EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 March 2022
EMA/205567/2022
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## ADCETRIS

International non-proprietary name: brentuximab vedotin

Procedure No. EMEA/H/C/002455/II/0099

## Note

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

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| Steps taken for the assessment | |
|---|---|
| **Description** | **Actual Date** |
| Start of procedure | 24 Jan 2022 |
| CHMP Rapporteur Assessment Report | 22 Feb 2022 |
| PRAC Rapporteur Assessment Report | 22 Feb 2022 |
| PRAC members comments | 02 Mar 2022 |
| Updated PRAC Rapporteur Assessment Report | 03 Mar 2022 |
| PRAC endorsed relevant sections of the assessment report | 10 Mar 2022 |
| CHMP members comments | 14 Mar 2022 |
| Updated CHMP Rapporteur Assessment Report | 18 Mar 2022 |
| Opinion | 24 Mar 2022 |

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# 1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Takeda Pharma A/S submitted to the European Medicines Agency on 21 December 2021 an application for a variation.

The following changes were proposed:

| **Variation requested** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.4 | C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | Type II | I, II and IIIB |

Update of sections 4.8 and 5.1 of the SmPC, based on final results from study C25006, a multi-centre open-label, phase 4 study of 50 patients with r/r sALCL undertaken to further evaluate the efficacy and safety of brentuximab vedotin as a single agent in adult patients who had previously received at least 1 multiagent chemotherapy regimen. This study is listed as an interventional cat 2 PASS in the RMP (SOB 010). In addition, the MAH took the opportunity to delete SOB 010 from the annex II and to delete the mention of conditional approval from annex II and the package leaflet. The RMP version 16.1 has also been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

# 2. Overall conclusion and impact on the benefit/risk balance

In this procedure the MAH has submitted the study report for Study C25006 containing this study's primary analysis of its overall response rate primary endpoint. As this study is subject of a SOB, this variation serves to fulfil the final specific obligation for conversion of brentuximab vedotin's conditional marketing authorisation to a marketing authorisation not subject to specific obligations. Study C25006 was designed to be similar to the pivotal phase 2 study, SG035-0004, the results of which supported the initial conditional marketing authorization application in the r/r sALCL indication. Study C25006 contains pharmacokinetic, efficacy, and safety data for patients with relapsed or refractory systemic anaplastic large-cell lymphoma (sALCL).

The pharmacokinetics and immunogenicity in study C25006 in subjects with sALCL are consistent with previously reported data and have been evaluated sufficiently.

Although the results of study C25006 seem to indicate a slightly lower activity than was reported for the registration study, the anti-tumour activity was still high with an ORR of >60% and a substantial duration of response as indicated by the lower bound of the CI (median DoR not estimable (95% CI, 19.71 months-NE)), the two endpoints, which combined are considered to be indicative of clinical benefit in a single arm study.

The safety profile in study C25006 shows the substantial but manageable toxicity of brentuximab vedotin monotherapy. The safety profile is in line with what has previously been reported and no new safety signal has been identified.

In conclusion, data from study C25006 is considered to confirm the positive benefit-risk of brentuximab vedotin monotherapy for the targeted population i.e. adult patients with relapsed or refractory sALCL. As such the SOB 010: *To perform a single-arm study in a similar patient population as the sALCL population investigating response rate, duration of response, rate of (second) ASCT and data in subpopulations (including but not necessarily restricted to ALK status and age) based on a CHMP-agreed protocol (Study C25006)* can be considered fulfilled and on that basis, the CHMP is of the

view that there are no remaining grounds for the marketing authorisation to remain conditional and therefore recommends the granting of a marketing authorisation no longer subject to specific obligations, and deletion of the last specific obligation from Annex II can be agreed.

Based on the final results from study C25006, update of sections 4.8 and 5.1 of the SmPC were proposed. The MAH has adapted the SmPC as suggested in the preliminary AR circulated on 22 February. The updates of sections 4.8 and 5.1 are now agreed. Furthermore, the MAH added an editorial update in section 5.1; update of the ATC code from L01XC12 to L01FX05 following the latest WHO classification.

The benefit-risk balance of ADCETRIS, remains positive.

# 3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

| **Variation requested** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.4 | C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | Type II | I, II and IIIB |

Update of sections 4.8 and 5.1 of the SmPC, based on final results from study C25006, a multi-centre open-label, phase 4 study of 50 patients with r/r sALCL undertaken to further evaluate the efficacy and safety of brentuximab vedotin as a single agent in adult patients who had previously received at least 1 multiagent chemotherapy regimen. This study was listed as an interventional category 2 PASS in the RMP (SOB 010). In addition, the MAH took the opportunity to request the granting of a marketing authorisation not subject to specific obligations and valid for five years, in accordance with Article 14-a(8) of Regulation (EC) No 726/2004, thereby deleting SOB 010 from the annex II and of the reference to the conditional marketing authorisation from annex II and the package leaflet. The revised RMP version 16.1 has also been submitted. An editorial update under section 5.1 of the SmPC (update of the ATC code) has been implemented.

In addition, the CHMP, having considered the application as set out in the appended assessment report and having reviewed the data submitted by the marketing authorisation holder including the evidence concerning compliance with specific obligations, is of the opinion that the risk-benefit balance of the above mentioned medicinal product remains favourable, that all specific obligations laid down in Annex II have been fulfilled and that comprehensive data supports a favourable benefit-risk balance of the above mentioned medicinal product. Therefore, pursuant to Article 14-a(8) of Regulation (EC) No 726/2004, the CHMP recommends by consensus the granting of a marketing authorisation in accordance with Article 14(1) of Regulation (EC) No 726/2004 for the above mentioned medicinal product for which the draft Summary of Product Characteristics is set out in Annex I.

☒is recommended for approval.

## *Amendments to the marketing authorisation*

In view of the data submitted with the variation, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

The following obligation has been fulfilled, and therefore it is recommended that it be deleted from the

Annex II to the Opinion:

| | | |
|---|---|---|
| **SOB 010** | To perform a single-arm study in a similar patient population as the sALCL population investigating response rate, duration of response, rate of (second) ASCT and data in subpopulations (including but not necessarily restricted to ALK status and age) based on a CHMP-agreed protocol (Study C25006) | Outstanding; Reporting date extended during reporting period.<br><br>Demographic and safety data are presented for Study C25006 in patients with relapsed or refractory sALCL, which was closed to enrolment for the entire reporting period with patients remaining in long-term follow-up. A revised due date of 4Q 2021 for reporting of study results was agreed with CHMP on 25 September 2020 (EMEA/H/C/002455/IB/0081). |

# 4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

## *Scope*

Please refer to the Recommendations section above

## *Summary*

Please refer to Scientific Discussion "Adcetris EMEA/H/C/002455/II/0099"

For more information, please refer to the Summary of Product Characteristics.

# Annex: Rapporteur’s assessment comments on the type II variation

# 5. Introduction

Adcetris (brentuximab vedotin) is a CD30-directed antibody-drug conjugate (recombinant chimeric IgG1, produced by recombinant DNA technology in Chinese Hamster ovary cells) consisting of 3 components:

1. the chimeric IgG1 antibody cAC10, specific for human CD30;
2. the microtubule-disrupting agent monomethyl auristatin E (MMAE); and
3. a protease-cleavable linker that covalently attaches MMAE to cAC10.

Brentuximab vedotin is proposed to have a multi-step mechanism of action that is initiated by binding to CD30 on the cell surface and internalization of the antibody-drug conjugate. Upon trafficking to lysosomes, MMAE is released from the conjugate through proteolytic degradation of the drug linker. Binding of released MMAE to tubulin disrupts the microtubule network, leading to G2/M phase cell cycle arrest and apoptosis.

Adcetris is indicated for adult patients with previously untreated CD30+ Stage IV Hodgkin lymphoma in combination with doxorubicin, vinblastine and dacarbazine, for the treatment of adult patients with CD30+ Hodgkin lymphoma at increased risk of relapse or progression following autologous stem cell transplant and for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma. In addition, Adcetris is indicated for adult patients with previously untreated systemic anaplastic large cell lymphoma (in combination with cyclophosphamide, doxorubicin and prednisone and for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma after at least 1 prior systemic therapy. The recommended dose for monotherapy and in combination with chemotherapy (cyclophosphamide, doxorubicin and prednisone) is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. The recommended dose in combination with chemotherapy (doxorubicin, vinblastine and dacarbazine) 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. If the patient's weight is more than 100 kg, the dose calculation should use 100 kg.

