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Eribulin (liposarcoma) –

Addendum to Commission A16-31[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
AJCC	American Joint Committee on Cancer
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
QLQ-C30	Quality of Life Questionnaire-Core 30
SAE	serious adverse events
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
VAS	visual analogue scale

1 Background

On 11 October 2016, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A16-31 (Eribulin – Benefit assessment according to §35a Social Code Book (SGB) V [1]).

The pharmaceutical company (hereinafter referred to as "the company") had presented study E7389-G000-309 (hereinafter referred to as "study 309") in its dossier on eribulin [2]. Based on the information provided in the dossier, the study was assessed as unsuitable in dossier assessment A16-31 for answering the research question of the benefit assessment of eribulin. The reason for this was that the regimen with dacarbazine administered to the patients in the comparator arm of study 309 was not in compliance with the information provided in the Summary of Product Characteristics (SPC) for the treatment of soft tissue sarcoma, which constituted an off-label use [1,3].

To be able to make a decision on the added benefit of eribulin, the G-BA commissioned IQWiG with the assessment of study 309.

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

In accordance with the commission, study 309 is assessed in the following sections [4-7].

2.1 Study design and study characteristics

Tables presenting the characteristics of the study and of the interventions can be found in Appendix A of dossier assessment A16-31 [1].

Study 309 was a multicentre, randomized, controlled, unblinded study. The study was conducted in 110 centres worldwide. Adult patients with unresectable liposarcoma or leiomyosarcoma were included in the study. A further criterion required for inclusion in the study was pretreatment with at least 2 standard systemic regimens for advanced soft tissue sarcoma, one of which had to include an anthracycline (unless contraindicated). The patients were stratified by histology (liposarcoma versus leiomyosarcoma), geographical region (USA/Canada versus Western Europe/Australia/Israel versus Eastern Europe/Latin America/Asia) and number of prior therapies for advanced soft tissue sarcoma (2 versus > 2). A total of 452 patients were randomized in a ratio of 1:1, 228 patients to the eribulin arm and 224 patients to the comparator arm (dacarbazine monotherapy). The patient population included in the study only partly concurred with the approved therapeutic indication. The relevant subpopulation of the patients with liposarcoma (according to stratification) comprised 71 patients (31.1%) in the eribulin arm and 72 patients (32.1%) in the comparator arm.

The patients in the eribulin arm received a dosage of 1.23 mg/m² body surface area as an intravenous infusion over 2 to 5 minutes on day 1 and day 8 of every 21-day cycle. This treatment regimen concurs with the description in the SPC [8]. The criteria for dose delay, dose modification or treatment discontinuation also concur with the SPC. Patients in the comparator arm received dacarbazine as monotherapy at a dosage of 850 mg/m^2, 1000 mg/m^2 or 1200 mg/m^2 body surface area as an intravenous infusion over 15 to 30 minutes on day 1 of every 21-day cycle. The respective dose of dacarbazine was determined by the investigator for each patient before randomization. As described in dossier assessment A16-31, this treatment regimen does not comply with the regimen described in the SPC for the treatment of soft tissue sarcoma [1,3].

All patients could receive or continue concomitant medication that was necessary for the patient's health and that was not expected to interact with the study medication or influence the analysis of the study. Any other anti-tumour treatment including radiotherapy was not allowed.

The patients were to be treated until progression of the disease or unacceptable toxicity occurred or consent was withdrawn.

The primary analysis was planned after about 353 deaths. The data cut-off was on 2 January 2015. 357 patients had died at this time point. In study 309, this first treatment and follow-up phase until the primary analysis was designated as randomization phase. Patients who were still under treatment or observation at the time point of the primary analysis continued treatment according to their randomization and were observed in the extension phase. There was no crossover. A planned interim analysis was conducted after 247 deaths (70% of the events required for the primary analysis).

Overall survival was the primary outcome of study 309. Further patient-relevant outcomes were symptoms, health status, health-related quality of life and side effects.

