IQWiG Reports – Commission No. A16-06

Regorafenib – Addendum to Commission A15-43[1]

Addendum

Commission: A16-06
Version: 1.0
Status: 26 February 2016

[1] Translation of addendum A16-06 *Regorafenib – Addendum zum Auftrag A15-43* (Version 1.0; Status: 26 February 2016). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Regorafenib – Addendum to Commission A15-43

Commissioning agency:
Federal Joint Committee

Commission awarded on:
9 February 2016

Internal Commission No.:
A16-06

Address of publisher:
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

IQWiG employees involved in the addendum[2]:

- Thomas Kaiser
- Katharina Biester
- Charlotte Guddat

Keywords: regorafenib, colorectal neoplasms, benefit assessment

[2] Due to legal data protection regulations, employees have the right not to be named.

Table of contents

Page

List of tables

Page

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
BSC	best supportive care
CI	confidence interval
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LSMD	least square mean difference
MMRM	mixed-effects model repeated measures
SD	standard deviation
SE	standard error
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference

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 A15-43 (Regorafenib – Benefit assessment according to §35a Social Code Book [SGB] V).

In its dossier [1], the pharmaceutical (hereinafter referred to as "the company") presented results from the studies CORRECT and CONCUR to prove the added benefit of regorafenib in the therapeutic indication "metastatic colorectal cancer". They also included analyses on health-related quality of life and symptoms. These analyses were not usable, however, because the company had not appropriately analysed the data [2].

With its written comments, the company presented changed analyses on health-related quality of life and symptoms [3]. The G-BA commissioned IQWiG to assess these analyses.

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

2.1 Data availability

New analyses presented on the studies CORRECT and CONCUR

The company had presented 2 studies for the benefit assessment of regorafenib in comparison with the appropriate comparator therapy (ACT) best supportive care (BSC), which were assessed in dossier assessment A15-43 [1,2]:

- the CORRECT study; this study had also been presented in the first benefit assessment procedure on regorafenib in 2013; 760 patients were included in this study; the study was conducted in Asia, Australia, North America, Eastern Europe and Western Europe
- the CONCUR study; this study was presented for the first time in the current benefit assessment procedure; 75 patients were included in this study (relevant subpopulation); the study was only conducted in Asia

Both in the CORRECT and in the CONCUR study, symptoms and health-related quality of life were recorded with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 (EORTC QLQ-C30). Already in the first benefit assessment procedure, the company had not presented an appropriate analysis on this for the CORRECT study because it had not adequately considered the high drop-out rates in its analyses [2,4]. In its dossier on the current assessment procedure, the company had adequately considered the drop-out rates in its analyses (analyses based on a mixed-effects model repeated measures [MMRM]). However, the analyses did not comply with the specifications provided in the manual of the questionnaire [2], whereas the company had considered these specifications in the first assessment procedure [5].

With the comments on the current assessment procedure, the company presented analyses in which both the high drop-out rates and the specifications in the manual of the questionnaire were considered [3].

Only the data on the CORRECT study were relevant for the present assessment

As described in dossier assessment A15-43 [2], the data on health-related quality of life from the CONCUR study were not usable with regard to content, irrespective of the type of analysis, because the results in the area of individual adverse events differed from the ones in the CORRECT study to an important degree. This also applied to several symptoms recorded with the EORTC QLQ-C30 [3]. Furthermore, as also described in dossier assessment A15-43 [2], the median treatment duration in the CONCUR study differed by a factor of about 1.5 between the treatment arms (information for the total population, there was no information for the subpopulation), without the company addressing this in the analyses presented (e.g. using survival time analyses).

In summary, the results of the CONCUR study on health-related quality of life and on symptoms could neither confirm nor raise doubts about the CORRECT study. Hereinafter, the assessment is only conducted on the basis of the results of the CORRECT study.

Responder analyses missing; analyses of the company for assessing the relevance of the effects unsuitable

Results on symptoms and health-related quality of life that are recorded with questionnaires need to be considered regarding the relevance of the observed group differences. Ideally, this is done with responder analyses based on validated response criteria [6]. The company did not present such analyses.

