IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Pomalidomide (Addendum to Commission A15-42)[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC QLQ-MY20	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Multiple Myeloma Module 20
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HD-dex	high-dose dexamethasone
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LD-dex	low-dose dexamethasone
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

1 Background

On 9 February 2016, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A15-42 (Pomalidomide – Benefit assessment according to §35a Social Code Book (SGB) V [1]).

The pharmaceutical company (hereinafter referred to as "the company") had presented study MM-003 in its dossier on pomalidomide [2]. Based on the information provided in the dossier, the study was assessed as unsuitable in dossier assessment A15-42 for answering the research question of the benefit assessment of pomalidomide. The reason was that the uniform regimen of high-dose dexamethasone (HD-dex) administered to all patients in the comparator arm of the MM-003 study did not concur with the appropriate comparator therapy (ACT) specified by the G-BA (individual targeted therapy specified by the physician), particularly because, in the MM-003 study, HD-dex was not used in compliance with the specifications of the Summary of Product Characteristics (SPC) of dexamethasone [1,3].

To be able to make a decision on the added benefit of pomalidomide, the G-BA commissioned IQWiG with the analysis of the MM-003 study under inclusion of the data cut-offs from 7 September 2012, 1 March 2013 and 1 September 2013.

The responsibility for the present assessment and the results of the assessment lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment of study MM-003

In accordance with the commission, the MM-003 study is assessed in the following sections [4-7]. The company used the MM-003 study for answering the following research question in its dossier [2]: the assessment of the added benefit of pomalidomide in comparison with individual targeted therapy in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 2 prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy, and who are eligible for targeted therapy.

2.1 Study design and study characteristics

Tables presenting the study characteristics and the characteristics of the interventions and the study population can be found in Appendix A of dossier assessment A15-42 [1].

The MM-003 study was a randomized, active-controlled, parallel, open-label approval study. It was conducted in Australia, Europe, North America and Russia. Adult patients with relapsed and refractory multiple myeloma who had received at least 2 prior treatment regimens (including both lenalidomide and bortezomib) and had demonstrated disease progression on the last therapy, were included in the study. The patient population included in the study therefore concurred with the approved therapeutic indication of pomalidomide. 455 patients were randomly assigned in a ratio of 2:1, 302 patients to the pomalidomide arm, and 153 patients to the comparator arm (HD-dex).

The patients in the pomalidomide arm received 4 mg pomalidomide once daily on days 1 to 21 of a 28-day cycle. The patients additionally received 40 mg (patients ≤ 75 years) or 20 mg (patients > 75 years) dexamethasone daily on days 1, 8, 15 and 22 of the 28-day cycle. The treatment regimen of the randomized study treatment with pomalidomide concurred with the description in the SPC [8].

All patients in the HD-dex arm received 40 mg (patients ≤ 75 years) or 20 mg (patients > 75 years) dexamethasone daily on days 1 to 4, 9 to 12, and 17 to 20 of a 28-day cycle. About 92% of the patients in both study arms were aged ≤ 75 years and therefore received the 40 mg dosage of dexamethasone. About 98% of the patients had already been pretreated with dexamethasone at the start of the MM-003 study. As described in dossier assessment A15-42, the dosage in the HD-dex arm was outside the dose range described in the SPC [1].

The patients were to be followed-up over a period of 5 years for the outcomes “overall survival” and “disease progression”; hence the study is still ongoing. Progression-free survival is the primary outcome of the study. The study medication is stopped on achieving the primary outcome; treatment switch (e.g. from HD-dex to pomalidomide) is then possible. The recording of the patient-reported outcomes (symptoms and health-related quality of life) ends with the end of the study medication so that these outcomes are not biased by a possible treatment switch from HD-dex to pomalidomide. Adverse events (AEs) are continued to be

recorded until 28 days after the end of the study medication, which is why they were not affected by relevant bias due to possible treatment switching.

Following the study treatment, the patients in the pomalidomide arm could switch to individually optimized treatment. On achieving the primary outcome, the patients in the HD-dex arm could switch to the one-arm study MM-003/C and hence also to pomalidomide monotherapy, or also to individually optimized treatment. Such individually optimized treatment was frequently chosen in both arms (see Table 6 in Appendix A). It can therefore be assumed that HD-dex was not the only treatment option (besides pomalidomide) for the patients included in the study.

Data cut-offs and data availability

The final analysis for the primary outcome was planned for the time point at which about 242 patients had achieved the primary outcome (progression or death). It was conducted with the data cut-off from 7 September 2012 (first data cut-off). At this time point, the median treatment duration was 12.4 weeks in the pomalidomide arm and 8.0 weeks in the HD-dex arm. The recruitment phase for the MM-003 study ended shortly before this first data cut-off (the first patient was included in the study on 18 March 2011, the last patient on 31 August 2012).

Since the outcome criteria of the study had already been achieved at the time point of the first data cut-off, the data monitoring committee decided on 8 November 2012, with immediate effect, to allow all patients in the HD-dex arm to switch to pomalidomide treatment, irrespective of whether they had already had disease progression. At the time point of the second data cut-off (1 March 2013), 81 (52.9%) of the patients in the HD-dex arm were receiving pomalidomide, at the time point of the third data cut-off (1 September 2013), these were 85 (55.6%) of the patients. The median treatment duration at the first and second data cut-off was 18.2 weeks in the pomalidomide arm and 8.0 weeks in the HD-dex arm.

Table 1 shows for which outcomes data from the individual data cut-off dates were available in the company's dossier.