Table 1 shows the planned duration of follow-up of the patients for the individual outcomes.

Table 1: Planned duration of follow-up – RCT, direct comparison: eribulin vs. dacarbazine monotherapy

Study **Outcome category** **Outcome**	**Planned follow-up**
309	
Mortality	
Overall survival	Every 12 weeks until death
Morbidity	
Symptoms (EORTC QLQ-C30)	Until the last study visit within 30 days after the end of treatment; no follow-up planned afterwards
Health status (EQ-5D VAS)	Until the last study visit within 30 days after the end of treatment; no follow-up planned afterwards
Health-related quality of life	
EORTC QLQ-C30	Until the last study visit within 30 days after the end of treatment; no follow-up planned afterwards
Side effects	
AEs/SAEs/AEs CTCAE grade 3 or 4	30 days after administration of the last treatment dose

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Table 2 shows the characteristics of the patients with liposarcoma in study 309.

Table 2: Characteristics of the study population – RCT, direct comparison: eribulin vs. dacarbazine monotherapy

Study **Characteristics** **Category**	**Eribulin**	**Dacarbazine**
309	N[a] = 71	N[a] = 72
Age [years], mean (SD)	55 (11)	56 (11)
Sex [F/M], %	46/54	29/71
Ethnicity, n (%)		
Caucasian	52 (73.2)	51 (70.8)
Non-Caucasian	6 (8.5)[b]	7 (9.7)[b]
Not determined	13 (18.3)	14 (19.4)
ECOG PS, n (%)		
0	35 (49.3)	24 (33.3)
1	34 (47.9)	42 (58.3)
2	2 (2.8)	6 (8.3)
Disease duration: time between first diagnosis and randomization [months], mean (SD)	ND[c]	ND[c]
Tumour grade, n (%)		
High	38 (53.5)	39 (54.2)
Intermediate	32 (45.1)	32 (44.4)
Not conducted	1 (1.4)	1 (1.4)
Number of prior regimens for advanced soft tissue sarcoma, n (%)		
2	39 (54.9[b])	41 (56.9[b])
> 2	32 (45.1[b])	31 (43.1[b])
Geographical region, n (%)		
Region 1: USA and Canada	25 (35.2)	25 (34.7)
Region 2: Western Europe, Australia, Israel	36 (50.7)	37 (51.4)
Region 3: Eastern Europe, Latin America, Asia	10 (14.1)	10 (13.9)
Treatment discontinuation, n (%)	ND[c]	ND[c]
Study discontinuation, n (%)	ND[c]	ND[c]

a: Number of randomized patients.
b: Institute's calculation.
c: No information for the relevant subpopulation of the patients with liposarcoma.
ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The demographic and disease-specific patient characteristics were mostly comparable between the study arms. The mean age of the patients in the relevant subpopulation of study 309 was 55 and 56 years (eribulin and dacarbazine arm). The majority of the patients in both treatment arms were male; the proportion of men was notably larger in the dacarbazine arm (71%) than in the eribulin arm (54%). The majority of the patients were of Caucasian

origin (73.2% in the eribulin arm and 70.8% in the dacarbazine arm); ethnicity was not determined in almost 20% of the patients due to country-specific requirements. About half of the patients were from Western Europe, Australia and Israel; slightly over one third of the patients were from the United States and Canada. Overall, the Eastern Cooperative Oncology Group Performance Status (ECOG PS) in patients in the dacarbazine arm was worse than in the eribulin arm. About half of the patients in the eribulin arm and only one third of the patients in the dacarbazine arm had an ECOG PS of 0. The proportion of patients with an ECOG PS of 1 or 2 was higher in each case in the dacarbazine arm than in the eribulin arm. The number of prior regimens for advanced soft tissue sarcoma in both treatment arms was comparable: About 55% of the patients had received 2 regimens; about 45% of the patients had received more than 2 regimens. There was no information on disease duration since first diagnosis for the relevant subpopulation. The same applied to the proportion of patients who discontinued treatment or the total study.