Since the granting of the conditional marketing authorisation (CMA), the MAH has submitted the following specific obligations (SOBs):

**Table 1. Full list of SOBs as adopted with the initial marketing authorisation**

| Number | Description | Status |
|---|---|---|
| **SOB 007** | Study SG035-0003<br>Study SG035-0004 | Fulfilled |
| **SOB 008** | Interim Report of the SOB 009 PASS study in sALCL (Study MA25101). | Fulfilled |
| **SOB 009** | Provision of the results of the ongoing Non-Interventional Post-Authorization Safety Study (PASS) conducted in HL and sALCL patient populations (Study MA25101). | Fulfilled |
| **SOB 010** | To perform a single-arm study in a similar patient population as the sALCL population investigating response rate, duration of response, rate of (second) ASCT and data in subpopulations (including but not necessarily restricted to ALK status and age) based on a CHMP-agreed protocol (Study C25006) | Outstanding; Reporting date extended during reporting period.<br><br>Demographic and safety data are presented for Study C25006 in patients with relapsed or refractory sALCL, which was closed to enrollment for the entire reporting period with patients remaining in long-term follow-up. A revised due date of 4Q 2021 for reporting of study results was agreed with CHMP on 25 September 2020 |

| Number | Description | Status |
|---|---|---|
| | | (EMEA/H/C/002455/IB/0081). |
| **SOB 011** | To perform a single-arm study in the r/r HL population not eligible for ASCT investigating response rate, PFS, OS, proportion of patients proceeding to transplant and safety (n = approx. 60 pts) based on a CHMP agreed protocol. | Fulfilled |

This Type II Variation is intended to update the EU SmPC to add data for post-marketing commitment specific obligation study C25006 alone and pooled with similar predecessor study SG035-0004. Submission of the C25006 clinical study report containing this study's primary analysis of its overall response rate primary endpoint further serves to fulfil the final specific obligation for conversion of brentuximab vedotin's conditional authorisation to full marketing authorisation not subject to specific obligations. The study contains pharmacokinetic, efficacy, and safety data for patients with relapsed or refractory systemic anaplastic large-cell lymphoma (sALCL).

Study C25006 was designed to be similar to the pivotal phase 2 study, SG035-0004 the results of which supported the initial marketing authorization application in the r/r sALCL indication.

Study C25006 was a single-arm, open-label, multi-centre Phase 4 clinical study, which was designed to evaluate the efficacy and safety of brentuximab vedotin as a single agent in adult patients with relapsed or refractory sALCL who had previously received at least 1 multi-agent chemotherapy such as cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate (Oncovin), and prednisone or an equivalent multiagent chemotherapy regimen with curative intent. The study was conducted between 23rd of January 2014 and 4th of May 2021. The study's primary objective was to determine the antitumour efficacy of single-agent brentuximab vedotin in this patient population, as measured by overall objective response rate. A total of 50 patients were enrolled and treated in the study. Brentuximab vedotin was administered as a single outpatient 1.8 mg/kg intravenous infusion over ~30 minutes on Day 1 of each 3-week cycle. Patients who achieved stable disease or better should have received a minimum of 8 treatment cycles and all patients were to be given the opportunity to complete a maximum of 16 cycles.

# 6. Clinical Pharmacology aspects

A clinical study was conducted in adult patients with relapsed or refractory sALCL who had previously received at least 1 multi-agent chemotherapy such as cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate (Oncovin), and prednisone or an equivalent multiagent chemotherapy regimen with curative intent in which the PK and immunogenicity was measured and compared with previous obtained PK results (study C25006).

## *6.1. Methods*

The study consisted of 50 patients. Blood samples were obtained each treatment cycle pre-dose and relative to the end of the brentuximab vedotin infusion for the measurement of serum/plasma concentrations of brentuximab vedotin, free cytotoxic payload (MMAE), total antibody, and anti-drug antibody (including neutralising anti-drug antibodies).

The analysis of serum concentrations of brentuximab vedotin and total antibody was performed by Labcorp Early Development Laboratories Inc. (Chantilly, Virginia) using validated enzyme-linked immunosorbent assay (ELISA) methods (methods ELISA-0198-021 and ELISA-0202-016). Neutralising

antibodies were analysed using a validated ELISA method (method ICDIM 227 V 1.01) by PPD® laboratories (Richmond, Virginia, USA). Samples with a mean response less than or equal to the neutralising antibody assay cut point were classified as positive for the presence of anti-SGN-35 neutralising antibodies. This analytical method has been used for the analysis of neutralising antibodies in previous procedure EMEA/H/C/002455/II/0093. The analysis of plasma concentrations of MMAE was performed by Labcorp Early Development Laboratories Inc. (Madison, Wisconsin, USA) using validated liquid chromatography tandem mass spectrometry method (method MMAHPP). This analytical method has been used for the analysis of MMAE in previous procedure EMEA/H/C/002455/II/0093.

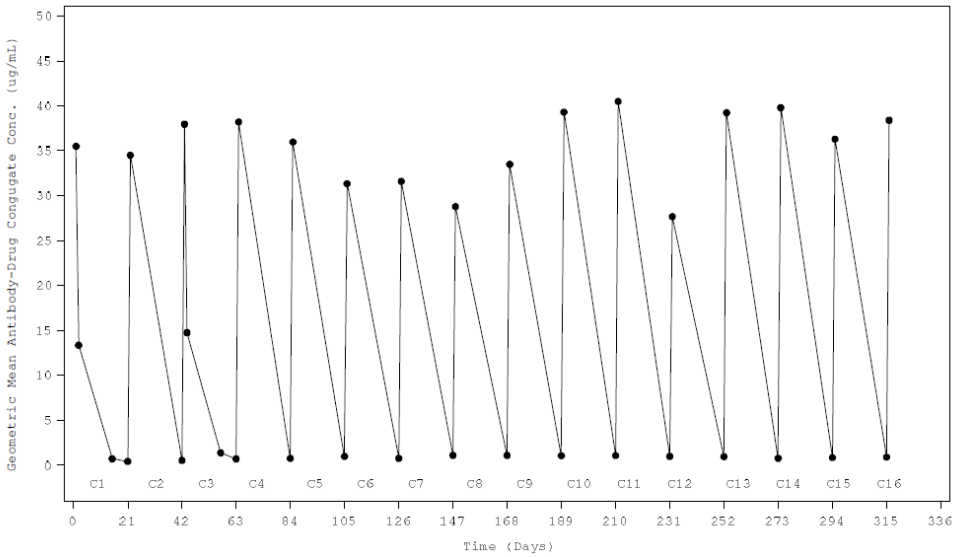
## *6.2. Results*

Blood samples were obtained from 50 patients using a sparse PK sampling scheme. Serum brentuximab vedotin (antibody-drug conjugate) concentration data were obtained from 49 patients. Serum total antibody concentration data were obtained from 48 patients. Plasma MMAE concentration data were obtained from 50 patients. A baseline sample and at least 1 post-baseline sample were available for 44 patients in the safety population for anti-drug antibody assessment.

