADCETRIS is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. Alternatively, treatment may be started at the last tolerated dose (see section 5.1).

Treatment should be continued until disease progression or unacceptable toxicity (see section 4.4).

Patients who achieve stable disease or better should receive a minimum of 8 cycles and up to a maximum of 16 cycles (approximately 1 year) (see section 5.1).

Relapsed or refractory sALCL

The recommended dose 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 who have previously responded to treatment with ADCETRIS is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. Alternatively, treatment may be started at the last tolerated dose (see section 5.1).

Treatment should be continued until disease progression or unacceptable toxicity (see section 4.4).

Patients who achieve stable disease or better should receive a minimum of 8 cycles and up to a maximum of 16 cycles (approximately 1 year) (see section 5.1).

CTCL

The recommended dose is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks.

Patients with CTCL should receive up to 16 cycles (see section 5.1).

General

If the patient's weight is more than 100 kg, the dose calculation should use 100 kg (see section 6.6).

Complete blood counts should be monitored prior to administration of each dose of this treatment (see section 4.4).

Patients should be monitored during and after infusion (see section 4.4).

Dose adjustments

Neutropenia

If neutropenia develops during treatment it should be managed by dose delays. See Table 1 below for appropriate dosing recommendations (see also section 4.4).

Table 1: Dosing recommendations for neutropenia

	Monotherapy	Combination therapy Note: Primary prophylaxis with G-CSF is recommended for all patients receiving combination therapy beginning with the first dose.
Severity grade of neutropenia (signs and symptoms [abbreviated description of CTCAE^a])	Modification of dosing schedule	Modification of dosing schedule
Grade 1 (< LLN-1500/mm ³ < LLN-1.5 x 10 ⁹ /L) or Grade 2 (< 1500-1000/mm ³ < 1.5-1.0 x 10 ⁹ /L)	Continue with the same dose and schedule	Continue with the same dose and schedule
Grade 3 (< 1,000-500/mm ³ < 1.0-0.5 x 10 ⁹ /L) or Grade 4 (< 500/mm ³ < 0.5 x 10 ⁹ /L)	Withhold dose until toxicity returns to ≤ Grade 2 or baseline then resume treatment at the same dose and schedule ^b . Consider G-CSF or GM-CSF in subsequent cycles for patients who develop Grade 3 or Grade 4 neutropenia.	Consider G-CSF or GM-CSF in subsequent cycles for patients who develop Grade 3 or Grade 4 neutropenia.

^a. Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0; see Neutrophils/granulocytes; LLN = lower limit of normal

^b. Patients who develop Grade 3 or Grade 4 lymphopenia may continue treatment without interruption.

Peripheral neuropathy

If peripheral sensory or motor neuropathy emerges or worsens during treatment see Table 2 below for appropriate dosing recommendations (see section 4.4).

Table 2: Dosing recommendations for new or worsening peripheral sensory or motor neuropathy

	Monotherapy	Combination therapy
Severity of peripheral sensory or motor neuropathy (signs and symptoms [abbreviated description of CTCAE^a])	Modification of dose and schedule	Modification of dose and schedule
Grade 1 (paraesthesia and/or loss of reflexes, with no loss of function)	Continue with the same dose and schedule	Continue with the same dose and schedule
Grade 2 (interfering with function but not with activities of daily living) or	Withhold dose until toxicity returns to \leq Grade 1 or baseline, then restart treatment at a reduced dose of 1.2 mg/kg up to a maximum of 120 mg every 3 weeks	Reduce dose to 0.9 mg/kg up to a maximum of 90 mg every 2 weeks
Grade 3 (interfering with activities of daily living)	Withhold dose until toxicity returns to \leq Grade 1 or baseline, then restart treatment at a reduced dose of 1.2 mg/kg every 3 weeks	Withhold treatment with ADCETRIS until toxicity is \leq Grade 2, then restart treatment at a reduced dose to 0.9 mg/kg every 2 weeks.
Grade 4 (sensory neuropathy which is disabling or motor neuropathy that is life threatening or leads to paralysis)	Discontinue treatment	Discontinue treatment

^a. Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0; see neuropathy: motor; neuropathy: sensory; and neuropathic pain.

Special patient populations

Renal and hepatic impairment

Combination therapy

Patients with renal impairment should be closely monitored for adverse events. There is no clinical trial experience using ADCETRIS in combination with chemotherapy in patients with renal impairment, where serum creatinine is \geq 2.0 mg/dL and/or creatinine clearance or calculated creatinine clearance is \leq 40 mL/minute. Use of ADCETRIS in combination with chemotherapy should be avoided in patients with severe renal impairment.

Patients with hepatic impairment should be closely monitored for adverse events. The recommended starting dose in patients with mild hepatic impairment is 0.9 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. There is no clinical trial experience using ADCETRIS in combination with chemotherapy in patients with hepatic impairment, where total bilirubin is $>$ 1.5 times the upper limit of normal (ULN) (unless due to Gilbert syndrome), or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) are $>$ 3 times the ULN, or $>$ 5 times the ULN if their elevation may be reasonably ascribed to the presence of HL in the liver. Use of ADCETRIS in combination with chemotherapy should be avoided in patients with moderate and severe hepatic impairment.

Monotherapy

The recommended starting dose in patients with severe renal impairment is 1.2 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. Patients with renal impairment should be closely monitored for adverse events (see section 5.2).

The recommended starting dose in patients with hepatic impairment is 1.2 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. Patients with hepatic impairment should be closely monitored for adverse events (see section 5.2).

Elderly

The dosing recommendations for patients aged 65 and older are the same as for adults. Currently available data are described in sections 4.8, 5.1 and 5.2.

Paediatric population

The safety and efficacy of ADCETRIS in children less than 18 years have not yet been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

In nonclinical studies, thymus depletion has been observed (see section 5.3).

Method of administration

The recommended dose of ADCETRIS is infused over 30 minutes.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

ADCETRIS must not be administered as an intravenous push or bolus. ADCETRIS should be administered through a dedicated intravenous line and it must not be mixed with other medicinal products (see section 6.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Combined use of bleomycin and ADCETRIS causes pulmonary toxicity (see section 4.5).

4.4 Special warnings and precautions for use

Progressive multifocal leukoencephalopathy

John Cunningham virus (JCV) reactivation resulting in progressive multifocal leukoencephalopathy (PML) and death can occur in ADCETRIS-treated patients. PML has been reported in patients who received this treatment after receiving multiple prior chemotherapy regimens. PML is a rare demyelinating disease of the central nervous system that results from reactivation of latent JCV and is often fatal.

Patients should be closely monitored for new or worsening neurological, cognitive, or behavioural signs or symptoms, which may be suggestive of PML. ADCETRIS should be held for any suspected case of PML. Suggested evaluation of PML includes neurology consultation, gadolinium-enhanced magnetic resonance imaging of the brain and cerebrospinal fluid analysis for JCV DNA by polymerase chain reaction or a brain biopsy with evidence of JCV. A negative JCV PCR does not

exclude PML. Additional follow up and evaluation may be warranted if no alternative diagnosis can be established. ADCETRIS dosing should be permanently discontinued if a diagnosis of PML is confirmed.

The physician should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g., cognitive, neurological, or psychiatric symptoms).

Pancreatitis

Acute pancreatitis has been observed in patients treated with ADCETRIS. Fatal outcomes have been reported.

Patients should be closely monitored for new or worsening abdominal pain, which may be suggestive of acute pancreatitis. Patient evaluation may include physical examination, laboratory evaluation for serum amylase and serum lipase, and abdominal imaging, such as ultrasound and other appropriate diagnostic measures. ADCETRIS should be held for any suspected case of acute pancreatitis. ADCETRIS should be discontinued if a diagnosis of acute pancreatitis is confirmed.

Pulmonary toxicity

Cases of pulmonary toxicity, including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome (ARDS), some with fatal outcomes, have been reported in patients receiving ADCETRIS. Although a causal association with ADCETRIS 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, dyspnoea), a prompt diagnostic evaluation should be performed and patients should be treated appropriately. Consider holding ADCETRIS dosing during evaluation and until symptomatic improvement.

Serious infections and opportunistic infections

Serious infections such as pneumonia, staphylococcal bacteraemia, sepsis/septic shock (including fatal outcomes) and herpes zoster, cytomegalovirus (CMV) (reactivation) and opportunistic infections such as *Pneumocystis jirovecii* pneumonia and oral candidiasis have been reported in patients treated with ADCETRIS. Patients should be carefully monitored during treatment for the emergence of possible serious and opportunistic infections.

Infusion-related reactions

Immediate and delayed infusion-related reactions (IRR), as well as anaphylactic reactions, have been reported.

Patients should be carefully monitored during and after infusion. If an anaphylactic reaction occurs, administration of ADCETRIS 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 (see section 4.8).

Tumour lysis syndrome

Tumour lysis syndrome (TLS) has been reported with ADCETRIS. Patients with rapidly proliferating tumour and high tumour burden are at risk of tumour lysis syndrome. These patients should be monitored closely and managed according to best medical practice. Management of TLS may include aggressive hydration, monitoring of renal function, correction of electrolyte abnormalities, anti-hyperuricaemic therapy, and supportive care.

Peripheral neuropathy

ADCETRIS may cause peripheral neuropathy, both sensory and motor. ADCETRIS-induced peripheral neuropathy is typically an effect of cumulative exposure to this medicinal product and is reversible in most cases. In clinical trials, the majority of patients had resolution or improvement of their symptoms (see section 4.8). 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 peripheral neuropathy may require a delay and a dose reduction of ADCETRIS or discontinuation of treatment (see section 4.2).

Haematological toxicities

Grade 3 or Grade 4 anaemia, thrombocytopenia, and prolonged (≥ 1 week) Grade 3 or Grade 4 neutropenia can occur with ADCETRIS. Complete blood counts should be monitored prior to administration of each dose. If Grade 3 or Grade 4 neutropenia develops, refer to section 4.2.

Febrile neutropenia

Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection with an absolute neutrophil count $< 1.0 \times 10^9/L$, fever ≥ 38.5 °C; ref CTCAE v3) has been reported with treatment with ADCETRIS. Complete blood counts should be monitored prior to administration of each dose of treatment. Patients should be monitored closely for fever and managed according to best medical practice if febrile neutropenia develops.

In combination therapy with AVD, advanced age was a risk factor for febrile neutropenia. When ADCETRIS is administered in combination with AVD, primary prophylaxis with G-CSF is recommended for all patients regardless of age beginning with the first dose.

Stevens-Johnson syndrome and toxic epidermal necrolysis

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with ADCETRIS. Fatal outcomes have been reported. If SJS or TEN occur, ADCETRIS should be discontinued and appropriate medical therapy should be administered.

Gastrointestinal complications

Gastrointestinal (GI) complications including intestinal obstruction, ileus, enterocolitis, neutropenic colitis, erosion, ulcer, perforation and haemorrhage, some with fatal outcomes, have been reported in patients treated with ADCETRIS. In the event of new or worsening GI symptoms, perform a prompt diagnostic evaluation and treat appropriately.

Hepatotoxicity

Hepatotoxicity in the form of elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) has been reported with ADCETRIS. Serious cases of hepatotoxicity, including fatal outcomes, have also occurred. Pre-existing liver disease, comorbidities, and concomitant medications may also increase the risk. Liver function should be tested before initiating

the treatment and routinely monitored in patients receiving ADCETRIS. Patients experiencing hepatotoxicity may require a delay, change in dose or discontinuation of ADCETRIS.