Instead, the company considered the standardized mean difference (SMD; Hedges' g) to derive its conclusions on the relevance of the effects. Consideration of the SMD is an adequate possibility for the evaluation of relevance in case that no responder analyses are available. The concrete approach of the company for the calculation of the SMD was inadequate, however (see also Appendix A):

- The company's calculations resulted in inconsistent results between the initial analyses (MMRM) and the SMD determined by the company for the evaluation of relevance because the method used by the company was unsuitable.
- A suitable method for the calculation of the SMD, in contrast, resulted in consistent results between the initial analyses (MMRM) and the SMD.

For the evaluation of the relevance of the effects, the SMD was therefore calculated by the Institute with the suitable method.

2.2 Results

The following Table 1 shows the results on symptoms and health-related quality of life from the CORRECT study.

Table 1: Results on symptoms and health-related quality of life – study CORRECT, regorafenib + BSC vs. placebo + BSC

Study Category Scale	Regorafenib + BSC			Placebo + BSC			Regorafenib vs. placebo
	N[a]	Baseline values mean (SD)	Change at end of study LS mean (SE)	N[a]	Baseline values mean (SD)	Change at end of study LS mean (SE)	LSMD[b] [95% CI]; p-value SMD [95% CI][c]
CORRECT							
Symptom scales (EORTC QLQ-C30)[d]							
Fatigue	478	35.6 (25.0)	9.33 (1.79)	243	32.2 (23.6)	7.08 (1.89)	2.26 [0.52; 4.00]; 0.011 Hedges' g: 0.20 [0.05; 0.36]
Nausea and vomiting	478	8.5 (17.6)	2.24 (0.68)	243	6.8 (14.7)	3.00 (0.82)	−0.75 [−2.03; 0.52]; 0.248
Pain	479	27.2 (28.1)	7.99 (1.64)	243	26.2 (29.1)	3.57 (1.80)	4.42 [2.42; 6.43]; < 0.001 Hedges' g: 0.34 [0.18; 0.50]
Dyspnoea	476	20.2 (26.7)	6.22 (1.44)	243	17.3 (24.5)	4.88 (1.61)	1.34 [−0.64; 3.32]; 0.184
Insomnia	477	23.6 (28.2)	2.44 (1.55)	243	25.2 (29.9)	1.59 (1.73)	0.84 [−1.29; 2.98]; 0.439
Appetite loss	478	24.9 (33.1)	12.33 (2.06)	243	20.3 (28.4)	7.18 (2.22)	5.15 [2.83; 7.46]; < 0.001 Hedges' g: 0.34 [0.19; 0.50]
Constipation	478	15.9 (25.5)	2.55 (0.85)	243	16.5 (26.8)	4.23 (1.11)	−1.68 [−3.65; 0.28]; 0.093
Diarrhoea	477	12.7 (22.9)	5.95 (0.89)	240	12.1 (21.9)	–1.17 (1.16)	7.12 [5.07; 9.16]; < 0.001 Hedges' g: 0.54 [0.38; 0.70]

(continued)

Table 1: Results on symptoms and health-related quality of life – study CORRECT, regorafenib + BSC vs. placebo + BSC (continued)

Study Category Scale	Regorafenib + BSC			Placebo + BSC			Regorafenib vs. placebo
	N[a]	Baseline values mean (SD)	Change at end of study LS mean (SE)	N[a]	Baseline values mean (SD)	Change at end of study LS mean (SE)	LSMD[b] [95% CI]; p-value SMD [95% CI][c]
Scales on health-related quality of life (EORTC QLQ-C30)							
Global health status	476	62.6 (21.6)	−7.83 (1.5)	240	64.7 (22.4)	−6.23 (1.59)	−1.61 [−3.1; −0.11]; 0.035 Hedges' g: −0.17 [−0.32; −0.01]
Physical functioning	477	78 (19.7)	−6.91 (1.57)	243	79.7 (19.6)	−4.46 (1.65)	−2.44 [−3.91; −0.98]; 0.001 Hedges' g: −0.26 [−0.41; −0.10]
Role functioning	478	74.5 (29.3)	−13.27 (2.29)	243	77.6 (27.3)	−7.78 (2.4)	−5.49 [−7.57; −3.41]; < 0.001 Hedges' g: −0.41 [−0.56; −0.25]
Emotional functioning	477	78.2 (20.8)	−2.37 (1.33)	241	79.3 (20.0)	0.5 (1.43)	−2.87 [−4.38; −1.37]; < 0.001 Hedges' g: −0.30 [−0.45; −0.14]
Cognitive functioning	477	88.7 (15.8)	−4.46 (1.16)	241	87.3 (16.6)	−2.15 (1.25)	−2.31 [−3.63; −1.00]; < 0.001 Hedges' g: −0.27 [−0.43; −0.12]
Social functioning	477	77.3 (25.7)	−7.45 (1.82)	241	80.5 (24.3)	0.19 (1.96)	−7.64 [−9.63; −5.64]; < 0.001 Hedges' g: −0.59 [−0.75; −0.43]
Financial difficulties	476	15.6 (26.2)	0.22 (0.53)	240	13.6 (23.8)	−0.57 (0.82)	0.79 [−0.92; 2.50]; 0.363

