# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 125388Orig1s000

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

# OFFICE OF CLINICAL PHARMACOLOGY REVIEW

| | |
|---|---|
| **BLA** | 125388-0 and 125399-0 |
| **Submission Date** | February 25, 2011 |
| **Brand Name** | ADCETRIS™ |
| **Generic Name** | Brentuximab Vedotin |
| **Formulation/Strength** | 30 mL single-use vials (50 mg/vial) |
| **OCP Reviewer** | Aakanksha Khandelwal, Ph.D. |
| **OCP Team Leader** | Julie Bullock, Pharm.D. |
| **Pharmacometrics Reviewer** | Bahru Habtemariam, Pharm.D. |
| **Pharmacometrics Team Leader** | Christine Garnett, Pharm.D. |
| **OCP Division** | Division of Clinical Pharmacology 5 |
| **ORM Division** | Division of Hematology Products |
| **Sponsor** | Seattle Genetics |
| **Submission Type; Code** | Original BLA; 000 |
| **Dosing regimen** | 1.8 mg/kg IV Q3W |
| **Indication** | BLA 125388: Hodgkin's lymphoma<br>BLA 125399: Anaplastic large cell lymphoma |

## TABLE OF CONTENTS

## LIST OF ABBREVIATIONS

| | |
|---|---|
| ADC | Antibody drug conjugate |
| ALCL | Anaplastic large cell lymphoma |
| AUC | Area under the curve |
| cAC10 | CD-30 targeted monoclonal antibody |
| CL | Clearance |
| Cmax | Maximum concentration |
| CR | Complete remission |
| DAR | Drug to antibody ratio |
| DP | Drug product |
| ELISA | Enzyme-linked immunosorbent assay |
| HL | Hodgkin's lymphoma |
| HPLC-MS/MS | High-performance liquid chromatography-tandem mass spectrometry |
| IRF | Independent review facility |
| IV | Intravenous |
| kDa | Kilodaltons |
| LC-MS/MS | Liquid chromatography and tandem mass spectrometry |
| MMAE | Monomethyl auristatin E |
| OR | Objective response |
| ORR | Objective response rate |
| PFS | Progression free survival |
| PMC | Post-marketing commitment |
| PMR | Post-marketing requirement |
| PN | Peripheral neuropathy |
| PR | Partial remission |
| Q3W | Once every three weeks |
| Vss | Volume at steady state |

## LIST OF TABLES

## LIST OF FIGURES

# 1. EXECUTIVE SUMMARY

Brentuximab vedotin, submitted under BLAs 125388 and 125399, is a new molecular entity developed by Seattle Genetics for the treatment of relapsed or refractory Hodgkin's lymphoma (HL) or anaplastic large cell lymphoma (ALCL). Two phase 2 registration trials were conducted to support the proposed indication at a dose of 1.8 mg/kg brentuximab vedotin given as an intravenous infusion over 30 minutes once every three weeks.

## 1.1 Recommendations

The Office of Clinical Pharmacology has reviewed BLAs 125388 and 125399 and has found the clinical pharmacology data submitted to support the proposed dose and indication to be acceptable.

## 1.2 Phase IV Commitments and Requirements

The Office of Clinical Pharmacology does not recommend any PMCs or PMRs. There is one comment to be conveyed to the sponsor.

### *1.2.1 Additional Comments*

Submit the completed clinical study reports for SGN35-008B to address the impact of renal or hepatic impairment on brentuximab vedotin pharmacokinetics.

## 1.1 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Brentuximab vedotin is an antibody drug conjugate (ADC) that targets CD30. Brentuximab vedotin is comprised of a CD30-targeted monoclonal antibody (cAC10) linked to the small molecule monomethyl auristatin E (MMAE).

*Mechanism of Action:* The mechanism of action of brentuximab vedotin consists of a multi-step process. Binding of the ADC to CD30 on the cell surface initiates internalization 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 tumor cell.

*Efficacy:* The proposed indication is for relapsed or refractory HL or ALCL. Two phase 2 registration trials were completed, one for each proposed indication. Both of these trials were open-label, multicenter, single-arm trials with 1.8 mg/kg brentuximab vedotin administered as an IV infusion over 30 minutes given once every three weeks for 16 cycles. Brentuximab vedotin demonstrated an objective response rate (ORR) in the majority of treated patients, 75% in HL and 86% in ALCL. The objective response rate was defined as the sum of the partial and complete remission rates.

*Pharmacokinetics:* Data on the pharmacokinetics of brentuximab vedotin, total antibody, and MMAE is available from four phase 1 studies and two phase 2 studies. Brentuximab vedotin exhibited linear PK from 1.2 to 2.7 mg/kg. The half-life ranged from 4 to 6 days with minimal accumulation; steady-state was achieved in 21 days.

*Exposure-Response:* The concentrations of total antibody and ADC increase with increasing brentuximab vedotin dose, while the average concentration of MMAE flattens at doses greater than 0.8 mg/kg. The probability of ORR increases with increasing ADC concentrations, however, decreases with increasing MMAE concentrations.

*Safety:* Brentuximab vedotin treatment was associated with Grade 2+ neutropenia, peripheral neuropathy, and thrombocytopenia. Based on exposure-response analysis, the probability of Grade 2+ peripheral neuropathy or Grade 3/4 neutropenia increased with increasing ADC concentration, but was not affected by increasing MMAE concentration. Brentuximab vedotin did not prolong the QT interval at the proposed dose and doing interval.

---

8/03/11

Aakanksha Khandelwal, Ph.D.
Reviewer
Division of Clinical Pharmacology 5

8/3/2011

Julie Bullock, Pharm.D.
Team Leader
Division of Clinical Pharmacology 5

for Bahru Habtemariam 8/3/2011

Bahru Habtemariam, Pharm.D.
Reviewer
Division of Clinical Pharmacology 5

8/3/2011

Christine Garnett, Pharm.D.
Team Leader
Division of Pharmacometrics

## 2. QUESTION-BASED REVIEW

### 2.1 General Attributes

***2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?***

Brentuximab vedotin is a CD30-directed antibody-drug conjugate (ADC) consisting of three components:

- A CD30 specific monoclonal antibody, cAC10
- An antimicrotubule agent, monomethyl auristatin E (MMAE)
- A protease-cleavable linker that covalently attaches MMAE to cAC10

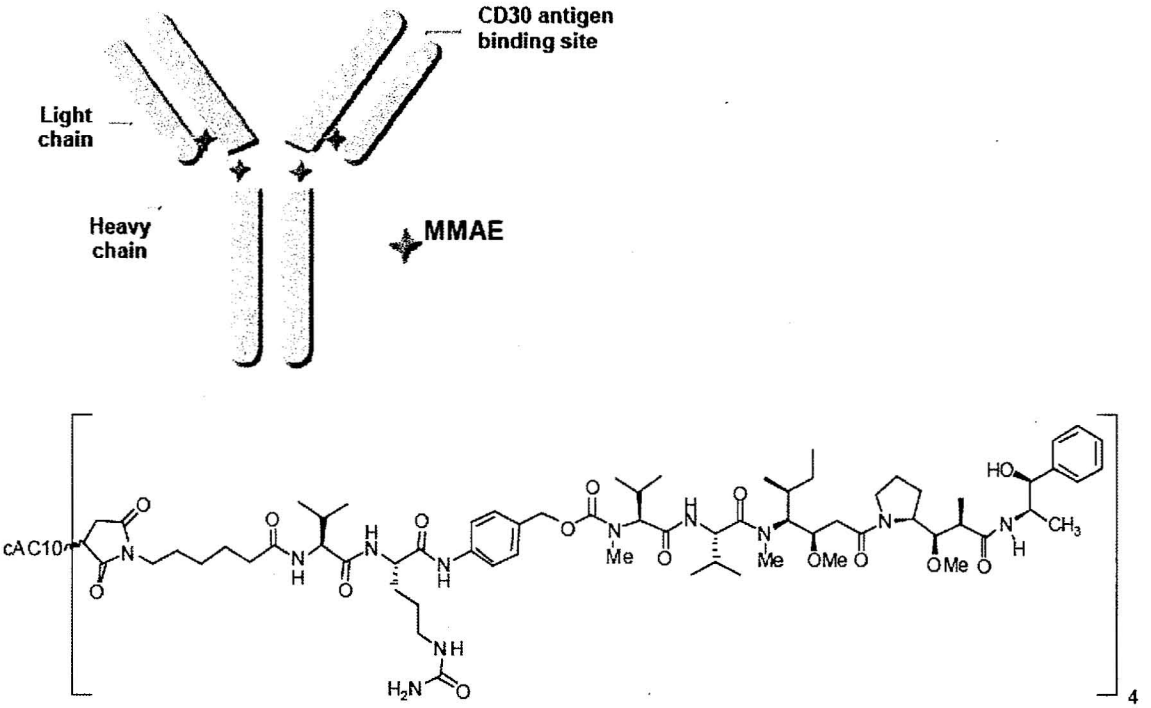



**Figure 1.** Structure of brentuximab vedotin

The IgG1 antibody is conjugated to MMAE at specific sites. The sites of attachment are cysteines [redacted] (b) (4) of the antibody. The linker consists of a thiol-reactive maleimide, a caproyl spacer, the dipeptide valine-citrulline, and p-aminobenzyloxycarbonyl, a self-immolative fragmenting group. The average drug-to-antibody molar ratio (DAR) is approximately 4:1 (range 0 to 8:1) and the molecular mass of brentuximab vedotin is approximately 153 kDa.

Brentuximab vedotin is a sterile, preservative-free, white to off-white lyophilized cake, supplied in single-use vials. Brentuximab vedotin drug product (DP) is reconstituted with sterile water for injection and further diluted for intravenous (IV) infusion. The reconstituted brentuximab vedotin DP is a clear to slightly opalescent, colorless solution

with no visible particulate matter. Each vial contains brentuximab vedotin and the excipients trehalose, sodium citrate, and polysorbate 80. The DP vial is reconstituted with the appropriate amount of sterile water for injection. The pH of reconstituted product is approximately 6.6.

***2.1.2 What are proposed mechanism(s) of action and therapeutic indication(s)?***

The mechanism of action of brentuximab vedotin consists of a multi-step process. Binding of the ADC to CD30 on the cell surface initiates internalization 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 tumor cell.

The proposed indication for brentuximab vedotin is for relapsed or refractory Hodgkin's lymphoma (HL) and relapsed or refractory systemic anaplastic large cell lymphoma (ALCL).

***2.1.3 What are the proposed dosage(s) and route(s) of administration?***

The proposed dosing regimen is 1.8 mg/kg brentuximab vedotin administered as an IV infusion over 30 minutes once every three weeks (Q3W).

## 2.2 General Clinical Pharmacology

***2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?***

A summary of completed clinical trials with brentuximab vedotin to support the BLA application is shown in Table 1.

**Table 1.** Summary of Completed Clinical Studies with Brentuximab Vedotin to Support the BLA Application

| Study Number | Primary Study Objective and Patient Population | Study Type | No. of Subjects Analyzed | Treatment Regimen |
|---|---|---|---|---|
| Phase 1 | | | | |
| SG035-0001 | Safety in patients with CD30+ heme malignancies | Open-label, single-arm, dose-escalation | 45 | 0.1 – 3.6 mg/kg IV Q3W |
| SG035-0002 | Safety in patients with CD30+ heme malignancies | Open-label, single-arm, dose-escalation | 44 | 0.4 – 1.4 mg/kg IV QW for 12 cycles |
| SGN35-007 (on-going) | Clinical pharmacology in patients with CD30+ heme malignancies | Open-label, single-arm 1°:Duration of ventricular repolarization | 46 | 1.8 mg/kg IV Q3W for 16 cycles |
| SGN35-008A | Clinical pharmacology in patients with CD30+ heme malignancies | Open-label, nonrandomized, 3-arm, DDI, excretion | 45 | 1.2 or 1.8 mg/kg IV Q3W for 2 cycles |
| SGN35-008B (on-going) | Clinical pharmacology in patients with CD30+ heme malignancies | Open-label, nonrandomized, hepatic or renal impairment | 12 planned | 1.2 mg/kg IV Q2W for 2 cycles |
| Phase 2 | | | | |
| SG035-0003 | Efficacy and safety in HL patients | Open-label, single-arm 1°: ORR | 102 | 1.8 mg/kg IV Q3W for 16 cycles |
| SG035-0004 | Efficacy and safety in systemic ALCL patients | Open-label, single-arm 1°: ORR | 58 | 1.8 mg/kg IV Q3W for 16 cycles |

*2.2.1.1 Registration Clinical Trial(s)*

Two separate phase 2 studies were submitted to support the efficacy and safety of brentuximab vedotin.

Study SG035-0003 entitled, "*A pivotal study of SGN-35 in treatment of patients with relapsed or refractory Hodgkin lymphoma (HL)*" was completed to support the HL indication. SGN035-0003 was a single-arm, open-label, multicenter trial in which patients received 1.8 mg/kg brentuximab vedotin Q3W for a maximum of 16 cycles. 75% of patients had an objective response (OR) (complete remission (CR) or partial remission (PR)) with median duration of approximately 7 months (Table 2). The median progression-free survival (PFS) was 25.1 weeks based on an independent review facility (IRF) assessment.

Study SG035-0004 entitled, "*A Phase 2 study of SGN-35 in treatment of patients with relapsed or refractory systemic anaplastic large cell lymphoma (ALCL)*" was completed to support the ALCL indication. SG035-0004 was a single-arm, open-label, multicenter, trial where patients received the same regimen of brentuximab vedotin as in SG035-0003. 86% of patients achieved a complete or partial remission. The median duration of OR was not estimable because of few events of progression or death, the lower limit of the 95% CI was 8.3 months (Table 2). The data submitted reflect an interim analysis since 18

patients continue to receive therapy. At the time of analysis, the median PFS per IRF had not yet been reached, but the median PFS per investigator was 41.1 weeks.

**Table 2**. Summary of Key Efficacy Endpoints from SG035-0003 (HL) and SG035-0004 (ALCL)

| Efficacy Endpoint (95% CI) | HL (N=102) | ALCL (N=58)[a] |
|---|---|---|
| ORR | 75% (64.9, 82.6) | 86% (74.6, 93.9) |
| Median duration of ORR | 6.7 months (3.6, 12.0) | Not reached (8.3 mo, NE) |
| CR | 34% (25.2, 44.4) | 53% (39.9, 66.7) |
| Median duration of OR in patients with CR | Not reached (8.8 mo, NE) | Not reached (8.3 mo, NE) |

NE-not estimable; [a]18 patients continued to receive therapy at the time of the data cut (reflects interim data through August 11, 2010)

*2.2.1.2 Clinical Pharmacology Studies*

Data on the pharmacokinetics of brentuximab vedotin is available from four phase 1 studies and two phase 2 studies as listed in Table 1. One phase 1 study, SGN35-008B, is currently on-going. All studies enrolled patients with CD30+ hematologic malignancies, including patients with HL and ALCL. The clinical pharmacology program characterized the PK of three analytes using traditional and population methods:

- ADC- brentuximab vedotin ADC
- MMAE- released small molecule drug
- TAb- total antibody (ADC plus unconjugated cAC10 antibody)

***2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints and how are they measured in clinical pharmacology and clinical studies?***

The primary endpoint use in the registration clinical trials is ORR, which is defined as the sum of the complete and partial remission rates. In both trials, review of response was performed by an independent radiological facility to assure unbiased assessment of brentuximab vedotin. For further comment on the selection of ORR as the clinical endpoint, refer to the Clinical review.

***2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?***

Yes. Three analytes were measured to characterize the PK of brentuximab vedotin: ADC, MMAE, and TAb. ADC and TAb were measured in serum by enzyme-linked immunosorbent assays (ELISA). MMAE was measured in plasma by liquid chromatography and tandem mass spectrometry (LC-MS/MS). The MMAE assay was also validated in urine and feces for use in an excretion study (SGN35-008A). The three analytes were measured in all 7 clinical studies listed in Table 1.

### *2.2.4 Exposure-response*

*2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicated the time to the onset and offset of the desirable pharmacological response or clinical endpoint.*

Plasma concentrations of TAb consisting of free and bound antibody, ADC, and free MMAE were measured in the phase 1 and phase 2 trials. Figure 2 showed that the concentration of TAb and ADC increase with increasing brentuximab vedotin dose, while the average concentration of MMAE appears to flatten at dose greater than 0.8 mg/kg. The concentrations of TAb and ADC were highly correlated; therefore, exposure-response analyses were performed using ADC and MMAE concentrations.

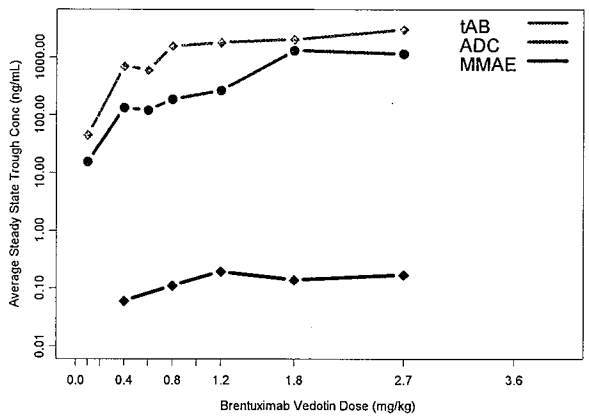



**Figure 2.** Median steady state trough concentration of TAb, ADC, and MMAE

As shown below, the probability of ORR increases with increasing ADC trough concentrations, but decreases with increasing MMAE trough concentrations (Figure 3 A and B). There is no clear explanation as to why the probability of ORR appears to decrease with increasing MMAE concentrations. It can be speculated that MMAE needs to be bound to the antibody in order to reach to the site of action and the unbound MMAE is unavailable to reach the site of actions, therefore higher free MMAE would lead to lower efficacy.

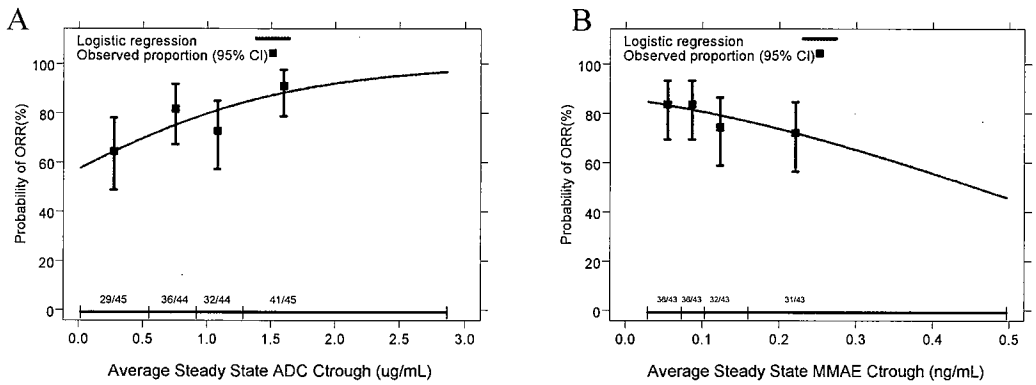



**Figure 3.** The probability of ORR increases with increasing average steady state ADC trough concentration (A) and shows a decreasing trend with increasing steady state MMAE trough concentrations (B)

*2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.*

Peripheral neuropathy, neutropenia, and thrombocytopenia were identified as the most frequent adverse events (AEs) observed in brentuximab vedotin clinical trials. To investigate whether these AEs were influenced by drug concentrations, logistic regression analysis was performed for peripheral neuropathy, neutropenia, and thrombocytopenia at ADC and MMAE average steady state concentrations.