Table 1: Overview of the data from the MM-003 study available for the assessment

Study **Outcome category** **Outcome**	**Data cut-off**		
	7 September 2012 (first data cut-off)	1 March 2013 (second data cut-off)	1 September 2013 (third data cut-off)
Study MM-003			
Mortality			
All-cause mortality	Yes	Yes	Yes
Morbidity			
Symptom scales EORTC QLQ-C30 and EORTC QLQ-MY20	No[a]	Yes	No
Health-related quality of life			
Scales of the EORTC QLQ-C30 and of the EORTC QLQ-MY20	No[a]	Yes	No
Adverse events			
AEs; SAEs; CTCAE grade 3 to 4, discontinuation due to AEs	Yes	Yes	Yes

a: According to the CSR, a separate result report was to be prepared for this. This report is neither contained in the dossier presented by the company nor in the comments. Further analyses on the first data cut-off are also missing for these outcomes.

AE: adverse event; CSR: clinical study report; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; SAE: serious adverse event

As shown in Table 1, analyses on all relevant outcomes were only available for the second data cut-off from 1 March 2013.

For the first data cut-off from 7 September 2012, in contrast, the company presented the analyses of the patient-reported outcomes (symptoms and health-related quality of life) neither in the dossier nor in the comments. An assessment based on the first data cut-off is therefore not meaningful except for all-cause mortality (due to the lower bias in comparison with the other data cut-offs).

The company did not analyse the data on the patient-reported outcomes for the third data cut-off from 1 September 2013. In its comment [9], the company justified the missing analysis with the fact that the improvement in the quality of life shown with the second data cut-off was considered to be unambiguous. This justification is inadequate. However, it could be inferred from the other analyses on the third data cut-off that no important change of the results for these outcomes could be expected at the third data cut-off: Only few patients (about 10%) in the pomalidomide arm and hardly any patients in the HD-dex arm were continued to be observed after the second data cut-off (see Table 7 and Table 8 in Appendix A). The incompleteness of the data provided at the third data cut-off therefore did not impede conclusions on the basis of the second data cut-off.

In summary, the second data cut-off from 1 March 2013 formed the basis for the present assessment. An exception was the outcome "all-cause mortality", for which the results of the first data cut-off from 7 September 2012 were primarily used because of the very high rate of patients who had switched treatment at the second data cut-off.

2.2 Presentation of the results

Risk of bias

The risk of bias at the study level was rated as low, but there was a high risk of outcome-specific bias for all outcomes. The risk of bias for the outcome "all-cause mortality" was rated as high because of the high number of patients who switched treatment (also at the first data cut-off). The risk or bias for the patient-reported outcomes on symptoms and health-related quality of life was rated as high because of the open-label study design and the great differences in treatment duration. The risk of bias for the outcomes "SAEs", "Common Terminology Criteria for Adverse Events (CTCAE) grade 3 to 4" and "discontinuation due to AEs" was also rated as high because of the great differences in treatment duration between the study arms.

Results

Table 2, Table 3 and Table 4 summarize the results on the comparison of pomalidomide in combination with low-dose dexamethasone (LD-dex) with HD-dex. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations.

Table 2: Results on mortality (survival time analyses) – RCT, direct comparison: pomalidomide + LD-dex vs. HD-dex

Study **Outcome category**	**Pomalidomide + LD-dex**		**HD-dex**		**Pomalidomide + LD-dex vs. HD-dex**
Outcome **Time point**	**N**	**Median survival time in weeks W [95% CI]** **Patients with event n (%)**	**N**	**Median survival time in weeks W [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value**
Study MM-003					
Mortality					
All-cause mortality					
First data cut-off (7 September 2012)	302	NA [48.1; NA] 76 (25.2)	153	34 [23.4; 39.9] 58 (37.9)	0.53 [0.37; 0.74]; < 0.001
Second data cut-off (1 March 2013)	302	54[a] [45.3; 66.4] 147 (48.7)[a]	153	34.9[a] [29.9; 39.1] 86 (56.2)[a]	0.70 [0.54; 0.92]; 0.009[a]

a: Discrepancy between data in Module 4 and 5 of the dossier; presentation of the data from Module 5.
CI: confidence interval; dex: dexamethasone; HD: high-dose; HR: hazard ratio; LD: low-dose; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial; vs.: versus; W: weeks

Table 3: Results on morbidity and health-related quality of life (survival time analyses) – RCT, direct comparison: pomalidomide + LD-dex vs. HD-dex

