London, 15 November 2007
EMEA/37144/2008
EMEA/H/C/000089/II/0045

SCIENTIFIC DISCUSSION

Invented name/Name: **Caelyx**
International non-proprietary name/Common name: doxorubicin hydrochloride

Extension of the indication to include:

Treatment in combination with bortezomib for progressive multiple myeloma in patients who have received at least one prior therapy and who have undergone or are unsuitable for bone marrow transplant.

1. Introduction

The MAH applied to extend the indications to include: *"Caelyx is indicated: In combination with bortezomib for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplant"* The rationale for combining Caelyx and Bortezomib (Velcade) for the treatment of patients with multiple myeloma was based on:

- The different mechanisms of action for the both drugs
- Their non-overlapping side-effect profiles
- Data from preclinical studies suggesting synergistic anti-myeloma activity when proteasome inhibitors and doxorubicin are combined
- Promising initial results from a Phase I study of Caelyx and Bortezomib in the treatment for patients with relapsed or refractory multiple myeloma

The indication is supported by the pivotal clinical study, MMY-3001 which aims to demonstrate the efficacy of Caelyx when combined with Bortezomib, compared to Bortezomib monotherapy, in subjects with relapsed or refractory multiple myeloma.

Multiple myeloma is a disseminated malignancy of monoclonal plasma cells. In the EU in 2000, it was estimated that 10,800 deaths were attributed to the disease. The median age of presentation is 70 years. The 5-year survival rate for all patients treated with conventional therapy is approximately 25%-30%. The aetiology of the disease is unknown but it is more common in certain racial groups. The disease is characterized by the unregulated proliferation of plasma cells producing a monoclonal immunoglobulin heavy and/or light chain in most cases. The accumulation of plasma cells in the bone marrow results in the typical clinical features of bone resorption, bone pain, features of anaemia, renal insufficiency, hypercalcaemia, increased susceptibility to infections and amyloidosis. Supportive care for renal disease, bone disease, anaemia and infections is an important component of the treatment regimen. For the vast majority of patients, the treatment of the disease involves combination chemotherapy. Standard of care for multiple myeloma includes high dose Dexamethasone alone or the combination of vincristine, doxorubicin, and Dexamethasone (VAD regimen). Alternate first line standard therapies include the combination of melphalan, and prednisone or the combination of thalidomide and Dexamethasone. Following initial treatment to reduce tumour mass, haematopoietic stem cell transplantation offers the best chance for long-term survival. However, not all patients with multiple myeloma are candidates for this procedure and many patients who do receive transplants will relapse. A few patients may be cured by allogenic stem cell transplantation, though the procedure carries a high risk of mortality. Relapsed or refractory multiple myeloma is a devastating disease that currently has limited treatment options.

Doxorubicin is frequently used in combination chemotherapy regimen involving other cytotoxic drugs. Caelyx is doxorubicin hydrochloride (HCl) encapsulated in pegylated liposomes for intravenous administration. Doxorubicin is a cytotoxic anthracycline antibiotic isolated from *Streptomyces peucetius*. Doxorubicin has multiple mechanisms of anti-cancer activity, including the formation of covalent topoisomerase-DNA complexes, interference with the function of topoisomerase II, acting as a DNA intercalator, and generation of free radical intermediates. Caelyx is currently used in the treatment of patients with metastatic breast cancer, advanced ovarian cancer and AIDS-related Kaposi's sarcoma (KS). Caelyx has been shown to have reduced cardiotoxicity and myelosuppression effects, when compared to conventional Doxorubicin.

Bortezomib is a reversible inhibitor of the 26S proteasome. Inhibition of the 26S proteasome prevents targeted proteolysis and affects multiple signalling cascades within the cell, ultimately resulting in cancer cell death. Bortezomib monotherapy is an accepted treatment option, in patients with progressive multiple myeloma, who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplantation.

2. Clinical aspects

The **Pivotal Study (MMY-3001)** was a Phase III, randomized, 1:1 ratio, parallel-group, open-label, active-controlled multi-centre study, with 646 subjects in 18 countries carried out between the 20/12/04-8/03/06. The aim was to compare the safety and efficacy of Caelyx/Bortezomib combination therapy with Bortezomib monotherapy in adult subjects with multiple myeloma, whose disease has progressed after at least one regimen of prior chemotherapy or was refractory to initial treatment.

The primary endpoint was time to progression (TTP, interval between the date of randomization and the date of disease progression or death due to progression using algorithm-driven EBMT [European Group for Blood and Marrow Transplantation] criteria). The secondary objectives were overall survival, response rate and safety (Overall survival [the interval between the date of randomization and the subject's death from any cause] and response rate [complete response + partial response per EBMT criteria]). The Applicant has provided a statement confirming that the pivotal clinical trail was conducted in accordance with GCP and that ethical requirements of directive 2001/20/EC were met.

The sample size for the study was estimated by assuming that the time to progression on the Bortezomib monotherapy arm was 6 months. An improvement in median time to progression from 6 months to 7.8 months was considered to be clinically relevant. This corresponds to a hazard ratio of 1.3. With these assumptions 460 events (progression or death due to progression) were needed to give 80% power to detect a treatment difference at the 2-sided 5% level. Approximately 630 subjects were to be randomised to observe these events.

One interim analysis was to be performed after approximately 230 events had been observed. The critical significance levels for the interim and final analysis based on the O'Brien-Fleming group sequential procedure were 0.003 for the interim analysis and 0.048 for the final analysis.

2. 1. Study Results

646 subjects were randomly assigned 1:1 to treatment with Caelyx/Bortezomib combination therapy (n=324) or Bortezomib monotherapy (n=322). Randomisation was performed using a centralised interactive voice response system, and was stratified by serum β_2-microglobulin levels ($\leq$2.5 mg/L, > 2.5 mg/L and $\leq$ 5.5 mg/L, > 5.5 mg/L) and response to prior treatment (disease responded to initial therapy and later progressed, disease progressed during initial treatment).

The stratification worked well and the treatment groups were balanced across all stratification factors.

Patient groups by stratification factors

Stratification factor	Bortezomib (N=322)	PLD + Bortezomib (N=324)
β2-microglobulin group		
≤ 2.5 mg/L	45 (14%)	45 (14%)
> 2.5 mg/L and ≤ 5.5 mg/L	178 (55%)	181 (56%)
> 5.5 mg/L	99 (31%)	98 (30%)
Response to Prior treatment		
Responded to initial therapy then progressed	295 (92%)	295 (91%)
Progressed during initial treatment	27 (8%)	29 (9%)

Therefore the 2 treatment groups were balanced with respect to relevant demographics, baseline disease characteristics, laboratory characteristics, prognostic factors and the types of prior systemic therapies for multiple myeloma. Most subjects had received prior corticosteroids (>99%) and alkylating agents (91%). The overall median age was 61 years and all subjects had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 (44%) or 1 (56%), except for 2 subjects with missing scores. The majority of subjects (92%) were white; 5% were black, and 2% were Asian. The presence of progression was demonstrated using the EBMT algorithm. IgG was the most common multiple myeloma class (59%). The ITT population was essentially either anthracycline-naive (33% of subjects) or not refractory to anthracycline (66%).

In both treatment arms, Bortezomib 1.3 mg/m^2 was given as an IV bolus on Days 1, 4, 8, and 11 of each 21-day cycle, per the approved licensed regimen. In the combination therapy arm, Caelyx 30 mg/m^2 was administered (following the Bortezomib bolus) as at least a 1-hour IV infusion on Day 4 of each 21-day cycle (the Caelyx regimen is consistent with the previously conducted Phase I study by Orlowski et al). Treatment was continued until disease progression, the occurrence of unacceptable treatment-related toxicity or until 8 cycles of therapy had been received. 'Permitted' concomitant therapy included pyridoxine (hand-foot syndrome prevention), bisphosphonates, Corticosteroids (Anti-emetic/infusion reactions: Dexamethasone up 8mg per dose, 24 mg per cycle), haematopoietic cytokines (use in second cycle onwards), anti-infective therapy, anti-emetics, midodrine and local irradiation/surgery. Anti-cancer drugs, other than the study drugs were not permitted.

2. 2. Clinical Efficacy

The median number of cycles received was 5 and the median duration of treatment was approximately 105 days in both arms. The median of the mean dose of Bortezomib administered per dose was approximately 1.28 mg/m^2, consistent with the protocol-specified initial dose and the median of the mean dose of Caelyx administered per dose combined arm was 29.83 mg/m^2/day. Dose reductions of Bortezomib were required for 35% of subjects in the monotherapy group, compared with 39% of subjects in the combined group. 82 (25%) subjects discontinued treatment in the monotherapy arm compared to 37 (11%) subjects in the Caelyx/Bortezomib arm due to disease progression. 66 (20%) subjects discontinued study treatment in the monotherapy arm compared to 86 (27%) subjects in the Caelyx/Bortezomib arm due to adverse events (Serious adverse events: 12 (4%) in the monotherapy arm Vs 24 (7%) in the Caelyx/Bortezomib).

Thirty-three randomized subjects, 12 in the Bortezomib arm and 21 in the Caelyx/Bortezomib arm were excluded from the evaluable population: 10 did not receive any dose of study drugs and 22 did not have measurable disease per protocol criteria at baseline and 1 for both reasons.

At the planned interim analysis (cut-off 28th April, 2006), there were a total of 249 subjects with a TTP event (39% of ITT population, 99 in Bortezomib/Caelyx arm, 150 in Bortezomib arm), and a median follow-up of 3.9 months. The median time to disease progression was 6.5 months (197 days) for the Bortezomib monotherapy group compared with 9.3 months (282 days) for the Caelyx/Bortezomib combination group. The P-value for the time to progression comparison was 0.000004 (stratified log-rank test). The hazard ratio for the two treatment groups (Bortezomib monotherapy relative to Caelyx/Bortezomib) was 1.82 (95% CI [1.41, 2.35]) obtained from a stratified Cox proportional hazards regression. The p-value of p=0.000004 more than satisfied the pre-specified criterion ($p<0.003$) for claiming a statistically significant benefit at the interim analysis.

Time to progression

Table 2 Time to Progression: Adjusted for Strata (Intent-to-Treat Analysis Set)

Study MMY-3001

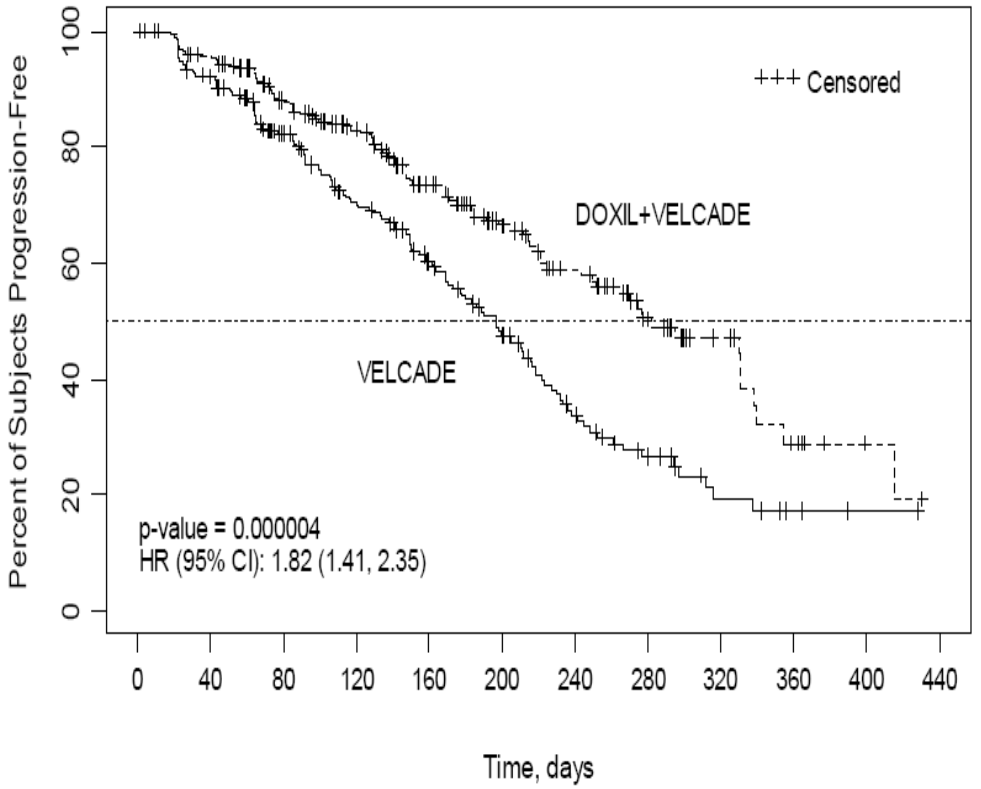
	Bortezomib (N=322)	PLD + bortezomib (N=324)
Time to Progression (Days)		
Censored (%)	172 (53.4)	225 (69.4)
Progressed or died due to progression (%)	150 (46.6)	99 (30.6)
25% Quantile (95% CI) [a]	105.0 (89.0; 127.0)	148.0 (131.0; 183.0)
Median (95% CI) [a]	197.0 (170.0; 217.0)	282.0 (250.0; 338.0)
75% Quantile (95% CI) [a]	297.0 (245.0; N/A)	415.0 (338.0; N/A)
P value [b]	0.000004	
Hazard ratio (95% CI) [c]	1.82 (1.41; 2.35)	

CI = confidence interval; N/A = not available.

a: Based on Kaplan-Meier product-limit estimates.

b: Based on stratified Log-rank test.

c: Bortezomib vs PLD and bortezomib. A hazard ratio >1 indicates an advantage for PLD and bortezomib.



Number of Subjects at Risk												
DOXIL+VELCADE	324	299	223	173	120	80	57	34	18	8	3	0
VELCADE	322	286	213	154	106	68	37	22	9	4	1	0

CI = confidence interval; DOXIL = PLD; HR=hazard ratio; VELCADE = bortezomib.