Pharmacokinetics

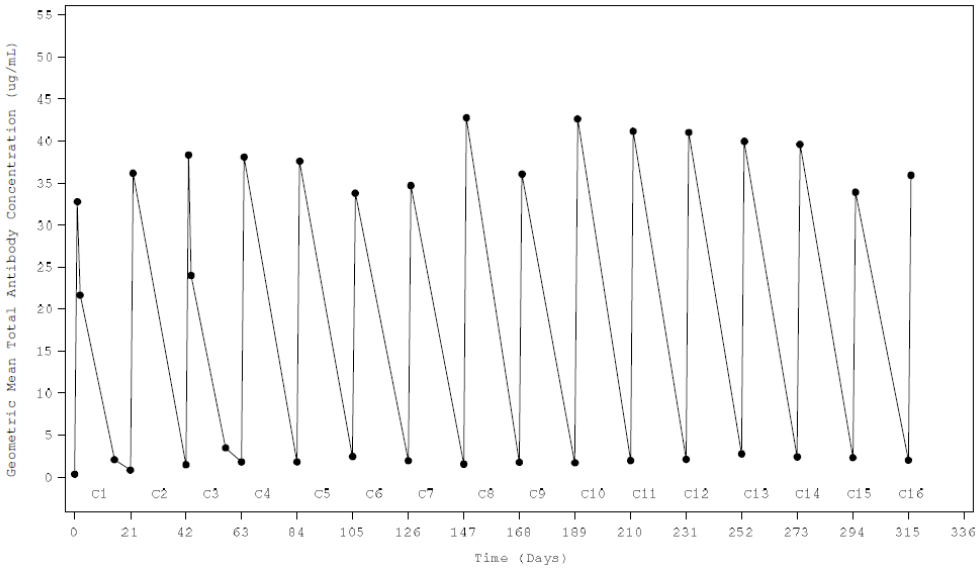
Serum brentuximab vedotin (antibody-drug conjugate) concentration-time profiles are shown in Figure 1. The geometric mean brentuximab vedotin concentrations at approximately the end of the brentuximab vedotin infusion was 35 µg/mL at Cycle 1 Day 1 (CV%=35; n=48) and 38 µg/mL at Cycle 3 Day 1 (CV%=25; n=38).

***Figure 1.*** *geometric mean antibody-drug conjugate concentration time curve (study C25006)*



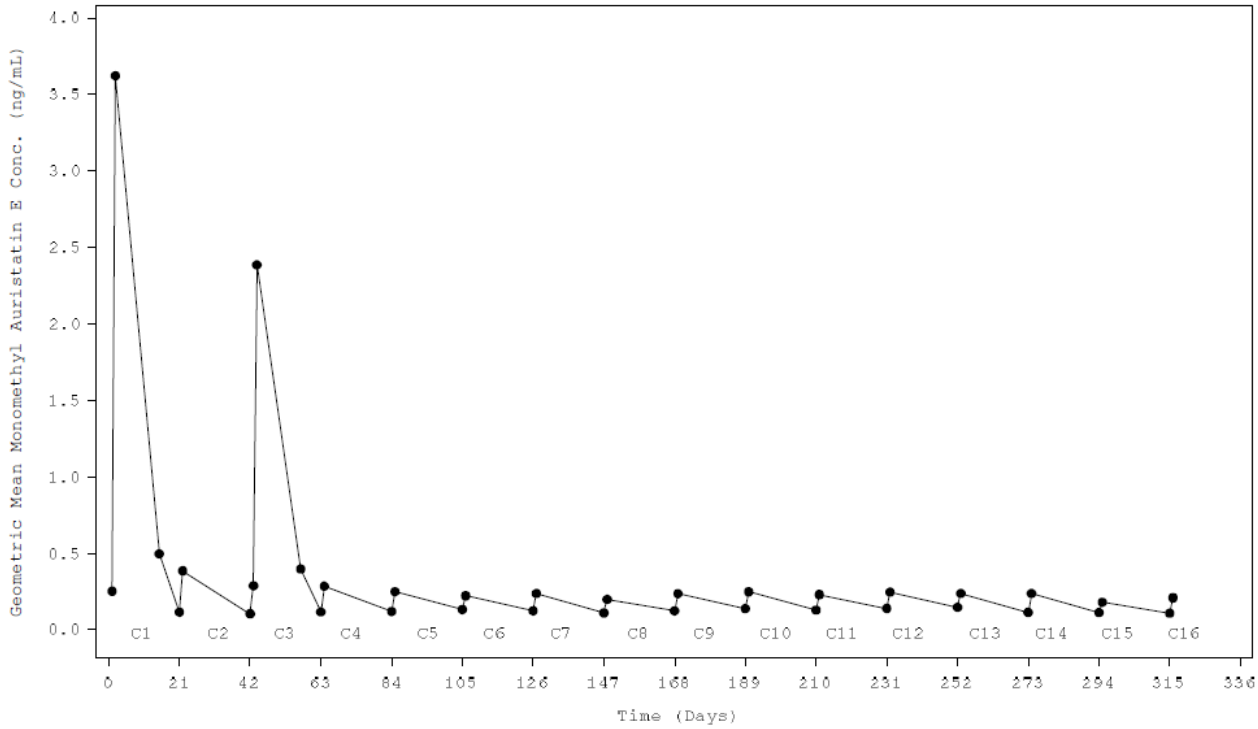

Serum TAb concentration-time profiles are shown in Figure 2. The geometric mean total antibody concentrations at approximately the end of the brentuximab vedotin infusion was 33 µg/mL at Cycle 1 Day 1 (CV%=29; n=48) and 38 µg/mL at Cycle 3 Day 1 (CV%=23; n=36).

***Figure 2.*** *geometric mean total antibody concentration time curve (study C25006)*




Plasma MMAE concentration-time profiles are shown in Figure 3. The mean MMAE concentrations at approximately the end of the brentuximab vedotin infusion was 0.33 ng/mL at Cycle 1 Day 1 (CV%=87; n=49) and 0.36 ng/mL at Cycle 3 Day 1 (CV%=88; n=38). The geometric $C_{max}$ was 3.6 ng/mL at Cycle 1 and 2.4 ng/mL at Cycle 3 as measured by the 24 hours post-dose sample.

***Figure 3.*** *Geometric mean MMAE concentration time curve (study C25006)*




Immunogenicity

A baseline sample and at least 1 post-baseline sample were available for 44 patients in the safety population for anti-drug antibody assessment; these 44 patients were considered immunogenicity evaluable. All 44 patients (100%) were anti-drug antibody negative at baseline. After treatment with brentuximab vedotin, 13 patients (30%) were confirmed anti-drug antibody positive. Among the 13

patients with confirmed anti-drug antibody-positive samples, 9 patients (20%) were transiently anti-drug antibody positive (1 or 2 post-baseline samples confirmed anti-drug antibody positive), and 4 patients (9%) were persistently anti-drug antibody positive (>2 post-baseline samples confirmed anti-drug antibody positive). All confirmed anti-drug antibody-positive samples had low titres of ≤25 (ranging between <5 and 25) and neutralising antibodies were not detected in any of the confirmed anti-drug antibody-positive samples. In short, all postbaseline anti-drug antibody-positive samples were neutralising antibody negative.

### *6.3. Discussion*

Study C25006 was a Phase 4, single-arm, open-label, multi-centre clinical study, which was designed to evaluate the efficacy and safety of brentuximab vedotin as a single agent in adult patients with relapsed or refractory sALCL who had previously received at least 1 multi-agent chemotherapy regimen. The pharmacokinetics (brentuximab vedotin, MMAE, and total antibody) and (neutralising) anti-drug antibody formation was investigated as secondary objective. The analytical methods for the analysis brentuximab vedotin (antibody-drug conjugate), MMAE, total antibody, and neutralising antibodies have been used in previous procedure EMEA/H/C/002455/II/0093 and are therefore acceptable. The geometric mean brentuximab vedotin concentrations at approximately end of infusion was 35 µg/mL on Cycle 1 Day 1 and 38 µg/mL on Cycle 3 Day 1. The geometric mean total antibody concentration at approximately the end of infusion was 33 µg/mL on Cycle 1 Day 1 and 38 µg/mL on Cycle 3 Day 1. The geometric $C_{max}$ of MMAE was 3.6 ng/mL at Cycle 1 and 2.4 ng/mL at Cycle 3.

The PK profiles were consistent with previously observed PK profiles for brentuximab vedotin, total antibody, and MMAE in subjects with HL and sALCL. After treatment with brentuximab vedotin, 13 patients (30%) were confirmed anti-drug antibody positive of which 9 patients were transiently positive (1 or 2 post-baseline samples positive) and 4 patients were persistently positive (>2 postbaseline samples positive). All post-baseline anti-drug antibody-positive samples were neutralising antibody negative.

In conclusion, pharmacokinetics and immunogenicity in study C25006 in subjects with sALCL are consistent with previously reported data and have been evaluated sufficiently.

## 7. Clinical Efficacy aspects

Study C25006 was conducted in compliance with the institutional review board (IRB) regulations, GCP regulations and guidelines, and all applicable local regulations.

### *7.1. Methods – analysis of data submitted*

**Study participants**

The target population of the study were male or female patients aged 18 years or older, with histologically confirmed r/r sALCL who had previously received at least 1 multiagent chemotherapy regimen such as CHOP or equivalent multiagent chemotherapy regimens with curative intent.