Study Outcome category Outcome	Pomalidomide + LD-dex N	Pomalidomide + LD-dex Median time to deterioration in days D [95% CI] Patients with event n (%)	HD-dex N	HD-dex Median time to deterioration in days D [95% CI] Patients with event n (%)	Pomalidomide + LD-dex vs. HD-dex HR [95% CI]; p-value
Study MM-003 (second data cut-off)					
Morbidity					
Symptoms (EORTC QLQ-C30)					
Fatigue	289	57.0 [56.00; 64.00] 166 (57.4)	144	57.0 [37.00; 58.00] 71 (49.3)	0.77 [0.58; 1.02]; 0.052
Nausea/vomiting	289	197.0 [143.00; 338.00] 103 (35.6)	144	197.0 [127.00; NA] 30 (20.8)	1.13 [0.75; 1.71]; 0.547
Pain	289	92.0 [85.00; 140.00] 136 (47.1)	144	67.0 [57.00; 141.00] 56 (38.9)	0.75 [0.55; 1.03]; 0.070
Dyspnoea	289	76.0 [60.00; 113.00] 154 (53.3)	144	84.0 [57.00; 222.00] 50 (34.7)	1.17 [0.85; 1.61]; 0.330
Insomnia	289	169.0 [123.00; 257.00] 114 (39.4)	144	57.0 [37.00; 64.00] 64 (44.4)	0.48 [0.35; 0.65]; < 0.001
Appetite loss	289	197.0 [142.00; 254.00] 108 (37.4)	144	131.0 [91.00; 222;00] 40 (27.8)	0.79 [0.55; 1.14]; 0.200
Constipation	289	86.0 [59.00; 121.00] 134 (46.4)	144	265.0 [92.00; NA] 30 (20.8)	1.85 [1.24; 2.75]; 0.002
Diarrhoea	289	255.0 [206.00; 462.00] 85 (29.4)	144	141.0 [106.00; 317.00] 30 (20.8)	0.72 [0.47; 1.10]; 0.122
Symptoms (EORTC QLQ-MY20)					
Disease-related symptoms	289	115.0 [89.00; 143.00] 135 (46.7)	144	86.0 [66.00; 141.00] 55 (38.2)	0.76 [0.55; 1.04]; 0.080
AEs of treatment	289	89.0 [71.00; 120.00] 143 (49.5)	144	71.0 [57.00; 86.00] 63 (43.8)	0.72 [0.53; 0.97]; 0.026

(continued)

Table 3: Results on morbidity and health-related quality of life (survival time analyses) – RCT, direct comparison: pomalidomide + LD-dex vs. HD-dex (continued)

Study Outcome category Outcome	Pomalidomide + LD-dex N	Pomalidomide + LD-dex Median time to deterioration in days D [95% CI] Patients with event n (%)	HD-dex N	HD-dex Median time to deterioration in days D [95% CI] Patients with event n (%)	Pomalidomide + LD-dex vs. HD-dex HR [95% CI]; p-value
Health-related quality of life					
EORTC QLQ-C30					
General health status/ quality of life	289	65.0 [58.00; 86.00] 158 (54.7)	144	57.0 [34.00; 76.00] 64 (44.4)	0.80 [0.60; 1.07]; 0.117
Physical functioning	289	113.0 [86.00; 176.00] 141 (48.8)	144	58.0 [57.00; 84.00] 61 (42.4)	0.63 [0.47; 0.86]; 0.002
Role functioning	289	85.0 [64.00; 108.00] 154 (53.3)	144	57.0 [46.00; 62.00] 69 (47.9)	0.64 [0.48; 0.86]; 0.002
Emotional functioning	289	145.0 [114.00; 230;00] 122 (42.2)	144	64.0 [57.00; 112.00] 59 (41.0)	0.57 [0.41; 0.79]; < 0.001
Social functioning	289	85.0 [58.00; 100.00] 149 (51.6)	144	57.0 [37.00; 85.00] 63 (43.8)	0.80 [0.59; 1.08]; 0.123
Cognitive functioning	289	85.0 [58.00; 112.00] 155 (53.6)	144	58.0 [57.00; 69.00] 64 (44.4)	0.78 [0.58; 1.05]; 0.091
EORTC QLQ-MY20					
Future perspective	289	127.0 [97.00; 229.00] 121 (41.9)	144	66.0 [57.00; 120.00] 54 (37.5)	0.66 [0.47; 0.91]; 0.009
Body image	289	203.0 [150.00; 337.00] 103 (35.6)	144	109.0 [64.00; 219.00] 47 (32.6)	0.68 [0.48; 0.96]; 0.027

AE: adverse event; CI: confidence interval; D: days; dex: dexamethasone; EORTC: European Organisation for Research and Treatment of Cancer; HD: high-dose; HR: hazard ratio; LD: low-dose; N: number of analysed patients; NA: not achieved; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RCT: randomized controlled trial; vs.: versus

Table 4: Results (AEs) – RCT, direct comparison: pomalidomide + LD-dex vs. HD-dex

Study Outcome category	Pomalidomide + LD-dex		HD-dex		Pomalidomide + LD-dex vs. HD-dex
Outcome Time point	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
Study MM-003					
Adverse events					
AEs (supplementary information)	300	297 (99.0)	150	149 (99.3)	
SAEs	300	183 (61.0)	150	80 (53.3)	1.14 [0.96; 1.36]; 0.126
Severe AEs (CTCAE grade 3 to 4)	300	259 (86.3)	150	127 (84.7)	1.02 [0.94; 1.11]; 0.736
Discontinuation due to AEs	300	31 (10.3)	150	16 (10.7)	0.97 [0.55; 1.71]; 0.949

a: Institute's calculation, asymptotic, unconditional exact test (CSZ method according to [10]).

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; dex: dexamethasone; HD: high-dose; LD: low-dose; N: number of analysed patients; n: number of patients with (at least one) event; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Mortality

All-cause mortality

The MM-003 study showed a statistically significant effect in favour of pomalidomide for the outcome "all-cause mortality" at the first data cut-off. This was also shown in the second data cut-off with the effect being of lesser informative value at the second data cut-off due to the high number of patients who had switched treatment.

Morbidity

Disease-related symptoms (EORTC QLQ-C30)

The MM-003 study showed a statistically significant effect in favour of pomalidomide for the outcome **"insomnia"**.

The MM-003 study showed a statistically significant effect to the disadvantage of pomalidomide for the outcome **"constipation**".

The MM-003 study showed no statistically significant difference between the intervention and the control group for the outcomes **"fatigue", "nausea/vomiting", "pain", "dyspnoea", "diarrhoea"** and **"appetite loss"**.