Hyperglycaemia

Hyperglycaemia has been reported during clinical trials in patients with an elevated Body Mass Index (BMI) with or without a history of diabetes mellitus. However, any patient who experiences an event of hyperglycaemia should have their serum glucose closely monitored. Anti-diabetic treatment should be administered as appropriate.

Renal and hepatic impairment

There is limited experience in patients with renal and hepatic impairment. Available data indicate that MMAE clearance might be affected by severe renal impairment, hepatic impairment, and by low serum albumin concentrations (see section 5.2).

CD30+ CTCL

The size of the treatment effect in CD30 + CTCL subtypes other than mycosis fungoides (MF) and primary cutaneous anaplastic large cell lymphoma (pcALCL) is not clear due to lack of high level evidence. In two single arm phase II studies of ADCETRIS, disease activity has been shown in the subtypes Sézary syndrome (SS), lymphomatoid papulosis (LyP) and mixed CTCL histology. These data suggest that efficacy and safety can be extrapolated to other CTCL CD30+ subtypes. Nevertheless, ADCETRIS should be used with caution in other CD30+ CTCL patients after careful consideration of the potential benefit-risk on an individual basis (see section 5.1).

Sodium content in excipients

This medicinal product contains 13.2 mg sodium per vial, equivalent to 0.7% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Traceability

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

4.5 Interaction with other medicinal products and other forms of interaction

Interaction with medicinal products metabolised through CYP3A4 route (CYP3A4 inhibitors/inducers)

Co-administration of brentuximab vedotin with ketoconazole, a strong CYP3A4 and P-gp inhibitor, increased the exposure to the antimicrotubule agent MMAE by approximately 73%, and did not alter the plasma exposure to brentuximab vedotin. Therefore, co-administration of brentuximab vedotin with strong CYP3A4 and P-gp inhibitors may increase the incidence of neutropenia. If neutropenia develops, refer to Table 1: Dosing recommendations for neutropenia (see section 4.2).

Co-administration of brentuximab vedotin with rifampicin, a strong CYP3A4 inducer, did not alter the plasma exposure to brentuximab vedotin. Though PK data are limited, co administration of rifampicin appeared to reduce plasma concentrations of MMAE metabolites that could be assayed.

Co-administration of midazolam, a CYP3A4 substrate, with brentuximab vedotin did not alter the metabolism of midazolam; therefore brentuximab vedotin is not expected to alter the exposure to medicines that are metabolized by CYP3A4 enzymes.

Doxorubicin, vinblastine and dacarbazine (AVD)

The serum and plasma pharmacokinetic characteristics of ADC and MMAE respectively following administration of brentuximab vedotin in combination with AVD were similar to that in monotherapy.

Co-administration of brentuximab vedotin did not affect the plasma exposure of AVD.

Bleomycin

There were no formal drug-drug interaction studies with brentuximab vedotin and bleomycin(B). In a phase 1 dose finding and safety study (SGN35-009), unacceptable pulmonary toxicity (including 2 fatal events) was noted in 11 of 25 patients (44%) treated with brentuximab vedotin plus ABVD. No pulmonary toxicity or fatal events were reported with brentuximab vedotin + AVD. Therefore, co-administration of ADCETRIS with bleomycin is contraindicated (see section 4.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be using two methods of effective contraception during treatment with ADCETRIS and until 6 months after treatment.

Pregnancy

There are no data from the use of ADCETRIS in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

ADCETRIS 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.

See the fertility section below pertaining to advice for women whose male partners are being treated with ADCETRIS.

Breastfeeding

There are no data as to whether brentuximab vedotin or its metabolites are excreted in human milk.

A risk to the newborn/infant cannot be excluded.

A decision should be made whether to discontinue breast-feeding or to discontinue/abstain from this therapy, taking into account a potential risk of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

In non-clinical studies, brentuximab vedotin treatment has resulted in testicular toxicity, and may alter male fertility. MMAE has been shown to have aneugenic properties (see section 5.3). Therefore, men being treated with this medicine are advised to have sperm samples frozen and stored before treatment. Men being treated with this medicine are advised not to father a child during treatment and for up to 6 months following the last dose.

4.7 Effects on ability to drive and use machines

ADCETRIS may have a moderate influence on the ability to drive and use machines (e.g. dizziness), see section 4.8.

4.8 Undesirable effects

Summary of the safety profile

The safety profile of ADCETRIS is based on available clinical trial data, the Named Patient Program (NPP), and post-marketing experience to date. Frequencies of adverse reactions described below and in Table 3 have been determined based on data generated from clinical studies.

Monotherapy

In the pooled dataset of ADCETRIS as monotherapy across HL, sALCL and CTCL studies (SG035-0003, SG035-0004, SGN35-005, SGN35-006, C25001 and C25007, see section 5.1) the most frequent adverse reactions ($\geq 10\%$) were infections, peripheral sensory neuropathy, nausea, fatigue, diarrhoea, pyrexia, upper respiratory tract infection, neutropenia, rash, cough, vomiting, arthralgia, peripheral motor neuropathy, infusion-related reactions, pruritus, constipation, dyspnoea, weight decreased, myalgia and abdominal pain.

Serious adverse drug reactions occurred in 12% of patients. The frequency of unique serious adverse drug reactions was $\leq 1\%$.

Adverse events led to treatment discontinuation in 24% of patients receiving ADCETRIS.

The safety data in patients retreated with ADCETRIS (SGN35-006, see section 5.1) were consistent with those observed in the combined pivotal phase 2 studies, with the exception of peripheral motor neuropathy, which had a higher incidence (28% vs. 9% in the pivotal phase 2 studies) and was primarily Grade 2. Patients also had a higher incidence of arthralgia, Grade 3 anaemia, and back pain compared to patients observed in the combined pivotal phase 2 studies.

The safety data in patients with relapsed or refractory HL who had not received an autologous stem cell transplant and were treated with the recommended dose of 1.8 mg/kg every three weeks in a single-arm phase 4 study (n = 60), the phase 1 dose escalation and clinical pharmacology studies (n = 15 patients) and in the NPP (n = 26 patients) (see section 5.1) were consistent with the safety profile of the pivotal clinical studies.

Combination therapy

For safety information of chemotherapy agents given in combination with ADCETRIS (doxorubicin, vinblastine and dacarbazine) for newly diagnosed patients with HL, refer to their summary of product characteristics.

In the study of ADCETRIS as combination therapy with AVD in 662 patients with previously untreated advanced HL (C25003), the most common adverse reactions ($\geq 10\%$) were: neutropenia, nausea, constipation, vomiting, fatigue, peripheral sensory neuropathy, diarrhoea, pyrexia, alopecia, peripheral motor neuropathy, decreased weight, abdominal pain, anaemia, stomatitis, febrile neutropenia, bone pain, insomnia, decreased appetite, cough, headache, arthralgia, back pain, dyspnoea, myalgia, upper respiratory tract infection, alanine aminotransferase increased.

In patients receiving ADCETRIS combination therapy, serious adverse reactions occurred in 36% of patients. Serious adverse reactions occurring in $\geq 3\%$ of patients included febrile neutropenia (17%), pyrexia (6%), and neutropenia (3%).

Adverse events led to treatment discontinuation in 13% of patients. Adverse events that led to treatment discontinuation in $\geq 2\%$ of patients included peripheral sensory neuropathy, peripheral neuropathy, and peripheral motor neuropathy.

Tabulated list of adverse reactions

Adverse reactions for ADCETRIS are listed by MedDRA System Organ Class and Preferred Term (see Table 3). Within each System Organ Class, adverse reactions are listed under frequency categories of: Very common ($\geq 1/10$); Common ($\geq 1/100$ to $< 1/10$); Uncommon ($\geq 1/1,000$ to $< 1/100$); Rare ($\geq 1/10,000$ to $< 1/1,000$); Very rare ($< 1/10,000$); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3: Adverse reactions to ADCETRIS

System organ class	Adverse reactions (monotherapy)	Adverse reactions (combination therapy)
Infections and infestations		
Very common:	Infection ^a , upper respiratory tract infection	Infection ^a , upper respiratory tract infection
Common:	Herpes zoster, pneumonia, herpes simplex, oral candidiasis	Pneumonia, oral candidiasis, sepsis/septic shock, herpes simplex
Uncommon:	Pneumocystis jiroveci pneumonia, staphylococcal bacteraemia, cytomegalovirus infection or reactivation, sepsis/septic shock	Herpes zoster, Pneumocystis jiroveci pneumonia
Frequency not known:	Progressive multifocal leukoencephalopathy	
Blood and lymphatic system disorders		
Very common:	Neutropenia	Neutropenia ^a , anaemia, febrile neutropenia
Common:	Anaemia, thrombocytopenia	Thrombocytopenia
Uncommon:	Febrile neutropenia	
Immune system disorders		
Uncommon:	Anaphylactic reaction	Anaphylactic reaction
Metabolism and nutrition disorders		
Very common:		Decreased appetite
Common:	Hyperglycaemia	Hyperglycaemia
Uncommon:	Tumour lysis syndrome	Tumour lysis syndrome
Nervous system disorders		
Very common:	Peripheral sensory neuropathy, peripheral motor neuropathy	Peripheral sensory neuropathy, peripheral motor neuropathy ^a , dizziness
Common:	Dizziness	
Uncommon:	Demyelinating polyneuropathy	
Respiratory, thoracic and mediastinal disorders		
Very common:	Cough, dyspnoea	Cough, dyspnoea
Gastro-intestinal disorders		
Very common:	Nausea, diarrhoea vomiting, constipation, abdominal pain	Nausea, constipation, vomiting, diarrhoea, abdominal pain, stomatitis
Uncommon:	Pancreatitis acute	Pancreatitis acute

System organ class	Adverse reactions (monotherapy)	Adverse reactions (combination therapy)
Hepatobiliary disorders		
Very common:		Alanine aminotransferase (ALT) increased
Common:	Alanine aminotransferase/aspartate aminotransferase (ALT/AST) increased	Alanine aminotransferase/aspartate aminotransferase (ALT/AST) increased
Skin and subcutaneous tissue disorders		
Very common:	Rash ^a , pruritus	Alopecia, rash ^a
Common:	Alopecia	Pruritus
Uncommon:	Stevens-Johnson syndrome/toxic epidermal necrolysis	Stevens-Johnson syndrome ^b
Musculoskeletal and connective tissue disorders		
Very common:	Arthralgia, myalgia	Bone pain, arthralgia, back pain, myalgia
Common:	Back pain	
General disorders and administration site conditions		
Very common:	Fatigue, pyrexia, infusion-related reactions ^a	Fatigue, pyrexia
Common:	Chills	Infusion-related reactions ^a , chills
Investigations		
Very common:	Weight decreased	Weight decreased
Psychiatric Disorders		
Very common:		Insomnia

^a. Represents pooling of preferred terms.

^b. Toxic epidermal necrolysis was not reported in the combination therapy setting.

Description of selected adverse reactions

Neutropenia and febrile neutropenia

Monotherapy

In clinical trials, neutropenia led to dose delays in 14% of patients. Grade 3 neutropenia was reported in 13% and Grade 4 neutropenia was reported in 5% of patients. No patients required dose reduction or discontinued treatment for neutropenia.

Severe and prolonged (≥ 1 week) neutropenia can occur with this treatment which may increase the risk of patients developing serious infections. Febrile neutropenia reported in $< 1\%$ of the patients (see section 4.2).

