The format of this insert was determined by the Ministry of Health and its content was checked and approved on July 2016

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).

Excipients 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 the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL):

1. following autologous stem cell transplant (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 CD30+ HL at increased risk of relapse or progression following ASCT (see section 5.1).

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

4.2 Posology and method of administration

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

Posology

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 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 3 weeks. Alternatively, treatment may be started at the last tolerated dose (see section 5.1).

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).

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

Patients with relapsed or refractory HL or sALCL 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).

For patients with HL at increased risk of relapse or progression following ASCT, ADCETRIS treatment should start following recovery from ASCT based on clinical judgment. These patients should receive up to 16 cycles (see section 5.1).

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

Severity grade of neutropenia (signs and symptoms [abbreviated description of CTCAE[a]])	**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
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 growth factor support (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

Severity of peripheral sensory or motor neuropathy (signs and symptoms [abbreviated description of CTCAE[a]])	**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
Grade 2 (interfering with function but not with activities of daily living) or Grade 3 (interfering with activities of daily living)	Withhold dose until toxicity returns to ≤ Grade 1 or baseline, then restart treatment at a reduced dose of 1.2 mg/kg every 3 weeks
Grade 4 (sensory neuropathy which is disabling or motor neuropathy that is life threatening or leads to paralysis)	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.

Renal impairment

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 monitored carefully (see section 5.2).

Hepatic impairment

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 monitored carefully (see section 5.2).

Elderly

The safety and efficacy in patients aged 65 and older have not been established. No data are available.

Paediatric population

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

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.

Brentuximab vedotin must not be administered as an intravenous push or bolus. Brentuximab vedotin 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 brentuximab vedotin causes pulmonary toxicity.

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 brentuximab vedotin-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. Brentuximab vedotin dosing 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. Brentuximab vedotin 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 brentuximab vedotin. 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. Brentuximab vedotin should be held for any suspected case of acute pancreatitis. Brentuximab vedotin 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 brentuximab vedotin.
Although a causal association with brentuximab vedotin 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 brentuximab vedotin 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, and opportunistic infections such as Pneumocystis jiroveci 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.

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 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 (see section 4.8).

Tumour lysis syndrome

Tumour lysis syndrome (TLS) has been reported with brentuximab vedotin. 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

Brentuximab vedotin treatment may cause peripheral neuropathy, both sensory and motor. Brentuximab vedotin-induced peripheral neuropathy is typically an effect of cumulative exposure to this medicinal product and is reversible in most cases.

In the pivotal phase 2 (SG035-0003 and SG035-0004) population, the incidence of pre-existing peripheral neuropathy was 24%. Treatment emergent neuropathy occurred in 56% of the population. At the time of last evaluation, the majority of patients (83%) had improvement or resolution of their peripheral neuropathy symptoms. For patients who reported peripheral neuropathy, brentuximab vedotin treatment discontinuation occurred in 17%, dose reductions were reported in 13%, and dose delays occurred in 21% of patients. The incidence of pre-existing peripheral neuropathy in patients with relapsed or refractory HL or sALCL who were retreated with brentuximab vedotin was 48%. Treatment emergent neuropathy occurred in 69% of the population. At the time of last evaluation, the majority of patients who were retreated and experienced treatment-emergent peripheral neuropathy (80%) had improvement or resolution of their peripheral neuropathy symptoms. Peripheral neuropathy led to discontinuation in 21% and dose modifications in 34% of patients who were retreated.

In the phase 3 population, at the time of last evaluation, the majority of patients in the brentuximab vedotin arm (85%) had improvement or resolution of their peripheral neuropathy symptoms. For patients who reported peripheral neuropathy, brentuximab vedotin treatment discontinuation occurred in 23%, dose reductions were reported in 29%, and dose delays occurred in 22% of patients.

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 brentuximab vedotin 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 brentuximab vedotin. 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 brentuximab vedotin. Complete blood counts should be monitored prior to administration of each dose of this treatment. Patients should be monitored closely for fever and managed according to best medical practice if febrile neutropenia develops.

Stevens-Johnson syndrome and toxic epidermal necrolysis

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with brentuximab vedotin. Fatal outcomes have been reported. If SJS or TEN occur, treatment with brentuximab vedotin 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 brentuximab vedotin. 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 brentuximab vedotin. 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 brentuximab vedotin. Patients experiencing hepatotoxicity may require a delay, change in dose or discontinuation of brentuximab vedotin.