Table 3 shows the mean/median treatment duration of the patients with liposarcoma and the follow-up period for individual outcomes.

Table 3: Information on the course of the study – RCT, direct comparison: eribulin vs. dacarbazine monotherapy

Study **Duration of the study phase** **Outcome category**	**Eribulin**	**Dacarbazine**
309	N = 71	N = 72
Treatment duration [weeks][a]		
Median [min; max]	ND	ND
Mean (SD)	ND	ND
Observation period [days]		
Overall survival	ND	ND
Morbidity	ND	ND
Health-related quality of life	ND	ND
Side effects[b]		
Median [min; max]	97.5 [15; 478]	51.0 [7; 407]
Mean (SD)	151.3 (131.95)	79.7 (68.95)

a: There are no data for the relevant subpopulation.
b: Number of patients in the "safety analysis set": eribulin N=70; dacarbazine N=70 (information in Table 4-49 of Module 4; according to the tables on results on side effects, the „safety analysis set" comprises 72 patients under dacarbazine).
max: maximum; min: minimum; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

2.2 Presentation of the results

Risk of bias

The risk of bias at study level was rated as low. However, there was a high risk of bias at outcome level for all outcomes except overall survival. Due to the open-label study design in subjective recording of outcomes and potentially informative censoring, the risk of bias was rated as high for the patient-reported outcomes on symptoms (symptom scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30]), health status (visual analogue scale [VAS] of the European Quality of Life-5 Dimensions [EQ-5D]) and health-related quality of life (functional scales of the EORTC QLQ-C30). In addition, there was a high risk of bias for the outcome "health status" (EQ-5D VAS) because more than 10% of the patients in the relevant subpopulation were not considered in the analysis or because the proportion of patients not considered differed by more than 5 percentage points between the study arms (eribulin: 15.5%; dacarbazine: 20.8%). The outcomes "serious adverse events (SAEs)", "severe adverse events (AEs)" (Common Terminology Criteria for Adverse Events [CTCAE] grade 3 or 4) and "discontinuation due to AEs" were also considered to have a high risk of bias due to the great differences in follow-up period between the treatment arms and potentially informative censoring.

Results

Table 4, Table 5 and Table 6 summarize the results on the comparison of eribulin and dacarbazine. The Kaplan-Meier curve on overall survival is presented in Appendix A of the full dossier assessment. Where necessary, the data from the company's dossier were supplemented with the Institute's calculations.

Table 4: Results on mortality (survival time analyses) – RCT, direct comparison: eribulin vs. dacarbazine monotherapy

Study	**Eribulin**		**Dacarbazine**		**Eribulin vs. dacarbazine**
Outcome category **Outcome**	**N**	**Median survival time in months [95% CI]** **Patients with event n (%)**	**N**	**Median survival time in months [95% CI]** **Patients with event n (%)**	**HR[a] [95% CI]; p-value**
309					
Mortality					
Overall survival	71	15.6 [10.2; 18.6] 52 (73.2)	72	8.4 [5.2; 10.1] 63 (87.5)	0.51 [0.35; 0.75] < 0.001

a: Cox proportional hazards model stratified by geographical region and number of prior regimens for advanced soft tissue sarcoma.

CI: confidence interval; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; RCT: randomized controlled trial; vs.: versus

Table 5: Results on morbidity (symptoms), health-related quality of life, side effects (survival time analyses) – RCT, direct comparison: eribulin vs. dacarbazine monotherapy