Main inclusion criteria:

- Patients with r/r sALCL who had previously received at least 1 multiagent chemotherapy regimen (CHOP or equivalent multiagent chemotherapy regimens with curative intent).
- Histologically-confirmed sALCL based on local pathology report.

- Aged 18 years or older.
- Bidimensional measurable disease of ≥1.5 cm as documented by radiographic technique (spiral CT preferred) per the IWG Revised Response Criteria for Malignant Lymphoma.
- Evidence of r/r sALCL (positive biopsy subsequent to most recent therapy, evidence of tumour growth, or new tumour mass)

Main exclusion criteria:

- Previous treatment with brentuximab vedotin.
- Previous allogeneic SCT.
- Current diagnosis of primary cutaneous ALCL (patients whose ALCL had transformed to sALCL were eligible).

Treatment

Brentuximab vedotin was administered as a single outpatient 1.8 mg/kg IV infusion on Day 1 of each 3-week cycle. Patients who achieved stable disease or better should have received a minimum of 8 treatment cycles and all patients were to be given the opportunity to complete a maximum of 16 cycles. Patients could continue on study treatment until disease progression or unacceptable toxicity.

All drug-related toxicity must have been resolved before starting a new treatment cycle, delays of longer than 3 weeks for study drug-related toxicities required study drug discontinuation, unless the sponsor agreed the benefit-risk assessment supported continued treatment. In case of grade 3 or 4 hematologic toxicity, growth factor support (G-CSF or GM-CSF) for treatment of neutropenia or for prophylaxis in subsequent cycles could be considered. For grade 4 hematologic toxicity and grade 3 peripheral neuropathy a reduced dose of 1.2 mg/kg is recommended, while for grade 4 neuropathy treatment discontinuation was indicated.

**Assessments**

Dedicated computed tomography (CT) scans (spiral preferred) of chest, neck, abdomen, and pelvis were to be performed at baseline and at Cycles 2, 4, 7, 10, 13, and 16. Patients who discontinued study treatment with stable disease or better were to have CT scans performed every 3 months for 18 months from EOT or until the sooner of disease progression, death, or study closure. Positron emission tomography (PET) scans were to be performed at baseline, and at Cycles 4 and 7, or at the end of treatment (EOT) for patients who discontinued study treatment without a postbaseline PET assessment. Measures of anticancer activity were assessed by an independent review facility (IRF) according to the International Working Group (IWG) Revised Response Criteria for Malignant Lymphoma.

Clinical laboratory samples were scheduled before dose administration on Day 1 of each 3-week cycle. Cycle 1 Day 1 clinical laboratory samples could have been collected within 4 days before dose administration to ensure patient eligibility on Study Day 1. Physical examination, including vital signs, weight, Eastern Cooperative Oncology Group (ECOG) performance status, and B symptoms assessment; brentuximab vedotin PK; immunogenicity; serum biomarkers; HU; and QOL assessments were scheduled to be performed on Day 1 of each cycle. In addition, a bone marrow biopsy was required to confirm responses in patients who had bone marrow involvement at baseline.

**Objectives:**

The primary objective of study C25006 is to assess the antitumor efficacy of single agent brentuximab vedotin (1.8 mg/kg administered intravenously every 3 weeks) as measured by the overall objective

response rate (ORR) in patients with relapsed or refractory sALCL following at least 1 multi-agent chemotherapy regimen (CHOP or equivalent multi-agent chemotherapy regimens with curative intent).

Secondary objectives included the determination of the duration of tumour control (duration of response (DOR), PFS and CR rate), proportion of patients receiving hematopoietic stem cell transplant, OS, safety and tolerability, PK and immunogenicity. Exploratory objectives were time to progression (TTP), time to response (TTR), disease-related symptoms, correlation biomarkers with outcomes, patient-reported health-related quality of life (QOL) and health care utilization (HU).

**Statistical methods**

The original C25006 protocol was approved on 29 November 2012, and the conduct of the study was modified by 1 amendment to the original protocol. No patients were enrolled under the original protocol. Amendment 1 was authored to clearly specify a minimum sample size, clarify the duration of posttreatment follow up (PTFU) to ensure mature efficacy data, delete several redundant assessments, and, where it was considered necessary, further clarify study procedures.

Final OS analysis is planned after the sooner of 50% of OS events in patients with a confirmed diagnosis of sALCL by central pathology review or 5 years after enrolment of the last patient.

Study data were analyzed as described in the SAP, approved on 18 June 2021 before clinical database lock, based on the study objectives and endpoints defined in Protocol C25006 Amendment 1. No changes were made to the planned analyses. The study was conducted for all enrolled patients according to the procedures described in Protocol Amendment 1.

*Primary efficacy endpoint*

The primary endpoint of the study was ORR by IRF assessment in patients with r/r sALCL following at least 1 multiagent chemotherapy regimen (CHOP or equivalent) with ORR as the proportion of patients with either a CR or PR according to IWG Revised Response Criteria for Malignant Lymphoma. A minimum of 45 patients with r/r sALCL were to be enrolled in the study. Based on previous study results, with a sample size of 45 patients, observing 31 objective responses, either CR or PR (69%), would provide the lower bound of the 95% CI (2-sided) that the true ORR is greater than 53%.Subgroup analyses by age group and ALK tumor status were performed for ORR, and the time-to-event efficacy endpoints, DOR, DOCR, PFS, and OS.

**comments**

The design of the study is very similar to the registration study for sALCL (SG035-0004) and has been agreed by CHMP.

## *7.2. Results*

**Accrual**

The first patient was enrolled in Study C25006 on 30 January 2014 and the last patient was enrolled on 31 October 2019. A total of 62 patients were screened for study eligibility and 12 of these patients were determined to be ineligible for study enrolment because of not meeting all inclusion criteria (n=8) or by meeting an exclusion criterion (n=4). A total of 50 patients were enrolled in the study. The ITT, safety, PK, and biomarker analysis populations consisted of 50 patients, and the PP analysis population consisted of 46 patients. The primary reason for study drug discontinuation was reported as disease progression for 17 patients (34%), an AE for 16 patients (32%), completion of the maximum number of cycles of therapy for 8 patients (16%), and initiation of hematopoietic SCT for 5 patients (10%).

The death of 22 patients (44%) was reported at the time of data cut-off for analysis of the primary endpoint of ORR. Death was considered disease related for 14 patients and not disease related for 8 patients. On study death of 5 patients (10%) are discussed in the safety section.

As of the 04 May 2021 cut-off for primary endpoint analysis, the treatment period of the study had been completed for all study participants and the study was ongoing for 23 patients in either PFS and/or OS follow-up. The data cut-off date represents approximately 1.6 years' follow-up since enrolment of the last patient. However, due to slow enrolment, earlier-enrolled patients have been followed for 7+ years and the median duration of overall survival (OS) follow-up for the study is 44 months.

The intent-to-treat (ITT) analysis population included all enrolled patients and was used for the primary efficacy analysis, and analysis of secondary and exploratory efficacy endpoints. All 50 enrolled patients were counted in the ITT population.

**Conduct of the study**

Important protocol deviations, which pertained to the study's inclusion /exclusion criteria, were identified for 6 patients. Clinical laboratory criteria were not met for 5 patients within 4 days of administration and an ECOG performance score of 2 was reported for 1 patient at screening, which should have precluded study enrolment.

**comments**

The MAH indicated that none of the protocol deviations were considered to have a significant impact on the assessment of the tumour response. This assessment is agreed.

**Baseline characteristics**

A total of 50 patients were enrolled, of whom 46 diagnoses of sALCL confirmed by a central lab, against a planned total enrolment of 45 patients. The population consisted of 19 men (38%) and 31 women (62%), with a mean age of 59.5± 16.7 years (range of 19-87 years) and a mean body weight of 75.2 ± 20.7 kg (range of 39 to 137 kg). A total of 33 patients (66%) were aged ≤65 years and 17 patients (34%) were aged ≥65 years. All 50 patients (100%) were white. A total of 14 patients (28%) had a primary diagnosis of ALK+ ALCL, and 36 patients (72%) had a diagnosis of ALK− ALCL (see Table 1).