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).

Sodium content in excipients

This medicinal product contains a maximum of 2.1 mmol (or 47 mg) of sodium per dose. To be taken into consideration for patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction with medicinal products metabolized 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.

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 brentuximab vedotin and until 6 months after treatment.

Pregnancy

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

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.

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

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

Brentuximab vedotin may have a minor influence on the ability to drive and use machines.

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.

ADCETRIS was administered as monotherapy in 160 patients in two phase 2 studies in patients with relapsed or refractory HL or sALCL. The median number of cycles was 9 in patients with relapsed or refractory HL and 7 in patients with relapsed or refractory sALCL. ADCETRIS was also administered as monotherapy in 167 out of 329 patients in a randomized, placebo-controlled phase 3 study in patients with HL at increased risk of relapse or progression following ASCT. The median number of cycles received in both arms was 15.

Serious infections and opportunistic infections were very common in patients treated with this medicine (see section 4.4). In the phase 2 and the phase 3 population, the most commonly reported opportunistic infections were herpes zoster and herpes simplex.

Serious adverse drug reactions in the pivotal phase 2 and the phase 3 population were: pneumonia, acute respiratory distress syndrome, headache, neutropenia, thrombocytopenia, constipation, diarrhoea, vomiting, nausea, pyrexia, peripheral motor neuropathy, peripheral sensory neuropathy, hyperglycaemia, demyelinating polyneuropathy, tumour lysis syndrome and Stevens-Johnson syndrome.

The most frequently observed (≥20%) adverse reactions in the pivotal phase 2 and the phase 3 population were: peripheral sensory neuropathy, fatigue, nausea, diarrhoea, upper respiratory tract infection, neutropenia, and cough. In addition, adverse reactions also observed at ≥20% were vomiting and pyrexia in the phase 2 studies and peripheral motor neuropathy was also observed in the phase 3 population.

Adverse reactions led to treatment discontinuation in 23% and 32% of patients receiving brentuximab vedotin in the phase 2 and the phase 3 population, respectively. Serious adverse reactions that led to treatment discontinuation in two or more patients in either the phase 2 or the phase 3 population were peripheral sensory neuropathy , peripheral motor neuropathy, demyelinating polyneuropathy, recurrent Hodgkin's disease, vomiting, and acute respiratory distress syndrome. Paresthesia also led to discontinuation in two or more patients in either the phase 2 or the phase 3 population.

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 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.

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 (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 3: Adverse reactions to ADCETRIS

System organ class	Adverse reactions
Infections and infestations	
Very common:	Infection[a], upper respiratory tract infection
Common:	Sepsis/septic shock, herpes zoster, pneumonia, herpes simplex
Uncommon:	Oral candidiasis, Pneumocystis jiroveci pneumonia, staphylococcal bacteraemia
Frequency not known:	Progressive multifocal leukoencephalopathy
Blood and lymphatic system disorders	
Very common:	Neutropenia
Common:	Anaemia, thrombocytopenia
Frequency not known:	Febrile neutropenia
Immune system disorders	
Frequency not known:	Anaphylactic reaction
Metabolism and nutrition disorders	
Common	Hyperglycaemia
Uncommon:	Tumour lysis syndrome
Nervous system disorders	
Very common:	Peripheral sensory neuropathy, peripheral motor neuropathy
Common:	Dizziness, demyelinating polyneuropathy
Respiratory, thoracic and mediastinal disorders	
Very Common:	Cough, dyspnoea
Gastro-intestinal disorders	
Very common:	Diarrhoea, nausea, vomiting, constipation, abdominal pain
Uncommon:	Pancreatitis acute
Hepatobiliary disorders	
Common:	Alanine aminotransferase/aspartate aminotransferase (ALT/AST) increased
Skin and subcutaneous tissue disorders	
Very common:	Alopecia, pruritus
Common	Rash
Rare:	Stevens-Johnson syndrome/ toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	
Very common:	Myalgia, arthralgia
Common:	Back pain
General disorders and administration site conditions	
Very common:	Fatigue, chills, pyrexia, infusion-related reactions[b]
Investigations	
Very common:	Weight decreased

a. Preferred terms that were reported under the Infections and Infestations SOC include sepsis/septic shock, upper respiratory tract infection, herpes zoster, and pneumonia.

b. Preferred terms associated with IRRs were headache, rash, back pain, vomiting, chills, nausea, dyspnoea, pruritus and cough.