Study Outcome category Outcome Subscale	Eribulin N	Eribulin Median time to event in days [95% CI] Patients with event n (%)	Dacarbazine N	Dacarbazine Median time to event in days [95% CI] Patients with event n (%)	Eribulin vs. dacarbazine HR[a] [95% CI]; p-value
Morbidity (symptoms)					
EORTC QLQ-C30 symptom scales – time to deterioration[b]					
Fatigue	65	43 [29; 50] 47 (72.3)	66	43 [41; 50] 46 (69.7)	1.02 [0.66; 1.57]; 0.927
Nausea and vomiting	65	165 [78; 421] 29 (44.6)	66	218 [78; 218] 20 (30.3)	1.01 [0.55; 1.86]; 0.983
Pain	65	93 [64; 116] 35 (53.8)	66	57 [42; 176] 34 (51.5)	0.74 [0.45; 1.23]; 0.244
Dyspnoea	65	127 [85; NC] 28 (43.1)	66	77 [50; 142] 29 (43.9)	0.69 [0.40; 1.17]; 0.167
Insomnia	63	110 [70; 239] 31 (49.2)	65	64 [43; 78] 36 (55.4)	0.52 [0.32; 0.88]; 0.012
Appetite loss	65	106 [64; 232] 34 (52.3)	66	69 [43; 113] 31 (47.0)	0.64 [0.38; 1.08]; 0.094
Constipation	65	123 [64; 176] 34 (52.3)	66	78 [50; NC] 28 (42.4)	0.86 [0.50; 1.46]; 0.568
Diarrhoea	65	378 [127; NC] 21 (32.3)	66	330 [NC; NC] 13 (19.7)	1.14 [0.55; 2.34]; 0.725
Health-related quality of life					
EORTC QLQ-C30 functional scales – time to deterioration[c]					
Global health status	65	113 [64; 197] 34 (52.3)	66	50 [43; 64] 36 (54.5)	0.62 [0.38; 1.03]; 0.065
Physical functioning	65	176 [50; 386] 30 (46.2)	65	50 [43; 69] 38 (58.5)	0.55 [0.33; 0.91]; 0.019
Role functioning	65	71 [43; 125] 38 (58.5)	66	43 [41; 64] 42 (63.6)	0.76 [0.48; 1.21]; 0.251
Emotional functioning	65	267 [165; NC] 24 (36.9)	65	176 [50; NC] 25 (38.5)	0.56 [0.30; 1.02]; 0.055
Cognitive functioning	64	78 [50; 160] 36 (56.2)	63	113 [50; NC] 25 (39.7)	1.29 [0.76; 2.18]; 0.342
Social functioning	65	244 [106; NC] 24 (36.9)	66	64 [43; 85] 37 (56.1)	0.35 [0.20; 0.62]; < 0.001

(continued)

Table 5: Results on morbidity (symptoms), health-related quality of life, side effects (survival time analyses) – RCT, direct comparison: eribulin vs. dacarbazine monotherapy (continued)

Study Outcome category Outcome Subscale	Eribulin N	Eribulin Median time to event in days [95% CI] Patients with event n (%)	Dacarbazine N	Dacarbazine Median time to event in days [95% CI] Patients with event n (%)	Eribulin vs. dacarbazine HR[a] [95% CI]; p-value
Side effects					
AEs (supplementary information)	70	3.5 [2.0; 7.0] 70 (100[d])	72	4.0 [3.0; 7.0] 69 (95.8[d])	-
SAEs	70	442.0 [148.0; NC] 22 (31.4[d])	72	NA [88.0; NC] 22 (30.6[d])	0.78 [0.42; 1.46]; 0.434
Discontinuation due to AEs	70	NA [442.0; NC] 5 (7.1[d])	72	NA [NC; NC] 4 (5.6[d])	0.41 [0.09; 1.96]; 0.257
Severe AEs (CTCAE grade 3 or 4)	70	49.5 [18.0; 109.0] 44 (62.9[d])	72	81.0 [31.0; NC] 37 (51.4[d])	1.24 [0.79; 1.94]; 0.348

a: Cox proportional hazards model stratified by geographical region and number of prior regimens for advanced soft tissue sarcoma.
b: Increase in score by at least 10 points versus the baseline value.
c: Decrease in score by at least 10 points versus the baseline value.
d: Institute's calculation.
AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Table 6: Results on morbidity (health status) (continuous outcomes) – RCT, direct comparison: eribulin vs. dacarbazine monotherapy