Disease-related symptoms (EORTC QLQ-MY20)

The MM-003 study showed no statistically significant difference between the intervention and the control group for the outcome **"disease-related symptoms"**.

The MM-003 study showed a statistically significant effect in favour of pomalidomide for the outcome **"AEs of treatment"**.

Health-related quality of life

Health-related quality of life (EORTC QLQ-C30)

The MM-003 study showed a statistically significant effect in favour of pomalidomide for each of the outcomes **"physical functioning", "emotional functioning"** and **"role functioning"**.

The MM-003 study showed no statistically significant difference between the intervention and the control group for the outcomes **"general health status/quality of life", "social functioning"** and **"cognitive functioning"**.

Health-related quality of life (EORTC QLQ-MY20)

The MM-003 study showed a statistically significant effect in favour of pomalidomide for each of the outcomes **"future perspective"** and **"body image"**.

Adverse events

Due to the great differences in observation periods between the study arms, a quantitative interpretation of the results on the outcomes "serious adverse events (SAEs)" and "CTCAE grade 3 and 4" based on the rates is not meaningful. The company did not address this problem and presented no survival time analyses of these outcomes for the second data cut-off (also not for the third data cut-off from 1 September 2013). Despite the longer observation period in the pomalidomide arm, no statistically significant difference between the intervention and the control group was shown for the outcomes "SAEs", "severe AEs (CTCAE grade 3 to 4)" and "discontinuations due to AEs", however. Hence a relevant disadvantage of pomalidomide for these outcomes can be excluded.

The company also presented no survival time analyses on specific AEs (only selectively for events with CTCAE grade 3 and 4 for the third data cut-off). The information on specific AEs is therefore presented only as additional information in Appendix B.

2.3 Summary

The following Table 5 shows an overview of the positive and negative effects resulting from the MM-003 study for pomalidomide in combination with LD-dex treatment in comparison with HD-dex treatment.

Table 5: Positive and negative effects for pomalidomide in combination with LD-dex treatment in comparison with HD-dex treatment – study MM-003

Positive effects	**Negative effects**
Mortality ▪ overall survival Health-related quality of life ▪ EORTC QLQ-C30: physical functioning, emotional functioning, role functioning ▪ EORTC QLQ-MY20: future perspective, body image Non-serious/non-severe symptoms ▪ EORTC QLQ-C30: insomnia ▪ EORTC QLQ-MY20: AEs of treatment	Non-serious/non-severe symptoms: EORTC QLQ-C30: constipation
dex: dexamethasone; EORTC: European Organisation for Research and Treatment of Cancer; HD: high-dose; LD: low-dose; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20	

Overall, there was an advantage of pomalidomide in combination with LD-dex treatment in comparison with HD-dex treatment, but dexamethasone was not used in compliance with the specifications in the SPC of dexamethasone in the comparator arm of the underlying MM-003 study.

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Appendix A – Subsequent therapies and treatment duration in the MM-003 study

Table 6: Overview of the subsequent therapies for the treatment of multiple myeloma in the MM-003 study

Celgene Corporation
Protocol: CC-4047-MM-003

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Cutoff Date:01Mar2013

Table 14.2.12.1 UM
Summary of Subsequent Anti Myeloma Therapy- (Intent-to-Treat Population)

Preferred Term [1]	POM+LD-DEX (N=302)	HD-DEX (N=153)	Overall (N=455)
Subjects Who Used at Least One Post Anti-Myeloma Drug	119 (39.4)	88 (57.5)	207 (45.5)
DEXAMETHASONE	76 (25.2)	33 (21.6)	109 (24.0)
CYCLOPHOSPHAMIDE	51 (16.9)	15 (9.8)	66 (14.5)
BORTEZOMIB	45 (14.9)	17 (11.1)	62 (13.6)
BENDAMUSTINE	31 (10.3)	11 (7.2)	42 (9.2)
MELPHALAN	24 (7.9)	7 (4.6)	31 (6.8)
THALIDOMIDE	22 (7.3)	6 (3.9)	28 (6.2)
PREDNISONE	18 (6.0)	9 (5.9)	27 (5.9)
LENALIDOMIDE	14 (4.6)	5 (3.3)	19 (4.2)
ETOPOSIDE	9 (3.0)	3 (2.0)	12 (2.6)
METHYLPREDNISOLONE	9 (3.0)	2 (1.3)	11 (2.4)
DOXORUBICIN HYDROCHLORIDE	8 (2.6)	2 (1.3)	10 (2.2)
CARFILZOMIB	7 (2.3)	0 (0.0)	7 (1.5)
CISPLATIN	6 (2.0)	2 (1.3)	8 (1.8)
DOXORUBICIN	6 (2.0)	3 (2.0)	9 (2.0)
PREDNISOLONE	5 (1.7)	2 (1.3)	7 (1.5)
VINCRISTINE	5 (1.7)	1 (0.7)	6 (1.3)
BLOOD AND BLOOD FORMING ORGANS	3 (1.0)	1 (0.7)	4 (0.9)
ELOTUZUMAB	3 (1.0)	0 (0.0)	3 (0.7)

[1] Preferred terms are based on WHODD March 2011. They are listed in descending order of frequency of POM+LD-DEX Group.
This table is generated by ADATM and ADSL analysis datasets.
Program Path: S:\FRD\projects\CC-4047\CC-4047-MM-003\Programs\Tables\CSR_Label_Update\rpamt01.sas
Run Date: 15OCT2013 Data Extraction Date: 11SEP13:13:13:56

(continued)

Table 6: Overview of the subsequent therapies for the treatment of multiple myeloma in the MM-003 study (continued)