Description of selected adverse reactions

Neutropenia led to dose delays in 14% and 22% of patients in the phase 2 and the phase 3 population, respectively .

Severe and prolonged (≥1 week) neutropenia can occur with this treatment which may increase the risk of patients developing serious infections. In the phase 2 population, 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.

In the phase 3 population, Grade 3 neutropenia was reported in 22% of patients in the brentuximab vedotin arm and Grade 4 neutropenia was reported in 7% of patients in the brentuximab vedotin arm. No patients required dose reduction or discontinued treatment for neutropenia.

In the phase 3 population, serious infections were reported in 9% of patients in the brentuximab vedotin arm. No events of bacteraemia, sepsis or septic shock were reported in the brentuximab vedotin arm.

Peripheral sensory neuropathy led to dose delays in 13% and 16% of patients in the phase 2 and the phase 3 population, respectively. In addition, peripheral motor neuropathy and upper respiratory tract infection both led to dose delays in 6% of patients in the phase 3 population.

Peripheral sensory neuropathy led to dose reductions in 9% and 22% of patients in the phase 2 and the phase 3 population, respectively. In addition, peripheral motor neuropathy also led to dose reductions in 6% of patients in the phase 3 population. Ninety percent (90%) and sixty-eight percent (68%) of patients in the phase 2 population and the phase 3 population, respectively, remained at the recommended dose of 1.8 mg/kg while on treatment.

Among patients who experienced peripheral neuropathy in the phase 2 population, the median follow up time from end of treatment until last evaluation was approximately 48.9 weeks. At the time of last evaluation, 83% of the 89 patients 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 was 16 weeks (range from 0.3 weeks to 106.6 weeks).

Among patients who experienced peripheral neuropathy in the phase 3 population, the median follow up time from end of treatment until last evaluation was approximately 98 weeks. At the time of last evaluation, 85% of patients who experienced peripheral neuropathy in the brentuximab vedotin arm experienced resolution or improvement of their peripheral neuropathy symptoms. Overall, the median time to resolution or improvement of peripheral neuropathy events in the brentuximab vedotin arm was 23.4 weeks (range from 0.1 weeks to 138.3 weeks).

IRRs were reported in 11% and 15% of patients in the phase 2 and the phase 3 population, respectively. In either the phase 2 population or the phase 3 population, the adverse events most commonly associated with IRRs were mild to moderate (Grade 1 or Grade 2) and included headache, rash, back pain, vomiting, chills, nausea, dyspnoea, pruritus and cough.

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.

Febrile neutropenia has been reported (see section 4.2). A patient enrolled in a phase 1 dose escalation trial experienced Grade 5 febrile neutropenia after receiving a single dose of 3.6 mg/kg of brentuximab vedotin.

Immunogenicity

Patients with relapsed or refractory HL or sALCL in two pivotal phase 2 studies were tested for antibodies to brentuximab vedotin every 3 weeks using a sensitive electrochemiluminescent immunoassay. Patients with HL at increased risk of relapse or progression following ASCT in the phase 3 study were also tested. Approximately 7% of patients in the phase 2 studies and 6% of patients in the brentuximab vedotin arm of the phase 3 study developed persistently positive anti-drug antibodies (ADA).Two patients in the phase 2 studies and two patients in the phase 3 study experienced adverse reactions consistent with IRRs that led to discontinuation of treatment.

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 ADA relative to patients with transiently positive ADA and never positive ADA.

Retreatment

Retreatment with ADCETRIS was administered in 21 patients with relapsed or refractory HL and 8 patients with relapsed sALCL. The median number of cycles was 7 (range, 2 to 37 cycles) (see section 5.1). The types and rates of adverse reactions reported for patients retreated with ADCETRIS 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 1 or 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.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il).

4.9 Overdose

There is no known antidote for overdose of brentuximab vedotin. 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 and sALCL 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 and sALCL disease and therapeutic spectrums and clinical evidence in two CD30-positive malignancies following multiple lines of treatment provide a biologic rationale for its use in patients with relapsed and refractory classical HL and sALCL with or without prior ASCT. 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 hematologic 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 SG035-0003

The efficacy and safety of brentuximab vedotin 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 4 below for a summary of baseline patient and disease characteristics.