In the pivotal phase 2 population (SG035-0003 and SG035-0004), the median duration of Grade 3 or Grade 4 neutropenia was limited (1 week); 2% of patients had Grade 4 neutropenia that lasted ≥ 7 days. Less than half of the patients in the pivotal phase 2 population with Grade 3 or Grade 4 neutropenia had temporally associated infections, and the majority of temporally associated infections were Grade 1 or Grade 2.

Combination therapy

In the clinical trial of ADCETRIS as combination therapy, neutropenia led to dose delays in 24% of patients. Grade 3 neutropenia was reported in 18% and Grade 4 neutropenia was reported in 47% of patients. Two percent of patients required dose reduction and $< 1\%$ discontinued one of more of the study drugs due to neutropenia.

Febrile neutropenia was reported in 21% of the patients who did not receive primary prophylaxis with G-CSF (see section 4.2). The frequency of febrile neutropenia was 11% in patients who received primary prophylaxis with G-CSF.

Serious infections and opportunistic infections

Monotherapy

In clinical trials, serious infections and opportunistic infections occurred in 10% of patients, sepsis or septic shock occurred in < 1% of the patients. The most commonly reported opportunistic infections were herpes zoster and herpes simplex.

Combination therapy

In the clinical trial of ADCETRIS as combination therapy, serious infections including opportunistic infections occurred in 15% of patients; sepsis, neutropenic sepsis, septic shock or bacteraemia occurred in 4% of the patients. The most commonly reported opportunistic infections were herpes viral infections.

Peripheral neuropathy

Monotherapy

In clinical trials treatment emergent neuropathy occurred in 59% of the population, peripheral motor neuropathy occurred in 14% of patients. Peripheral neuropathy led to treatment discontinuation in 15%, dose reductions in 15%, and dose delays in 17% of patients. For patients who experienced peripheral neuropathy the median time of onset of peripheral neuropathy was 12 weeks. The median duration of treatment for patients who discontinued due to peripheral neuropathy was 12 cycles.

Among patients who experienced peripheral neuropathy in the pivotal phase 2 studies (SG035-0003 and SG035-0004) and randomised phase 3 monotherapy studies (SGN35-005 and C25001), the median follow up time from end of treatment until last evaluation ranged from 48.9 to 98 weeks. At the time of last evaluation, most of the patients (82-85%) who experienced peripheral neuropathy had resolution or improvement of their peripheral neuropathy symptoms. The median time from onset to resolution or improvement for all events ranged from 16 to 23.4 weeks.

In patients with relapsed or refractory HL or sALCL who were retreated with ADCETRIS (SGN35-006), the majority of patients (80%) also had improvement or resolution of their peripheral neuropathy symptoms at the time of last evaluation.

Combination therapy

In the clinical trial of ADCETRIS as combination therapy, treatment emergent neuropathy occurred in 67% of the population; peripheral motor neuropathy occurred in 11% of patients. Peripheral neuropathy led to treatment discontinuation in 7%, dose reductions in 21%, and dose delays in 1% of patients. For patients who experienced peripheral neuropathy the median time of onset of peripheral neuropathy was 8 weeks. Patients who discontinued due to peripheral neuropathy received a median of 8 doses of ADCETRIS+AVD (A+AVD) before discontinuation of one or more agents.

Among patients who experienced peripheral neuropathy, the median follow up time from end of treatment until last evaluation was approximately 91 weeks. At the time of last evaluation, most of the patients (76%) who experienced peripheral neuropathy had resolution or improvement of their peripheral neuropathy symptoms. The median time from onset to resolution or improvement of peripheral neuropathy events was 10 weeks (ranged from 0 weeks to 139 weeks).

Infusion-related reactions

Monotherapy

IRRs, such as headache, rash, back pain, vomiting, chills, nausea, dyspnoea, pruritus and cough were reported in 13% of patients. Anaphylactic reactions have been reported (see section 4.4). Symptoms of an anaphylactic reaction may include, but are not limited to, urticaria, angioedema, hypotension and bronchospasm.

Combination therapy

IRRs, such as headache, rash, back pain, vomiting, chills, nausea, dyspnoea, pruritus, cough, infusion site pain and pyrexia were reported in 9% of patients. Anaphylactic reactions have been reported (see section 4.4). Symptoms of an anaphylactic reaction may include, but are not limited to, urticaria, angioedema, hypotension and bronchospasm.

Immunogenicity

In clinical trials, patients were periodically tested for antibodies to brentuximab vedotin using a sensitive electrochemiluminescent immunoassay. There was a higher incidence of infusion-related reactions observed in patients with antibodies to brentuximab vedotin relative to patients who tested transiently positive or negative.

The presence of antibodies to brentuximab vedotin did not correlate with a clinically meaningful reduction in serum brentuximab vedotin levels and did not result in a decrease in the efficacy of brentuximab vedotin. While the presence of antibodies to brentuximab vedotin does not necessarily predict the development of an IRR, there was a higher incidence of IRRs observed in patients with persistently positive anti-drug antibodies (ADA) relative to patients with transiently positive ADA and never positive ADA.

There was a trend of increased clearance of brentuximab vedotin in paediatric patients confirmed positive for ADAs. No patients aged < 12 years (0 of 11) and 2 patients aged \geq 12 years (2 of 23) became persistently ADA positive.

Paediatric population

Safety was evaluated in a phase 1/2 study in paediatric patients aged 7-17 years of age (n = 36) with relapsed or refractory (r/r) HL and sALCL (see section 5.1). In this study in 36 patients, no new safety concerns were reported.

Elderly

Monotherapy

The safety profile in elderly patients was consistent with that of adult patients.

Combination therapy

In older patients (\geq 60 years of age; n = 83 [13%]), the incidence of adverse events was similar across treatment arms. More serious adverse events and dose modifications (including dose delays, reductions, and discontinuations) were reported in the older patients compared with the overall study population. Advanced age was a risk factor for febrile neutropenia in patients in both arms. Older patients who received G-CSF primary prophylaxis had lower incidence of neutropenia and febrile neutropenia than those who did not receive G-CSF primary prophylaxis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website:

www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

There is no known antidote for overdose of ADCETRIS. In case of overdose, the patient should be closely monitored for adverse reactions, particularly neutropenia, and supportive treatment should be administered (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents; other antineoplastic agents; monoclonal antibodies, ATC code: L01XC12

Mechanism of action

Brentuximab vedotin is an antibody drug conjugate (ADC) that delivers an antineoplastic agent that results in apoptotic cell death selectively in CD30-expressing tumour cells. Nonclinical data suggest that the biological activity of brentuximab vedotin results from a multi-step 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 cell cycle arrest and results in apoptotic death of the CD30-expressing tumour cell.

Classical HL, sALCL and subtypes of CTCL (including MF and pcALCL) express CD30 as an antigen on the surface of their malignant cells. This expression is independent of disease stage, line of therapy or transplant status. These features make CD30 a target for therapeutic intervention. Because of the CD30-targeted mechanism of action brentuximab vedotin is able to overcome chemo-resistance as CD30 is consistently expressed in patients who are refractory to multi-agent chemotherapy, irrespective of prior transplant status. The CD30-targeted mechanism of action of brentuximab vedotin, the consistent expression of CD30 throughout the classical HL, sALCL and CD30+ CTCL disease and therapeutic spectrums and clinical evidence in CD30-positive malignancies following multiple lines of treatment provide a biologic rationale for its use in patients with relapsed and refractory classical HL, sALCL with or without prior ASCT and CD30+ CTCL after at least 1 prior systemic therapy.

Contributions to the mechanism of action by other antibody associated functions have not been excluded.

Pharmacodynamic effects

Cardiac electrophysiology

Forty-six (46) patients with CD30-expressing haematologic malignancies were evaluable of the 52 patients who received 1.8 mg/kg of brentuximab vedotin every 3 weeks as part of a phase 1, single-arm, open-label, multicenter cardiac safety study. The primary objective was to evaluate the

effect of brentuximab vedotin on cardiac ventricular re-polarization and the predefined primary analysis was the change in QTc from baseline to multiple time points in Cycle 1.

The upper 90% confidence interval (CI) around the mean effect on QTc was < 10 msec at each of the Cycle 1 and Cycle 3 post-baseline time points. These data indicate the absence of clinically relevant QT prolongation due to brentuximab vedotin administered at a dose of 1.8 mg/kg every 3 weeks in patients with CD30-expressing malignancies.

Clinical efficacy

Hodgkin lymphoma

Study C25003

The efficacy and safety of ADCETRIS were evaluated in a randomised, open-label, 2-arm, multicenter trial in 1334 patients with previously untreated advanced HL in combination with chemotherapy (doxorubicin [A], vinblastine [V] and dacarbazine [D] [AVD]). All patients had a histologically confirmed CD30-expressing disease. Sixty-two percent of patients had extranodal site involvement. Of the 1334 patients, 664 patients were randomised to the ADCETRIS + AVD arm and 670 patients were randomised to the ABVD (doxorubicin [A], bleomycin [B], vinblastine [V] and dacarbazine [D]) arm and stratified by number of International Prognostic Factor Project (IPFP) risk factors and region. Patients were treated on days 1 and 15 of each 28-day cycle with 1.2 mg/kg of ADCETRIS administered as an intravenous infusion over 30 minutes + doxorubicin 25 mg/m², vinblastine 6 mg/m², and dacarbazine 375 mg/m². The median number of cycles received was 6 (range, 1 to 6 cycles). Table 4 provides a summary of the baseline patient and disease characteristics. There were no relevant differences in the patient and disease characteristics between the two arms.

Table 4: Summary of baseline patient and disease characteristics in the phase 3 previously untreated-HL study

Patient Characteristics	ADCETRIS + AVD n = 664	ABVD n = 670
Median age (range)	35 years (18-82)	37 years (18-83)
Patients ≥ 65 years old n (%)	60 (9)	62 (9)
Gender, n (%)	378M (57) 286F (43)	398M (59) 272F (41)
ECOG status, n (%)		
0	376 (57)	378 (57)
1	260 (39)	263 (39)
2	28 (4)	27 (4)
Missing	0	2
Disease Characteristics		
Median time from HL diagnosis to first dose (range)	0.92 mo (0.1-21.4)	0.89 mo (0.0-81.4)
Disease stage ^a at initial diagnosis of HL, n (%)		
III	237 (36)	246 (37)
IV	425 (64)	421 (63)
Not applicable	1 (< 1)	1 (< 1)
Missing	0	2 (<1)
Extranodal involvement at time of diagnosis, n (%)	411 (62)	416 (62)
IPFP ^b risk factors, n (%)		
0-1	141 (21)	141 (21)
2-3	354 (53)	351 (52)
4-7	169 (25)	178 (27)
Bone marrow involvement at time of diagnosis or study entry, n (%)	147(22)	151 (23)
B symptoms ^a n (%)	400 (60)	381 (57)

^a Per Ann Arbor Staging

^bIPFP = International Prognostic Factor Project

The primary endpoint in Study C25003 was modified PFS (mPFS) per independent review facility (IRF), defined as time from randomisation to disease progression, death, or evidence of non-complete response (non-CR) after completion of first-line therapy per IRF followed by subsequent anticancer therapy. Timing of the modified event was the date of the first PET scan post completion of first-line therapy demonstrating the absence of complete response (CR), defined as Deauville score of ≥3. The median modified PFS by IRF assessment was not reached in either treatment arm. The results in the intent-to-treat (ITT) population showed a statistically significant improvement in modified PFS for ADCETRIS+ AVD, with a stratified hazard ratio of 0.770 (95% CI, 0.603; 0.983, p = 0.035), indicating a 23% reduction in the risk of modified PFS events for ADCETRIS+ AVD versus ABVD.