*Table 1 Study C25006: Baseline Disease Characteristics (Safety Population) Brentuximab vedotin*

| | Brentuximab Vedotin N=50 |
|---|---|
| **Disease type, n (%)** | |
| Mature T-cell and NK-cell neoplasm | 50 (100) |
| Anaplastic large cell lymphoma, ALK-positive | 14 (28) |
| Anaplastic large cell lymphoma, ALK-negative | 36 (72) |
| **Time from initial sALCL diagnosis to first dose (months)** | |
| n | 50 |
| Mean (std dev) | 38.1 (68.19) |
| Median | 12.0 |
| Minimum, maximum | 1, 412 |
| **Baseline SPD of dominant nodes or nodal masses per IRF ($cm^2$)** | |
| n | 42 |
| Mean (std dev) | 17.48 (17.779) |
| Median | 11.73 |
| Minimum, maximum | 1.4, 77.3 |
| **Ann Arbor stage at initial diagnosis, n (%)** | |
| I | 3 (6) |
| II | 12 (24) |
| III | 9 (18) |
| IV | 23 (46) |
| Unknown | 3 (6) |
| **Evidence of bone marrow involvement, n (%)** | |
| Yes | 4 (8) |
| No | 39 (78) |
| Unknown | 7 (14) |

| | Brentuximab Vedotin N=50 |
|---|---|
| **Evidence of extranodal involvement**, n (%) | |
| Yes | 29 (58) |
| No | 21 (42) |
| **History of bone marrow involvement**, n (%) | |
| Yes | 4 (8) |
| No | 42 (84) |
| Unknown | 4 (8) |
| **ALK status**, n (%) | |
| ALK-positive | 14 (28) |
| ALK-negative | 36 (72) |
| **Any baseline B symptoms**, n (%) | |
| Yes | 14 (28) |
| No | 36 (72) |
| **Any baseline B symptoms or evidence of bone marrow involvement**, n (%) | |
| Yes | 16 (32) |
| No | 34 (68) |
| **All 3 baseline B symptoms present**, n (%) | |
| Yes | 1 (2) |
| No | 49 (98) |
| **Unexplained weight loss of >10% of the body weight**, [a] n (%) | |
| Yes | 1 (2) |
| No | 49 (98) |
| **Unexplained, persistent, or recurrent fever >38°C**, [a] n (%) | |
| Yes | 5 (10) |
| No | 45 (90) |
| **Recurrent drenching night sweats**, [a] n (%) | |
| Yes | 10 (20) |
| No | 40 (80) |

| | Brentuximab Vedotin N=50 |
|---|---|
| **ECOG performance status**, n (%) | |
| 0 | 17 (34) |
| 1 | 31 (62) |
| 2 | 1 (2) |
| 3 | 1 (2) |

Source: Table 15.1.1.3.

ALK: anaplastic lymphoma kinase; ECOG: Eastern Cooperative Oncology Group; IRF: independent review facility; NK: natural killer; sALCL: systemic anaplastic large cell lymphoma; SPD: sum of the products of the diameters; std dev: standard deviation.

Percentages are based on the number of patients in the safety population.

Baseline SPD is the SPD of up to 6 of the largest dominant nodes or nodal masses.

[a] Unexplained weight loss, unexplained persistent or recurrent fever, and recurrent drenching night sweats are the 3 individual baseline B symptoms.

A median of 1 prior anticancer therapy (range, 1-10 prior therapies) was reported, prior anticancer therapies included prior ASCT for 4 patients (8%), a prior surgical procedure related to the cancer under study for 13 patients (26%), and prior radiation therapy for 5 patients (10%). Relative to the most recent prior therapy, a CR was reported for 16 patients (32%), PR for 8 patients (16%) and progressive disease for 15 patients (30%) in the safety population.

**comments**

The baseline patient and disease characteristics are similar to the predecessor study SG035-0004, with the exception median number of prior therapies 2 vs 1, respectively, but with the same range (1-6 prior therapies).

Demographic data presented for Study C25006 are indicative of a patient with relapsed or refractory sALCL.

**Outcomes**

**comments**

In addition to the study result for C25006 the MAH has also provided a pooled analysis of this study with the similar and predecessor study SG035-0004. For efficacy parameters (ORR, PFS and OS) the pooled analyses are also presented in this AR.

Of note: The Study SG035-0004 data used for pooling are current to the study's closure in June 2016, approximately 5 years after enrolment of the last patient. At that time the median overall survival (OS) follow-up duration was 74 months.

Primary endpoint

*Study C25006*

The ORR for the ITT population was 64% (95% CI, 49%-77%). Objective responses were reported for 32 patients and included a best response of CR for 15 patients (30%) and PR for 17 patients (34%). Stable disease was reported for 7 patients (14%) in the ITT population by IRF assessment. No postbaseline tumor response assessment was performed for 4 patients (see Table 2).

A high concordance was reported between IRF and investigator in the response assessment (response reported for 32 vs 33 patients respectively). Discordance was noted between the depth of the objective response adjudicated by IRF compared with that of the investigator, 15 (30%) vs 20 (40%) respectively.

The ORR for the PP (n=46) population was 67% (95% CI, 52%-80%). An objective response was reported for 31 patients and included a best response of CR for 14 patients (30%) and PR for 17 patients (37%). Stable disease was reported for 6 patients (13%).

The ORR was 79% (95% CI, 49%-95%) for patients with ALK-positive sALCL (n=14) consisting of 9 CR and 2 PR. For patients with ALK-negative sALCL (n=36) the ORR was 58% (95% CI, 41%-74%) with 6 patients achieving a CR and 15 a PR.

*Pooled population*

The ORR and CR rates per IRF in the pooled population were 76% ORR and 45% CR (see Table 2) .

*Table 2 Studies C25006 and SG035-0004: Summary of Overall Survival (ITT population)*

| | C25006 (N=50) n (%) (95% CI) | SG035-0004 (N=58) n (%) (95% CI) | Total (N=108) n (%) (95% CI) |
|---|---|---|---|
| Objective Response Rate (CR+PR) | 32 (64.0) (49.2, 77.1) | 50 (86.2) (74.6, 93.9) | 82 (75.9) (66.7, 83.6) |
| Best Clinical Response | | | |
| Complete Remission (CR) | 15 (30.0) (17.9, 44.6) | 34 (58.6) (44.9, 71.4) | 49 (45.4) (35.8, 55.2) |
| Partial Remission (PR) | 17 (34.0) (21.2, 48.8) | 16 (27.6) (16.7, 40.9) | 33 (30.6) (22.1, 40.2) |
| Stable Disease (SD) | 7 (14.0) (5.8, 26.7) | 2 (3.4) (0.4, 11.9) | 9 (8.3) (3.9, 15.2) |
| Progressive Disease (PD) | 7 (14.0) (5.8, 26.7) | 3 (5.2) (1.1, 14.4) | 10 (9.3) (4.5, 16.4) |
| Not Evaluable (NE) | 4 (8.0) (2.2, 19.2) | 3 (5.2) (1.1, 14.4) | 7 (6.5) (2.6, 12.9) |

Source: Addendum to m2.7.3 – sALCL, Table 3.b.

Abbreviations: CI, confidence interval; CR, complete remission; NE, not evaluable; PD, progressive disease; PR, partial remission; SD, stable disease.

[a] 95% confidence interval is based on exact binomial distribution.

[b] NE includes patients with Histological Ineligible and No Assessment Performed

Among the immunogenicity evaluable population (subjects with baseline and at leat 1 post treatment sample) 13 of 44 were considered (transiently) ADA positive (see pharmacology section) with only low levels of ADA and neutralising Abs were not detected. Of these 13 subjects an objective response (a CR or PR) was reported for 8 ADA-positive patients (1 CR and 7 PR). Stable disease was reported for 2 ADA-positive patients

**comments**

It is noticable that the ORR and CR rate in study C25006 are lower than reported for the predecessor study with limited or even no overlap in 95% CI for ORR and CR.

The ORR in the ADA positive population is in line with the overall population.

Secondary endpoints:

*DOR:* The median DOR for patients who had an objective response (CR or PR) was not estimable (NE) (95% CI, 19.71 months-NE).

**comments**

The currently reported duration of response is longer than reported in study SG035-004 study where median duration of response was estimated to be 13.2 months [95% CI (5.7,-)] (range, 0.1 to 21.7 months).