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: Mean treatment effect of the changes to baseline over time, based on an MMRM. The factor "visit" was included in the model as random effect. The model contained the factors "baseline value", "treatment", "day of visit after randomization" and "interaction from treatment and day".
c: Institute's calculation.
d: Positive changes correspond to deterioration (on a scale of 0 to 100).
e: Negative changes correspond to deterioration (on a scale of 0 to 100).

BSC: best supportive care; CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; LS: least square; LSMD: least square mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; QLQ-C30: Quality of Life Questionnaire - Core 30; SD: standard deviation; SE: standard error; SMD: standardized mean difference; vs.: versus

Symptoms

A statistically significant result to the disadvantage of regorafenib was shown for the scales of fatigue, pain, appetite loss and diarrhoea. Since responder analyses were lacking, the SMD (Hedges' g) was used for the evaluation of the relevance of the corresponding effects:

- For the diarrhoea scale, the 95% confidence interval (CI) of the SMD was completely above the irrelevance threshold of 0.2. This was interpreted to be a relevant effect. There was therefore a hint of lesser benefit of regorafenib in comparison with BSC for this outcome.
- For the scales of fatigue, pain and appetite loss, the 95% CI of the SMD was not completely above the irrelevance threshold of 0.2. It could therefore not be inferred that the effect in these cases was relevant. Hence there was no hint of lesser benefit of regorafenib in comparison with BSC; an added benefit for these outcomes is therefore not proven.

No statistically significant group difference was shown for the scales of nausea and vomiting, dyspnoea, insomnia and constipation. Hence there was no hint of an added benefit of regorafenib in comparison with BSC; an added benefit of regorafenib for these outcomes is not proven.

Health-related quality of life

A statistically significant result to the disadvantage of regorafenib was shown for each of the scales of global health status, role functioning, physical, emotional, cognitive and social functioning. Since responder analyses were lacking, the SMD (Hedges' g) was used for the evaluation of the relevance of the corresponding effects:

- For the scales of role functioning and social functioning, the 95% CI of the SMD was completely below the irrelevance threshold of −0.2. This was interpreted to be a relevant effect in each case. There was therefore a hint of lesser benefit of regorafenib in comparison with BSC for each of these outcomes.
- For the scales of global health status and physical, emotional and cognitive functioning, the 95% CI of the SMD was not completely below the irrelevance threshold of −0.2. It could therefore not be inferred that the effect in these cases was relevant. Hence there was no hint of lesser benefit of regorafenib in comparison with BSC; an added benefit for these outcomes is therefore not proven.

No statistically significant group difference was shown for the scale of financial difficulties. Hence there was no hint of an added benefit of regorafenib in comparison with BSC; an added benefit of regorafenib for this outcome is not proven.

2.3 Overall conclusion on added benefit

In comparison with dossier assessment A15-43, the analyses subsequently submitted by the company resulted in additional negative effects of regorafenib for health-related quality of life (role functioning and social functioning) with the extent "non-quantifiable". Such a negative effect was also shown for the symptom "diarrhoea"; a negative effect of regorafenib for diarrhoea had already been determined in the assessment of severe adverse events in dossier assessment A15-43, however.

The results included in the overall conclusion on the extent of added benefit are summarized in Table 2, taking into account dossier assessment A15-43 and the present addendum.