Table 4: Summary of baseline patient and disease characteristics in the phase 2 relapsed or refractory HL study

Patient characteristics	**N = 102**
Median age, yrs (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 brentuximab vedotin; and the median number of cycles received was 9 (ranging from 1 to 16).

Response to treatment with brentuximab vedotin 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 5.

Table 5: Efficacy results in relapsed or refractory Hodgkin lymphoma patients treated with 1.8 mg/kg of brentuximab vedotin 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 brentuximab vedotin 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 brentuximab vedotin.

Data were 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 brentuximab vedotin 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 brentuximab vedotin. 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 brentuximab vedotin.

Study SGN35-005

The efficacy and safety of brentuximab vedotin were evaluated in a randomized, 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 randomized to the treatment arm and 164 patients were randomized 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	**Brentuximab vedotin N = 165**	**Placebo N = 164**
Median age, yrs (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 Response	47 (28%)	46 (28%)
HL Status after the end of frontline standard chemotherapy [b]		
Refractory	99 (60%)	97 (59%)
Refractory 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 randomization.

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 Brentuximab Vedotin Every 3 Weeks

	Brentuximab Vedotin 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 brentuximab vedotin 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 brentuximab vedotin 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**	
	Brentuximab Vedotin N = 21	**Placebo N = 28**	**Brentuximab Vedotin N = 144**	**Placebo N = 136**	**Brentuximab Vedotin 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**	
	Brentuximab Vedotin N = 21	**Placebo N = 28**	**Brentuximab Vedotin N = 144**	**Placebo N = 136**	**Brentuximab Vedotin 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 1 and 2).

Figure 1: Kaplan-Meier Plot of PFS per IRF in Patients with ≥ 2 Risk Factors

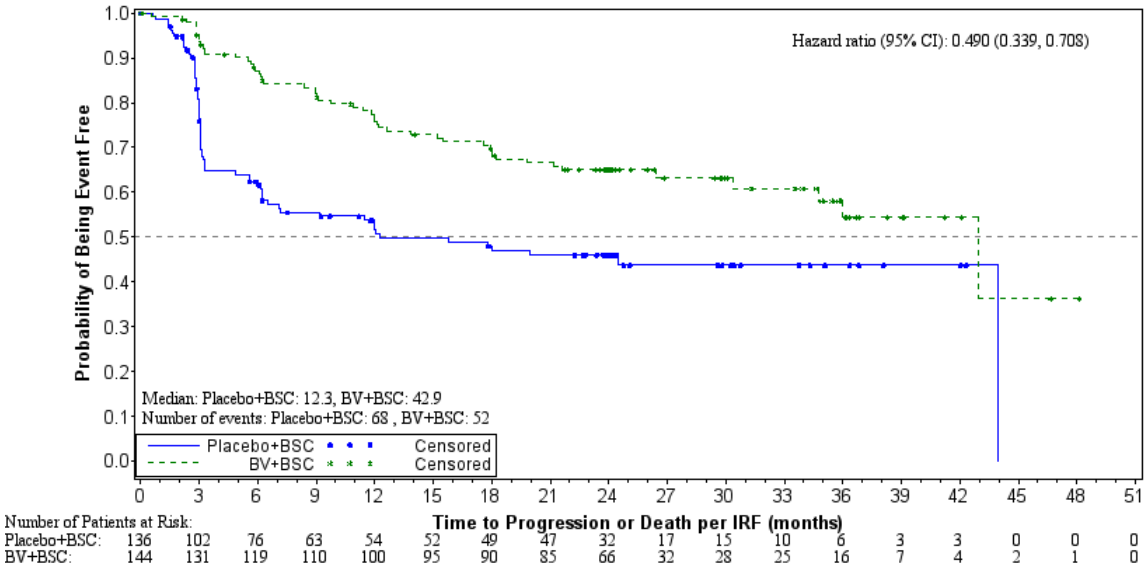
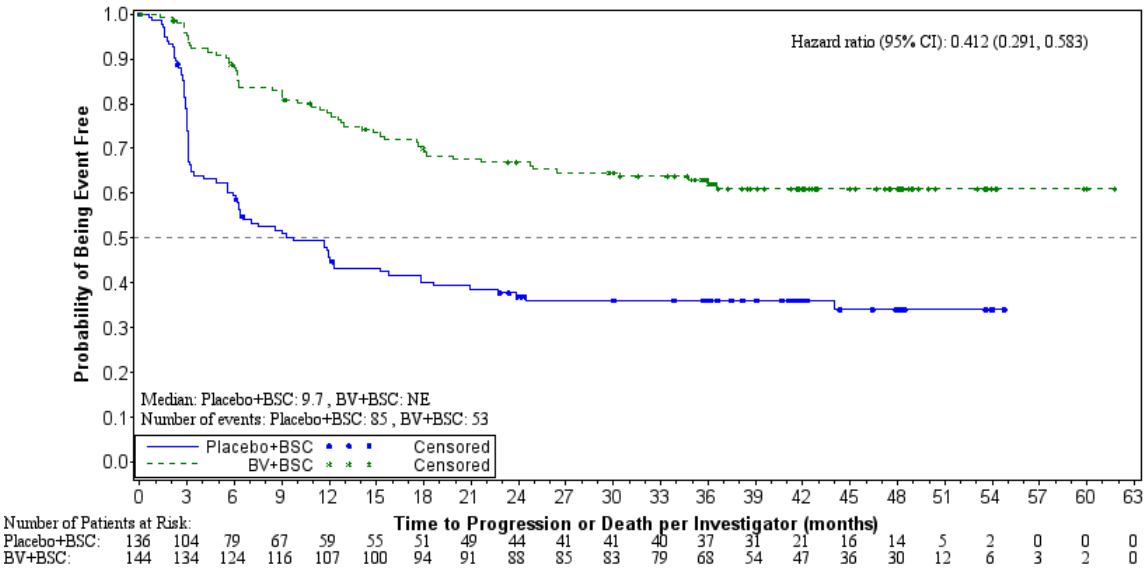