Celgene Corporation
Protocol: CC-4047-MM-003

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Cutoff Date:01Mar2013

Table 14.2.12.1 UM
Summary of Subsequent Anti Myeloma Therapy- (Intent-to-Treat Population)

Preferred Term [1]	POM+LD-DEX (N=302)	HD-DEX (N=153)	Overall (N=455)
BLOOD AND RELATED PRODUCTS	2 (0.7)	0 (0.0)	2 (0.4)
LOMUSTINE	2 (0.7)	0 (0.0)	2 (0.4)
MONOCLONAL ANTIBODIES	2 (0.7)	0 (0.0)	2 (0.4)
ANTINEOPLASTIC AGENTS	1 (0.3)	0 (0.0)	1 (0.2)
BUSULFAN	1 (0.3)	0 (0.0)	1 (0.2)
CARMUSTINE	1 (0.3)	0 (0.0)	1 (0.2)
CYTARABINE	1 (0.3)	0 (0.0)	1 (0.2)
DENOSUMAB	1 (0.3)	0 (0.0)	1 (0.2)
DEXAMETHASONE ACETATE	1 (0.3)	0 (0.0)	1 (0.2)
ENZYME INHIBITORS	1 (0.3)	0 (0.0)	1 (0.2)
HYDROCORTISONE	1 (0.3)	0 (0.0)	1 (0.2)
INTERFERON	1 (0.3)	0 (0.0)	1 (0.2)
INVESTIGATIONAL DRUG	1 (0.3)	0 (0.0)	1 (0.2)
LIPOSOMAL DOXORUBICIN HYDROCHLORIDE	1 (0.3)	0 (0.0)	1 (0.2)
MARIZOMIB	1 (0.3)	0 (0.0)	1 (0.2)
METHYLPREDNISOLONE SODIUM SUCCINATE	1 (0.3)	0 (0.0)	1 (0.2)
PAMIDRONATE DISODIUM	1 (0.3)	0 (0.0)	1 (0.2)
PROTEIN KINASE INHIBITORS	1 (0.3)	0 (0.0)	1 (0.2)
RITUXIMAB	1 (0.3)	0 (0.0)	1 (0.2)

[1] Preferred terms are based on WHODD March 2011. They are listed in descending order of frequency of POM+LD-DEX Group.
This table is generated by ADATM and ADSL analysis datasets.
Program Path: S:\PRD\projects\CC-4047\CC-4047-MM-003\Programs\Tables\CSR_Label_Update\rpamt01.sas
Run Date: 15OCT2013 Data Extraction Date: 11SEP13:13:13:56

(continued)

Table 6: Overview of the subsequent therapies for the treatment of multiple myeloma in the MM-003 study (continued)

Celgene Corporation
Protocol: CC-4047-MM-003

Cutoff Date:01Mar2013

Table 14.2.12.1 UM
Summary of Subsequent Anti Myeloma Therapy- (Intent-to-Treat Population)

Preferred Term [1]	POM+LD-DEX (N=302)	HD-DEX (N=153)	Overall (N=455)
THIOTEPA	1 (0.3)	0 (0.0)	1 (0.2)
VINCRISTINE SULFATE	1 (0.3)	0 (0.0)	1 (0.2)
VINDESINE	1 (0.3)	0 (0.0)	1 (0.2)
VORINOSTAT	1 (0.3)	0 (0.0)	1 (0.2)
ZOLEDRONIC ACID	1 (0.3)	0 (0.0)	1 (0.2)
DEXCHLORPHENIRAMINE MALEATE	0 (0.0)	1 (0.7)	1 (0.2)
DOXYCYCLINE	0 (0.0)	1 (0.7)	1 (0.2)
ONDANSETRON	0 (0.0)	1 (0.7)	1 (0.2)
PARACETAMOL	0 (0.0)	1 (0.7)	1 (0.2)
POMALIDOMIDE	0 (0.0)	72 (47.1)	72 (15.8)

[1] Preferred terms are based on WHODD March 2011. They are listed in descending order of frequency of POM+LD-DEX Group.
This table is generated by ADATM and ADSL analysis datasets.
Program Path: S:\PRD\projects\CC-4047\CC-4047-MM-003\Programs\Tables\CSR_Label_Update\rpamt01.sas
Run Date: 15OCT2013 Data Extraction Date: 11SEP13:13:13:56

Table 7: Overview of the treatment duration in the MM-003 study at the second data cut-off (1 March 2013)

Celgene Corporation
Protocol: CC-4047-MM-003

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Cutoff Date:01Mar2013

Table 14.1.2.1 UM
Summary of Treatment Duration for Overall Treatment - (Safety Population)