Table 2: Positive and negative effects from the assessment of regorafenib + BSC compared with placebo + BSC

Positive effects	**Negative effects**
▪ Hint of an added benefit - extent: "considerable" (mortality: overall survival)	▪ Hint of greater harm – extent: "major" (severe/serious AEs: severe AEs CTCAE grade ≥ 3; including diarrhoea, exanthema, hand-foot syndrome, in each case CTCAE grade 3 – extent: "major", fatigue CTCAE grade 3 – extent: "considerable") ▪ Hint of lesser benefit – extent: "non-quantifiable" (symptoms: diarrhoea) ▪ Hint of lesser benefit – extent: "non-quantifiable" (health-related quality of life: role functioning, social functioning)
AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; vs.: versus	

In contrast to dossier assessment A15-43, besides the positive effect on all-cause mortality, there were not only severe adverse events, but there was particularly also lesser benefit in the area of health-related quality of life (role functioning and social functioning). This resulted in a change of the assessment raising doubts about the overall added benefit in the area of all-cause mortality. The added benefit of regorafenib in comparison with BSC in patients with metastatic colorectal cancer is therefore not proven.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

3 References

1. Bayer Vital. Regorafenib (Stivarga): Dossier zur Nutzenbewertung gemäß §35a SGB V; Modul 4 A; Behandlung von erwachsenen Patienten mit metastasiertem Kolorektalkarzinom, die zuvor mit verfügbaren Therapien behandelt wurden oder die für diese nicht geeignet sind; diese Therapien umfassen Fluoropyrimidin-basierte Chemotherapie, eine Anti-VEGF-Therapie und eine Anti-EGFR-Therapie; medizinischer Nutzen und medizinischer Zusatznutzen, Patientengruppen mit therapeutisch bedeutsamem Zusatznutzen [online]. 29.09.2015 [accessed: 22.02.2016]. URL: https://www.g-ba.de/downloads/92-975-1197/2015-09-29_Modul4A_Regorafenib.pdf.

2. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Regorafenib: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A15-43 [online]. 23.12.2015 [accessed: 22.02.2016]. (IQWiG-Berichte; Volume 352). URL: https://www.iqwig.de/download/A15-43_Regorafenib_Nutzenbewertung-35a-SGB-V.pdf.

3. Bayer Vital. Stellungnahme zum IQWiG-Bericht Nr. 352: Regorafenib; Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A15-43. [Soon available under: https://www.g-ba.de/informationen/nutzenbewertung/195/#tab/beschluesse in the document "Zusammenfassende Dokumentation"].

4. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Addendum zum Auftrag A13-37 (Regorafenib): Auftrag A14-09 [online]. 26.02.2014 [accessed: 01.04.2014]. (IQWiG-Berichte; Volume 207). URL: https://www.iqwig.de/download/A14-09_Addendum-zum-Auftrag-A13-37_Regorafenib.pdf.

5. Bayer Vital. Regorafenib (Stivarga): Dossier zur Nutzenbewertung gemäß §35a SGB V; Modul 4 A; Behandlung von erwachsenen Patienten mit metastasiertem Kolorektalkarzinom, die zuvor mit verfügbaren Therapien behandelt wurden oder die für diese nicht geeignet sind; diese Therapien umfassen Fluoropyrimidin-basierte Chemotherapie, eine Anti-VEGF-Therapie und eine Anti-EGFR-Therapie; medizinischer Nutzen und medizinischer Zusatznutzen, Patientengruppen mit therapeutisch bedeutsamem Zusatznutzen [online]. 30.09.2013 [accessed: 22.02.2016]. URL: https://www.g-ba.de/downloads/92-975-385/2013-09-30_Modul4_Regorafenib_mCRC.pdf.

6. Institute for Quality and Efficiency in Health Care. General Methods: version 4.2 [online]. 22 April 2015 [accessed: 20 October 2015]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-2.pdf.

Appendix A – Comparison of the results on mean differences from the MMRM analyses with the standardized mean differences

Starting points for the considerations were the least square mean differences (LSMDs) of the individual symptom and quality of life scales. These were the result of the company's MMRM analyses under consideration of the high drop-out rates. The MMRM analyses showed statistically significant group differences, which were only to the disadvantage of regorafenib and mostly with very small p-values, for 4 of the 8 symptom scales (fatigue, pain, appetite loss and diarrhoea) and in 6 of the 7 scales on health-related quality of life (global health status, role functioning as well as physical, emotional, cognitive and social functioning) (see Table 1).

The company calculated SMDs for each of the individual scales. Such analyses serve the assessment of the effect size (consideration of relevance), but they should not fundamentally change the conclusions on statistical significance. However, substantial discrepancies in comparison with the MMRM analyses were notable in the consideration of the SMD presented by the company: The SMD calculated by the company showed a statistically significant result in only 2 of the 10 scales with statistically significant group difference based on the MMRM analyses (diarrhoea and social functioning).

A pooled standard deviation (SD) is required for the calculation of the SMD. It can be inferred that the company had used the two standard errors (SEs) of the mean change since the start of the study per treatment arm for their calculation. Ultimately, the causes of the notable discrepancy between its calculation of the SMD and the LSMD were not clear from the available data and from the information presented by the company. Possibly, dependence between the LSMD estimators of the 2 treatment arms was not taken into account in the company's calculation variant and was responsible for this.

In contrast, if the pooled SD is determined using the SE of the LSMD (i.e. of the group difference based on the MMRM analyses), the statements on significance are consistent between LSMD and SMD. It has to be assumed that the estimation including SE for the group difference with the MMRM approach is stable because otherwise these analyses in total were not usable. Hence the LSMDs with corresponding SEs had to be used for the calculation of the SMDs, which resulted in consistent results between the group differences based on the MMRM analyses and the SMDs.

Hereinafter, the results on the LSMDs are visually compared with the ones calculated by the company and with the SMDs calculated by the Institute on the basis of the SE of the LSMD. It was shown both for the symptom scales (Figure 1 to Figure 3) and for the scales on health-related quality of life (Figure 4 to Figure 6) that the company's calculations (see second figure in each case) resulted in marked discrepancies in comparison with the LSMDs (see first figure in each case). The Institute's calculations (see third figure in each case), in contrast, were consistent with the LSMDs.

Symptom scales

Regorafenib vs. Placebo
Symptoms (EORTC QLQ-C30), LSMD

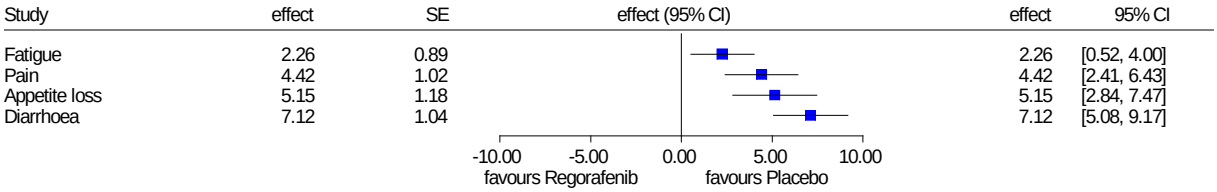

Figure 1: LSMD with statistically significant group difference – symptom scales

Regorafenib vs. Placebo
Symptoms (EORTC QLQ-C30), SMD variant 1

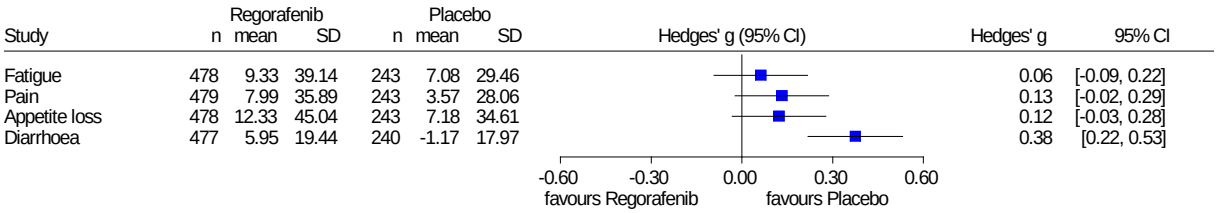

Figure 2: SMD calculated by the company – symptom scales

Regorafenib vs. Placebo
Symptoms (EORTC QLQ-C30), SMD variant 2

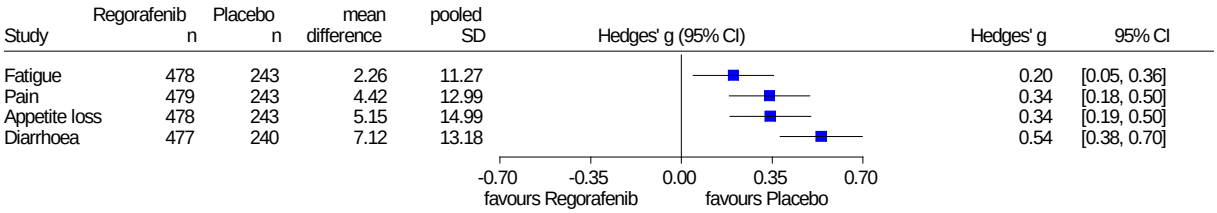

Figure 3: SMD calculated by the Institute – symptom scales

Scales on health-related quality of life

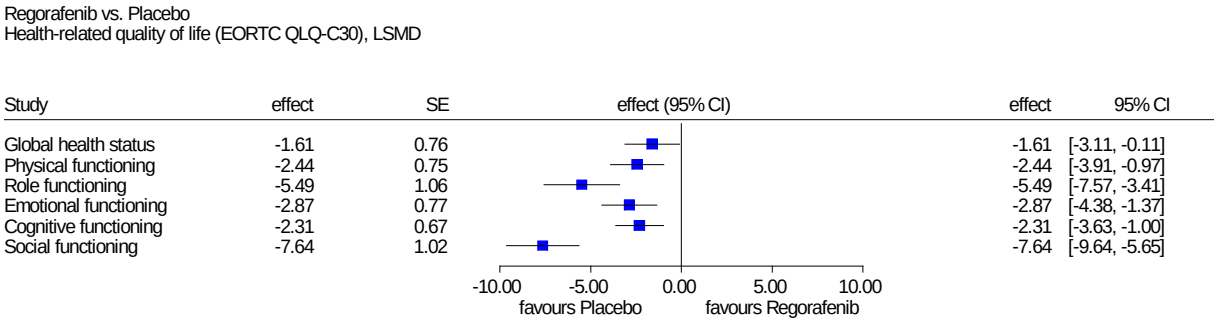

Figure 4: LSMD with statistically significant group difference – scales on health-related quality of life

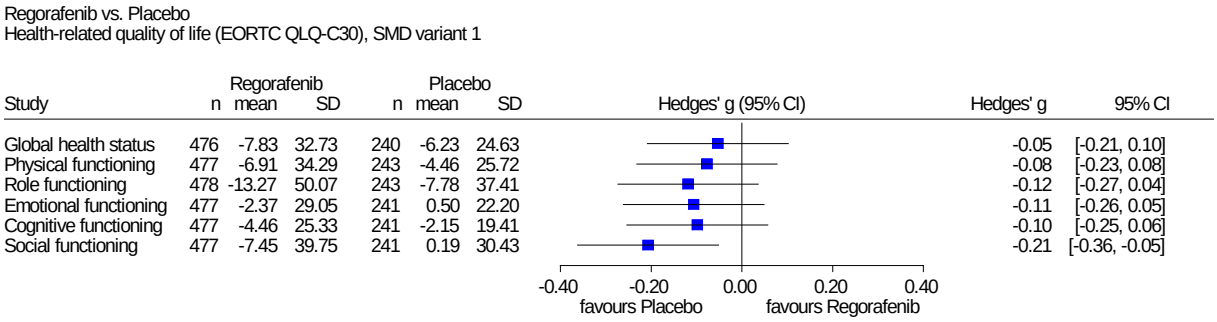

Figure 5: SMD calculated by the company – scales on health-related quality of life

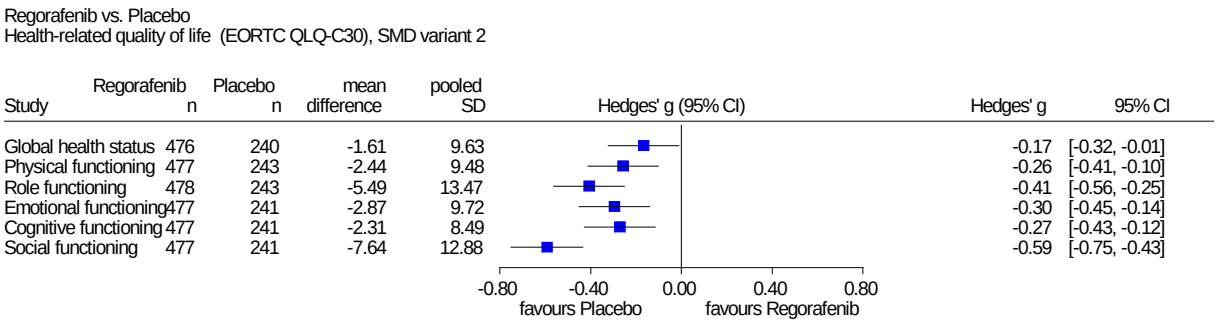

Figure 6: SMD calculated by the Institute – scales on health-related quality of life