*PFS*

The median PFS for the ITT population was 20.9 months (95% CI, 4.17 months-NE) with a median follow-up duration of 10.6 months. At 12 and 24 months, the estimated progression free rate was 51.1% (95% CI, 34.99% 65.03%) and 38.3% (95% CI, 15.4% 61.1%), respectively. A total of 23 PFS events (46%), including disease progression for 15 patients (30%) were reported and 27 PFS observations (54%) were censored.

When patients who started a new anticancer therapy other than SCT before progressive disease were not treated as having had disease progression until it was documented and data were not censored at the date of the last disease assessment (sensitivity analysis PFS), the median PFS was 8.5 months (95% CI, 4.17-26.84 months). When patients who started new alternative anticancer therapy before

disease progression were treated as having progressive disease on the date of the last disease assessment (sensitivity analysis 2) the median PFS was 4.7 months (95% CI, 2.76-6.77 months).

For the patients with ALK-positive sALCL, median PFS was not estimable. For patients with ALK-negative sALCL median PFS was 4.9 months (95% CI, 2.83-26.84 months).

*Pooled population:* For the pooled population, the median duration of PFS per IRF was 14 months (range 7 to 20).

**comments**

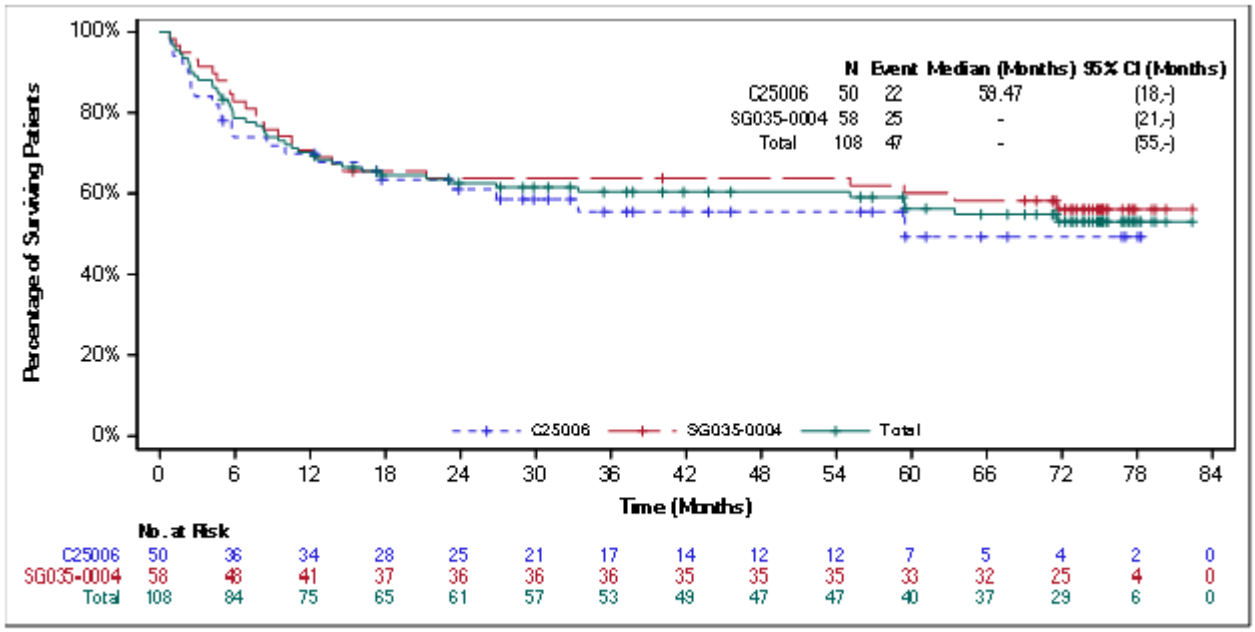
The impact of censoring on PFS is substantial. Apparently, a significant number of subjects received next line therapy before progression was detected. No question is asked on this difference considering the purpose of this study, i.e. confirmation of results from study SG035-04.

The longer PFS for subjects with ALK positive disease is not surprising given that ALK negative status is a worse prognostic factor.

*OS*

As of the 04 May 2021 cut-off for data analysis, 22 deaths were reported in the study, including 20 patients with a histologically confirmed diagnosis of sALCL by central pathology review. As of a median duration of OS follow up of 43.8 months, median OS was 59.5 months (95% CI, 17.68 months NE) for the ITT population with a total of 22 deaths (44%) reported and 28 OS observations censored. The estimated OS rate was 69.8% (95% CI, 54.96% 80.56%) at 12 months, 61.0% (95% CI, 45.84% 73.15%) at 24 months, and 49.3% (95% CI, 31.41% 64.99%) at 60 months (see Figure 1).

For the patients with ALK-positive sALCL median OS was not reached (endpoints of the 95% CI NE). The estimated 12-month OS rate for this subgroup was 85.7% (95% CI, 53.94%-96.22%). For the patients with ALK-negative sALCL median OS was 26.8 months (95% CI, 8.51 months-NE). The estimated 12-month OS rate for this subgroup was 63.6% (95% CI, 45.61%-76.98%).




Source: Addendum to m2.7.3 – sALCL, Figure 3.b.

Abbreviations: CI, confidence interval; ITT, intent-to-treat; OS, overall survival.

*Figure 1 Studies C25006 and SG035-0004: Kaplan-Meier Plot of OS (ITT Population)*

*Pooled analysis:* As a pooled intent-to-treat (ITT) population (N=108), the median duration of OS has not been reached despite a long follow-up duration for the majority of patients (Figure 1). As of a median duration of OS follow-up of 72 months, the median duration of OS was not estimable (95% CI, 55 months to not estimable). Of note for the predecessor study the median duration of OS had also not been reached (95% CI, 21 months to not estimable)

**comments**

Of note at the time of this data cut-off, the number of specified OS events (50%) has not been reached. Instead the analysis was performed using a data cut-off date of 04 May 2021 when it became clear that the specified OS event total would not be reached in time to support a Type II variation submission package at the agreed data of 31 December 2021. As a consequence, final OS analysis (at 50% of OS events or 5 years after enrolment of the last patient) is not yet available. The study was ongoing for 23 patients in either PFS and/or OS follow-up. So formally the OS data could be considered to be immature. However, at a median duration of OS follow up of 43.8 months, the KM curve may be considered sufficient interpretable.

Both studies show a plateau phase in OS indicating long term survival for a significant portion of the subjects.

Similarly to PFS, the better survival of subjects with ALK+ disease is in line with what can be expected from this prognostic marker.

*Proportion of patients who received an SCT*

Subsequent SCT was reported for 13 patients (26%) in the ITT population, after a median of 10 cycles (range, 1 16 cycles).

Pooled analysis: Across the pooled studies, 31 of 108 patients (29%) were known to have received subsequent SCT. As of closure of Study SG035-0004, subsequent SCT was reported for 18 patients

(31%) in the ITT population, although it is noted that SCT enabled by other intervening subsequent therapies was not captured in this total.

**comments**

Rates for proceeding to SCT are similar between the studies, which is re-assuring.

Exploratory endpoints

*Time to progression*: at a median follow-up of 8.0 months, median TTP for the ITT population was 20.9 months (95% CI, 5.13 months-NE),

*Time to response:* Median time to response was 5.8 weeks (range, 4-41.9 weeks) for the ITT population by IRF assessment. Median time to best response was 6.98 weeks (range, 4.0-44.7 weeks). Median time to CR was 12.53 weeks (range, 5.7-44.7 weeks)

*B symptom resolution rate:* The B symptom resolution rate was 79% (95% CI, 49%-95%). Resolution of all symptoms was reported for 11 patients of the 14 patients for whom at least 1 B symptom was reported at baseline with resolution reported at a median of 3.84 weeks (range, 3.1-9.1 weeks).

*PRO:* An overall compliance rate of 96% was reported for the EORTC-QLQ-C30 and EQ-5D-3L questionnaires. PRO as measured by EORTC-QLQ-C30 and EQ-5D-3L questionnaires were constant with no clinically meaningful changes from baseline reported during the treatment period and during PFS and OS follow-up.