	POM+LD-DEX (N=300)	HD-DEX (N=150)	Overall (N=450)
Treatment Duration (Weeks) [1]			
n	300	150	450
Mean	24.0	13.3	20.5
SD	18.26	12.56	17.32
Median	18.2	8.0	13.7
Min, Max	0.4, 93.1	0.7, 69.3	0.4, 93.1
Treatment Duration (Weeks) [1] n(%)			
LESS THAN 1 WEEK	3 (1.0)	3 (2.0)	6 (1.3)
1 TO <4 WEEKS	12 (4.0)	10 (6.7)	22 (4.9)
4 TO <8 WEEKS	41 (13.7)	44 (29.3)	85 (18.9)
8 TO <12 WEEKS	38 (12.7)	39 (26.0)	77 (17.1)
12 TO <16 WEEKS	37 (12.3)	14 (9.3)	51 (11.3)
16 TO <20 WEEKS	25 (8.3)	11 (7.3)	36 (8.0)
20 TO <24 WEEKS	14 (4.7)	3 (2.0)	17 (3.8)
24 TO <28 WEEKS	13 (4.3)	7 (4.7)	20 (4.4)
28 TO <32 WEEKS	18 (6.0)	7 (4.7)	25 (5.6)
32 TO <36 WEEKS	25 (8.3)	1 (0.7)	26 (5.8)
36 TO <40 WEEKS	17 (5.7)	3 (2.0)	20 (4.4)
40 TO <44 WEEKS	12 (4.0)	1 (0.7)	13 (2.9)
44 TO <48 WEEKS	6 (2.0)	2 (1.3)	8 (1.8)
48 TO <52 WEEKS	10 (3.3)	1 (0.7)	11 (2.4)
52 TO <56 WEEKS	9 (3.0)	1 (0.7)	10 (2.2)
56 TO <60 WEEKS	5 (1.7)	2 (1.3)	7 (1.6)
60 TO <64 WEEKS	2 (0.7)	0 (0.0)	2 (0.4)
>=64 WEEKS	13 (4.3)	1 (0.7)	14 (3.1)
Number of Cycles on Study Medications			
n	300	150	450
Mean	5.9	3.5	5.1
SD	4.35	2.99	4.11
Median	5.0	2.0	4.0
Min, Max	1.0, 23.0	1.0, 17.0	1.0, 23.0

[1] Treatment duration is calculated by [(last cycle end date of the study drug) - (the first dose date of the study drug) + 1]/7.
This table is generated by ADEX and ADSL analysis datasets.
Program Path: S:\PRD\projects\CC-4047\CC-4047-MM-003\Programs\Tables\CSR_Label_Update\rex01.sas
Run Date: 15OCT2013

Data Extraction Date: 11SEP13:13:13:56

Table 8: Overview of the treatment duration in the MM-003 study at the third data cut-off (1 September 2013)

Celgene Corporation
Protocol: CC-4047-MM-003

Page 1 of 1
Cutoff Date:01SEP2013

Table 14.1.2.1 UM
Summary of Treatment Duration for Overall Treatment - (Safety Population)

	POM+LD-DEX (N=300)	HD-DEX (N=150)	Overall (N=450)
Treatment Duration (Weeks) [1]			
n	300	150	450
Mean	28.1	14.7	23.6
SD	24.68	16.57	23.16
Median	18.2	8.0	13.7
Min, Max	0.4, 114.1	0.7, 95.3	0.4, 114.1
Treatment Duration (Weeks) [1] n(%)			
LESS THAN 1 WEEK	3 (1.0)	3 (2.0)	6 (1.3)
1 TO <4 WEEKS	12 (4.0)	10 (6.7)	22 (4.9)
4 TO <8 WEEKS	41 (13.7)	44 (29.3)	85 (18.9)
8 TO <12 WEEKS	38 (12.7)	39 (26.0)	77 (17.1)
12 TO <16 WEEKS	37 (12.3)	14 (9.3)	51 (11.3)
16 TO <20 WEEKS	25 (8.3)	11 (7.3)	36 (8.0)
20 TO <24 WEEKS	14 (4.7)	3 (2.0)	17 (3.8)
24 TO <28 WEEKS	12 (4.0)	7 (4.7)	19 (4.2)
28 TO <32 WEEKS	15 (5.0)	4 (2.7)	19 (4.2)
32 TO <36 WEEKS	12 (4.0)	1 (0.7)	13 (2.9)
36 TO <40 WEEKS	11 (3.7)	1 (0.7)	12 (2.7)
40 TO <44 WEEKS	12 (4.0)	0 (0.0)	12 (2.7)
44 TO <48 WEEKS	8 (2.7)	2 (1.3)	10 (2.2)
48 TO <52 WEEKS	3 (1.0)	1 (0.7)	4 (0.9)
52 TO <56 WEEKS	9 (3.0)	0 (0.0)	9 (2.0)
56 TO <60 WEEKS	9 (3.0)	4 (2.7)	13 (2.9)
60 TO <64 WEEKS	8 (2.7)	3 (2.0)	11 (2.4)
>=64 WEEKS	31 (10.3)	3 (2.0)	34 (7.6)
Number of Cycles on Study Medications			
n	300	150	450
Mean	6.9	3.8	5.9
SD	5.91	3.84	5.51
Median	5.0	2.0	4.0
Min, Max	1.0, 29.0	1.0, 23.0	1.0, 29.0

[1] Treatment duration is calculated by [(last cycle end date of the study drug) - (the first dose date of the study drug) + 1]/7.
This table is generated by ADEX and ADSL analysis datasets.
Program Path: S:\DEV\projects\CC-4047\CC-4047-MM-003\Programs\Tables\CSR_Label_Update\rex01.sas
Run Date: 25NOV2013

Data Extraction Date: 13NOV13:08:49:51

Appendix B – Results on AEs, naive proportions of patients with events

Table 9: Common AEs (≥ 5% in at least one study arm) – RCT, direct comparison: pomalidomide + LD-dex vs. HD-dex