Study Outcome category Outcome	Eribulin N[a]	Eribulin Values at start of study mean[b] (SD)	Eribulin Change until cycle 9 mean[b] (SE)	Dacarbazine N[a]	Dacarbazine Values at start of study mean (SD)	Dacarbazine Change until cycle 9 mean[b] (SE)	Eribulin vs. dacarbazine MD[b] [95% CI]; p-value
309							
Morbidity							
Health status (EQ-5D VAS)	60	69.8 (22.4)	5.07 (1.13)	57	66.5 (17.1)	1.54 (1.72)	3.52 [−0.37; 7.42]; 0.076

a: Number of patients considered in the analysis for the calculation of the effect estimate. The values at the start of the study may be based on other patient numbers.
b: MMRM analysis of the ITT population, stratified by geographical region and number of prior regimens for advanced soft tissue sarcoma.
CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus

Mortality

Overall survival

Study 309 showed a statistically significant effect in favour of eribulin for the outcome "overall survival".

Morbidity

Symptoms (EORTC QLQ-C30)

Study 309 showed a statistically significant effect in favour of eribulin for the outcome "insomnia".

Study 309 showed no statistically significant difference between the intervention and the control group for the following outcomes: fatigue, nausea and vomiting, pain, dyspnoea, appetite loss, constipation and diarrhoea.

Study 309 showed proof of an effect modification for the characteristic "sex" for the outcome "pain" (see Table 8). For men, there was a statistically significant effect in favour of eribulin for the outcome "pain". No statistically significant difference between the intervention and the control group was shown for women.

Health status

Study 309 showed no statistically significant difference between the intervention and the control group for the outcome "health status" (EQ-5D VAS).

Health-related quality of life

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

Study 309 showed a statistically significant effect in favour of eribulin for the outcomes "physical functioning" and "social functioning".

Study 309 showed no statistically significant difference between the intervention and the control group for the following outcomes: global health status, role functioning, emotional functioning and cognitive functioning.

Side effects

Study 309 showed no statistically significant difference between the intervention and the control group for the outcomes "SAEs", "discontinuation due to AEs" and "severe AEs" (CTCAE grade 3 or 4).

There was proof of an effect modification by the characteristic "number of prior regimens for advanced soft tissue sarcoma" for the outcome "severe AEs" (CTCAE grade 3 or 4). For patients who had received 2 prior regimens, study 309 showed a statistically significant effect to the disadvantage of eribulin. For patients who had received more than 2 prior regimens, in

contrast, study 309 showed no statistically significant difference between the intervention and the control group.

The choice of specific AEs for the benefit assessment was to be conducted based on notable differences between the treatment arms and under consideration of the patient relevance. In addition, specific AEs of particular importance for the disease or for the drugs used in the study were to be chosen. No specific AEs could be chosen with this method, however, because the company provided no data on individual events based on which specific AEs were to be chosen for the relevant subpopulation.

Since data on AEs in the relevant subpopulation of patients with liposarcoma were missing, the most common AEs, SAEs, severe AEs and AEs that led to treatment discontinuation can also not be presented.

Subgroups and other effect modifiers

The following subgroup characteristics were considered to be relevant for the present benefit assessment:

- sex (men/women)
- age (< 65/≥ 65 years)
- ethnicity (Caucasian/non-Caucasian)
- number of prior regimens for advanced soft tissue sarcoma (2/< 2)
- region (USA, Canada/Eastern Europe, Latin America, Asia/Western Europe, Australia, Israel)
- ECOG PS (0, 1/2)
- American Joint Committee on Cancer (AJCC) score (high/intermediate)

The results of the subgroup analyses for the 2 characteristics “ethnicity” and “ECOG PS” were considered to be not interpretable because in each case one subgroup was very small. The AJCC score is a relevant characteristic for the severity of the disease. Since it was unclear how the allocation to the categories “high” and “intermediate” was conducted, the data on this characteristic are not presented.