*Peripheral Neuropathy*

Consistent with the dose reductions in the phase 2 trials, the proposed draft labeling for brentuximab vedotin recommends a dose reduction for patients with Grade 2 or more (Grade 2+) peripheral neuropathy. Exposure-response analyses were performed to investigate the relationship between the probability of Grade 2+ neutropenia and average steady state trough concentrations of ADC and MMAE. The probability of Grade 2+ peripheral neuropathy increases with increasing steady state ADC trough concentrations (Figure 4A), but stays flat with increasing average steady state MMAE trough concentrations (Figure 4B).

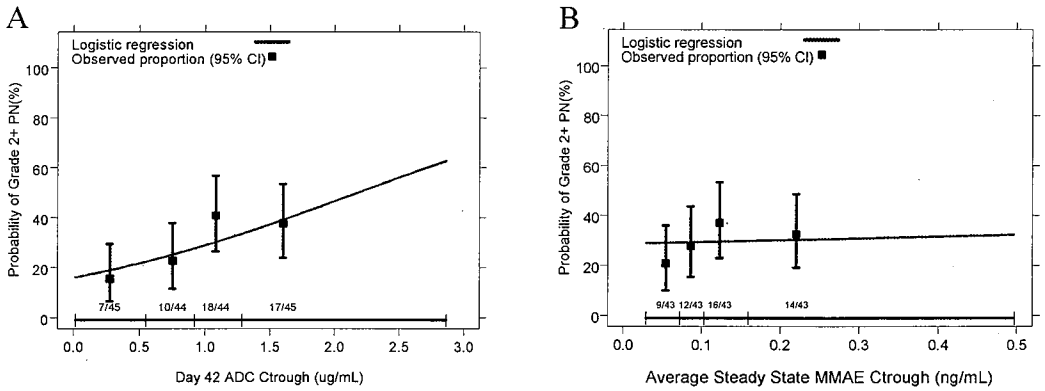



**Figure 4.** Probability of Grade 2+ peripheral neuropathy increases with increasing average steady state ADC trough concentrations (A) and remains flat with increasing steady state MMAE trough concentrations (B)

*Neutropenia*

There are no proposed dose reductions in the product label for Neutropenia. The phase 2 trials incorporated holding the dose for Grade 3 or 4 neutropenia. The probability of Grade 3 or 4 neutropenia (Grade 3+) increases with increasing average steady state ADC trough concentrations (Figure 5A). At the lowest ADC concentration quartile, 6 of the 45 (13%) patients had Grade 3+ neutropenia compared to 12 of the 45 patients (27%) in the top quartile (Figure 5A). Based on these results, it is recommended that the dose be reduced in patients who experience Grade 3 or 4 neutropenia. Logistic regression analysis was also performed using MMAE concentrations, and the probability of Grade 3+neutropenia (Figure 5B) shows a decreasing trend with increasing MMAE concentrations.

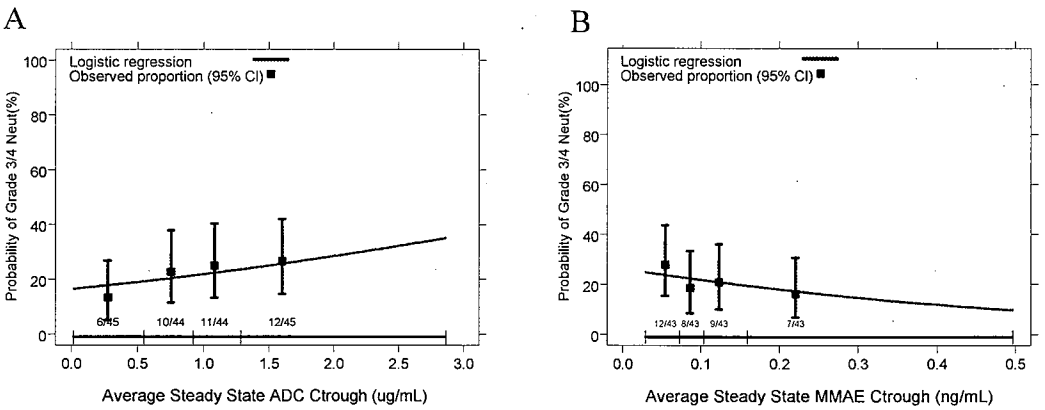



**Figure 5.** Probability of Grade 3+ neutropenia increases with increasing average steady state ADC trough concentrations (A) and shows a decreasing trend with increasing steady state MMAE trough concentrations (B)

*Thrombocytopenia*

Thrombocytopenia is one of the most frequently reported AEs in clinical trials of brentuximab vedotin. We investigated whether the proportion of Grade 3 or 4 thrombocytopenia increases with increasing ADC or MMAE concentrations. As shown in

Figure 6 below, there is no clear exposure-response relationship between thrombocytopenia and either ADC or MMAE concentration.

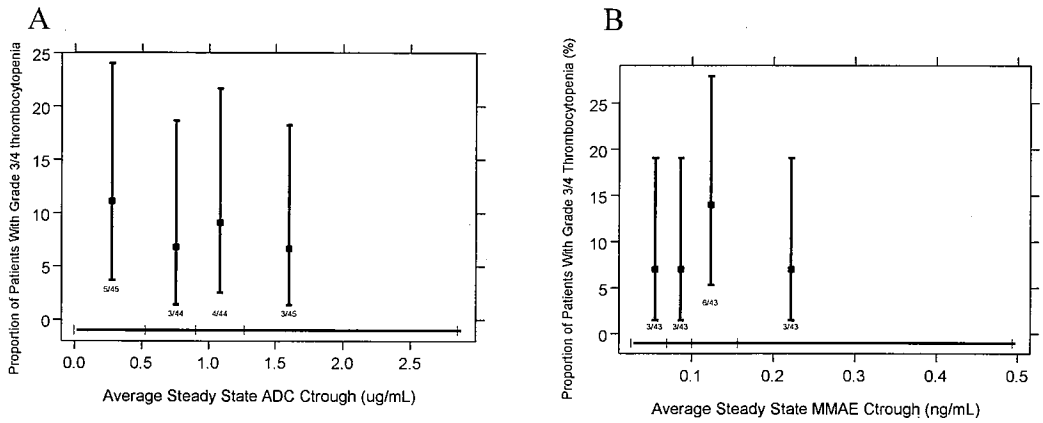



**Figure 6.** Proportion of Grade 3+ thrombocytopenia does not increase with increasing average steady state trough concentrations of ADC (A) or MMAE and (B)

The exposure-response analyses based on the ADC trough concentrations for neutropenia and peripheral neuropathy support a dose reduction or modification for patients that experience Grade 3 or 4 symptoms of these AEs. Hence, it is recommended that patients with these symptoms receive a dose of 1.2 mg/kg brentuximab vedotin instead of 1.8 mg/kg. There is no strong trend of increase of neutropenia, peripheral neuropathy, or thrombocytopenia with increasing trough MMAE levels.

*2.2.4.3 Does this drug prolong the QT/QTc interval?*

Study SGN35-007 assessed the influence of brentuximab vedotin (1.8 mg/kg Q3W) on the QTc interval of patients with CD30-positive hematologic malignancies (n=46 evaluable patients). A 12-lead Holter monitor was applied to patients approximately 2 hours and 15 minutes before the Day 1 dosing on Cycle 1. ECGs were extracted in quadruplicate at 30, 60, 90 and 120 minutes pre-dose and 30, 60, 90 and 120 minutes post-dose. On Days 2, 3 and 4 the 12-lead Holter was reapplied to the patient as close as possible to the start time of the pre-dose ECGs on Day 1. ECGs were extracted at 30, 60, 90and 120 minutes after start of ECG monitoring. Serum and plasma samples for PK were collected in Cycle 1 on Day 1 at 30 minutes post-dose. On Days 2, 3 and 4, samples were collected 120 minutes after start of ECG monitoring. Measurements of the ADC, TAb, and MMAE were evaluated.

No large changes (i.e., >20 ms) in the QTc interval were detected following brentuximab vedotin dosing. The largest upper bound of the 2-sided 90% CI for the mean change from baseline was 2.9 ms, observed at one hour post-dose on Day 1 of Cycle 1. In addition, within the range of concentrations observed in this study, no apparent concentration-QT relationship was identified. However, small increases in QTc interval (i.e., <10ms) with the use of brentuximab vedotin cannot be excluded due to study design limitations. Further details can be found in the Interdisciplinary Review Team Memo.

*2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues.*

The dose for the phase 2 studies (1.8 mg/kg Q3W) was selected based on a phase 1 dose escalation study using the traditional 3+3 dose escalation rule. The sponsor did not conduct a dedicated phase 2 dose selection or optimization study. However, available data suggest the selected dose reasonably balances safety and efficacy (Figure 7).

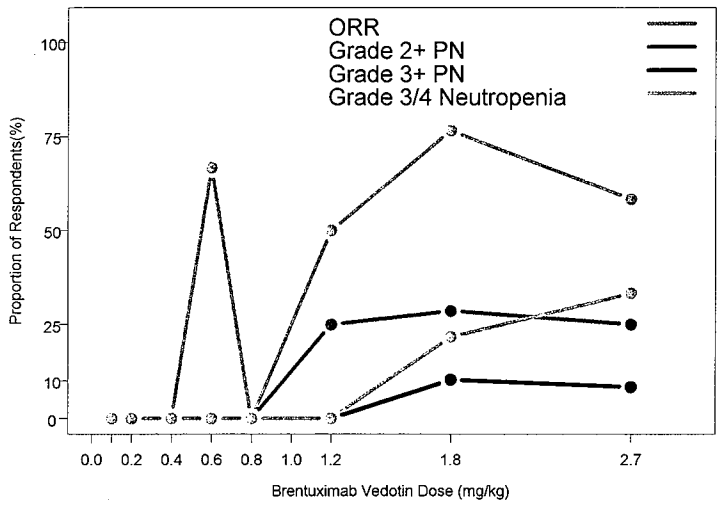



**Figure 7.** Proportions of ORR, Grade2+ and Grade 3+ peripheral neuropathy (PN), and Grade 3+ neutropenia

***2.2.5 What are the PK characteristics of the drug and its major metabolite?***

The PK of brentuximab vedotin at 1.8 mg/kg Q3W, the proposed commercial dose, was characterized by traditional methods in SG035-0001 and SGN35-008A. Sparse PK samples at this dose were collected for population PK analysis in study SGN35-007 and the two registration trials, SG035-0003 and SG035-0004. SG035-0002 used a different dose and dosing regimen and thus, results from this study are not summarized below.

PK parameters for ADC, TAb, and MMAE have been presented separately.

*2.2.5.1 What are the single dose and multiple dose PK parameters?*

*Antibody-drug conjugate*

The PK of the ADC was linear over the doses of 1.2, 1.8, and 2.7 mg/kg Q3W. A multiexponential decline in ADC serum concentrations was observed with a $t_{1/2}$ of approximately 4-6 days. Steady-state was achieved by 21 days after multiple doses of brentuximab vedotin. Minimal accumulation was observed with the Q3W regimen and ADC exposure did not decrease with subsequent doses.

**Table 3.** First-dose PK Parameters of the ADC

| Study | Dose[b] (mg/kg) | Pharmacokinetic Parameters[a] | | | | | |
|---|---|---|---|---|---|---|---|
| | | $AUC_{0-\infty}$ (day·µg/mL) | $C_{max}$ (µg/mL) | $T_{max}$ (day)[c] | $t_{1/2}$ (day) | CL (L/day) | $V_{ss}$ (L) |
| SG035-0001 | 1.2 (n=4) | 46.14 (62) | 18.89 (27) | 0.09 (0.08,0.09) | 3.79 (11) | 1.96 (105) | 5.85 (260) |
| | 1.8 (n=12) | 79.41 (30) | 31.98 (29) | 0.09 (0.08,0.25) | 4.43 (38) | 1.76 (17) | 8.21 (24) |
| | 2.7 (n=12) | 125.75 (19) | 45.01 (16) | 0.09 (0.09,0.18) | 5.98 (30) | 1.71 (33) | 10.18 (39) |
| SGN35-008A | 1.2 (n=16)[d] | 52.77 (28) | 22.57 (23) | 0.02 (0.02,0.17) | 5.70 (33) | 1.78 (27) | 9.41 (25) |
| | 1.8 (n=11) | 89.84 (25) | 36.74 (34) | 0.02 (0.02,0.09) | 5.87 (66) | 1.62 (26) | 10.02 (34) |

[a]Data presented as geometric mean (%CV); [b]all doses administered Q3W; [c]data for $T_{max}$ presented as median (min, max); [d]n=16 for $C_{max}$ and $T_{max}$, n=11 for all other parameters

Results were similar between studies SG035-0001 and SGN35-008A at the 1.2 and 1.8 mg/kg doses. The $t_{1/2}$ was longer in study SGN35-008A and Tmax occurred close to the end of the 30 minute infusion. The clearance (CL) and volume at steady-state ($V_{ss}$) at 1.2 mg/kg from study SG035-0001 displayed large variability, but this may be attributed to the small sample size. The concentration-time profile of the ADC after the first dose at three different dose levels from study SG035-0001 is shown in Figure 8.

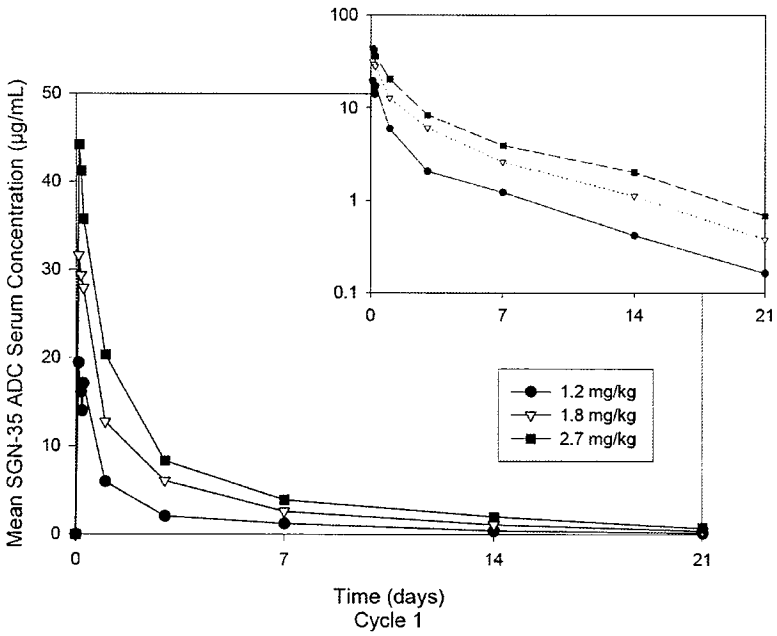



**Figure 8.** ADC serum concentration-time profile following the first dose of brentuximab vedotin in study SG035-0001

*MMAE*

The single and multiple dose plasma PK of MMAE was characterized after doses of 1.2, 1.8, and 2.7 mg/kg brentuximab vedotin. The PK was linear with $AUC_{0-\infty}$ and $C_{max}$ increasing in an almost dose-proportional manner. MMAE elimination appeared to be dependent on the rate of its release from the ADC. The $T_{max}$ of MMAE was much longer

than that of the ADC indicating delayed release of MMAE as indicated by the mechanism of action for an ADC (Table 4).

**Table 4.** First-dose PK Parameters of MMAE

| Study | Dose[b] (mg/kg) | Pharmacokinetic Parameters [a] | | | |
|---|---|---|---|---|---|
| | | $AUC_{0-\infty}$ (day·ng/mL) | $C_{max}$ (ng/mL) | $T_{max}$ (day)[c] | Apparent $t_{1/2}$ (day) |
| SG035-0001 | 1.2 (n=4) | 20.29 (212) | 2.72 (272) | 1.07 (0.21, 3.09) | 3.13 (28) |
| | 1.8 (n=12) | 37.03 (47) | 4.97 (43) | 2.09 (1.09, 3.93) | 3.60 (25) |
| | 2.7 (n=12)[d] | 53.20 (41) | 7.00 (44) | 2.99 (1.09, 7.81) | 3.43 (22) |
| SGN35-008A | 1.2 (n=16)[e] | 26.65 (71) | 4.11 (71) | 1.97 (0.97, 6.99) | 3.06 (13) |
| | 1.8 (n=14) | 40.06 (53) | 4.98 (67) | 3.00 (0.99, 5.01) | 3.71 (19) |

[a]Data presented as geometric mean (%CV); [b]all doses administered Q3W; [c]data for $T_{max}$ presented as median (min, max); [d]n=12 for $C_{max}$ and $T_{max}$, n=11 for all other parameters; [e]n=16 for $C_{max}$ and $T_{max}$, n=14 for all other parameters

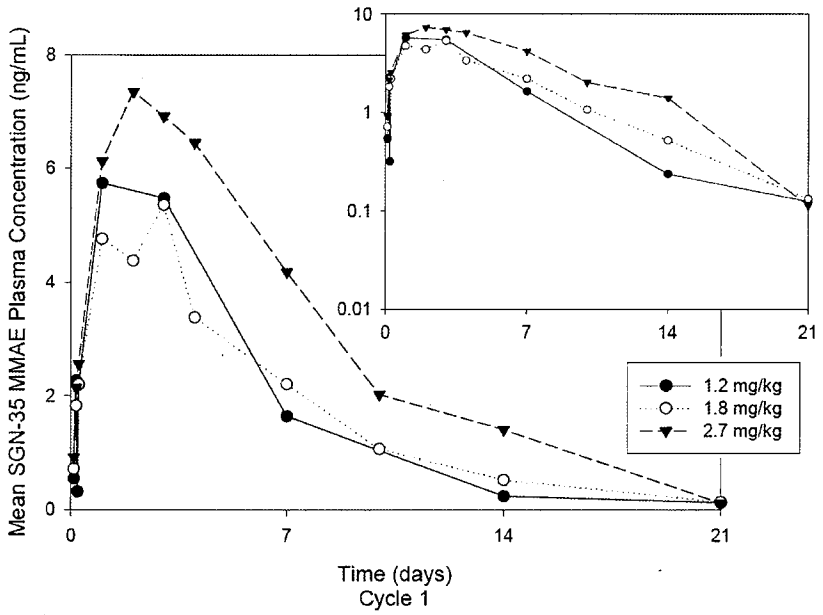



**Figure 9.** MMAE plasma concentration-time profile following the first dose of brentuximab vedotin in study SG035-0001

**Table 5.** Multiple Dose PK Parameters of MMAE in Study SG035-0001

| Dose[b] (mg/kg) | Pharmacokinetic Parameters (Accumulation Ratio) [a] | | | |
|---|---|---|---|---|
| | $AUC_{0-21d}$ Cycle 2/Cycle 1 | $AUC_{0-21d}$ Cycle 3/Cycle 1 | $C_{max}$ Cycle 2/Cycle 1 | $C_{max}$ Cycle 3/Cycle 1 |
| 1.8 | 0.79 (0.57, 1.09) n=10 | 0.69 (0.47, 1.00) n=9 | 0.54 (0.33, 0.87) n=11 | 0.54 (0.36, 0.80) n=10 |
| 2.7 | 0.67 (0.49, 0.90) n=10 | 0.60 (0.45, 0.79) n=8 | 0.57 (0.38, 0.87) n=10 | 0.50 (0.36, 0.71) n=9 |

[a]Data presented as geometric mean ratio (90% CI); [b]all doses administered Q3W

Ratios below for AUC and Cmax for Cycle 2/Cycle 1 and Cycle 3/Cycle 1 were below 1, indicating little or no accumulation (Table 5).

*Total Antibody*
Single dose serum PK of the TAb was characterized after doses of 1.2, 1.8, and 2.7 mg/kg of brentuximab vedotin. Exposure was dose proportional in study SG035-0001, but was greater than dose proportional in SGN35-008A (Table 6). In general, levels of TAb where higher than ADC, suggesting that the unconjugated antibody has a longer half-life than the ADC. This increase in unconjugated antibody relative to ADC is consistent with the proposed mechanism of action.

**Table 6.** First-dose PK Parameters of Total Antibody

| Study | Dose[b] (mg/kg) | Pharmacokinetic Parameters [a] | | |
|---|---|---|---|---|
| | | $AUC_{0\text{-}21d}$ (day·μg/mL) | $C_{max}$ (μg/mL) | $T_{max}$ (day)[c] |
| SG035-0001 | 1.2 (n=4) | 112.0 (27) | 24.7 (26) | 0.13 (0.08, 0.24) |
| | 1.8 (n=12) | 169.1 (29) | 36.6 (28) | 0.13 (0.08, 1.10) |
| | 2.7 (n=12) | 243.5 (22) | 53.3 (21) | 0.09 (0.09, 0.76) |
| SGN35-008A | 1.2 (n=16)[d] | 93.5 (37) | 22.3 (38) | 0.03 (0.02, 0.17) |
| | 1.8 (n=14) | 172.26 (30) | 40.3 (35) | 0.08 (0.02, 0.17) |

[a]Data presented as geometric mean (%CV); [b]all doses administered Q3W; [c]data for $T_{max}$ presented as median (min, max); [d]n=16 for $C_{max}$ and $T_{max}$, n=11 for AUC

*2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?*
Not applicable. Brentuximab vedotin has not been administered to healthy volunteers because of its safety profile. For information on drug metabolism, refer to section 2.2.5.6.

*2.2.5.3 What are the characteristics of drug absorption?*
Not applicable. Brentuximab vedotin is administered as an IV infusion. No studies of drug absorption have been performed.

*2.2.5.4 What are the characteristics of drug distribution?*
Following an IV infusion of 1.2, 1.8, or 2.7 mg/kg of brentuximab vedotin, the steady-state volume of distribution was approximately 6-10 L, indicating that brentuximab vedotin is primarily limited to the vascular space.

No radiolabeled tissue distribution studies for brentuximab vedotin have been performed. It is not characteristic to have tissue distribution studies for biologic agents.

*2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?*
No radiolabeled mass balance study of brentuximab vedotin has been performed in man to determine the proportion of administered dose cleared through specific mechanisms. Since brentuximab vedotin consists of a monoclonal antibody and MMAE, a mass balance study was performed for MMAE. Mass balance studies are not generally performed for biologic products, such as monoclonal antibodies, because they are proteins which are degraded into amino acids that are then recycled into other proteins.

A study examining the excretion of MMAE suggests that the primary route of excretion of MMAE is via feces. See response to 2.2.5.7 below for detailed information.

*2.2.5.6 What are the characteristics of drug metabolism?*

Metabolism studies were conducted for MMAE as part of the study SGN35-008A (Arm A-rif). Excreted metabolites were measured in unconcentrated and concentrated urine and feces bulk pools using HPCL-MS/MS (high-performance liquid chromatography-tandem mass spectrometry). MMAE was the only observed species in unconcentrated bulk pools. However, in urine and feces bulk pools which were concentrated 10-fold, 8 human metabolites of MMAE were observed. Seven of these 8 had been previously identified in non-clinical studies. The one metabolite which was not previously observed contains two individual biotransformations that had been identified *in vitro*.

Five key metabolic pathways were identified: N-demethylation (CYP3A4), O-demethylation (CYP3A4), dehydrogenation (CYP3A4), amide hydrolysis, and oxidation (Figure 10). Additional metabolites which were formed were found to be combinations of the some of the five biotransformations listed above.

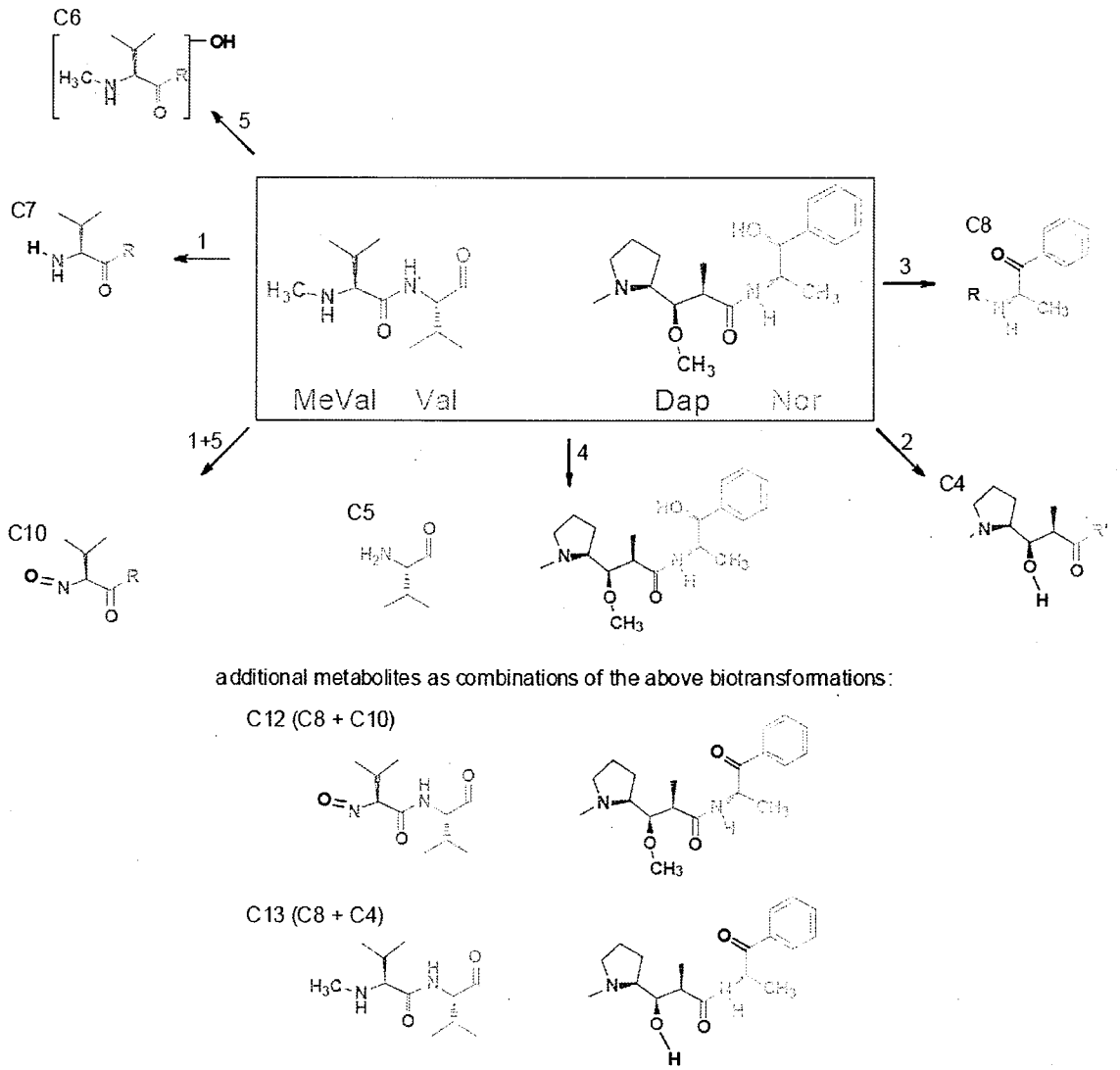



**Figure 10**. Metabolic pathway of MMAE in humans

**Table 7**. MMAE Metabolites Identified in Humans

| Metabolite Designation[a] | Metabolic Pathway | Urine n=8 n (%) | Feces n=8 n (%) |
|---|---|---|---|
| C1 | Oxidation | 0 | 0 |
| C2 | Oxidation | 0 | 0 |
| C3 | Oxidation | 0 | 0 |
| C4 | O-demethylation | 0 | 8 (100) |
| C5 | Amide hydrolysis | 3 (38) | 8 (100) |
| C6 | Oxidation | 4 (50) | 0 |
| C7 | N-demethylation | 4 (50) | 0 |
| C8 | Dehydrogenation | 8 (100) | 6 (75) |
| C9 | Oxidation | 0 | 0 |
| C10 | N-demethylation, oxidation | 3 (38) | 0 |
| C11 | Oxidation | 0 | 0 |
| C12 | Dehydrogenation, N-demethylation, Oxidation (C8+C10) | 2 (25) | 0 |
| C13[b] | O-demethylation, dehydrogenation (C4+C8) | 3 (38) | 8 (100) |

[a]Metabolites C1 through C12 were previously identified in *in vitro* and nonclinical *in vivo* studies
[b]C13 was not previously observed but contains two individual biotransformations that had been identified in C4 and C8

No metabolism study has been conducted for the antibody portion of brentuximab vedotin or for the ADC itself. Brentuximab vedotin is a biologic product. Metabolism studies are not generally performed for biologic products because these products are proteins that are degraded into amino acids which are then recycled into other proteins.

*2.2.5.7 What are the characteristics of drug excretion?*

The excretion of MMAE was evaluated in eight patients as part of study SGN35-008A (Arm A-rif). Urine and fecal sample were collected for a week after the first dose of 1.8 mg/kg brentuximab vedotin and prior to treatment with rifampin. A median of 23.5% of MMAE was recovered over the 1 week period, broken down into 6.3% from urine and 17.2% from feces, hence mass balance was not achieved (Figure 11). The mean percentage of MMAE excreted in feces was 72% of the total MMAE excreted (range 59-77%).

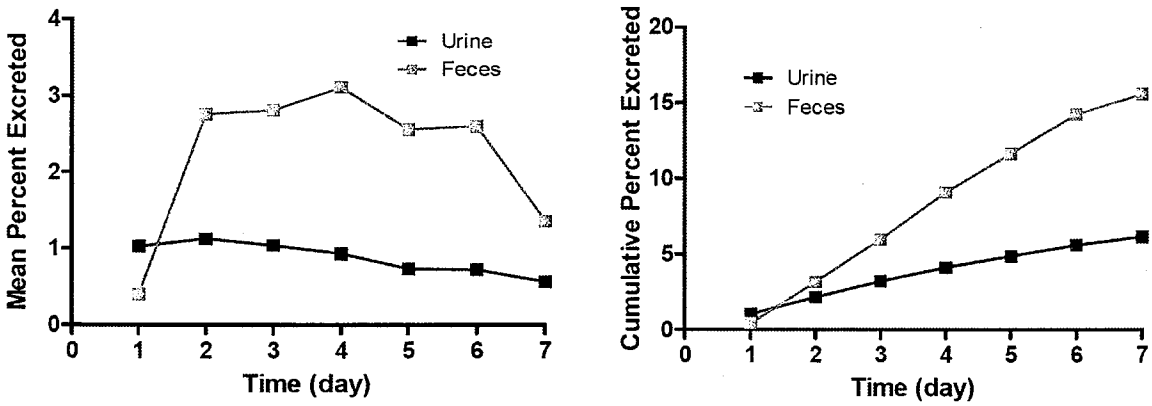



**Figure 11**. Excretion of MMAE over time (mean and cumulative)

*2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?*

The PK of the ADC was adequately described by a three-compartment model with zero-order input and first-order elimination linear elimination.

The sponsor claims that PK of MMAE was adequately described by a two-compartment model with first-order elimination and formation of MMAE both directly from ADC and through binding of ADC to the target with a delay in the formation of MMAE described with a lag compartment. However, the MMAE population PK model appeared to be quite complex. There were too many parameters that would have only been identifiable by administering MMAE alone. The results of the MMAE model were not used to assess covariate effects for labeling statements. Therefore, further review of the MMAE model was not performed.

*2.2.5.9 How do the PK parameters change with time following chronic dosing?*

The plasma concentration of ADC remained constant throughout all treatment cycles. Therefore time variant PK parameters are neither expected nor identified in the population PK model.

*2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?*

In the final population PK model constructed by the sponsor, the inter-individual variability of CL and central volume parameters were estimated to be 46.7 and 13.3 %, respectively. The intra-individual variability was estimated to be 33%. Since these inter- and intra-subject variability estimates were obtained in the final population PK model, the sources of variability are unidentified.

## 2.3 Intrinsic Factors

***2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence -exposure and/or -response and what is the impact of any differences in exposure on efficacy or safety responses?***

The CL and volume parameters of the ADC following brentuximab vedotin administration increased with weight. As a result, the dose of brentuximab vedotin is body weight based with the drug being dosed on a kg basis. No other intrinsic factors influenced the PK of ADC.

***2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dose regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.***

*2.3.2.1 Elderly Patients*

Age did not influence the PK of the ADC.

*2.3.2.2 Pediatric Patients*
There were an insufficient number of pediatric patients enrolled in the clinical studies to determine if the PK was different in this population or whether any dose adjustment would be needed.

*2.3.2.3 Gender*
Gender did not meaningfully influence the PK of the ADC.

*2.3.2.4 Race*
Race did not influence the PK of the ADC.

*2.3.2.5 Renal Impairment*
Renal function did not influence the PK of the ADC.

*2.3.2.6 Hepatic Impairment*
Hepatic function did not influence the PK of the ADC.

*2.3.2.7 What pharmacogenetics information is in the application and is it important or not?*
The sponsor only carried out exploratory pharmacogenomics analysis. Analyses of the effects of brentuximab vedotin on cytokines, chemokines, and soluble CD30 were performed as part of studies SG035-0001 and SG035-0002. The set of cytokines and chemokines evaluated were interleukin-6 (IL-6), interleukin-1 receptor antagonist, thymus and activation-regulated chemokine (TARC), tumor necrosis factor-alpha, and soluble CD30. No relationships between brentuximab vedotin dose levels and cytokine and chemokine concentrations were identified. The sponsor states that although some correlations were found, none of these analytes has been established as a biomarker for clinical efficacy, or as predictive of the effect of brentuximab vedotin.

*2.3.2.8 What pregnancy and lactation use information is in the application?*
Brentuximab vedotin was studied for effects on embryo-fetal development in pregnant female rats. The no-observed-adverse-effect-level of brentuximab vedotin when administered to pregnant rats was 1 mg/kg/dose. It is not known whether brentuximab vedotin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Since human $IgG_1$ is known to cross the placental barrier, brentuximab vedotin has the potential to be transmitted from the mother to the developing fetus. The product label recommends that brentuximab vedotin not be given to pregnant women unless clearly needed.

No study has been conducted to determine whether brentuximab vedotin is secreted into breast milk. Because, human $IgG_1$ is known to be secreted into human breast milk, there is a potential for brentuximab vedotin to be passed from mother to nursing child. The product label recommends that women who are taking brentuximab vedotin not breast-feed.

### *2.3.3 Immunogenicity*

*2.3.3.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?*

Patients were tested for anti-product antibodies (APAs) against brentuximab vedotin in all clinical studies. In studies SG035-0003 and SG035-0004, samples were collected at baseline (within 2 hours prior to the first dose), pre-dose in each subsequent treatment cycle ($C_{trough}$; approximately 3 weeks following the previous dose), and at the End of Treatment visit.

Serum APA was tested using an ELISA immunoassay in study SG035-0001; drug tolerance for this assay was below the observed serum concentration of the ADC. Hence, results from this study are not included in the summary below. In SG035-0001 all patients tested negative for APAs at baseline. Two patients tested positive for the presence of APA post-baseline. One was in the 0.1 mg/kg dose cohort and had a positive test beginning at Cycle 6 Day 1 and remained positive through the last assessment at Cycle 16, Day 1. The other patient was in the 1.2 mg/kg cohort and tested positive at the End of Treatment visit. An ECL (electrochemiluminescence) assay was used in all of the other clinical studies.

Study SG035-0002 employed a different dosing schedule than the other clinical studies. Five patients (11%) in SG035-0002 had APAs at the Cycle 1 Day 1 visit. Of the 42 patients who were evaluable for APA (defined as patients with a sample at baseline and at least one post-baseline visit), 14 patients (33%) had APA at any post-baseline visit. Two patients (14%) who had an acute infusion reaction also had APA at a post-baseline visit.

Study SGN35-008A employed an abbreviated sampling schedule. Samples were assessed for APAs at baseline (Cycle 1 Day 1); Cycle 2 Day 1; and at the End of Treatment visit. Six (11%) of 56 patients had confirmed APA at baseline; 3 of these patients also tested positive for confirmed APA post-baseline. Eighteen patients were free of confirmed APA at baseline but tested positive at one or both post-baseline timepoints. Due to the short duration of the study, the transience or persistence of the APA could not be assessed.

Study SGN35-007 is currently on-going and only the interim study results have been submitted. Information on APA response has not been included in the intern clinical study report dated December 20, 2010.

Studies SG035-0003 and SG035-0004 employed similar sampling schedules for APA detection. APA status was grouped into 3 categories:

- Negative - defined as patients who did not have confirmed positive APA in any post-baseline sample
- Transiently positive - defined as patients with confirmed positive APA in 1 or 2 post-baseline samples

- Persistently positive - defined as patients with confirmed APA in more than 2 post-baseline samples (note: not necessarily APA-positive at the end of treatment)

Studies SG035-0003 and SG035-0004 employed similar sampling schedules for APA detection; results are summarized in Table 8.

**Table 8**. Immunogenicity Incidence in Studies SG035-0003 and SG035-0004[a]

| Baseline APA Status | Pose-baseline APA Status | Number of Patients n=156[b] n (%) |
|---|---|---|
| Baseline negative | | 148 (95) |
| | Negative post-baseline | 96 (62) |
| | Transiently positive post-baseline | 42 (27) |
| | Persistently positive post-baseline | 10 (6) |
| Baseline positive | | 8 (5) |
| | Negative post-baseline | 2 (1) |
| | Transiently positive post-baseline | 5 (3) |
| | Persistently positive post-baseline | 1 (1) |

[a]Immunogenicity incidence represents anti-brentuximab vedotin antibodies
[b]4 patients from the Phase 2 population are not included in this analysis: 2 because they did not have a baseline result, and 2 because they did not have any post-baseline results

In studies SG035-0003 and SG035-0004, where immunogenicity was assessed at each cycle, the beginning of Cycle 2 (approximately 3 weeks after initiating treatment) is when the most patients tested positive for APAs. When this data was further categorized for those patients who were transiently positive and those who were persistently positive, again the beginning of Cycle 2 was when most patients were positive for both.

**Table 9**. Immunogenicity (APA Incidence) by Treatment Cycle in SG035-0003 and SG035-0004

| | APA Incidence | |
|---|---|---|
| First Positive Cycle (Pre-dose)[a] | Transiently Positive n=47 n (%) | Persistently Positive n=11 n 9%) |
| Cycle 1 (predose, baseline positive) | 5 (11) | 1 (9) |
| Cycle 2 | 32 (68) | 9 (82) |
| Cycle 3 | 7 (15) | 0 |
| Cycle 4 | 1 (2) | 0 |
| Cycle 5 | 1 (2) | 0 |
| Cycle 6 | 0 | 0 |
| Cycle 7 | 1 (2) | 0 |
| Cycle 8 | 0 | 1 (9) |

[a]Samples taken within 2 hours prior to dosing in each indicated cycle

Overall, 30% of the patients from the two registration studies became transiently positive and 7% became persistently positive (more than 2 instances of a positive confirmed APA response) for APA after treatment with brentuximab vedotin.

*2.3.3.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?*
Immunogenicity does not affect the PK and/or PD of brentuximab vedotin. In SG035-0001, positive APA status did not appear to affect the PK of brentuximab vedotin. An

exploratory analysis was conducted in SGN35-008A to determine whether excluding patients who were post-baseline APA positive would impact ADC or MMAE PK. As stated in Section 2.3.3.1, 18 patients were positive for APAs for at least one post-baseline measurement. Three patients were positive for APAs at- and post-baseline. Of the 21 patients in total, 5 were in Arm-A mid, 8 were in Arm A-rif, and 8 were in Arm A-ket. An analysis comparing the geometric mean ratios of several PK parameters with and without patients with positive post-baseline APA results showed that the GMRs were similar for the two groups. This analysis was performed for the Arm A-rif and Arm A-ket groups, but not for the Arm A-mid group, most likely because of the small number of patients in the Arm-A mid group. Data from this analysis is provided in the Appendix (Tables A-1 and A-2).

Based on population PK analysis, ADC CL was 18% higher in cycles when patients had positive APA response. However, the increased CL does not have an impact on the PK profile of the ADC based on a simulation (Figure 12).

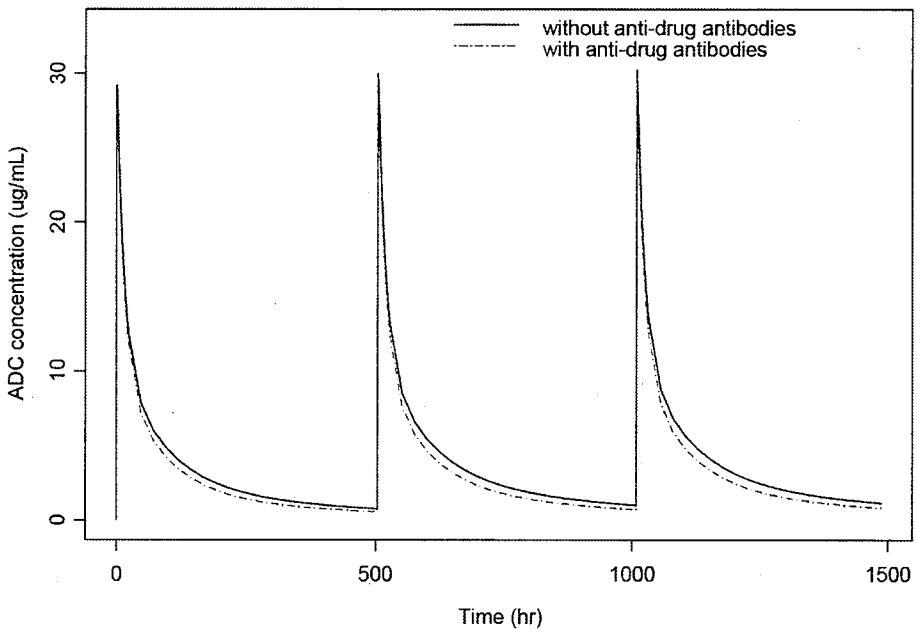



**Figure 12.** Simulated typical ADC profiles for a patient receiving 1.8 mg/kg brentuximab vedotin over 3 cycles with and without APAs

*2.3.3.3 Do the anti-product antibodies have neutralizing activity?*

Samples from studies SG035-0003 and SG035-0004 which were confirmed to be APA positive were tested for the presence of neutralizing antibodies. A total of 58 patient samples were found to be either transiently or persistently APA positive post-baseline. Of the 58 patients, 18 (31%) were negative for the presence of neutralizing antibodies, 36 (62%) had at least one sample that was positive for the presence of neutralizing antibodies, and 4 (7%) were of unknown status due to insufficient sample.

Thirty-four (34) of 40 patients in study SG035-0003 who screened positive for APAs were tested for neutralizing antibodies. Thirty of these patients were positive for neutralizing antibodies. Patient's positive for neutralizing antibodies had similar ORR and higher CR rates (Table 10). The median duration of response was not reached in patients positive for neutralizing antibodies. For safety, the incidence of neuropathy, neutropenia, or thrombocytopenia was similar to the overall population. Infusion reactions were more common in patients with positive neutralizing antibodies (27%) compared to the overall safety population (14%).

**Table 10.** Effect of Neutralizing Antibodies on Select Efficacy and Safety Parameters for SG035-0003 (HL)

| Clinical Measure | All Patients (n=102) | Neutralizing antibody positive (n=30) |
|---|---|---|
| Overall response rate (CR+PR) | 74 (73%) | 24 (80%) |
| Complete remission rate | 33 (32%) | 17 (57%) |
| Peripheral neuropathy | 56 (55%) | 18 (60%) |
| Neutropenia | 55 (54%) | 17 (57%) |
| Thrombocytopenia | 29 (28%) | 8 (27%) |
| Infusion reaction | 14 (14%) | 8 (27%) |

Twenty (20) of 23 patients in study SG035-0004 who screened positive for APAs were tested for neutralizing antibodies. Six of these patients were positive for neutralizing antibodies. The ORR for the patients who tested positive for neutralizing antibodies was 100% (5 CRs and 1 PR). Fifty percent of neutralizing antibody positive patients had peripheral neuropathy, all had neutropenia, 17% had thrombocytopenia and none had an infusion reaction. The small number of patients with neutralizing antibodies in study SG035-0004 limits the utility of this data.

**Table 11.** Effect of Neutralizing Antibodies on Select Efficacy and Safety Parameters for SG035-0004 (ALCL)

| Clinical Measure | All Patients (n=58) | Neutralizing antibody positive (n=6) |
|---|---|---|
| Overall response rate (CR+PR) | 50 (86%) | 6 (100%) |
| Complete remission rate | 33 (57%) | 5 (83%) |
| Peripheral neuropathy | 17 (29%) | 3 (50%) |
| Neutropenia | 32 (55%) | 6 (100%) |
| Thrombocytopenia | 9 (16%) | 1 (17%) |
| Infusion reaction | 5 ( 9%) | ----- |

*2.3.3.4 What is the impact of anti-product antibodies on clinical efficacy?*

There is no impact of immunogenicity on brentuximab vedotin efficacy. Clinical response was summarized by post-baseline immunogenicity status (negative, transiently positive, persistently positive). Studies SG035-0002 and SG035-0003 were used for this analysis for the HL indication and studies SG035-0002 and SG035-0004 were used for the ALCL indication. For both indications, various measures of clinical response were compared between APA negative patients and those that became transiently or

persistently positive. The data suggests the emergence of APA post-baseline does not influence clinical response (Appendix- Tables A-3 and A-4).

*2.3.3.5 What is the impact of anti-product antibodies on clinical safety? (e.g., infusion-related reactions, hypersensitivity reactions, cross-reactivity to endogenous counterparts, etc.)?*

Patients from studies SG035-0003 and SG035-0004 were pooled for an assessment of the impact of APAs on brentuximab vedotin safety. A total of 42 (27%) of patients who had a negative baseline APA sample were transiently positive post-baseline, an additional 10 (6%) of patients were persistently positive. Overall, the incidence of adverse events (AEs) and severe adverse events (SAEs) were similar regardless of whether a patient tested transiently or persistently positive for APAs (Appendix- Table A-5). The incidence of treatment-emergent AEs by system organ class was also similar regardless of whether the patient tested transiently or persistently positive for APAs (data not shown). It is important to note that the smaller number of persistently positive patients compared to transiently positive patients makes it more difficult to detect AEs in the smaller population.

A higher incidence of infusion related reactions (IRRs) was observed in the persistenly positive patients (3/10, 30%) relative to transiently positive (5/42, 12%), and never positive (7/96, 7%) patients (Appendix- Table A-6).

Two patients from study SG35-0003 discontinued treatment with brentuximab vedotin because of infusion reactions or AEs consistent with IRRs. Both patients were categorized at persistently positive and had APA titers of 3125.

## 2.4 Extrinsic Factors

***2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or –response and what is the impact of any differences in exposure on response?***

None.

***2.4.2 Drug-drug interactions***

Drug-drug interactions were addressed in study SGN35-008A, in which patients with CD30+ hematologic malignancies were assigned to one of three arms. Patients received a maximum of 2 cycles of brentuximab vedotin and also received midazolam (mid), rifampin (rif), or ketoconazole (ket) as shown in Table 12. Although 56 patients were enrolled in the study, 45 patients were evaluable for PK: 15 in Arm A-mid, 14 in Arm A-rif, and 16 in Arm A-ket.

**Table 12**. Administration of Brentuximab Vedotin and CYP3A4 Drugs in SGN35-008A

| Treatment Arm | Dose of Brentuximab Vedotin [a] | Dose of CYP3A4 Drug |
|---|---|---|
| Arm A-mid | 1.8 mg/kg IV, 30 min infusion | Midazolam 1 mg IV over 2 min (Day -3 and Day 3 of Cycle 1) |
| Arm A-rif | 1.8 mg/kg IV, 30 min infusion | Rifampin, 600 mg orally/day (Cycle 1, Day 14 through Cycle 2, Day 21) |
| Arm A-ket | 1.2 mg/kg IV, 30 min infusion [b] | Ketoconazole, 400 mg orally/day (Cycle 1, Day 19 through Cycle 2, Day 21) |

[a] Brentuximab vedotin administered on Day 1 of each cycle; patients received a maximum of two cycles
[b] To minimize potential increased exposures in the event that CYP3A4 inhibition altered the PK of brentuximab vedotin, a dose of 1.2 mg/kg brentuximab vedotin was used in Arm A-ket

*2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?*
Several *in vitro* non-GLP studies were conducted to characterize the metabolism of MMAE. The *in vitro* metabolism of tritium-labeled MMAE ([$^3$H]MMAE, 0.9 – 104 μM) in human liver microsomes suggested minimal biotransformation by CYP enzymes. *In vitro*, 3 of 8 radioactive components (C4, C7, and C8 in Table 7) appeared to be the most abundant metabolites and appeared to be generated primarily through CYP3A4 and possibly CYP2D6. The role of CYP3A4 was confirmed by strong inhibition of the formation of components C4, C7, and C8 by the chemical inhibitor ketoconazole and by a monoclonal antibody against CYP3A4.

Several metabolites were formed at low levels, following incubation of [$^3$H]MMAE (10 μM) with cryopreserved human hepatocytes,. The substrate initial rate and overall extent of [$^3$H]MMAE metabolism by hepatocytes was low.

It was also determined that MMAE (0.1 μM, 1 μM, or 10 μM) did not appear to be an inducer of CYP1A2, 2B6, 2C8, 2C9, 2C19, or 3A4/5 in cultured human hepatocytes. However, MMAE appeared to cause direct inhibition of CYP3A4/5 as measured by midazolam 1′-hydroxylation with an $IC_{50}$ value of 10 μM. There was little or no direct inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or of CYP3A4/5 when measured by testosterone 6β-hydroxylation. MMAE was also determined to be potentially a mechanism-based time-dependent inhibitor of CYP3A4/5 with a $k_{inact}$ value of 0.10 $min^{-1}$, and a $K_I$ value of 1.12 μM, yielding a $k_{inact}$ / $K_I$ ratio of ~90 $min^{-1}$ $mM^{-1}$. Based on these results, MMAE is a potential substrate of CYP3A4 and inhibitor of CYP3A4/5.

*2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?*
The effect of rifampin, a CYP3A4 and P-gp (P-glycoprotein) inducer, on the PK of brentuximab vedotin and MMAE was determined.

**Table 13**. Geometric Mean Ratios for Brentuximab Vedotin ± Rifampin

| Analyte | PK Parameter | N | Geometric Mean | | |
|---|---|---|---|---|---|
| | | | Brentuximab Vedotin Alone | Brentuximab Vedotin with Rifampin | GMR (90% CI) [a] |
| ADC | $AUC_{0-\infty}$ (d·μg/mL) | 11 | 89.8 | 93.4 | 1.04 (0.87-1.24) |
| | $C_{max}$ (μg/mL) | | 36.7 | 34.1 | 0.93 (0.81-1.06) |
| MMAE | $AUC_{0-\infty}$ (d·ng/mL) | 14 | 40.1 | 21.5 | 0.54 (0.43-0.68) |
| | $AUC_{0-10d}$ (d·ng/mL) | | 31.8 | 17.7 | 0.55 (0.44-0.71) |
| | $C_{max}$ (ng/mL) | | 4.98 | 2.80 | 0.56 (0.42-0.76) |

[a] Geometric mean ratio of (brentuximab vedotin + rifampin)/(brentuximab vedotin alone)

The 90% CI for the geometric mean ratio (GMR) fell within the equivalence bounds of (0.80, 1.25) for the ADC, but failed to meet the equivalence criteria for MMAE (Table 13). The AUC and $C_{max}$ for MMAE were lower when brentuximab vedotin was coadministered with rifampin and the upper limit of the 90% CI for the GMR was below 1.0, indicating that MMAE is a substrate for CYP3A4 and/or P-gp.

The effect of ketoconazole, a strong CYP3A4 and P-gp inhibitor, on the PK of brentuximab vedotin was tested in a similar fashion as rifampin. The 90% CI for AUC for the GMR fell within the equivalence bounds for the ADC; however, the 90% CI for $C_{max}$ fell outside of the limits (Table 14). Because the GMR was close to 1.0 for both AUC and $C_{max}$, it is unlikely for a CYP3A4 inhibitor to have an effect on the ADC. The AUC and $C_{max}$ of MMAE were higher when brentuximab was coadministered with ketoconazole. Consequently, the upper limit of the 90% CI for exposure of MMAE fell outside of the equivalence bound. The higher exposures and GMR above 1.0 in the presence of ketoconazole suggest that MMAE is a substrate of CYP3A4 and/or P-gp.

**Table 14**. Geometric Mean Ratios for Brentuximab Vedotin ± Ketoconazole

| Analyte | PK Parameter | N | Geometric Mean | | |
|---|---|---|---|---|---|
| | | | Brentuximab Vedotin Alone | Brentuximab Vedotin with Ketoconazole | GMR (90% CI) [a] |
| ADC | $AUC_{0-\infty}$ (d·μg/mL) | 11 | 52.8 | 56.3 | 1.07 (0.95-1.19) |
| | $C_{max}$ (μg/mL) | 16 | 22.6 | 22.4 | 0.99 (0.75-1.31) |
| MMAE | $AUC_{0-\infty}$ (d·ng/mL) | 14 | 26.7 | 35.7 | 1.34 (0.98-1.84) |
| | $AUC_{0-17d}$ (d·ng/mL) | 14 | 25.8 | 32.1 | 1.24 (0.95-1.61) |
| | $C_{max}$ (ng/mL) | 16 | 4.11 | 5.13 | 1.25 (0.90-1.72) |

[a] Geometric mean ratio of (brentuximab vedotin + ketoconazole)/(brentuximab vedotin alone)

*2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?*

The AUC and $C_{max}$ for midazolam, a CYP3A4 substrate, were determined for midazolam alone and midazolam coadministered with brentuximab vedotin. Parameters were estimated at the $T_{max}$ of MMAE, approximately 2 days after brentuximab vedotin administration. The 90% CI for the GMR for $AUC_{0-\infty}$ was within the equivalence bounds of (0.80, 1.25) (Table 15). The 90% CI for the GMR for $C_{max}$ falls out of the equivalence bounds; however, the ratio is close to 1. This does not rule out the possibility of a drug interaction, but brentuximab vedotin is unlikely to affect midazolam $C_{max}$. Hence, brentuximab vedotin is neither an inhibitor nor an inducer of CYP3A4.

**Table 15**. Geometric Mean Ratios for Midazolam ± Brentuximab Vedotin

| PK Parameter | N | Geometric Mean | | |
|---|---|---|---|---|
| | | Midazolam Alone | Midazolam with Brentuximab Vedotin | GMR (90% CI) [a] |
| $AUC_{0-\infty}$ (hr·μg/mL) | 15 | 0.079 | 0.074 | 0.94 (0.81-1.10) |
| $C_{max}$ (μg/mL) | 14 | 0.073 | 0.085 | 1.15 (0.76-1.74) |

[a] Geometric mean ratio of (midazolam + brentuximab vedotin)/(midazolam alone)

*2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?*
MMAE is a substrate of CYP3A4 and/or P-gp. See response to 2.4.2.3.

*2.4.2.5 Are there other metabolic/transporter pathways that may be important?*
Yes. See response to 2.2.5.6.

*2.4.2.6 Does the label specify co-administration of another drug (e.g. combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?*
No. The proposed dosing regimen involves the use of brentuximab vedotin as a monotherapy.

*2.4.2.7 What other co-medications are likely to be administered to the target patient population?*
None. The current proposed use of brentuximab vedotin is as a monotherapy. Additional medications may be given concomitantly to alleviate symptoms arising from adverse events.

*2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?*
Yes. The concentration of MMAE was altered when coadministered with ketoconazole and rifampin. However, since the contribution of free MMAE is extremely low and the contribution of free MMAE to efficacy and safety is minimal, dose modifications are not nessesary when brentuximab vedotin is co-administered with drugs that inhibit or induce CYP3A4.

*2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?*
No.

***2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?***
None.

## 2.5 General Biopharmaceutics

***2.5.1 What are the manufacturing differences between the to-be-marketed formulation and the formulation used in the pivotal clinical trial?***

Three different processes have been used to manufacture brentuximab vedotin. Process A was the initial investigational process used to produce brentuximab vedotin for some Phase 1 studies and at the beginning of the Phase 2 studies. Process B was also used in some Phase 1 studies and during the Phase 2 studies. Brentuximab vedotin produced using Process C was used to complete the Phase 2 studies, is being used in current clinical studies, and is the commercial process.

Table 16 below shows the changes in the manufacturing processes for brentuximab vedotin. Physiochemical, immunological, and biological assays were used to assess the comparability between the different manufacturing processes. The three processes were found to be comparable from a CMC standpoint, refer to the CMC review for further details. No PK comparability studies were conducted in humans.