Figure 2: Kaplan-Meier Plot of PFS per Investigator in Patients with ≥ 2 Risk Factors



Study SGN35-006 (Retreatment Study)

The efficacy of retreatment in patients who had previously responded (CR or PR) to treatment with brentuximab vedotin 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 brentuximab vedotin 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 brentuximab vedotin as a single agent was evaluated in an open-label, single-arm, multicenter study in 58 patients with relapsed or refractory sALCL. 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 sALCL study

Patient characteristics	**N = 58**
Median age, yrs (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 brentuximab vedotin was 16.8 months.

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

Response to treatment with brentuximab vedotin 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 was achieved in 97% of patients. The estimated 36 month overall survival was 63% (the median observation time (time to death or last contact) from first dose was 33.4 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 7 responding patients went on to autologous SCT. For further efficacy results, see Table 10.

Table 10: Efficacy results in relapsed or refractory sALCL patients treated with 1.8 mg/kg of brentuximab vedotin 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, NE[b]
Complete remission (CR)	Not reached	13.0, NE
Overall survival	**Median**	**95% CI**
Median	Not reached[c]	21.3, NE

a. The range of DOR was 0.1+ months to 21.7+ months and the median follow-up time from first dose for patients who achieved objective response (OR) per IRF was 11.8 months.

b. Not estimable.

c. The estimated 36 month overall survival was 63% (the median observation time (time to death or last contact) from first dose was 33.4 months).

An exploratory intra-patient analysis showed that approximately 69% of the sALCL patients treated with brentuximab vedotin 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 brentuximab vedotin 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 brentuximab vedotin 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 brentuximab vedotin 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.

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

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 μg/ml and 79.41 μg/ml x 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 metabolized 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.

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 volume of distribution (VM and VMP) of MMAE were 7.37 l and 36.4 l respectively.

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 metabolized. 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 1.457 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
Clinical studies of brentuximab vedotin did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

Paediatric population

Clinical studies of brentuximab vedotin did not include sufficient numbers of patients below 18 years of age to determine whether the PK profile differs from adult patients.

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
Sodium citrate dihydrate
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

3 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 discoloration. 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):

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

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 11: 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*

a. For a reduced dose, use 1.2 mg/kg for the calculation.
b. To be diluted in 150 ml of diluent and administered by intravenous infusion over 30 minutes every 3 weeks.
c. If patient's weight is more than 100 kg, the dose calculation should use 100 kg.
d. The maximal recommended dose is 180 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 Israel Ltd.
Efal 25
P.O.B 4140 Kiryat Arie
Petach Tikva 4951125

8. MANUFACTURER

Takeda Italia
Via Crosa, 86
Cerano, 28065
Italy

9. MARKETING AUTHORISATION NUMBER(S)

152-09-33991-00

10. DATE OF REVISION OF THE TEXT

July 2016