The treatment durations and resulting observation periods that may differ for the relevant subpopulation (see Table 3) and the potentially informative censorings may differ between the subgroups. These differences may have an important influence on the result of the interaction test. Only effect modifiers for which there was proof of an interaction were therefore considered for the following outcomes: morbidity (symptoms, health status), health-related quality of life and side effects. For the outcome “overall survival”, results are presented if there was at least an indication of an interaction between treatment and subgroup characteristic.

The prerequisite for proof of an effect modification is a statistically significant interaction with a p-value < 0.05. A p-value ≥ 0.05 and < 0.2 provides an indication of an effect modification. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Table 7 and Table 8 summarize the subgroup results on the comparison of eribulin with dacarbazine for the relevant subpopulation of study 309. Where necessary, the data from the company's dossier were supplemented with the Institute's calculations.

Table 7: Subgroups (overall survival) – RCT, direct comparison: eribulin vs. dacarbazine monotherapy

Study Outcome Characteristic Subgroup	Eribulin N	Eribulin Median survival time in months [95% CI] Patients with event n (%)	Dacarbazine N	Dacarbazine Median survival time in months [95% CI] Patients with event n (%)	Eribulin vs. dacarbazine HR[a] [95% CI]	Eribulin vs. dacarbazine p-value
309						
Overall survival						
Age						
< 65	55	18.0 [10.5; 22.2] 38 (69.1[b])	54	8.2 [5.1; 10.1] 50 (92.6[b])	0.43 [0.27; 0.68]	< 0.001
≥ 65	16	7.7 [3.1; 17.9] 14 (87.5[b])	18	9.5 [2.8; 13.2] 13 (72.2[b])	0.55 [0.22; 1.39]	0.203
					Interaction:	0.073
Number of prior regimens for advanced soft tissue sarcoma						
2	39	18.0 [6.8; 20.1] 29 (74.4[b])	41	9.5 [6.6; 11.5] 34 (82.9[b])	0.60 [0.36; 1.02]	0.057
> 2	32	14.7 [10.1; 23; 3] 23 (71.9[b])	31	6.3 [3.3; 10.6] 29 (93.5[b])	0.42 [0.24; 0.75]	0.002
					Interaction:	0.165

a: Cox proportional hazards model stratified by geographical region and number of prior regimens for advanced soft tissue sarcoma.

b: Institute's calculation.

CI: confidence interval; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; vs.: versus

Table 8: Subgroups (symptoms, side effects) – RCT, direct comparison: eribulin vs. dacarbazine monotherapy

Study Outcome Characteristic Subgroup	Eribulin N	Eribulin Median time to event in days [95% CI] Patients with event n (%)	Dacarbazine N	Dacarbazine Median time to event in days [95% CI] Patients with event n (%)	Eribulin vs. dacarbazine HR[a] [95% CI]	 p-value
309						
EORTC QLQ-C30 symptom scales – time to deterioration[b]						
Pain						
Sex						
Men	35	116 [71; NC] 14 (40.0)	45	44 [34; 64] 27 (60.0)	0.30 [0.13; 0.67]	0.002
Women	30	71 [29; 102] 21 (70.0)	21	176 [50; NC] 7 (33.3)	2.10 [0.79; 5.59]	0.130
					Interaction:	0.001
Side effects						
AEs CTCAE grade 3 or 4						
Number of prior regimens for advanced soft tissue sarcoma						
2	38	42.0 [15.0; 102.0] 27 (71.1[c])	41	NA [43.0; NC] 17 (41.5[c])	2.00 [1.08; 3.73]	ND
> 2	32	96.0 [16.0; NC] 17 (53.1[c])	31	44.0 [22.0; 113.0] 20 (64.5[c])	0.70 [0.36; 1.36]	ND
					Interaction:	0.036

a: Cox proportional hazards model stratified by geographical region and number of prior regimens for advanced soft tissue sarcoma.
b: Increase in score by at least 10 points versus the baseline value.
c: Institute's calculation.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; vs.: versus