*HU:* At least 1 hospitalization was reported for 12 patients in the ITT population. A median of 1 hospitalization (range, 1-4 hospitalizations) and a mean of 1.8 hospitalizations (standard deviation, 1.06 days) were reported and a median of 21 days (range, 7-69 days) was reported for each hospital stay. The median hospitalization rate per patient-year was 0.4 (95% CI, 0.3-0.7). The outpatient visit rate was 0.7 (95% CI, 0.5-1.0) per patient-year. At least 1 ICU (intensive care unit) visit was reported for 5 patients, at least 1 emergency room visit for 3 patients, and at least 1 hospice care stay for 1 patient in the ITT population.

**comments**

The TTP is in line with PFS data.

The Time to response is difficult to interpret given that the interval between tumour assessments was rather long as these were performed at the end of cycle 2 (6 weeks) and cycle 4 (12 weeks). Even so, the data suggest that response can be deepened upon treatment duration. Also, the TTR data are in line with what has been reported in SG35-004.

The impact of treatment on QoL is difficult to evaluate. Presumably the resolution of B cell symptoms would be of benefit to patients.

## *7.3. Discussion*

Study C25006 shows clear anti-tumour effect of brentuximab vedotin in subjects with R/R sALCL. No evident differences were noted in treatment effect in subgroups according to age (< and > 65years). Also the known prognostic value of ALK status, where patients with ALK-negative ALCL generally have a worse prognosis than patients with ALK-positive disease, is confirmed. It is however noted that while data from study C25006 confirm the high anti-tumour effect from registrational (predecessor) study, the activity seems slightly less (ORR 64% 95CI 49-77 vs 86% 95%CI 75-94). It is not clear whether these differences are real or mere chance findings (caused by limited sample size, heterogeneity in study population, differences in actual dosing, cross study comparison). A discussion on this issue by

the MAH is lacking. While more insight would be of interest, it would not change the conclusion that significant anti-tumour activity of substantial duration is noted in study C25006 and indicative of clinical benefit, thereby confirming the results that were available at the time of the MAA.

# 8. Clinical Safety aspects

The overview of safety was provided for the C25006 population and for the pooled (C25006 and SG035-0004) population.

**comments**

In the previous renewal, an interim report on the safety observations in study C25006 had been submitted and discussed. At that point, the study had already been closed for enrolment for over 1 year and during that procedure it was concluded that the safety data were in line with what has been reported for this study during the previous renewal and was in line with the already known safety profile of Adcetris. The current data for study C25006 'only' encompasses additional follow up.

In this assessment the data for the pooled population are presented. In case observations in the C25006 study deviate from the previous reporting period or from pooled analyses (and thus from the data collected in the predecessor study SG035-0004) this is mentioned below.

## *8.1. Methods – analysis of data submitted*

The safety analysis population included all patients who received at least 1 dose of brentuximab vedotin and was used for patient demographics and baseline disease characteristics. All 50 enrolled patients were counted in the safety population.

The safety population in study C25006 is the same as the ITT, for description of the population see above in the efficacy section.

## *8.2. Results*

In the pooled analyses a median of 7 cycles of brentuximab vedotin (range, 1 16 cycles) was reported for the pooled safety population, administered over a median of 149 days (range, 6 525 days). A total of 49 patients (45%) completed at least 8 cycles and 18 patients (17%) completed the maximum 16 cycles of brentuximab vedotin.

Adverse events

At least 1 TEAE of any grade was reported for 105 patients (97%) and at least 1 drug related TEAE of any grade for 88 patients (81%) (see Table 3). The TEAE PTs of any grade reported for at least 15% of patients were peripheral sensory neuropathy (31% of patients), pyrexia (27%), fatigue and nausea (26% each), diarrhoea (24%), neutropenia (19%), constipation (16%), and rash (15%) (see Table 4). The drug related TEAEs reported for at least 10% of patients were peripheral sensory neuropathy (31% of patients), nausea (18%), neutropenia (15%), fatigue (14%), diarrhoea (12%), and myalgia and pyrexia (10% each).

At least 1 Grade 3 or higher TEAE was reported for 65 patients (60%) and at least 1 drug related Grade 3 or higher TEAE for 43 patients (40%) (see Table 3). The Grade 3 or higher TEAE PTs reported for at least 5% of patients were neutropenia (17% of patients), thrombocytopenia (9%), and anaemia and peripheral sensory neuropathy (7% each). The drug related Grade 3 or higher TEAEs reported for

at least 5% of patients were neutropenia (13% of patients), peripheral sensory neuropathy (7%), and thrombocytopenia (5%).

At least 1 SAE was reported for 40 patients (37%) and considered drug related for 18 patients (17%). On study death was reported for 11 patients (10%) (see Table 3). The most commonly reported SAE PTs for the pooled safety population, sALCL, diarrhoea and pneumonia, were reported for 3 patients each (3%). The most commonly reported drug related SAEs were diarrhoea (3 patients; 3%), and hypotension, neutropenia, pneumonia, and urinary tract infection (2 patients each; 2%).

An AE led to premature study drug discontinuation for 29 patients (27%) (see Table 3). Peripheral sensory neuropathy was reported to have led to premature study discontinuation for 7 patients (6%) in the pooled safety population. Other TEAE PTs that led to premature study drug discontinuation were reported for 1 patient each (1%) (see Table 5).

Analysis of the TEAEs that resulted in dose modification was not performed for the pooled safety population

*Table 3 Studies C25006 and SG035-0004: Overview of Safety Profile (Safety Population)*

| N (%) | C25006 N=50 | SG035-0004 N=58 | Total N=108 |
|---|---|---|---|
| Any adverse event | 47 (94) | 58 (100) | 105 (97) |
| Drug-related adverse event | 35 (70) | 53 (91) | 88 (81) |
| Grade 3 or higher adverse event | 29 (58) | 36 (62) | 65 (60) |
| Drug-related Grade 3 or higher adverse event | 17 (34) | 26 (45) | 43 (40) |
| Serious adverse event | 16 (32) | 24 (41) | 40 (37) |
| Drug-related serious adverse event | 7 (14) | 11 (19) | 18 (17) |
| AE resulting in study drug discontinuation | 13 (26) | 16 (28) | 29 (27) |
| On-study death | 5 (10) | 6 (10) | 11 (10) |

Source: Addendum to m2.7.4 – C25006, Table 2.a.
Abbreviation: AE, adverse event.

*Table 4 Studies C25006 and SG035 0004: TEAEs Reported For At Least 10% of Patients by PT (Safety Population)*

| PT, n (%) | C25006 N=50 | SG035-0004 N=58 | Total N=108 |
|---|---|---|---|
| Patients with at least 1 TEAE | 47 (94) | 58 (100) | 105 (97) |
| Peripheral sensory neuropathy | 9 (18) | 24 (41) | 33 (31) |
| Pyrexia | 9 (18) | 20 (34) | 29 (27) |
| Fatigue | 6 (12) | 22 (38) | 28 (26) |
| Nausea | 5 (10) | 23 (40) | 28 (26) |
| Diarrhoea | 9 (18) | 17 (29) | 26 (24) |
| Neutropenia | 9 (18) | 12 (21) | 21 (19) |
| Constipation | 4 (8) | 13 (22) | 17 (16) |
| Rash | 2 (4) | 14 (24) | 16 (15) |
| Upper respiratory tract infection | 4 (8) | 11 (19) | 15 (14) |
| Cough | 4 (8) | 10 (17) | 14 (13) |
| Decreased appetite | 5 (10) | 9 (16) | 14 (13) |
| Dyspnoea | 3 (6) | 11 (19) | 14 (13) |
| Vomiting | 4 (8) | 10 (17) | 14 (13) |
| Anaemia | 7 (14) | 6 (10) | 13 (12) |
| Arthralgia | 5 (10) | 8 (14) | 13 (12) |
| Headache | 2 (4) | 11 (19) | 13 (12) |
| Myalgia | 3 (6) | 9 (16) | 12 (11) |
| Pruritus | 1 (2) | 11 (19) | 12 (11) |
| Dizziness | 2 (4) | 9 (16) | 11 (10) |
| Insomnia | 2 (4) | 9 (16) | 11 (10) |
| Oedema peripheral | 3 (6) | 8 (14) | 11 (10) |
| Pain in extremity | 3 (6) | 8 (14) | 11 (10) |
| Thrombocytopenia | 3 (6) | 8 (14) | 11 (10) |

Source: Addendum to m2.7.4 – C25006, Table 2.b.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; TEAE: treatment-emergent adverse event.