A pre-specified subgroup analysis of mPFS by disease stage showed that patients with Stage IV disease had a larger effect compared with the ITT population, with an unstratified hazard ratio of 0.71 (95% CI, 0.53; 0.96), compatible with a 29% reduction in the risk of modified PFS events for ADCETRIS+ AVD versus ABVD. Of the ITT population, 846 patients (64%) had Stage IV disease.

Table 5 provides the efficacy results for modified PFS and overall survival (OS) in the ITT population and patients with Stage IV disease.

Table 5: Efficacy results for previously untreated HL patients treated with 1.2 mg/kg of ADCETRIS + AVD on days 1 and 15 of a 28-day cycle (ITT and Stage IV)

	Intent to Treat (ITT) Population			Patients with Stage IV Disease		
	ADCETRIS + AVD n = 664	ABVD n = 670	Stratified Hazard Ratio and p-value	ADCETRIS + AVD n = 425	ABVD n = 421	Unstratified Hazard Ratio and p-value
Number of events (%)	117 (18)	146 (22)	0.77 (95% CI [0.60, 0.98]) p-value=0.035	77 (18)	102 (24)	0.71 (95% CI [0.53, 0.96]) p-value=0.023
Estimated mPFS^a per IRF at 2 Year (%)	82.1 (95% CI [78.8, 85.0])	77.2 (95% CI [73.7, 80.4])		82.0 (95% CI [77.8, 85.5])	75.3 (95% CI [70.6, 79.3])	
Overall Survival^b Number of deaths (%)	28 (4)	39 (6)	0.73 (95% CI [0.45, 1.18]) p-value=0.199	14 (3)	26 (6)	0.51 (95% CI [0.27, 0.97]) p-value=0.037

^aAt the time of analysis, the median modified PFS follow-up time for both arms was 24.6 months

^bData from an interim OS analysis

Figure 1: Modified progression-free survival per IRF in the ITT population (ADCETRIS + AVD vs. ABVD)

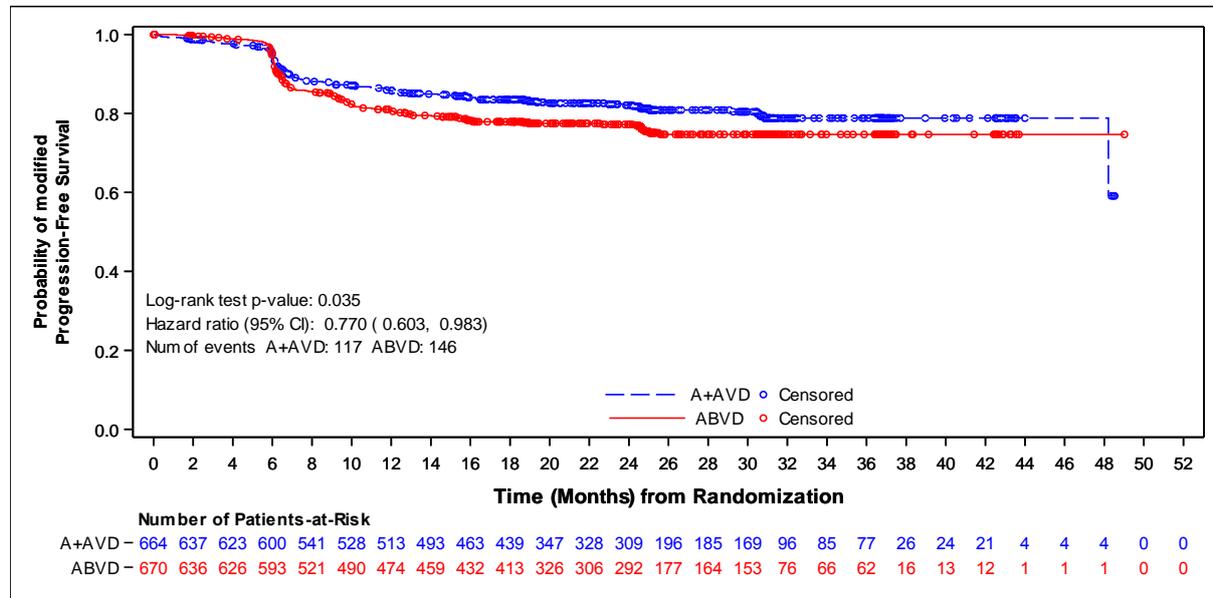
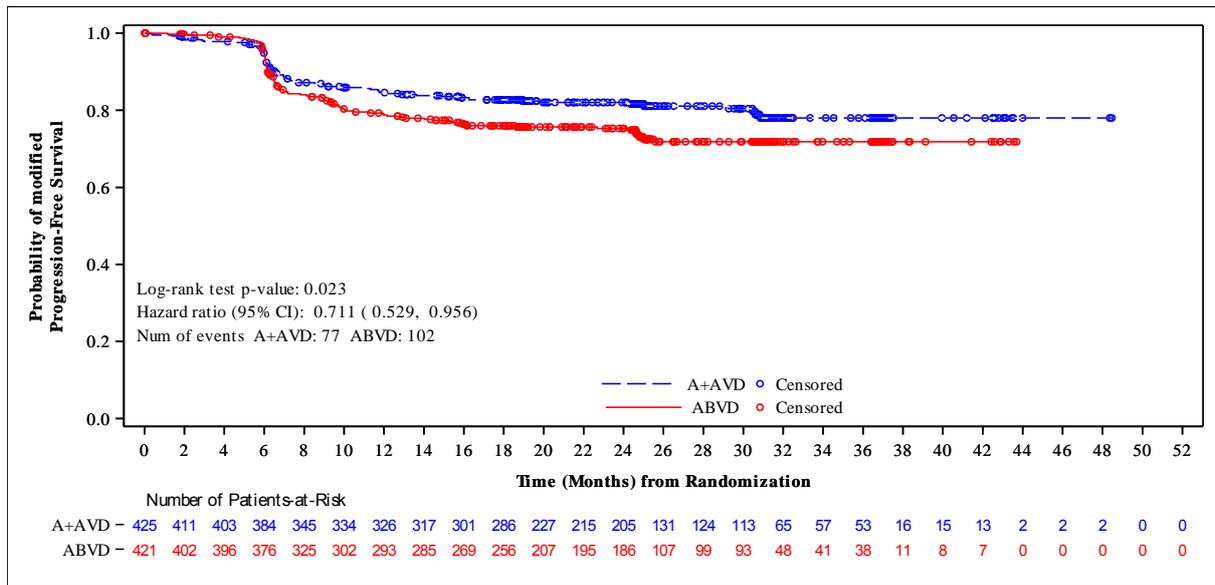


Figure 2: Modified progression-free survival per IRF in patients with Stage IV disease (ADCETRIS + AVD vs. ABVD)



Other secondary efficacy endpoints including CR rate and ORR at the end of randomisation regimen, CR rate at the end of first-line therapy, and the rate of PET negativity at the end of Cycle 2, duration of response (DOR), duration of complete remission (DOCR), disease-free survival (DFS,) and event-free survival (EFS) all trended in favour of ADCETRIS + AVD in both the ITT and Stage IV population.

Pre-specified subgroup analyses of modified PFS per IRF were performed for the ITT population including age, region, cancer stage at baseline, baseline extranodal sites, number of IPFP risk factors, baseline B symptoms, Cycle 2 PET assessment, Cycle 2 PET Deauville score, and receipt of alternative first-line medication (AFM). The analyses showed a consistent trend towards benefit for patients who received ADCETRIS + AVD compared with patients who received ABVD in most subgroups. The efficacy in elderly patient population (patients ≥ 60 years of age [n = 186] [HR = 1.00, 95% CI (0.58, 1.72)] and ≥ 65 years of age [n = 122] [HR = 1.01, 95% CI (0.53, 1.94)]) and patients with no extranodal sites (n = 445) (HR = 1.04, 95% CI [0.67, 1.62]) showed no clinically meaningful difference between the two arms.

Post-hoc subgroup analyses of modified PFS per IRF for patients with Stage IV disease were performed including age, region, baseline extranodal sites, number of IPFP risk factors, baseline B symptoms, baseline ECOG status and gender. The analyses showed a consistent trend towards benefit for patients who received ADCETRIS + AVD compared with patients who received ABVD in most subgroups. Patients with Stage IV disease for whom extranodal disease was reported ([n = 722] [HR = 0.69, 95% CI (0.50, 0.94)]) showed an mPFS (per IRF) benefit. In patients with Stage IV disease for whom no extranodal disease was reported, no benefit has been shown at time of analysis ([n = 85] [HR = 1.49, 95% CI (0.51, 4.31)]). The significance of this finding in stage IV HL patients with no extranodal disease is not established due to small patient numbers and low event rates (14 events). The efficacy in elderly patients with Stage IV disease in the A + AVD arm (patients ≥ 60 years of age [n = 118] [HR = 0.80, 95% CI (0.42, 1.53)] and ≥ 65 years of age [n = 78] [HR = 0.78, 95% CI (0.36, 1.67)]) showed better benefit compared with elderly patients in ITT population.

In the ITT population, 33% fewer patients treated with ADCETRIS + AVD in the ITT population received subsequent salvage chemotherapy (n = 66) and high-dose chemotherapy and transplant (n = 36) compared with those treated with ABVD (n = 99 and n = 54, respectively). In the Stage IV population, 35% fewer patients treated with ADCETRIS + AVD received subsequent salvage

chemotherapy (n = 45) compared with those treated with ABVD (n = 69) and 22% fewer patients treated with ADCETRIS + AVD received high-dose chemotherapy and transplant (n = 29) compared with those treated with ABVD (n = 37).

The European Organization for Research and Treatment of Cancer Quality of Life 30-Item Questionnaire (EORTC-QLQ-C30) showed no clinically meaningful difference between the two arms in both the ITT and Stage IV population.

Study SGN35-005

The efficacy and safety of ADCETRIS were evaluated in a randomised, double-blind, placebo-controlled, 2-arm multicenter trial in 329 patients with HL at risk of relapse or progression following ASCT. Patients with known cerebral/meningeal disease, including history of PML were excluded from the study. See Table 6 for patient characteristics. Of the 329 patients, 165 patients were randomised to the treatment arm and 164 patients were randomised to the placebo arm. In the study, patients were to receive their first dose after recovery from ASCT (between days 30-45 following ASCT). Patients were treated with 1.8 mg/kg of ADCETRIS or matching placebo intravenously over 30 minutes every 3 weeks for up to 16 cycles.

Eligible patients were required to have at least one of the following risk factors:

- HL that was refractory to frontline treatment
- Relapsed or progressive HL that occurred <12 months from the end of frontline treatment
- Extranodal involvement at time of pre-ASCT relapse, including extranodal extension of nodal masses into adjacent vital organs

Table 6: Summary of baseline patient and disease characteristics in the phase 3 HL post-ASCT Study

Patient characteristics	ADCETRIS n = 165	Placebo n = 164
Median age, years (range)	33 years (18-71)	32 years (18-76)
Gender	76M (46%)/89F (54%)	97M (59%)/67F (41%)
ECOG status		
0	87 (53%)	97 (59%)
1	77 (47%)	67 (41%)
2	1 (1%)	0
Disease characteristics		
Median number of prior chemotherapy regimens (range)	2 (2-8)	2 (2-7)
Median time from HL diagnosis to first dose (range)	18.7 mo (6.1-204.0)	18.8 mo (7.4-180.8)
Disease stage at initial diagnosis of HL		
Stage I	1 (1%)	5 (3%)
Stage II	73 (44%)	61 (37%)
Stage III	48 (29%)	45 (27%)
Stage IV	43 (26%)	51 (31%)
Unknown	0	2 (1%)
PET scan Status prior to ASCT		
FDG-AVID	64 (39%)	51 (31%)
FDG-NEGATIVE	56 (34%)	57 (35%)
NOT DONE	45 (27%)	56 (34%)
Extranodal involvement at time of pre-ASCT relapse	54 (33%)	53 (32%)
B symptoms ^a	47 (28%)	40 (24%)
Best response to salvage therapy pre-ASCT ^b		
Complete Response	61 (37%)	62 (38%)
Partial Response	57 (35%)	56 (34%)
Stable Disease	47 (28%)	46 (28%)
HL Status after the end of frontline standard chemotherapy ^b		
Refractory	99 (60%)	97 (59%)
Relapse occurred <12 months	53 (32%)	54 (33%)
Relapse occurred > = > 12 months	13 (8%)	13 (8%)

^{a.} For refractory disease, or upon progression or relapse after frontline therapy.