Study	Patients with event n (%)	
SOC[a] PT[a]	Pomalidomide + LD-dex N = 300	HD-dex N = 150
Study MM-003		
Overall rate of adverse events	297 (99.0)	149 (99.3)
Blood and lymphatic system disorders	229 (76.3)	101 (67.3)
Anaemia	156 (52.0)	78 (52.0)
Neutropenia	154 (51.3)	31 (20.7)
Thrombocytopenia	89 (29.7)	44 (29.3)
Leukopenia	38 (12.7)	8 (5.3)
Febrile neutropenia	28 (9.3)	0 (0)
Lymphopenia	13 (4.3)	8 (5.3)
General disorders and administration site conditions	224 (74.7)	96 (64.0)
Fatigue	101 (33.7)	41 (27.3)
Fever	80 (26.7)	35 (23.3)
Asthenia	50 (16.7)	28 (18.7)
Oedema peripheral	52 (17.3)	17 (11.3)
General physical health deterioration	35 (11.7)	16 (10.7)
Infections and infestations	203 (67.7)	79 (52.7)
Upper respiratory tract infection	48 (16.0)	11 (7.3)
Pneumonia	45 (15.0)	16 (10.7)
Bronchitis	30 (10.0)	8 (5.3)
Nasopharyngitis	25 (8.3)	1 (0.7)
Urinary tract infection	16 (5.3)	12 (8.0)
Respiratory tract infection	18 (6.0)	5 (3.3)
Lower respiratory tract infection	8 (2.7)	8 (5.3)
Gastrointestinal disorders	178 (59.3)	63 (42.0)
Diarrhoea	66 (22.0)	28 (18.7)
Constipation	65 (21.7)	22 (14.7)
Nausea	45 (15.0)	17 (11.3)
Vomiting	23 (7.7)	6 (4.0)

(continued)

Table 9: Common AEs (≥ 5% in at least one study arm) – RCT, direct comparison: pomalidomide + LD-dex vs. HD-dex (continued)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Pomalidomide + LD-dex N = 300**	**HD-dex N = 150**
Musculoskeletal and connective tissue disorders	162 (54.0)	84 (56.0)
Back pain	59 (19.7)	24 (16.0)
Bone pain	54 (18.0)	21 (14.0)
Muscle spasms	46 (15.3)	11 (7.3)
Muscular weakness	9 (3.0)	20 (13.3)
Arthralgia	26 (8.7)	7 (4.7)
Myopathy	3 (1.0)	11 (7.3)
Pain in extremity	20 (6.7)	9 (6.0)
Respiratory, thoracic and mediastinal disorders	151 (50.3)	49 (32.7)
Cough	60 (20.0)	15 (10.0)
Dyspnoea	59 (19.7)	22 (14.7)
Epistaxis	28 (9.3)	16 (10.7)
Exertional dyspnoea	18 (6.0)	3 (2.0)
Metabolism and nutrition disorders	117 (39.0)	65 (43.3)
Decreased appetite	38 (12.7)	12 (8.0)
Hypercalcaemia	21 (7.0)	16 (10.7)
Hypokalaemia	28 (9.3)	12 (8.0)
Hyperglycaemia	18 (6.0)	13 (8.7)
Dehydration	16 (5.3)	10 (6.7)
Hypocalcaemia	12 (4.0)	9 (6.0)
Nervous system disorders	129 (43.0)	56 (37.3)
Dizziness	37 (12.3)	14 (9.3)
Peripheral sensory neuropathy	24 (8.0)	4 (2.7)
Headache	23 (7.7)	8 (5.3)
Tremor	17 (5.7)	2 (1.3)
Psychiatric disorders	88 (29.3)	56 (37.3)
Insomnia	32 (10.7)	32 (21.3)
Confusional state	13 (4.3)	10 (6.7)
Anxiety	11 (3.7)	9 (6.0)
Agitation	15 (5.0)	7 (4.7)
Skin and subcutaneous tissue disorders	94 (31.3)	28 (18.7)
Rash	23 (7.7)	2 (1.3)
Pruritus	22 (7.3)	5 (3.3)
Hyperhidrosis	15 (5.0)	1 (0.7)

(continued)

Table 9: Common AEs (≥ 5% in at least one study arm) – RCT, direct comparison: pomalidomide + LD-dex vs. HD-dex (continued)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Pomalidomide + LD-dex N = 300**	**HD-dex N = 150**
Investigations	86 (28.7)	31 (20.7)
Blood creatinine increased	17 (5.7)	8 (5.3)
Neutrophil count decreased	15 (5.0)	1 (0.7)
Vascular disorders	54 (18.0)	21 (14.0)
Renal and urinary disorders	52 (17.3)	24 (16.0)
Renal failure acute	14 (4.7)	9 (6.0)
Renal failure	15 (5.0)	5 (3.3)
Cardiac disorders	48 (16.0)	24 (16.0)
Injury, poisoning and procedural complications	41 (13.7)	18 (12.0)
Eye disorders	37 (12.3)	16 (10.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	17 (5.7)	7 (4.7)

a: MedDRA version 14.0.

dex: dexamethasone; HD: high-dose; LD: low-dose; MedDRA: Medical Dictionary for Regulatory Activities; N: number of analysed patients; n: number of patients with (at least one) event; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 10: Common SAEs (≥ 2% in at least one study arm) – RCT, direct comparison: pomalidomide + LD-dex vs. HD-dex