A proportional hazards analysis was performed, which showed that the hazard ratio remained virtually unchanged (going from 1.82 to 1.83) after adjusting for potential prognostic factors.

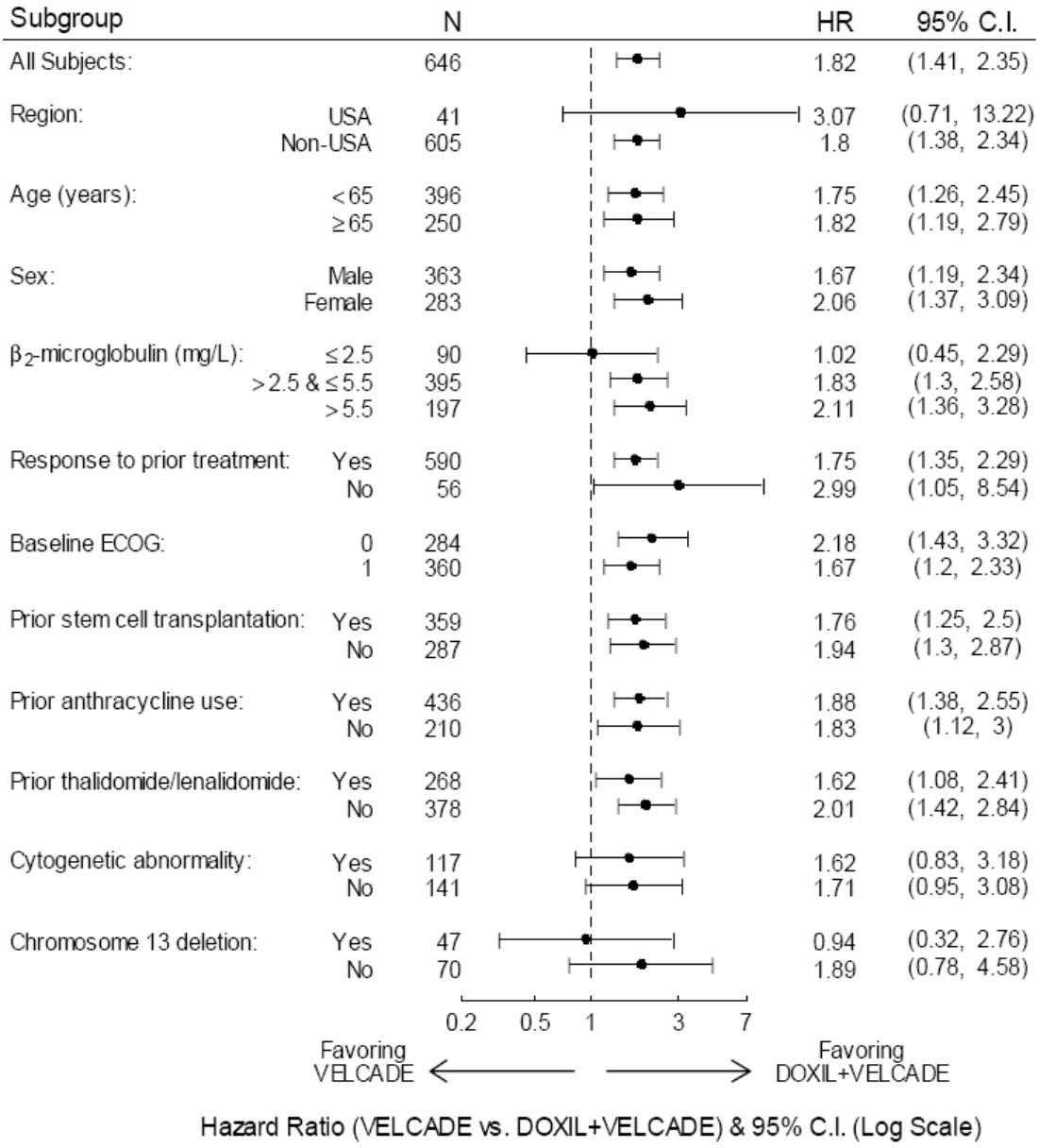
Adjusting for relevant prognostic factors in a proportional hazards model

The hazard ratio for time to progression favoured the combination therapy in nearly all subgroups after adjustment for prognostic factors (treatment, β-2 microglobulin, response to initial treatment, age,

baseline ECOG PS, sex, prior stem cell transplantation, prior anthracycline use, prior thalidomide or lenalinomide use). The trend was in the opposite direction only in some of the smaller sub-groups; confidence intervals in these sub-groups were wide and still consistent with there being a benefit in these groups.

Time to progression all subjects and subgroups (Hazard Ratios)

Progression-free survival (including all deaths, not just those attributable to progression as in the primary analysis) was planned as a secondary analysis to provide supportive evidence. The median progression-free survival duration was 7.3 months (222 days) for the Bortezomib monotherapy arm and 11.2 months (340 days) for the Caelyx/Bortezomib combination arm. The P-value for the progression-free survival comparison was 0.000038 (stratified log-rank test). This result is also extreme enough to be significant at the interim analysis and supports the findings from the primary efficacy analysis.



Unplanned Interim Analysis

An unplanned TTP and survival analysis was requested by the FDA (cut-off 28th November 2006). A total of 63% of ITT subjects reporting a TTP event, 223 Bortezomib arm and 184 Caelyx/Bortezomib arm and a median follow up of 6.3 months. The median TTP was 6.9 months (209 days) in the

Bortezomib arm and 8.9 months (271 days) in the Caelyx/Bortezomib arm. The observed p-value of p=0.000013 was still extreme enough to satisfy the stopping rule defined for the initial interim analysis.

Time to progression (unplanned)

Table 4 Time to Progression (Days), Adjusted for Strata: Intent-to-Treat Analysis Set (Data Cut-Off: 28 NOV 2006)

Study MMY-3001

	Bortezomib (N=322)	PLD + Bortezomib (N=324)
Censored (%)	99 (30.7)	140 (43.2)
Progressed or Died Due to Progression (%)	223 (69.3)	184 (56.8)
25% Quantile (95% CI)[a]	106.0 (87.0; 121.0)	148.0 (128.0; 174.0)
Median (95% CI)[a]	209.0 (185.0; 222.0)	271.0 (246.0; 298.0)
75% Quantile (95% CI)[a]	330.0 (294.0; 401.0)	435.0 (380.0; 557.0)
P value[b]	0.000013	
Hazard Ratio (95% CI)[c]	1.55 (1.27;1.89)	

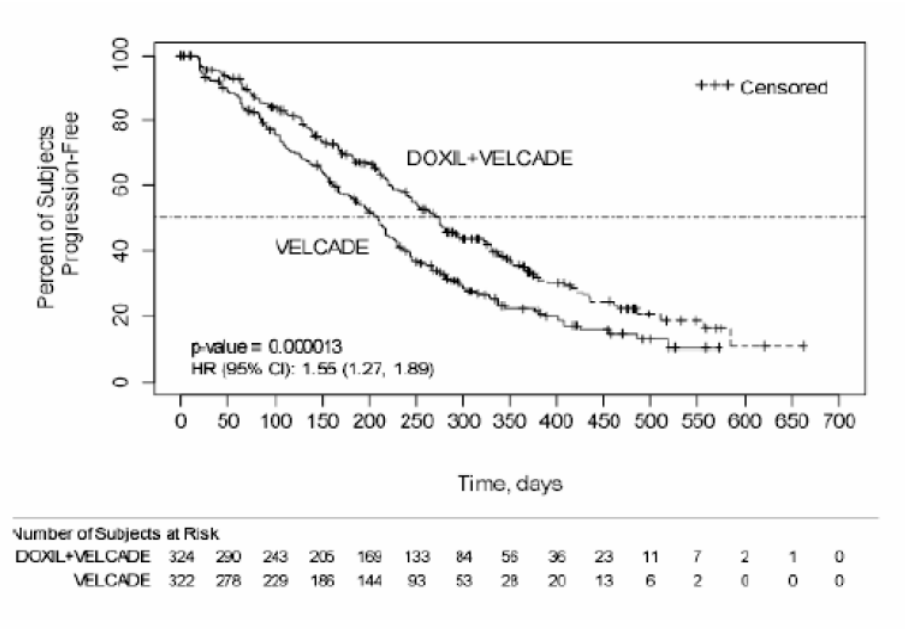
PLD = pegylated liposomal doxorubicin; CI = confidence interval.

a: Based on Kaplan-Meier product-limit estimates.

b: Based on stratified log-rank test.

c: Bortezomib vs PLD + bortezomib. A hazard ratio >1 indicates an advantage for PLD + bortezomib.

Cross-reference: Efficacy Update\Table 1.



CI = confidence interval; DOXIL = PLD; HR=hazard ratio; VELCADE = bortezomib.

Cross-reference: Efficacy Update\Figure 1

Secondary endpoints: Response rate, Overall survival and Quality of life

A total of 133 (43%) subjects (95% CI: 37.3; 48.6) achieved a complete or partial **response** in the Bortezomib monotherapy arm compared with 144 (48%) subjects (95% CI: 41.8; 53.3) in the Caelyx/Bortezomib combination arm (p=0.2514, Cochran-Mantel-Haenszel test).

	Caelyx/Bortezomib arm	Bortezomib arm
Complete Response (CR)	5%	3%
Near CR	9%	8%
Partial Response (PR)	43%	40%

The duration of response, measured as the time of first response to progression or death due to any cause, had a median of 7 months (213 days; 95% CI: 180 – 254) in the Bortezomib arm and 10.2 months (311 days; 95% CI: 309-394) in the Caelyx/Bortezomib arm.

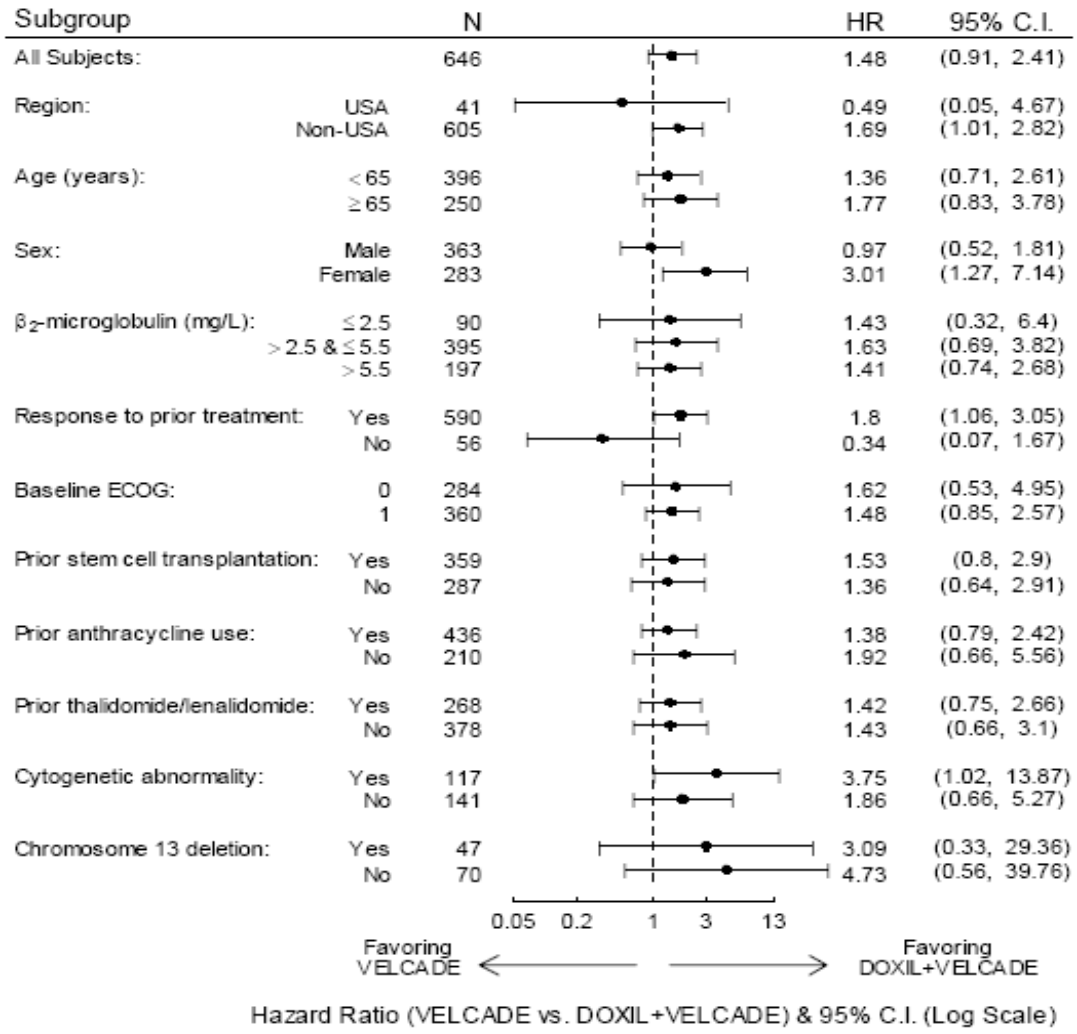
Overall survival

As of the 28 April 2006 clinical data collection cut-off, 12% of subjects (39) in the Bortezomib monotherapy arm and 9% (28) of subjects in the Caelyx/Bortezomib therapy arm had died (p=0.113 stratified log-rank test, hazard ratio = 1.48 with 95% CI [0.91, 2.41]). The trend is in favour of the combination group but statistical significance has not been achieved.

Overall survival for all Subjects and Subgroups

DOXIL/CAELYX (pegylated liposomal doxorubicin): MODULE 2.7.3 Clinical Efficacy

Figure 4: Overall Survival for All Subjects and Subgroups: Hazard Ratio and 95% Confidence Interval (Study DOXIL-MMY-3001: Intent-to-Treat Analysis Set)



C.I.=confidence interval; ECOG = Eastern Cooperative Oncology Group; HR=hazard ratio
Cross-reference: Mod5.3.5.1\MMY-3001\Fig4

The FDA requested unplanned analysis shows a total of 139 deaths, 81 subjects in the Bortezomib arm and 58 in the Caelyx/Bortezomib arm, and a median follow-up of 10.9 months and a mortality risk reduction point estimate of 29% (hazard ratio [95%CI]:1.406 [1.002 to 1.972]). This is an unplanned analysis (albeit requested by the FDA), so the precise interpretation of p-values is difficult, but the p-

value here is less than 0.048. Hence if this had been the final analysis a benefit in overall survival would have been shown.

Overall survival (unplanned)

Table 5 Overall Survival (Days), Adjusted for Strata: Intent-to-Treat Analysis Set (Data Cut-Off: 28 NOV 2006)

Study MMY-3001

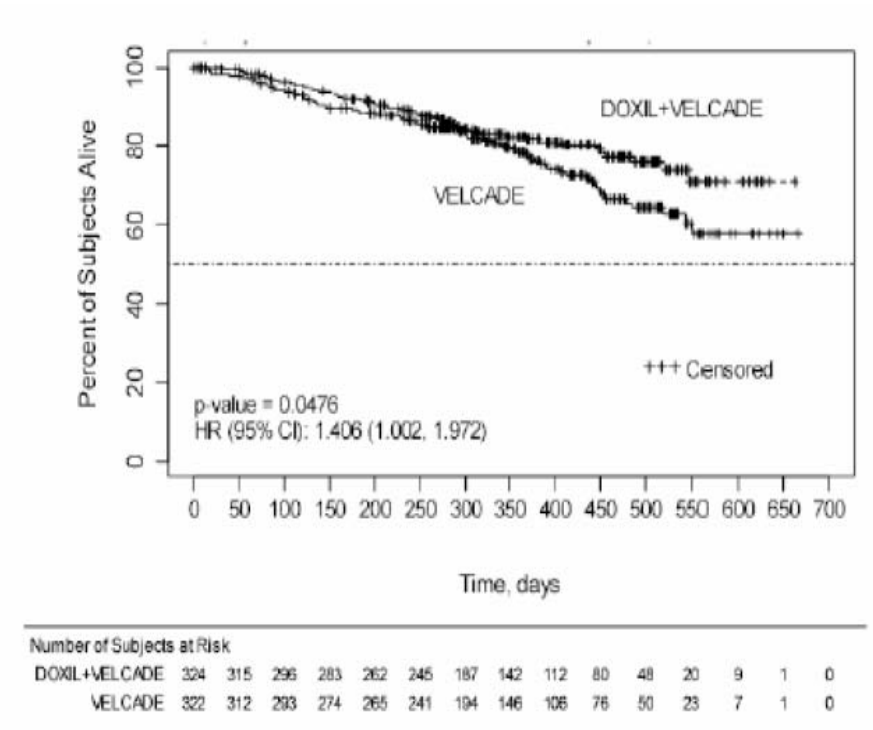
	Bortezomib (N=322)	PLD + Bortezomib (N=324)
Censored (%)	241 (74.8)	266 (82.1)
Died (%)	81 (25.2)	58 (17.9)
25% Quantile (95% CI)[a]	389.0 (344.0; 451.0)	518.0 (455.0; N/A)
Median (95% CI)[a]	(551.0; N/A)	(N/A; N/A)
Quantile (95% CI)[a]	(N/A; N/A)	(N/A; N/A)
P value[b]	0.0476	
Hazard Ratio (95% CI)[c]	1.406 (1.002; 1.972)	

PLD = pegylated liposomal doxorubicin; CI = confidence interval; N/A = not available.

a: Based on Kaplan-Meier product-limit estimates.

b: Based on stratified log-rank test.

c: Bortezomib vs PLD + bortezomib. A hazard ratio >1 indicates an advantage for PLD + bortezomib.



CI = confidence interval; DOXIL = PLD; HR = hazard ratio; VELCADE = bortezomib.
Cross-reference: Efficacy Update\Figure 2

Subject self-reported **quality of life** data were prospectively collected. Limitations of the quality of life data are anticipated due to the non-blinded design of the study.

Updated efficacy analysis

Although the current results in the primary endpoint TTP (time to progression) are favourable, these should be viewed in the context of overall clinical benefit. The improvement in TTP should be

supported by an improved in overall survival and/or improved quality of life. Therefore, an unplanned survival update to allow assessment of the latest available data was requested by the CHMP.
An additional 67 deaths (38 in the combination arm and 29 in the control) were reported in the unplanned overall survival update (cut off 10 August 2007).The hazard ratio moved from 0.68 to 0.71 and has now reached 0.86. The upper bound of the 95% confidence interval went from 1.098 to 0.998 and now is 1.127.

Table 4 Summary of the Overall Survival Analyses

Study MMY-3001

	Planned Analysis	FDA-Mandated Update	CHMP-Mandated Update
Clinical data collection cut-off date	28 APR 2006	28 NOV 2006	10 AUG 2007
Median follow-up (months)	3.9	10.9	18.0
No. of death events (% of ITT)	67 (10%)	139 (22%)	206 (32%)
No. of deaths in test arm	28	58	96
No. of deaths in control arm	39	81	110
Hazard ratio[a] (95% CI)	0.68 (0.415 - 1.098)	0.71 (0.507 - 0.998)	0.86 (0.649 – 1.127)
Risk reduction	32%	29%	14%
P value (stratified log-rank test)	0.113	0.0476	0.265

CI = confidence interval; ITT = intent-to-treat; PLD = pegylated liposomal doxorubicin.

a: Hazard ratio <1 is in favor of the PLD + bortezomib arm.

3. 2. 3. Clinical Safety

Adverse events

Adverse events were recorded from the first study-related procedure until 30 days after the last dose of study drug. Toxicities observed within the Caelyx/Bortezomib combination group were predictable, manageable, and consistent with the known safety profiles of both agents. No unexpected safety concerns were observed.
At least 1 adverse event was considered to be at least possibly drug-related for most subjects in both the Bortezomib monotherapy group (86%) and the Caelyx/Bortezomib combination therapy group (94%).

Summary of Treatment-Related AE's

Table 6 Overview of Treatment-Emergent Adverse Events (Safety Analysis Set)

Study MMY-3001

	Bortezomib (N=318)	PLD + bortezomib (N=318)	Total (N=636)
Any AEs, n (%)	307 (97)	312 (98)	619 (97)
Drug-related AEs, n (%)	273 (86)	299 (94)	572 (90)
Serious AEs, n (%)	98 (31)	115 (36)	213 (33)
Drug-related serious AEs, n (%)	47 (15)	69 (22)	116 (18)
Grade 3 or 4 AEs, n (%)	204 (64)	253 (80)	457 (72)
Drug-related Grade 3 or 4 AEs, n (%)	165 (52)	217 (68)	382 (60)
AEs leading to bortezomib discontinuation[b], n (%)	76 (24)	120 (38)	196 (31)
AEs with outcome of death, n (%)	11 (3)	13 (4)[a]	24 (4)[a]
Drug-related AEs with outcome of death, n (%)	5 (2)	5 (2)	10 (2)

AE = adverse event; PLD = pegylated liposomal doxorubicin.

Note: Incidence is based on the number of subjects, not the number of events. Adverse events reported any time during treatment or within 30 days of end of treatment are included. Drug-related means possible, probable, or very likely relationship to study drug.

a: This total includes 1 subject (113047) who was alive at the clinical cut-off date, and who had an adverse event for weight loss that was erroneously reported to have a fatal outcome.

b: Cross-reference: Additional Safety Data\Table 3.

Cross-reference: Mod5.3.5.1\MMY-3001\Table 22.

- Cardiac events: the incidence of all cardiac adverse events was 7% in the monotherapy arm and 10% in the combination arm. The incidence of symptomatic arrhythmia was more frequent in the Caelyx/Bortezomib combination therapy group, 3% versus 1% in the monotherapy arm. One subject in the Bortezomib monotherapy group and 1 subject in the Caelyx/Bortezomib combination group died as a result of cardiac events. Changes from baseline in left ventricular ejection fraction (LVEF) measurements were reported for 9% of subjects in the Caelyx/Bortezomib combination therapy group and 7% of subjects in the monotherapy group. Congestive heart failure, ventricular dysfunction, cardiac failure, right ventricular failure, congestive cardiac failure, chronic cardiac failure, acute pulmonary oedema and pulmonary oedema were reported in 3% of subjects in both arms.
- More Grade 3 or 4 AEs (adverse events) were seen with the combined therapy than the monotherapy (primarily due to an increase in Grade 3 or 4 myelosuppression and Grade 3 gastrointestinal events).

- Grade 3:Grade 4 haematological adverse events were reported for 26%:21% of subjects in the Caelyx/Bortezomib arm, compared with 20%:12% of subjects in the Bortezomib monotherapy

- Grade 3 gastrointestinal adverse events were reported for 16% of subjects in the Caelyx/Bortezomib arm, compared with 21% of subjects in the Bortezomib monotherapy

- Stomatitis was reported in 18% of patients receiving the combined therapy and 3% in the monotherapy arm

- Infusion-Related reactions were seen in 3% of subjects in the combined arm

- Haematological events: Haematological adverse events were reported for 44% of subjects in the monotherapy group and 55% of subjects in the Caelyx/Bortezomib arm. The most frequently reported events were thrombocytopenia (28%), neutropenia (27%), and anaemia (22%). Neutropenia was more frequent with the combination therapy (35%) than with the monotherapy (20%). The incidence of Grade 3 and 4 neutropenia was higher in the Caelyx/Bortezomib combination group (30%) compared with the monotherapy group (14%). The incidence of febrile neutropenia was 2% in the monotherapy arm and 3% in the combination arm. The incidence of other Grade 3 or 4 adverse events associated with neutropenia, such as septic shock, sepsis, and septic embolus, was 2% or less in both treatment groups. Granulocyte Colony-Stimulating Factor (G-CSF) was used in 17% of subjects for the combined arm and 9% of subjects for the monotherapy arm. More Grade 3 or greater bleeding or haemorrhage episodes were seen with the combined therapy (4%) than the monotherapy (1%). Thromboembolic events were rare (1%)

- Neuropathy-Related events: Grade 3 or 4 peripheral neuropathy was reported in 9% of subjects in the monotherapy group and 4% of subjects in the combined therapy group. Hand-foot syndrome was only seen in the combined therapy arm, with an overall incidence of 19%. The majority of cases were Grade 1 or 2 severity

- Alopecia: Alopecia occurred in 1% of patients in the monotherapy arm and 2% of patients in the combined therapy arm

- Renal: renal and urinary disorders were similar in the 2 groups, 7% in the monotherapy group and 9% in the combination group. Serum creatinine was monitored throughout the study. 35% of subjects in the monotherapy group and 40% of subjects in the Caelyx/Bortezomib combination group had elevated creatinine.

- Hepatobiliary: the incidence of adverse events classified as 'hepatobiliary' was 1% in the monotherapy group and 2% in the combination group. No liver-related toxicities were reported as serious adverse events.

Frequency of System Organ Class Adverse Events in each arm

Table 7 Treatment-Emergent Adverse Events Reported in at Least 10% of Subjects in Any Treatment Group (Safety Analysis Set)

Study MMY-3001

	Bortezomib (N=318)			PLD + bortezomib (N=318)			Total (N=636)		
System Organ Class	**Total**			**Total**			**Total**		
Preferred Term	n (%)	Grade 3	Grade 4	n (%)	Grade 3	Grade 4	n (%)	Grade 3	Grade 4
Total subjects with adverse event	**307 (97)**			**312 (98)**			**619 (97)**		
Blood and lymphatic system disorders	**140 (44)**	**65 (20)**	**39 (12)**	**176 (55)**	**83 (26)**	**68 (21)**	**316 (50)**	**148 (23)**	**107 (17)**
Anaemia	65 (20)	23 (7)	5 (2)	72 (23)	23 (7)	6 (2)	137 (22)	46 (7)	11 (2)
Neutropenia	64 (20)	34 (11)	12 (4)	110 (35)	65 (20)	29 (9)	174 (27)	99 (16)	41 (6)
Thrombocytopenia	81 (25)	25 (8)	24 (8)	95 (30)	34 (11)	37 (12)	176 (28)	59 (9)	61 (10)
Gastrointestinal disorders	**218 (69)**	**27 (8)**	**0**	**249 (78)**	**52 (16)**	**0**	**467 (73)**	**79 (12)**	**0**
Abdominal pain	23 (7)	4 (1)	0	32 (10)	2 (1)	0	55 (9)	6 (1)	0
Constipation	89 (28)	2 (1)	0	90 (28)	3 (1)	0	179 (28)	5 (1)	0
Diarrhoea	109 (34)	14 (4)	0	136 (43)	22 (7)	0	245 (39)	36 (6)	0
Nausea	117 (37)	1 (<1)	0	146 (46)	7 (2)	0	263 (41)	8 (1)	0
Stomatitis	10 (3)	1 (<1)	0	58 (18)	7 (2)	0	68 (11)	8 (1)	0
Vomiting	62 (19)	3 (1)	0	100 (31)	13 (4)	0	162 (25)	16 (3)	0
General disorders and administration site conditions	**187 (59)**	**24 (8)**	**2 (1)**	**217 (68)**	**42 (13)**	**3 (1)**	**404 (64)**	**66 (10)**	**5 (1)**
Asthenia	51 (16)	9 (3)	0	62 (19)	18 (6)	0	113 (18)	27 (4)	0
Fatigue	83 (26)	7 (2)	0	100 (31)	15 (5)	2 (1)	183 (29)	22 (3)	2 (<1)
Pyrexia	69 (22)	4 (1)	0	93 (29)	4 (1)	0	162 (25)	8 (1)	0
Infections and infestations	**171 (54)**	**40 (13)**	**8 (3)**	**193 (61)**	**44 (14)**	**7 (2)**	**364 (57)**	**84 (13)**	**15 (2)**
Herpes simplex	16 (5)	2 (1)	0	32 (10)	0	0	48 (8)	2 (<1)	0
Herpes zoster	28 (9)	6 (2)	0	31 (10)	6 (2)	0	59 (9)	12 (2)	0
Investigations	**48 (15)**	**7 (2)**	**1 (<1)**	**87 (27)**	**8 (3)**	**1 (<1)**	**135 (21)**	**15 (2)**	**2 (<1)**
Weight decreased	11 (3)	0	0	33 (10)	0	0	44 (7)	0	0
Metabolism and nutrition disorders	**77 (24)**	**14 (4)**	**1 (<1)**	**116 (36)**	**21 (7)**	**6 (2)**	**193 (30)**	**35 (6)**	**7 (1)**
Anorexia	36 (11)	0	0	57 (18)	5 (2)	0	93 (15)	5 (1)	0
Musculoskeletal and connective tissue disorders	**127 (40)**	**20 (6)**	**2 (1)**	**123 (39)**	**14 (4)**	**2 (1)**	**250 (39)**	**34 (5)**	**4 (1)**
Back pain	33 (10)	6 (2)	0	33 (10)	5 (2)	0	66 (10)	11 (2)	0
Pain in extremity	41 (13)	5 (2)	0	29 (9)	0	0	70 (11)	5 (1)	0

	Bortezomib (N=318)			PLD + bortezomib (N=318)			Total (N=636)		
System Organ Class	Total			Total			Total		
Preferred Term	n (%)	Grade 3	Grade 4	n (%)	Grade 3	Grade 4	n (%)	Grade 3	Grade 4
Nervous system disorders	**201 (63)**	**41 (13)**	**10 (3)**	**203 (64)**	**37 (12)**	**7 (2)**	**404 (64)**	**78 (12)**	**17 (3)**
Headache	50 (16)	0	0	58 (18)	2 (1)	1 (<1)	108 (17)	2 (<1)	1 (<1)
Neuralgia	51 (16)	12 (4)	2 (1)	44 (14)	9 (3)	0	95 (15)	21 (3)	2 (<1)
Neuropathy	33 (10)	4 (1)	0	29 (9)	4 (1)	0	62 (10)	8 (1)	0
Neuropathy peripheral	41 (13)	9 (3)	1 (<1)	31 (10)	6 (2)	0	72 (11)	15 (2)	1 (<1)
Paraesthesia	24 (8)	0	0	35 (11)	1 (<1)	0	59 (9)	1 (<1)	0
Peripheral sensory neuropathy	36 (11)	5 (2)	0	36 (11)	3 (1)	0	72 (11)	8 (1)	0
Psychiatric disorders	**63 (20)**	**5 (2)**	**1 (<1)**	**59 (19)**	**6 (2)**	**0**	**122 (19)**	**11 (2)**	**1 (<1)**
Insomnia	37 (12)	0	1 (<1)	32 (10)	0	0	69 (11)	0	1 (<1)
Respiratory, thoracic and mediastinal disorders	**85 (27)**	**13 (4)**	**4 (1)**	**110 (35)**	**11 (3)**	**4 (1)**	**195 (31)**	**24 (4)**	**8 (1)**
Cough	36 (11)	0	0	52 (16)	0	0	88 (14)	0	0
Skin and subcutaneous tissue disorders	**98 (31)**	**8 (3)**	**0**	**155 (49)**	**21 (7)**	**0**	**253 (40)**	**29 (5)**	**0**
Hand-foot syndrome	0	0	0	50 (16)	15 (5)	0	50 (8)	15 (2)	0
Rash	25 (8)	3 (1)	0	42 (13)	2 (1)	0	67 (11)	5 (1)	0

Serious Adverse Events (SAE'S)

Serious adverse events occurred more frequently in the combined arm (36%), than the monotherapy arm (31%). The most common SAE's for the combined arm were pneumonia (5%), pyrexia (3%), thrombocytopenia (3%) and vomiting (4%).

Deaths

Of the 646 subjects randomized in Study, 67 deaths were reported at the time of the clinical data collection cut-off date on the 28th April 2006.

- 39 (12%) subjects died in the Bortezomib monotherapy arm
- 28 (9%) subjects in the Caelyx/Bortezomib combination arm.

25 of the 67 subjects died within 30 days of treatment termination. 14 (4%) subjects in the Bortezomib monotherapy arm and 11 (3%) subjects in the Caelyx/Bortezomib combination therapy arm. 6/14 deaths in the monotherapy group and 1/11 deaths in the combination therapy group were due to disease progression. 1 subject (sudden cardiac death) in the monotherapy group and 1 subject (cardiac arrest) in the combination therapy group died as a result of cardiac events.

7 (2%) subjects in the monotherapy arm and 10 (3%) subjects in the combination therapy arm died due to an adverse event. Furthermore, 3 subjects died in the Bortezomib monotherapy arm and 4 subjects died in the Caelyx/Bortezomib combination arm, with the main cause considered by the investigator to be a drug-related adverse event.

3. 2. 4. Supporting clinical studies C-2000-003-03 and C-2000-002-01

In addition to the pivotal study, data are included from 2 additional studies. These were conducted in subjects with multiple myeloma. Caelyx was administered either in comparison to conventional doxorubicin or as a monotherapy.

C-2000-003-03

This was a Phase III, multi-centre, randomized, open-label study to compare the efficacy, clinical benefit, toxicity and safety of VDD treatment regimen (Vincristine/ Caelyx [40 mg/m^2 infusion over 1 hour] / Dexamethasone) with a VAD (Vincristine/ Doxorubicin [9 mg/m^2 infusion per day, days 1-4] /

Dexamethasone) treatment regimen in subjects with newly diagnosed multiple myeloma who had not received prior treatment for their disease. Subjects were randomly assigned 1:1. The primary efficacy endpoint was the objective response rate, defined as the % of subjects who attained an objective status of complete remission, remission, or partial remission. The 2 treatments were considered therapeutically equivalent if the corresponding 2-sided 95% CI of the difference in objective response rates fell within ±20%. Secondary efficacy endpoints included time to progression, defined as the time from first study drug administration until documented disease progression or death due to any cause, overall survival and clinical benefit. Hazard ratios were calculated for these secondary endpoints, such that a value greater than 1 indicated an advantage for the VDD group. A total of 192 adult subjects with untreated multiple myeloma were enrolled. Ninety-five subjects were randomized to receive VAD therapy and 97 subjects to receive VDD therapy. The treatment groups were balanced in terms of age and sex; the overall median age was 59 years.

For the primary efficacy endpoint, the overall objective response rate was 35.8% (34 of 95 subjects) in the VAD treatment group and 39.2% (95% CI 26.1- 45.4%) in the VDD treatment group (95% CI 29.5%-48.9%). The 95% CI for the difference in objective response was -17.1% to 10.3% (p=0.652). Secondary efficacy endpoints included progression-free survival and overall survival. The hazard ratio of VDD versus VAD for progression-free survival was 1.11 (p=0.69), and the hazard ratio for overall survival was 0.88 (p=0.67). Clinical benefit parameters showed that the incidence of Grade 3 or 4 neutropenia was significantly lower with VDD therapy (10.3%) than with VAD treatment (24.2%, p=0.0128).

No unexpected toxicity was observed.

- The most frequently reported adverse event was asthenia (VAD 48.4% VDD 55.7%)
- Serious adverse events (VAD 35.8%; VDD 37.1%)
- Four serious adverse events were reported more frequently in the VDD group compared with the VAD group: pneumonia (9.3% versus 4.2%), dehydration (6.2% versus 0%), asthenia (5.2% versus 0%), and nausea (5.2% versus 0%)
- Grade 4 adverse events (VAD 25.3%; VDD 21.6%)
- Grade 3 adverse events (VAD 62.1%; VDD 59.8%)
- Grade 3/4 neutropenia (VAD 10.3%; VDD 10.3%)
- Sepsis (VAD 8.4%; VDD 3.1%)
- VAD was associated with Grade 3 or 4 congestive heart failure in 2 subjects, whereas no subject treated with VDD experienced Grade 3 or 4 heart failure
- 2 subjects in the VAD group died due to adverse events, and 1 subject in the VDD group died due to progression of multiple myeloma. Additionally, 1 subject in the VAD group and 3 subjects in the VDD group died shortly after the 30-day follow-up period.

C-2000-002-01
This was a Phase II, multi-centre, open-label, single-agent study of Caelyx in the treatment of adult subjects with multiple myeloma who had achieved less than a partial response after receiving 3 to 4 cycles of VAD therapy or who had disease progression after 2 cycles of VAD therapy. Caelyx was give at a dose of 40 mg/m^2 iv infusion over 1 hour on day 1 of each 28-day cycle. The study was terminated after enrolment of only 15 subjects of the planned 100. The mean age was 58.3 years. The median time to progression was 99 days, and the median survival time was 110.5 days.

In terms of adverse events, the most common adverse events were nausea (7 subjects), anaemia (7 subjects), asthenia (6 subjects), anorexia (5 subjects), fever (5 subjects), and leukopenia (5 subjects).

Grade 3 adverse events were reported in 12 subjects and Grade 4 adverse events in 7 subjects. Serious adverse events reported for 2 or more subjects included anaemia (3 subjects), and hypercalcaemia, pneumonia, hypotension, sepsis, and fever (2 subjects each)
No formal evaluation of efficacy could be performed due to the limited number of participants. The reported adverse event profiles are in keeping with the known profile of Caelyx.

3. 3. Conclusion and Benefit/Risk analysis

The results from the Pivotal study support the use of Caelyx/Bortezomib combination in the treatment of patients with multiple myeloma. Overall, the efficacy results demonstrate that the combined therapy does provide clinical benefit in terms of extended time to disease progression. The Caelyx/Bortezomib combination therapy appears to be a well-tolerated regimen and unexpected adverse events were not documented.

In terms of overall survival, the updated overall survival data (following CHMP request) exhibited a trend that still favours the Caelyx/Bortezomib arm, although the advantage is not as impressive as seen at the planned interim analysis and the unplanned FDA analysis. Currently 32% of the ITT population has died. However, these results are not unexpected when considering the long-term follow-up of overall survival. Furthermore, 65% of patients (67% in the control arm and 62% in the combination arm) have now started using subsequent therapies (47% of ITT subjects received systemic corticosteroids, 31% thalidomide/lenalidomide, 19% cyclophosphamide, and 17% melphalan). It can be expected that the results in each group will become more similar over time and in the very long term the treatment difference would be further expected to diminish as the time from randomised increases. Therefore, any difference between treatments is likely to be at its greatest in the early stages when there is a clean comparison between both randomised groups. As such, the gradual increase of the hazard ratio over the repeated analyses is not felt to be a concern. While a benefit on overall survival cannot be considered to have been definitively established, it is strongly suggested, and there is certainly no suggestion of a detrimental effect. The Kaplan-Meier curves show separation of the curves, favouring the combination therapy.

Overall, in terms of overall survival, the updated OS data (unplanned CHMP request) exhibited a trend that still favours the Caelyx/Bortezomib arm. The Study MMY-3001 protocol planned long-term follow-up and survival analysis, expected not earlier than 2010. The Applicant has committed to this Follow up measure. The final analysis of overall survival is planned for when approximately 80% of ITT subjects have died. The Quality of Life data do not demonstrate any clinically relevant adversarial effect of adding Caelyx to the standard treatment of Bortezomib, at least during the treatment phase.

The overall benefit/risk in subjects with multiple myeloma who have received at least 1 prior therapy is favourable and the extension of indication is supported. The results of the protocol-planned long-term follow-up and survival analysis of study MMY-3001 will be submitted when 80% of events are anticipated to have occurred.

The MAH will be performing ongoing long-term safety follow-up of study MMY-3001, by reporting of all serious adverse events deemed related (possibly, probably, very likely) to study treatment to the extent permitted by the local circumstances (consent, records) while continuing the planned long-term overall survival follow-up.

The MAH has initiated a readability testing on the package leaflet as reviewed by the CHMP and will submit the results by mid 2008.

The MAH has provided a detailed description of the Risk Management Plan and Pharmacovigilance system confirming a commitment to on going product surveillance. Current ongoing safety concerns relate to cardiotoxicity, renal failure and interstitial lung disease.

Table Summary of the risk management plan

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation (routine and additional)
Infusion-related events	Routine Pharmacovigilance	Information included in the SPC. Routine Pharmacovigilance with specific monitoring of possible renal toxicity and interstitial lung disease, and changes in severity, characteristics of frequency of cardiotoxicity. Renal failure and interstitial lung disease have been identified as potential risks for PLD, but a causal relationship has not been established. Cardiotoxicty is a known risk for both PLD and bortezomib. There may be a concern whether PLD and bortezomib combination therapy would ultimately result in a different cardiac safety profile than that observed at the planned interim analysis of the pivotal trial.
Opportunistic infections	Routine Pharmacovigilance	
Haematologic toxicity	Routine Pharmacovigilance	

It is noted that within the community therapy is available for the treatment of multiple myeloma (MM) which have an orphan designation, this being Revlimid (lenalinomide). This medicinal product is a chemical entity with a different mechanism of action to Caelyx and could clearly be classified as not being similar to Caelyx. S-P has not applied for an orphan designation for the treatment of MM with liposomal doxorubicin, and as such no detail was supplied in the MAA in relation to this.

The three key issues relevant for assessing similarity are molecular structural features, mechanism of action and therapeutic indication.

Doxorubicin is structurally unrelated to lenalinomide and acts via a different mechanism of action. Therefore, doxorubicin and lenalinomide are not similar active substances as defined by Article 3.3c) of Commission Regulation (EC) No 847/2000.

As a result, the 10 year period of market exclusivity afforded to Revlimid for multiple myeloma by way of Article 8.1 “Market exclusivity” of Regulation (EC) No 141/2000 should not preclude the Community from accepting this Type II Variation Application to include use of doxorubicin for the treatment of patients with MM.