^{b.} Stratification factors at randomisation.

The efficacy results are shown in Table 7. The primary endpoint of PFS was met and showed a difference in median PFS of 18.8 months in favour of the treatment arm.

Table 7: Efficacy results in HL patients at increased risk of relapse or progression following ASCT treated with 1.8 mg/kg of ADCETRIS every 3 weeks

	ADCETRIS n = 165	Placebo n = 164	Stratified Hazard Ratio
Progression Free Survival^a	Median per IRF		
	42.9 months (95% CI [30.4, 42.9])	24.1 months (95% CI [11.5, -])	0.57 (95% CI [0.40, 0.81]) Stratified log-rank test p=0.001
	Median per Investigator		
	Not reached (95% CI [26.4, -])	15.8 months (95% CI [8.5, -])	0.5 (95% CI [0.36, 0.70]) ^b
Overall Survival	Number of deaths (%)		
	28 (17)	25 (15)	1.15 (95% CI [0.67, 1.97])

^a. At the time of the primary analysis, the median follow-up time for both arms was 30 months (range, 0 to 50).

^b. Stratified log-rank test was not performed for PFS per Investigator.

Pre-specified subgroup analyses of PFS per IRF were performed by patients' best response to pre-ASCT salvage therapy, HL status after frontline therapy, age, gender, baseline weight, baseline ECOG performance status, number of treatments pre-ASCT, geographic region, pre-ASCT PET status, B symptom status after failure of frontline therapy, and pre-ASCT extranodal disease status. The analyses showed a consistent trend towards benefit for patients who received ADCETRIS compared with patients who received placebo with the exception of patients ≥ 65 years of age (n = 8).

No differences were observed in quality of life between the treatment and placebo arms. Medical resource utilization (MRU) analysis showed that hospitalizations and outpatient visits, as well as working days/other activities missed by patients and caregivers were lower with ADCETRIS compared with placebo in patients with HL at increased risk of relapse.

An updated analysis conducted after 3 years of follow-up showed a sustained PFS improvement per IRF (HR = 0.58 [95% CI (0.41, 0.81)]).

Post-hoc Risk Factor Analyses

Post-hoc analyses were performed to evaluate the impact of increased risk (number of risk factors) on clinical benefit (Table 8). Representative risk factors for these analyses were:

- HL that occurred <12 months or HL that was refractory to frontline therapy
- Best response of PR or SD to most recent salvage therapy as determined by CT and/or PET scanning
- Extranodal disease at pre-ASCT relapse

- B symptoms at pre-ASCT relapse
- Two or more prior salvage therapies.

The results of these post-hoc analyses suggest increased clinical benefit for patients with two or more risk factors but no difference based on any of the individual risk factors. No benefit in terms of PFS or OS has been observed in patients with one risk factor for relapse or progression.

Table 8: Summary of PFS per IRF and OS by number of risk factors in the phase 3 HL post-ASCT Study

Progression Free Survival per IRF						
	Number of Risk Factors = 1		Number of Risk Factors ≥ 2		Number of Risk Factors ≥ 3	
	ADCETRIS n = 21	Placebo n = 28	ADCETRIS n = 144	Placebo n = 136	ADCETRIS n = 82	Placebo n = 84
Number of patients with disease progression or death ^a (%)	9 (43)	7 (25)	51 (35)	68 (50)	32 (39)	49 (58)
Stratified Hazard Ratio	1.65 (95% CI [0.60, 4.55]) ^b		0.49 (95% CI [0.34, 0.71])		0.43 (95% CI [0.27, 0.68])	
Overall Survival						
	Number of Risk Factors = 1		Number of Risk Factors ≥ 2		Number of Risk Factors ≥ 3	
	ADCETRIS n = 21	Placebo n = 28	ADCETRIS n = 144	Placebo n = 136	ADCETRIS n = 82	Placebo n = 84
Number of deaths ^c (%)	5 (24)	1 (4)	23 (16)	24 (18)	15 (18)	16 (19)
Stratified Hazard Ratio	7.94 (95% CI [0.93, 68.06]) ^b		0.94 (95% CI [0.53, 1.67])		0.92 (95% CI [0.45, 1.88])	

^{a.} Death without either prior progression or more than one missed assessment visit.

^{b.} Indicates results from non-stratified analysis.

^{c.} Events are death due to any cause.

At the time of the updated analysis (3 years of follow-up) for patients with 2 or more risk factors, the hazard ratio for PFS per IRF was 0.49 (95% CI [0.34, 0.71]) and the hazard ratio for PFS per investigator was 0.41 (95% CI [0.29, 0.58]) (see Figures 3 and 4).

Figure 3: Kaplan-Meier Plot of PFS per IRF in Patients with ≥ 2 Risk Factors

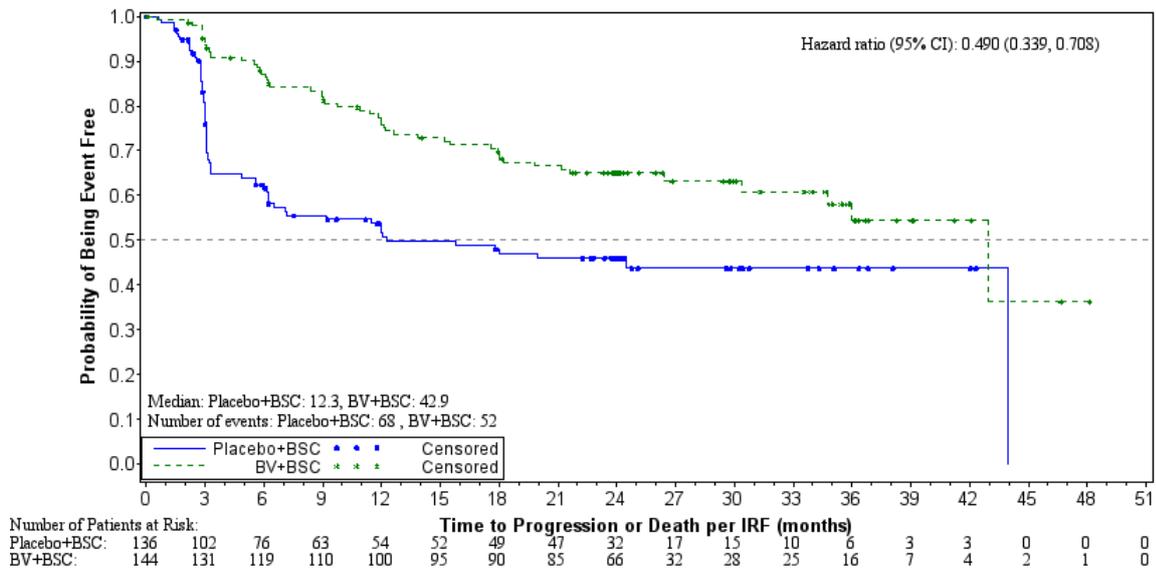
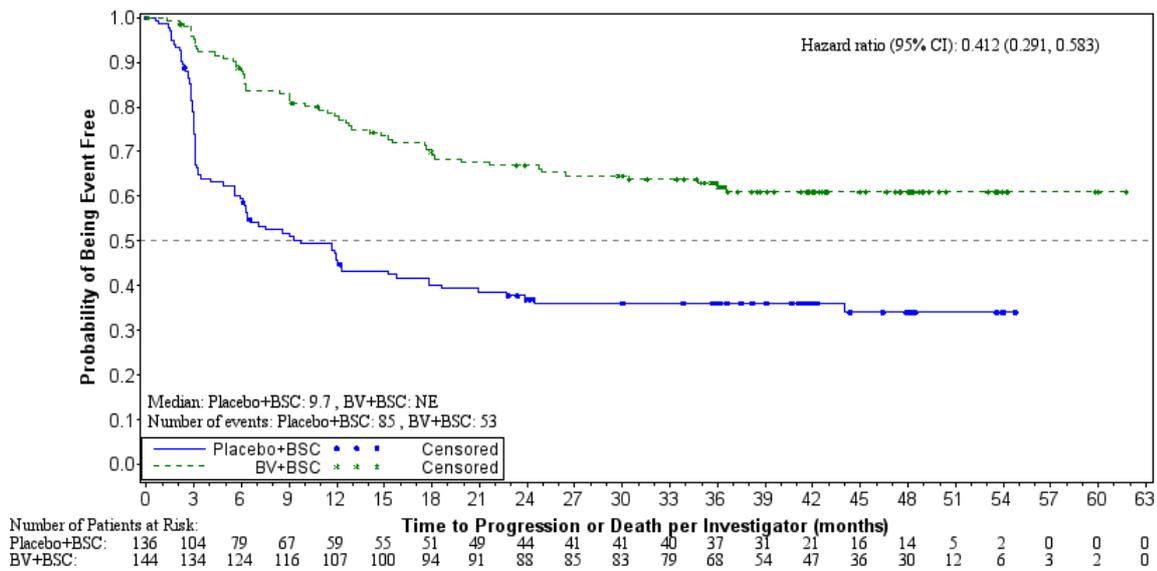


Figure 4: Kaplan-Meier Plot of PFS per Investigator in Patients with ≥ 2 Risk Factors



Study SG035-0003

The efficacy and safety of ADCETRIS as a single agent was evaluated in a pivotal open-label, single-arm, multicenter study in 102 patients with relapsed or refractory HL. See Table 9 below for a summary of baseline patient and disease characteristics.

Table 9: Summary of baseline patient and disease characteristics in the phase 2 relapsed or refractory HL study

Patient characteristics	n = 102
Median age, years (range)	31 years (15-77)
Gender	48M (47%)/54F (53%)
ECOG status	
0	42 (41%)
1	60 (59%)
Prior ASCT	102 (100%)
Prior chemotherapy Regimens	3.5 (1-13)
Time from ASCT to first post-transplant relapse	6.7 mo (0-131)
Histologically confirmed CD30-expressing disease	102 (100%)
Disease characteristics	
Primary Refractory to frontline therapy ^a	72 (71%)
Refractory to most recent therapy	43 (42%)
Baseline B symptoms	35 (33%)
Stage III at initial diagnosis	27 (26%)
Stage IV at initial diagnosis	20 (20%)

^a Primary refractory HL is defined as a failure to achieve a complete remission to, or progressed within 3 months of completing frontline therapy.

Eighteen (18) patients (18%) received 16 cycles of ADCETRIS; and the median number of cycles received was 9 (ranging from 1 to 16).