Table 9: Subgroups (health status) – RCT, direct comparison: eribulin vs. dacarbazine monotherapy

Study Outcome	Eribulin			Dacarbazine			Eribulin vs. dacarbazine
Characteristic Subgroup	N[a]	Values at start of study mean (SD)	Change until cycle 9 mean[b] (SE)	N[a]	Values at start of study mean (SD)	Change until cycle 9 mean[b] (SE)	MD[b] [95% CI]; p-value
309							
Health status (EQ-5D VAS)							
Age							
< 65	47	70.3 (23.1)	2.84 (1.29)	44	65.6 (16.9)	2.71 (1.99)	0.13 [-4.39; 4.65]; 0.954
≥ 65	13	68 (20.4)	17.1 (2.47)	13	69.2 (18)	-9.89 (3.94)	26.99 [16.84; 37.15]; < 0.001
						Interaction:	p-value < 0.001
Region							
USA/Canada	19	66.8 (29.8)	10.86 (2.15)	23	66.4 (15.5)	-5.22 (4.46)	16.08 [6.22; 25.94]; 0.002
Western Europe/ Australia/ Israel	31	70.4 (17.7)	-2.44 (1.35)	28	68.2 (17.4)	-1.59 (1.81)	-0.85 [-5.32; 3.62]; 0.708
Eastern Europe/ Latin America/Asia	10	73.5 (20.6)	4.03 (2.16)	6	58.3 (21.8)	4.38 (3.73)	-0.34 [-8.54; 7.85]; 0.933
						Interaction:	p-value = 0.002

a: Number of patients considered in the analysis for the calculation of the effect estimation. The values at the start of the study may be based on other patient numbers.
b: MMRM analysis of the ITT population, stratified by geographical region and number of prior regimens for advanced soft tissue sarcoma.
CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; ITT: intention to treat; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus

Mortality

Overall survival

There were indications of an effect modification by the characteristics “age” and “number of prior regimens for soft tissue sarcoma” for the outcome “overall survival”.

The subgroup results could not be meaningfully interpreted because data for the investigation of possible dependencies between the subgroup characteristics were missing. An effect in

favour or to the disadvantage of eribulin was therefore determined for the total relevant subpopulation of patients with liposarcoma in study 309.

Morbidity

Symptoms (EORTC QLQ-C30)

There was proof of an effect modification by the characteristic "sex" for the outcome "pain". Study 309 showed no statistically significant difference between the intervention and the control group for women, whereas for men a statistically significant effect in favour of eribulin was shown.

Health status (EQ-5D VAS)

There was discrepant information in Module 4 of the dossier and in the additional analyses presented by the company for the outcome "health status" (EQ-5D VAS). The data from Module 4 of the dossier (stratified mixed-effects model repeated measures [MMRM] analysis) are presented; the data from the additional analyses (unstratified) showed the same effect.

There was proof of an effect modification by the characteristic "age" for the outcome "health status" (EQ-5D VAS). Study 309 showed no statistically significant difference between the intervention and the control group for patients younger than 65 years of age, whereas there was a statistically significant and relevant effect in favour of eribulin for patients 65 years of age or older.

There was also proof of an effect modification by the characteristic "region". There was no statistically significant difference between the intervention and the control group for the subgroup of patients from Western Europe, Australia and Israel, which is the one of interest for the health care context.

The subgroup results could not be meaningfully interpreted because data for the investigation of possible dependencies between the subgroup characteristics were missing. An effect in favour or to the disadvantage of eribulin was therefore determined for the total relevant subpopulation of patients with liposarcoma in study 309.