**Table 16.** Brentuximab Vedotin Manufacturing Processes and Patient Exposures

| Process | A | B | C |
|---|---|---|---|
| | | | (b) (4) |
| Patient Exposures in Clinical Studies[a] | SG035-0001 (n = 45)<br>SG035-0002 (n = 36)<br>SG035-0003 (n = 43)<br>SG035-0004 (n = 14)<br>SGN35-007 (n = 10)<br>Total exposed = 148 | SG035-0002 (n = 16)<br>SG035-0003 (n = 83)<br>SG035-0004 (n = 23)<br>SGN35-007 (n = 1)<br>Total exposed = 123 | SG035-0002 (n = 12)<br>SG035-0004 (n = 36)<br>SGN35-007 (n = 41)<br>SGN35-008 (n = 60)<br>Total exposed = 149 |

[a]Patients could received brentuximab vedotin form more than one process and are included in the total for each process. SGN-35= brentuximab vedotin; BDS= bulk drug substance; DP= drug product

### *2.5.2 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?*

The sponsor did not conduct any *in vivo* comparability studies comparing Processes A, B, and C. (b) (4) . Similar numbers of patients have been exposed to brentuximab vedotin manufactured using each process. The proposed to-be-marketed formulation is not expected to present an efficacy or safety concern.

## 2.6 Analytical

### *2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?*

In order to characterize the PK and disposition of brentuximab vedotin, the concentrations of three analytes were measured: ADC, MMAE, and TAb. ADC and TAb were measured in serum by ELISA immunoassays. MMAE was measured in plasma by liquid chromatography and tandem mass spectrometry (LC-MS/MS). The MMAE assay was also validated in urine and feces for metabolism and elimination studies.

### *2.6.2 Which metabolites have been selected for analysis and why?*

No metabolites have been selected for further analysis. The metabolites of MMAE that were formed are present in very small amounts and do not warrant further characterization.

### *2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?*

For the ADC, the assay measures only intact conjugate. The assay is not able to differentiated between the conjugates with different drug to antibody ratios. For total antibody, both conjugated and unconjugated antibody was measured.

For MMAE the sponsor states that "free" MMAE was detected, unconjugated MMAE can still include free MMAE and MMAE attached to the linker or MMAE non-specifically bound to other plasma proteins. The assay used for the detection of "free" MMAE would not be able to distinguish between actual free MMAE and MMAE bound to other moieties as mentioned above. The sponsor did carry out a separate analysis to determined the extent of linker-MMAE transfer from the ADC to other plasma proteins. The results of this study showed that free MMAE was the predominant component of the MMAE in the sample following affinity chromatography for total MMAE. The transferred MMAE consisted of approximately 1.5% of all circulating conjugated and unconjugated MMAE in plasma.

### *2.6.4 What bioanalytical methods are used to assess therapeutic protein concentrations?*

Five different assays were used to assess the concentrations of the different components of the conjugate as described in Section 2.6.1 above. Each assay has been reviewed individually below.

*ADC Serum ELISA*

ADC concentrations in serum were measured with an ELISA immunoassay in a sandwich format (using different antibodies for capture and detection) (Table 17). (b) (4)

(b) (4) Assay performance was monitored by 3 levels of quality control samples and a set of calibration standards.

**Table 17.** ADC Serum ELISA Characteristics

| Characteristic | Results |
|---|---|
| Specificity | 95% of 20 samples at a spike of 49.5 ng/mL and 85% at a spike of 200 ng/mL met targeted %AR ranges |
| Accuracy | All QC levels were between 98.2 and 108% overall averaged AR |
| Precision | All QC levels had inter- and intra-assay %CV ≤10.1% |

AR = analytical recovery

*MMAE LC-MS/MS*

Free (unconjugated) MMAE concentrations in human plasma, urine, and feces were detected by liquid chromatography with tandem mass spectrometry (Table 18). Free MMAE and the internal standard D8-MMAE were extracted from the biological matrix by solid-phase extraction. While the sponsor states that "free" MMAE was detected, unconjugated MMAE can still include free MMAE and MMAE attached to the linker. This assay would not be able to differentiate between free MMAE and MMAE non-specifically bound to other moieties.

**Table 18.** MMAE Assay Characteristics

| Characteristic | Results |
|---|---|
| *Plasma* | |
| Selectivity | Mean RSD of 2.5%; mean accuracy of 96.0% |
| Accuracy | 95.4 to 103.6% for calibration standards<br>92.0 to 94.7% for QC samples |
| Precision | Inter- and intra-assay RSD ≤6.0% |
| *Urine* | |
| Selectivity | Mean RSD of 2.2%; mean accuracy of 100.7% |
| Accuracy | 108.0% at 0.300 ng/mL<br>102.4% at 5.00 ng/mL<br>101.8% at 40.0 ng/mL |
| Precision | Inter- and intra-assay RSD ≤3.8% |
| *Feces* | |
| Selectivity | Mean RSD of 9.3%; mean accuracy of 94.0% |
| Accuracy | 95.4 to 103.6% for calibration standards<br>105.3% at 15 ng/g<br>100.8% at 250 ng/g<br>98.5% at 2000 ng/g |
| Precision | Inter- and intra-assay RSD ≤4.6% |

RSD= relative standard deviation

*Total Antibody Serum ELISA*

Total antibody concentrations in serum were measured with an ELISA immunoassay in a bridging format (using the same antibody for capture and detection) (Table 19). (b) (4) Total antibody measurements include conjugated and unconjugated antibody.

**Table 19.** Total Antibody Serum ELISA Characteristics

| Characteristic | Results |
|---|---|
| Specificity | 65.0% of low spikes and 95.0% of high spikes within 80.0 to 120% AR |
| Accuracy | All QC levels were between 89.2 and 109% AR |
| Precision | All QC levels had inter- and intra-assay %CV ≤14.9%; the between-run %CV was 15.1% |

*2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?*

*ADC Serum ELISA*
Pools of human serum were screened to identify the lowest baseline signals and best recovery of low and high spikes against a buffer calibration curve as part of the feasibility assays. The SGN-35 ADC calibrators were prepared in the selected pool of human serum at concentrations of 3200, 1600, 800, 400, 300, 200, 100, 50, 25, 12.5, 6.25 and 3.13 ng/mL. Calibration curves were fit with a 4-parameter curve fit using SOFTmax Pro version 4.3.1 (Molecular Devices). The mean OD for the zero calibrator was 0.028 OD with a range of 0.021 to 0.066 OD.

*MMAE LC-MS/MS*
Calibration curves for MMAE in human plasma ranged from 25.0 to 1000 pg/mL and were generated using a weighted (1/x2) linear least-squares regression.

*Total Antibody Serum ELISA*
Calibrators were prepared in the human serum and tested in two-fold dilutions from 3200 to 3.13 ng/mL (prior to 1/100 dilution in assay buffer). A 300 ng/mL calibrator was also included in the calibrator backfit analysis. Calibration curves were fit using the 4-parameter curve-fitting program in SOFTmax Pro version 4.3.1 (Molecular Devices). The average zero calibrator OD was 0.104 (to ± 0.0403) with a range of 0.066 to 0.225 OD units.

*2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?*

**Table 20.** Analytical Methods Limits of Quantification

| Analyte | Matrix | Analytical Method | Limits of Quantification |
|---|---|---|---|
| ADC | Serum | ELISA | 12.5 – 400 ng/mL |
| TAb | Serum | ELISA | 12.5 – 400 ng/mL |
| MMAE | Plasma | LC-MS/MS | 0.025 – 1 ng/mL |
| MMAE | Urine | LC-MS/MS | 0.1 – 50 ng/mL |
| MMAE | Feces | LC-MS/MS | 5.00 – 2500 ng/g in human feces |

*2.6.4.3 What are the accuracy, precision, and selectivity at these limits?*
The accuracy, precision, and selectivity for each assay have been provided in Section 2.6.4 above.

*2.6.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?*

*ADC Serum ELISA*
Stability testing included six cycles of freeze/thaw, up to 16 hours bench top stability and up to 7 days refrigerator stability. Long-term stability is acceptable up to 24 months after storage at -60 to -90°C and up to nine months after storage at -15 to -30°C.

*MMAE LC-MS/MS*
Stability of free MMAE in human plasma was confirmed for three freeze/thaw cycles and was stable for 24 hours at room temperature. Long-term stability was acceptable up to 7.5 months after storage at -10 to 30°C and up to approximately 13 months after storage at -60 to -80°C.

*Total Antibody Serum ELISA*
The total antibody portion of brentuximab vedotin is stable for at least four months after storage at -10 to -30°C and for at least 24 months after storage at -60 to -80°C.

*2.6.4.5 What is the QC sample plan?*

*ADC Serum ELISA*
The LLOQ QC was evaluated at two levels: LLOQ1 at 12.5 ng/mL and LLOQ2 at 25.0 ng/mL. The ULOQ QC was also evaluated at two concentrations: 400 ng/mL (ULOQ1) and 800 ng/mL (ULOQ 2). Additional spikes, Low, Mid and High QCs, were prepared at 50, 100 and 200 ng/mL SGN-35 ADC in pooled human serum.

*MMAE LC-MS/MS*
Six replicates of QC samples at each of the LLOQ, low QC [LQC (75.0 pg/mL)], low/medium QC [LMQC (150 pg/mL)], medium QC [MQC (300 pg/mL)], and high QC [HQC (800 pg/mL)] concentrations were used.

*Total Antibody Serum ELISA*
SGN-35 was spiked into pooled human serum and tested at seven dilutions assay, three duplicate pairs of each QC were tested. Two levels of LLOQ (6.25 and 12.5 ng/mL) and two concentrations of ULOQ (400 and 800 ng/mL) were tested, along with a low (25.0 ng/mL), mid (100 ng/mL), and a high (200 ng/mL) QC.

### *2.6.6 What bioanalytical methods are used to assess the formation of the anti-product antibodies? Briefly describe the methods and assay performance including sensitivity, specificity, precision, cut point, interference and matrix, etc.*

APA in the serum of patients dosed with brentuximab vedotin was detected by immunoassay, initially by ELISA for the first-in-human study (SG035-0001), and by ECL for all subsequent clinical trials. A bridging format that used the same antibody, brentuximab vedotin, for capture and detection was employed in both immunoassays. However, the ECL method was more robust with regard to interference from therapeutic drug levels in the sample, with a 100-fold higher drug tolerance level than the ELISA method.

(b) (4)

Assay performance was monitored by three levels of quality control samples and a set of calibration standards.

*2.6.6.1 What is the performance of the binding assay(s)?*
The performance of the binding assays has been reviewed in the detail in the CMC review. Please refer to this review for further details.

*2.6.6.2 What is the performance of the neutralizing assay(s)?*
The performance of the neutralizing assay has been reviewed in the detail in the CMC review. Please refer to this review for further details.

## 3. DETALIED LABELING RECOMMENDATIONS

(b) (4)

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

# 4. APPENDICIES

## 4.1 ADDITIONAL TABLES

**Table A-1.** Effect of APA on GMRs for Brentuximab Vedotin (PK analysis set; Arm A-rif)

| | | All Patients in PK Analysis Set | | Excluding Patients With Confirmed ATA Postbaseline | |
|---|---|---|---|---|---|
| Analyte | PK Parameter | n | GMR[a] (90% CI) | n | GMR[a] (90% CI) |
| ADC | $AUC_{0-\infty}$[b] (d·µg/mL) | 11 | 1.04 (0.87–1.24) | 6 | 1.25 (1.09–1.43) |
| ADC | $C_{max}$ (µg/mL) | 11 | 0.93 (0.81–1.06) | 6 | 0.93 (0.71–1.22) |
| MMAE | $AUC_{0-\infty}$[b] (d·ng/mL) | 14 | 0.54 (0.43–0.68) | 9 | 0.50 (0.35–0.71) |
| MMAE | $AUC_{0-10d}$ (d·ng/mL) | 14 | 0.55 (0.44–0.71) | 9 | 0.50 (0.35–0.71) |
| MMAE | $C_{max}$ (ng/mL) | 14 | 0.56 (0.42–0.76) | 9 | 0.50 (0.32–0.78) |

a Brentuximab vedotin with rifampin/brentuximab vedotin alone.
b Primary AUC analysis.

**Table A-2.** Effect of APA on GMRs for Brentuximab Vedotin (PK analysis set; Arm A-ket)

| | | All Patients in PK Analysis Set | | Excluding Patients With Confirmed ATA Postbaseline | |
|---|---|---|---|---|---|
| Analyte | PK Parameter | n | GMR[a] (90% CI) | n | GMR[a] (90% CI) |
| ADC | $AUC_{0-\infty}$[b] (d·µg/mL) | 11 | 1.07 (0.95–1.19) | 7 | 1.15 (1.00–1.33) |
| ADC | $C_{max}$ (µg/mL) | 16 | 0.99 (0.75–1.31) | 8 | 1.33 (0.88–1.99) |
| MMAE | $AUC_{0-\infty}$[b] (d·ng/mL) | 14 | 1.34 (0.98–1.84) | 7 | 1.62 (0.92–2.84) |
| MMAE | $AUC_{0-17d}$ (d·ng/mL) | 14 | 1.24 (0.95–1.61) | 7 | 1.38 (0.91–2.11) |
| MMAE | $C_{max}$ (ng/mL) | 16 | 1.25 (0.90–1.72) | 8 | 1.14 (0.75–1.74) |

a Brentuximab vedotin with ketoconazole/brentuximab vedotin alone.
b Primary AUC analysis.

**Table A-3.** Best clinical response by post-baseline immunogenicity status in baseline negative patients in patients with HL

| | SG035-0003[a] (n=96) On-Study Immunogenicity Status | | | SG035-0002[b c] (n=33) On-Study Immunogenicity Status | | |
|---|---|---|---|---|---|---|
| | Negative (N=64) n (%) | Transient Positive (N=24) n (%) | Persistent Positive (N=7) n (%) | Negative (N=23) n (%) | Transient Positive (N=9) n (%) | Persistent Positive (N=1) n (%) |
| Best clinical response | | | | | | |
| Complete remission (CR) | 16 (25) | 12 (50) | 5 (71) | 6 (26) | 2 (22) | 0 |
| Partial remission (PR) | 33 (52) | 4 (17) | 1 (14) | 5 (22) | 3 (33) | 1 (100) |
| Stable disease (SD) | 14 (22) | 6 (25) | 1 (14) | 9 (39) | 3 (33) | 0 |
| Progressive disease (PD) | 1 (2) | 2 (8) | 0 | 3 (13) | 1 (11) | 0 |
| Histology ineligible (HI) | 0 | 0 | 0 | 0 | 0 | 0 |
| Not evaluable (NE) | 0 | 0 | 0 | 0 | 0 | 0 |
| Objective response rate (CR + PR) | 49 (77) | 16 (67) | 6 (86) | 11 (48) | 5 (56) | 1 (100) |
| Disease control rate (CR + PR + SD) | 63 (98) | 22 (92) | 7 (100) | 20 (87) | 8 (89) | 1 (100) |
| 95% CI[d] for objective response | 64.3, 86.2 | 44.7, 84.4 | 42.1, 99.6 | 26.8, 69.4 | 21.2, 86.3 | 2.5, 100 |
| 95% CI[d] for complete remission | 15, 37.4 | 29.1, 70.9 | 29, 96.3 | 10.2, 48.4 | 2.8, 60 | NE, NE |
| 95% CI[d] for disease control | 91.6, 100 | 73, 99 | 59, 100 | 66.4, 97.2 | 51.8, 99.7 | 2.5, 100 |

NE, not estimable

a Independent review facility assessment per Revised Response Criteria for Malignant Lymphoma.

b Investigator assessment per Revised Response Criteria for Malignant Lymphoma.

c Drug administered on Days 1, 8, and 15 of 28 day cycles

d Two-sided 95% exact confidence interval computed using the F distribution method of Collett (1991).

**Table A-4.** Best clinical response by post-baseline immunogenicity status in baseline negative patients in patients with ALCL

| | SG035-0004[a] (n=54) On-Study Immunogenicity Status | | | SG035-0002[b,c] (n=5) On-Study Immunogenicity Status | | |
|---|---|---|---|---|---|---|
| | Negative (N=32) n (%) | Transient Positive (N=18) n (%) | Persistent Positive (N=3) n (%) | Negative (N=4) n (%) | Transient Positive (N=1) n (%) | Persistent Positive (N=0) n (%) |
| Best Clinical Response | | | | | | |
| Complete Remission (CR) | 16 (50) | 11 (61) | 2 (67) | 3 (75) | 1 (100) | 0 |
| Partial Remission (PR) | 12 (38) | 4 (22) | 1 (33) | 0 | 0 | 0 |
| Stable Disease (SD) | 1 (3) | 1 (6) | 0 | 1 (25) | 0 | 0 |
| Progressive Disease (PD) | 2 (6) | 1 (6) | 0 | 0 | 0 | 0 |
| Histology Ineligible (HI) | 1 (3) | 1 (6) | 0 | 0 | 0 | 0 |
| Not Evaluable (NE) | 0 | 0 | 0 | 0 | 0 | 0 |
| Objective Response Rate (CR + PR) | 28 (88) | 15 (83) | 3 (100) | 3 (75) | 1 (100) | 0 |
| Disease Control Rate (CR + PR + SD) | 29 (91) | 16 (89) | 3 (100) | 4 (100) | 1 (100) | 0 |
| 95% CI[d] for Objective Response | 71, 96.5 | 58.6, 96.4 | 29.2, 100 | 19.4, 99.4 | 2.5, 100 | -, - |
| 95% CI[d] for Complete Remission | 31.9, 68.1 | 35.7, 82.7 | 9.4, 99.2 | 19.4, 99.4 | 2.5, 100 | -, - |
| 95% CI[d] for Disease Control | 75, 98 | 65.3, 98.6 | 29.2, 100 | 39.8, 100 | 2.5, 100 | -, - |

a Independent review facility assessment per Revised Response Criteria for Malignant Lymphoma.
b Investigator assessment per Revised Response Criteria for Malignant Lymphoma.
c Drug administered on Days 1, 8, and 15 of 28 day cycles
d Two-sided 95% exact confidence interval computed using the F distribution method of Collett.

**Table A-5.** Overall Summary of Adverse Events by Post-baseline Immunogenicity Status in the Phase 2 Population

| | | Never Positive (N=96) n(%) | Transiently Positive (N=42) n(%) | Persistently Positive (N=10) n(%) | Total (N=148) n(%) |
|---|---|---|---|---|---|
| Any treatment-emergent AE | | 94 (98) | 42 (100) | 10 (100) | 146 (99) |
| Max. severity | Grade 1 | 10 (10) | 3 (7) | 4 (40) | 17 (11) |
| | Grade 2 | 22 (23) | 23 (55) | 2 (20) | 47 (32) |
| | Grade 3 | 42 (44) | 12 (29) | 4 (40) | 58 (39) |
| | Grade 4 | 18 (19) | 2 (5) | 0 | 20 (14) |
| | Grade 5 | 2 (2) | 2 (5) | 0 | 4 (3) |
| | ≥ Grade 3 | 62 (65) | 16 (38) | 4 (40) | 82 (55) |
| Treatment-related AE[a] | | 89 (93) | 38 (90) | 10 (100) | 137 (93) |
| Discontinued due to AE | | 21 (22) | 6 (14) | 2 (20) | 29 (20) |
| SAE | | 33 (34) | 9 (21) | 2 (20) | 44 (30) |
| Treatment-related SAE[a] | | 19 (20) | 3 (7) | 1 (10) | 23 (16) |
| Death | | 15 (16) | 6 (14) | 0 | 21 (14) |
| Within 30 days of last dose | | 13 (14) | 4 (10) | 0 | 17 (11) |
| Post 30 days of last dose | | 2 (2) | 2 (5) | 0 | 4 (3) |

N = the number of patients who tested negative for ATA at baseline and had at least one postbaseline ATA assessment.
a Related to treatment with brentuximab vedotin as determined by the investigator.

**Table A-6.** Infusion-related Reactions by Post-baseline Immunogenicity Status in the Phase 2 Population

| | Never Positive (N=96) n (%) | Transiently Positive (N=42) n (%) | Persistently Positive (N=10) n (%) | Total (N=148) n (%) |
|---|---|---|---|---|
| Any IRR event | 7 (7) | 5 (12) | 3 (30) | 15 (10) |
| Chills | 1 (1) | 2 (5) | 3 (30) | 6 (4) |
| Dyspnoea | 0 | 1 (2) | 3 (30) | 4 (3) |
| Pruritus | 1 (1) | 1 (2) | 2 (20) | 4 (3) |
| Cough | 0 | 3 (7) | 0 | 3 (2) |
| Nausea | 1 (1) | 2 (5) | 0 | 3 (2) |
| Erythema | 1 (1) | 0 | 1 (10) | 2 (1) |
| Flushing | 0 | 1 (2) | 1 (10) | 2 (1) |
| Pyrexia | 1 (1) | 0 | 1 (10) | 2 (1) |
| Rash | 2 (2) | 0 | 0 | 2 (1) |
| Throat tightness | 0 | 0 | 2 (20) | 2 (1) |

Preferred terms are presented if 2 or more patients in any immunogenicity category experienced the event.
N = the number of patients who tested negative for ATA at baseline and had at least one postbaseline ATA assessment.

## 4.2 PHARMACOMETRICS REVIEW

# OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

| | |
|---|---|
| **Application Number** | BLA 125338 |
| **Submission Number (Date)** | February 25, 2011 |
| **Compound** | Brentuximab vedotin |
| **Clinical Division** | DHP |
| **Primary PM Reviewer** | Bahru A Habtemariam, Pharm.D. |
| **Secondary PM Reviewer** | Christine Garnett, Pharm.D. |



## Summary of Findings

### *Key Review Questions*

The purpose of this review is to address the following key questions.

**Is there evidence of exposure-response for efficacy in the pivotal phase 2 trials?**

Yes, there is evidence of exposure-response for effectiveness in the two pivotal phase 2 efficacy studies showing that the clinical endpoint, objective response rate (ORR), is

influenced by drug exposure at the proposed dose of 1.8 mg/kg every 3 weeks.

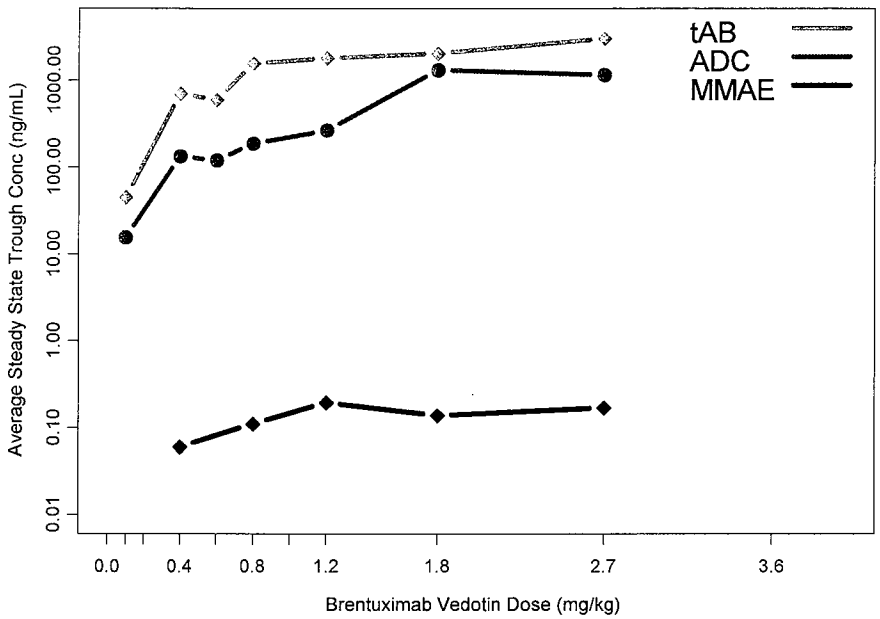
Efficacy, safety, and trough concentration data were available from one phase 1 trial and pivotal phase 2 trials as summarized in **Table 1** below. In the phase 1 study, patients received escalating doses of 0.1 to 3.6 mg/kg every three weeks. In the phase 2 studies, all patients received brentuximab vedotin doses of 1.8 mg/kg every three weeks. The studies were designed to show whether brentuximab vedotin improves ORR (either partial or complete response) in patients with hodgkin's lymphoma (HL) or patients with anaplastic large cell lymphoma (ALCL).

**Table 1. Summary of Clinical Studies and Data Used for Exposure-Response Analyses**

| Study (Phase) | Doses | Population | Endpoint | N | PK Subset |
|---|---|---|---|---|---|
| SG035-0001 (Ph 1) | 0.1 to 3.6 mg/kg | CD30-positive refractory hematologic malignancies | Safety | 48 | All |
| SG035-0003 (Ph 2) | 1.8 mg/kg | Refractory HL | ORR | 102 | All |
| SG035-0004 (Ph 2) | 1.8 mg/kg | relapsed or refractory systemic ALCL | ORR | 58 | All |

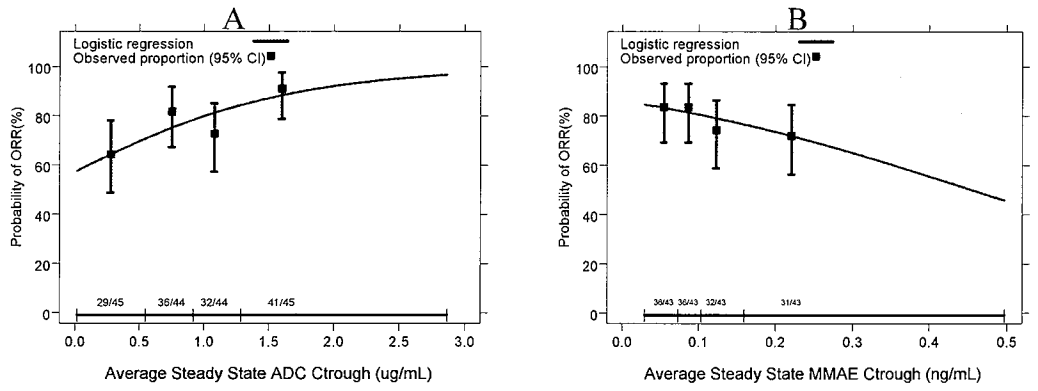
Plasma concentrations of total antibody (tAB) consisting of free and bound antibody, antibody-drug conjugate (ADC), and free MMAE were measured in the phase 1 and phase 2 trials. All reference to MMAE hereafter refers to free MMAE. **Figure 1** showed that the concentration of tAB and ADC increase with increasing brentuximab vedotin dose, while the average concentration of MMAE appears to flatten at dose greater than 0.8 mg/kg (**Figure 1**). The concentrations of tAB and ADC were highly correlated; therefore, exposure-response analyses were performed using ADC and MMAE concentrations.

**Figure 1.** Median steady state trough concentration of total antibody (tAB), antibody-drug conjugate (ADC) and MMAE.




As shown below, the probability of ORR increased with increasing antibody-drug conjugate (ADC) trough concentrations (**Figure 2A**). On the other hand, the probability of ORR decreases with increasing MMAE trough concentrations (**Figure 2B**). There is no clear explanation why probability of ORR appears to decrease with increasing MMAE concentrations. One possible explanation may be that MMAE needs to be bound to the antibody in order to reach to the site of action and the unbound MMAE is unavailable to reach the site of actions, therefore higher free MMAE would lead to lower efficacy; however, there is no data to support this explanation.

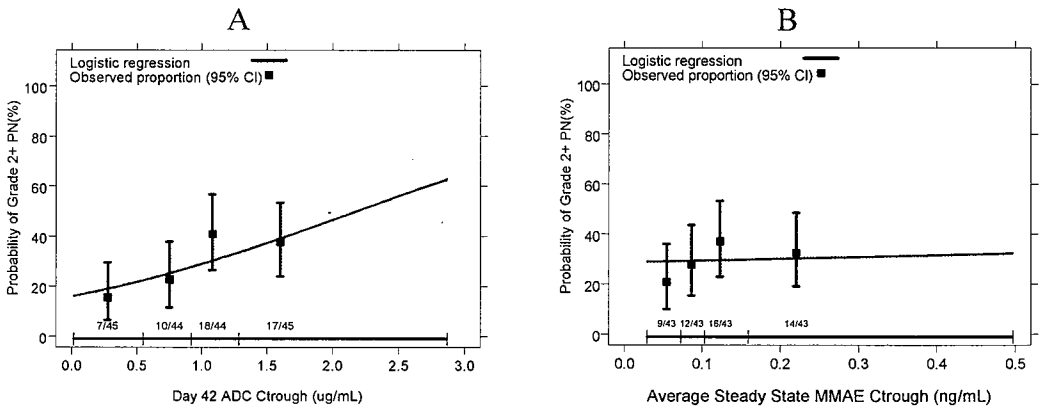
**Figure 2.** Probability of objective response rate (ORR) increases with increasing average steady state ADC trough concentration (A). Probability of ORR appears to show a decreasing trend with increasing steady state MMAE trough concentrations (B).




**Is there exposure-response relationship of peripheral neuropathy?**

The proposed draft labeling for brentuximab vedotin recommends dose reduction for patients with grade 2 or more (Grade 2+) peripheral neuropathy. To that end, exposure-response analyses were performed to investigate the relationship between the probability of Grade 2+ neutropenia and average steady state trough concentrations of ADC and free MMAE. **Figure 3A** below demonstrates that the probability of Grade 2+ peripheral neuropathy increases with increasing steady state ADC trough concentrations. On the other hand, the probability of Grade 2+ peripheral neuropathy stays flat with increasing average steady state MMAE trough concentrations (**Figure 3B**).

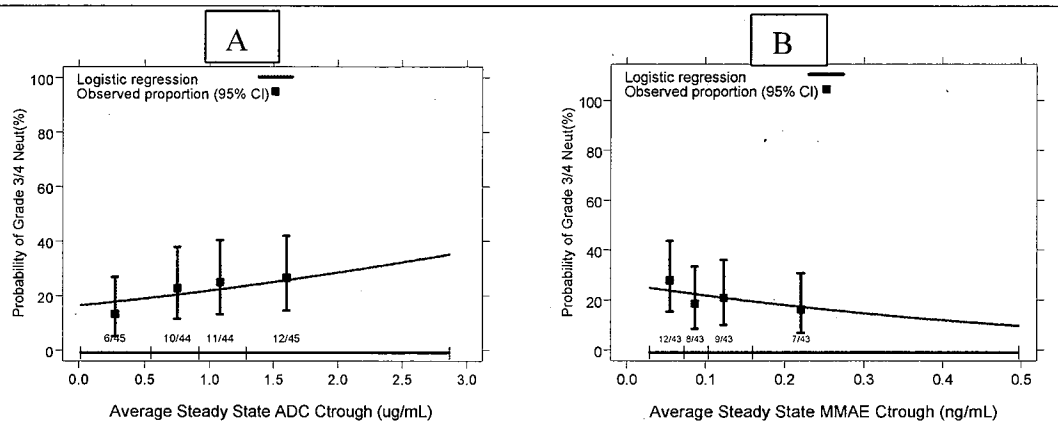
**Figure 3.** Probability of Grade 2+ peripheral neuropathy increases with increasing average steady state ADC trough concentration (A). Probability of Grade 2+ appears to a flat trend with increasing steady state MMAE trough concentrations (B).



**Is there exposure-response relationship for neutropenia?**

The probability of Grade 3 or 4 neutropenia (Grade 3+ neutropenia) increased with increasing average steady state ADC trough concentrations (**Figure 4A**). At the lowest ADC concentration quartile, 6 of the 45 (13%) patients had Grade 3+ neutropenia compared to 12 of the 45 patients (27%) in the top ADC concentration quartile (**Figure 4A**). Logistic regression analysis was also performed using free MMAE concentrations, and the probability of Grade 3+neutropenia (**Figure 4B**) show a decreasing trend with increasing MMAE concentrations.

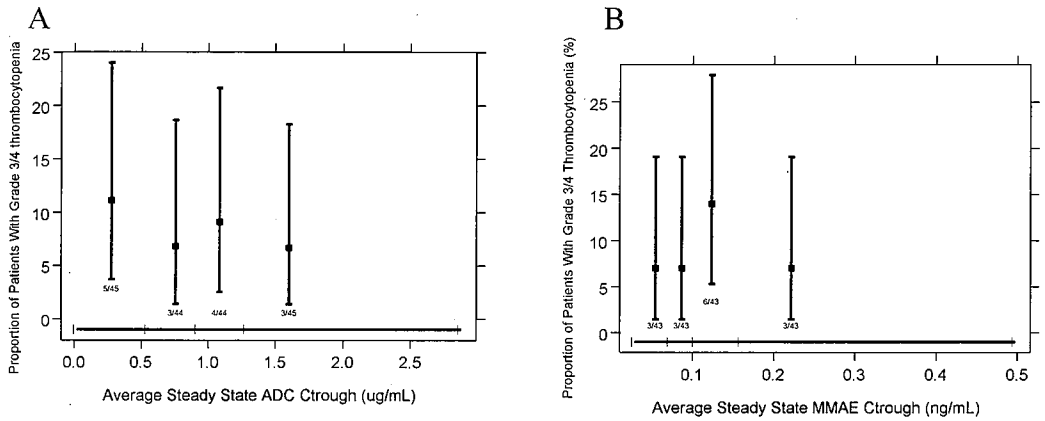
**Figure 4.** Probability of Grade 3+ neutropenia increases with increasing average steady state ADC trough concentrations (A). Probability of Grade 3+ neutropenia appears to show a decreasing trend with increasing steady state MMAE trough concentrations (B).




**Is there exposure-response relationship for thrombocytopenia?**

Thrombocytopenia is one of the most frequently reported adverse effects in clinical evolutions of brentuximab vedotin. We investigated whether the proportion of Grade 3 or 4 thrombocytopenia increases with increasing ADC or MMAE concentrations. As shown in **Figure 5** below, there is no clear exposure-response relationship that shows increasing proportion of thrombocytopenia with increasing concentrations of either ADC or MMAE.

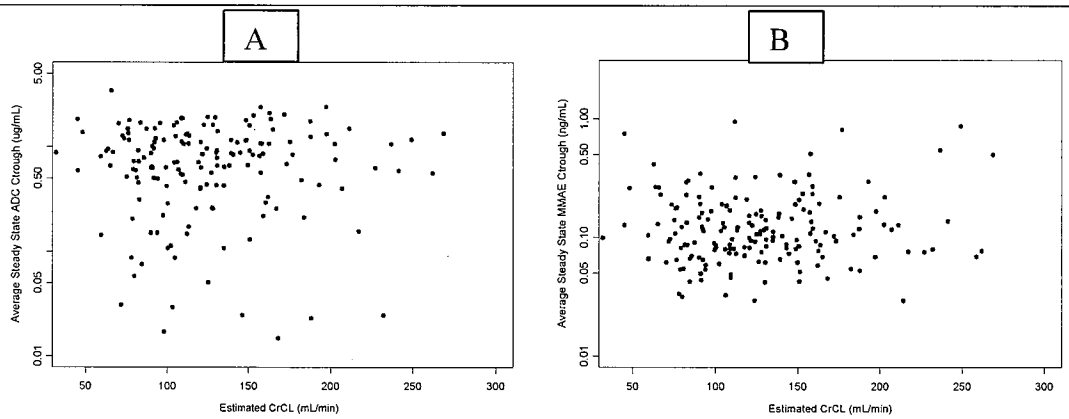
**Figure 5.** Proportion of Grade 3+ thrombocytopenia does not increase with increasing average steady state trough concentrations of ADC or MMAE (A) and (B).




**Is there relationship between creatinine clearance and peripheral neuropaty and neutropenia?**

The sponsor's population PK analysis showed a trend of lower ADC and MMAE clearance with decreasing creatinine clearance (CrCL). In order to confirm whether trough concentrations of MMAE and ADC were influence by CrCL, scattered plots of trough concentrations and CrCL were constructed. Baseline estimated creatinine clearance CrCL data and steady trough concentrations data (n= 173) were available from brentuximab vedotin treated patients that took part in studies SG035-0002, SG035-0003, and SG035-0004 (**Table 2**). As shown on **Figure 6** below, there is no clear relationship between creatinine clearance and ADC or MMAE concentrations.

**Figure 6.** Scatted plats of average steady state ADC and MMAE concentrations vs. estimated baseline CrCL (A) and (B).



**Is the proposed dose reduction for peripheral neuropathy and neutropenia appropriate?**

Yes, the exposure-response relationship for grade 2+ peripheral neuropathy and grade 3+ neutropenia support dose reductions to 1.2 mg/kg. The dose reduction proposal for peripheral neuropathy is consistent with the medical management of neuropathy in the clinical trials. However, in clinical trials, dose reduction for neutropenia was carried out for patients with Grade 4 neutropenia and not those with Grade 3. Therefore, to be consistent with the conduct of the clinical trial, the label will recommend dose reduction in the event of Grade 4 neutropenia.

***Recommendations***

The exposure-response analysis indicates that patients with higher steady state ADC concentrations have higher probability of clinical response (ORR) and adverse events (peripheral neuropathy and neutropenia). In the draft label, the sponsor has proposed dose reduction to 1.2 mg/kg to address Grade 2+ PN. However, the sponsor did not propose dose reduction scheme to address Grade 4 neutropenia. As shown above, there is a clear exposure-response relationship between Grade 3/4 neutropenia and ADC trough concentrations; therefore, we recommend dose reduction to 1.2 mg/kg to address Grade 4 neutropenia. This is also consistent the management of neutropenia in the clinical trial.

*Labeling Statements*

**2.2 Dose Modification**

(b) (4)

**Peripheral Neuropathy:** (b) (4)

(b) (4)

**5.1 Peripheral Neuropathy**

(b) (4)

**12.3 Pharmacokinetics**

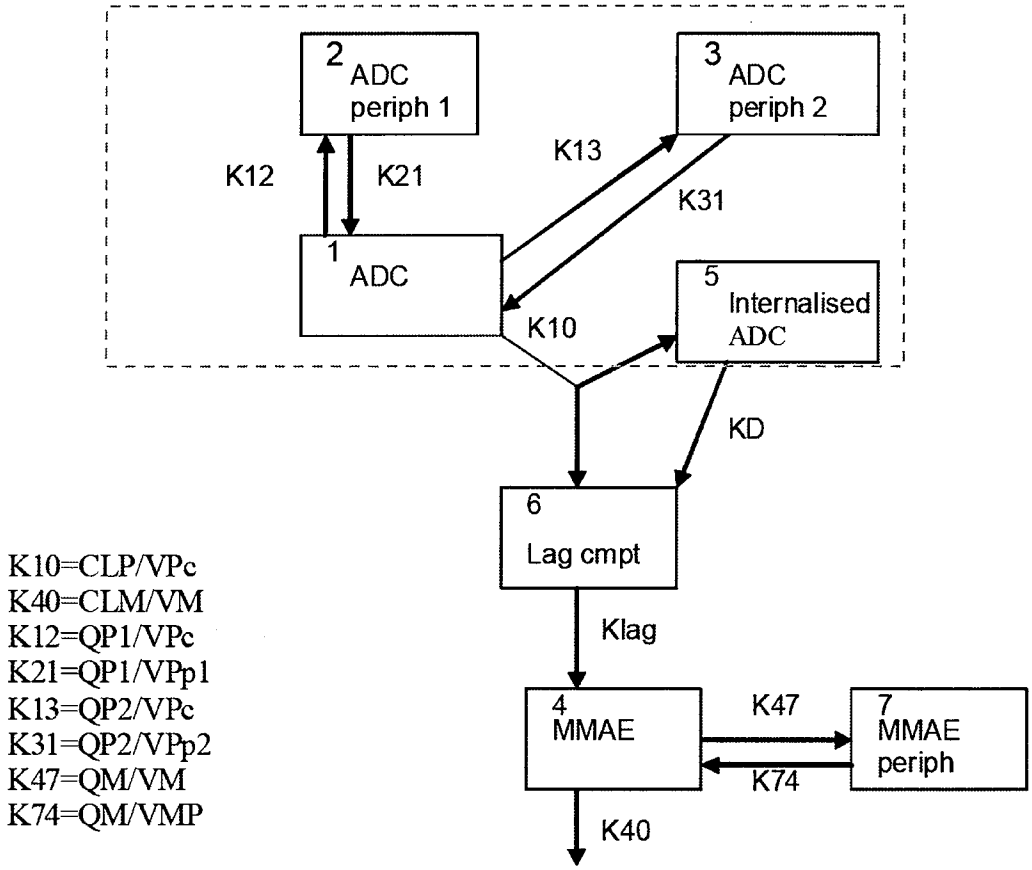
(b) (4)

***Effects of Gender, Age and Race***
***Based on the population pharmacokinetic analysis, gender, age and race do not have a meaningful effect on the pharmacokinetics of brentuximab vedotin.***

**Results of Sponsor's Analysis**

The sponsor conducted separate population PK analyses for ADC and MMAE. The population PK findings for ADC and MMAE are described below. For detailed information, including parameter estimates, see synopsis of sponsor's analysis provided as an appendix.

The figure below shows schematic representations of ADC and MMAE PK models. The model within the square represents ADC model and the diagram outside of the square represents MMAE model.




**Population PK Analysis Findings**

- The pharmacokinetics of ADC was adequately described by a three-compartment model with zero-order input and first-order elimination.
- ADC PK parameters were related to body weight, where clearance and volume parameters increased with increasing body weight.
- ADC clearance was 18% higher in cycles when patients had positive ATA response.
- ADC volume of the central compartment was 14% lower in females compared to males.

MMAE

- The pharmacokinetics of MMAE were adequately described by a two-compartment model with first-order elimination and formation of MMAE both directly from ADC and through binding of ADC to the target with a delay in the formation of MMAE described with a lag compartment. The fraction of MMAE formed directly from ADC decreased following ADC administration.
- MMAE volume parameters increased with increasing body weight.

- MMAE clearance and peripheral volume increased with increasing albumin concentrations, while KD decreased with increasing albumin. For the range of albumin in the current analysis (1.6 to 4.8 g/dL), predicted typical CLM, VMP and KD were in the ranges of 0.273 to 1.13 L/h, 9.77 to 51.9 L and 0.0820 to 0.00266 h-1, respectively compared to an individual with albumin of 3.8 g/dL.
- MMAE apparent clearance was 7% lower in patients administered brentuximab vedotin manufactured by process B, and within bioequivalence bounds. Only small changes in MMAE concentrations were observed indicating that the lower apparent clearance of MMAE detected is not clinically relevant.

*Reviewer's comments:*
*ADC: The sponsor's population PK analysis is adequate and the model appears to adequately describe the data. The PK parameter-weight relationship is consistent with the current weight based dosing recommendation. No major PK parameter-covariate relationships were discovered in the population PK model.*

*MMAE: The results of the MMAE model were not used to assess covariate effects for labeling statements. Therefore, further review of the MMAE model was not performed.*

**Reviewer's Analysis**

***Introduction***

The sponsor performed two population PK analyses: one for the antibody-drug conjugate (ADC), and one for the small molecule, MMAE. The population PK model for the ADC appears to have been adequate. The MMAE population PK model appeared complex and over-parameterized. However, the sponsor did not perform any exposure-response analysis beyond population the above described population PK analysis. The reviewers

performed additional analyses to further elucidate the exposure-response properties of brentuximab vedotin.

### *Objectives*

Exposure-response and dose-response analyses were performed to address the following:

1) To understand the exposure-response properties of ADC and MMAE for safety and effectiveness
2) The efficacy endpoint was ORR
3) Safety endpoints were:
    a. Grade 2 or more peripheral neuropathy
    b. Grade 3 and 4 neutropenia
    c. Grade 3 and 4 thrombocytopenia

### *Methods*

**Data Sets**

Data sets used are summarized in **Table 2** below.

**Table 2: Analysis Data Sets.**

| Study Number | Name (desctiption) | Link to EDR |
|---|---|---|
| SG035-0001 | pc.xpt (PK) | \\cber-fs3\M\eCTD_Submissions\STN125388\0000\m5\datasets\sg035-0001\tabulations |
| SG035-0003 | adpc.xpt (PK) | \\cber-fs3\M\eCTD_Submissions\STN125388\0000\m5\datasets\sg035-0003\analysis |
| SG035-0004 | adpc.xpt (PK) | \\cber-fs3\M\eCTD_Submissions\STN125388\0000\m5\datasets\sg035-0004\analysis |
| SG035-0001, SG035-0003, and SG035-0004 | Adae.xpt (safety) | \\cber-fs3\M\eCTD_Submissions\STN125388\0000\m5\datasets\iss-hl\analysis |
| SG035-0001, SG035-0003, and SG035-0004 | adeff.xpt (efficacy) | \\cber-fs3\M\eCTD_Submissions\STN125388\0000\m5\datasets\iss-hl\analysis |
| SG035-0001, SG035-0003, and SG035-0004 | adsl.xpt (safety) | \\cber-fs3\M\eCTD_Submissions\STN125388\0013\m5\datasets\iss-hl\analysis |
| SG035-0001 | lb.xpt (labs) | \\cber-fs3\M\eCTD_Submissions\STN125388\0000\m5\datasets\sg035-0001\tabulations |
| SG035-0003, and SG035-0004 | adlabs.xpt (labs) | \\cber-fs3\M\eCTD_Submissions\STN125388\0013\m5\datasets\iss-hl\analysis |

**Software**

S-PLUS was used for the reviewer's analyses.

***Results***

See section 1.1.

## Appendix A: Synopsis of Sponsor's Population PK Analysis

| |
|---|
| **Title:** Population Pharmacokinetic Analysis of Brentuximab Vedotin and Monomethyl Auristatin E Following Administration of Brentuximab Vedotin |
| **Phase of Development:** Phases 1 and 2 |
| **Introduction:**<br>Brentuximab vedotin is an antibody-drug conjugate (ADC) consisting of three components: 1) the antibody cAC10, specific for human CD30, 2) the highly potent antimicrotubule agent monomethyl auristatin E (MMAE), and 3) a protease-cleavable linker that covalently attaches MMAE to cAC10. The biological activity of brentuximab vedotin results from a multi-step process. Binding of the ADC to CD30 on the cell surface initiates internalization 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 tumor cell.<br>A population approach was taken to understand the effect of intrinsic factors that affect the pharmacokinetics (PK) of brentuximab vedotin ADC and MMAE in patients with CD30-positive hemataologic malignancies. The population PK model was developed primarily based on the two initial phase 1 dose escalation studies (SG035-0001 and SG035-0002), both of which contained dense blood sampling for PK assessment. Following availability of data from two phase 2 studies with sparse sampling (SG035-0003 and SG035-0004) and a phase 1 clinical pharmacology study with dense sampling (SGN35-008), those data were included in the analysis and model refinements made. This report details the model development process and the final results that describe the population PK of brentuximab vedotin ADC and MMAE. |
| **Objectives:**<br>The objectives based on the PK profiles for brentuximab vedotin ADC and MMAE, and clinical data from studies SG035-0001 and SG035-0002 were:<br>• to simultaneously model the PK of ADC and MMAE through the use of a single integrated model after administration of brentuximab vedotin in patients with relapsed/refractory CD30-positive hematologic malignancies (such as Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (ALCL));<br>• to characterize the magnitude of inter- and intra-patient variability in the PK parameters of both ADC and MMAE;<br>• to identify covariate (i.e. demographics, manufacturing process (A, B or C) used to produce brentuximab vedotin) factors that are significant predictors of variability in PK.<br>The model was refined as necessary and the influence of covariates were re-assessed following addition of data from studies SG035-0003, SG035-0004, and SGN35-008. |
| **Methodology:**<br>The population PK model was developed using a non-linear mixed-effect modeling approach; the NONMEM 7 software with the first-order conditional estimation method with interaction (FOCEI) was used. Initially, a simultaneous model using the combined ADC and MMAE data was attempted. However as the MMAE PK was not expected to alter the ADC PK, the model was simplified and a sequential approach was undertaken. First a model was developed initially for ADC alone using two available studies (SG035-0001 and SG035-0002) and following this, a model for MMAE was developed where |

Sponsor's Population PK Study Synopsis (Page 1)

MMAE formation was linked to ADC elimination using the individual parameter estimates from the ADC model to predict the ADC concentrations in the MMAE model. Population and empirical Bayesian (individual) estimates were generated for studies SG035-0003, SG035-0004, and SGN35-008 using the population PK models developed based on data from studies SG035-0001 and SG035-0002. If bias was evident for studies SG035-0003, SG035-0004 or SGN35-008, the PK models for ADC and MMAE were refined. All covariates were re-assessed using data from all studies. Once the final population PK models were developed, the ability of the model to describe the observed data was further evaluated using a visual predictive check procedure. Individual estimates of ADC and MMAE exposure (steady-state $AUC_{0\text{-}21d}$ and $C_{max}$) following repeat dosing of ADC (ADC administered on the first day of each 21-day cycle) were obtained and summarized by study and nominal dose.

**Number of Patients:** 314

**Results:**

**ADC**

The PK of ADC was described by a linear three-compartment model with zero-order input and first-order elimination.

The reference population was chosen to be a male 70 kg patient with no anti-therapeutic antibody (ATA) response. The estimated mean (95% CI) parameter values for the reference population were CLP=0.0607 (0.0556, 0.0658) L/h, VPc =4.16 (4.01, 4.31) L, VPp1=8.06 (6.79, 9.33) L, VPp2=3.47 (3.22, 3.72) L, QP1=0.0289 (0.0259, 0.0319) L/h, and QP2=0.110 (0.0981, 0.122) L/h.

**Parameter Estimates of Final Population Pharmacokinetic Model for ADC (Run 311cs, Studies SG035-0001, SG035-0002, SG035-0003, SG035-0004 & SGN35-008)**

| Parameter (Units) | NONMEM Estimates | | | |
|---|---|---|---|---|
| | Point Estimate | %RSE | 95% CI | |
| CLP (L/h) | 0.0607 | 4.25 | 0.0556, 0.0658 | |
| VPc (L) | 4.16 | 1.84 | 4.01, 4.31 | |
| QP1 (L/h) | 0.0289 | 5.22 | 0.0259, 0.0319 | |
| VPp1 (L) | 8.06 | 8.03 | 6.79, 9.33 | |
| QP2 (L/h) | 0.110 | 5.53 | 0.0981, 0.122 | |
| VPp2 (L) | 3.47 | 3.66 | 3.22, 3.72 | |
| CLP, QP1 and QP2 ~ WT | 0.718 | 10.1 | 0.576, 0.860 | |
| VPc, VPp1 and VPp2 ~ WT | 0.496 | 7.56 | 0.422, 0.570 | |
| VPc~gender | 0.863 | 2.42 | 0.822, 0.904 | |
| CLP~ATA titer by cycle | 1.18 | 0.864 | 1.16, 1.20 | |
| **Inter-individual** | | | | **CV%** |
| $\omega^2_{CLP}$ | 0.218 | 6.42 | 0.191, 0.245 | 46.7 |
| $\omega^2_{VPc}$ | 0.0176 | 9.60 | 0.0143, 0.0209 | 13.3 |
| $\omega^2_{QP1}$ | 0.194 | 13.6 | 0.142, 0.246 | 44.0 |
| $\omega^2_{VPp1}$ | 1.01 | 12.9 | 0.755, 1.26 | 100 |
| **Residual variability** | | | | **CV%** |
| $\sigma^2_{prop}$ | 0.109 | 0.600 | 0.108, 0.110 | 33.0 |

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100; CLP = ADC clearance, VPc = volume of ADC central compartment, QP1 = ADC inter-compartmental clearance from central to first peripheral compartment, QP2 = ADC inter-compartmental clearance from central to second peripheral compartment, VPp1 = volume of the first ADC peripheral compartment, VPp2 = volume of the second ADC peripheral compartment, $\omega^2_{CLP}$, $\omega^2_{VPc}$, $\omega^2_{QP1}$ and $\omega^2_{VPp1}$= variance of random effect of CLP, VPc, QP1 and VPp1, respectively, $\sigma^2_{prop}$ = variance of the proportional component of the residual error.

CLP, QP1 and QP2 ~ WT = dependence of CLP, QP1 and QP2 on WT (as $CLP*(WT/70)^{0.718}$, $QP1*(WT/70)^{0.718}$, $QP2*(WT/70)^{0.718}$).

VPc, VPp1 and VPp2 ~ WT = dependence of VPc, VPp1 and VPp2 on WT (as $VPc*(WT/70)^{0.496}$, $VPp1*(WT/70)^{0.496}$, $VPp2*(WT/70)^{0.496}$).

The reference population for PK parameters was a 70 kg male patient with negative ATA response.

Sponsor's Population PK Study Synopsis (Page 2)

The final ADC covariate model included the influence of body weight on CLP, QP1, QP2, VPc, VPp1 and VPp2, gender on VPc, and influence of ATA titer by cycle on CLP. Mean (95% CI) clearance was 18% (16%, 20%) higher in subjects with positive ATA response. Female patients had a 14% (18%, 10%) lower VPc compared to males.

Clearance and distributional clearances increased with weight with the power coefficient of 0.718 (i.e. as $(WT/70)^{0.718}$) and volumes of the central and peripheral compartments increased with weight with the power coefficient of 0.496 (i.e. as $(WT/70)^{0.496}$). For the range of weights in the current analysis (41 to 168 kg), predicted typical CLP, QP1, QP2, VPc, VPp1 and VPp2 are in the ranges of 0.0413 to 0.114 L/h, 0.0197 to 0.0542 L/h, 0.0749 to 0.206 L/h, 3.19 to 6.42 L, 6.18 to 12.4 L and 2.66 to 5.36 L, respectively. This translates to 32% lower to 87% higher CLP, QP1 and QP2 and 23% lower to 54% higher VPc, VPp1 and VPp2 for the range of weights compared to a 70-kg individual.

Other covariates evaluated for their effect on ADC exposure were found not to be significant (race, ethnicity, age, disease (HL vs. ALCL), baseline tumor size, albumin, aspartate transferase (AST), alanine transferase (ALT), bilirubin, creatinine clearance and manufacturing process).

**MMAE**

The PK of MMAE was described by a two-compartment model with first-order elimination and formation of MMAE both directly from ADC and through binding of ADC to a hypothetical target. The model included a lag compartment to describe the delay in formation of MMAE both directly from ADC and through binding of ADC to the target. The fraction of MMAE formed directly from ADC decreased following ADC administration, relative to time after dose (TAD).

The reference population was chosen to be a 70-kg male patient with negative ATA response, albumin of 3.8 g/dL and ADC administration with manufacturing process A/C. The estimated mean (95% CI) parameter values for the reference population were CLM=0.833 (0.769, 0.897) L/h, VM=7.37 (3.53, 11.2) L, VMP=36.4 (31.3, 41.5) L, QM=13.6 (9.52, 17.7) L/h, KD=0.00552 (0.00414, 0.00690) $h^{-1}$, ALFM=0.00204 (0.00321, 0.00337) $h^{-1}$ and Klag=2.04 (1.08, 3.00) $h^{-1}$.

Sponsor's Population PK Study Synopsis (Page 3)

**Parameter Estimates of Final Population Pharmacokinetic Model for MMAE (Run 508, Studies SG035-0001, SG035-0002, SG035-0003, SG035-0004 & SGN35-008)**

| Parameter (Units) | NONMEM Estimates | | | |
|---|---|---|---|---|
| | Point Estimate | %RSE | 95% CI | |
| CLM (L/h) | 0.833 | 3.89 | 0.769, 0.897 | |
| VM (L) | 7.37 | 26.6 | 3.53, 11.2 | |
| QM (L/h) | 13.6 | 15.3 | 9.52, 17.7 | |
| VMP (L) | 36.4 | 7.20 | 31.3, 41.5 | |
| KD ($h^{-1}$) | 0.00552 | 12.8 | 0.00414, 0.00690 | |
| ALFM ($h^{-1}$) | 0.00204 | 1.20 | 0.00321, 0.00337 | |
| Klag ($h^{-1}$) | 2.04 | 24.1 | 1.08, 3.00 | |
| CLM~PROCB | 0.934 | 0.777 | 0.920, 0.948 | |
| CLM~ALB | 1.29 | 12.2 | 0.982, 1.60 | |
| VMP~ALB | 1.52 | 15.5 | 1.06, 1.98 | |
| KD~ALB | -3.12 | 19.6 | -4,32, -1.92 | |
| VM and VMP ~ WT | 0.550 | 18.5 | 0.350, 0.750 | |
| **Inter-individual** | | | | **CV% or R** |
| $\omega^2_{CLM}$ | 0.270 | 12.7 | 0.203 | 52.0 |
| Corr($\omega^2_{CLM}$, $\omega^2_{VM}$) | 0.113 | 43.4 | 0.0170 | 0.280 |
| $\omega^2_{VM}$ | 0.603 | 18.9 | 0.380 | 77.7 |
| Corr($\omega^2_{CLM}$, $\omega^2_{KD}$) | 0.339 | 28.9 | 0.147 | 0.390 |
| Corr($\omega^2_{VM}$, $\omega^2_{KD}$) | 0.665 | 25.4 | 0.334 | 0.512 |
| $\omega^2_{KD}$ | 2.80 | 17.7 | 1.83 | 167 |
| Corr($\omega^2_{CLM}$, $\omega^2_{QM}$) | 0.327 | 25.9 | 0.161 | 0.561 |
| Corr($\omega^2_{VM}$, $\omega^2_{QM}$) | 0.292 | 27.9 | 0.132 | 0.335 |
| Corr($\omega^2_{KD}$, $\omega^2_{QM}$) | 0.0378 | 683 | -0.468 | 0.0201 |
| $\omega^2_{QM}$ | 1.26 | 22.7 | 0.699 | 112 |
| Corr($\omega^2_{CLM}$, $\omega^2_{VMP}$) | 0.245 | 14.3 | 0.176 | 0.792 |
| Corr($\omega^2_{VM}$, $\omega^2_{VMP}$) | 0.178 | 27.4 | 0.0824 | 0.385 |
| Corr($\omega^2_{KD}$, $\omega^2_{VMP}$) | 0.340 | 34.1 | 0.113 | 0.342 |
| Corr($\omega^2_{QM}$, $\omega^2_{VMP}$) | 0.343 | 27.8 | 0.156 | 0.514 |
| $\omega^2_{VMP}$ | 0.354 | 12.7 | 0.266 | 59.5 |
| **Residual variability** | | | | **CV%** |
| $\sigma^2_{add}$ | 0.000861 | 5.67 | 0.000765, 0.000957 | 0.0293 |
| $\sigma^2_{prop}$ | 0.115 | 1.03 | 0.113, 0.117 | 33.9 |

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100; CLM = apparent MMAE clearance, VM = apparent volume of MMAE central compartment, QM = apparent MMAE inter-compartmental clearance, VMP = apparent volume of the MMAE peripheral compartment, KD = binding rate constant, ALFM = rate constant to describe the decline in direct conversion of ADC to MMAE following time after dose, $K_{lag}$=rate constant for lag compartment, $\omega^2_{CLM}$, $\omega^2_{VM}$, $\omega^2_{KD}$, , $\omega^2_{QM}$, $\omega^2_{VMP}$ = variance of random effect of CLM, VM, KD, QM and VMP, respectively, $\sigma^2_{prop}$ = variance of the proportional component of the residual error, $\sigma^2_{add}$ = variance of the additive component of the residual error

The reference population for PK parameters was a 70 kg male patient administered ADC with manufacturing process A/C with negative ATA response and albumin concentration of 3.8 g/dL.

The final MMAE covariate model included the influence of body weight on VM and VMP, manufacturing process B on CLM, and albumin on CLM, VMP and KD. Mean (95% CI) clearance was 7% lower in subjects administered ADC with manufacturing process B. The impact of this decrease in CLM was hardly noticeable in the concentration profiles of MMAE (Figure 9-94) and the effect of manufacturing process B on CLM was considered not to be clinically meaningful.

Apparent volumes of the central and peripheral compartments increased with weight with the power coefficient of 0.550 (i.e. as $(WT/70)^{0.550}$). For the range of weights in the current analysis (41 to 168 kg),

Best Available Copy

Sponsor's Population PK Study Synopsis (Page 4)

predicted typical VM and VMP are in the ranges of 5.49 to 11.9 L and 27.1 to 58.9 L, respectively. This translates to 25% lower to 62% higher VM and VMP for the range of weights compared to a 70-kg individual.
Albumin was a significant covariate in the MMAE model with CLM, VMP increasing with increasing albumin and KD decreasing with increasing albumin. For the range of albumin concentrations in the current analysis (1.6 to 4.8 g/dL), predicted typical CLM, VMP and KD were in the ranges of 0.273 to 1.13 L/h, 9.77 to 51.9 L and 0.0820 to 0.00266 $h^{-1}$, respectively compared to an individual with albumin of 3.8 g/dL.
Although gender and ATA titer by cycle were not significant covariates in the MMAE model, they were significant covariates in the ADC model, therefore, impacting MMAE concentrations. However, the impact of gender on VPc and ATA titer by cycle on CLP was hardly noticeable in the concentration profiles of MMAE (Figure 9-95 and Figure 9-96, respectively) and therefore unlikely to be clinically meaningful.
Other covariates evaluated for their effect on MMAE exposure were found not to be significant (race, ethnicity, age, disease (HL vs. ALCL), baseline tumor size, AST, ALT, bilirubin, creatinine clearance and ATA titer).

Although several covariates (weight, gender, ATA, albumin, manufacturing process B) were statistically significant either in the ADC or MMAE models, gender, ATA and manufacturing process were shown to have little impact on the concentration profiles of ADC or MMAE, and therefore are unlikely to be clinically meaningful.

**Conclusions:**

- The pharmacokinetics of ADC were adequately described by a three-compartment model with zero-order input and first-order elimination.
- For a typical 70 kg male patient with negative ATA response, estimated mean (95% CI) ADC parameter values were CLP=0.0607 (0.0556, 0.0658) L/h, VPc =4.16 (4.01, 4.31) L, VPp1=8.06 (6.79, 9.33) L, VPp2=3.47 (3.22, 3.72) L, QP1=0.0289 (0.0259, 0.0319) L/h, and QP2=0.110 (0.0981, 0.122) L/h.
- ADC CLP, QP1, QP2, VPc, VPp1 and VPp2 increased with body weight for the range of weights in the analysis (41 to 168 kg), CLP, QP1 and QP2 ranged from 32% lower to 87% higher values and VPc, VPp1 and VPp2 ranged from 23% lower to 54% higher values than for 70-kg individuals.
- ADC clearance was 18% higher in cycles where patients had positive ATA response.
- ADC volume of the central compartment was 14% lower in females compared to males.
- The pharmacokinetics of MMAE were adequately described by a two-compartment model with first-order elimination and formation of MMAE both directly from ADC and through binding of ADC to the target with a delay in the formation of MMAE described with a lag compartment. The fraction of MMAE formed directly from ADC decreased following ADC administration.
- For a typical 70 kg male patient with negative ATA response and albumin of 3.8 g/dL administered ADC with manufacturing process A/C, estimated mean (95% CI) MMAE parameter values were CLM=0.833 (0.769, 0.897) L/h, VM=7.37 (3.53, 11.2) L, VMP=36.4 (31.3, 41.5) L, QM=13.6 (9.52, 17.7) L/h, KD=0.00552 (0.00414, 0.00690) $h^{-1}$, ALFM=0.00204 (0.00321, 0.00337) $h^{-1}$, and Klag=2.04 (1.08, 3.00) $h^{-1}$.
- Both MMAE VM and VMP increased with body weight for the range of weights in the analysis (41 to 168 kg), VM and VMP ranged from 25% lower to 62% higher values than for 70-kg individuals.

Sponsor's Population PK Study Synopsis (Page 5)

- MMAE CLM and VMP increased with increasing albumin concentrations, while KD decreased with increasing albumin. For the range of albumin in the current analysis (1.6 to 4.8 g/dL), predicted typical CLM, VMP and KD were in the ranges of 0.273 to 1.13 L/h, 9.77 to 51.9 L and 0.0820 to 0.00266 $h^{-1}$, respectively compared to an individual with albumin of 3.8 g/dL.
- MMAE apparent clearance was 7% lower in patients administered brentuximab vedotin manufactured by process B, and within bioequivalence bounds. Only small changes in MMAE concentrations were observed indicating that the lower apparent clearance of MMAE detected is not clinically relevant.

Date of Report: 03 February 2011

Sponsor's Population PK Study Synopsis (Page 6)

## 4.3 OCP FILING FORM

# Office of Clinical Pharmacology

*New Drug Application Filing and Review Form*

***General Information About the Submission***

| | Information | | Information |
|---|---|---|---|
| **NDA/BLA Number** | **BLA 125388/0 & 125399/0** | **Brand Name** | **ADCETRIS** |
| **OCP Division (I, II, III, IV, V)** | **DCPV** | **Generic Name** | **Brentuximab vedotin** |
| **Medical Division** | **DHP** | **Drug Class** | **Antibody-drug conjugate** |
| **OCP Reviewer** | **Aakanksha Khandelwal, Ph.D** | **Indication(s)** | **Hodgkin lymphoma and anaplastic large cell lymphoma** |
| **OCP Team Leader** | **Julie Bullock, Pharm.D.** | **Dosage Form** | **Single-use 30 mL vials (50 mg/vial)** |
| **Pharmacometrics Reviewer** | **Bahru Habtemariam, Pharm.D** | **Dosing Regimen** | **1.8 mg/kg IV Q3W** |
| **Date of Submission** | **February 25, 2011** | **Route of Administration** | **Intravenous Infusion** |
| **Estimated Due Date of OCP Review** | **August 2, 2011** | **Sponsor** | **Seattle Genetics** |
| **Medical Division Due Date** | **August 2, 2011** | **Priority Classification** | **Priority** |
| **PDUFA Due Date** | **August 30, 2011** | | |

### *Clin. Pharm. and Biopharm. Information*

| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
|---|---|---|---|---|
| **STUDY TYPE** | | | | |
| **Table of Contents present and sufficient to locate reports, tables, data, etc.** | **X** | | | |
| **Tabular Listing of All Human Studies** | **X** | | | |
| **HPK Summary** | **X** | | | |
| **Labeling** | **X** | | | |
| **Reference Bioanalytical and Analytical Methods** | **X** | | | |
| **I. Clinical Pharmacology** | | | | |
| **Mass balance:** | | | | |
| **Isozyme characterization:** | | | | |
| **Blood/plasma ratio:** | | | | |
| **Plasma protein binding:** | | | | |
| **Pharmacokinetics (e.g., Phase I) -** | **X** | **4** | **4** | **SGN35-007, SGN35-008A, SG035-0001, SG035-002; SGN35-008B on-going** |
| **Healthy Volunteers-** | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| Patients- | | | | |
| single dose: | | | | |
| multiple dose: | **X** | | | **SGN35-007, SGN35-008A, SG035-0001, SG035-0002, SG035-0003, SG035-0004** |
| **Dose proportionality -** | | | | |
| fasting / non-fasting single dose: | | | | |
| fasting / non-fasting multiple dose: | | | | |
| **Drug-drug interaction studies -** | | | | |
| In-vivo effects on primary drug: | **X** | **1** | **1** | **SGN35-008A** |
| In-vivo effects of primary drug: | **X** | **1** | **1** | **SGN35-008A** |
| In-vitro: | **X** | **1** | **1** | |
| **Subpopulation studies -** | | | | |

| | | | | |
|---|---|---|---|---|
| ethnicity: | X | | | PopPK |
| gender: | X | | | PopPK |
| pediatrics: | | | | |
| geriatrics: | X | | | PopPK |
| renal impairment: | X | 1 | 1 | On-going SGN35-008B |
| hepatic impairment: | X | 1 | 1 | On-going SGN35-008B |
| **PD -** | | | | |
| Phase 1: | X | 2 | 2 | SG035-0001, SG035-0002 |
| Phase 2/3: | | | | |
| **PK/PD -** | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| **Population Analyses -** | | | | |
| Data rich: | | | | |
| Data sparse: | X | 2 | 2 | SG035-0003, SG035-0004 |
| **II. Biopharmaceutics** | | | | |
| **Absolute bioavailability** | | | | |
| **Relative bioavailability -** | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| **Bioequivalence studies -** | | | | |
| traditional design; single / multi dose: | | | | |
| replicate design; single / multi dose: | X | | | Comparability through PopPK in several studes |
| **Food-drug interaction studies** | | | | |
| **Bio-waiver request based on BCS** | | | | |
| **BCS class** | | | | |
| **Dissolution study to evaluate alcohol induced dose-dumping** | | | | |
| **III. Other CPB Studies** | | | | |
| **Genotype/phenotype studies** | | | | |
| **Chronopharmacokinetics** | | | | |
| **Pediatric development plan** | X | | | Orphan drug status; pediatric waiver |
| **Literature References** | X | | | |
| **ECG Monitoring** | X | 1 | 1 | SGN35-007 |
| **Biomarkers** | | | | |
| **Immunogenicity Testing** | X | 2 | 2 | SG035-0003, SG035-0004 |
| **Total Number of Studies** | | 6 | 6 | +1 on-going (SGN35-008B) |
| | | | | |

On **initial** review of the NDA/BLA application for filing:

| | Content Parameter | Yes | No | N/A | Comment |
|---|---|---|---|---|---|
| **Criteria for Refusal to File (RTF)** | | | | | |
| 1 | Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials? | X | | | |
| 2 | Has the applicant provided metabolism and drug-drug interaction information? | X | | | |
| 3 | Has the sponsor submitted bioavailability data satisfying the CFR requirements? | | | X | |
| 4 | Did the sponsor submit data to allow the evaluation of the validity of the analytical assay? | X | | | |
| 5 | Has a rationale for dose selection been submitted? | X | | | |
| 6 | Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to | X | | | |

| | | | | | |
|---|---|---|---|---|---|
| | allow substantive review to begin? | | | | |
| 7 | Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin? | X | | | |
| 8 | Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work? | X | | | |
| | | | | | |
| | | | | | |
| 9 | Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)? | X | | | |
| 10 | If applicable, are the pharmacogenomic data sets submitted in the appropriate format? | X | | | |
| | | | | | |
| 11 | Is the appropriate pharmacokinetic information submitted? | X | | | |
| 12 | Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)? | X | | | |
| 13 | Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance? | X | | | |
| 14 | Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics? | X | | | |
| 15 | Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective? | | | X | Pediatric waiver |
| 16 | Did the applicant submit all the pediatric exclusivity data, as described in the WR? | | | X | Pediatric waiver |
| 17 | Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label? | X | | | |
| | | | | | |
| 18 | Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product? | X | | | |
| 19 | Was the translation (of study reports or other study information) from another language needed and provided in this submission? | | | X | |

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ____Yes____**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

There is no filing issue for this submission from a clinical pharmacology perspective.

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

## Office of Clinical Pharmacology

*New Drug Application Filing and Review Form*

*General Information About the Submission*

| | Information | | Information |
|---|---|---|---|
| NDA/BLA Number | BLA 125388/0 & 125399/0 | Brand Name | ADCETRIS |
| OCP Division (I, II, III, IV, V) | DCPV | Generic Name | Brentuximab vedotin |
| Medical Division | DHP | Drug Class | Antibody-drug conjugate |
| OCP Reviewer | Aakanksha Khandelwal, Ph.D | Indication(s) | Hodgkin lymphoma and anaplastic large cell lymphoma |
| OCP Team Leader | Julie Bullock, Pharm.D. | Dosage Form | Single-use 30 mL vials (50 mg/vial) |
| Pharmacometrics Reviewer | Bahru Habtemariam, Pharm.D | Dosing Regimen | 1.8 mg/kg IV Q3W |
| Date of Submission | February 25, 2011 | Route of Administration | Intravenous Infusion |
| Estimated Due Date of OCP Review | August 2, 2011 | Sponsor | Seattle Genetics |
| Medical Division Due Date | August 2, 2011 | Priority Classification | Priority |
| PDUFA Due Date | August 30, 2011 | | |

### *Clin. Pharm. and Biopharm. Information*

| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
|---|---|---|---|---|
| STUDY TYPE | | | | |
| Table of Contents present and sufficient to locate reports, tables, data, etc. | X | | | |
| Tabular Listing of All Human Studies | X | | | |
| HPK Summary | X | | | |
| Labeling | X | | | |
| Reference Bioanalytical and Analytical Methods | X | | | |
| I. Clinical Pharmacology | | | | |
| Mass balance: | | | | |
| Isozyme characterization: | | | | |
| Blood/plasma ratio: | | | | |
| Plasma protein binding: | | | | |
| Pharmacokinetics (e.g., Phase I) - | X | 4 | 4 | SGN35-007, SGN35-008A, SG035-0001, SG035-002; SGN35-008B on-going |
| Healthy Volunteers- | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| Patients- | | | | |
| single dose: | | | | |
| multiple dose: | X | | | SGN35-007, SGN35-008A, SG035-0001, SG035-0002, SG035-0003, SG035-0004 |
| Dose proportionality - | | | | |
| fasting / non-fasting single dose: | | | | |
| fasting / non-fasting multiple dose: | | | | |
| Drug-drug interaction studies - | | | | |
| In-vivo effects on primary drug: | X | 1 | 1 | SGN35-008A |

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

| | | | | |
|---|---|---|---|---|
| In-vivo effects of primary drug: | X | 1 | 1 | SGN35-008A |
| In-vitro: | X | 1 | 1 | |
| **Subpopulation studies -** | | | | |
| ethnicity: | X | | | PopPK |
| gender: | X | | | PopPK |
| pediatrics: | | | | |
| geriatrics: | X | | | PopPK |
| renal impairment: | X | 1 | 1 | On-going SGN35-008B |
| hepatic impairment: | X | 1 | 1 | On-going SGN35-008B |
| **PD -** | | | | |
| Phase 1: | X | 2 | 2 | SG035-0001, SG035-0002 |
| Phase 2/3: | | | | |
| **PK/PD -** | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| **Population Analyses -** | | | | |
| Data rich: | | | | |
| Data sparse: | X | 2 | 2 | SG035-0003, SG035-0004 |
| **II. Biopharmaceutics** | | | | |
| **Absolute bioavailability** | | | | |
| **Relative bioavailability -** | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| **Bioequivalence studies -** | | | | |
| traditional design; single / multi dose: | | | | |
| replicate design; single / multi dose: | X | | | Comparability through PopPK in several studes |
| **Food-drug interaction studies** | | | | |
| **Bio-waiver request based on BCS** | | | | |
| **BCS class** | | | | |
| **Dissolution study to evaluate alcohol induced dose-dumping** | | | | |
| **III. Other CPB Studies** | | | | |
| **Genotype/phenotype studies** | | | | |
| **Chronopharmacokinetics** | | | | |
| **Pediatric development plan** | X | | | Orphan drug status; pediatric waiver |
| **Literature References** | X | | | |
| **ECG Monitoring** | X | 1 | 1 | SGN35-007 |
| **Biomarkers** | | | | |
| **Immunogenicity Testing** | X | 2 | 2 | SG035-0003, SG035-0004 |
| **Total Number of Studies** | | 6 | 6 | +1 on-going (SGN35-008B) |
| | | | | |

On **initial** review of the NDA/BLA application for filing:

| | Content Parameter | Yes | No | N/A | Comment |
|---|---|---|---|---|---|
| **Criteria for Refusal to File (RTF)** | | | | | |
| 1 | Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials? | X | | | |
| 2 | Has the applicant provided metabolism and drug-drug interaction information? | X | | | |
| 3 | Has the sponsor submitted bioavailability data satisfying the CFR requirements? | | | X | |
| 4 | Did the sponsor submit data to allow the evaluation of the validity of the analytical assay? | X | | | |
| 5 | Has a rationale for dose selection been submitted? | X | | | |

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

| | | | | | |
|---|---|---|---|---|---|
| 6 | Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin? | X | | | |
| 7 | Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin? | X | | | |
| 8 | Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work? | X | | | |
| | | | | | |
| | | | | | |
| 9 | Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)? | X | | | |
| 10 | If applicable, are the pharmacogenomic data sets submitted in the appropriate format? | X | | | |
| | | | | | |
| 11 | Is the appropriate pharmacokinetic information submitted? | X | | | |
| 12 | Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)? | X | | | |
| 13 | Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance? | X | | | |
| 14 | Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics? | X | | | |
| 15 | Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective? | | | X | Pediatric waiver |
| 16 | Did the applicant submit all the pediatric exclusivity data, as described in the WR? | | | X | Pediatric waiver |
| 17 | Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label? | X | | | |
| | | | | | |
| 18 | Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product? | X | | | |
| 19 | Was the translation (of study reports or other study information) from another language needed and provided in this submission? | | | X | |

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**
**____Yes____**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

There is no filing issue for this submission from a clinical pharmacology perspective.

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Reviewing Clinical Pharmacologist — Date: 3/30/11

Team Leader/Supervisor — Date: 3/30/11

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808