Response to treatment with ADCETRIS was assessed by Independent Review Facility (IRF) using the Revised Response Criteria for Malignant Lymphoma (Cheson, 2007). Treatment response was assessed by spiral CT of chest, neck, abdomen and pelvis; PET scans and clinical data. Response assessments were performed at cycles 2, 4, 7, 10, 13, and 16 with PET at cycles 4 and 7.

The objective response rate (ORR) per IRF assessment was 75% (76 of 102 patients in the intent-to-treat [ITT] set) and tumour reduction was achieved in 94% of patients. Complete remission (CR) was 33% (34 of 102 patients in the ITT set). The median overall survival (OS) is 40.5 months (the median observation time (time to death or last contact) from first dose was 35.1 months (range 1.8 to 72.9+ months). The estimated overall survival rate at 5 years was 41% (95% CI [31%, 51%]). The investigator assessments were generally consistent with the independent review of the scans. Of the patients treated, 8 responding patients went on to receive an allogeneic SCT. For further efficacy results see Table 10.

Table 10: Efficacy results in relapsed or refractory Hodgkin lymphoma patients treated with 1.8 mg/kg of ADCETRIS every 3 weeks

Best clinical response (n = 102)	IRF n (%)	95% CI
Objective response rate (CR + PR)	76 (75)	64.9, 82.6
Complete remission (CR)	34 (33)	24.3, 43.4
Partial remission (PR)	42 (41)	NA
Disease control rate (CR + PR + SD)	98 (96)	90.3, 98.9
Duration of response	Median per IRF	95% CI
Objective response rate (CR + PR) ^a	6.7 months	3.6, 14.8
Complete remission (CR)	27.9 months	10.8, NE ^b
Overall survival		95% CI
Median	40.5 months	28.7, 61.9
Estimated 5-year OS Rate	41%	31%, 51%

^{a.} The range of DOR was 1.2+ months to 43+ months and the median follow-up time from first dose for patients who achieved objective response (OR) per IRF was 9.0 months.

^{b.} Not estimable.

An exploratory intra-patient analysis showed that approximately 64% of the HL patients treated with ADCETRIS as part of the SG035-0003 clinical study experienced an improvement in clinical benefit as measured by longer progression free survival (PFS) compared with their most recent prior line of therapy.

Of the 35 patients (33%) who had B symptoms at baseline, 27 patients (77%) experienced resolution of all B symptoms at a median time of 0.7 months from initiation of ADCETRIS.

Data in HL Patients Who Are Not Stem Cell Transplant (SCT) Candidates

Study-C25007

A phase 4 single-arm study was conducted in patients with relapsed or refractory HL (n = 60) who had received at least one prior chemotherapeutic regimen and at the time of treatment initiation with ADCETRIS were not considered candidates for SCT or multiagent chemotherapy. The median number of cycles was 7 (range 1 to 16 cycles). Patients were treated with 1.8 mg/kg of ADCETRIS every 3 weeks. Per IRF, the objective response rate (ORR) in the ITT population was 50% (95% CI, 37; 63%). A best overall response of CR was reported for 7 patients (12%); PR was reported for 23 patients (38%). Among these 30 patients, the median time to response, defined as the time from first dose to the soonest of PR or CR, was 6 weeks (range, 5 to 39 weeks). The median time to best overall response, defined as the time from first dose to the clinical best response of CR or PR, was 11 weeks (range, 5 to 60 weeks). Twenty-eight patients (47%) went on to receive SCT after a median of 7 cycles (range, 4 to 16 cycles) of ADCETRIS treatment. The 32 patients (53%) who did not receive subsequent SCT also received ADCETRIS for a median of 7 cycles (range, 1 to 16 cycles).

Of the study's 60 patients, 49 patients (82%) received > 1 prior cancer-related treatment and 11 patients (18%) received 1 prior cancer-related treatment. Per IRF, the ORR was 51% (95% CI [36%, 66%]) for the patients who had received > 1 prior cancer-related treatment and 45% (95% CI [17%, 77%]) for the patients who had received 1 prior cancer-related treatment. For the patients who received > 1 prior cancer-related treatment, a best overall response of CR was reported for 6 patients (12%); PR was reported for 19 patients (39%). For the patients who received 1 prior cancer-related treatment, CR was reported for 1 patient (9%) and PR was reported for 4 patients (36%). Out of the 49 patients receiving > 1 line of prior treatment, 22 patients (45%) received subsequent SCT; of the 11 patients who had received 1 prior treatment, 6 patients (55%) received subsequent SCT.

Data were also collected from patients (n = 15) in phase 1 dose escalation and clinical pharmacology studies, and from patients (n = 26) in a NPP, with relapsed or refractory HL who had not received an ASCT, and who were treated with 1.8 mg/kg of ADCETRIS every 3 weeks.

Baseline patient characteristics showed failure from multiple prior chemotherapy regimens (median of 3 with a range of 1 to 7) before first administration with ADCETRIS. Fifty nine percent (59%) of patients had advanced stage disease (Stage III or IV) at initial diagnosis.

Results from these phase 1 studies and from the NPP experience showed, that in patients with relapsed or refractory HL without prior ASCT, clinically meaningful responses can be achieved as evidenced by an investigator-assessed, objective response rate of 54% and a complete remission rate of 22% after a median of 5 cycles of ADCETRIS.

Study SGN35-006 (Retreatment Study)

The efficacy of retreatment in patients who had previously responded (CR or PR) to treatment with ADCETRIS was evaluated in a phase 2, open-label, multicenter trial. Twenty patients with relapsed or refractory HL received a starting dose of 1.8 mg/kg and one patient received a starting dose of 1.2 mg/kg of ADCETRIS administered intravenously over 30 minutes every 3 weeks. The median number of cycles was 7 (range, 2 to 37 cycles). Of the 20 evaluable patients with HL, 6 patients (30%) achieved a CR and 6 patients (30%) achieved a PR with ADCETRIS retreatment, for an ORR of 60%. The median duration of response was 9.2 and 9.4 months in patients who achieved OR (CR+PR) and CR, respectively.

Systemic anaplastic large cell lymphoma

Study SG035-0004

The efficacy and safety of ADCETRIS as a single agent was evaluated in an open-label, single-arm, multicenter study in 58 patients with relapsed or refractory sALCL. See Table 11 below for a summary of baseline patient and disease characteristics.

Table 11: Summary of baseline patient and disease characteristics in the phase 2 relapsed or refractory sALCL study

Patient characteristics	n = 58
Median age, years (range)	52 years (14-76)
Gender	33M (57%)/25F (43%)
ECOG status ^a	
0	19 (33%)
1	38 (66%)
Prior ASCT	15 (26%)
Prior chemotherapy Regimens (range)	2 (1-6)
Histologically confirmed CD30-expressing disease	57 (98%)
Anaplastic lymphoma kinase (ALK)-negative disease	42 (72%)
Disease characteristics	
Primary Refractory to frontline therapy ^b	36 (62%)
Refractory to most recent therapy	29 (50%)
Relapsed to most recent therapy	29 (50%)
Baseline B symptoms	17 (29%)
Stage III at initial diagnosis	8 (14%)
Stage IV at initial diagnosis	21 (36%)

a. One patient had a baseline ECOG status of 2, which was prohibited by protocol and is captured as Inclusion Criteria Not Met.

b. Primary refractory sALCL is defined as a failure to achieve a complete remission to, or progressed within 3 months of completing frontline therapy.

The median time from initial sALCL diagnosis to first dose with ADCETRIS was 16.8 months.

Ten (10) patients (17%) received 16 cycles of ADCETRIS; the median number of cycles received was 7 (range, 1 to 16).

Response to treatment with ADCETRIS was assessed by Independent Review Facility (IRF) using the Revised Response Criteria for Malignant Lymphoma (Cheson, 2007). Treatment response was assessed by spiral CT of chest, neck, abdomen and pelvis; PET scans and clinical data. Response assessments were performed at cycles 2, 4, 7, 10, 13 and 16 with PET at cycles 4 and 7.

The ORR per IRF assessment was 86% (50 of 58 patients in the ITT set). CR was 59% (34 of 58 patients in the ITT set) and tumour reduction (of any degree) was achieved in 97% of patients. The estimated overall survival at 5 years was 60% (95% CI [47%,73%]). The median observation time (time to death or last contact) from first dose was 71.4 months. The investigator assessments were generally consistent with the independent review of the scans. Of the patients treated, 9 responding patients went on to receive an allogeneic stem cell transplant (SCT) and 9 responding patients went on to autologous SCT. For further efficacy results, see Table 12 and Figure 5.

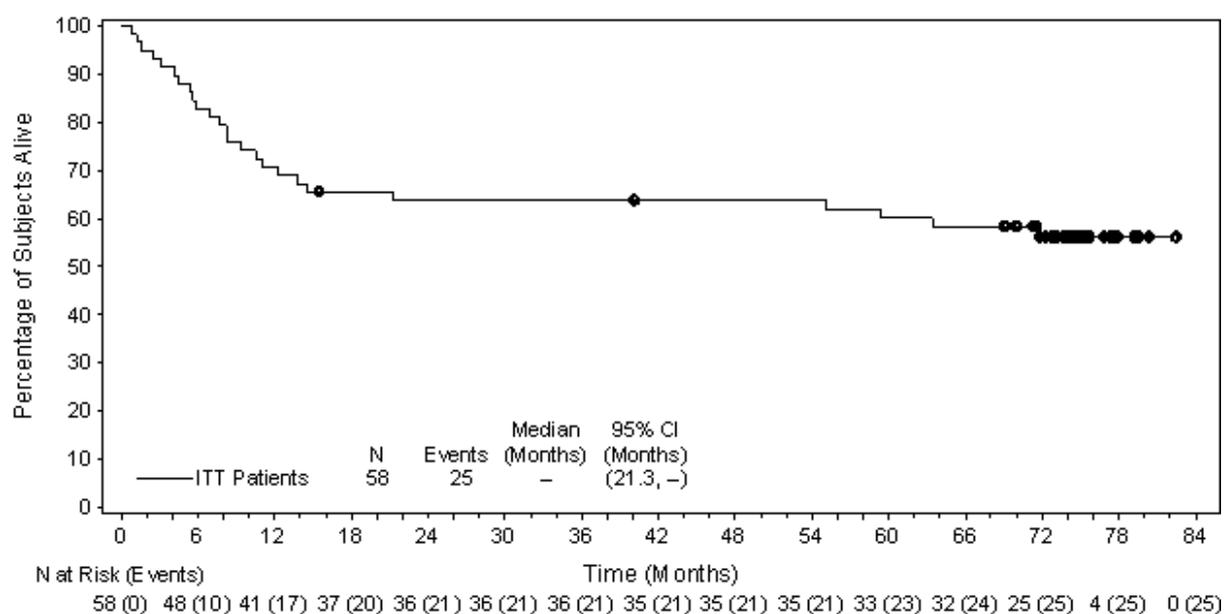
Table 12: Efficacy results in relapsed or refractory sALCL patients treated with 1.8 mg/kg of ADCETRIS every 3 weeks

Best clinical response (n = 58)	IRF n (%)	95% CI
Objective response rate (CR + PR)	50 (86)	74.6, 93.9
Complete remission (CR)	34 (59)	44.9, 71.4
Partial remission (PR)	16 (28)	NA
Disease control rate (CR + PR + SD)	52 (90)	78.8, 96.1
Duration of response	Median per IRF	95% CI
Objective response (CR + PR) ^a	13.2	5.7, 26.3
Complete remission (CR)	26.3	13.2, NE ^b
Progression Free Survival	Median per IRF	95% CI
Median	14.6	6.9, 20.6
Overall survival	Median	95% CI
Median	Not reached	21.3, NE ^b

^a. The range of DOR was 0.1 months to 39.1+ months and the median follow-up time from first dose for patients who achieved objective response (OR) per IRF was 15.5 months.

^b. Not estimable.

Figure 5: Kaplan-Meier Plot of OS



An exploratory intra-patient analysis showed that approximately 69% of the sALCL patients treated with ADCETRIS as part of the SG035-0004 clinical study experienced an improvement in clinical benefit as measured by longer progression free survival (PFS) compared with their most recent prior line of therapy.

Of the 17 patients (29%) who had B symptoms at baseline, 14 patients (82%) experienced resolution of all B symptoms in a median time from initiation of ADCETRIS of 0.7 months.

Study SGN35-006 (Retreatment study)

The efficacy of retreatment in patients who had previously responded (CR or PR) to treatment with ADCETRIS was evaluated in a phase 2, open-label, multicenter trial. Seven patients with relapsed sALCL received a starting dose of 1.8 mg/kg and one patient received a starting dose of 1.2 mg/kg of

ADCETRIS administered intravenously over 30 minutes every 3 weeks. The median number of cycles was 8.5 (range, 2 to 30 cycles). Of the 8 sALCL patients, 3 were retreated twice for a total of 11 retreatment experiences. Retreatment with ADCETRIS resulted in 6 CRs (55%) and 4 PRs (36%), for an ORR of 91%. The median duration of response was 8.8 and 12.3 months in patients who achieved OR (CR+PR) and CR, respectively.

Cutaneous T-cell lymphoma

Study C25001

The efficacy and safety of ADCETRIS as a single agent was evaluated in a pivotal phase 3, open-label, randomised, multicentre study in 128 patients with histologically confirmed CD30+ CTCL. CD30 positivity was defined as $\geq 10\%$ target lymphoid cells demonstrating membrane, cytoplasmic, and/or Golgi staining pattern based on an immunohistochemistry assay (Ventana anti-CD30 [Ber-H2]). Patients with a diagnosis of mycosis fungoides [MF] or primary cutaneous anaplastic large cell lymphoma [pcALCL] were considered eligible for the study. Patients were stratified by these disease types and randomised 1:1 to receive either ADCETRIS or the physician's choice of either methotrexate or bexarotene. Patients with pcALCL received either prior radiation therapy or at least 1 prior systemic therapy and patients with MF received at least 1 prior systemic therapy. Patients with a concurrent diagnosis of systemic ALCL, Sezary syndrome and other non-Hodgkin lymphoma (except for lymphomatoid papulosis [LyP]) were excluded from this study. Patients were treated with 1.8 mg/kg of ADCETRIS intravenously over 30 minutes every 3 weeks for up to 16 cycles or physician's choice for up to 48 weeks. The median number of cycles was approximately 12 cycles in the ADCETRIS arm. In the physician's choice arm, the median duration of treatment (number of cycles) for patients receiving bexarotene was approximately 16 weeks (5.5 cycles) and 11 weeks (3 cycles) for patients receiving methotrexate. Table 13 provides a summary of the baseline patient and disease characteristics.

Table 13: Summary of baseline patient and disease characteristics in the phase 3 CTCL Study (ITT Population)

Patient characteristics	ADCETRIS n = 64	Physician's Choice (Methotrexate or Bexarotene) n = 64
Median age (range)	62 years (22-83)	58.5 years (22-83)
Patients ≥ 65 years old n (%)	28 (44%)	24 (38%)
Gender n (%)	33M (52%)/31F (48%)	37M (58%)/27F (42%)
ECOG status n (%)		
0	43 (67)	46 (72)
1	18 (28)	16 (25)
2	3 (5)	2 (3)
Disease characteristics		
Median number of prior therapies (range)	4 (0-13)	3.5 (1-15)
Median number of skin-directed therapies (range)	1 (0-6)	1 (0-9)
Median number of systemic therapies (range)	2 (0-11)	2 (1-8)
MF, n (%)	48 (75)	49 (77)
Early (IA-IIA)	15 (31)	18 (37)
Advanced (IIB-IVB ^a)	32 (67)	30 (61)
pcALCL, n (%)	16 (25)	15 (23)
Skin only	9 (56)	11 (73)
Extracutaneous disease	7 (44)	4 (27)

^a One patient in each arm had incomplete staging data and are not included in the table

The most common prior skin directed therapies in the ITT population were radiotherapy (64%), phototherapy (48%) and topical steroids (17%). The most common prior systemic therapies in the ITT population were chemotherapy (71%), immunotherapy (43%) and bexarotene (38%).

The primary endpoint was objective response rate that lasts at least 4 months (ORR4) (duration from first response to last response ≥ 4 months), as determined by an independent review of the Global Response Score (GRS) consisting of skin evaluations (modified severity weighted assessment tool [mSWAT] as assessed per investigator), nodal and visceral radiographic assessment, and detection of circulating Sézary cells (Olsen 2011). Table 14 includes the results for ORR4 and other key secondary endpoints.

Table 14: Efficacy results in CTCL patients treated with 1.8 mg/kg of ADCETRIS every 3 weeks (ITT population)

	ADCETRIS (n = 64)	Physician's Choice (Methotrexate or Bexarotene) n = 64
Objective Response Rate lasting at least 4 months (ORR4) per IRF		
n (%)	36 (56.3)	8 (12.5)
Percent Difference (95% CI)		43.8 (29.1, 58.4)
p-value		<0.001
Complete Response (CR) per IRF		
n (%)	10 (15.6)	1 (1.6)
Percent Difference (95% CI)		14.1 (-4.0, 31.5)
Adjusted p-value ^a		0.0046
Progression Free Survival (PFS) per IRF		
Median (months)	16.7	3.5
Hazard Ratio		0.270
95% CI		(0.17, 0.43)
Adjusted p-value ^a		<0.001

^a Calculated from a weighted Holm's procedure

Pre-specified subgroup analyses of ORR4 per IRF were performed by patients' CTCL subtype, physicians' choice of treatment, baseline ECOG status, age, gender, and geographic region. The analyses showed a consistent trend towards benefit for patients who received ADCETRIS compared with patients who received physician's choice. ORR4 was 50% and 75% in the ADCETRIS arm versus 10.2% and 20% in the physician's choice arm for MF and pcALCL, respectively.

No meaningful differences in quality of life (assessed by the EuroQol five dimensions questionnaire [EQ-5D] and Functional Assessment of Cancer Therapy-General [FACT-G]) were observed between the treatment arms.

The efficacy and safety of ADCETRIS were evaluated in two additional open-label studies in 108 patients with relapsed CD30+ CTCL (including MF and pcALCL as well as SS, LyP and mixed CTCL histology), regardless of CD30 expression level. Patients were treated with ADCETRIS 1.8 mg/kg intravenously over 30 minutes every 3 weeks for up to 16 cycles. The safety and efficacy results in these studies were consistent with results in Study C25001. Overall response rates for MF were 54-66%; pcALCL, 67%; SS, 50%; LyP, 92%; and mixed CTCL histology, 82-85%.

Paediatric population

The safety, pharmacokinetics and anti-tumour activity of ADCETRIS in 36 paediatric patients (7-17 years of age) with r/r HL and sALCL (children aged 7-11 years, n = 12 and adolescents aged 12 to 17 years, n = 24) were evaluated in a phase 1/2 open-label, single-agent, multicentre dose-escalation study (C25002). Phase 1 of the study assessed the safety profile (see section 4.8), determined the paediatric maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D), and assessed the pharmacokinetics of ADCETRIS (see section 5.2). Phase 1 included 3 r/r HL patients treated at 1.4 mg/kg and 9 patients (7 r/r HL and 2 sALCL) treated at 1.8 mg/kg. The MTD was not reached. The RP2D was determined to be 1.8 mg/kg. Across the study, a total of 16 patients with r/r HL and 17 patients with r/r sALCL, of whom 10 were in first relapse, were treated with 1.8 mg/kg of ADCETRIS. The best overall response rate (ORR) per independent review facility (IRF) was analysed across both study phases at the RP2D. Of these 33 patients who received the RP2D, 32 were evaluable for response. The ORR was 47% in response-evaluable patients with r/r HL,

53% in patients with r/r sALCL and 60% in sALCL patients in first relapse. Eight HL patients and 9 sALCL patients went on to receive SCT following treatment with ADCETRIS.

The European Medicines Agency has deferred the obligation to submit the results of studies with ADCETRIS in one or more subsets of the paediatric population in the treatment of Hodgkin lymphoma and treatment of anaplastic large cell lymphoma (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited.

The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Monotherapy

The pharmacokinetics of brentuximab vedotin were evaluated in phase 1 studies and in a population pharmacokinetic analysis of data from 314 patients. In all clinical trials, brentuximab vedotin was administered as an intravenous infusion.

Maximum concentrations of brentuximab vedotin ADC were typically observed at the end of infusion or the sampling timepoint closest to the end of infusion. A multiexponential decline in ADC serum concentrations was observed with a terminal half-life of approximately 4 to 6 days. Exposures were approximately dose proportional. Minimal to no accumulation of ADC was observed with multiple doses at the every 3-week schedule, consistent with the terminal half-life estimate. Typical C_{max} and AUC of ADC after a single 1.8 mg/kg in a phase 1 study was approximately 31.98 $\mu\text{g}/\text{mL}$ and 79.41 $\mu\text{g}/\text{mL} \times \text{day}$ respectively.

MMAE is the major metabolite of brentuximab vedotin. Median C_{max} , AUC and T_{max} of MMAE after a single 1.8 mg/kg of the ADC in a phase 1 study was approximately 4.97 ng/mL, 37.03 ng/mL x day and 2.09 days respectively. MMAE exposures decreased after multiple doses of brentuximab vedotin with approximately 50% to 80% of the exposure of the first dose being observed at subsequent doses. MMAE is further metabolised mainly to an equally potent metabolite; however, its exposure is an order of magnitude lower than that of MMAE. Thus, it is not likely to have any substantial contribution to the systemic effects of MMAE.

In the first cycle, higher MMAE exposure was associated with an absolute decrease in neutrophil count.

Combination therapy

The pharmacokinetics of ADCETRIS in combination with AVD were evaluated in a single phase 3 study in 661 patients. Population pharmacokinetic analysis indicated that the pharmacokinetics of ADCETRIS in combination with AVD were consistent to that in monotherapy.

After multiple-dose, IV infusion of 1.2 mg/kg brentuximab vedotin every two weeks, maximal serum concentrations of ADC were observed near the end of the infusion and elimination exhibited a multi-exponential decline with a $t_{1/2z}$ of approximately 4 to 5 days. Maximal plasma concentrations of MMAE were observed approximately 2 days after the end of infusion, and exhibited a mono-exponential decline with a $t_{1/2z}$ of approximately 3 to 4 days.

After multiple-dose, IV infusion of 1.2 mg/kg brentuximab vedotin every two weeks, steady-state trough concentrations of ADC and MMAE were achieved by Cycle 3. Once steady-state was achieved, the PK of ADC did not appear to change with time. ADC accumulation (as assessed by

AUC_{14D} between Cycle 1 and Cycle 3) was 1.27-fold. The exposure of MMAE (as assessed by AUC_{14D} between Cycle 1 and Cycle 3) appeared to decrease with time by approximately 50%.

Distribution

In vitro, the binding of MMAE to human serum plasma proteins ranged from 68-82%. MMAE is not likely to displace or to be displaced by highly protein-bound medicines. *In vitro*, MMAE was a substrate of P-gp and was not an inhibitor of P-gp at clinical concentrations.

In humans, the mean steady state volume of distribution was approximately 6-10 l for ADC. Based on population PK estimation the typical apparent central volume of distribution of MMAE was 35.5l.

Metabolism

The ADC is expected to be catabolised as a protein with component amino acids recycled or eliminated.

In vivo data in animals and humans suggest that only a small fraction of MMAE released from brentuximab vedotin is metabolised. The levels of MMAE metabolites have not been measured in human plasma. At least one metabolite of MMAE has been shown to be active *in vitro*.

MMAE is a substrate of CYP3A4 and possibly CYP2D6. *In vitro* data indicate that the MMAE metabolism that occurs is primarily via oxidation by CYP3A4/5. *In vitro* studies using human liver microsomes indicate that MMAE inhibits only CYP3A4/5 at concentrations much higher than was achieved during clinical application. MMAE does not inhibit other isoforms.

MMAE did not induce any major CYP450 enzymes in primary cultures of human hepatocytes.

Elimination

The ADC is eliminated by catabolism with a typical estimated CL and half life of 1.5 l/day and 4-6 days respectively.

The elimination of MMAE was limited by its rate of release from ADC, typical apparent CL and half life of MMAE was 19.99 l/day and 3-4 days respectively.

An excretion study was undertaken in patients who received a dose of 1.8 mg/kg of brentuximab vedotin. Approximately 24% of the total MMAE administered as part of the ADC during a brentuximab vedotin infusion was recovered in both urine and faeces over a 1-week period. Of the recovered MMAE, approximately 72% was recovered in the faeces. A lesser amount of MMAE (28%) was excreted in the urine.

Pharmacokinetics in special populations

Population PK analysis showed that baseline serum albumin concentration was a significant covariate of MMAE clearance. The analysis indicated that MMAE clearance was 2-fold lower in patients with low serum albumin concentrations <3.0 g/dl compared with patients with serum albumin concentrations within the normal range.

Hepatic impairment

A study evaluated the PK of brentuximab vedotin and MMAE after the administration of 1.2 mg/kg of ADCETRIS to patients with mild (Child-Pugh A; n = 1), moderate (Child-Pugh B; n = 5) and severe (Child-Pugh C; n = 1) hepatic impairment. Compared to patients with normal hepatic function,

MMAE exposure increased approximately 2.3-fold (90% CI 1.27-4.12-fold) in patients with hepatic impairment.

Renal impairment

A study evaluated the PK of brentuximab vedotin and MMAE after the administration of 1.2 mg/kg of ADCETRIS to patients with mild (n = 4), moderate (n = 3) and severe (n = 3) renal impairment. Compared to patients with normal renal function, MMAE exposure increased approximately 1.9-fold (90% CI 0.85-4.21-fold) in patients with severe renal impairment (creatinine clearance < 30 mL/min). No effect was observed in patients with mild or moderate renal impairment.

Elderly

The population pharmacokinetics of brentuximab vedotin were examined from several studies, including data from 380 patients up to 87 years old (34 patients ≥ 65 -< 75 and 17 patients ≥ 75 years of age). Additionally, the population pharmacokinetics of brentuximab vedotin in combination with AVD were examined, including data from 661 patients up to 82 years old (42 patients ≥ 65 -< 75 and 17 patients ≥ 75 years of age). The influence of age on pharmacokinetics was investigated in each analysis and it was not a significant covariate.

Paediatric population

The pharmacokinetics of brentuximab vedotin ADC and MMAE following a 30-minute intravenous infusion of BV administered at 1.4 mg/kg or 1.8 mg/kg given every 3 weeks were evaluated in a phase 1/2 clinical trial of 36 paediatric patients (7-17 years of age) with r/r HL and sALCL (children aged 7-11 years, n = 12 and adolescents aged 12 to 17 years, n = 24) (see section 5.1). The C_{max} of ADC was typically observed at the end of infusion or the sampling closest to the end of infusion. A multi-exponential decline in ADC serum concentrations was observed with a terminal half-life of approximately 4 to 5 days. Exposures were approximately dose proportional with a trend observed for lower ADC exposures at lower ages/ body weights in the study population.

Median ADC AUC in children and adolescents from this study was approx. 14% and 3% lower than in adult patients, respectively, while MMAE exposures were 53% lower and 13% higher, respectively, than in adult patients. Median C_{max} and AUC of ADC after a single 1.8 mg/kg dose were 29.8 $\mu\text{g}/\text{mL}$ and 67.9 $\mu\text{g}\cdot\text{day}/\text{mL}$, respectively, in patients < 12 years of age and 34.4 $\mu\text{g}/\text{mL}$ and 77.8 $\mu\text{g}\cdot\text{day}/\text{mL}$, respectively, in patients ≥ 12 years of age. Median C_{max} , AUC, and T_{max} of MMAE after a single 1.8 mg/kg dose were 3.73 ng/mL, 17.3 ng $\cdot\text{day}/\text{mL}$, and 1.92 days, respectively, in patients < 12 years of age and 6.33 ng/mL, 42.3 ng $\cdot\text{day}/\text{mL}$, and 1.82 days, respectively, in patients ≥ 12 years of age. There was a trend of increased clearance of brentuximab vedotin in paediatric patients confirmed positive for ADAs. No patients aged < 12 years (0 of 11) and 2 patients aged ≥ 12 years (2 of 23) became persistently ADA positive.

5.3 Preclinical safety data

MMAE has been shown to have aneugenic properties in an *in vivo* rat bone marrow micronucleus study. These results were consistent with the pharmacological effect of MMAE on the mitotic apparatus (disruption of the microtubule network) in cells.

The effects of brentuximab vedotin on human male and female fertility have not been studied. However, results of repeat-dose toxicity studies in rats indicate the potential for brentuximab vedotin to impair male reproductive function and fertility. Testicular atrophy and degeneration were partially reversible following a 16-week treatment-free period.

Brentuximab vedotin caused embryo-foetal lethality in pregnant female rats.

In nonclinical studies, lymphoid depletion and reduced thymic weight were observed, consistent with the pharmacologic disruption of microtubules caused by MMAE derived from brentuximab vedotin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate (for pH-adjustment)
Sodium citrate dihydrate (for pH-adjustment)
 α,α -Trehalose dihydrate
Polysorbate 80

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

4 years.

After reconstitution/dilution, from a microbiological point of view, the product should be used immediately. However, chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C-8 °C.

6.4 Special precautions for storage

Store in a refrigerator (2 °C-8 °C).

Do not freeze.

Keep the vial in the original carton in order to protect from light.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I glass vial with a butyl rubber stopper and an aluminium/plastic flip-off seal, containing 50 mg powder.

Pack of 1 vial.

6.6 Special precautions for disposal and other handling

General precautions

Procedures for proper handling and disposal of anticancer medicines should be considered.

Proper aseptic technique throughout the handling of this medicinal product should be followed.

Instructions for reconstitution

Each single use vial must be reconstituted with 10.5 mL of water for injections to a final concentration of 5 mg/ mL. Each vial contains a 10% overfill giving 55 mg of ADCETRIS per vial and a total reconstituted volume of 11 mL.

1. Direct the stream toward the wall of the vial and not directly at the cake or powder.
2. Gently swirl the vial to aid dissolution. DO NOT SHAKE.
3. The reconstituted solution in the vial is a clear to slightly opalescent, colourless solution with a final pH of 6.6.
4. The reconstituted solution should be inspected visually for any foreign particulate matter and/or discolouration. In the event of either being observed, discard the medicinal product.

Preparation of infusion solution

The appropriate amount of reconstituted ADCETRIS must be withdrawn from the vial(s) and added to an infusion bag containing sodium chloride 9 mg/ mL (0.9%) solution for injection in order to achieve a final concentration of 0.4-1.2 mg/ mL ADCETRIS. The recommended diluent volume is 150 mL. The already reconstituted ADCETRIS can also be diluted into 5% dextrose for injection or Lactated Ringer's for injection.

Gently invert the bag to mix the solution containing ADCETRIS. DO NOT SHAKE.

Any portion left in the vial, after withdrawal of the volume to be diluted, must be disposed of in accordance with local requirements.

Do not add other medicinal products to the prepared ADCETRIS infusion solution or intravenous infusion set. The infusion line should be flushed following administration with sodium chloride 9 mg/ mL (0.9%) solution for injection, 5% dextrose for injection, or Lactated Ringer's for injection.

Following dilution, infuse the ADCETRIS solution immediately at the recommended infusion rate.

Total storage time of the solution from reconstitution to infusion should not exceed 24 hours.

Determining dosage amount:

Calculation to determine the total ADCETRIS dose (mL) to be further diluted (see section 4.2):

$$\frac{\text{ADCETRIS dose (mg/kg)} \times \text{patient's body weight (kg)}}{\text{Reconstituted vial concentration (5 mg/ml)}} = \text{Total ADCETRIS dose (mL) to be further diluted}$$

Note: If patient's weight is more than 100 kg, the dose calculation should use 100 kg. The maximal recommended dose is 180 mg.

Calculation to determine the total number of ADCETRIS vials needed:

$$\frac{\text{Total ADCETRIS dose (mL) to be administered}}{\text{Total volume per vial (10 mL/vial)}} = \text{Number of ADCETRIS vials needed}$$

Table 15: Sample calculations for patients receiving the recommended dose of 1.8 mg/kg of ADCETRIS for weights ranging from 60 kg to 120 kg

Patient weight (kg)	Total dose = patient weight multiplied by recommended dose [1.8 mg/kg ^a]	Total volume to be diluted ^b = total dose divided by reconstituted vial concentration [5 mg/ mL])	Number of vials needed = total volume to be diluted divided by total volume per vial [10 mL/vial])
60 kg	108 mg	21.6 mL	2.16 vials
80 kg	144 mg	28.8 mL	2.88 vials
100 kg	180 mg	36 mL	3.6 vials
120 kg ^c	180 mg ^d	36 mL	3.6 vials

- For a reduced dose, use 1.2 mg/kg for the calculation.
- To be diluted in 150 mL of diluent and administered by intravenous infusion over 30 minutes every 3 weeks.
- If patient's weight is more than 100 kg, the dose calculation should use 100 kg.
- The maximal recommended dose is 180 mg.

Table 16: Sample calculations for patients receiving the recommended dose of 1.2 mg/kg of ADCETRIS for weights ranging from 60 kg to 120 kg as combination therapy or when a reduced dose is required

Patient weight (kg)	Total dose = patient weight multiplied by recommended dose [1.2 mg/kg ^a]	Total volume to be diluted ^b = total dose divided by reconstituted vial concentration [5 mg/mL])	Number of vials needed = total volume to be diluted divided by total volume per vial [10 mL/vial])
60 kg	72 mg	14.4 mL	1.44 vials
80 kg	96 mg	19.2 mL	1.92 vials
100 kg	120 mg	24 mL	2.4 vials
120 kg ^c	120 mg ^d	24 mL	2.4 vials

- For a reduced dose, use 0.9 mg/kg for the calculation
- To be diluted in 150 mL of diluent and administered by intravenous infusion over 30 minutes every 3 weeks.
- If patient's weight is more than 100 kg, the dose calculation should use 100 kg.
- The maximal recommended dose for combination therapy is 120 mg.

Disposal

ADCETRIS is for single use only.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S
Dybendal Alle 10
2630 Taastrup
Denmark

8. MARKETING AUTHORISATION NUMBER

EU/1/12/794/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 October 2012

Date of renewal: 10 September 2018

10. DATE OF REVISION OF THE TEXT

6 February 2019

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>