A TEAE was defined as any AE that occurred after administration of the first dose of study drug and up through 30 days after the last dose of study drug. A patient was counted once for each PT. AEs were coded using MedDRA Version 24.0. Percentages were calculated using the number of treated patients as the denominator. AEs were sorted by PT and descending total frequency.

*Table 5 Studies C25006 and SG035 0004: TEAEs Resulting in Study Drug Discontinuation by PT (Safety Population)*

| PT, n (%) | C25006 N=50 | SG035-0004 N=58 | Total N=108 |
|---|---|---|---|
| Patients with any AE that resulted in study drug discontinuation | 13 (26) | 16 (28) | 29 (27) |
| Peripheral sensory neuropathy | 1 (2) | 6 (10) | 7 (6) |
| Acute kidney injury | 0 | 1 (2) | 1 (1) |
| Acute respiratory failure | 1 (2) | 0 | 1 (1) |
| ALCL T- and null-cell types recurrent | 0 | 1 (2) | 1 (1) |
| Autonomic neuropathy | 1 (2) | 0 | 1 (1) |
| Colitis | 1 (2) | 0 | 1 (1) |
| Demyelinating polyneuropathy | 0 | 1 (2) | 1 (1) |
| Dermatitis | 0 | 1 (2) | 1 (1) |
| General physical health deterioration | 1 (2) | 0 | 1 (1) |
| Haematemesis | 1 (2) | 0 | 1 (1) |
| Haemorrhage intracranial | 0 | 1 (2) | 1 (1) |
| Hypotension | 1 (2) | 0 | 1 (1) |
| Invasive lobular breast carcinoma | 1 (2) | 0 | 1 (1) |
| Large intestinal haemorrhage | 1 (2) | 0 | 1 (1) |
| Neuralgia | 0 | 1 (2) | 1 (1) |
| Neuropathy peripheral | 1 (2) | 0 | 1 (1) |
| Neutrophil count decreased | 1 (2) | 0 | 1 (1) |
| Orthostatic hypotension | 1 (2) | 0 | 1 (1) |
| Paraesthesia | 1 (2) | 0 | 1 (1) |
| Peripheral motor neuropathy | 1 (2) | 0 | 1 (1) |
| Pneumonitis | 1 (2) | 0 | 1 (1) |
| Renal failure | 0 | 1 (2) | 1 (1) |
| Respiratory failure | 1 (2) | 0 | 1 (1) |
| Retinal vein occlusion | 0 | 1 (2) | 1 (1) |
| Sudden death | 0 | 1 (2) | 1 (1) |
| Transaminases increased | 0 | 1 (2) | 1 (1) |
| Upper gastrointestinal haemorrhage | 1 (2) | 0 | 1 (1) |

Source: Addendum to m2.7.4 – C25006, Table 2.h.
Abbreviations: AE, adverse event; ALCL, systemic anaplastic large cell lymphoma; MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term; SAE, serious adverse event.
A patient was counted once for each PT.
Percentages used the number of treated patients as the denominator.
AEs were coded using MedDRA Version 24.0.

Death

On study death (i.e. death death reported within 30 days of the last dose of brentuximab vedotin) was reported for 11 patients in the pooled safety population. The primary causes of death were reported as sALCL for 3 patients, respiratory failure for 2 patients, and acute myocardial infarction, sudden death, CNS haemorrhage, acute kidney injury, general physical health deterioration, and pneumonitis for 1 patient each.

**comments**

On-treatment death in C25006 study was reported for 5 patients, with the primary causes of death general physical health deterioration, CNS haemorrhage, respiratory failure, and pneumonitis and not specified for 1 patient. Pneumonitis was the only reported on study death that was considered drug related, according to investigator assessment.

Posttreatment follow-up deaths were not captured for Study SG035-0004 but follow from OS follow-up data.

In Study C25006, death was reported for 17 patients more than 30 days after the last dose of the study drug. The death of 11 patients was considered to be related to the primary disease or associated complications. For an additional 2 patients, the cause of death was reported as pulmonary fibrosis, reported 774 days after the last dose of study drug and considered drug related, and vena cava thrombosis, reported 318 days after the last dose of study drug and considered not drug related, according to the investigator assessment

AE of special interest.

*Peripheral Neuropathy (PN):* At least 1 treatment emergent PN (SMQ) AE of any grade was reported for 49 patients (45%) in the pooled safety population (onset at a median of 12.14 weeks, resolution at a median of 13.07 weeks). Peripheral sensory neuropathy was the most commonly reported PN (SMQ) AE of any grade (33 patients; 31%). Paraesthesia was reported for 8 patients (7%), and peripheral motor neuropathy for 6 patients (6%) in the pooled safety population.

*Infusion Reactions:* at least IRR of any grade was reported for 9 patients (8%). Grade 2 rash was reported for 2 patients (2%), and Grade 2 nausea, vomiting, pyrexia, chills, swelling, dizziness, and urticaria, and Grade 1 diarrhoea, pyrexia, and infusion related reaction were reported for 1 patient each (1%).

**comments**

Safety data for study C25006 are in line with what had been reported during the previous reporting period. Changes in frequencies, if any, are marginal.

No qualitative and only limited numerical differences in AE profile are noted between the two studies.

### *8.3. Discussion*

Overall the safety profile of brentuximab vedotin as reported in the two studies is consistent and also in line with what has been described previously. No new safety signals were identified. Thus the conclusion of the MAH that the safety findings in study C25006 are consistent with the known safety profile of brentuximab vedotin in the monotherapy setting is agreed.

## 9. PRAC advice

Not applicable.

## 10. Risk management plan

The MAH submitted an updated RMP version 16.1 dated 10 December 2021 with a DLP of 18 August 2021 with this variation. The purpose of this RMP update is to reflect the completion of the C25006 study as a category 2 study in the RMP and the removal of the important identified risk of "anti-drug antibodies". The (main) proposed RMP changes were the following:

- Updates in Part II to include data from C25006 Study, Post-marketing exposure update, removal of anti-drug antibodies as important identified risk
- Updates in part III and IV to remove C25006 study
- Updates in part V to remove anti-drug antibody as a safety concern

**Part II safety specification:**

Module SIII:

Clinical trial exposure was updated to include safety data from the C25006 study.

Module SV:

Updated post authorisation experience data with a DLP 18 August 2021.

Module SVII:

Removal of the important identified risk of anti-drug antibodies and updated exposure detail with a DLP 18 August 2021.

Module SVIII:

The MAH proposed to remove anti-drug antibody as important identified risk.

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

***PRAC assessment comment:***

The proposed changes to modules SIII-SVII are acceptable.

Following CHMP review of the study results, no new safety signal was identified. The AEs and risks are similar to what has been identified and described from MA studies. Based on the C25006 study data, the risk for anti-drug antibodies is consistent with previously reported data and has been characterised sufficiently. SmPC section 4.8 includes information on anti-drug antibodies. Therefore, the removal of this important identified risk from the list of safety concerns is considered acceptable.

**Part III Pharmacovigilance plan**

The pharmacovigilance plan was updated to remove the C25006 study as category 2 study, as a specific obligation in the context of conditional marketing authorisation.

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

**Part IV Plans for post-authorisation efficacy studies**

Removal of the C25006 study as post authorisation SOB.

***PRAC Rapporteurs assessment comment**:*

The removal of the C25006 study from part III and Part IV can be accepted.

**Part V Risk minimisation measures**

Part V was updated to reflect the removal of safety concern anti-drug antibodies.

***PRAC Rapporteurs assessment comment:***

The changes to part V can be accepted.

**Part VII Annexes**

Removal of the C25006 study from Annex 5.

***PRAC Rapporteurs assessment comment:***

The changes to part VII can be accepted.

### *10.1. Overall conclusion on the RMP*

☒The changes to the RMP and the changes to the conditions and obligations of the MA are acceptable.

# 11. Changes to the Product Information

As a result of this variation, section(s) 4.8 and 5.1 of the SmPC are updated based on the final results of study C25006. The Package Leaflet (PL) is updated accordingly.

Changes are made to the Opinion Annex II conditions as detailed in the recommendations section above.

Please refer to the published product information.