Side effects

There was proof of an effect modification by the characteristic "number of prior regimens for advanced soft tissue sarcoma" for the outcome "severe AEs" (CTCAE grade 3 or 4). For patients who had received 2 prior regimens, study 309 showed a statistically significant effect to the disadvantage of eribulin. For patients who had received more than 2 prior regimens, in contrast, study 309 showed no statistically significant difference between the intervention and the control group.

2.3 Summary

The following Table 10 shows an overview of the positive and negative effects resulting from study 309 for eribulin in comparison with dacarbazine.

Table 10: Positive and negative effects from the assessment of eribulin in comparison with dacarbazine monotherapy

Positive effects	**Negative effects**
Mortality ▪ Overall survival Non-serious/non-severe symptoms ▪ EORTC QLQ-C30: insomnia ▪ EORTC QLQ-C30: pain ▫ men Health-related quality of life ▪ EORTC QLQ-C30: physical functioning, social functioning	Serious/severe side effects ▪ Severe AEs (CTCAE grade 3 or 4) ▫ 2 prior regimens for advanced soft tissue sarcoma
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire-Core 30	

In the overall consideration, there is a positive effect for the total relevant subpopulation for the outcomes “overall survival”, “insomnia”, “physical functioning” and “social functioning”. For the outcome “pain”, there is a positive effect for men. This is accompanied by a negative effect in severe AEs (CTCAE grade 3 or 4) for patients with 2 prior regimens for advanced soft tissue sarcoma. It is to be noted that in the comparator arm of the underlying study 309, dacarbazine was not used as combination therapy, but as monotherapy, and in a different dosage than recommended in the SPC on dacarbazine for the treatment of soft tissue sarcoma.

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Appendix A – Kaplan-Meier curve for the outcome "overall survival"

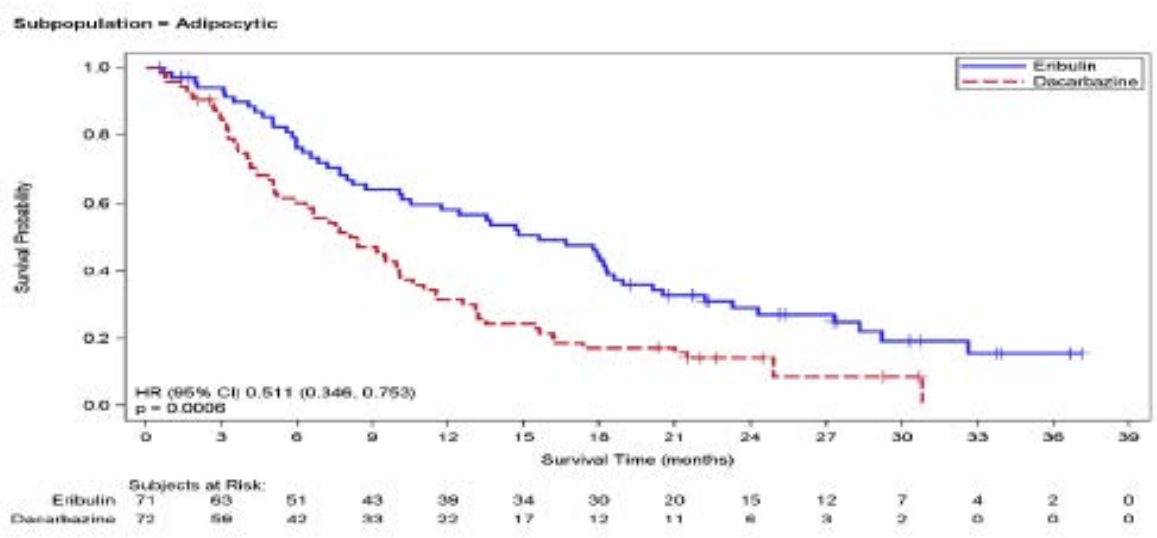

Figure 1: Kaplan-Meier curves on the outcome "overall survival" from study 309 (relevant subpopulation: patients with liposarcoma) – eribulin versus dacarbazine monotherapy