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Pomalidomide + LD-dex N = 300**	**HD-dex N = 150**
Study MM-003		
Overall rate of serious adverse events	183 (61.0)	80 (53.3)
Infections and infestations	96 (32.0)	39 (26.0)
Pneumonia	39 (13.0)	13 (8.7)
Sepsis	7 (2.3)	3 (2.0)
Upper respiratory tract infection	6 (2.0)	1 (0.7)
Lower respiratory tract infection	5 (1.7)	4 (2.7)
Septic shock	3 (1.0)	6 (4.0)
Urinary tract infection	0 (0)	5 (3.3)
General disorders and administration site conditions	57 (19.0)	22 (14.7)
General physical health deterioration	26 (8.7)	12 (8.0)
Fever	23 (7.7)	7 (4.7)
Blood and lymphatic system disorders	33 (11.0)	14 (9.3)
Febrile neutropenia	17 (5.7)	0 (0)
Anaemia	10 (3.3)	7 (4.7)
Neutropenia	9 (3.0)	1 (0.7)
Thrombocytopenia	6 (2.0)	4 (2.7)
Renal and urinary disorders	25 (8.3)	10 (6.7)
Renal failure acute	11 (3.7)	7 (4.7)
Renal failure	8 (2.7)	1 (0.7)
Musculoskeletal and connective tissue disorders	25 (8.3)	8 (5.3)
Bone pain	10 (3.3)	1 (0.7)
Back pain	8 (2.7)	2 (1.3)
Metabolism and nutrition disorders	22 (7.3)	12 (8.0)
Hypercalcaemia	13 (4.3)	5 (3.3)
Hyperglycaemia	1 (0.3)	3 (2.0)
Nervous system disorders	19 (6.3)	10 (6.7)
Cardiac disorders	18 (6.0)	8 (5.3)
Respiratory, thoracic and mediastinal disorders	20 (6.7)	8 (5.3)
Dyspnoea	7 (2.3)	1 (0.7)
Gastrointestinal disorders	12 (4.0)	5 (3.3)

(continued)

Table 10: Common SAEs (≥ 2% in at least one study arm) – RCT, direct comparison: pomalidomide + LD-dex vs. HD-dex (continued)

Study	Patients with event n (%)	
SOC[a] PT[a]	Pomalidomide + LD-dex N = 300	HD-dex N = 150
Injury, poisoning and procedural complications	12 (4.0)	4 (2.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (2.3)	5 (3.3)
Psychiatric disorders	4 (1.3)	4 (2.7)
Confusional state	3 (1.0)	3 (2.0)
Vascular disorders	7 (2.3)	1 (0.7)
Investigations	3 (1.0)	3 (2.0)

a: MedDRA version 14.0.

dex: dexamethasone; HD: high-dose; LD: low-dose; MedDRA: Medical Dictionary for Regulatory Activities; N: number of analysed patients; n: number of patients with (at least one) event; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 11: Common discontinuation due to AEs (≥ 1% in at least one study arm) – RCT, direct comparison: pomalidomide + LD-dex vs. HD-dex

Study	Patients with event n (%)	
SOC[a] PT[a]	Pomalidomide + LD-dex[b] N = 300	HD-dex N = 150
Study MM-003		
Overall rate of discontinuations due to AEs	28 (9.3)	16 (10.7)
Infections and infestations	8 (2.7)	4 (2.7)
Lower respiratory tract infection	0 (0)	2 (1.3)
Blood and lymphatic system disorders	4 (1.3)	0 (0)
Thrombocytopenia	3 (1.0)	0 (0)
Renal and urinary disorders	3 (1.0)	1 (0.7)
General disorders and administration site conditions	2 (0.7)	2 (1.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3)	2 (1.3)
Psychiatric disorders	1 (0.3)	2 (1.3)

a: MedDRA version 14.0.
b: AEs that led to discontinuation of dexamethasone.

AE: adverse event; dex: dexamethasone; HD: high-dose; LD: low-dose; MedDRA: Medical Dictionary for Regulatory Activities; N: number of analysed patients; n: number of patients with (at least one) event; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 12: Common AEs with CTCAE grade 3 to 4 (≥ 5% in at least one study arm) – RCT, direct comparison: pomalidomide + LD-dex vs. HD-dex

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Pomalidomide + LD-dex N = 300**	**HD-dex N = 150**
Study MM-003		
Overall rate of common AEs with CTCAE grade 3 to 4	259 (86.3)	127 (84.7)
Blood and lymphatic system disorders	203 (67.7)	85 (56.7)
Neutropenia	145 (48.3)	24 (16.0)
Anaemia	98 (32.7)	58 (38.7)
Thrombocytopenia	66 (22.0)	39 (26.0)
Febrile neutropenia	28 (9.3)	0 (0)
Leukopenia	27 (9.0)	5 (3.3)
Infections and infestations	90 (30.0)	36 (24.0)
Pneumonia	38 (12.7)	12 (8.0)
General disorders and administration site conditions	62 (20.7)	37 (24.7)
General physical health deterioration	24 (8.0)	12 (8.0)
Asthenia	11 (3.7)	10 (6.7)
Fatigue	16 (5.3)	9 (6.0)
Metabolism and nutrition disorders	58 (19.3)	33 (22.0)
Hyperglycaemia	11 (3.7)	11 (7.3)
Musculoskeletal and connective tissue disorders	49 (16.3)	30 (20.0)
Bone pain	22 (7.3)	7 (4.7)
Back pain	15 (5.0)	6 (4.0)
Investigations	40 (13.3)	12 (8.0)
Nervous system disorders	30 (10.0)	18 (12.0)
Respiratory, thoracic and mediastinal disorders	36 (12.0)	13 (8.7)
Dyspnoea	15 (5.0)	7 (4.7)
Psychiatric disorders	17 (5.7)	15 (10.0)
Gastrointestinal disorders	24 (8.0)	10 (6.7)
Renal and urinary disorders	22 (7.3)	8 (5.3)
Cardiac disorders	17 (5.7)	10 (6.7)

a: MedDRA version 14.0.
b: CTCAE version: 4.0.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; HD: high-dose; LD: low-dose; MedDRA: Medical Dictionary for Regulatory Activities; N: number of analysed patients; n: number of patients with (at least one) event; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus