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EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

EUnetHTA Joint Action 2 (2012-2015)
WP5 Strand A, Rapid assessment of pharmaceutical

Pilot rapid assessment of pharmaceuticals using the HTA Core Model® for Rapid Relative Effectiveness Assessment

RAMUCIRUMAB IN COMBINATION WITH PACLITAXEL AS SECOND-LINE TREATMENT FOR ADULT PATIENTS WITH ADVANCED GASTRIC OR GASTRO-OESOPHAGEAL JUNCTION ADENOCARCINOMA

Pilot ID: WP5 – SA4

Final version, March 2015

DISCLAIMER

During the Scoping Phase of this jointly produced rapid Relative Effectiveness Assessments, the manufacturer was asked to compile a EUnetHTA submission file. This submission file includes all important and relevant information regarding the compound under assessment. Within the submission file from the manufacturer on ramucirumab, data was presented regarding indirect comparison and network analyses. This data was planned to be presented within the publicly available EUnetHTA assessment report. During the assessment phase the manufacturer indicated that they wanted to publish the results of the indirect comparison in an abstract for an international conference and the committee responsible for assessing these abstracts indicated that pre-publication of these results in the EUnetHTA report could seriously decrease the chances of these data being accepted. After discussion with the manufacturer, the main authors of this report and the coordinator, it was decided that in order to support the opportunity for the manufacturer to publish this data, until the publication of the abstract results at the international conference, only directions of findings would be presented in this public assessment report. However, it was also indicated that all the results of the indirect comparisons would be immediately shared with all WP5 partners.

During the discussion with the manufacturer we had to acknowledge the fact that it was not sufficiently clearly stated in the procedure manual of WP5 Strand A that all information included within the submission file must be available to be used within this public assessment. Moreover, the pilot team felt that a pragmatic approach in the pilot phase of this project would be beneficial to bring these activities forward. However, the coordination team has as a consequence, ensured that the procedure of the REA has been adapted and that it is now clearly stated in all relevant documents that all information included in the submission file must be available for usage in the publicly available rapid Relative Effectiveness Assessments.

As EUnetHTA is working based on transparency guidelines it also has been decided that an additional appendix to this assessment report with a complete overview of all data will be published. This appendix will be made publicly available in June 2015.

This note is intended to notify the reader of this assessment is aware of the discussed issue and to raise awareness that an additional appendix will be published in June.

The assessment represents a consolidated view of the EUnetHTA network members and is in no case the official opinion of the participating institutions or individuals.

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CONSULTATION OF THE DRAFT RAPID ASSESSMENT

The following WP5 Strand A members have provided comments during WP5 consultation [v 1.4]	HAS, France FIMEA, Finland Ministry of Health, Slovakia Scottish Medicine Consortium, Scotland Ministry of Energy and Health, Malta Ministry of Health, Czech Republic AETSA, Spain ZIN, The Netherlands AIFA, Italy
Manufacturer/ Marketing Authorisation Holder	Eli Lilly and Company Ltd., United Kingdom

CONFLICT OF INTEREST

All authors and reviewers involved in the production of this pilot assessment have declared they have no conflicts of interest in relation to the technology assessed according to the EUnetHTA conflicts of interest (COI) statement form.

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SUMMARY OF RELATIVE EFFECTIVENESS OF RAMUCIRUMAB

Scope

In short, we examined the clinical effectiveness and safety of ramucirumab in combination with paclitaxel compared to other treatments for adults with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma previously treated with chemotherapy and with good performance status (Eastern Cooperative Oncology Group [ECOG] score of 0 or 1).

Introduction

Description of technology

Ramucirumab (Cyramza®) is a human receptor-targeted antibody, which specifically binds vascular endothelial growth factor (VEGF) receptor 2 and blocks binding of the activating ligands (VEGF-A, VEGF-C, and VEGF-D) and inhibits downstream signalling [B0001].

Ramucirumab in combination with paclitaxel is indicated for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction (GEJ) adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy [A0020].

Currently, ramucirumab alone, or in combination with paclitaxel is the only approved treatment option for those patients [A0020].

Paclitaxel, docetaxel and irinotecan are not approved drugs for second-line treatment and represent off-label second-line chemotherapy for patients with advanced disease whose cancer has progressed [B0003].

Health problem

Gastric cancers include malignancies that arise from the lining of the stomach and the GEJ. Stomach cancers occur in any part of the stomach, whereas GEJ cancers occur “within 5 cm proximal and distal of the anatomic cardia”. The vast majority of gastric cancers are adenocarcinomas histopathologically (about 90%), and in a minority of cases include lymphomas, gastrointestinal stromal tumours, or carcinoid tumours [A0002].

The prevalence of gastric cancer (which includes GEJ cancer, as per International Classification of Diseases [ICD] codes), in 2014, was estimated to range from 2.80 to 4.24 per 10,000 in the European Union (EU) community. This is below the threshold of 5 per 10,000 patients required by the European Commission for an orphan drug designation. Based on UK data in 2011, the proportion of gastric cancer patients (including GEJ) who have metastatic disease is estimated to be 80%, which is equal to approximately 4,700 people in UK of patients with advanced disease, it is estimated that 66% have inoperable cancer, of these 53% are estimated to be fit enough to receive first-line chemotherapy (all of these patients will probably relapse) [A0023].

In the EU there is currently no standard second-line treatment for patients with advanced gastric or gastro-oesophageal junction adenocarcinoma following progression despite prior chemotherapy.

In second-line clinical trials the following chemotherapy regimens have been used: irinotecan plus cisplatin or fluoropyrimidines; single-agent irinotecan; single-agent docetaxel; docetaxel plus oxaliplatin (expert opinion indicates that docetaxel is used more commonly with cisplatin or 5-fluorouracil [5-FU]); paclitaxel single-agent or plus platinum agents; and FOLFOX (folinic acid, 5-FU, oxaliplatin) [A0025].

According the most current European ESMO-ESSO-ESTRO clinical practice guidelines in patients of adequate performance status, second-line chemotherapy is associated with improvements in overall survival and quality of life compared with best supportive care, with treatment options including

irinotecan, docetaxel, or paclitaxel. In patients with disease progression 3 months or more after first-line chemotherapy, it may be appropriate to consider a re-challenge with the same drug combination [A0025].

The National Comprehensive Cancer Network clinical practice guideline for gastric cancer now includes the use of ramucirumab for second-line treatment of metastatic or locally advanced disease [A0025].

Methods

We mainly used 3 sources of information, submitted by the marketing authorisation holder (MAH): the submission dossier, the draft and published European public assessment report (EPAR) for ramucirumab and a meta-analysis report. The MAH performed a systematic literature search as a part of their submission dossier. They used a combination of subject terms and text words to define the population and all interventions and controls relevant for this assessment, and searched in several relevant databases. The search strategy was adapted to each database. When necessary, we performed additional non-systematic searches.
No quality assessment tool was used for the domains Description and Technical Characteristics of the Technology and Health Problem and Current Use of Technology, but multiple sources were used in order to validate individual, possibly biased, sources. Descriptive analysis was performed on different information sources.

The study types included in the clinical effectiveness and safety domains were limited to randomised controlled trials. We used the Cochrane risk of bias tool to assess the internal validity. We assessed external validity formally only for direct evidence for the major outcomes. The evidence was assessed as part of assessing the overall documentation for each outcome using GRADE (Grading of Recommendations, Assessment, Development and Evaluation).

Results

Available evidence
For the patients and intervention of interest in this assessment, there is direct evidence from one randomised study only. The RAINBOW study (N = 665) compared ramucirumab plus paclitaxel with placebo plus paclitaxel in relevant patient population. Other studies were used to make an evidence network and indirect comparisons for ramucirumab.
The following comparisons were identified:

- Ramucirumab plus paclitaxel vs placebo plus paclitaxel
- Irinotecan vs paclitaxel
- Docetaxel vs active symptom control
- Irinotecan vs best supportive care
- Irinotecan vs docetaxel (used only to connect the evidence network for selected outcomes)

Clinical effectiveness

Patients aged 18 years or older with advanced gastric or gastro-oesophageal junction carcinoma and disease progression on or within 4 months after first-line chemotherapy (platinum plus fluoropyrimidine with or without an anthracycline) were randomised to receive ramucirumab 8 mg/kg or placebo intravenously (iv) on days 1 and 15, plus paclitaxel 80 mg/m^2 intravenously on days 1, 8 and 15 of a 28 days cycle. Results from a direct comparison of ramucirumab plus paclitaxel compared with placebo plus paclitaxel showed a benefit for overall survival with a hazard ratio (HR) of 0.81 (95% confidence interval (CI) 0.68 to 0.96) corresponding to an absolute difference in median overall survival of 2.27 months (9.63 vs 7.36 months) [D0001].

The treatment difference in median progression-free survival was 1.5 month in favour of the ramucirumab and paclitaxel group compared with the placebo and paclitaxel group (4.4 vs 2.9 months) with a statistically significant lower hazard of disease progression HR 0.64 (95% CI 0.54 to 0.75 [D0006]. A greater proportion of patients reported an objective response to treatment in the ramucirumab and paclitaxel group compared with the placebo and paclitaxel group (odds ratio (OR) = 2.1 (95% CI 1.45 to 3.16)) [D0005].

The indirect evidence comparing ramucirumab plus paclitaxel to irinotecan, docetaxel and best supportive care showed a mix of statistical significant and not statistical significant findings. Many of the results were associated with wide confidence intervals around the point estimates and were thus considered uncertain. For overall survival ramucirumab plus paclitaxel was favoured compared to irinotecan and best supportive care [D0001].

Indirect comparisons of progression-free survival and objective response rate favoured ramucirumab plus paclitaxel compared with irinotecan [D0006, D0016]. The indirect comparisons of ramucirumab plus paclitaxel with docetaxel for overall survival, progression-free survival or objective response rate was not statistically significant, however, the point estimate of the HR was less than 1 for both progression-free and overall survival, and the point estimate of the OR was greater than 1 for objective response rate [D0001, D0006, D0016].

Indirect comparisons was performed by using the Bucher method.

Safety

Direct comparison of the frequency of reported adverse events with ramucirumab plus paclitaxel compared with placebo plus paclitaxel, showed that nearly all patients experienced an adverse event. There were no statistically significant differences between the treatment groups [C0008a]. Similarly, we did not find differences between the groups in withdrawal due to adverse events [C0008b], the frequency of serious adverse events [C0008c], or adverse events leading to death [C0008d]. However, for adverse events of grade 3 or higher, we identified a statistically significant difference in favour of placebo plus paclitaxel, risk ratio (RR) 1.30 (95% CI 1.18 to 1.44) [C0008a].

Evidence networks (direct and indirect comparisons) indicate that withdrawal due to adverse events could be higher for ramucirumab plus paclitaxel than for best supportive care or placebo. There were no statistically significant differences when this ramucirumab combination was compared with paclitaxel, irinotecan or docetaxel [C0008b].

The submission dossier identified specific adverse events that occurred very often (in 10% or more) in patients treated with ramucirumab plus paclitaxel. Most studies are not designed to show statistically significant differences in safety outcomes. This is also the case here. However, sometimes specific adverse reactions do reach significant differences. Comparing the odds of experiencing these adverse events with the ramucirumab combination with that of other treatment alternatives analysed shows that certain events appear to occur more often with this intervention, while others seem to occur more often

with the comparator alternatives [C0008e]. It appears that in the tested comparisons ramucirumab plus paclitaxel is less favourable for neutropenia, leukocytopenia, all grades thrombocytopenia (vs paclitaxel), all grade diarrhoea, all grades anorexia (vs paclitaxel), peripheral sensory neuropathy or neuropathy (vs irinotecan). Ramucirumab plus paclitaxel was however favourable compared to irinotecan for all grade anemia, all grade nausea and for anorexia. If not otherwise specified the same direction applies for both all grades and grade 3 and 4 events.

Upcoming evidence

We identified 5 planned, ongoing or unpublished studies using ramucirumab in patients with gastric cancer and/or GEJ adenocarcinoma, 4 non-randomised open- label studies and one registry (Table A5). The registry will run until 2021, but data from the remaining studies can be expected in 2015-2016. We did not identify any planned or ongoing RCT of ramucirumab in combination with paclitaxel against the adequate comparators in the population of interest.

Reimbursement

The reimbursement status of ramucirumab plus paclitaxel in different EU countries will be decided at the national level after marketing authorisation [A0021].

Summary table of relative effectiveness of ramucirumab plus paclitaxel

Adults with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma previously treated with chemotherapy and with good performance status (ECOG score of 0 or 1)						
	Health benefit			**Harm**		
	Overall mortality HR (95% CI)	**Progression-free survival** HR (95% CI)	**Quality of life (end of treatment)** RR (95% CI)	**Adverse events (any type, all severity grades)** RR (95% CI)	**Serious adverse events** RR (95% CI)	**Withdrawal due to adverse events** OR (95% CI)
Ramucirumab plus paclitaxel **Placebo plus paclitaxel**	***0.81 (0.68 to 0.96), p= 0.0169*** ***Absolute risk* 701 per 1000 (637 to 763)*** ***[D0001][1]***	***0.64 (0.54 to 0.75), p<0.0001*** ***4.4 (4.2 to 5.3) months vs 2.9 (2.8 to 3.0) months = 1.5 months absolute difference in effect*** ***[D0006][2]***	***0.92 (0.74 to 1.15)*** ***[D0013][3]***	***1.01 (0.99 to 1.03)*** ***Absolute risk*: 989 per 1000 (969 to 1000)*** ***[C0008a][2]***	***1.11 (0.93 to 1.31)*** ***Absolute risk* 469 per 1000 (393 to 553)*** ***[C0008c][2]***	***1.05 (0.65 to 1.68)*** ***Absolute effect* 123 per 1000 (80 to 188)*** ***[C0008b][4]***
Quality of body of evidence+	⊕⊕⊕◯ MODERATE [1]	⊕⊕⊕◯ MODERATE [1]	⊕⊕⊕◯ MODERATE [1]	⊕⊕⊕◯ MODERATE [1]	⊕⊕◯◯ LOW [1,2]	⊕⊕◯◯ LOW [1,2]
Ramucirumab plus paclitaxel **Irinotecan**	***<1 (CI does not include 1)*** [1]	***<1 (CI does not include 1)*** [1]	***Not available***	***Not available***	***Not available***	***<1 (CI includes 1)*** [1]

Adults with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma previously treated with chemotherapy and with good performance status (ECOG score of 0 or 1)

	Health benefit			**Harm**		
	Overall mortality HR (95% CI)	**Progression-free survival** HR (95% CI)	**Quality of life (end of treatment)** RR (95% CI)	**Adverse events (any type, all severity grades)** RR (95% CI)	**Serious adverse events** RR (95% CI)	**Withdrawal due to adverse events** OR (95% CI)
Quality of body of evidence [+]	⊕⊕◯◯ LOW [2,3]	⊕⊕◯◯ LOW [2,3]	….	….	….	⊕◯◯◯ VERY LOW [2,3]
Ramucirumab plus paclitaxel / **Docetaxel**	***<1 (CI includes 1)*** [1]	***<1 (CI includes 1)*** [1]	***Not available***	***Not available***	***Not available***	***<1 (CI includes 1)*** [1]
Quality of body of evidence [+]	⊕⊕◯◯ LOW [2,3]	⊕⊕◯◯ LOW [2,3]	….	….	….	⊕◯◯◯ VERY LOW [2,3]
Ramucirumab plus paclitaxel / **Best supportive care**	***<1 (CI does not include 1)*** [1]	***Not available***	***Not available***	***Not available***	***Not available***	***>1 (CI does not include 1)*** [1]

Adults with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma previously treated with chemotherapy and with good performance status (ECOG score of 0 or 1)						
	Health benefit			**Harm**		
	Overall mortality HR (95% CI)	**Progression-free survival** HR (95% CI)	**Quality of life (end of treatment)** RR (95% CI)	**Adverse events (any type, all severity grades)** RR (95% CI)	**Serious adverse events** RR (95% CI)	**Withdrawal due to adverse events** OR (95% CI)
***Quality of body of evidence*[+]**	⊕⊕◯◯ LOW [2,3]	….	….	….	….	⊕◯◯◯ VERY LOW [2,3]

Abbreviations: ECOG=Eastern Cooperative Oncology Group; HR=hazard ratio; CI=confidence interval; RR=risk ratio; QoL=quality of life.
*We present the absolute risk for ramucirumab plus paclitaxel.
[+]Quality of the Body of Evidence was rated using GRADE. The interpretation is: High = We are very confident that the true effect lies close to that of the estimate of the effect; Moderate = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; Low = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect; Very Low: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

1. Single study, thus results not confirmed /shown consistently across different studies
2. Confidence interval include both no difference and clear harm or benefit
3. Based on indirect evidence. Limited evidence network with only one study for each comparison.

Discussion

The direct evidence for ramucirumab plus paclitaxel is based on one randomised controlled trial with a low risk of bias (RAINBOW study). RAINBOW is the largest clinical trial of second-line therapy in this patient population to date. The endpoints: overall survival, progression- free survival and objective response rate are representative of those used in other oncology studies and are in line with Committee for Medicinal Products for Human Use (CHMP) recommendations.
Defining the size of clinically meaningful outcomes is challenging. There are no published recommendations for what effect size on overall survival or progression-free survival is acceptable as clinically meaningful for this particular patient population, even though the topic has been discussed for example by the American Society of Oncology (ASCO). The difference of approximately 2 months in median overall survival achieved in RAINBOW seems a good result in this poor-prognosis population since patients whose disease progresses after first-line treatment can expect median survival under 6 months. The submitted disease specific global health status measures (European Organisation for Research and Treatment of Cancer quality of life questionnaire EORTC QLQ-C30) indicate more favourable results for patients treated with ramucirumab plus paclitaxel compared with those treated with placebo plus paclitaxel. Quality of life was maintained for a longer duration and more patients had stable or improved EORTC QLQ-C30 Global Health status compared to the placebo plus paclitaxel arm at each visit during the treatment. By the end of treatment, a higher proportion in the placebo plus paclitaxel arm had a stable or improved global health status.

Direct comparisons between the treatment alternatives were limited by the number of studies. The evidence for the comparators was based on data from 4 randomised controlled trials, all with open-label designs and rather small sample sizes (40 to 223 patients). Each linage was supported by only one RCT, making the evidence network linear and limited. The choice of methods used for the evidence networks was appropriate for the research question. There was some heterogeneity due to differences in inclusion and exclusion criteria, definition of primary and secondary endpoints in the studies and standard of care.

The direct comparison of ramucirumab plus paclitaxel compared with placebo plus paclitaxel indicated that nearly all patients can expect to experience adverse events with both treatment combinations. We did not find differences between the groups for withdrawals due to adverse events, frequency of serious adverse events or adverse events leading to death. The reporting of adverse events in the studies included in evidence networks was heterogeneous, limiting several comparisons. Indirect data on withdrawal due to adverse events was presented and gave important insight into estimates for the risk of reaching the point when the adverse events outweigh the potential benefits of treatment.

A second-line gastric cancer population is inevitably a selected population due to the fact that only a fraction of all patients diagnosed with advanced gastric cancer are candidates for first-line chemotherapy and even fewer will be offered second-line treatment. Patients from clinical trials in general are more homogeneous in terms of higher performance status and fewer comorbidities than patients in regular clinical practice. The patient populations in the included studies are probably as close to the intended population for this treatment combination as can be expected in a trial.

There is no direct head-to-head evidence to position ramucirumab plus paclitaxel compared with the other treatment alternatives used in second-line treatment of advanced gastric cancer or GEJ adenocarcinoma except for paclitaxel alone. Direct comparisons and large observational studies and data are needed to confirm the findings of indirect comparisons, and to facilitate more robust conclusions.

Upcoming evidence from registries will provide results that should help to clarify these issues.

Conclusion

One study constitutes the evidence for direct comparison of ramucirumab plus paclitaxel compared with paclitaxel. The overall survival benefit for combination ramucirumab and paclitaxel is considered clinically relevant in this population of patients with a poor prognosis. Results in secondary endpoints such as progression-free survival and objective response rate supported the observed improvement in overall survival. Quality of life was maintained for a longer duration in the ramucirumab plus paclitaxel arm with more patients reported stable or improved quality of life.

Direct comparison of ramucirumab plus paclitaxel compared with placebo plus paclitaxel indicated that nearly all patients can expect to experience adverse events of treatment, but the differences between the treatments were not statistically significant. Similarly, we did not find differences in withdrawal due to adverse events, frequency of serious adverse events or adverse event leading to death. Differences in quality of life between the treatment groups were small and may indicate that ramucirumab plus paclitaxel does not impose an extra burden on the patients compared with paclitaxel treatment.

LIST OF ABBREVIATIONS

AAZ	Agency for Quality and Accreditation in Health Care and Social Welfare (Croatia)
AE	Adverse event
BSC	Best supportive care
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events (National Cancer Institute)
DALY	Disability-adjusted life year
ECOG PS	Eastern Cooperative Oncology Group performance status
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer quality of life questionnaire
EPAR	European public assessment report
EQ-5D-3L	EuroQol five-dimensions, three-level scale
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
5-FU	5-Fluorouracil
GEJ	Gastro-oesophageal junction
GIST	Gastrointestinal stromal tumour
HR	Hazard ratio
HRQoL	Health-related quality of life
ICD	International Classification of Diseases
ITT	Intention-to-treat
IV	Intravenous
MAH	Marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
MeSH	Medical Subject Headings
NOKC	Norwegian Knowledge Centre for the Health Services

NR	Not reached; not reported
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PS	Performance status
QoL	Quality of life
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria In Solid Tumours
RR	Risk ratio; relative risk
SAE	Serious adverse event
SD	Standard deviation
TE-AE	Treatment-emergent adverse event
TE-SAE	Treatment-emergent serious adverse event
TTP	Time to progression
UK	United Kingdom
VEGF	Vascular endothelial growth factor
WHO	World Health Organization
WJOG	West Japan Oncology Group
ZIN	Zorginstituut Nederland

1 SCOPE

Description	Project Scope
Population	Adults with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma previously treated with chemotherapy and with good performance status (Eastern Cooperative Oncology Group [ECOG] score of 0 or 1). International Classification of diseases (ICD)-10 code: C 16; C16.0 MeSH-terms: stomach neoplasms; esophageal neoplasms or non-MeSH term gastro oesophageal junction adenocarcinoma
Intervention	Ramucirumab in combination with paclitaxel (as second- line therapy). Ramucirumab is not yet mapped as a MeSH term. Alternative MeSH terms: antineoplastic agents; antibodies; submapped to: antibodies, monoclonal; or non-MeSH term ramucirumab
Comparison	• Docetaxel monotherapy • Paclitaxel monotherapy • Irinotecan monotherapy • Best supportive care At present there are no other technologies (pharmaceuticals) than ramucirumab with marketing authorisation for the intended patient population. The off-label comparators were chosen based on information in published guidelines [ESMO-ESSO-ESTRO, 2013; EUnetHTA, 2013] MeSH terms: antineoplastic agents; taxoids; paclitaxel; antineoplastic agents, phytogenic; or non-MeSH term docetaxel; irinotecan; best supportive care.
Outcomes	Efficacy • Overall survival (OS); • Progression-free survival (PFS); • Objective response rate (ORR); • Health-related quality of life (HRQoL);

	Safety • Adverse events (AEs) of treatment (Any AEs, serious AE [SAE], discontinuation due to AE, AE of special interest, most frequent, death as SAE) Rationale for choosing the outcomes: commonly used outcomes in cancer studies and outcomes important for relative effectiveness assessment; based on recommendations from the EUnetHTA methods guideline on clinical and surrogate endpoints and safety.

2 METHODS AND EVIDENCE INCLUDED

2.1. Pilot team

The pilot team consisted of employees of the Norwegian Knowledge Centre for the Health Services (NOKC), in collaboration with the Norwegian Medicines Agency, employees of the Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ; Croatia) and of the Zorginstituut Nederland (ZIN).

ZIN was responsible for coordination between the involved parties throughout the duration of the pilot. NOKC was responsible for the descriptions of *Clinical Effectiveness, Safety* and miscellaneous parts. AAZ was responsible for the description of the *Technical Characteristics of the Technology*, the section on the *Health Problem and Current use of the Technology*, and the Checklist for potential ethical, organisational, social and legal aspects. We received comments from dedicated reviewers and stakeholders. NOKC and AAZ were responsible for assessing all comments and incorporating relevant changes. NOKC and AAZ are responsible for the final scientific content.

2.2. Identification of evidence

Search

The marketing authorisation holder (MAH) submitted both published and unpublished material divided into 3 separate documents: the submission dossier [2], the draft European public assessment report (EPAR) for ramucirumab [3] and a meta-analysis report [4]. When necessary, we performed additional non-systematic searches.

The marketing authorisation holder (MAH) performed the searches as part of their submission dossier. They used a combination of subject terms and text words to define the population and all interventions and controls relevant for this assessment. In addition, they used search terms to isolate randomised controlled trials and exclude other publication types such as case reports, letters and reviews. The search was adapted for each database. The search was undertaken in December 2013 and updated on 28 May 2014 with no date limits. The following databases were searched:

- MEDLINE (R) In-Process and Other Non-Indexed Citations
- Ovid MEDLINE (R) 1946 to present (via OVID)
- EMBASE, 1980 to present (via OVID)
- The Cochrane Library (via OVID), searching the following databases:
- The Cochrane Central Register of Controlled Trials (CENTRAL)
- The Cochrane Database of Systematic Reviews (Cochrane Reviews)
- The Database of Abstracts of Reviews of Effects (DARE)
- The Health Technology Assessment Database (HTA)

They also searched for conference abstracts from ESMO (European Society for Medical Oncology) and ASCO (American Society of Clinical Oncology).

The MAH used the same search strategy to search for direct and indirect evidence. The author team assessed the quality of the submitted search strategy. No errors were discovered. The author team searched the international clinical trials registry platform search portal at the World Health Organization for registered clinical trials using ramucirumab and did not identify any missing studies [5].

In total, the searches identified 11,056 records. Based on clear inclusion criteria in the screening process, the MAH identified 30 publications of 23 unique studies. However, after limiting the focus to

the intervention and controls for this assessment, the included studies were reduced to 1 study for direct evidence [1], and 3 studies comparing the comparator treatments [6-8]. Only randomised controlled studies in the English language were included. To view the full search strategy and description of the selection process for identification of studies, see Appendix 1.

Data extraction and calculation of estimates

Questions from the domains Description and technical characteristics of the technology and Health Problem and Current Use of Technology were answered by data from Manufacturer's submission file, EPAR and Summary of Product Characteristics on ramucirumab, Micromedex Drugdex Database and basic literatures identified through the systematic literature search.

For Clinical Effectiveness and Safety Domains one reviewer extracted data from submitted documents or otherwise identified sources. Another reviewer checked it for accuracy. We calculated effect estimates and risk ratio with 95% confidence intervals, for selected major outcomes if the submission dossier presented data only as frequencies. In these cases, we used RevMan 5.3 to perform the analyses. Such analyses are labelled as our calculations.

2.3. Quality rating of studies

No quality assessment tool was used for the domains Description and technical characteristics of the technology and Health Problem and Current Use of Technology, but multiple sources were used in order to validate individual, possibly biased, sources. Descriptive analysis was performed on different information sources.

We assessed the quality of identified trials and outcomes.

According to EUnetHTA guidelines, we used the Cochrane risk of bias too to assess internal validity. It includes evaluation of how the study was performed regarding randomisation, allocation concealment, blinding of participants, blinding of personnel and outcome assessments, data reporting (incomplete outcome data and selective reporting) and other potential risks of bias [9,10].

We assessed external validity using GRADE (Grading of Recommendations, Assessment, Development and Evaluation, www.gradeworkinggroup.org) only for the following outcomes: OS, PFS, QoL of direct evidence. The GRADE method involves an evaluation of factors influencing our confidence in the reported estimates. It includes an evaluation of study type, study quality (risk of bias), consistency of results between trials, directness (how similar the population, intervention, and outcomes are among the trials and the objectives of this report), precision of the estimates and publication bias. GRADE may also take into account whether there are strong associations between the intervention and the outcome such as a very large effect, whether there are dose–response associations or whether all confounding variables would have reduced the effect. Results are as far as possible presented as absolute and relative terms. Finally, the overall quality, or confidence in the estimate, was categorised as high, moderate, low or very low.

The categories should be interpreted as follows:

- **High quality:** We are very confident that the true effect lies close to that of the estimate of the effect
- **Moderate quality:** We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
- **Low quality:** Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
- **Very low quality:** We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect

We assessed the choice of methodology for making indirect comparisons. We used the EUnetHTA methods guideline on direct and indirect comparisons together with suggestions from the GRADE Working Group on how to rate the quality of the evidence from network meta-analysis [11,12]. Due to the limited evidence supporting the networks for indirect comparisons, we decided to use only a simplified approach for quality assessments.

We used the quality of the evidence for the direct comparison as the starting level. Further, we consequently deducted one level from the starting level due to the indirect nature of the evidence. When using indirect comparisons, there may be more heterogeneity in study design and study population characteristics such as performance status, background medication and outcome evaluation compared to direct evidence. Details of individual GRADE assessments are shown only for clinical effectiveness outcomes and for aggregated safety outcomes of direct evidence.

2.4. Description of the evidence used

Table 2.1 gives an overview of the main characteristics of studies included. We present further details of the studies in the evidence tables in Appendix 1.

One study, RAINBOW, presents direct evidence of ramucirumab plus paclitaxel for previously treated advanced gastric and gastro-oesophageal junction cancer. The remaining studies are used for indirect comparisons.

Table 2.1 Main characteristics of studies included

Author and year or study name	Study type	Number of patients (ITT)	Intervention(s)	Main endpoints	Included in clinical effectiveness and/or safety domain
RAINBOW[§] [1]	RCT, double-blind	665	Ramucirumab plus paclitaxel Placebo plus paclitaxel	Primary: OS Secondary: PFS, TTP, ORR, QoL and health status, safety,	Clinical effectiveness and safety
WJOG 4007 [7]	RCT, open label	223	Paclitaxel	Primary: OS	Clinical effectiveness

Author and year or study name	Study type	Number of patients (ITT)	Intervention(s)	Main endpoints	Included in clinical effectiveness and/or safety domain
			Irinotecan	Secondary: PFS, ORR, toxicity, rate of post-subsequent chemotherapy	and safety
COUGAR-02 [6]	RCT, open label	168	Docetaxel Active symptom control	Primary: OS Secondary: best response to docetaxel, time to progression (for docetaxel), toxicity, QoL	Clinical effectiveness and safety
Thuss-Patience [8]	RCT, open label	40	Irinotecan Best supportive care	Primary: OS Secondary: ORR, time to progression, toxicity	Clinical effectiveness and safety
Roy[13]	RCT, open label	88	Irinotecan Docetaxel	Survival, response, progression, safety	Used only to connect the evidence network for selected outcomes

§. Direct evidence. **Abbreviations:** ITT = intention-to-treat, all enrolled patients; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RCT = randomised controlled trial; TTP =time to progression; QoL = quality of life; WJOG=West Japan Oncology Group
Sources:[2]

2.5. Deviations from project plan

There were no deviations from the project plan, except for the need to publish only directions of results from indirect comparisons in the main report.

Participation in the EUnetHTA Joint Action 2 Work Package 5 is voluntary. The MAH submitted data for evaluation. This submission consisted of both published and unpublished material. The MAH performed new analyses of indirect comparisons to supplement data used as part of the marketing authorisation application. We are not able to present further details on the analysis and estimates of the original data for which the indirect estimates are based on, including the image of the network which shows the actual linkage of the studies. The MAH indicated that these data are to be submitted for publication and that presenting the data in our assessment would prevent acceptance.

To respect their willingness to participate in this pilot, we compromised on how to present the data. In this version of the assessment report, we present only the direction of results from indirect comparisons. We will publish an appendix with all actual estimates and confidence intervals by June 2015.

3 DESCRIPTION AND TECHNICAL CHARACTERISTICS OF THE TECHNOLOGY

3.1. Research questions

Element ID	Research question
B0001	What is ramucirumab and the comparators?
A0020	For which indications has ramucirumab received marketing authorisation?
B0002	What is the claimed benefit of ramucirumab in relation to the comparators?
B0003	What is the phase of implementation of ramucirumab and the comparator(s)?
A0021	What is the reimbursement status of ramucirumab?

3.2. Results

[B0001] What is ramucirumab and the comparators?

Ramucirumab

Ramucirumab is a human immunoglobulin G1 (IgG1) monoclonal antibody produced in murine (NS0) cells by recombinant DNA technology. Vascular endothelial growth factor (VEGF) receptor 2 is the key mediator of VEGF induced angiogenesis (Table 3.1).

Ramucirumab, is a human receptor-targeted antibody that specifically binds VEGF receptor 2 (VEGF R2; the extracellular domain) and blocks binding of VEGF-A, VEGF-C, and VEGF-D, preventing the interaction of VEGF R2 with activating ligands (VEGF-A, VEGF-C, and VEGF-D). As a result, ramucirumab inhibits ligand-stimulated activation of VEGF R2 and its downstream signalling components, including p44/p42 mitogen-activated protein kinases, neutralising ligand-induced proliferation and migration of human endothelial cells [14,15].

The affinity of ramucirumab for the VEGF-binding epitope on the extracellular domain of VEGFR-2 (dissociation constant = 50 pM) is much higher than the natural VEGF-A ligand which is important for biological activity of drug [16].

According the Summary of Product Characteristic (SmPC) the most serious adverse reactions associated with ramucirumab treatment (as a single agent or in combination with cytotoxic chemotherapy) were gastrointestinal perforation, severe gastrointestinal haemorrhage (including fatal events) and arterial thromboembolic events. The most common adverse reactions are fatigue/asthenia, neutropenia, leukopenia, diarrhoea, epistaxis and hypertension. Contraindications and special warnings and precautions for use are listed in Table 3.1. Ramucirumab has the potential to increase the risk of severe bleeding and should be permanently discontinued in patients who experience Grade 3 or 4 bleeding.

Ramucirumab has U.S. Food and Drug Administration's Pregnancy Category C (All Trimesters) [17].

Table 3.1 Summary data on ramucirumab

Ramucirumab (Cyramza)	
Active substance	ramucirumab
ATC code	Antineoplastic agents, monoclonal antibodies
Approved indication in advanced gastric cancer or gastro-oesophageal junction adenocarcinoma	**Yes**
Contraindications	Hypersensitivity to the active substance or to any of the excipients in Cyramza
SAEs	Gastrointestinal perforation; Severe gastrointestinal haemorrhage; Arterial thromboembolic events
SpecialWarnings and precautions for use	Arterial thromboembolic events; Gastrointestinal perforations; Severe bleeding; Infusion-related reactions; Hypertension; Impaired wound healing; Hepatic impairment; Fistula; Proteinuria; Renal Impairment; Sodium restricted diet.
Adult dosing	*Cyramza in combination with paclitaxel* The recommended dose of ramucirumab is 8 mg/kg on days 1 and 15 of a 28 day cycle, prior to paclitaxel infusion. The recommended dose of paclitaxel is 80 mg/m2 administered by intravenous infusion over approximately 60 minutes on days 1, 8 and 15 of a 28 day cycle.
Premedication	Histamine H1 antagonist (for example diphenhydramine) prior to infusion of ramucirumab. If a patient experiences a Grade 1 or 2 infusion-related reaction (as per the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]), premedication must be given for all subsequent infusions. If a patient experiences a second Grade 1 or 2 infusion-related reaction (IRR) administer dexamethasone (or equivalent); for subsequent infusions, premedicate with the following or equivalent medicinal products: an intravenous histamine H1 antagonist (for example diphenhydramine hydrochloride), paracetamol and dexamethasone.
Recommended duration of treatment	Until disease progression or until unacceptable toxicity has occurred.

Source: Summary of Product Characteristic (SmPC)

Comparators (paclitaxel, docetaxel, irinotecan, best supportive care)

In this assessment paclitaxel, docetaxel and irinotecan are used as comparators, as well as best supportive care (BSC), according the rationale given in the Scope. None of the 3 above-mentioned drugs is approved for second-line treatment but all are used off-label for patients with advanced disease whose cancer has progressed despite prior first-line chemotherapy (Table A13 in Appendix 2, Table A3 in Appendix 1). They are the most common agents recommended in treatment guidelines and the only agents listed in the most recent European ESMO- ESSO-ESTRO guidelines as second-line therapies, except when patients have a progression-free interval of >3 months after first-line therapy when patients could be re-challenged with first-line therapy (Table A3 in Appendix 1) [18]. Best supportive care is also an option since none of the comparators have regulatory approval in this treatment setting and relatively few patients in Western countries receive second-line treatment (please see A0025). According the manufacturers file data paclitaxel and docetaxel are used in between 16% and 46%, irinotecan in between 17% and 41% and BSC in between 15% and 37% of patients as a second line treatment [2]. Paclitaxel, docetaxel and irinotecan are all administered as intravenous infusions, generally in oncology-specific clinics. Pre-medications for each agent are based on label recommendations (for non-gastric cancer indications for all comparators), as well as local or institutional guidelines; corticosteroid regimens may require initiating dosing 12 to 24 hours prior to the infusion. Laboratory monitoring is generally recommended prior to each infusion, but conducted only once if multiple infusions are given on the same day. The frequency of radiological assessments is based on local or institutional guidelines. Toxicity is also assessed prior to each infusion and is customised based on the common or unique toxicities of each agent [2,17].

Paclitaxel is classified as a taxane (Table 3.2). Paclitaxel binds to tubulin and inhibits the disassembly of microtubules, thereby inhibiting of cell division. Treatment of gastric cancer is not an approved indication for paclitaxel in the USA or in the EU. Paclitaxel dosing regimens include weekly administration, weekly for 3 weeks followed by 1 week of rest (same dose regimen used in combination with ramucirumab), and every 3 weeks. Pre-medications generally include an H1-antagonist, an H2-antagonist, and a corticosteroid. According to the published data, in 2 small studies, treatment with paclitaxel produced overall response rates of 17% and 20% in patients with metastatic gastric cancer.

Paclitaxel had minimal activity in patients with previously untreated advanced adenocarcinoma of the upper gastrointestinal tract in a phase 2 trial (n=23).

Evidence supports the use of paclitaxel, in combination therapy, as reasonable medical therapy at some point in the management of advanced gastric carcinoma. Paclitaxel monotherapy has demonstrated only minimal activity against gastric cancer. Paclitaxel plus radiation has shown some activity against gastric cancer [2,17,19-22].

Table 3.2 Summary data on paclitaxel

Paclitaxel	
Active substance	paclitaxel
ATC code	Antineoplastic Agent, Mitotic Inhibitor
Approved indication in advanced gastric	No, **off-label use**

Paclitaxel	
cancer or gastro-oesophageal junction adenocarcinoma	
Contraindications	Baseline neutrophil counts of less than 1500 cells/mm^3 in patients with solid tumours or less than 1000 cells/mm^3 in patients with AIDS-related Kaposi's sarcoma; hypersensitivity to paclitaxel or to other drugs formulated in Cremophor(R) EL (polyoxyethylated castor oil)
SAEs	**Cardiovascular:** Atrial fibrillation, cardiac dysrhythmia (less than 1%), cardiotoxicity, congestive heart failure, myocardial infarction, supraventricular tachycardia; **dermatologic:** Stevens-Johnson syndrome, toxic epidermal necrolysis; **gastrointestinal:** gastrointestinal perforation, nausea and vomiting, grade 3 or greater (10% to 29%); **haematologic:** anaemia, grade 3 or greater (2% to 34%), deep venous thrombosis, febrile neutropenia (2% to 55%), neutropenia, grade 4 (14% to 81%), thrombocytopenia, grade 3 or greater (1% to 17%); **immunologic:** anaphylaxis, hypersensitivity reaction, grade 3 or greater (up to 4%), opportunistic infection (up to 76%), sepsis; **neurologic:** grand mal seizure (less than 1%), peripheral neuropathy, grade 3 or greater (up to 10%), seizure; **respiratory:** pulmonary embolism, respiratory failure
Black Box Warning	Anaphylaxis and severe hypersensitivity reactions characterised by dyspnoea and hypotension requiring treatment, angioedema, and generalised urticaria have occurred in clinical trials. Fatal reactions have occurred in patients despite premedication and all patients should be pretreated with corticosteroids, diphenhydramine, and H2 antagonists. Patients who experience severe hypersensitivity reactions to paclitaxel should not be rechallenged with the drug. Paclitaxel therapy should not be given to patients with solid tumours who have baseline neutrophil counts of less than 1500 cells/mm^3 and should not be given to patients with AIDS-related Kaposi's sarcoma if the baseline neutrophil count is less than 1000 cells/mm^3. Monitor peripheral blood cell counts frequently.
Adult dosing	Optimal dose and timing not defined in gastric cancer and carcinoma of oesophagus, used as weekly, weekly for 3 weeks followed by 1 week of rest (same dose regimen used in combination with ramucirumab), and every 3 weeks
Premedication	Corticosteroids, diphenhydramine, and H2 antagonists
Recommended duration of treatment	NA

Docetaxel is classified as a taxane (Table 3.3). Docetaxel binds to tubulin and inhibits the disassembly of microtubules, thereby resulting in the inhibition of cell division. Docetaxel is indicated in combination with cisplatin and fluorouracil for the treatment of advanced gastric adenocarcinoma, including adenocarcinoma of the gastro-oesophageal junction (GEJ), in patients who have not received prior chemotherapy for advanced disease (first-line treatment). In a randomised trial of patients with advanced gastric adenocarcinoma docetaxel, added to cisplatin and fluorouracil (TCF), improved median survival from 8.6 to 9.2 months as compared with cisplatin and fluorouracil (CF), with overall response rate of 36.7% for the TCF group vs 25.4% for the CF group [23].

Docetaxel dosing regimens include weekly and every 3 weeks administration. Pre-medications include corticosteroids. Literature data showed that a regimen consisting of docetaxel, cisplatin, and fluorouracil, administered sequentially, improved overall survival (OS) compared with cisplatin and fluorouracil in patients with advanced gastric adenocarcinoma (n=445), including adenocarcinoma of the GEJ. Premedicate with dexamethasone 8 mg orally twice daily for 3 days, starting 1 day prior to docetaxel (day 0); docetaxel 75 mg/m^2 intravenously over 1 hour on day 1, followed by cisplatin 75 mg/m^2 intravenously over 1 to 3 hours on day 1, followed by fluorouracil 750 mg/m^2/day intravenously over 24 hours on days 1, 2, 3, 4, and 5; repeat all doses every 3 weeks [17,24].

Table 3.3 Summary data on docetaxel

Docetaxel	
Active substance	Docetaxel
ATC code	Antineoplastic Agent, Mitotic Inhibitor
Approved indication in advanced gastric cancer or gastro-oesophageal junction adenocarcinoma	**Yes**, in **first-line therapy**: in combination with cisplatin and fluorouracil for the treatment of advanced gastric adenocarcinoma, including adenocarcinoma of the GEJ, in patients who have not received prior chemotherapy for advanced disease In **second-line** therapy: **off-label**
Contraindications	Neutrophil count less than 1500 cells/mm^3; severe hypersensitivity to docetaxel or any other drugs formulated with polysorbate 80
SAEs	Anaphylaxis; anaemia, grade 3 or 4; colitis; febrile neutropenia; infectious disease; interstitial pneumonia; leukopenia, grade 3 or 4; liver function tests abnormal; neutropenia, grade 3 or 4; pulmonary embolism; renal failure; Stevens-Johnson syndrome; thrombocytopenia; toxic epidermal necrolysis
Black Box Warning	Treatment-related mortality increases with abnormal liver function, at higher doses, and in patients with non-small cell lung carcinoma and a history of prior treatment with platinum-based therapy receiving docetaxel at 100 mg/m^2. Docetaxel should generally not be given to patients with bilirubin greater than the ULN, or to patients with AST and/or ALT greater than 1.5 x ULN concomitant with alkaline phosphatase greater than 2.5 x ULN. These patients are at increased risk for developing severe or life-threatening toxicities. Monitor LFTs prior to each treatment cycle. Docetaxel therapy should not be given to patients with neutrophil counts of less than 1500 cells/mm^3; obtain frequent blood counts to monitor for neutropenia. Severe hypersensitivity reactions, including fatal anaphylaxis, has been reported in patients who received dexamethasone premedication. Use is contraindicated in patients with a severe hypersensitivity to docetaxel or polysorbate 80. Severe fluid retention may occur.
Adult dosing	Docetaxel 75 mg/m^2 IV over 1 hour followed by cisplatin 75 mg/m^2 IV over 1 to 3 hours, both on day 1 only, followed by fluorouracil 750 mg/m^2/day IV over 24 hours daily for 5 days (starting at the end of the cisplatin infusion); repeat every 3 weeks
Premedication	Premedicate docetaxel with oral corticosteroids, such as dexamethasone 8 mg orally twice daily for 3 days, starting 1 day before docetaxel administration; premedicate cisplatin with

Docetaxel	
	anti-emetics and appropriate hydration
Recommended duration of treatment	Please see above

Abbreviations: ALT= alanine aminotransferase; AST=aspartate aminotransferase; LFT=liver function tests; ULN= upper limit of normal

Irinotecan is classified as a topoisomerase I inhibitor (Table 3.4). Irinotecan inhibits topoisomerase I activity by stabilising the cleavable complex between topoisomerase I and DNA, resulting in DNA breaks that inhibit DNA replication and trigger apoptotic cell death. Treatment of gastric cancer is not an approved indication for irinotecan in the USA or in the EU. Irinotecan dosing regimens include weekly, every 2 weeks, and every 3 weeks administration. Pre-medications include corticosteroids, anti-emetics such as 5-hydroxytryptamine antagonists, and atropine for diarrhoea. Based on literature data, median OS was statistically significantly improved with salvage chemotherapy with docetaxel or irinotecan in addition to BSC compared with BSC alone (5.3 vs 3.8 months) in patients with advanced gastric cancer in a multicentre, open-label, randomised, controlled, phase 3 Korean trial (n=202) [25].

Irinotecan has shown some activity as a single-agent or in combination with cisplatin in the treatment of advanced or metastatic gastric cancer [17,26-28].

Table 3.4 Summary data on irinotecan

Irinotecan	
Active substance	Irinotecan
ATC code	Antineoplastic agent , topoisomerase I inhibitor
Approved indication in advanced gastric cancer or gastro-oesophageal junction adenocarcinoma	No; **off-label use**
Contraindications	Hypersensitivity to irinotecan or any component of the product
SAEs	**Cardiovascular:** disorder of cardiovascular system; **gastrointestinal:** diarrhoea, grade 3 and 4 (4.9% to 31%), gastrointestinal perforation; **haematologic:** anaemia, grade 3 and 4 (2.1% to 8.4%), febrile neutropenia (adults, 2% to 7.1%; paediatrics, 8.8%), haemorrhage (1% to 5%), infectious disease, neutropenic (1% to 2.2%), leukopenia, grade 3 and 4 (17.4% to 37.8%), neutropenia, grade 3 or 4 (adults, 26% to 53.8%; paediatrics, 31.8%), thrombocytopenia, grade 3 and 4 (up to 4%), thromboembolic disorder (5.4% to 11.7%);

Irinotecan	
	immunologic: hypersensitivity reaction; **respiratory:** interstitial lung disease
Black Box Warning	Irinotecan can induce both early and late forms of diarrhoea. Early diarrhoea may be accompanied by cholinergic symptoms that may be prevented or ameliorated by atropine. Late diarrhoea can be life threatening and should be treated promptly with loperamide. Initiate antibiotic therapy if ileus, fever, or severe neutropenia develop. Administration of irinotecan should be interrupted and subsequent doses reduced if severe diarrhoea occurs. Severe myelosuppression may occur with irinotecan administration.
Adult dosing	Regimens include weekly, every 2 weeks, and every 3 weeks
Premedication	Corticosteroids, anti-emetics such as $5HT_3$-antagonists, and atropine for diarrhoea
Recommended duration of treatment	NA

Abbreviations: $5HT_3$=5-hydroxytryptamine; NA=not applicable

Best supportive care (BSC)

BSC is neither well defined nor standardised. The National Cancer Institute at the National Institutes of Health (USA) defines supportive care as “Care given to improve the quality of life of patients who have a serious or life-threatening disease. The goal of supportive care is to prevent or treat as early as possible the symptoms of a disease, side effects caused by treatment of a disease, and psychological, social, and spiritual problems related to a disease or its treatment. Also called comfort care, palliative care, and symptom management” [29].

The American Cancer Society define palliative or supportive care as care that focuses on relieving symptoms caused by serious illnesses like cancer. It can be given at any point during a person’s illness to help them feel more comfortable [30].

Zafar et al. (2008) raised a key issue in clinical trials when BSC is used in the control group: it is not well defined and is not standardised, which hampers the internal and external validity of clinical trials [31].

According to the data from ClinicalTrial.gov on the REGARD trial, BSC is described as the care determined to be appropriate by the investigator(s). BSC may include but is not limited to antiemetic agents, opiate and non-opiate analgesic agents, appetite stimulants, and granulocyte and erythroid growth factors [32].

Kang et al. (2012), in a randomized phase III trial comparing salvage chemotherapy plus best supportive care with best supportive care alone, reported that all patients received a standard BSC regimen predefined in the study protocol (multiprofessional attention to the patient’s overall physical, psychosocial, spiritual, and cultural needs was available at all stages of the illness; it included, but was not restricted to, analgesics, paracentesis, psychosocial care, nutritional support, and blood transfusion; localised radiotherapy to alleviate pain was allowed, provided that the radiation dose was in the palliative range) [25]. Investigators were free to provide non-protocol supportive care measures at any

time during the study if it was felt to be in the patient's best interest. BSC patients could exit BSC and were allowed to receive chemotherapy.

Ahmed et al. (2004), in a systematic review of trials comparing chemotherapy to BSC in gastrointestinal cancers revealed that BSC was not consistently defined in the 4 trials included, but shared some similarities (all reported the use of analgesics as part of the supportive care; 2 reported the use of antibiotics to control infections as part of supportive care and only one trial reported the use of psychological support as part of the supportive care) [33].

Kim et al. (2013) in a systematic review reported that the authors of RCTs included in the analysis were aware of the risk of bias and tried to provide consistent and pre-planned BSC intervention [34].
In 2012, a panel of 36 experts developed a consensus statement for BSC in clinical trials in advanced cancer identifying 4 domains of BSC: multidisciplinary care; supportive care documentation; symptom assessment and symptom management. Symptoms should be managed according the available evidence-based clinical guidelines.
A meta-analysis of clinical trials, along with the COUGAR-02 (2013) study, showed that docetaxel and irinotecan chemotherapy, compared with BSC, resulted in a significantly reduced risk of death (hazard ratio [HR] = 0.64, 95% CI: 0.52 to 0.79, $p < 0.0001$) [34]. Nonetheless, in patients without positive prognostic factors, BSC may remain as a treatment alternative. Literature data showed that supportive care could improve quality of life and potentially affect survival [35-38].

To provide recommendations for the best standards of cancer care ESMO recently published different evidence-based Clinical Practice Guidelines: Prevention of chemotherapy and radiotherapy-induced nausea; Erythropoiesis-stimulating agents in the treatment of anaemia in cancer patients; Management of cancer pain; Management of oral and gastrointestinal mucositis; Cancer, fertility and pregnancy; Management of venous thromboembolism (VTE) in cancer patients; Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy; Management of chemotherapy extravasation [39].

[A0020] For which indications has ramucirumab received marketing authorisation?

The European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) [40] issued a positive opinion on ramucirumab in combination with paclitaxel intended for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy during the meeting of 22-25 September 2014 (Table A13 in Appendix 2).

This recommendation was forwarded to the European Commission, which approved the product on 19 December 2014.

Ramucirumab plus paclitaxel is indicated for the treatment of adult patients with advanced gastric cancer or GEJ adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy.

Ramucirumab monotherapy is indicated for the treatment of adult patients with advanced gastric cancer or GEJ adenocarcinoma with disease progression after prior platinum or fluoropyrimidine chemotherapy and for whom treatment in combination with paclitaxel is not appropriate.

In the USA, ramucirumab was given marketing authorisation with the following FDA-approved indications: 1) Gastric cancer, as monotherapy (on 21 April 2014) or in combination with paclitaxel (on 5

November 2014) for advanced or metastatic disease, progressing after treatment with fluoropyrimidine- or platinum-containing chemotherapy; 2) Malignant neoplasm of the cardio-esophageal junction of the stomach, as monotherapy (on 21 April 2014) or in combination with paclitaxel (on 5 November 2014) for advanced or metastatic disease, progressing after treatment with fluoropyrimidine- or platinum-containing chemotherapy [41].

[B0002] What is the claimed benefit of ramucirumab in relation to the comparators?

Rational multi-target approaches to angiogenesis are needed to overcome resistance mechanisms. Inhibition of VEGFR2 (or VEGFA) may have some impact on these elements given pathway crosstalk, but is likely insufficient to prevent all escape mechanisms from occurring. Despite these potential mechanisms of resistance, ramucirumab may have distinct mechanistic advantages compared to other anti-angiogenic modalities. Although a number of tyrosine kinase inhibitors are being used, their biochemical promiscuity and potential for off-target toxicities present potential limitations in cancer therapy.

Ramucirumab offers a novel mechanism for anti-angiogenic therapy with the potential for both high affinity and high specificity blockade of VEGFR-2. Because ramucirumab binds to VEGFR-2 specifically and with high affinity, it may offer a rational modulation advantage. In contrast to other agents directed against the VEGFR-2/VEGF axis, ramucirumab binds a specific epitope on the extracellular domain of VEGFR-2, thereby blocking all VEGF ligands from binding to this therapeutically validated target.

Moreover, in contrast to bevacizumab, which binds to VEGF-A only, ramucirumab blocks all known VEGFs from binding to VEGFR-2. The combined effects of high specificity and more complete target inhibition could lead to a more complete blockade of angiogenesis [15] .

[B0003] What is the phase of implementation of ramucirumab and the comparator(s)?

In the USA and EU, ramucirumab was given a marketing authorisation in 2014 with approved indications: Gastric or GEJ adenocarcinoma, as monotherapy or in combination with paclitaxel for advanced or metastatic disease, progressing after treatment with fluoropyrimidine- or platinum-containing chemotherapy [17].

In contrast to other off-label second-line chemotherapy options, ramucirumab alone, or in combination with paclitaxel, is the only approved treatment option for patients with advanced disease whose cancer has progressed despite prior fluoropyrimidine and platinum chemotherapy (see A0025 and overview of European guidelines for advanced disease, in Table A3 Appendix 1).

[A0021] What is the reimbursement status of ramucirumab?

The reimbursement status of ramucirumab in combination with paclitaxel in different European Union (EU) countries will be decided at the national level after marketing authorisation.

3.3. Discussion

Ramucirumab alone, or in combination with paclitaxel is the only approved second-line treatment option for advanced gastric cancer or GEJ adenocarcinoma patients with disease progression after prior first-line chemotherapy. Other drugs are used as off-label second-line therapy. Off-label cancer treatment is

associated with various clinical, safety and ethical issues, and should be prescribed according national laws and only when the potential benefit outweighs the potential toxic effects. It should be used only where there is no licensed product available that meets the medical needs of the patient or in cases of serious adverse drug reactions connected with approved drugs.

Ramucirumab, among other serious adverse effects, increased the risk of haemorrhage, which could be severe and sometimes fatal haemorrhagic events. Ramucirumab should be permanently discontinued in patients who experience severe bleeding.

4 HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY

4.1. Research questions

Element ID	Research question
A0002	What is the precise definition of advanced gastric cancer or gastro-oesophageal junction adenocarcinoma and which diagnosis is given according to ICD-10?
A0004	What is the natural course of advanced gastric cancer or gastro-oesophageal junction adenocarcinoma?
A0005	What are the symptoms and the burden of advanced gastric cancer or gastro-oesophageal junction adenocarcinoma for the patient?
A0006	What is the burden of advanced gastric cancer or gastro-oesophageal junction adenocarcinoma for society?
A0025	How is advanced gastric cancer or gastro-oesophageal junction adenocarcinoma currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?

4.2. Results

Overview of the disease or health condition

[A0002] What is the precise definition of advanced gastric cancer or gastro-oesophageal junction adenocarcinoma and which diagnosis is given according to ICD-10?

Gastric cancers include malignancies that arise from the lining of the stomach and the gastro-oesophageal junction (GEJ) [42,43]. Whereas stomach cancers occur in any part of the stomach, GEJ cancers occur “within 5 cm proximal and distal of the anatomic cardia” [44]. The vast majority of gastric cancers are adenocarcinomas histopathological (about 90%), and in a minority of cases include lymphomas, gastrointestinal stromal tumours, or carcinoid tumours [42].

Current World Health Organization (WHO) International Statistical Classification of Diseases and Related Health Problems 10th Revision [45] uses C16 to code for ‘Malignant neoplasm of stomach’, with specific code extensions (0-8) for different anatomical localisations within the stomach, such as C16.0 for cardia (including cardiac orifice, cardio-oesophageal junction, GEJ, oesophagus and stomach). Extended code C16.9 is used for stomach, unspecified (gastric cancer, not otherwise

specified - NOS). The previous (9th) ICD [46] used 151 to code for 'Malignant neoplasm of stomach', and specific code extensions (0-9) were used in a similar manner as in ICD-10, including 151.9 for stomach, unspecified and 151.0 (cardia), which includes GEJ.

The commonly used Lauren classification of gastric adenocarcinoma defines 2 subtypes, diffuse and intestinal, based on location and histopathological features [47,48]. Diffuse cancers develop in the stomach wall and mucosa, usually in the distal part of the stomach and often in younger patients; they commonly metastasise to the peritoneum, and have a poor prognosis. Intestinal-type adenocarcinomas are characterised by gland formation, and are microscopically similar to colonic mucosa and commonly affect older patients. Gland formation includes a range from well to poorly differentiated carcinomas, which grow by expansion, and not by infiltration [47,49].

Dietary (nitroso compounds, high salt diet with low vegetables) and lifestyle risk factors (smoking and alcohol consumption) account for one-third to one-half of all gastric cancers. An important risk factor is *H. pylori* infection, especially certain genotypes (vacAs1-, vacAm1-, and cagA-positive). The risk is increased in hosts who possess specific types of cytokine polymorphisms (IL-1B-511*T/*T or IL-1B-511*T/*C). Gastric ulcers, adenomatous polyps, and intestinal metaplasia have been associated with an increased risk of gastric cancer [50].

[A0004] What is the natural course of advanced gastric cancer or gastro-oesophageal junction adenocarcinoma?

Patients who present with advanced gastric cancer at diagnosis have a poor prognosis and expected survival times of less than a year. They typically have lymph node metastases and surgery is not considered curative (but palliative if performed) [49,51,52]. Different chemotherapy regimens can result in median PFS and OS times of several months to about a year [53-57]. This seems to depend on different prognostic factors such as Eastern Cooperative Oncology Group (ECOG) performance status, baseline haemoglobin and carcino-embryonic antigen levels, the length of time from the start of first-line treatment of the disease until disease progression, tumour localisation, number of metastatic sites, peritoneal metastases, weight loss of less than 10%, ascites, tumour differentiation, prior gastrectomy, disease status (locally advanced versus metastatic disease) and geography [1,6,58-60].

European [61] mean 5-year age-standardised relative survival for stomach cancer was 25.1%, whereas Japan [49] had better survival outcomes of around 70%, possibly due to differences in the underlying subtypes of gastric cancers, but also due to differences in the care provided [51]. Mass gastric cancer screening was introduced in Japan in the 1960s, resulting in earlier diagnosis compared with Western countries where screening to a similar extent has not so far been introduced [51,62]. About 80% of patients presenting with locally advanced gastric cancer in Japan can be cured with resection of the tumour, whereas in the West this is the case for a lower proportion (below 55%) of such patients [49].

Effects of the disease or health condition

[A0005] What are the symptoms and the burden of advanced gastric cancer or gastro-oesophageal junction adenocarcinoma for the patient?

The symptoms and burden of advanced gastric cancer for the patient commonly include fatigue, nausea, vomiting, anorexia, abdominal pain, diarrhoea or constipation, melaena, haematemesis, weight loss, and anaemia [63-67].

[A0006] What is the burden of advanced gastric cancer or gastro-oesophageal junction adenocarcinoma for society?

According to the EUCAN [68,69] database, in 2012 the estimates of age-standardised (European) incidence rates (per 100 000) of gastric cancer (ICD C16) in men in the EU ranged from 33.7 in Latvia to 7.4 in Sweden, the overall EU (27) rate being 15.2 (Table A1, Appendix 1). The age-standardised incidence rates of gastric cancer in 2012 in women ranged from 14.9 in Estonia to 4.1 in Sweden, the overall EU (27) rate being 7.1. (Table A2, Appendix 1) [68,69].

Although there has been some progress in the treatment of gastric cancer, the prognosis still remains poor, in particular in Western countries; for patient diagnosed with advanced gastric cancer is approximately 1 year median survival [51]. Asian countries, such as Japan, Taiwan and South Korea, have somewhat more favourable outcomes [70,71]. The results of the EUROCARE-5 study showed that for patients diagnosed in 2000-2007 the European mean 5-year age-standardised relative survival for stomach cancer was 25.1% (95% CI 24.8% to 25.4%), the second lowest rate (after lung cancer) among all the common cancer sites studied [61]. The Central European and Southern European regions had survival rates above the European mean (28.1% and 29.6% respectively), whereas survival rates of 21.9% in Northern Europe, 17.2% in the UK and Ireland, and of 18.8% in Eastern Europe were below the mean [61]. The 5-year relative and period survival by stage was different for localised gastric cancer and that with distant metastases, namely 28.8% versus 4.2% [72]. A study in France found that the 5-year survival rate for patients diagnosed with metastatic disease was 2% for distal stomach tumours and 0% for cardia tumours [73]. Another study in the Netherlands found the 5-year survival rate for patients with Stage IV disease to be 1% for cardia tumours and 2% for non-cardia tumours [74].

In 2008, stomach cancer caused an estimated total loss of 378, 103, 197 and 108 disability-adjusted life years (DALYs) per age- adjusted 100 000 population in men in the Europe East, North, South and West WHO regions, respectively. For women the corresponding estimated losses were 185, 60, 107 and 63 DALYs per age-adjusted 100 000 population [75].

Current clinical management of the disease or health condition

[A0025] How is advanced gastric cancer or gastro-oesophageal junction adenocarcinoma currently managed according to published guidelines and in practice?

In Western countries, 80% to 90% of patients with gastric cancer (in more than 90 percent adenocarcinomas) are either diagnosed at an advanced stage, when the tumour is inoperable and/or metastatic, or develop recurrence within 5 years after initial surgery [51]. Most patients present with advanced-stage disease, and therefore need palliative chemotherapy. Not all patients with advanced disease receive first-line therapy; primarily because they are not considered fit enough to receive chemotherapy. Some chemotherapy regimens have been well established as first-line therapy, and have been shown to increase survival; however, almost all patients with metastatic gastric cancer develop progressive disease after first-line therapy. With the availability of several active chemotherapy drugs, many patients who retain a good performance status after the initial treatment remain good candidates for additional therapy [76]. Relatively few patients in Western countries (approximately 15% to 50% of patients receiving first-line treatment) receive second-line treatment [54,77-81].

An overview of European guidelines for advanced disease, including both first-line and subsequent therapy is given in Table A3, Appendix 1.

According the most current ESMO-ESSO-ESTRO clinical practice guidelines [18] for patients with advanced disease, *first-line palliative chemotherapy* combination regimens based upon a platinum–fluoropyrimidine doublet are generally used. Other doublet and triplet combinations are also sometimes used, including addition of an anthracycline (epirubicin) or a taxane (docetaxel).

In the EU there is currently no standard *second-line* treatment for patients with advanced gastric or gastro-oesophageal junction adenocarcinoma following progression despite prior chemotherapy. According the above mentioned ESMO-ESSO-ESTRO guidelines, in patients of adequate performance status, second-line chemotherapy is associated with proven improvements in OS and quality of life (QoL) compared with BSC, with treatment options including irinotecan, docetaxel, or paclitaxel (Level of evidence I, Grade of recommendation A) [18].

In patients with disease progression 3 months or more after first-line chemotherapy, it may be appropriate to consider a re-challenge with the same drug combination (Level of evidence IV, Grade of recommendation C). Additionally, consideration should always be given to inclusion of patients in appropriate clinical trials (Level of evidence V, Grade of recommendation B) [18].

In second-line clinical trials the following chemotherapy regimens have been used: irinotecan plus cisplatin or fluoropyrimidines; single-agent irinotecan; single-agent docetaxel; docetaxel plus oxaliplatin (expert opinion indicates that docetaxel is used more commonly with cisplatin or 5-fluorouracil [5-FU]); paclitaxel single-agent or plus platinum agents; and FOLFOX (folinic acid, 5-FU, oxaliplatin) [82].

Ramucirumab alone or in combination with paclitaxel is currently only approved treatment option for patients with advanced disease whose cancer has progressed despite prior fluoropyrimidine and platinum chemotherapy, and for whom there are currently no standard therapies available.

The National Comprehensive Cancer Network (NCCN) clinical practice guideline for gastric cancer [83] now includes the use of ramucirumab for second-line treatment of metastatic or locally advanced disease (NCCN Categories of Evidence and Consensus: Category 1).

Further treatment options include: palliative radiotherapy; endoscopic methods for relieving dysphagia such as oesophageal intubation, oesophageal dilatation, brachytherapy and stents; laser therapy and stents; and palliative surgery – to bypass obstruction in patients with distal stomach cancers that are obstructing the passage of food out of the stomach [82].

Target population

[A0007] What is the target population in this assessment?

In accordance with the proposed indication for ramucirumab in combination with paclitaxel, the target population in this assessment is adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy.

According to treatment guidelines, only patients who have good performance status at the time of progression after first-line treatment are considered to be candidates for second-line therapy [18].

[A0023] How many people belong to the target population**?**

Based on the estimated prevalence in the European countries of interest in the calendar year of 2011 the prevalence of gastric cancer, including GEJ cancer, was estimated to range from 2.8 to 3.6 per 10,000 in the EU community. Based on an updated literature review conducted in October 2014 and indirect methods (estimation of gastric cancer prevalence as a function of incidence and mean duration of disease) the population prevalence of gastric cancer (which includes GEJ cancer, as per ICD codes) in the European countries of interest (EU-28, plus Norway and Iceland) in the calendar year of 2014, was estimated to range from 2.80 to 4.24 per 10,000 in the EU community. This is below the threshold of 5 per 10,000 required by the European Commission for an orphan drug designation [2].

Based on UK data in 2011, the proportion of gastric cancer patients who have metastatic disease is estimated to be 80%, which is equal to approximately 4,700 people in UK [82,84]. Of patients with advanced disease, it is estimated that 66% have inoperable cancer, of whom 53% are estimated to be fit enough to receive first-line chemotherapy (all of these patients will probably relapse) [76,82].

4.3. Discussion

Particularly in Western countries, where up to 90% of patients are diagnosed at an advanced stage when curative resection is not possible, or develop recurrence within 5 years following resection that was intended to be curative, the prognosis remains poor despite some progress in the treatment of gastric cancer. Currently in the EU there is no standard second-line treatment for patients with advanced gastric or gastro-oesophageal junction adenocarcinoma following progression after first-line chemotherapy and ramucirumab alone or in combination with paclitaxel is only approved treatment option for these patients.

5 CLINICAL EFFECTIVENESS

5.1. Research questions

Element ID	Research question
D0001	What is the effect on overall mortality of ramucirumab in combination with paclitaxel compared to other treatments in second-line therapy?
D0005	How does ramucirumab in combination with paclitaxel affect symptoms and findings (severity, frequency) of patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma compared to other treatments in second-line therapy?
D0006	How does ramucirumab in combination with paclitaxel affect progression-free survival (PFS) of patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma compared to other treatments in second-line therapy?
D0016	How does ramucirumab in combination with paclitaxel affect performance status, such as ECOG score, compared to other treatments in second-line therapy?
D0012	What is the effect on health-related quality of life for ramucirumab in combination with paclitaxel compared to other treatments in second-line therapy?
D0013	What is the effect on disease-specific quality of life for ramucirumab in combination with paclitaxel compared to other treatments in second-line therapy?

5.2. Results

Included studies

Available evidence on the clinical effectiveness of ramucirumab plus paclitaxel is limited. The choice of comparator is justified in the sections on the description and technical characteristics of the technology and the health problem and current use of the technology. The relative effectiveness of ramucirumab plus paclitaxel is assessed using both direct and indirect evidence.

For the patients of interest in this assessment, there is direct evidence only for the comparison with placebo plus paclitaxel [1]. The indirect evidence for the relevant patient group consists of 3 additional randomised controlled studies with treatments that are considered to be relevant comparators (docetaxel, irinotecan and best supportive care) for ramucirumab plus paclitaxel treatment [6-8].

The RAINBOW study is a global, multicentre, randomised, double-blind phase 3 study comparing the efficacy and safety of ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with metastatic gastric cancer or GEJ adenocarcinoma whose disease progressed while on or within 4 months after the last dose of standard first-line platinum- and fluoropyrimidine-based combination chemotherapy [1]. All 665 patients were randomised in a ratio of 1:1 to receive either ramucirumab plus paclitaxel or placebo plus paclitaxel. Ramucirumab (8 mg/m^2) or an equivalent dose of placebo was administered as an intravenous (IV) infusion on days 1 and 15 in combination with paclitaxel (80 mg/m^2) on days 1, 8 and 15 of a 28-day cycle. The primary endpoint in RAINBOW was OS, and the secondary

endpoints included PFS, ORR, and QoL. Median duration of treatment with ramucirumab was 18 weeks (approximately 4 to 5 cycles) in the ramucirumab and paclitaxel group and 12 weeks in the placebo and paclitaxel group. Tumour assessments were made every 6 weeks (more details in Appendix 1).

Indirect evidence

Indirect comparisons with irinotecan, docetaxel, and BSC were limited by the number of studies as each linkage was supported by only one RCT each. Exclusion of heterogeneous trials was not feasible.

The WJOG study enrolled only Japanese patients (N = 223), and the vast majority received third-line therapy [7]. This open-label, phase III study compared treatment with weekly paclitaxel and biweekly irinotecan in patients with advanced gastric cancer refractory to treatment with fluoropyrimidine plus platinum. Patients were excluded if they had severe peritoneal metastases or GEJ tumours or if they were more than 75 years of age. Patients with ECOG performance status (PS) = 2 were allowed to enrol, but accounted for only 4% of the randomised population. Tumour assessments were made every 2 months in both treatment groups (more details in Appendix 1).

The COUGAR-02 study was conducted only in the UK (N = 168) and less than 20% of patients received third-line therapy [6].This open-label, phase III study compared the effect of docetaxel versus active symptom control with no placebo use. Docetaxel treatment was limited to 6 cycles. Patients with oesophageal cancer were allowed to enrol, as were patients with ECOG PS=2 (15% of population). Tumour assessments were made every 9 weeks in the docetaxel group but not in the active symptom control group. The study assessed health-related quality of life in addition to survival benefits (more details in Appendix 1).

The study by Thuss-Patience et al. was conducted only in Germany (N = 40) and less than 15% of patients received third-line therapy [8]. This open-label phase III study compared irinotecan plus BSC vs BSC alone. The study was ended early because of recruitment issues, and results are based on a total of 40 patients. Patients with ECOG PS=2 were allowed to enrol and represented 23% of the population. Prior fluoropyrimidine plus platinum therapy was not mandated, but almost all patients had received agents from both classes. Patients were excluded if they were more than 75 years of age. Tumour assessments were made every 6 weeks in the irinotecan group only (more details in Appendix 1).

The study by Roy et al. is only used to connect the evidence network for selected outcomes. In short, it is an open-label, phase II study (N=135) comparing irinotecan and docetaxel (more details in Appendix 1).

The MAH stated that the base-case analysis was conducted as a series of pairwise analyses using the Bucher method since there is no closed network [10]. The evidence networks were analysed via single pairwise meta-analysis and/or a series of indirect comparisons.

The results presented for the comparative effectiveness of ramucirumab (+ paclitaxel) for defined endpoints are based both on direct comparisons and indirect comparisons for each outcome.

Mortality

[D0001] What is the effect on overall mortality for ramucirumab in combination with paclitaxel compared to other treatments in second-line therapy?

Direct evidence

In the RAINBOW study, ramucirumab plus paclitaxel reduced the risk of death from any cause by 19% (HR= 0.81; 95% CI: 0.68 to 0.96; p=0.0169) compared with placebo plus paclitaxel. OS, the primary endpoint in the RAINBOW study, was defined as the interval between the date of randomisation and the date of death from any cause. The study demonstrated a statistically significant improvement in OS, with an improvement in median survival of 2.27 months among patients treated with ramucirumab plus paclitaxel compared with those in the placebo plus paclitaxel group. Median OS was 9.63 (95% CI 8.6 to 10.8) months among patients treated with ramucirumab plus paclitaxel compared with 7.36 (95% CI 6.3 to 8.4) months among those treated with placebo and paclitaxel (31% increase in survival time) [1]. The OS curves separated early, by 2 months of treatment, and remained separated beyond 1 year.

The quality of the direct evidence for OS according to GRADE is medium since the direct evidence is limited to only one clinical study. Details of individual GRADE assessments are shown in Table 5.1.

Table 5.1 Survival

Outcomes	***Anticipated absolute effects**** *(95% CI)*		*Relative effect (95% CI)*	*№ of participants (Studies)*	*Quality of the evidence (GRADE)*
	Risk with placebo+paclitaxel	**Risk with ramucirumab+paclitaxel**			
Mortality	Study population				
	776 per 1000	701 per 1000 (637 to 763)	HR 0.807 (0.678 to 0.962)	665 (1 RCT)	⊕⊕⊕◯ MODERATE [1]
Median survival	The median survival in the control group was 7.36 months	The median survival in the intervention group was 9.63 months (95% CI 8.48 to 10.81 months)	-	665 (1 RCT)	⊕⊕⊕◯ MODERATE [1]

Abbreviations: CI=confidence interval; HR=hazard ratio; RCT=randomised controlled trial
*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
1. Single study, thus results not confirmed /shown consistently across different studies

Indirect evidence

Only 4 studies informed the base-case analysis for OS [1,6-8]. Results of the base-case OS analysis for comparison with ramucirumab plus paclitaxel are presented in Table 5.2 below, based on the manufacturer's submission. The hazard ratios for OS (95% CI) all favoured ramucirumab plus paclitaxel

and were statistically significant versus placebo plus paclitaxel (based on the RAINBOW trial), irinotecan and BSC. There was no significant difference in the hazard of death for ramucirumab plus paclitaxel when compared with docetaxel. Sensitivity analyses were limited due to single study linkages.

Table 5.2 Indirect comparison: results for base-case overall survival for comparisons of ramucirimab plus paclitaxel against placebo/BSC, docetaxel and irinotecan.

Comparator→ Intervention↓	Paclitaxel	Irinotecan	Docetaxel	Placebo/BSC
Ramucirumab+ paclitaxel	*0.81 (0.68 - 0.96)*	<1 (CI does not include 1)	<1 (CI includes 1)	<1 (CI does not include 1)

All estimates are hazard ratio and 95% confidence intervals (CIs). Grey cells and italics = direct evidence

The quality of the evidence for indirect comparisons is assessed as low since the results are based on one study per comparison, wide confidence intervals, and the indirect nature of the comparison. There may be more heterogeneity between study design, study population characteristics such as performance status, background medication and outcome evaluation.

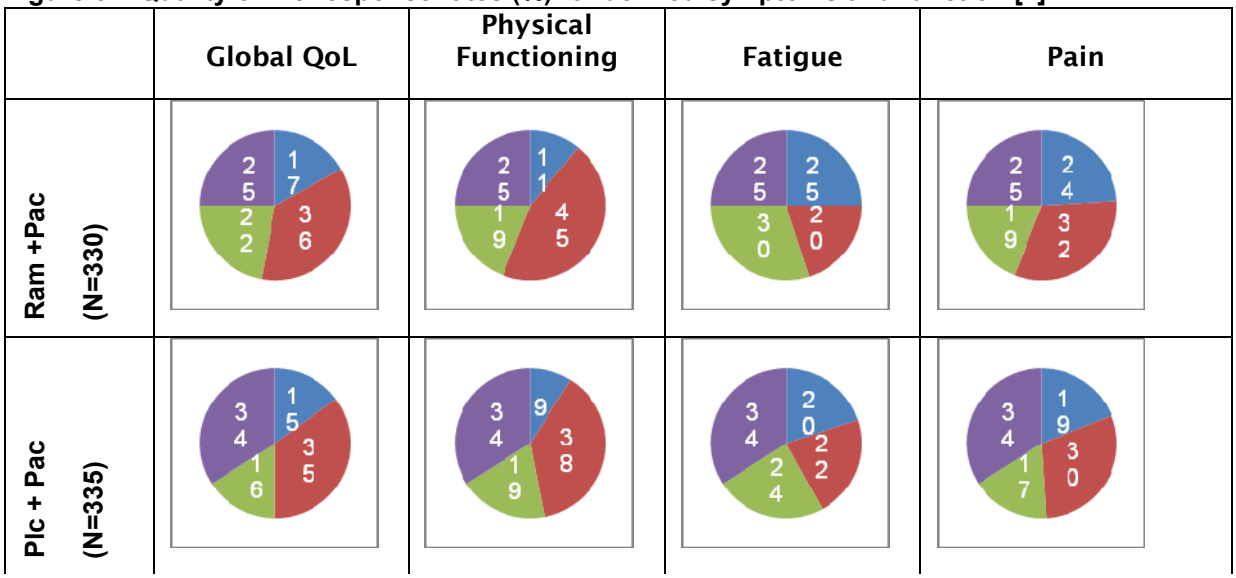
Morbidity

[D0005] How does ramucirumab in combination with paclitaxel affect symptoms and findings (severity, frequency) of patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma compared to other treatments in second-line therapy?

Direct evidence

Figure 5.1 below, submitted by the manufacturer, shows that a slightly greater proportion of patients in the ramucirumab plus paclitaxel group compared with the placebo plus paclitaxel group in the RAINBOW study experienced stability or improvement in symptoms such as fatigue (45% vs 42%) and pain (56% vs 49%) [2]. Slightly more patients reported better or stable physical functioning in the ramucirumab plus paclitaxel group compared with the placebo plus paclitaxel group (56% vs 47%). The results presented were collected after 6 weeks of treatment and are based on data collected from 75% of patients in the ramucirumab plus paclitaxel group and only 66% of patients in the placebo plus paclitaxel group.

Figure 5.1 Quality of life response rates (%) for defined symptoms and function [2]



Legend: blue: improved, red: stable, green: worsened, purple: no data
Abbreviations: Pac = paclitaxel; plc = placebo; QoL = quality of life; ram = ramucirumab.
Source:[2]

Indirect evidence (symptoms)

There are no indirect comparisons for symptoms such as pain and fatique due to lack of available data. The RAINBOW study reported an ORR, defined as patients achieving either a complete response or a partial response. ORR may possibly be considered an indirect measure of cancer-related morbidity. A significantly greater proportion of patients achieved an objective response in the ramucirumab plus paclitaxel group (92 of 330 patients [27.9%; 95% CI 23.3 to 33.0]) than in the placebo plus paclitaxel group (54 of 335 patients [16.1%; 95% CI 12.6 to 20.4]. The odds ratio for ORR was 2.14 (95% CI 1.45 to 3.16), p= 0.0001 (Table 5.3).

Table 5.3 Objective response rate

Outcomes	***Anticipated absolute effects**** *(95% CI)*		*Relative effect (95% CI)*	*No. of participants (Studies)*	*Quality of evidence (GRADE)*
	Risk with placebo + paclitaxel	**Risk with ramucirumab+paclitaxel**			
Objective response rate (ORR) assessed as: complete or partial response	Study population		OR 2.14 (1.45 to 3.16)	665 (1 RCT)	⊕⊕⊕◯ MODERATE [1]
	161 per 1000	291 per 1000 (218 to 378)			

Abbreviations: CI=confidence interval; OR=odds ratio; RCT=randomised controlled trial
*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
1. Single study, thus results not confirmed /shown consistently across different studies

The results for ORR are driven by the difference in partial responses (28% in the ramucirumab plus paclitaxel group compared with 16% in the paclitaxel plus placebo group). Complete response was achieved only in less than 1% of patients in both groups (0.6% vs 0.3%).

Indirect evidence

A significantly greater proportion of patients achieved an objective response in the ramucirumab and paclitaxel group, compared with paclitaxel and irinotecan, but not compared with docetaxel (Table 5.4). A sensitivity analysis was done for the outcomes of disease control rate and ORR using the intention-to-treat (ITT) population as opposed to the evaluable population. Results were consistent for analyses based on the evaluable population and the ITT population.

Table 5.4 Indirect comparison for objective response rate (evaluable population). Comparisons of treatment: ramucirumab plus paclitaxel against paclitaxel, docetaxel and irinotecan.

Comparator→ Intervention↓	Paclitaxel	Irinotecan	Docetaxel	Placebo/BSC
Ramucirumab + paclitaxel	*2.01 (1.38 to 2.93)*	>1 (CI does not include 1)	>1 (CI includes 1)	Not available

All estimates are hazard ratio and 95% confidence intervals (CIs). Grey cells and italics = direct evidence

The quality of the evidence for indirect comparisons is assessed as low since the results are based on one study per comparison. The reduction in the assessment from medium to low quality of the evidence comes from the indirect nature of the comparison. As a result there is likely to be more heterogeneity between study design, study population characteristics such as performance status, background medication and outcome evaluation.

[D0006] How does ramucirumab in combination with paclitaxel affect progression-free survival (PFS) of patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma compared to other treatments in second-line therapy?

Direct evidence

PFS in the RAINBOW study was defined as the time from the date of randomisation until the date of objectively determined radiographic disease progression (RECIST 1.1) or death due to any cause, whichever was first.

Treatment with ramucirumab plus paclitaxel significantly reduced the risk of disease progression or death (Table 5.5; HR=0.64; 95% CI: 0.54-0.75; p<0.0001); the median PFS was 1.5 months longer in the ramucirumab plus paclitaxel group compared with the placebo plus paclitaxel group. Median PFS in the ramucirumab plus paclitaxel group was 4.4 (95% CI 4.2 to 5.3) months vs 2.9 (95% CI 2.8 to 3.0) months in the placebo plus paclitaxel group. The robustness of the main PFS analysis results was supported by pre-specified sensitivity analyses, as demonstrated by consistent HRs between 0.599 and 0.649 with p<0.0001.

Table 5.5 Patients with progression of disease

Outcomes	***Anticipated absolute effects**** *(95% CI)*		Relative effect HR (95% CI)	№ of participants (Studies)	Quality of the evidence (GRADE)
	Risk with placebo+paclitaxel	**Risk with ramucirumab+paclitaxel**			
Patients with progression	Study population		0.635 (0.536 to 0.752)	665 (1 RCT)	⊕⊕⊕◯ MODERATE [1]
	884 per 1000	745 per 1000 (684 to 802)			

Abbreviations: CI=confidence interval; OR=odds ratio; RCT=randomised controlled trial
*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
1. Single study, thus results not confirmed /shown consistently across different studies

Indirect evidence

There was no significant difference in the hazard of progression or death for ramucirumab plus paclitaxel compared with docetaxel (Table 5.6). The hazard of progression or death for ramucirumab plus paclitaxel was lower compared with irinotecan.

Table 5.6 Indirect comparisons for progression-free survival

Comparator→ Intervention↓	Paclitaxel HR (95%CI)	Irinotecan HR (95%CI)	Docetaxel HR (95%CI)	Placebo/BSC
Ramucirumab plus paclitaxel	*0.64 (0.54 to 0.75)*	<1 (CI does not include 1)	<1 (CI includes 1)	Not available

All estimates are hazard ratio and 95% confidence intervals (CIs). Grey cells and italics = direct evidence

The quality of the evidence for indirect comparisons is assessed as very low since the results are based on one study per comparison. The reduction in the assessment from low to very low quality of the evidence comes from the indirect nature of the comparison. As a result there is likely to be more heterogeneity between study design, study population characteristics such as performance status, background medication and outcome evaluation.

[D0016] How does ramucirumab in combination with paclitaxel affect performance status, such as ECOG score, compared to other treatments in second-line therapy?

Activities of daily living were not assessed in the RAINBOW or in the comparator clinical trials. ECOG PS was used as an approximation. The time to deterioration in ECOG PS assessed the risk of functional status worsening to the extent that patients were no longer able to work and may have been confined to bed for at least part of the day.

Direct evidence

Treatment with ramucirumab plus paclitaxel was associated with a delay in the time to worsening of functional status, as measured with the ECOG PS compared with treatment with placebo plus paclitaxel. The median time to deterioration, that is to ECOG PS=2 or higher was 10.0 months (95% CI 8.3 to 15.0) in the ramucirumab plus paclitaxel group versus 8.6 months (95% CI 6.3 to 14.3) in the placebo plus paclitaxel group. The difference between the medians was 1.4 months (HR=0.798 (95% CI 0.612 to 1.040), p=0.094). The results are based on less than 50% of the patients from the RAINBOW study.

Indirect evidence

There are no indirect comparisons for this outcome due to the lack of available data on comparators for this specific outcome

Health-related quality of life

Quality of life assessments were performed using the European Organisation for Research and Treatment of Cancer Quality of Life questionnaire (EORTC QLQ-C30) and the EuroQol five-dimensions, three-level scale (EQ-5D-3L).

[D0012] What is the effect on health-related quality of life for ramucirumab in combination with paclitaxel compared to other treatments in second-line therapy?

The EQ-5D quality of life questionnaire is a generic scale for assessing quality of life and incorporates five functional scales: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

Direct evidence

The RAINBOW study presents limited EQ-5D-3L results [1], restricted to the data for baseline and for the end of treatment. The scale is from -0.59 to 1 with 1 representing perfect health [1].The EQ-5D-3L index scores were similar at baseline and at end of treatment. For the ramucirumab plus paclitaxel group mean at baseline and end of treatment were (0.75 (SD 0.22) and 0.61 (SD 0.32) and for the placebo plus paclitaxel group 0.75 (SD 0.24) and 0.60 (SD 0.35).

Indirect evidence

There are no indirect comparisons for this outcome due to the lack of available data on comparators for this specific outcome EQ 5 D was not assessed in the clinical trials for comparators.

[D0013] What is the effect on disease-specific quality of life for ramucirumab in combination with paclitaxel compared to other treatments in second-line therapy?

The EORTC quality of life questionnaire (QLQ) is an integrated system for assessing the health related quality of life (QoL) of cancer patients participating in international clinical trials. The QLQ-C30 incorporates five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status / QoL scale, and a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea) and perceived financial impact of the disease.

Direct evidence

Patients in RAINBOW completed the EORTC QLQ-C30 (v3) at baseline, every 6 weeks from start to discontinuation. Time to deterioration (TtD) was defined as time from randomization to first worsening of

≥10 points (on 100-point scale). In addition, scores were classified as improved or worsened if changed by ≥10 points relative to baseline, otherwise classified as stable.
More patients in the ramucirumab plus paclitaxel group reported improved or stable EORTC QLQ-C30 global health status compared with the placebo plus paclitaxel group at each visit during the treatment, mostly due to stabile status. By the end of treatment however a higher proportion of patients in the placebo plus paclitaxel group had a stable or improved global health status (RR= 0.92 [95%CI 0.74 to 1.15]) (Table 5.7 and 5.8) [3,85].

Table 5.7 Global health status at each visit during the RAINBOW trial[86]

	Ramucirumab + Paclitaxel N = 330				Placebo + Paclitaxel N = 335				
Visit	Improved	Stable	Deteriorated	No Data	Improved	Stable	Deteriorated	No Data	p-Value[a]
Cycle 2 Day 15	57 (17.3)	118 (35.8)	72 (21.8)	83 (25.2)	50 (14.9)	116 (34.6)	54 (16.1)	115 (34.3)	0.3937
Cycle 4 Day 1	45 (13.6)	74 (22.4)	58 (17.6)	153 (46.4)	27 (8.1)	65 (19.4)	34 (10.1)	209 (62.4)	0.0196
Cycle 5 Day 15	27 (8.2)	53 (16.1)	39 (11.8)	211 (63.9)	14 (4.2)	38 (11.3)	23 (6.9)	260 (77.6)	0.0063
Cycle 7 Day 1	25 (7.6)	23 (7.0)	23 (7.0)	259 (78.5)	11 (3.3)	19 (5.7)	11 (3.3)	294 (87.8)	0.0298
Cycle 8 Day 15	15 (4.5)	24 (7.3)	18 (5.5)	273 (82.7)	6 (1.8)	12 (3.6)	3 (0.9)	314 (93.7)	0.0034
Cycle 10 Day 1	13 (3.9)	12 (3.6)	10 (3.0)	295 (89.4)	6 (1.8)	7 (2.1)	4 (1.2)	318 (94.9)	0.0453
End of Treatment	21 (6.4)	80 (24.2)	108 (32.7)	121 (36.7)	25 (7.5)	86 (25.7)	91 (27.2)	133 (39.7)	0.5062

Abbreviations: EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer, Questionnaire-C30; ITT = intent-to-treat; N = number of randomized patients; n = number of patients in category.
a 2-sided p-value of Fisher's exact test for Not Deteriorated (Improved or Stable) versus Deteriorated/No Data comparing the treatment groups.
Note 1: Assessment is based on a 6-week schedule.
Note 2: Percentages are based on the number of patients in the ITT population in the corresponding treatment arm.

Table 5.8 Quality of life reported at the end of treatment and at 18 weeks

Outcomes	***Anticipated absolute effects**** *(95% CI)*		*Relative effect (95% CI)*	*№ of participants (Studies)*	*Quality of the evidence (GRADE)*
	Risk with placebo+ paclitaxel	**Risk with ramucirumab+paclitaxel**			
Quality of Life (end of treatment) assessed with: EORTC QLQ-C30	Study population		RR 0.92 (0.74 to 1.15)	665 (1 RCT)	⊕⊕⊕◯ MODERATE [1]
	331 per 1000	305 per 1000 (245 to 381)			
Quality of Life (18 weeks) assessed with: EORTC QLQ-C30	Study population		RR 1.56 (1.14 to 2.14)	665 (1 RCT)	⊕⊕⊕◯ MODERATE [1]
	155 per 1000	242 per 1000 (177 to 332)			

Abbreviations: CI=confidence interval; RR: risk ratio; RCT=randomised controlled trial
*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
1. Single study, thus results not confirmed /shown consistently across different studies

Indirect evidence
There are no indirect comparisons for this outcome. Only COUGAR-02 study assessed quality of life but the results were not reported in a manner to allow for any comparisons.

5.3. Discussion

The patient population in the studies included in the submission are most likely representative of the relevant patients within the scope of this assessment. A second-line gastric cancer population is already a selected population due to the fact that only a fraction of all patients diagnosed with advanced gastric cancer receive first-line chemotherapy. Relatively few patients in Western countries receive second-line treatment (approximately 15% to 50% of patients receiving first-line treatment; see [A0025]).

Intervention and choice of comparator treatment
Ramucirumab alone, or in combination with paclitaxel will be the first approved second-line treatment option for patients with advanced disease whose cancer has progressed despite prior first-line chemotherapy. Other drugs currently available (docetaxel, irinotecan, paclitaxel) are used as off-label second-line therapy.
Paclitaxel seems an appropriate choice for the control group of the RAINBOW trial since paclitaxel had been shown to have similar activity to other single-agent (including docetaxel and irinotecan) or combination chemotherapy regimens in off-label use in second-line treatment of advanced gastric cancer. Irinotecan, docetaxel and BSC are relevant comparators for the indirect comparison based on the network meta-analysis.

Outcomes
OS is considered a very important outcome for studies of advanced cancer. The studies of ramucirumab plus paclitaxel and comparators were all designed with OS as the primary endpoint. Except for the study of Thuss-Patience et al. that ended early due to poor enrolment, the other studies followed patients until the pre-specified number of deaths had occurred.
PFS represents the time during which a patient is directly benefiting from an intervention. In the RAINBOW trial [1], radiological assessments were conducted every 6 weeks, allowing for early detection of tumour progression. In the WJOG study [7], radiological assessments were conducted every 8 weeks. In the study reported by Thuss-Patience et al. [8], radiological assessments were conducted every 6 weeks but only in the experimental arm. In COUGAR -02 study, radiological assessments were conducted at 9 and 18 weeks, but only in the experimental arm.

ORR was assessed at the same frequency as PFS. Assessments at intervals of 6 to 9 weeks are reasonable in terms of expectations of when tumour shrinkage might occur.

Interpretation and consideration of the direct evidence
The results are based on only one single study. The RAINBOW study demonstrated a statistically significant improvement in OS and PFS and a benefit in ORR and maintained quality of life.
The randomisation and stratification in RAINBOW resulted in balance across treatment groups with respect to potential prognostic factors. The demographic, disease, and other baseline characteristics (ECOG PS; age; previous treatment) reflect a typical clinical trial population of advanced gastric cancer patients and are largely representative of the target patient population. The primary endpoint of improved OS was met in addition to improvements in PFS, while maintaining QoL. The robustness of the OS and PFS results was supported by sensitivity analyses. The RAINBOW study has provided evidence of the clinical efficacy of ramucirumab plus paclitaxel compared with placebo plus paclitaxel, in terms of the primary endpoint OS, in patients with advanced gastric cancer or gastro-oesophageal

junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy.

Defining the size of clinically meaningful outcomes is challenging as was recently discussed by ASCO [87]. So far there are no published recommendations for what effect size on OS or PFS is acceptable as clinically meaningful for this particular patient population. The difference in overall survival achieved in RAINBOW seems a good result in this poor-prognosis population since patients whose disease progresses after first-line treatment can expect median survival under 6 months.

The RAINBOW study has a low risk of bias and high internal validity, but its external validity is more uncertain. The quality of the evidence is considered moderate according to GRADE because it was limited to only one clinical study. Details of individual GRADE assessments are shown in Appendix 1.

Interpretations and considerations of the indirect evidence

The MAH presented results from evidence networks for OS, PFS and ORR. The approach seems appropriate for this assessment. Evidence of the relative effectiveness of ramucirumab plus paclitaxel compared with relevant alternative therapy either with docetaxel, irinotecan or BSC is very limited, consisting entirely of studies with open-label designs and rather small sample sizes. The results are based on indirect comparisons made between single studies for each comparator treatment.

Ramucirumab in combination with paclitaxel treatment was associated with a statistically significant lower hazard of death compared with placebo/BSC, paclitaxel monotherapy and irinotecan. There was no significant difference in the hazard of death for ramucirumab plus paclitaxel compared with docetaxel.

The studies used show heterogeneity of the study population characteristics such as performance status, background medication and outcome evaluation, and some differences in secondary outcomes. Details of individual GRADE assessments are not shown for indirect evidence. The quality of this evidence is considered low due to the indirect nature of the comparison.

There is no direct head-to-head evidence to position ramucirumab plus paclitaxel compared with the other off-label treatment alternatives used in second-line except for paclitaxel. There is little information available from real world care settings, and direct evidence for off-label treatments is limited. Direct comparisons and/or observational data are necessary to formally confirm the findings of indirect comparisons, and facilitate conclusions that are more robust.

Evidence gaps

Predictive biomarkers for ramucirumab have not yet been identified.

There are no studies that include direct comparisons of all potentially relevant comparators with ramucirumab plus paclitaxel.

The RAINBOW study included patients with ECOG PS 0 and 1. For patient with performance status worse than 1, efficacy data are not available. In the absence of clear signals against the generalizability of results, the CHMP concluded against a restriction of the indication to patients with good performance status.

6 SAFETY

6.1. Research questions

Element ID	Research question
C0008	How safe is the technology in relation to (the) comparator(s)? Divided into 5 more specific questions: a) What is the frequency of all adverse events with ramucirumab in combination with paclitaxel compared to other treatments in second-line therapy? b) What is the frequency of discontinuation of treatment due to adverse events with ramucirumab in combination with paclitaxel compared to other treatments in second-line therapy? c) What is the frequency of and what are the serious adverse events (SAEs) with ramucirumab in combination with paclitaxel compared to other treatments in second-line therapy? d) What is the frequency of serious adverse events (SAEs) leading to death with ramucirumab in combination with paclitaxel compared to other treatments in second-line therapy? e) What are the most frequent adverse events with ramucirumab in combination with paclitaxel compared to other treatments in second-line therapy?
C0005	What are the susceptible patient groups that are more likely to be harmed with ramucirumab treatment in combination with paclitaxel?

6.2. Results

Limited evidence is available for the use of ramucirumab in combination with paclitaxel. Currently, no treatment options with regulatory approval exist for second-line treatment for advanced gastric cancer. As described in the sections on the Description and Technical Characteristics of the Technology and on the Health Problem and the Current Use of the Technology, the most commonly used treatments are paclitaxel, irinotecan, docetaxel and BSC. For the patients of interest in this assessment, there is direct evidence only for ramucirumab plus paclitaxel compared with placebo plus paclitaxel.

Patient safety

[C0008] How safe is the technology in relation to (the) comparator(s)?

We formulated 5 different sub-questions to address different aspects of how safe ramucirumab plus paclitaxel are compared with other treatments in second-line therapy of gastric cancer and gastro-oesophageal junction carcinoma previously treated with chemotherapy.

Information on safety given in the labelling is based on knowledge of monoclonal antibodies and of the ramucirumab mechanism of action, and on studies of ramucirumab as monotherapy and in combination

with paclitaxel. This information also includes information from studies in patient populations other than the one indicated in the labelling. However, in this assessment, we focus on comparative safety within our selected population. In Appendix 1 we present details of the studies used as evidence for the safety domain, evidence tables and risk of bias tables.

For the RAINBOW trial all numbers relate to the safety population (all patients that received at least one dose of study drug) unless otherwise specified. Adverse events were identified through reports, physical examinations, and clinical laboratory assessments. They used the National Cancer Institute common terminology criteria for adverse events (NCI-CTCAE; version 4.02) [88]. Each term is a lowest level term in the Medical Dictionary for Regulatory Activities (MedDRA) [89]. It is divided based on the severity of the adverse event giving the following:

> Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
> Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
> Grade 3 Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self care activities of daily living.
> Grade 4 Life-threatening consequences; urgent intervention indicated.
> Grade 5 Death related to adverse event.

[C0008a] What is the frequency of all adverse events of ramucirumab in combination with paclitaxel compared to other treatments in second-line therapy?

Direct evidence

An adverse event was considered treatment-emergent if it occurred during or after the first administration of the study drug, and up to 30 days after the last dose. It could also be an event that occurred prior to study drug administration, if it worsened during therapy or up to 30 days after the last dose. Results from the RAINBOW trial show that most patients experience adverse events, but there is no indication of a different frequency of adverse events in patients treated with ramucirumab plus paclitaxel compared with placebo plus paclitaxel treatment, RR 1.01 (95% CI 0.99 to 1.03) moderate quality of the evidence (Table 6.1). If we focus on adverse events of grade 3 or higher, the RR is 1.30 (95% CI 1.18 to 1.44), which is a statistically significant difference in favour of the control group.

Table 6.1 Adverse events for ramucirumab plus paclitaxel compared with placebo plus paclitaxel

Outcomes	***Anticipated absolute effects**** *(95% CI)*		*Relative effect (95% CI)*	*№ of participants (Studies)*	*Quality of the evidence (GRADE)*
	Risk with placebo+paclitaxel	**Risk with ramucirumab+paclitaxel**			
Patients with one or more adverse events vs placebo+ paclitaxel	Study population		RR 1.01 (0.99 to 1.03)	656 (1 RCT)	⊕⊕⊕◯ MODERATE [1]
	979 per 1000	989 per 1000 (969 to 1000)			
Patients with adverse events of grade 3 or higher	Study population		RR 1.3 (1.18 to 1.44)	656 (1 RCT)	⊕⊕⊕◯ MODERATE [1]
	626 per 1000	814 per 1000 (739 to 902)			

Abbreviations: CI=confidence interval; RR=risk ratio; RCT:=randomised controlled trial
*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
[1] Single study, thus results not confirmed /shown consistently across different studies

Indirect evidence
No indirect evidence calculations were presented for this outcome due to lack of available data.

[C0008b] What is the frequency of discontinuation of treatment due to adverse events of ramucirumab in combination with paclitaxel compared to other treatments in second-line therapy?

Direct evidence
Direct evidence is from the RAINBOW trial. The frequency of patients that discontinued treatment because of adverse events was similar between patients treated with ramucirumab plus paclitaxel and placebo plus paclitaxel. Calculations based on the ITT population give an RR of 1.04 (95% CI 0.68 to 1.59). The quality of the evidence is low (Table 6.2).

Table 6.2 Withdrawal due to adverse events

Outcomes	***Anticipated absolute effects**** *(95% CI)*		*Relative effect (95% CI)*	*№ of participants (Studies)*	*Quality of the evidence (GRADE)*
	Risk with placebo+ paclitaxel	**Risk with ramucirumab+paclitaxel**			
Patients who discontinued treatment due to adverse events	Study population		RR 1.04 (0.68 to 1.59)§	665 (1 RCT)	⊕⊕◯◯ LOW [1] [2]
	118 per 1000	123 per 1000 (80 to 188)			

Abbreviations: CI=confidence interval; RR=risk ratio; RCT=randomised controlled trial

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
§Calculated by author team based on events presented in submission file [2] and publication by Wilke et al. of the RAINBOW trial [1]. It correspond to the odds ratio and 95% CI presented in the submitted meta-analysis report 1.05 (0.65-1.68) [4].

1. Single study, thus results not confirmed /shown consistently across different studies
2. Confidence interval include both no difference and clear harm or benefit

Indirect evidence

Calculations based on the studies comparing other second-line treatments used, indicate that all active treatments show higher withdrawal due to adverse events than BSC. There were no statistically significant differences between any of the active treatment alternatives, ramucirumab plus paclitaxel, paclitaxel, docetaxel and irinotecan as presented in Table 6.3.

The quality of the evidence for indirect comparisons shown here is very low. As for the direct evidence, the results are based on only one study per comparison, with few patients and/or events. The reduction of the quality of the evidence from low to very low is due to the indirect nature of the comparison. This leads to greater heterogeneity in the study design, study population characteristics such as performance status, background medication and outcome evaluation. Details of individual GRADE assessments are not shown for indirect evidence.

Table 6.3 Treatment withdrawal due to adverse events – from evidence network

Comparator→ Intervention↓	Paclitaxel	Irinotecan	Docetaxel	Best supportive care
Ramucirumab+ paclitaxel	*1.05 (0.65-1.68)*	<1 (CI includes 1)	<1 (CI includes 1)	>1 (CI does not include 1)

All estimates are odds ratio and 95% confidence intervals (CIs). Grey cells and italics = direct evidence

[C0008c] What is the frequency of and what are the serious adverse events (SAEs) with ramucirumab in combination with paclitaxel compared to other treatments in second-line therapy?

Direct evidence

Direct evidence is from the RAINBOW trial. Treatment-emergent SAEs were reported for the time that patients were on the study drug and for 30 days after treatment. The time could be extended to include any time past treatment as long as the SAE was considered possibly, probably, or definitely related to study treatment by the investigator. The proportion of patients who experienced any SAE was similar among patients treated with ramucirumab plus paclitaxel and those treated with placebo plus paclitaxel.

Based on the frequencies of SAE submitted by the MAH, we calculated an RR of 1.11 (95%CI 0.93 to 1.31) (Table 6.4). The quality of the evidence is low. Calculations based on selecting SAEs of grade 3 or above gave a similar result, RR 1.15 (95%CI 0.95 to 1.38).
The following SAEs occurred in 2% or more of patients receiving ramucirumab plus paclitaxel and are listed in order of decreasing frequency: malignant neoplasm progression, neutropenia, abdominal pain, febrile neutropenia, general physical health deterioration, anaemia, pyrexia and vomiting. Our control calculation of risk ratio and 95%CI for the top 2 events at any grade gave an RR 0.89 (95%CI 0.60-1.33) for malignant neoplasm progression and RR 4.02 (95%CI 1.15-14.13) for neutropenia (statistically significant in favour of the control group).

Table 6.4 Serious adverse events

Outcomes	***Anticipated* absolute effects*** (95% CI)		*Relative effect (95% CI)*	*№ of participants (Studies)*	*Quality of the evidence (GRADE)*
	Risk with placebo+paclitaxel	**Risk with ramucirumab+paclitaxel**			
Patients with serious adverse events	Study population		RR 1.11 (0.93 to 1.31)§	656 (1 RCT)	⊕⊕◯◯ LOW [1,2]
	422 per 1000	469 per 1000 (393 to 553)			

Abbreviations: CI=confidence interval; RR=risk ratio; RCT=randomised controlled trial
*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
§ calculated by author team based on events in presented in submission file [2] and publication by Wilke et al. of the RAINBOW trial [1].
1. Single study, thus results not confirmed /shown consistently across different studies
2. Confidence interval include both no difference and clear harm or benefit

Indirect evidence
The submission dossier does not present indirect evidence for the frequency of SAEs due to lack of available data.

[C008d] What is the frequency of serious adverse events (SAEs) leading to death for ramucirumab in combination with paclitaxel compared to other treatments in second-line therapy?

Direct evidence
Direct evidence is from the RAINBOW trial. The number of deaths due to an adverse event was similar in patients treated with ramucirumab plus paclitaxel and those treated with placebo plus paclitaxel, 13/327(4%) vs 15/329 (4.6%); RR 0.87 (95%CI 0.42- 1.80) [2,3]. This includes deaths due to adverse events that occurred during treatment or up to 30 days after the last dose of study drugs. The quality of the evidence is low (Table 6.5). Details of the deaths that occurred within 30 days of the last dose are given in the manufacturer's submission. However, the numbers of patients with an adverse event leading to death are also reported to be 39/327 vs 51/329, giving an RR of 0.77 (95%CI 0.52-1.13) [1,2]. Further, the numbers of deaths with a causal relationship to any study drug are reported as 6/327 vs 5/329 patients for the ramucirumab plus paclitaxel and placebo plus paclitaxel groups, respectively [1,17].

Table 6.5 Deaths due to an adverse event

Outcomes	***Anticipated absolute effects**** *(95% CI)*		*Relative effect (95% CI)*	*№ of participants (Studies)*	*Quality of the evidence (GRADE)*
	Risk with placebo+ paclitaxel	**Risk with ramucirumab+paclitaxel**			
Deaths due to an adverse events	Study population		RR 0.87 (0.42 to 1.8)	656 (1 RCT)	⊕⊕◯◯ LOW [1] [2]
	46 per 1000	40 per 1000 (19 to 82)			

Abbreviations: CI=confidence interval; RR=risk ratio; RCT=randomised controlled trial
*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

1. Single study, thus results not confirmed /shown consistently across different studies
2. Confidence interval include both no difference and clear harm or benefit

Indirect evidence

The submission dossier does not present indirect evidence for the frequency of SAEs leading to death due to lack of available data.

[C0008e] What are the most frequent adverse events of ramucirumab in combination with paclitaxel compared to other treatments in second-line therapy?

Direct evidence

Direct evidence is from the RAINBOW trial. The following adverse events occurred in 10% or more of the patients in the ramucirumab plus paclitaxel group, and based on the safety population (listed in order of decreasing frequency): fatigue, neutropenia, neuropathy, decreased appetite, abdominal pain, nausea, anaemia, leukopenia, alopecia, diarrhoea, epistaxis, vomiting, oedema peripheral, hypertension, constipation, asthenia, stomatitis, pyrexia, proteinuria, malignant neoplasm progression, peripheral neuropathy, weight decrease, thrombocytopenia, dyspnoea, cough, back pain, rash, hypoalbuminaemia, myalgia and ascites [1,2]. Actual numbers for adverse drug reactions occurring in 5% or more of patients treated with ramucirumab plus paclitaxel will be presented in the EPAR, both as events of any grade and as events of grade 3 or higher [3].

Investigating the frequency of adverse events of special interest gave the following risk ratios when comparing any grade event occurring in the ramucirumab plus paclitaxel group with that in the placebo plus paclitaxel group: bleeding/haemorrhage RR 2.34 (95% CI 1.79 to 3.04), epistaxis RR 4.37 (95% CI 2.86 to 6.70), hypertension RR 4.34 (95% CI 2.70 to 6.98), arterial thromboembolic events RR 1.21 (95% CI 0.37 to 3.92), venous thromboembolic events RR 0.73 (95% CI 0.36 to 1.46), proteinuria RR 2.77 (95% CI 1.70 to 4.51), gastrointestinal haemorrhage RR 1.66 (95% CI 0.97 to 2.83), gastrointestinal perforation RR 4.02 (95% CI 0.45 to 35.8), congestive heart failure RR 2.01 (95% CI 0.61 to 6.62), infusion related reaction RR 1.59 (95% CI 0.79 to 3.23) and liver failure/liver injury RR 1.33 (95% CI 0.91 to 1.93) [2]. In addition, the EPAR lists wound healing complications, fistula, and reversible posterior leukoencephalopathy syndrome (RPLS) as warnings and precautions [3].

Indirect evidence

Indirect evidence is based on the following studies:

- West Japan Oncology Group 4007 (WJOG) [7] – irinotecan vs paclitaxel
- COUGAR-02 [6] – docetaxel vs active symptom control (BSC?)
- Thuss-Patience et al. [8] – irinotecan vs BSC
- Roy et al. [13] – irinotecan vs docetaxel

The MAH presented evidence networks with direct and indirect comparisons. Analyses are based on the safety population unless otherwise stated. Table 6.6 summarises the comparative safety estimates. We used the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use MedDRA Terminology to group the types of adverse events into system organ classes (SOCs) [89]. We used the frequency of the specific adverse events in the ramucirumab plus paclitaxel group to illustrate actual frequencies (based on the RAINBOW trial). Frequencies can be divided into very common (>10%), common (1% to 10%), uncommon (0.1% to 1%), rare (0.01% to 0.1%), very rare (<0.001%=1/10 000) and not known.

Most studies are not designed to show statistically significant differences in safety outcomes. This is also the case here. However, sometimes specific adverse reactions do reach significant differences (Table 6.6). It appears that neutropenia and leukocytopenia occur more often with ramucirumab plus paclitaxel than with the comparator treatments. Any grade thrombocytopenia was also statistically significantly more frequent with the ramucirumab combination compared with paclitaxel. The likelihood of any grade diarrhoea was higher for patients treated with ramucirumab plus paclitaxel than for those treated with paclitaxel or irinotecan. The likelihood of all grade nausea was higher for the ramucirumab-combination than for irinotecan. The risk of anorexia was higher for ramucirumab plus paclitaxel than for paclitaxel (all grades), but lower for the ramucirumab-combination than for irinotecan. The risk of peripheral sensory neuropathy or neuropathy was significantly higher for ramucirumab plus paclitaxel compared with irinotecan.

Table 6.6 Summary of comparative safety estimates for specific adverse events

Ramucirumab +paclitaxel vs: → Adverse event↓	**Paclitaxel**	**Irinotecan**	**Docetaxel**	**Best supportive care**	**Frequency#**
Blood and lymphatic system disorders					
All grade anaemia	*0.94 (0.69-1.30)*	<1 (CI does not include 1)	NA	NA	34.5%
Grade 3+4*	*0.88 (0.52-1.47)*	<1 (CI includes 1)	<1 (CI includes 1)	<1 (CI includes 1)	9.2%
All grade bleeding	*NA*	NA	NA	NA	
All grade neutropenia	*2.66 (1.93-3.66)*	>1 (CI does not include 1)	NA	NA	54.4%
Grade 3+4*	*2.95 (2.07-4.20)*	>1 (CI includes 1)	>1 (CI does not include 1)	>1 (CI does not include 1)	40.7%
All grade	*1.94 (1.36-2.75)*	>1 (CI does	NA	NA	33.9%

Ramucirumab +paclitaxel vs: → **Adverse event↓**	**Paclitaxel**	**Irinotecan**	**Docetaxel**	**Best supportive care**	**Frequency#**
leukocytopenia		not include 1)			
Grade 3+4*	*2.95 (1.75-4.95)*	>1 (CI does not include 1)	NA	NA	17.4%
All grade thrompcytopenia	*2.34 (1.34-4.07)*	<1 (CI includes 1)	NA	NA	13.1%
Grade 3+4*	*0.84 (0.25-2.77)*	<1 (CI includes 1)	>1 (CI includes 1)	NA	1.5%
All grade febrile neutropenia	*1.27 (0.49-3.25)*	<1 (CI includes 1)	NA	NA	3.1%
Grade 3+4*	*1.27 (0.49-3.25)*	<1 (CI includes 1)	<1 (CI includes 1)	>1 (CI includes 1)	3.1%
Gastrointestinal disorders					
All grade vomiting	*1.41 (0.98-2.03)*	<1 (CI includes 1)	NA	NA	26.9%
Grade 3+4*	*0.83 (0.35-1.96)*	>1 (CI includes 1)	>1 (CI includes 1)	NA	3.1%
All grade diarrhoea	*1.60 (1.13-2.26)*	>1 (CI do not includes 1)	NA	NA	32.4%
Grade 3+4*	*2.47 (0.86-7.09)*	<1 (CI includes 1)	>1 (CI includes 1)	NA	3.7%
All grade nausea	*1.11 (0.80-1.53)*	<1 (CI does not include 1)	NA	NA	35.2%
Grade 3+4*	*0.75 (0.26-2.19)*	<1 (CI includes 1)	>1 (CI includes 1)	NA	1.8%
All grade anorexia	*1.43 (1.03-1.96)*	<1 (CI does not include 1	NA	NA	40.1%
Grade 3+4*	*0.77 (0.33-1.77)*	<1 (CI does not include 1)	>1 (CI includes 1)	NA	3.1%
Nervous system disorders					
All grade peripheral sensory neuropathy	*1.72 (1.10-2.69)*	>1 (CI does not include 1)	NA	NA	17.4%
Grade 3+4	*2.03 (0.50-8.19)*	>1 (CI does not include 1)	NA	NA	1.8%
All grade neuropathy	*1.50 (0.09-2.04)*	>1 (CI does not include 1)	NA	NA	45.9%
Grade 3+4	*1.88 (0.98-3.61)*	>1 (CI does	NA	NA	8.3%

Ramucirumab +paclitaxel vs: → Adverse event↓	Paclitaxel	Irinotecan	Docetaxel	Best supportive care	Frequency#
		not include 1)			
Investigations					
All grade increased bilirubin	*1.01 (0.35-2.90)*	<1 (CI includes 1)	NA	NA	2.1%
Grade 3+4	*0.50 (0.05-5.56)*	<1 (CI includes 1)	NA	NA	0.3%
All grade increased AST	*1.65 (0.88-3.09)*	>1 (CI includes 1)	NA	NA	8.3%
Grade 3+4	*1.21 (0.37-4.01)*	<1 (CI includes 1)	NA	NA	1.8%
All grade increased ALT	*1.13 (0.58-2.17)*	<1 (CI includes 1)	NA	NA	6.1%
Grade 3+4	*1.35 (0.30-60.6)*	>1 (CI includes 1)	NA	NA	1.2%
All grade hyponatremia	*2.19 (0.98-4.92)*	>1 (CI includes 1)	NA	NA	5.8%
Grade 3+4	*2.83 (0.89-8.98)*	<1 (CI includes 1)	NA	NA	3.4%

Abbreviations: CI=confidence interval; NA=not available
All estimates are odds ratio and 95% confidence intervals. Grey cells and italics = direct evidence
*Results are consistent with sensitivity analyses using the ITT analysis instead of the safety population.
Frequency of the specific adverse events in the ramucirumab plus paclitaxel group to illustrate actual frequencies (based on the RAINBOW trial).

[C0005] What are the susceptible patient groups that are more likely to be harmed with ramucirumab in combination with paclitaxel?

The draft EPAR state that no studies were conducted in special populations [3].

The submission dossier does comment on whether there is a need to optimise the use of the technology, or monitor the use of the technology to minimise the potential risks to safety. Labelling for ramucirumab will include the following warnings and precautions; arterial thromboembolism (ATEs), hypertension, infusion related reactions (IRRs), gastrointestinal perforation, severe bleeding, impaired wound healing, and hepatic impairment and severe gastrointestinal haemorrhage. If patients are predisposed towards any of these events, they may be more likely to be harmed. Wound healing and changes in the blood and lymphatic systems may be of importance if emergency operations are necessary. As far as possible, this will be handled by the warning statements and the fact that the drug can be prescribed only by doctors experienced in oncology [2].

In addition, the draft EPAR states that data on VEGF over-expression was not collected during the RAINBOW trial [3]. Based on data from the REGARD trial of ramucirumab monotherapy it appeared that those with higher VEGFR-2 neoplastic vessel staining may have better OS and/or PFS. However, this was mainly due to differences in the placebo group, so it may be a prognostic factor [3].

The draft EPAR also comments on the issue that with both treatment alternatives in the RAINBOW study, patients with a previous history of hypertension had an increased incidence of Grade 3 or higher hypertension, older patients had an increased incidence of Grade 3 or higher neutropenia, and Asian patients had an increased incidence of grade 3 or higher neutropenia and leukopenia. In view of these findings it is not possible to attribute the increased risk to ramucirumab, but these risk factors are still issues that could be considered when selecting treatment for individuals.

6.3. Discussion

Interpretation and consideration of the direct evidence

Based on the direct comparison of ramucirumab plus paclitaxel with placebo plus paclitaxel, nearly all patients experienced an adverse event. There were no statistically significant differences between the treatments. However, limiting the adverse events to those of grade 3 adding ramucirumab increased the risk from 626 per 1000 treated to 814 (95% CI 739 to 902), which some may find clinically important. We did not find differences between the groups in withdrawal due to adverse events, frequency of SAEs or adverse events leading to death. The evidence suggest that the addition of ramucirumab to paclitaxel did not add to the burden of treatment in an unmanageable way. Finally, caution is needed, because the results are based on only one study. The study itself, RAINBOW [1], has a low risk of bias and high internal validity, but its external validity is more uncertain. In addition, for some outcomes there are few events, resulting in wide confidence intervals.

Interpretation and consideration of the indirect evidence

In the absence of, or with limited, direct evidence we can use indirect evidence to inform decisions and provide a larger evidence base [11]. For the assessment of safety, the MAH presented direct evidence as frequencies and risk ratios. In addition, they presented evidence networks for safety outcomes reported for comparators, which could analyzed via the network. These networks were analysed via single pairwise meta-analysis and/or a series of indirect comparisons [4].

Direct comparisons among the treatment alternatives are limited to one direct study for each comparison, making the evidence network linear and limited in size (see Appendix 1, for a description of the evidence used). Several assumptions are necessary to develop the network. The assumptions used here were validated by clinical opinion and are listed in Appendix 1 [4]. The choice of methods used for evidence networks was appropriate for the research question in this assessment. The analyses are limited by inconsistent reporting of adverse events, lack of definitions of outcomes and heterogeneity between studies [4]. Indirect data on withdrawal due to adverse events were presented and give important insight into the risk of reaching the point where the adverse events outweigh the potential benefit of treatment.

An extension to the CONSORT statement focuses on reporting of harms in randomised trials [90]. Studies designed to support a marketing authorisation application may collect data in a form that the regulatory authorities demand. Coding of adverse events and reporting in primary studies and systematic reviews remains challenging and heterogeneous [91-93]. Hence the limitations identified in this assessment are not unique.

Analyses of separate adverse events used the safety population (all treated patients). Sensitivity analysis using the ITT population (all randomised patients) yielded similar results. We chose not to use GRADE formally on the numerous reported specific adverse events. However, generally considering the limitations presented and the wide confidence intervals, our confidence in the accuracy of result estimates is limited. Additional evidence may substantially change the estimates.

Reporting of adverse events

Adverse events are usually divided into adverse events and SAEs. The CTCAE classification system described above and in the EUnetHTA guideline for safety, grades events based on their severity [94]. The EUnetHTA guideline also discusses the difference between severe and serious, in relation to adverse events. Severe relates to intensity, while a serious adverse reaction results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect, and is a medically important event or reaction. There is clearly some overlap between severe and serious adverse events. In this report we have used the terminology used in the references cited. We present the risk of experiencing an adverse event of any type and any grade. Because ramucirumab is used in combination with paclitaxel, and the control group receive paclitaxel most patients experienced an adverse event, it may be difficult to detect an increase in the frequency of events due to ramucirumab. Many adverse events can be handled without too much impact on the patient's quality of life. We present a separate analysis for grade 3 or higher adverse events, as we expect these to have more impact on the patient. The absolute frequencies of these adverse events are lower.

The calculations of comparative adverse events in this assessment were based on events reported during the included randomised controlled trials. Adverse events were collected from routine monitoring and spontaneous reporting. One study collected data in the experimental group only [8]. Differences in frequency of monitoring in clinical studies may influence on detection of adverse events. Adverse events were defined as those that were treatment emergent. The investigators assessed causality and severity. Although the risk is low, this approach does lead to a potential risk of bias in open-label studies.

Ramucirumab plus paclitaxel is on the verge of market access. Available evidence is consequently limited. However, all trials in the ramucirumab development program collected adverse events. These studies include non-randomised trials and trials in study populations other than gastric cancer patients. The EPAR lists such supportive trials and included evidence from these studies as part of the identification of the overall risk-benefit evaluation.

Use in a substantially larger patient population, and perhaps in a more heterogeneous patient group with more comorbidities could lead to the discovery of additional adverse events or changes in the expected frequencies. Ramucirumab has a risk management plan, a pharmacovigilance plan and a risk minimisation plan. This includes a large observational study to collect systematically additional data from real-life use.

Choice of endpoints

We report adverse events on an aggregate level, such as risk of experiencing any type of adverse event, SAE or need to withdraw from the study due to adverse events. Such risks are important when assessing the potential for harms and contribute to the overall risk-benefit ratio of the treatment. Individuals may have different preferences and values that influence their decision.

We also present briefly the most common adverse events, and indirect comparative evidence when available. The different treatments may have different adverse event profiles that may be important when selecting the appropriate treatment for individual patients.

Evidence gaps

There is no direct head-to-head evidence to position ramucirumab plus paclitaxel compared with the other treatment alternatives used in second-line treatment of gastric cancer or GEJ adenocarcinoma except for paclitaxel. Such direct comparisons and large observational studies and data could

contribute to confirm the findings of indirect comparisons, and facilitate conclusions that are more robust.

The choice, and definition, of outcomes for safety presented in the direct evidence and in the studies that are part of evidence networks are not necessarily the same, as described above. Due to more limited and heterogeneous reporting of adverse events for the studies of irinotecan and docetaxel, made particularly few comparisons with docetaxel were feasible. This makes it challenging to get a full overview of the harms in a comparative setting.

The RAINBOW study included patients with ECOG PS 0 and 1, so for patients with performance status worse than 1, safety data are lacking. Studies used to inform indirect analysis, however, also included patients with ECOG PS 2, even if they constituted only a small proportion of the included patients.

7 POTENTIAL ETHICAL, ORGANISATIONAL, SOCIAL AND LEGAL ASPECTS

7.1 Research questions

We used the Checklist for potential ethical, organisational, social and legal aspects (see Appendix 3). On the basis of this, we formulated the following research questions connected with ethical and legal issues:

Element ID	Research question
F0007	Does the implementation or withdrawal of ramucirumab in combination with paclitaxel in comparisons with treatments in second-line therapy challenge or change professional values, ethics or traditional roles?
H0012	Are there factors that could prevent a group or person from gaining access to ramucirumab in combination with paclitaxel?
F0017	What are the ethical consequences of the choice of comparators/controls in the assessment?
I0012	What are the consequences of various EU level and national regulations for equal access to ramucirumab in combination with paclitaxel in comparison with off-label second-line therapy?

7.2. Results

After the first-line therapy for advanced gastric cancer, there are currently no options for second-line therapy that have received regulatory approval. Ramucirumab is the first pharmaceutical with marketing authorisation for second-line treatment for patients with this kind of cancer. The manufacturer's submission file indicates a positive risk–benefit ratio for the treatment. Continuing with use of alternative treatments outside their intended use (outside of indication, off-label) should be discussed.
Four further questions connected with ethical and legal issues could be relevant due to the current off-label prescribing of comparators in this assessment and will be answered together. (Off-label prescribing is defined as prescribing a registered medicine for a use that is not included or is disclaimed in the product information, and is not approved by the regulatory authorities, such as use in a different indication or age group, at a different dose or by a different route).

[F0007] Does the implementation or withdrawal of ramucirumab in combination with paclitaxel in comparisons with treatments in second-line therapy challenge or change professional values, ethics or traditional roles?

[H0012] Are there factors that could prevent a group or person from gaining access to ramucirumab in combination with paclitaxel?

[F0017] What are the ethical consequences of the choice of comparators/controls in the assessment?

[I0012] What are the consequences of various EU level and national regulations for equal access to ramucirumab in combination with paclitaxel in comparison with off-label second-line therapy?

Prevalence of off-label use of cancer drugs for different cancer treatments ranges from one third to more than one half to three quarters [95-99]. A recent study in the USA, which evaluated the prevalence and cost of off-label prescribing of 10 commonly prescribed drugs in 2010, found that 30% were prescribed off label, with annual costs of approximately $4.5 billion. Of these prescriptions, 14% conformed to NCCN supported off-label indications [100]. Similarly in Europe Joerger et al. [101] reported off-label prescribing of anticancer drugs in one-third of all cancer patients; only in 6.6% of patients unsupported by the current ESMO treatment recommendations (but higher for bevacizumab, 29.6% and lenalidomide, 22.6%). Similar findings were reported in Australia, in which over 90% of off-label protocols are supported by established treatment guidelines or published peer-reviewed research, but are unfunded by the Pharmaceutical Benefits Scheme [102].

Off-label use is challenging for different stakeholders due to clinical, safety and ethical issues, especially for physicians. In situations where no authorised treatment is available, they are ethically obliged to find alternatives, but should take into account that safety and efficacy have not been fully established. In a case of serious harm they are exposed to civil liability claims for fault/negligence or even criminal and disciplinary sanctions [98,103,104]. For responsible off-label prescribing physicians should find sufficient evidence to justify off-label use, ask for research when evidence is lacking and inform patients about uncertainties, safety and potential costs [103,105,106]. Oncologists often rely on compendia for up-to-date evidence and reimbursement information for off-label indications, but such compendia may lack transparency and systematic approaches to reviewing or updating evidence and they may cite little current evidence [107]. In the UK a new tool has been established (evidence summaries: unlicensed and off-label medicines, ESUOM) [108], providing a summary and critical review of the best available evidence for selected off-label drugs.

Off-label prescribing by physicians in Europe is generally allowed, but individual Member States have their own rules on prescribing and reimbursement. In some this is regulated by law and in others by good practice guidance such as treatment guidelines, general professional recommendations and reimbursement decisions [97,98,109].

7.3. Discussion

Off-label use of anticancer drugs is widespread for most cancer types. Before marketing authorisation of ramucirumab plus paclitaxel, after the first-line therapy for advanced gastric cancer, there were no other regulatory approved options for second-line therapy. Off-label cancer treatment is not illegal but is connected with different clinical, safety and ethical issues. Off-label cancer treatment must be prescribed according national laws and only when the potential benefit outweighs the potential toxic effects. It should be used only where there is no licensed product available that meets the medical needs of the patient or in cases of serious adverse drug reactions connected with approved drugs. Individual patient values and preferences should always be considered.

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APPENDIX 1: METHODS AND DESCRIPTION OF THE EVIDENCE USED

DOCUMENTATION OF THE SEARCH STRATEGIES

The manufacturer's submission file described the search strategy they had used for identification of clinical effectiveness studies. It was undertaken in December 2013 and updated 28 May 2014. The search included subject headings and text words for the disease and the possible treatments, and run in several relevant databases (see below).

The search identified 11,056 records via databases but only 43 remained after exclusion of duplicates and of studies that did not meet eligibility criteria (based on title/abstract); additional publications were identified from conference abstracts and hand-searching. Final is 30 publications for 23 unique studies. However, after limiting the focus to the intervention and controls for this assessment the included studies was reduced to one study for direct evidence [1], and 3 studies comparing the comparator treatments [6-8].

- MEDLINE (R) In-Process & Other Non-Indexed Citations
- Ovid MEDLINE (R) 1946 to present (via OVID)
- EMBASE, 1980 to present (via OVID)
- The Cochrane Library (via OVID), searching the following databases:
    - The Cochrane Central Register of Controlled Trials (CENTRAL)
    - The Cochrane Database of Systematic Reviews (Cochrane Reviews)
    - The Database of Abstracts of Reviews of Effects (DARE)
- The Health Technology Assessment Database (HTA)

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present (accessed May 28th 2014)

	Search	Result
1	exp Stomach Neoplasms/	73482
2	((stomach or gastric) adj4 (neoplas$ or cancer$ or carcin$ or tumo$ or malig$ or adenocarcin$ or nonsquamous or non squamous)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	91651
3	((gastroesophag$ or gastro-oesophag$ or gastrointestin$) adj4 (neoplas$ or cancer$ or carcin$ or tumo$ or malig$ or adenocarcin$ or nonsquamous or non squamous)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	30007
4	exp Esophagogastric Junction/	6818
5	(distal adj2 (esophag$ or oesophag$)).tw.	3271
6	((gastroesophag$ or gastro-oesophag$) adj2 junction).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	2151
7	gastroesophageal.tw.	16588
8	esophagogastric.tw.	2681

9	oesophagogastric.tw.	541
10	exp Cardia/	3653
11	((gastric or stomach) adj3 cardia).tw.	1783
12	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	29045
13	1 or 2	91651
14	exp Neoplasms/	2546539
15	exp Carcinoma/	484098
16	exp Carcinoma, Adenosquamous/	1489
17	exp Adenocarcinoma/	282443
18	exp Adenocarcinoma, Mucinous/	7552
19	(neoplas$ or cancer$ or carcin$ or tumo$ or malig$ or adenocarcin$ or nonsquamous or non squamous).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	2970632
20	14 or 15 or 16 or 17 or 18 or 19	3251518
21	12 and 20	8886
22	3 or 13 or 21	118185
23	(capecitabine or Xeloda).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	3997
24	exp Paclitaxel/	19212
25	(paclitaxel or Taxol).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	26502
26	(nab-paclitaxel or Abraxane).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	267
27	(docetaxel or Taxceus or Taxotere).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	10077
28	(trastuzumab or Herceptin or Herclon).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	6315
29	(irinotecan or Campto or Camptosar).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	7716
30	(everolimus or Afinitor).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare	3013

	disease supplementary concept word, unique identifier]	
31	(cetuximab or Erbitux).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	3965
32	exp Cisplatin/	40173
33	(cisplatin or cisplatinum or CDDP or Platin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	55785
34	(CAPOX or XELOX or Xeloda).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	590
35	*Antineoplastic Combined Chemotherapy Protocols/ae, mo, tu, to	57525
36	FOLFIRI.mp.	718
37	FLOT.mp.	54
38	EOX.mp.	109
39	ramucirumab.mp.	45
40	(oxaliplatin or eloxatin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	6222
41	tegafur.mp. or exp Tegafur/	4872
42	exp Fluorouracil/	37677
43	(5-fluorouracil or 5-FU).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	29650
44	S-1.mp.	41539
45	(lapatinib or tyverb).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1441
46	apatinib.mp.	10
47	(bevacizumab or avastin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	9330
48	mitomycin.mp. or exp Mitomycin/	17517
49	exp Etoposide/	14373
50	(Etoposide or Eposin or Etopophos or Vepesid).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	20753
51	exp Epirubicin/	4322

52	(Epirubicin or Pharmorubicin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	5706
53	mFOLFIRI.mp.	5
54	exp Carboplatin/	8959
55	(carboplatin or paraplatin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	12672
56	23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55	231712
57	Randomized controlled trials as Topic/	92859
58	Randomized controlled trial/	373734
59	Random allocation/	80493
60	Double blind method/	125699
61	Single blind method/	19046
62	Clinical trial/	487601
63	exp Clinical Trials as Topic/	280117
64	or/57-63	911690
65	(clinic$ adj trial$1).tw.	215839
66	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	129471
67	Placebos/	32546
68	Placebo$.tw.	159107
69	Randomly allocated.tw.	17046
70	(allocated adj2 random).tw.	713
71	or/65-70	419942
72	64 or 71	1063476
73	Case report.tw.	204850
74	Letter/	841185
75	Historical article/	300975
76	Review of reported cases.pt.	0
77	Review, multicase.pt.	0

78	or/73-77	1335457
79	72 not 78	1035130
80	22 and 56 and 79	2554
81	limit 80 to yr="2013 -Current"	149

EBM Reviews - Cochrane Central Register of Controlled Trials April 2014, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to April 2014, EBM Reviews - Database of Abstracts of Reviews of Effects 2nd Quarter 2014, EBM Reviews - Health Technology Assessment 2nd Quarter 2014, EBM Reviews - NHS Economic Evaluation Database 2nd Quarter 2014: accessed May 28th 2014

# ▲# ▲	Searches	Results
1	exp Stomach Neoplasms/	1419
2	((stomach or gastric) adj4 (neoplas$ or cancer$ or carcin$ or tumo$ or malig$ or adenocarcin$ or nonsquamous or non squamous)).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	3167
3	((gastroesophag$ or gastro-oesophag$ or gastrointestin$) adj4 (neoplas$ or cancer$ or carcin$ or tumo$ or malig$ or adenocarcin$ or nonsquamous or non squamous)).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	1389
4	exp Esophagogastric Junction/	318
5	(distal adj2 (esophag$ or oesophag$)).tw.	228
6	((gastroesophag$ or gastro-oesophag$) adj2 junction).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	129
7	gastroesophageal.tw.	1452
8	esophagogastric.tw.	157
9	oesophagogastric.tw.	65
10	exp Cardia/	50
11	((gastric or stomach) adj3 cardia).tw.	104
12	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	2079
13	1 or 2	3167
14	exp Neoplasms/	46086
15	exp Carcinoma/	8345
16	exp Carcinoma, Adenosquamous/	35
17	exp Adenocarcinoma/	4164
18	exp Adenocarcinoma, Mucinous/	59
19	(neoplas$ or cancer$ or carcin$ or tumo$ or malig$ or adenocarcin$ or nonsquamous or non squamous).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	87885
20	14 or 15 or 16 or 17 or 18 or 19	92789
21	12 and 20	403

# ▲# ▲	Searches	Results
22	3 or 13 or 21	4395
23	(capecitabine or Xeloda).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	785
24	exp Paclitaxel/	1380
25	(paclitaxel or Taxol).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	3272
26	(nab-paclitaxel or Abraxane).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	42
27	(docetaxel or Taxceus or Taxotere).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	1970
28	(trastuzumab or Herceptin or Herclon).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	479
29	(irinotecan or Campto or Camptosar).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	871
30	(everolimus or Afinitor).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	571
31	(cetuximab or Erbitux).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	510
32	exp Cisplatin/	3179
33	(cisplatin or cisplatinum or CDDP or Platin).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	7224
34	(CAPOX or XELOX or Xeloda).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	175
35	*Antineoplastic Combined Chemotherapy Protocols/ae, mo, tu, to	0
36	FOLFIRI.mp.	139
37	FLOT.mp.	6
38	EOX.mp.	4
39	ramucirumab.mp.	4
40	(oxaliplatin or eloxatin).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	922
41	tegafur.mp. or exp Tegafur/	570
42	exp Fluorouracil/	3768
43	(5-fluorouracil or 5-FU).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	4420
44	S-1.mp.	744
45	(lapatinib or tyverb).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	167
46	apatinib.mp.	1
47	(bevacizumab or avastin).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	1050
48	mitomycin.mp. or exp Mitomycin/	2045
49	exp Etoposide/	1180

# ▲# ▲	Searches	Results
50	(Etoposide or Eposin or Etopophos or Vepesid).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	2378
51	exp Epirubicin/	766
52	(Epirubicin or Pharmorubicin).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	1756
53	mFOLFIRI.mp.	2
54	exp Carboplatin/	953
55	(carboplatin or paraplatin).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	2505
56	23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55	21854
57	22 and 56	1295
58	limit 57 to yr="2013 -Current" [Limit not valid in DARE; records were retained]	165

Embase 1974 to 2014 May 27: accessed May 28th 2014

# ▲# ▲	Searches	Results
1	exp stomach tumor/	106543
2	((stomach or gastric) adj4 (neoplas$ or cancer$ or carcin$ or tumo$ or malig$ or adenocarcin$ or nonsquamous or non squamous)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	122404
3	((gastroesophag$ or gastro-oesophag$ or gastrointestin$) adj4 (neoplas$ or cancer$ or carcin$ or tumo$ or malig$ or adenocarcin$ or nonsquamous or non squamous)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	85567
4	exp lower esophagus sphincter/	10231
5	(distal adj2 (esophag$ or oesophag$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	4815
6	((gastroesophag$ or gastro-oesophag$) adj2 junction).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	3122
7	gastroesophageal.mp.	44196
8	esophagogastric.mp.	3774
9	oesophagogastric.mp.	704
10	exp cardia/	3894
11	((gastric or stomach) adj3 cardia).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	2612
12	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	58458
13	1 or 2	125478
14	exp neoplasm/	3370228
15	carcinoma/	43807
16	exp adenosquamous carcinoma/	4638
17	exp adenocarcinoma/	72603
18	(neoplas$ or cancer$ or carcin$ or tumo$ or malig$ or adenocarcin$ or nonsquamous or	3641465

# ▲# ▲	Searches	Results
	non squamous).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	
19	14 or 15 or 16 or 17 or 18	4106084
20	12 and 19	16247
21	3 or 13 or 20	202241
22	exp capecitabine/	16594
23	(capecitabine or Xeloda).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	17127
24	exp paclitaxel/	66504
25	(paclitaxel or Taxol).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	69721
26	(nab-paclitaxel or Abraxane).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1300
27	exp docetaxel/	34411
28	(docetaxel or Taxceus or Taxotere).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	35300
29	exp trastuzumab/	22276
30	(trastuzumab or Herceptin or Herclon).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	23273
31	exp irinotecan/	24469
32	(irinotecan or Campto or Camptosar).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	25114
33	exp everolimus/	13202
34	(everolimus or Afinitor).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	13472

# ▲# ▲	Searches	Results
35	exp cetuximab/	16483
36	(cetuximab or Erbitux).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	16885
37	exp cisplatin/	124966
38	(cisplatin or cisplatinum or CDDP or Platin).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	131197
39	(CAPOX or XELOX or Xeloda).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	2661
40	FOLFIRI.mp.	1532
41	FLOT.mp.	95
42	EOX.mp.	234
43	exp ramucirumab/	343
44	ramucirumab.mp.	348
45	exp oxaliplatin/	20879
46	(oxaliplatin or eloxatin).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	21567
47	exp tegafur/	5799
48	(tegafur or uftoral).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	8856
49	exp fluorouracil/	104383
50	(5-fluorouracil or 5-FU).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	38095
51	S-1.mp.	41891
52	exp lapatinib/	7021

# ▲# ▲	Searches	Results
53	(lapatinib or tyverb).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	7167
54	apatinib.mp.	27
55	exp bevacizumab/	31205
56	(bevacizumab or avastin).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	31908
57	Mitomycin.mp. or mitomycin/	41245
58	exp etoposide/	65500
59	(Etoposide or Eposin or Etopophos or Vepesid).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	67333
60	exp epirubicin/	21431
61	(Epirubicin or Pharmorubicin).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	21829
62	exp panitumumab/	4691
63	(Panitumumab or Vectibix).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	4822
64	mFOLFIRI.mp.	12
65	exp carboplatin/	44359
66	(carboplatin or paraplatin).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	45705
67	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66	416139
68	Clinical trial/	835382
69	Randomized controlled trial/	344690

# ▲# ▲	Searches	Results
70	Randomization/	62070
71	Single blind procedure/	18298
72	Double blind procedure/	115773
73	Crossover procedure/	38979
74	Placebo/	252227
75	Randomi?ed controlled trial$.tw.	98292
76	Rct.tw.	13826
77	Random allocation.tw.	1344
78	Randomly allocated.tw.	20362
79	Allocated randomly.tw.	1937
80	(allocated adj2 random).tw.	792
81	Single blind$.tw.	14455
82	Double blind$.tw.	146423
83	((treble or triple) adj blind$).tw.	387
84	Placebo$.tw.	201924
85	Prospective study/	250840
86	or/68-85	1374276
87	Case study/	25926
88	Case report.tw.	266509
89	Abstract report/ or letter/	908589
90	or/87-89	1195442
91	86 not 90	1336301

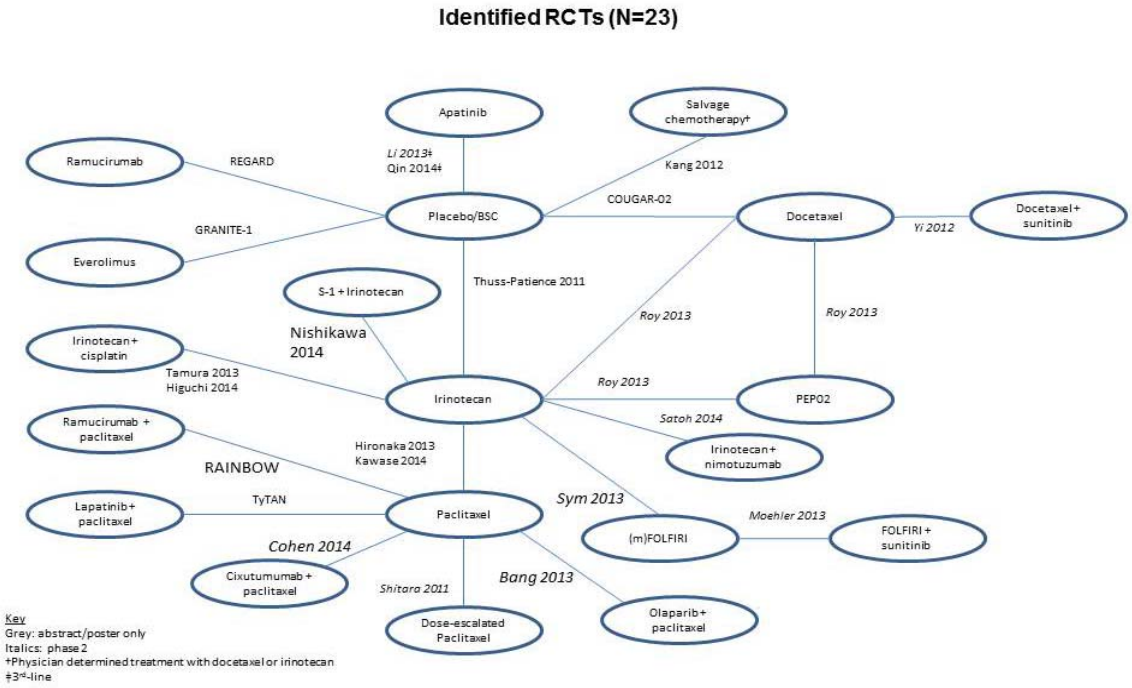
# ▲# ▲	Searches	Results
92	21 and 67 and 91	10516
93	limit 92 to yr="2013 -Current"	543

DESCRIPTION OF EVIDENCE USED

We used the manufacturer's submission file. The search was newer than one year, so according to our project plan, we did not re-run it. Figure A1 show the complete network of identified studies. Four studies inform the submission's major analysis. They connect the network in a series of single studies.

- Ramucirumab+paclitaxel vs placebo + paclitaxel
- Paclitaxel vs irinotecan
- Irinotecan vs best supportive care
- Docetaxel vs best supportive care
- Irinotecan vs docetaxel (used only to connect the evidence network for selected outcomes)

Figure A1. Network diagram of randomised controlled trials in previously treated advanced gastric cancer as presented in the MAH submission dossier [2].



The MAH made several assumptions to form the evidence networks for the analyses. The assumptions were validated with clinical opinions [4]. Assumptions are:

- No interaction between treatment effects and:
  - primary disease site
  - disease status
  - number of prior chemotherapy regimens
  - treatment duration
- Active symptom control, best supportive care and best supportive care+placebo are considered equivalent
- Dosing regimens of the individual treatments are considered equivalent
- No interaction between treatment effects and post-protocol treatments

The estimated incidence, mortality and prevalence for gastric cancer in men and women (2012)

Table A1. Estimated incidence, mortality and prevalence of gastric cancer in men, 2012.

Country	Incidence rate[1]	Mortality rate[1]	1-Year prevalence[2]	3-Year prevalence[2]	5-Year prevalence[2]
Europe	19.5	14.6	40192	87458	117903
European Union (27)	15.2	10.4	24281	53785	73379
Austria	13.9	8.3	379	882	1244
Belgium	12.2	7.8	487	1119	1561
Bulgaria	21.4	17.9	433	906	1191
Croatia	21.8	17.6	321	735	1022
Cyprus	11.4	7.5	33	78	108
Czech Republic	15.5	10.6	426	888	1161
Denmark	12.3	6.0	191	378	480
Estonia	28.7	23.8	85	180	237
Finland	10.2	7.4	187	432	606
France	10.5	6.8	2282	5105	6971
Germany	16.2	8.8	4980	11269	15575
Greece	11.1	9.6	482	1107	1539
Hungary	20.3	16.1	503	1038	1351
Iceland	9.6	4.9	8	18	26
Ireland	13.4	8.8	113	245	333
Italy	16.5	12.0	4213	9716	13545
Latvia	33.7	24.0	169	356	469

Country	Incidence rate[1]	Mortality rate[1]	1-Year prevalence[2]	3-Year prevalence[2]	5-Year prevalence[2]
Lithuania	33.5	24.8	239	500	657
Luxembourg	14.7	6.4	23	53	74
Malta	17.0	9.3	15	32	40
Netherlands	11.6	7.6	566	1197	1580
Norway	8.7	5.2	123	271	366
Poland	19.7	16.8	1593	3203	4126
Portugal	26.7	19.5	939	2182	3080
Romania	23.7	19.2	1186	2475	3249
Slovakia	21.0	14.6	249	521	684
Slovenia	23.3	16.2	126	283	385
Spain	16.4	10.8	2455	5651	7913
Sweden	7.4	5.7	238	513	691
Switzerland	7.5	5.1	212	470	637
UK	10.0	6.6	1689	3476	4529

Source: EUCAN website [68,69]
[1]age-standardised rates (European) per 100 000
[2] 1/3/5-year cancer prevalence used in the EUCAN website is the number of patients diagnosed with cancer and still alive one/three/five year(s) after the diagnosis in the given population. For example, 5-year prevalence in 2012 includes all cases diagnosed within 5 previous years and still alive in 2012.

Table A2. Estimated incidence, mortality and prevalence of gastric cancer in women, 2012.

Country	Incidence rate[1]	Mortality rate[1]	1-Year prevalence[2]	3-Year prevalence[2]	5-Year prevalence[2]
Europe	9.3	7.0	25379	55404	74975
European Union (27)	7.1	4.9	14517	32366	44404
Austria	7.3	4.8	270	629	888
Belgium	5.7	3.5	288	667	935
Bulgaria	10.4	8.0	285	599	790
Croatia	9.5	7.4	198	456	635
Cyprus	4.8	4.6	18	43	62
Czech Republic	7.8	5.2	284	595	779
Denmark	4.4	3.0	77	156	204
Estonia	14.9	9.0	74	157	205
Finland	5.9	4.3	136	310	432

Country	Incidence rate[1]	Mortality rate[1]	1-Year prevalence[2]	3-Year prevalence[2]	5-Year prevalence[2]
France	4.2	2.7	1168	2618	3584
Germany	8.0	4.8	2827	6403	8879
Greece	5.4	4.7	302	698	978
Hungary	9.7	7.5	350	737	975
Iceland	5.7	4.4	9	17	24
Ireland	6.7	4.4	66	142	193
Italy	8.9	6.1	2960	6857	9601
Latvia	12.6	9.8	107	227	300
Lithuania	11.8	9.2	140	294	388
Luxembourg	7.2	3.4	16	34	47
Malta	8.1	2.5	10	20	25
Netherlands	5.8	4.2	328	699	930
Norway	5.7	3.9	94	205	275
Poland	7.3	6.0	815	1677	2196
Portugal	12.8	8.9	587	1373	1948
Romania	8.5	6.9	590	1220	1593
Slovakia	9.8	6.9	164	342	450
Slovenia	9.6	6.5	74	164	225
Spain	7.5	4.8	1445	3341	4698
Sweden	4.1	2.8	148	325	436
Switzerland	5.1	3.1	163	365	496
UK	4.8	3.1	988	2039	2663

Source: EUCAN website [68,69]
[1]age-standardised rates (European) per 100 000
[2] 1/3/5-year cancer prevalence used in the EUCAN website is the number of patients diagnosed with cancer and still alive one/three/five year(s) after the diagnosis in the given population. For example, 5-year prevalence in 2012 includes all cases diagnosed within 5 previous years and still alive in 2012.

Guidelines for diagnosis and management

Table A3. Overview of European guidelines for advanced disease, including both first-line and subsequent therapy

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation (Level of evidence/Grade of recommendation for 2nd line treatment)
UK National Health Service; Guidelines for the Management of Oesophageal and Gastric Cancer [110]	2011	United Kingdom	**1st-line palliative combination chemotherapy** - ECF is the preferred regimen (triplet regimes containing anthracyclines, cisplatin and 5-FU (e.g., ECF) are superior for OS than doublet regimens containing either cisplatin/5-FU or anthracyclines/5-FU). Capecitabine can be substituted for 5-FU, and oxaliplatin for cisplatin in ECF; therefore, EOX or ECX can also be used. **2nd-line** - it is recommended that patients of good performance status are enrolled into a RCT, if available. Data from phase II trials have demonstrated activity in the second-line setting for the following agents/combination regimes: irinotecan in combination with cisplatin or fluoropyrimidines, FOLFOX (folinic acid, 5-FU, oxaliplatin), docetaxel monotherapy, docetaxel in combination with oxaliplatin, and paclitaxel alone or in combination with platinum agents. Second-line irinotecan confers a small survival benefit over best supportive care (BSC), but is not currently approved by the National Institute for Health and Clinical Excellence (NICE) (**Ib; grade A)** **Advanced HER2-positive cancer**: Targeted agents with chemotherapy - trastuzumab to a cisplatin and fluoropyrimidine (5-FU or capecitabine) chemotherapy doublet.
Association of the Scientific Medical Societies of Germany (AWMF); German S3 – Guideline: diagnosis and treatment of Oesophagogastric cancer – In German [111]	2011	Germany	**Palliative chemotherapy** should be initiated as soon as possible (duration of therapy depends on tumour response, treatment associated toxicity and patient preference). **2nd-line** chemotherapy only for patients with good general condition. **No recommendations.** **HER2 positive**, consider trastuzumab. Alleviate Symptoms: Decision for tumour stenosis of the stomach depends on tumour location and dimension, and severity of symptoms (partial gastric resection should only be performed in exceptional cases). Choice of therapy (that is, endoscopic haemostasis, palliative resection, angiographic embolisation, and palliative radiotherapy) depends on localisation and strength of bleeding
Haute Autorité de Santé, Institut	2011	France	**For locally advanced stages**: chemotherapy

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation (Level of evidence/Grade of recommendation for 2nd line treatment)
National du Cancer; Guide – affection de longue duree – Cancer de l'estomac – In French [112]			before and after surgery, postsurgery radiochemotherapy, or only symptomatic treatments. **For metastatic stage**: palliative chemotherapy. The most common protocols used, according to their marketing authorisation, could include cisplatin, 5-FU, capecitabine, docetaxel, epirubicin (**N.A**) and trastuzumab for HER2+.
French National Society of Gastroenterology (SNFGE); National Thesaurus of Digestive Cancers, Section 2.4.2.2. [113]	2014	France	**2nd-line** chemotherapy for patients with good general condition could be discussed in multidisciplinary consultation meeting. Chemotherapy choice according to patient age and general condition. Reference: docetaxel in monotherapy (75 mg/m²/3 weeks) (**grade** **B**) (Cook N 2013), ramucirumab 8mg/kg/2weeks (**grade B**) [Fuchs 2014], ramucirumab 8mg/Kg/2weeks-paclitaxel 80 mg/m²J1,8,15 (**not graded**, congress abstract) [Wilke 2014]. Options: FOLFIRI, FOLFOX, 5FU-mitomycine C, paclitaxel monotherapy (**experts agreement**).
ESMO, ESSO, ESTRO Gastric Cancer. Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up [18]	2013	Europe	**1st-line** palliative chemotherapy: combination regimens including ‡platinum agent and a fluoropyrimidine are generally used, but ECF, ECX, EOF, EOX can also be used. Alternatively, taxane based regimens‡‡ or irinotecan and 5-FU can be used. **2nd-line** chemotherapy: in patients with adequate performance status, proven improvements in OS and quality of life compared with best supportive care, with treatment options including irinotecan, docetaxel or paclitaxel (**I, A**) Considerations should be given to clinical trial (**V, B**) and in patients with disease progression after 3 months of 1st-line chemotherapy, re-challenge with the same drugs (**IV, C**). **HER2-positive cancer** Palliative chemotherapy with targeted agents (e.g., trastuzumab with cisplatin and fluoropyrimidine). GEJ carcinomas Ramucirumab has recently been shown to have single-agent activity in the second-line setting with improved overall survival, but is not being used in routine clinical use Control symptoms – bleeding,

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation (Level of evidence/Grade of recommendation for 2nd line treatment)
			obstruction, pain, and perforation: Palliative radiotherapy and surgery is recommended.
Alleanza Contro il Cancro (Alliance Against Cancer); Documenti Carcinoma Gastrico – In Italian [114]	2011	Italy	**1st-line** palliative combination chemotherapy - ECF is the preferred regimen (combination of epirubicin, cisplatin and 5- FU) and considered superior than FAMTX (5-FU, Adriamycin, methotrexate). 5-FU can be substituted by capecitabine (ECX) and cisplatin by oxaliplatin (EOX) in ECF; therefore, EOX or ECX can also be used. Alternative treatments: regimen with combination of docetaxel and cisplatin+5-FU (DCF). **2nd-line** chemotherapy only for patients with good general condition that show diseases progression after the 1st-line therapy (**N.A**). Control symptoms – bleeding, obstruction, and pain: Palliative radiotherapy is recommended.
Associazione Italiana di Oncologia; Linee guida neoplasie Dello stomaco, AIOM Guideline [115]	2014	Italy	**1st-line** palliative chemotherapy: combined chemotherapy is preferred to monochemotherapy. Combined therapy with cisplatin, 5-FU and anthracyclines is the preferred regimen. 5-FU can be substituted by capecitabine (ECX) and cisplatin by oxaliplatin (EOX) in ECF; therefore, EOX or ECX can also be used. Alternative treatments: regimen with combination of docetaxel and cisplatin+5-FU (DCF) or S-1 and cisplatin. HER2-positive cancer: chemotherapy with combination of trastuzumab with fluoropyrimidine/cisplatin. **2nd-line** chemotherapy only for patients with good general condition that show diseases progression after the 1st-line therapy (**A**). The choice of chemotherapy depends of treatment in 1-st line (**D**).
ACCC; Gastric Carcinoma – Nation-wide guideline V1.0, [116]	2009	The Netherlands	**1st-line** palliative chemotherapy: combination regimen of epirubicin, platinum (cisplatin or oxaliplatin) and fluoropyrimidine (5-FU or capecitabine) recommended for patients in good condition. Alternative treatment: combination regimen including irinotecan or docetaxel. If contraindication

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation (Level of evidence/Grade of recommendation for 2nd line treatment)
			for combination chemotherapy, monotherapy with capecitabine may be considered.
Belgian Healthcare Knowledge Centre – College of Oncology [117]	2012	Belgium	**Locally advanced or metastatic gastric cancer**: Patients with good performance status may receive combination chemotherapy (**high level of evidence, strong recommendation**). Palliative gastric surgery is limited to symptomatic stenoses, bleeding tumours and perforation. For patients with gastric outlet obstruction, endoscopic stenting or surgical gastroenterostomy is recommended. Recurrent gastric Cancer: Treatment options should be discussed in the multidisciplinary team.

Abbreviations: 5-FU= 5- fluorouracil; ACCC= Association of Comprehensive Cancer Centres; AWMF = Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V ECF = epirubicin, cisplatin, and 5-FU; ECX =epirubicin, cisplatin, and capecitabine;EOF = epirubicin, oxaliplatin, and 5-FU; EOX = epirubicin, oxaliplatin, and capecitabine; GEJ = gastro-oesophageal junction; HER2 = human epidermal growth factor receptor 2; HRQOL = health-related quality of life; OS = overall survival; QoL = quality of life; RCT = randomised controlled trial; UK = United Kingdom. *Relevant information extracted for population of interest (i.e., non-resectable locally advanced and/or metastatic gastric cancer). **Capecitabine is designed to generate 5-FU in tumour tissue via a 3-step enzymatic cascade. (Van et al. 2004). Although ECF chemotherapy regimen remains the standard of care in Ontario, especially in patients with difficulty taking oral medication, ECX is preferred due to significant survival benefit reported in a meta-analysis.

Note: Due to the high number of dosing regimens in the US and British Columbia guidelines, doses for these jurisdictions have not been included in the table.

***Recommended doses for 1st-line palliative chemotherapy regimens:a) Cisplatin/ 5-FU: cisplatin 75 mg/m2 Day 1 or 25 mg/m2 Days 1-3, 5-FU 1000 mg/m2 Days 1-4 (q21 days, up to 6 cycles) b) ECF: epirubicin 50 mg/m2, cisplatin 60 mg/m2, 5-FU 200 mg/m2 CVI (q21 days, up to 6 cycles) c) ECX: epirubicin 50 mg/m2, cisplatin 60 mg/m2, capecitabine 625 mg/m2 continuous (q21 days, up to 6 cycles) d) For adenocarcinoma of GEJ cancer patients the following chemotherapy regimen is recommended: cisplatin 80 mg/m2 Day 1, 5-FU 800mg/m2 Days 1-5 CVI, herceptin 8mg/kg LD after 6 cycles if no progression, herceptin 6mg/kg MD (q21 days, up to 6 cycles. herceptin can be continued after 6 cycles if no progression). Capecitabine can be substituted for 5-FU. If poor performance status or reduced creatinine clearance, consider carboplatin instead of cisplatin.

+The following are the recommended doses of ECX, ECF and ELF palliative chemotherapy regimens:

 ECX: Three-week cycles where epirubicin (50 mg/m2 I.V. over 20 minutes) and cisplatin (60 mg/m2 I.V. over 1 hour along with hydration) are administered on Day 1, and capecitabine; 625 mg/m2 orally Q12h is administered for 21 consecutive days.; ECF: Three-week cycles where epirubicin (50 mg/m2 I.V. over 20 minutes) and cisplatin (60 mg/m2 I.V. over 1 hour along with hydration) are administered on Day 1 and 5-FU (200 mg/m2/day) is administered as a continuous I.V. infusion through a CVC, PICC line, or port.; ELF: Three-week cycles where etoposide (120 mg/m2 I.V. over 1 hour), leucovorin (300 mg/m2 I.V. over 15 minutes), and 5-FU (500 mg/m2 I.V.) are administered on Days 1, 2, and 3.; ++S-1 combines the oral 5-FU prodrug tegafur with oteracil (lowers bowel toxicity) and gimeracil (an inhibitor of dihydropyrimidine dehydrogenase, which prevents degradation of 5-FU and permits oral bioavailability of the agent). S-1 and cisplatin should be carefully determined in patients with limited oral intake, moderate volume of ascites, intestinal stenosis/obstruction and/or elderly. Irinotecan and cisplatin, and S-1 and irinotecan are not acceptable 1st-line chemotherapy regimens as they did not show significant superiority over 5-FU alone, and S-1 alone in an RCT.

‡Triplet therapy is controversial, but a meta-analysis showed significant benefit from adding an anthracycline agent to platinum and fluoropyrimidine doublet. Also, the triplet regimen ECF is amongst the most active and well-tolerated regimens.

‡‡ Weekly docetaxel schedule combined with cisplatin and infused 5-FU or capecitabine is associated with increased activity, but is also related to toxic effects. Modified DCF regimens are currently being explored.

‡‡‡Although not required to be used by every facility, the NCCN guidelines are commonly used nationally; there are, however, other guidelines available in the US.

Sources: Manufacturer submission file

Evidence Tables of individual studies included for clinical effectiveness and safety

Table A4. Summary of Efficacy for RAINBOW Trial

Title: A Phase 3, Randomized, Double-Blinded Study of IMC-1121B and Paclitaxel Versus Placebo and Paclitaxel in the Treatment of Metastatic Gastric Adenocarcinoma, Refractory to or Progressive After First-Line Therapy with Platinum and Fluoropyrimidine				
Study identifier	I4T-IE-JVBE, (IMCL CP12-0922), RAINBOW			
Design	Phase 3, randomized, multicentre, placebo-controlled, double-blinded study.			
	Duration of Main phase:		Until progressive disease (PD), unacceptable toxicity, withdrawal of consent, or until other withdrawal criteria were met.	
Hypothesis	Superiority			
Treatments groups	Ramucirumab+ Paclitaxel		Ramucirumab 8 mg/Kg + Paclitaxel 80 mg/m^2 intravenous over approximately 60 minutes administered on a 28-day cycle. 330 patients randomized.	
	Placebo+Paclitaxel		Placebo + Paclitaxel 80 mg/m^2 intravenous over approximately 60 minutes administered on a 28-day cycle. 335 patients randomized.	
Endpoints and definitions	Primary endpoint	Overall survival (OS)	The interval between date of randomization and the date of death from any cause.	
	Secondary	Progression free survival (PFS)	The time from the date of randomization until the date of objectively determined PD (RECIST 1.0) or death due to any cause, whichever was first.	
	Secondary	Overall response rate (ORR)	The proportion of patients achieving a best overall response of partial (PR) or complete response (CR).	
Database lock	31 December 2012			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	ITT (cut-off date at 12 July 2013)(all randomized patients):665			
Descriptive statistics and estimate variability	Treatment group		Ramucirumab+paclitaxel	Placebo+paclitaxel
	Number of patients		330	335
	Median OS (months)		9.6	7.4
	95% CI for median		(8.5,10.8)	(6.3,8.4)
	Median PFS (months)		4.4	2.9
	95% CI for median		(4.2,5.3)	(2.8,3.0)
	Objective Response Rate (%)		27.9%	16.1
	95% CI		23.3-33.0%	12.6-20.4%
Effect estimate per comparison	Primary Endpoint (OS)		Comparison groups	Ramucirumab vs Placebo
			Hazard Ratio (stratified)	0.807
			(95% CI)	(0.678 - 0.962)
			p-value	0.0169
	Secondary Endpoint (PFS)		Comparison groups	Ramucirumab vs Placebo
			Hazard Ratio (stratified)	0.635
			(95% CI)	(0.536, 0.752)
			p-value	<0.0001
	Secondary Endpoint (ORR)		Comparison groups	Ramucirumab vs Placebo
			Odd Ratio	2.140
			(95% CI)	(1.449, 3.160)
			p-value (stratified)	0.0001
Notes	Stratification factors for the primary analysis: time to Progression (TTP) from the start of the first-line chemotherapy (<6 months vs. ≥6 months), geographic region (North America, Europe (including Israel), Australia vs. South and Central America vs. Asia) and disease measurability (measurable vs no measurable disease)			

Table A5. Characteristics of studies used for direct and indirect comparisons

Primary reference source	Study type	Number of patients	Intervention(s)	Comparator (Number of patients)	Patient population	Endpoints	Duplicate publications from the same study
RAINBOW [1]	RCT, double-blind	665	Ramucirumab (8 mg/kg I.V. on Days 1 & 15) plus paclitaxel (80 mg/m2 I.V. on Days 1, 8, & 15) every 28 Days (n=330)	Placebo (Days 1 & 15) plus paclitaxel (80 mg/m2 I.V. on Days 1, 8, & 15) every 28 days (n=335)	Patients with advanced gastric or GEJ adenocarcinoma after failure on platinum- and fluoropyrimidine-containing chemotherapy EGOG PS 0-1.	**Primary:** OS **Secondary:** PFS, TTP, ORR, QoL and health status, safety, PK, pharmacodynamics, Immunogenicity	Wilke et al. (2014a, 2014b, 2014c, 2014d), Wilke et al. (2012) Al-Batran et al. (2014a, 2014b), Hironaka et al. (2014), Carlson et al. 2014
West Japan Oncology Group 4007 [7]	RCT, open label	223 enrolled, but only 219 eligible for overall survival and PFS analyses (179 for ORR analysis; 218 for safety analysis)	Paclitaxel (80 mg/m2 I.V. on Days 1, 8, & 15) every 28 days	Irinotecan (150 mg/m2 I.V. on Days 1 & 15) every 28 days	Patients with advanced gastric adenocarcinoma after failure on platinumand fluoropyrimidine-containing chemotherapy EGOG PS 0-2	**Primary:** OS **Secondary:** PFS, ORR, toxicity, rate of post-subsequent chemotherapy	
COUGAR-02 [6]	RCT, open label	168	Docetaxel (75 mg/m2 I.V. on Day 1) every 21 days; up to 6 cycles	Active symptom control (no details of any interventions provided in publication)	Patients with advanced gastric, oesophageal, or GEJ adenocarcinoma after failure on platinumand fluoropyrimidine-containing chemotherapy. EGOG PS 0-2.	**Primary:** OS **Secondary:** best response to docetaxel, time to progression (for docetaxel), toxicity, QoL	
Thuss- Patience et al. [8]	RCT, open label	40 enrolled; study was closed early due to poor accrual	Irinotecan (250 mg/m2 x 1, then 350 mg/m2 I.V. on Day 1) every 21 days: up to 10 cycles	Best supportive care (no details of any interventions provided in publication, but patients were evaluated at same frequency as in experimental arm)	Patients with advanced gastric or GEJ adenocarcinoma after failure on prior chemotherapy (not including irinotecan). EGOG PS 0-2.	**Primary:** OS **Secondary:** ORR, time to progression, toxicity	

Primary reference source	Study type	Number of patients	Intervention(s)	Comparator (Number of patients)	Patient population	Endpoints	Duplicate publications from the same study
Roy et al. [13]	RCT, open label, phase 2	135 randomised. ITT for irinotecan n=44, and docetacel n=44 (One additional arm; PEP02 (highly stable liposomal nanocarrier formulation of irinotecan)	Irinotecan: 300 mg/m2(90-min infusion on day 1 of each cycle)	Docetaxel: 75 mg/m2 (60-min infusion on day 1 of each cycle) intravenously as monotherapy administered every 3 weeks.	Locally advanced or metastatic gastric or GEJ junction adenocarcinoma, with at least one measurable lesion. Failed one prior systemic chemotherapy. ECOG PS 0–2.	**Primary:** ORR **Secondary** PFS, time to disease progression or death, OS, 1 year survival rate toxicity	

Abbreviations: GEJ = gastro-oesophageal junction; I.V. = intravenous; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; RCT = randomised controlled trial; TTP = time to progression; QoL = quality of life.

Table A6. Additional studies used to inform safety information in the labelling of ramucirumab

Primary reference source	Study type and phase of development	Patient population, cancer type	Intervention(s)	Comparator (Number of patients)
I4T-IE-JVBJ[$] (IMCL CP12-0708)	Phase 2	NSCLC	Ramucirumab (10 mg/kg every 3 weeks)+ paclitaxel + carboplatin (n=40)	
I4T-IE-JVCA (IMCL CP12-1032)	Phase 2	Adv. Solid Tumours	Part A: *Ram + Paclitaxel Population* Cycle 2+: 8 mg/kg on Days 1 and 15 of every 4- week cycle, (n=31) Part B *Single-Agent Ram Population* Cycle 1: 8 mg/kg on Day 1 Cycle 2+: 8 mg/kg on Days 1 and 15 of q 4- week cycle	
ROSE; I4T-IE-JVBC (IMCL CP12-0606)	Phase 3	Breast Cancer (first-line unresectable, locally recurrent or metastatic (HER-2 negative))	Ramucirumab + Docetaxel (n=752)	Placebo + docetaxel (n=382)

Primary reference source	Study type and phase of development	Patient population, cancer type	Intervention(s)	Comparator (Number of patients)
I4T-IE-JVBX (IMCL CP12-1028)	Phase 1b	Breast Cancer	Ramucirumab + Docetaxel (n=7)	
I4T-IE-JVCCb (IMCL CP12-0713)	Phase 2	Adv Solid Tumours	Ramucirumab + Docetaxel (n=18)	
REGARD; I4T-IE-JVBD (IMCL CP12-0715)	Phase 3|	Gastric	Ramucirumab (n=236)	Placebo (n=115)

Source [2]

List of ongoing and planned studies

Identification of ongoing trials

On 9th December 2014, we searched the international clinical trials registry platform search portal (ICTRP search portal), using the term „ramucirumab“ [5]. It resulted 112 records in 35 trials. We removed one duplicate entry and selected the studies in patients with gastric cancers. We include the 2 studies referenced and used to inform results in the manufacturer submission dossier to complete all studies regarding patients with gastric cancer. Table A5 lists details of the identified studies. The MAH informs us that the JVCL and JVCP have expected completion in 2015, and that a manuscript has been submitted for study JVBW.

In addition, the draft EPAR list a study called I4T-MC-JVDD: Safety and Effectiveness of Ramucirumab in Patients with Advanced Gastric Cancer in the European Union and North America: A Prospective Observational Registry. The final study report is estimated for completion in Q4 2021 [3].

Table A7. List of trials using ramucirumab in patients with gastric cancers in second-line treatment

Study identifier	Date of first enrolment	Study type	Number of patients	Intervention	Comparator	Patient population	Primary endpoints
NCT02082210 I4C-MC-JTBF	03.2014	Non-RCT, open label	70	Ramucirumab in Combination With LY2875358	no	Advanced Cancers (any type solid tumour, gastric or GEJ, Hepatocellular cancer, Renal cell carcinoma, Non-small cell lung cancer	Dose-Limiting Toxicities (DLTs), Complete Response (CR) or Partial Response (PR) [Overall Response Rate (ORR)]
NCT02065765 I4T-MC-JVCP	02.2014	Expanded Access	NR	Ramucirumab	no	Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma Following Disease Progression After Prior Fluoropyrimidine and/or Platinum-Containing Chemotherapy	NR
NCT01983878 I4T-JE-JVCL	12.2013	Phase 2, Non-RCT, open label	33	Ramucirumab	no	Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma Following Disease Progression on First Line Platinum- or Fluoropyrimidine-Containing Combination Therapy in Japanese Patients	Progression Free Survival (PFS) Rate at 12 Weeks
NCT01253525 I4T-IE-JVBW	12.2010 Completed	Phase 1, Non-RCT, open label	6	Weekly Paclitaxel With Ramucirumab	No	Advanced Gastric Adenocarcinomas	Dose-Limiting Toxicities (DLT), Adverse events

Study identifier	Date of first enrolment	Study type	Number of patients	Intervention	Comparator	Patient population	Primary endpoints
NCT01170663 I4T-IE-JVBE	= RAINBOW trial. It is published and used for direct evidence						
NCT00917384 I4T-IE-JVBD	= REGARD trial. It is published and used to inform safety issues.						

Abbreviations: NR = not reported; RCT = randomised controlled trial
Sources: ICTRP search portal

Risk of bias tables

Table A8. Risk of bias – study level

Trial	Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding		Selective outcome reporting unlikely	No other aspects which increase the risk of bias	Risk of bias – study level
			Patient	Medicinal personnel and other staff			
RAINBOW (I4T-IE-JVBE/ IMCL CP12- 0922) [1]	Yes	Yes	Yes	Yes	Yes	Yes	Low
West Japan Oncology Group 4007 [7]	Yes	Yes	No[2]	No[2]	Yes	Unclear[3]	Unclear
COUGAR-02 [6]	Yes	Yes	No[2]	No[2]	Unclear[4]	Unclear[3,5]	Unclear
Thuss- Patience et al. [8]	Yes	Unclear[1]	No[2]	No[2]	Unclear[6]	No[5,7,8]	High
Roy et al. [13] (Used in evidence networks, not discussed otherwise)	Unclear[1]	Unclear[1]	No[2]	No[2]	Unclear[4]	Unclear[3]	High

comments:

1: not described 2: open-label study, 3: assessors aware of treatment assignment could influence results for some outcomes. Could have used a blinded independent assessor to validate results, 4: ITT-principle not used for all outcomes, 5: tumour assessment only scheduled or mandatory for experimental group, 6: quality of life not assessed due to poor return of questionnaires 7:study terminated early due to poor recruitment, 8: long recruitment of few patients may impact on what is considered best practice, missing data and no or unclear for several elements of the evaluation of validity

Table A9. Risk of bias – outcome level

Outcome Trial	Blinding – outcome assessors	ITT principle adequately realized	Selective outcome reporting unlikely	No other aspects according to risk of bias	Risk of bias – outcome level
Overall survival (OS)					
RAINBOW	Low	Low	Low	Low	Low
WJOG	Low[0]	Low[1]	Low	Low	Low
COUGAR-02	Low[0]	Low	Low	Low	Low
Thuss-Patience	Low[0]	Low	Low	Low	Low
Progression free survival (PFS)					
RAINBOW	Low	Low	Low	Low	Low
WJOG	Unclear[13]	Low	Low	Low	Unclear
COUGAR-02	Not reported[3]				

Outcome Trial	**Blinding – outcome assessors**	**ITT principle adequately realized**	**Selective outcome reporting unlikely**	**No other aspects according to risk of bias**	**Risk of bias – outcome level**
Thuss-Patience	Not reported[5]				
Objective response rate (ORR)					
RAINBOW	Low	Low	Low	Low	Low
WJOG	Unclear[13]	Low[4]	Low	Low	Unclear
COUGAR-02	Not reported [2,3]				
Thuss-Patience	Not reported[5]				
Health-related quality of life (HRQoL)					
RAINBOW	Low	Low	Low	Low	Low
WJOG	Not reported				
COUGAR-02	High[7]	Unclear[8]	Low	Low	High
Thuss-Patience	Not reported[6]				
Adverse events					
RAINBOW	Low	Low[9]	Low	Low	Low
WJOG	Unclear[12]	Low[9]	Low	Low	Unclear
COUGAR-02	Unclear[12]	High[10]	Low	Low	High
Thuss-Patience	Not reported[11]				

comments:

0: awareness of study treatment not expected to influence mortality 1:Four of 223 patients excluded from analysis set, not optimal but unlikely to alter results, 2: ORR only in patients with assessable disease (56/84 in docetaxel group), 3:not assessed in control group, 4: response rate assessed in all patients with ≥measurable lesion at baseline, CT every 2 months RECIST criteria, 5:Staging by imaging was mandatory only in the irinotecan arm and optional in the BSC arm.6: Quote: “Assessment of quality of life using the EORTC QLQ C30 questionnaire was planned but return of the forms was too poor to undertake meaningful analyses”, 7: answered by patients on open-label, unsure if it could affect results (one group had only BSC), 8: Acceptable, 72% and 65% return of forms, description of handling missing data and sensitivity analyses 9:Adverse events was reported for the safety population (all patients that received at least one dose of any study drug) instead of all randomised patients 10:exclusion form AE reporting unclear; 11: only reported for experimental arm of the study, 12: assessors aware of treatment assignment could influence assessment of adverse events. 13: assessors given rating templates such as RECIST, but being aware of treatment assignment could influence assessment

Evidence Profiles

Table A10. GRADE evidence profile for direct evidence and effectiveness outcomes

Quality assessment							№ of patients		Effect		Quality
№ of studies	**Study design**	**Risk of bias**	**Inconsis-tency**	**Indirect-ness**	**Impreci-sion**	**Other considera-tions**	**ramucirumab+ paclitaxel**	**placebo+ paclitaxel**	**Relative (95% CI)**	**Absolute (95% CI)**	
Mortality											
1	randomised trials	not serious	serious [1]	not serious	not serious	none	256/330 (77.6%)	260/335 (77.6%)	**HR 0.807** (0.678 to 0.962)	75 fewer per 1000 (from 13 fewer to 139 fewer)	⊕⊕⊕◯ MODERATE
Patients with progression											
1	randomised trials	not serious	serious [1]	not serious	not serious	none	279/330 (84.5%)	296/335 (88.4%)	**HR 0.635** (0.536 to 0.752)	139 fewer per 1000 (from 82 fewer to 199 fewer)	⊕⊕⊕◯ MODERATE
Median survival											
1	randomised trials	not serious	serious [1]	not serious	not serious	none	330	335	-	median **9.63 higher** (8.48 higher to 10.81 higher)	⊕⊕⊕◯ MODERATE

Objective response rate (ORR) (assessed with: complete or partial response)											
1	randomised trials	not serious	serious [1]	not serious	not serious	none	92/330 (27.9%)	54/335 (16.1%)	**OR 2.14** (1.45 to 3.16)	130 more per 1000 (from 57 more to 217 more)	⊕⊕⊕◯ MODERATE
Quality of Life (end of treatment) (assessed with: EORTC QLQ-C30)											
1	randomised trials	not serious	serious [1]	not serious	not serious	none	101/330 (30.6%)	111/335 (33.1%)	**RR 0.92** (0.74 to 1.15)	27 fewer per 1000 (from 50 more to 86 fewer)	⊕⊕⊕◯ MODERATE
Quality of Life (18 weeks) (assessed with: EORTC QLQ-C30)											
1	randomised trials	not serious	serious [1]	not serious	not serious	none	80/330 (24.2%)	52/335 (15.5%)	**RR 1.56** (1.14 to 2.14)	87 more per 1000 (from 22 more to 177 more)	⊕⊕⊕◯ MODERATE

Question: Ramucirumab+paclitaxel compared to placebo + paclitaxel for patients with gastric cancer or gastro-oesophageal junction adenocarcinoma
Settings: after treatment with chemotherapy
MD – mean difference, RR – relative risk
1. Single study, thus results not confirmed /shown consistently across different studies

Table A11. GRADE evidence profile for direct evidence and safety outcomes

Quality assessment							№ of patients		Effect		Quality
№ of studies	**Study design**	**Risk of bias**	**Inconsis-tency**	**Indirect-ness**	**Impreci-sion**	**Other considerat-ions**	**ramucirumab+ paclitaxel**	**placebo+ paclitaxel**	**Relative (95% CI)**	**Absolute (95% CI)**	
Patients with one or more adverse events vs placebo+paclitaxel											
1	randomised trials	not serious	serious [1]	not serious	not serious	none	324/327 (99.1%)	322/329 (97.9%)	**RR 1.01** (0.99 to 1.03)	10 more per 1000 (from 10 fewer to 29 more)	⊕⊕⊕◯ MODERATE
Patients with AE of grade 3 or higher											
1	randomised trials	not serious	serious [1]	not serious	not serious	none	267/327 (81.7%)	206/329 (62.6%)	**RR 1.3** (1.18 to 1.44)	188 more per 1000 (from 113 more to 276 more)	⊕⊕⊕◯ MODERATE
Patients who discontinued treatment due to adverse events											
1	randomised trials	not serious	serious [1]	not serious	serious [2]	none	38/335 (11.3%)	39/330 (11.8%)	**RR 1.04** (0.68 to 1.59)	5 more per 1000 (from 38 fewer to 70 more)	⊕⊕◯◯ LOW
Patients with serious adverse event (TE-SAE)											

1	randomised trials	not serious	serious [1]	not serious	serious [2]	none	153/327 (46.8%)	139/329 (42.2%)	**RR 1.11** (0.93 to 1.31)	46 more per 1000 (from 30 fewer to 131 more)	⊕⊕◯◯ LOW
deaths due to an AE											
1	randomised trials	not serious	serious [1]	not serious	serious [2]	none	13/327 (4.0%)	15/329 (4.6%)	**RR 0.87** (0.42 to 1.8)	6 fewer per 1000 (from 26 fewer to 36 more)	⊕⊕◯◯ LOW

Question: Ramucirumab+paclitaxel compared to placebo + paclitaxel for patients with gastric cancer or gastro-oesophageal junction adenocarcinoma
Settings: after treatment with chemotherapy
MD – mean difference, RR – relative risk

1. Single study, thus results not confirmed /shown consistently across different studies
2. Confidence interval include both no difference and clear harm or benefit

Applicability tables

Table A12. Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	The population included in the RAINBOW trial is representative of patients usually included in clinical trials. The study only included patients with ECOG PS 0 and 1, while the studies used for indirect evidence/evidence networks also included patients with ECGO PS 2. Baseline characteristics show that the studies included more men than women (approx.70-85%). The median age was approx. 60 to 65 years. Hence, the enrolled population is representative of the intended use. Patient population in studies included in the indirect comparisons in the submission seems to be representative for patient relevant for the scope of this assessment.
Intervention	The way of administration, dosing and frequency of cycles used for ramucirumab in combination with paclitaxel is according to the upcoming approved licence. Paclitaxel seems to be one of the routine used 2nd line treatments (off-label) and the combination with ramucirumab, if licensed, could be regarded as a new standard 2nd line therapy for patients relevant for the scope of this assessment. Patients received study treatment until disease progression, unacceptable toxicity, or withdrawal of consent. This is in line with treatment recommendations. All patients received supportive care if indicated as it is done in clinical practice.
Comparators	Currently, no regulatory approved treatment options exist for second-line treatment for advanced gastric cancer, but the most commonly used treatments are paclitaxel, irinotecan, docetaxel and best supportive care.
Outcomes	The choice of outcomes is representative, and according to guidelines, for oncology studies. Overall survival (OS) is considered the gold standard for studies of advanced cancer. Most studies reported on this outcome. Except for the study by Thuss-Patience et al. that ended early due to poor enrolment, the other studies followed patients until the pre-specified number of survival events had occurred. Secondary outcomes were progression-free survival, defined as time from randomisation to radiographic progression or death; objective tumour response, defined as the proportion of patients who had best response of complete response or partial response; disease control, defined as the proportion of patients who had a best response of complete response, partial response or stable disease. Disease progression and tumour response was assessed by investigators according to the RECIST criteria. Patient reported outcomes were assessed using EORTC QLQ-C30 and EQ-5D-3L, both are known quality of life measurement scales. This will aid in comparing to other treatments.
Setting	The RAINBOW trial included patients worldwide. This is representative of expected use. There has been data showing that stage of disease discovery and prognosis vary between regions such as Asia and Europe. Subgroup analyses have been performed and relative benefit is consistent across regions. The combination treatment with ramucirumab and paclitaxel requires some premedication and it has to be administered in an in-patient setting as it was done in the studies.

APPENDIX 2. REGULATORY STATUS

Table A13. Regulatory status of ramucirumab in combination with paclitaxel and comparators (paclitaxel, docetaxel, irinotecan) by EMA and FDA in second-line therapy in advance gastric cancer or gastro-oesophageal junction adenocarcinoma

Second-line therapy in advance gastric cancer or gastro-oesophageal junction adenocarcinoma	EMA	FDA
Ramucirumab in combination with paclitaxel	Yes	Yes
Paclitaxel	No, Off-label use	No, Off-label use
Docetaxel	No, Off-label use	No, Off-label use
Irinotecan	No, Off-label use	No, Off-label use

APPENDIX 3. CHECKLIST FOR POTENTIAL ETHICAL, ORGANISATIONAL, SOCIAL AND LEGAL ASPECTS

1. Ethical	
1.1. Does the introduction of the new medicine and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues?	Yes
1.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be ethically relevant?	No
After the first-line therapy for advanced gastric cancer, there are no other regulatory approved options for second-line therapy. Relevant questions are: • F0007 Does the implementation or withdrawal of the ramucirumab in combination with paclitaxel in comparisons with treatments in second-line therapy challenge or change professional values, ethics or traditional roles? • H0012 Are there factors that could prevent a group or person from gaining access to the ramucirumab in combination with paclitaxel? • F0017 What are the ethical consequences of the choice of comparators/controls in the assessment?	
2. Organisational	
2.1. Does the introduction of the new medicine and its potential use/non-use instead of the defined, existing comparators require organisational changes?	No

2.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be organisationally relevant?	No
We assume that the departments dealing with cancer treatment are well equipped to handle potential minor changes between the intervention and other treatments.	
3. Social	
3.1. Does the introduction of the new medicine and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new social issues?	No
3.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be socially relevant?	No
None detected.	
4. Legal	
4.1. Does the introduction of the new medicine and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues?	Yes
4.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be legally relevant?	Yes

Ramucirumab is the first pharmaceutical with marketing authorisation for second-line treatment patients with this kind of cancer. The Manufacturer's submission file indicates a positive risk/benefit ratio for the treatment. Continuing with use of treatments outside their intended use (outside of indication, off-label) should be discussed.

I0012 What are the consequences of various EU level and national regulations to the equal access to the ramucirumab in combination with paclitaxel in comparison with off-label second-line therapy?

APPENDIX 4. COMMENTS RECEIVED BY DEDICATED REVIEWERS ON THE FIRST ASSESSMENT DRAFT

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
Part I: Scope				
1. Was there a need to deviate from the Project Plan (protocol) in terms of clinical problem, population, intervention(s), comparison(s) and outcome(s)? If the answer is **NO**, please move directly to the Part II of the reviewer form.			**GYEMSZI**: No **HAS:** No **FIMEA:** No **A.Gemelli**: No **SlovakMoH**: No	
2. Was a rationale included for the deviation of the scope that was proposed in the project plan?				
Part II: Methods				
1. If there was a need to deviate from the Project Plan (protocol) in terms of methods used, is it described in the Method's section of the pilot?	**GYEMSZI**: N/A			**HAS:** Not relevant **FIMEA:** No need to deviate from the project plan **SlovakMoH:** Not applicable (authors have no deviations from the project plan.)
2. If there was no manufacturer's submission file available or the received submission file was incomplete, biased or outdated, did	**SlovakMoH**: Yes	**GYEMSZI:** Performed additional non-systematic searches		**HAS:** Not relevant **FIMEA:** MAH submission file was quality assessed

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
the authors conduct a more detailed search?		**A.Gemelli:** A non-systematic review has been done because of the short timelines.		by author team
3. Are inclusion/exclusion criteria for selection of the studies described in appropriate detail?	**GYEMSZI:** Yes **HAS:** Yes **A.Gemelli**: Yes **SlovakMoH:** Yes	**FIMEA:** Details for exclusion and inclusion are missing A: Covered by:" Based on clear inclusion criterial in the screening process, the MAH identified 30 publications of 23 unique studies. However, after limiting the focus to the intervention and controls for this assessment the included studies was reduced."		
4. Are the quality appraisal tools appropriate?	**GYEMSZI**: Yes **HAS**: Yes **FIMEA**: Yes **A.Gemelli:** Yes **SlovakMoH:** Yes			
5. Is the type/presentation of evidence (e.g. Meta analysis, qualitative synthesis, GRADE) appropriate for this analysis?	**GYEMSZI:** Yes **HAS**: Yes **FIMEA**: Yes **A.Gemelli**: Yes **SlovakMoH:** Yes			
6. Is the risk of bias sufficiently assessed, both on study level and on	**GYEMSZI**: Yes			

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
an outcome level?	**HAS**: Yes **FIMEA:** Yes **A.Gemelli**: Yes **SlovakMoH:** Yes			
7. Is the choice of study types appropriate to the population, intervention(s), comparison(s) and outcome(s)?	**GYEMSZI:** Yes **HAS:** Yes **FIMEA:** Yes **A.Gemelli:** Yes **SlovakMoH:** Yes	**HAS:** The choice is appropriate although, we should underline as the authorship team the limited number of evidence used : only 4 RCTs were included in the discussion - one RCT on ramucirumab, which served as a basis for direct evidence - and 3 RCTs on comparators for the indirect evidence which 1- are all open label studies performed in one single country with a rather small sample size and 2 - are different one from another in terms of inclusion/exclusion criteria, endpoints, standard of care etc A: (to HAS) We understand the desire for additional studies, but currently they do not exist. We discuss this issue under evidence gaps.		

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
8. Are the types of studies to be included (randomised trials, quasi-randomised trials or other designs) described?	**GYEMSZI**: Yes **FIMEA**: Yes **A.Gemelli**: Yes **SlovakMoH**: Yes	**HAS:** More information on patients populations (line of treatment, disease extension, ECOG PS) study location would be important. It would be helpful if a study is designated the same way across the report (i.e. WJOG 4007/Hironaka 2013 and COUGAR-02/Ford 2014) A: (to HAS) An overview of patient population and ECOG is part of Table 22.We also present the studies including location in the start of Clinical Effectiveness Chapter. Updated the naming of studies		
9. If it was relevant to include data from indirect comparisons, is this step justified and the methods of indirect comparisons sufficiently described?	**GYEMSZI**: Yes **A.Gemelli**: Yes **SlovakMoH**: Yes	**HAS:** Yes, even if more information on how the heterogeneity across the studies has been measured and handled would be welcome.	**FIMEA:** Practically all details including original data related to indirect analyses are unfortunately missing. Extensive description of the methodology and selection of studies is necessary in case results from indirect comparisons are reported. Furthermore, proper evaluation of the assumptions should be	

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
			discussed A: A short description of all included studies and methodology for selection of studies is included in the Appendix 1. Discussion of the assumptions in the report has to be limited because the analysis is not published yet. More information in Appendix.	
10. Are appropriate methods of measuring each outcome and appropriate time points for measurement identified?	**GYEMSZI:** Yes **FIMEA**: Yes **A.Gemelli**: Yes **SlovakMoH:** Yes			

11. Details on sources of information and literature search strategies provided?					
Search strategy	Databases	Year range	Language restriction	Primary data	Other kind of information resources
GYEMSZI: Yes **HAS:** Yes **FIMEA:** NO (permission to report detailed search strategy has been asked)	**GYEMSZI:** Yes **HAS**: Yes **FIMEA:** Yes **A.Gemelli:** Yes **SlovakMoH:** Yes	**GYEMSZI**: Yes **HAS:** Yes **FIMEA:** Yes **A.Gemelli:** Not stated **SlovakMoH:**	**HAS**: ? **FIMEA:** No **A.Gemelli**: I couldn't find any reference to this point **SlovakMoH:** Yes A: Only studies in English were	**HAS:** Yes **FIMEA:** Yes **A.Gemelli**: Yes **SlovakMoH:** Yes	**GYEMSZI:** Yes **HAS:** Yes **FIMEA**: Yes **A.Gemelli:** Yes **SlovakMoH:** Yes

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
A.Gemelli: Yes **SlovakMoH**: Yes	Yes	included. Clarified in text.		
12. Information on basis for the assessment and interpretation of selected data and information?				
Method of data extraction described?	Critical appraisal method (for quality assessment of the literature) described?		Method of data synthesis described?	
GYEMSZI: Yes **HAS:** Yes **FIMEA**: Yes **A.Gemelli:** Yes **SlovakMoH:** Yes	**GYEMSZI:** Yes **FIMEA:** Yes **A.Gemelli:** The applicability tables well summarize applicability criteria. Additionally, It is reported for each study/outcome results of the assessment of risk of bias **SlovakMoH:** Yes		**FIMEA:** NO/PARTLY (indirect comparison methodology missing all the details) **A.Gemelli:** Yes **SlovakMoH:** Yes A: Data from indirect comparisons are of low quality and yet unpublished. We were not able to use them in the tables or to present them in a proper way before expected publication. All data will be presented in Appendix.	
13. Do you agree on the selection of the assessment elements and the justification for not including specific elements?	**GYEMSZI**: Yes **HAS**: Yes **FIMEA:** Yes **A.Gemelli:** Yes **SlovakMoH:** Yes			
14. If there was a need to deviate from the Project Plan in terms selection of assessment elements, is	**A.Gemelli:** Not applicable			**HAS:** Not relevant **FIMEA:** Not applicable;

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
the change justified?				no need to deviate from the project plan **SlovakMoH:** Not applicable
Part III: Description of the evidence				
1. Do you agree on the data extracted from the included studies? (See Table [X]. Characteristics of the randomized controlled studies and Table [X]. Relevant non-RCTs identified)	**GYEMSZI:** Yes **FIMEA**: Yes **SlovakMoH:** Yes	**HAS:** More information on patients populations (line of treatment, disease extension, ECOG PS) study location would be important. It would be helpful if a study is designated the same way across the report (i.e. WJOG 4007/Hironaka 2013) **A.Gemelli:** In Table 23, it isn't clear the meaning text "None?" in Comparator column A: (to HAS), see Q8 above A: (to A-Gemelli). Text deleted. Empty cells= no comparator		
2. Do you agree on the risk of bias tables?	**GYEMSZI**: Yes **HAS:** Yes **A.Gemelli:** Yes **SlovakMoH:** Yes	**FIMEA:** Risk of bias at study level should be justified; it remains unclear to us why e.g. RAINBOW, WJOG 4007 and COUGAR-02 leads to same study level risk of bias. Secondly, the industrial sponsorship should be reflected in the RoB assessment.		

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
		Homogeneous practice within WP5 should be discussed on how to deal with industrial sponsorship in RoB assessment. A: (to FIMEA) Risk of bias at overall study level is an estimate across all outcomes, please see individual outcomes for details Tables and legends updated for clarity (Appendix 1). We did not suspect industrial sponsorship to influence these study results. We agree that we should aim for a WP5 discussion on the topic		
3. Do you agree on the applicability tables?	**GYEMSZI:** Yes **HAS:** Yes **A.Gemelli:** Yes **SlovakMoH:** Yes	**FIMEA:** In principle we agree on the applicability tables. However, this can not be evaluated based on the information given in the report. A: See our explanation above		
Part IV: Results				
Health problem and current use of the technology				
1. Does the section describe the health issue including incidence and prevalence, how it occurs, who is affected (including high-risk groups, vulnerable/disadvantaged	**A.Gemelli:** Yes **SlovakMoH:** Yes	**GYEMSZI:** Incidence? how it is diagnosed? symptoms?		

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
populations, where it occurs, how it is diagnosed, symptoms and consequences)?		**HAS:** Yes in general even if more Information on risk factors for the disease should be developed **FIMEA:** Risk factors and specific high-risk groups could be further discussed if possible A: Thank you very much for your valuable comments. The symptoms have been covered in A0005 Element. A0024 Element (diagnosis) and A0003 Element (risk factors) were planned to be excluded from the assessment, as optional assessment elements judged not so important for this assessment. In case of further kind requests on these data during the next phases of assessment, could be envisage adding the most important risk factors but not as separate assessment element. We have added additional text and two tables on estimated incidence, mortality & prevalence from gastric cancer in 2012 for men and for women for EU-countries, Iceland, Norway and Switzerland, and a reference to those tables (please see in the text) in assessment elements A0006/A007/A0023 and		

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
		Appendix 1. Reference used: Steliarova-Foucher E, O'Callaghan M, Ferlay J, Masuyer E, Forman D, Comber H, Bray F: European Cancer Observatory: Cancer Incidence, Mortality, Prevalence and Survival in Europe. Version 1.0 (September 2012) European Network of Cancer Registries, International Agency for Research on Cancer. Available from http://eco.iarc.fr, accessed on 16/January/2015.		
2. Are the supporting references current?	**GYEMSZI:** Yes **HAS**: Yes **FIMEA:** Yes **A.Gemelli:** Yes **SlovakMoH:** Yes			
3. Do the supporting references provide an international picture of the problem?	**GYEMSZI**: Yes **HAS:** Yes **FIMEA:** Yes **SlovakMoH:** Yes	**A.Gemelli:** The attention paid to Asian countries (in A0004) seems to be not appropriate for the European Assessment. A: Thank you very much; We agree with the referee that somewhat inappropriate attention was paid to Japan, considering the European context of the report. We have tried to address this and re-order paragraphs in A004. We have also		

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
		rewritten the paragraph on the differences between Japan and Western countries (adding more data on European countries and reducing data on Japan), please see in the text, thank you.		
Description and technical characteristics of the technology				
4. Does the section describe the intervention under review including how it works and how it may have an impact on potential recipients?	**GYEMSZI:** Yes **HAS:** Yes **FIMEA**: Yes **SlovakMoH:** Yes	**A.Gemelli:** Discussion section seems to be not fully appropriate for this Domain. In the Discussion are reported adverse effects associated with ramucirumab. It isn't the correct place where to place that evidence. Furthermore,is it necessary to report the definition of BSC, as done? A: Thank you for your comments; Data from SmPC, also on adverse events, are parts of this Domain, after the marketing authorization data will be changed accordingly. We consider Adverse events as a part of the description of clinical effects and potential harms. According BSC, yes, this is necessary due the fact that even general definition is reported in different way by investigators; BSC		

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
		is neither well-defined nor standardized, please see below.		
5.. Does the section describe the comparator(s) under review including how it works and how it may have an impact on potential recipients?	**GYEMSZI**: Yes **HAS**: Yes **FIMEA:** Yes **A.Gemelli:** Yes **SlovakMoH:** Yes	**HAS:** Definition and distinction of best supportive care versus active symptom control would be beneficial, especially as both are comparators in the 3 open label RCTs used for the indirect comparison A: The distinction is not made clear in the included studies. It is briefly discussed as general problem in text (Discussion). According the definitions - best supportive care versus active symptom control has the same meaning, and could be used as expression for BSC. For example, in REGARD trial (data from ClinicalTrial.gov): Best Supportive Care (BSC) - as determined appropriate by the investigator(s). BSC may include but are not limited to antiemetic agents, opiate and nonopiate analgesic agents, appetite stimulants, and granulocyte and erythroid growth factors. According the Kang et al. 2012., all patients received standard BSC		

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
		regimen a priori defined in the study protocol. “In general, BSC had to be understood as multiprofessional attention to the patient’s overall physical, psychosocial, spiritual, and cultural needs available at all stages of illness. It included, but was not restricted to, analgesics, paracentesis, psychosocial care, nutritional support, and blood transfusion. Localized radiotherapy to alleviate pain was allowed, provided that the radiation dose was in the palliative range. Investigators were free to provide nonprotocol supportive care measures at any time during the study if it was felt to be in the patient’s best interest. BSC patients could exit BSC and were allowed to receive chemotherapy.” According Cochrane Systematic Review from Ahmed et al, 2004, comparing chemotherapy to BSC in GI cancers revealed that BSC was not consistently defined in the four trials included.		
6. Are the supporting references current and do they provide an international picture of the problem?	**HAS:** Yes **FIMEA:** Yes **SlovakMoH**: Yes	**A.Gemelli**: Some references are missing. A: References are current and provide clear picture of the		

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
		problem; some new are added, thank you.		
Safety and effectiveness				
7. Is the risk of bias clearly reported?	**GYEMSZI:** Yes **HAS:** Yes **SlovakMoH:** Yes	**FIMEA:** Justifications for some issues are missing; see comment above	**A.Gemelli:** Only in Appendix and not discussed, just reported. A: See response above, RoB is also included in the GRADE assessments that are in the main report.	
8. Is quality of data sufficiently evaluated?	**GYEMSZI**: Yes **HAS**: Yes **FIMEA**: Yes **A.Gemelli:** Yes **SlovakMoH**: Yes			
9. Are both relative and absolute effect measures presented for each dichotomous outcome?	**GYEMSZI:** Yes **HAS:** Yes **FIMEA:** Yes **A.Gemelli:** Yes **SlovakMoH:** Yes			
10. Are continuous data reported according to appropriate statistics	**HAS:** Yes	**A.Gemelli:** For instance, in Table 7 Survival only “mean		

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
(e.g. 'standardised mean difference' or 'weighted mean difference')?	**FIMEA**: Yes **SlovakMoH:** Yes	median survival" is reported. No'standardised mean difference' or 'weighted mean difference'. Which is the meaning of "mean median survival"? A: We have added missing confidence intervals around point estimates. Median OS is reported correct now. Thank you for your feedback		
11. In case of time-to event analysis, are hazard ratios (HR) and ratios of medians presented	**GYEMSZI:** Yes **FIMEA:** Yes **A.Gemelli**: Yes **SlovakMoH:** Yes			
12. Are measures of the precision of the effect estimates presented or, in case of absence of this essential information, is this fact reported	**GYEMSZI:** Yes **FIMEA**: Yes **A.Gemelli:** Results are reported always with confidence intervals. **SlovakMoH:** Yes			
13. Is frequency of adverse events, frequency of occurrence, relative risk	**GYEMSZI:** Yes	**HAS**: No NNH data presented **A.Gemelli:** Odds ratio are		

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
or number needed to harm (NNH) presented for the safety data	**FIMEA:** Yes **SlovakMoH:** Yes	reported A: We did not present all possible output styles, but used the style from the submission.		
14. In case where adverse events are incorporated in utility values of quality of life, is the source of quantification accessible?	**SlovakMoH:** Yes	**A.Gemelli:** QoL is addressed in D0012, which could be improved investigated data for each symptom scale (if feasible). It isn't clear the utility of the table taken from EPAR A: Unfortunately not. It is not clear how the adverse events were incorporated in the quality of life assessments reported by patients. The table is removed.		**HAS:** Not relevant **FIMEA:** Not applicable
15. Do you agree that the results of this REA do not contain any errors or deficiencies?	**GYEMSZI**: Yes **HAS**: Mostly **A.Gemelli:** Yes **SlovakMoH:** Yes	**FIMEA:** We agree on the results for direct comparisons; Based on the report, the indirect comparison results can not be checked in necessary detail in order to be confident about them A: For indirect comparisons we have added a bit more detail in the report. As described above we have data on hold, which will be added in an Appendix.		

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
16. If applicable, was the transformation of the surrogate outcomes into patient-relevant final outcomes considered?	**FIMEA:** Yes **SlovakMoH:** Yes			**HAS:** Not relevant **A.Gemelli:** Not applicable
General				
17. Do you agree that the data extracted are relevant to the research questions formulated in the beginning and that analysed and synthesised data still answer the question?	**GYEMSZI:** Yes **HAS**: Yes **FIMEA**: Yes **A.Gemelli:** Yes **SlovakMoH:** Yes			
18. Can the results be applied to the intended population?	**GYEMSZI:** Yes **HAS:** Yes **FIMEA:** Yes **A.Gemelli:** Yes **SlovakMoH:** Yes			
19. Is the assessment sufficiently transparent and evidence ('facts') distinguished from judgements (including values and preferences)?	**GYEMSZI:** Yes **HAS**: Yes **A.Gemelli:** Yes **SlovakMoH**: Yes	**FIMEA:** Indirect comparisons lack transparency and all the details required for critically appraisal of them are missing. Evidence is mostly well distinguished from the judgements A: See response to Q 15. We agree, but not feasible for the		

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
		time being to write in more details. See Appendix.		
Part V: Summary of Relative Effectiveness				
1. Does the summary present a balanced representation of the content of the report?	**GYEMSZI:** Yes **HAS**: Yes **FIMEA**: Yes **SlovakMoH:** Yes	**A.Gemelli:** Conform to template. Minor revisions to perform. A: Updated in version 2.		
2. Does the discussion of the summary clearly address the uncertainty in the available evidence, the evidence gaps and the applicability of the evidence?	**GYEMSZI**: Yes **HAS:** Yes **FIMEA:** Yes **A.Gemelli:** Yes **SlovakMoH:** Yes			
Part VI: Other Considerations				
1. Have all relevant ethical, organisational, social and legal aspects been considered? (See Appendix 3 of the Pilot assessment)	**GYEMSZI:** Yes **FIMEA**: Yes **SlovakMoH:** Yes		**A.Gemelli**: It isn't available a final version for Appendix 3. At the moment Appendix 3 is incomplete and the Discussion section must be written.	**HAS:** To be reviewed when the report will be completed with this part A: Updated in version 2, appropriate references were found to answer on these assessment element questions.

GENERAL AND SPECIFIC COMMENTS FOR THE AUTHORS

Page	Line	Comments	Comments from the author
General		**HAS:** As pre-warned by the coordinator team, table numbers and language check should and will be done. Therefore, no comment on language will be given.	OK
General		**HAS:** The glossary should be updated as well with some missing abbreviations (PS, DP etc).	PS is in the abbrev., DP is not in use? However, we will check the abbreviations again.
General		**HAS:** I suggest that if acronyms have to be used in the executive summary, then the full definition is given as well.	Updated. We use the full name the first time, with abbreviation in brackets. Further text use the abbreviation.
General		**FIMEA:** This report is well written and includes relevant data. Secondly, we find this relatively complete considering that this is the first draft. Thirdly, the timelines were respected which is appreciated by collaborators. Furthermore, inclusion of off-label comparators brings additional clinical value for the report. More detailed and specific comments can be found below.	Thank you.
5	12-18	**A.Gemelli:** Duplication of information. Text could be simplified in „Ramucirumab (Cyramza) in combination with paclitaxel is indicated for the treatment of adult patients with advanced gastric cancer or GEJ adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy [A0020]. Ramucirumab will be the only approved treatment option for those patients“.	Thank you, we revised text according suggestion, the second sentence is written as “Ramucirumab alone, or in combination with paclitaxel will be the only approved treatment option for those patients.”
6	16-18	**FIMEA:** Does this refer to situation in U.S?	Currently yes.
7	5-7	**A.Gemelli:** This sentence could be moved in Health Problem or removed. It doesn’t refer to available evidence and doesn’t add new information.	This is for background information, first two domain text

Page	Line	Comments	Comments from the author
7	26-28	**FIMEA:** Reference should be to D0005 instead of D0016.	Updated
7	29-30	**FIMEA:** From our point of view, statistical significances are quite irrelevant with these indirect comparisons. Representation including estimates and their CIs could be useful.	We agree that CI give more information than p-values. However, this need to be read with the next sentences too "Many of the results were associated with wide confidence intervals around the point estimates and thus considered uncertain." Listing all details would too extensive in the summary.
8	4	**FIMEA:** Please note that statistical significance is not quite relevant in terms of safety. Trials have not been powered to detect differences in safety parameters (eventhough sometimes these differences can be statistically significant). More focus could be put on the differences in safety profiles instead of purely statistically orientated comparisons.	We agree (see above). Also see below, as we updated other sections.
8	14-18	**A.Gemelli:** Please specify to which adverse events you refers. To clarify the meaning of „Comparing the odds of experiencing these adverse events to other treatment alternatives show that some appear to occur more often with this intervention, while others seem to occur more often in the other treatment alternatives".	New text added.
8	14-20	**FIMEA:** Please provide more details on the specific events and the type of events. As it stands currently, the summary section related to safety does not provide any information on the types of adverse events.	New text added.
9	Table1	**FIMEA**: With respect to overall mortality, the incidece of death seem to be the same for both groups (77.6%) and HR is 0.81. This can be possible but usually the proportional hazards assumption related to survival analysis is likely to be not valid in such situation. Secondly, these incidence numbers are different than those reported on page 41. This should be checked further.	Overall mortality vs. median overall survival The incidence numbers seems to be different because they are reported differently: number events in study group (256/330) vs number events per 1000 but both are correct.

Page	Line	Comments	Comments from the author
		Also median survial times could be reported here instead of incidence proportions.	Median survival time is reported in the text.
11	28-29	**FIMEA:** Clinical relevance of the 2.2 months survival benefit is debatable. This is fine as author's judgement but a reference or more justification could be useful. Please refer to Ellis et al. Journal of clinical oncology 2014:32(12), p. 1277-1280 try to reflect the estimate to these specifications.	Thanks for your suggestion. Ellis et al.2014 gives some recommendation for what effect size of OS and PFS for specified patient populations should be expected in order to be recognize as clinically meaningful. Metastatic gastric cancer is not included in the examples but we may discuss suggestions in the reference.
12	1	**FIMEA:** Please consider removing the rest of the sentence ",but not showing…" since it is quite irrelevant in this context (see comment on safety and statistics above).	Done
18	9-12	**FIMEA:** Note: While representing the results, it could be useful to indicate which estimates are calculated by the authors.	Updated: "Such analyses are labelled as our calculation." Results sections updated with information of calculation done by us.
22	2-4	**FIMEA:** Please consider removing these two sentences since they may be too detailed and irrelevant information for this context.	Thank you, we agree with your comment, sentences are deleted.
22	12-18	**FIMEA:** To our understanding, this section should belong to safety domain?	Thank you for your comment; We think that data from SmPC, also on adverse events, are parts of this Domain and after the marketing authorization data will be changed accordingly.
23	20-21	**A.Gemelli:** I suggest to move in a most appropriate paragraph „Treatment of gastric cancer is not approved indication for paclitaxel in US „. Here you don't discuss about marketing authorization. Before you mentioned dosing, then available evidence. I suggest to move at the end approved indications or open with a sentence dedicated to them.	Text is partially rewritten to raise more clarity.
23	21	**FIMEA:** …. In US and in EU	Thank you.

Page	Line	Comments	Comments from the author
23	24-29	**FIMEA**: References are missing	References were added, thank you.
23	28-29	**A.Gemelli:** „. Paclitaxel plus radiation has shown some activity against gastric cancer“ is a too generic sentence.	Thank you, these data are in line with given references.
25	3-14	**FIMEA:** References are missing	References were added, thank you.
26	7-12	**FIMEA:** References are missing. Line 7: in US and in EU.	References were added, thank you.
27	3-12	**A.Gemelli:** Please motivate the need to report a general (not disease specific) definition of BSC and palliative/supportive care.	Even general definition is reported in different way by investigators; BSC is neither well-defined nor standardized. Please see also text already given above.
30	17	**FIMEA:** …will be the only…=> is currently the only (when this report comes out).	Will be changed according suggestion (changes were envisage through different draft versions).
30	21-24	**A.Gemelli:** It isn't the appropriate domain for the sentence „Ramucirumab, among other serious adverse effect, increased the risk of hemorrhage, which could be severe and sometimes fatal hemorrhagic events. Ramucirumab should be permanently discontinued in patients who experience severe bleeding“. You mentioned it at pag.22 and investigated it in C0008e (pag. 55) where (to me) it's more appropriate	Thank you for your comment; We think that data from SmPC, also on adverse events, are parts of this Domain and after the marketing authorization data will be changed accordingly. Due possible serious AEs clinicians and patients could opt against it or use again off-label drugs in case of discontinuation of ramucirumab.
32-33	3-5	**A.Gemelli:** You dedicated a lot of space to differences among Japan and Western countries. I suggest to begin A0004 with the paragraph of pag. 33 line 6-18 and then with a shorter paragraph on the differences Japan-Western countries. Now, you give it too much relevance.	We considered this comment and the European context of our report. We have re-ordered paragraphs in A0004, and rewritten the paragraph on the differences between Japan and Western countries as suggested; please see the new text, thank you.
33	4	**FIMEA:** The actual percentage in the west could be useful in case it is available in the reference.	We have rewritten this paragraph, added more specific survival data for European countries and Japan, and the percentages from the references used throughout the paragraph, thank you.

Page	Line	Comments	Comments from the author
38	5-8	**A.Gemelli**: Reference is missing for the literature review on prevalence in EU countries. It will be useful for national adaptation of this REA.	Added, thank you.
38	12	**FIMEA:** Does this number of patients (4.700) refer to UK only?	Yes.
40	35	**FIMEA:** Clinical relevance of the 2.2 months survival benefit is debatable. This is fine as author's judgement but a reference or more justification could be useful. Please refer to Ellis et al. Journal of clinical oncology 2014:32(12), p. 1277-1280 try to reflect the estimate to these specifications. Furthermore, consider reporting this judgement in the discussion part and not with the results.	See above: Thanks for your suggestion. Ellis et al.2014 gives some recommendation for what effect size of OS and PFS for specified patient populations should be expected in order to be recognize as clinically meaningful. Metastatic gastric cancer is not included in the examples but we may discuss suggestions in the reference.
41	Table7	**FIMEA:** Are these numbers means or medians (mean median survival in case of one study?). Secondly, please remove the word "higher" if 9.63 refers to median survival and not to difference in median survial.	Updated. The data reflect median overall survival. We edited the text as suggested.
41	13-26	**A.Gemelli:** Are methods for indirect comparison here reported be valid for all indirect comparison conducted for the REA? Could be a section in „Appendix 1 – Methods" dedicated to your indirect comparison methods?	New text: <u>Indirect evidence</u> The base-case analysis was conducted as a series of pairwise analyses using the Bucher method since there is no closed network (REF: Bucher et al. 1997). The evidence networks were analysed via single pair-wise meta-analysis and/or a series of indirect comparisons.
41	13-26	**FIMEA:** Please provide further details on the analysis and estimates of the original data for which the indirect estimates are based on. In order to do this, please consider reporting the table 17 (draft submission file; page 71) and consider also providing the image of the network which shows the actual linkage of the	We have updated the text with additional information on the network and show the complete network in Appendix 1. Based on the actual scope of this assessment and discussion with MAH we will focus on the final results estimates.

Page	Line	Comments	Comments from the author
		studies (draft submission file; figure 6 on page 70). Furthermore, NMA is not described or referred anywhere else in this assessment. Referring to NMA brings more questions than clarity. Please consider removing this sentence referring to NMA.	
42	13	**A.Gemelli:** Which is the information provided by the table taken from EPAR? Do you want to discuss QoL according to patient status (improved, stable, deteriorated)? It would be useful to have data for QoL subscales.	We only have data on change over time as presented in the table.
42	16	**HAS:** I would suggest to use instead of this table the table 17 from the MAH application file (p71)	See above response for page 41. Will not be able to use those figures/tables.
42	18-25	**FIMEA**: In terms of interpretation, please note the differences in “no data proportions” between groups.	We are not sure we understand the comment. Text is updated with frequencies
43	5-6	**FIMEA:** In terms of interpretation, please note the differences in “no data proportions” between groups.	New text: The RAINBOW study reported objective response rate (ORR), defined as patients achieving either a complete response or a partial response.
43	4-9	**FIMEA:** Please consider reporting complete and partial responses separately in case there data available.	This was not our scope, but we added the information to clarify objective response rate.
43	6	**HAS:** The legend is missing: „QoL responses rates (%) for W6 for select scales“	Updated.
47	21	**A.Gemelli:** Frequency of radiologic assessment appears only in Discussion and not somewhere else in the domain.	It is also part of the introductory description of the studies in the beginning of the section/chapter
47-49		**FIMEA:** There is no results from sub-group analysis shown in the clinical effectiveness domain and the short note in the discussion part related to subgroup analysis is not sufficient. Please consider adding data from sub-group analyses.	Subgroups were not part of the project plan. We have removed text referring to subgroups.

Page	Line	Comments	Comments from the author
50-61		**FIMEA:** Indirect comparisons: Please provide further details on how the assumtions of the indirect analyses were validated? Single clinical opinion may not be enough to convince critical reader with this respect.	Details on validation process not described. We have added the assumptions in Appendix 1. Assumptions are necessary to form the network.
52	1	**HAS:** I would specify : „in the MAH application file“	I can not find the reference. Line 1 is the assessment element question
53	Table16	**HAS:** Confidence interval for BSC is pretty wide. Is it reliable?	One can get quite wide CI if e.g. the number of events is low. This can be expected here as it relates to treatment withdrawal of best supportive care/active symptom control. Other issues may add to this uncertainty.
56-58	Table19	**HAS:** For this table, that was created by the authorship team, would it be possible to summarize in a few lines the main elements which should be few results that are statistically significant in the table (neutropenia, leukopenia, thrombocytopenia, diarrhoea, anorexia, peripheral sensory neuropathy)?	New text added as suggested.
59	7-10	**A.Gemelli:** Duplication of information. You first write „However, caution is in order, as the results are based on only one study” and after few rows you write “The main concern relates to the fact that the results originate from only one study.”.	Updated.
59	11	**A.Gemelli**: Do you refer to direct or indirect comparisons with „Direct comparisons among the treatment alternatives are limited to one direct study for each comparison, making the evidence network linear and limited.”?	Both. It is probably easier to see now as we have been able to add the network diagram and description in Appendix 1.
59	11-14 Vs. 22-25	**A.Gemelli:** It looks like the same paragraph. Before you write:“ Direct comparisons among the treatment alternatives are limited to one direct study for each comparison, making the evidence network linear and limited. Several	Updated. Duplication error. Deleted.

Page	Line	Comments	Comments from the author
		assumptions are necessary to make the network. These were validated with clinical opinion. The choice of methods used for evidence networks was appropriate for the research question.“. Then you write:“ Direct comparisons among the treatment alternatives is limited to one direct study for each comparison, making the evidence network linear and limited in size. Several assumptions are necessary to make the network. These assumptions used here were validated with clinical opinion [2]. The choice of methods used for evidence networks was appropriate for the research question.“. Apart minor differences, both for Interpretations and considerations of the direct evidence and for Interpretations and considerations of the indirect evidence, you report the same comment.	
59-60	3-4	**A.Gemelli:** Why do you discussed coding of adverse events and safety population in the section „Interpretations and considerations of the indirect evidence“? Do your comments refer only to studies involved in the indirect comparion?	We assume that they use the same coding within the same study, so it should only be an issue across studies, for indirect comparisons. Nonblinded treatment could influence coding within a study, but that is coved in the risk of bias assessments.
62-63		**A.Gemelli:** This section must be completed. No discussion is provided yet.	Text will be written in version 2, appropriate references were found to answer on these assessment element questions.
68		**A.Gemelli**: In case you get the permission to use the graph, please introduce it. Now for an external reader, who hasn’t read the MAH file, it’s quite unclear what it represents.	Updated.
71		**A.Gemelli:** You mentioned the italian guidelines by AIOM. Please correct the text „Associazio ne Italiana di Oncologia“ in „Associazione Italiana di Oncologia“.	Corrected, thank you.
75	Table22	**A.Gemelli:** For Roy et al. 2013 you report in the column „Duplicate publications from the same study“ the following text „One additional arm; PEP02 (highly stable liposomal nanocarrier	Deleted, thank you.

Page	Line	Comments	Comments from the author
		formulation of irinotecan)". It doesn't seem a publication.	
76	Table23	**A.Gemelli:** Comparator column: what does it mean „None?" for two studies? Does it means Information Not Available? Please, clarify.	Updated. See comment in table above.
80	Table26	**A.Gemelli:** COUGAR 02 – Risk of bias- Outcome level. How is it possible that ORR was assessed in a subgroup of patients and, at the same time, outcomes weren't assessed in the control group? Do you mean that information is available only for the treatment group anyway even for ORR?	Yes. Assessments were only done for the treatment group.
82	Table28	**A.Gemelli:** There is a formatting issue in the last row on TE-SAE. Not all text is visible.	It continues on page 83. We will check all formatting in the final version to eliminate such unfortunate dividing of tables.
84	Table29	**A.Gemelli:** In Outcomes you mention EQ-5D-3L for patient reported outcomes. EQ-5D-3L isn't mentioned before in the REA. Why?	Additional text added and clarified under [D0012] and [D0013]. According to the publication by Wilke et al. 2014 further details on quality of life will be published separately.
85-87		**FIMEA:** Appendix 3 is well documented and arises important issues.	Thank you.

APPENDIX 5. INPUT FROM THE MARKETING AUTHORIZATION HOLDER AND THE WP5 MEMBERS ON THE EDITORIAL DRAFT ASSESSMENT

Input from the Marketing Authorization Holder on the Editorial Draft Assessment

GENERAL AND SPECIFIC COMMENTS FOR THE AUTHORS

Page	Line	Comments	Comments from the author
General Comment	Full Report	Eli Lilly and Company appreciates the opportunity to provide comments on the draft rapid relative effectiveness assessment report 'Ramucirumab in Combination With Paclitaxel as Second-Line Treatment for Adults with Advanced Gastric or Gastro-Oesophageal Junction Adenocarcinoma'. We commend EUnetHTA and the participating health technology assessment agencies on the overall quality of this report which demonstrates that the rapid REA pilots are evolving through experience. In particular, we are pleased to see that EUnetHTA have responded to recommendations resulting from the previous pilots by (i) removing the extensive duplication and reworking of the European Medicines Agency assessments of safety and efficacy, (ii) by increasing the focus of the assessment on relative efficacy and relative safety, (iii) by improving the transparency relating to the use of the GRADE assessment approach and (iv) by removing the extensive internal duplication previously seen with the full inclusion of the Core Model assessment 'Results Cards' (eg 221 pages in length in the second pilot). Therefore, we consider that this report is a significant step forwards in terms of achieving a balance in content, where the report is streamlined enough that it could be practically conducted for all products at launch, while sufficiently detailed to provide a source of factual information that is relevant to Member States. We do have comments on this report, with a few areas of major concern that we highlight within the general comments section given that they apply to the entire report. Otherwise, our	Thank you very much for that. This two layers structure was recognized as added value from the Rapid REA team and Coordinator as well. We appreciate the work you have put into reviewing the document.

Page	Line	Comments	Comments from the author
		comments herein are mainly clarifications and factual corrections. We believe such clarifications may be necessary since some text makes sense in context of the information around it, but could be misleading as stand-alone text in particular if translated into Results Cards. Where possible, we have included suggested text for consideration. Given that this is a draft, we are not commenting on minor editorial issues.	
General Comment	Full Report	We commend EUnetHTA for providing transparency around the Risk of Bias and Quality Assessments. However, we are concerned about how these data are assessed. We are concerned that the GRADE criteria do not take into account the fact that this is an orphan indication in oncology where multiple trials might not be feasible for ethical and practical reasons (e.g., patient finding). Two phase 3 trials (RAINBOW and REGARD) with OS benefit is unique in the oncology setting and while we acknowledge that REGARD was not part of the relative efficacy review, it could have been considered relative to assessment of the strength of evidence. Further, while it is not usual to provide multiple duplicated phase III clinical trials with the same active comparator for the purposes of efficacy studies, it is usual practice to provide several phase II/III studies for the purposes of studying safety. We think it is important that with respect to the GRADE analysis conducted by EUnetHTA to note that this analysis concerns only the relative safety as the safety of ramucirumab has been comprehensively analysed by the EMA. Finally, we are concerned about a lack of clarity in the GRADE Quality Assessment Inconsistency category. This was termed serious for the reason 'One study, results not shown consistently across studies' which we consider could be interpreted in multiple ways, either - as likely intended - that there was simply a single study and so no duplication of studies existed with which to confirm results, or alternatively that there was inconsistency in	We acknowledge that GRADE have strengths and weaknesses. The main benefit is however the transparency. As you state, our assessments are based on the evidence base for the relative effectiveness in our scope. Decision makers should use the GRADE evaluations, but could other issues as well. It is under continuous development. Relevant is e.g the DECIDE project http://www.decide-collaboration.eu/ The interpretation of "one study, results not shown consistently across studies" is as you say. Those results have not been reproduced in another study. It may be that such duplication is unusual, but it does influence how sure we are on the results. Changed to: Single study, thus results not confirmed /shown consistently across different studies

Page	Line	Comments	Comments from the author
		results across studies which we view as much more serious.	
General Comment	Full Report	A checklist on ethical, organisational, social and legal aspects (Appendix 3) could be of value if issues specific to that product and are also common across Europe are identified. However such a checklist will not be of value if there is speculative discussion on 'potential' aspects where there is no supporting evidence, or if the aspects raised are so common that they will apply to every new technology since the information will have no value. In the case of this draft assessment, the authors identify an issue that we agree is important and appropriate for discussion in the context of the checklist and which relates to off label use of comparators as discussed on page 71, beginning line 21 and in the discussion in section 7.3 However, we view speculation about the price of ramucirumab (eg page 70 lines 14-15) as totally inappropriate in the context of a clinical assessment and urge that this line be deleted. We are also very concerned about the discussion that mixes the financial cost of off-label prescribing with guideline support (page 71, lines 10-20). There appears to be some inference that a significant proportion of off label prescribing is supported by guidelines although no context is supplied. We are unclear as to what point the authors are attempting to make with this discussion and what evidence is being used to support this point. We do not see how this discussion relates to the current situation of off label use prior to the introduction of an approved therapy and think the following section on off label use is more relevant and appropriate. Therefore, we urge that this paragraph is deleted.	Thank you very much for your valuable comments. For the future joint work it will be important to have clear explanation or SOP within EUnetHTA how to deal with Checklist in case of „Yes" answers; to leave answering on raised issue to local (national/regional HTA doers) or try to give answers by Rapid REA team: in this assessment we choose 2nd approach. We agree on your comment about the price, so this line is now deleted. We do not agree with your further comment and this paragraph was not deleted; in case of any clarification needed readers could approach original literature data.
7	21-23	Some of the off-label treatments may not be limited to prior	Thank you very much; sentence is now written according

Page	Line	Comments	Comments from the author
		fluoropyrimidine and platinum chemotherapy. Therefore, we suggest the following text: *Paclitaxel, docetaxel and irinotecan are not approved drugs for second-line treatment and represent off-label second-line chemotherapy for patients with advanced disease whose cancer has progressed*.	suggestion.
8	14-18	We suggest clarifying that this is referring to second-line trials and reword for ease of reading. Thus, we suggest the following: *In second-line clinical trials the following chemotherapy regimens have been used: irinotecan plus cisplatin or fluoropyrimidines; single-agent irinotecan; docetaxel plus oxaliplatin (expert opinion indicates that docetaxel is used more commonly with cisplatin or 5-fluorouracil [5-FU]); single-agent docetaxel; paclitaxel plus platinum agents; paclitaxel single-agent; and FOLFOX (folinic acid, 5-FU, oxaliplatin)*.	Thank you very much; sentence is now rewritten for clarity reasons: In second-line clinical trials the following chemotherapy regimens have been used: irinotecan plus cisplatin or fluoropyrimidines; single-agent irinotecan; single-agent docetaxel; docetaxel plus oxaliplatin (expert opinion indicates that docetaxel is used more commonly with cisplatin or 5-fluorouracil [5-FU]); paclitaxel single-agent or plus platinum agents; and FOLFOX (folinic acid, 5-FU, oxaliplatin) [A0025].
8	23-25	The information needed for this section may not have been available at the time this draft report was written, but it is now available. We request the authors update the indication statement per the Summary of Product Characteristics (SmPC).	This paragraph is now deleted as duplication of the text on page 7.
9	30	We believe there is a factual correction needed to the difference in overall survival. We request it be changed to *2.3 months* (2.27 months actual).	Changed to 2,27 keep 2 decimal points as in the CI.
10	9-11	The current sentence does not convey the directionality of the results, and we suggest the following be added to the end of the sentence: "*The indirect comparisons of ramucirumab plus paclitaxel with docetaxel for overall survival, progression-free survival or objective response rate was not statistically significant; however, the point estimate of the HR was less than 1 for both progression-free and overall survival, and the point estimate of the OR was greater than 1 for objective response rate.*"	Text revised.

Page	Line	Comments	Comments from the author
10	18, 31-32	The higher incidence of neutropenia (any grade and Grade ≥3) observed in the ramucirumab plus paclitaxel arm was not associated with severe clinical consequences.The incidence of febrile neutropenia, a severe complication of neutropenia, was low and similar in both treatments arms (3.1% in the Ramucirumab plus paclitaxel arm vs 2.4% in the placebo plus paclitaxel arm).	We have tried to be compact in summary. We only state direction and statistical significant findings. More detail and clinical implications need to be presented in the main text and discussions.
10	30-36	-Because reporting of adverse events was more limited and heterogeneous for studies of irinotecan and docetaxel, these limitations should be reflected in the summary, particularly that few comparisons with docetaxel were feasible. -Furthermore, the current summary does not discuss any adverse events where there were no differences. -Alternatively, the results reported in the summary could be limited to the direct comparison with paclitaxel, along with absolute values to provide additional context.	This section is a result of previous feedback. We do not highlight missing data or non-significant findings, as space is limited in the summary. Your comment on reporting on adverse events have been included for clarification of evidence gaps in discussion of safety domain.
12	Summary Table	-We are concerned about the potential interpretations of the text “Not Reported” in the Ramucirumab plus paclitaxel versus Docetaxel and Ramucirumab plus paclitaxel versus Best supportive care rows of the Summary table of relative effectiveness. We were unable to present any comparisons mainly as data needed to do so were not available for these comparators. Instead, we propose EUnetHTA change “Not Reported” to be “Data Unavailable for Comparisons.” -For the Quality of Life column of the summary table, the end of treatment values are used to represent the QoL impact. We consider that the end-of-treatment values are not reflective of the totality of the QoL data and tumor progression (experienced by both arms) rather treatment is likely the most significant determinant of QoL at this time. Please consider reporting the 18-week results. If not changed, then these results should be	Changed to Not available.

Page	Line	Comments	Comments from the author
		clearly reported as "*end of treatment*".	Added «end of treatment"
15	10-11	We suggest clarifying that this statement is referring to the median overall survival. Therefore, we suggest the following: *The median overall survival of approximately 2 months achieved in RAINBOW seems a good result in this poor-prognosis population since patients whose disease progress after first-line treatment can expect median survival under 6 months*.	Accepted- the text has been edited.
15	17-18	"The extent of quality of life data ..." applies to the REGARD study (CHMP assessment report). The text should be updated to the corresponding statement for RAINBOW is: *More patients in the ramucirumab plus paclitaxel arm had improved or stable EORTC QLQ-C30 Global Health status compared to the placebo plus paclitaxel arm at each visit during the treatment however a higher proportion in the placebo+paclitaxel arm had a stable or improved global health status by the end of treatment (p 67).* In addition, the following statement is in the Benefit-risk section: Furthermore, measures of EORTC QLQ-C30 Global Health status also tended to favour ramucirumab + paclitaxel treated patients over placebo+paclitaxel ones (p 94).	The text has been edited.
15	18-20	"There are no published further data on disease-specific quality of life . . ." is an inaccurate statement as there have been several presentations of data at congresses. Two specific examples were cited in the MAH submission (Al-Batran et al).	The text has been updated with relevant references.
15	22	Comparator evidence was based on 4 studies. We believe Roy et al. Which is cited later in the report on page 63 may not have been included.	Done.
16	23-25	The summary of the QoL data is not consistent with the discussion on page 54 where QoL was considered to be maintained. We recommend the summary be updated to be	The summary has been updated.

Page	Line	Comments	Comments from the author
		consistent with the information in the discussion.	
22	10	We are concerned that the sentence “No obvious errors were discovered” could potentially imply that there are some less obvious errors within the strategy. We would request that this text be changed to the following: *No ~~obvious~~ errors were discovered*.	Done.
24	13-15	We are concerned that the ‘temporary compromise’ from EUnetHTA to not publish certain new data in this pilot report was an exemption rather than standard practice. HTA processes value evidence based on whether is it published or not. A standard practice of peer review journals is to refuse publication of data previously released, including in HTA reports. Some HTA organisations that routinely conduct early review of manufacturer’s data recognise the need to keep such material out of the public domain until after publication. NICE have termed this ‘academic-in-confidence’. In our case, the information we released for the pilot assessment was intended for publication in a journal that indicated to us that they would refuse publication if such information was present in the pilot report. We suggest the following change to the text on lines 13-14 to clarify this matter: *The MAH indicated that these data are to be submitted for publication and that presenting the data in our assessment would prevent acceptance.* In addition, we ask that EUnetHTA consider the impact of confidentially issues (commercial and academic) given that the rapid REA is intentionally an early assessment and that the report will be placed into the public domain. We do agree that it is important to update the report when the confidential information is available and suggest that rather than an annex, that it would be better to simply update the whole report while noting where the updates have occurred. A process for tracking such changes could be modelling on the EPAR updates.	Text revised. How to deal with confidential information/ information to be published in coming pilots is forwarded to WP5 coordinating team and EUnetHTA.

Page	Line	Comments	Comments from the author
25	22-25	We want to clarify that anemia, impaired wound healing, RPLS, and clinical deterioration have not be identified ADRs in the list of “serious adverse effects” in the SmPC. It would be more appropriate to refer to the approved SmPC for warnings and precautions, and we recommend this section is updated to be consistent with it. With respect to severe haemorrhage, the warning is: Severe bleeding: Ramucirumab is an antiangiogenic therapy and has the potential to increase the risk of severe bleeding. Ramucirumab should be permanently discontinued in patients who experience Grade 3 or 4 bleeding (see section 4.2). Blood counts and coagulation parameters should be monitored in patients with conditions predisposing to bleeding, and in those treated with anticoagulants or other concomitant medicinal products that increase the risk of bleeding. Severe gastrointestinal haemorrhage, including fatal events, were reported in patients with gastric cancer treated with ramucirumab in combination with paclitaxel.	Thank you very much. This section is now rewritten according to the SmPC.
26	Table 3.1	The information needed for this table may not have been available at the time this draft report was written, but it is now available. We request the authors update Table 3.1 per the Summary of Product Characteristics (SmPC).	Thank you very much. This Table is now updated according the SmPC.
28	6-9	We question if there is an error in this sentence, and the percentages at the end of it should instead be median survival which is usually reported in months. Based on the publication, we believe the following changes could be appropriate: *In a randomised trial of patients with advanced gastric adenocarcinoma docetaxel, added to cisplatin and fluorouracil (TCF), improved median survival from 8.6 to 9.2 months as*	Thank you very much. The text is now changed according data presented in reference: In a randomised trial of patients with advanced gastric adenocarcinoma docetaxel, added to cisplatin and fluorouracil (TCF), improved median survival from 8.6 to 9.2 months as

Page	Line	Comments	Comments from the author
		compared with cisplatin and fluorouracil ~~(36.7% vs 25.4%)~~ [21].	compared with cisplatin and fluorouracil (CF), with overall response rate of36.7% for the TCF group vs 25.4% for the CF group [23].
32	25	The information needed for this section may not have been available at the time this draft report was written, but it is now available. The date of approval by the European Commission was 19th December 2014.	The date of marketing authorization approval is now added in the text.
32-33	32-2	We would like to clarify that ramucirumab was approved by the US FDA as a single agent (21 April 2014) or in combination with paclitaxel (5 November 2014), for treatment of advanced gastric or gastro-esophageal junction adenocarcinoma, with disease progression on or after prior fluoropyrimidine-or platinum-containing chemotherapy. In addition, ramucirumab in combination with docetaxel, for treatment of metastatic non-small cell lung cancer with disease progression on or after platinum-based chemotherapy was approved by the US FDA on 12 December 2014. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving ramucirumab.	Thank you, the text is now changed according two different dates of FDA approval.
34	23-25	Please clarify that the comments relating to Best Supportive Care apply to the evidence regarding the off-label comparators. As it is currently written this could be misconstrued as a criticism of the evidence relating to ramucirumab, in particular with respect to the focus of this assessment report. Having said that, while BSC might vary between clinical trials it is usually very well defined within high quality RCTs (Kim et al 2013) and is important both where BSC reflects the standard of care and for external validity.	Thank you, this text is now deleted, and should be read in more broader context written above in the text on BSC.
41	14-15	We recommend that that specific designation from the National Comprehensive Cancer Network be included in this section. Therefore, we would suggest rewording this text to say: *The*	Thank you. The sentence is now written as „The National Comprehensive Cancer Network (NCCN) clinical practice guideline for gastric cancer [83] now includes the use of

Page	Line	Comments	Comments from the author
		National Comprehensive Cancer Network clinical practice guideline for gastric cancer [82] now includes the use of ramucirumab and has awarded it a designation of 1 for second-line treatment of metastatic or locally advanced disease.	ramucirumab for second-line treatment of metastatic or locally advanced disease (NCCN Categories of Evidence and Consensus: Category 1)."
41	16-18	As ramucirumab has now been licensed in the EU, please update this sentence*: When licensed in the EU, ramucirumab will offer an additional treatment option for patients with advanced disease whose cancer has progressed despite prior fluoropyrimidine and platinum chemotherapy, and for whom there are currently no standard therapies available*.	The sentence is updated as: Ramucirumab alone or in combination with paclitaxel is currently only approved treatment option for patients with advanced disease whose cancer has progressed despite prior fluoropyrimidine and platinum chemotherapy, and for whom there are currently no standard therapies available.
41	21	We would suggest removing "iatrogenic perforation and tracheo-oesophageal fistulae" from the text as this is a medical complication and not a treatment option.	Thank you, we remove this part of the text.
42	20-22	We suggest lines 20-22 be reworded to say: *Currently in the EU there is no standard second-line treatment other than ramucirumab for patients with advanced gastric or gastro-oesophageal junction adenocarcinoma following progression after first-line chemotherapy*.	Sentence is now written as: Currently in the EU there is no standard second-line treatment for patients with advanced gastric or gastro-oesophageal junction adenocarcinoma following progression after first-line chemotherapy and ramucirumab alone or in combination with paclitaxel is only approved treatment option for these patients.
44	2	Please reword lines 1-2 to read: *4 months after the last dose of standard first-line platinum- and fluoropyrimidine-based combination chemotherapy.*	Done
44	11-36	We recommend that the sample size for each study be added to provide the necessary context for the percentages in this section.	Done
44	13	Please reword line 13 to clarify the linkages within the network. We suggest the following text: Indirect comparisons with irinotecan, docetaxel, and BSC were limited by the number of	Done

Page	Line	Comments	Comments from the author
		studies as each linkage was supported by only one RCT *each*.	
44	36	We are concerned that the study Roy et al has not been included in this section, and we suggest it be added.	Short description added.
47	14-15	The statement, "No such data collected at the end of treatment are available" is not an accurate statement as >60% of patients provided data at this time point (See Table 5.7). This statement would be accurate for the REGARD study. This error may be related to the inaccurate statement on page 15 which applies to REGARD and not RAINBOW.	The text has been edited.
47	23-24	We want to clarify that the higher rate of events cited in line 24 (as compared to line 20) is because investigators reported progressive disease as an adverse event.	OK, no changes made.
49	5-9	We suggest adding a column for BSC to Table 5.4 (for consistency across all outcomes, given that this was in scope) with the results stating that this comparison could not be made based on available data.	Added. Included information that comparison not available.
49	16	For accuracy, please reword line 16 to read: *of objectively determined radiographic disease progression (RECIST 1.1)*	Done
50	4-5	We recommend rewording line 4 to state: *The hazard of progression or death for ramucirumab plus paclitaxel was lower compared with irinotecan.*	Done
50	9	We suggest adding a column for BSC to Table 5.6 (for consistency across all outcomes, given that this was in scope) with the results stating that this comparison could not be made based on available data.	Added. Included information that comparison not available.
51	1-2	We would suggest lines 1 -2 are reworded for clarity to say: *The results are based on more than 50% of the patients being*	Not changed

Page	Line	Comments	Comments from the author
		censored due no observed deterioration of performance status to ≥ 2.	
51	4	We recommend clarifying that the reason there are no indirect comparisons for this outcome is due to the lack of available data on comparators for this specific outcome.	Done. The text has been edited.
51	19-20	We suggest removing lines 19-20 from this section as performance status is not relevant to the QoL section.	Done
52	2	We recommend clarifying that the reason there are no indirect comparisons for this outcome is due to the lack of available data on comparators for this specific outcome. EQ-5D was not assessed in clinical trials for comparators.	Done. The text has been edited.
52	7	Table 5.7 does not present baseline data. We are concerned that the statement does not correspond to the data presented in this table. We suggest this sentence be revised to Week 6 instead of baseline.	Done. The table has been updated
52	10-12	We request the following sentence be removed: “In contrast, by the end of treatment, a higher proportion of patients in the placebo plus paclitaxel group had a stable or improved global health status (RR= 0.92 [95%CI 0.74 to 1.15]) [2].” This information is already addressed in lines 7-8 and details in Table 5.8. There is no justification as to why this particular assessment period is considered more important than others in terms of discussing the numerical results.	Not changed. This happens quite often in palliative treatment.
53	3	We recommend this section be clarified and revised to state that only COUGAR-02 assessed quality of life but results were not reported in a manner to allow for any comparisons.	Done
53	9-14	We suggest that this section be reworded for clarity and to prevent misinterpretation. Therefore, we suggest: “*The patient*	Done

Page	Line	Comments	Comments from the author
		population in the studies included in the submission are most likely representative of the relevant patients within the scope of this assessment. A second-line gastric cancer population is already a selected population due to the fact that only a fraction of all patients diagnosed with advanced gastric cancer receive first-line chemotherapy. Relatively few patients in Western countries receive second-line treatment (approximately 15% to 50% of patients receiving first-line treatment; see [A0025]).	
54	10-12	We recommend revising this sentence for greater clarity and suggest the following text*: In the WJOG study, radiological assessments were conducted every 8 weeks. In the study reported by Thuss-Patience et al., radiological assessments were conducted every 6 weeks, but only in the experimental arm. In the COUGAR-02 study, radiological assessments were conducted at 9 and 18 weeks, but only in the experimental arm*.	Done. The text has been revised.
55	15-16	For clarity and accuracy, we suggest the following text be added to the sentence: *There was no significant difference in the hazard of death for ramucirumab plus paclitaxel compared with docetaxel, however, the point estimate of the HR was less than 1.*	Not changed as we generally do not present estimates and CI in this discussion.
55	24	Given the legal and regulatory connotations that are implied by the word 'required', we suggest it be replaced with 'suggested'. We also think this sentence could benefit from some precision as what a 'large' study is in the context of an orphan population. We agree that it is important to develop robust evidence between alternative authorised interventions. However, at this point in ramucirumab's development, there is little information available from real world care settings, and we do not think it appropriate to conduct follow on studies against off label comparators, particularly given their limited direct evidence.	The text has been edited

Page	Line	Comments	Comments from the author
55	29-32	So as not to overestimate the size of the gap, it would be appropriate to state that *HER-2 expression is observed in only 10-15% of patients with gastric cancer* and add the following statement included in the SmPC: *Based on limited data from REGARD patients with HER2-positive gastric or GEJ adenocarcinoma and patients previously treated with trastuzumab (in RAINBOW), it is considered unlikely that Cyramza has a detrimental effect or that it has no effect in patients with HER2-positive gastric cancer. Post hoc unstratified subgroup analyses from RAINBOW patients previously treated with trastuzumab (n= 39) suggested a survival benefit in such patients (HR 0.679, 95% CI 0.327, 1.419) and demonstrated a benefit for progression free survival (PFS) (HR 0.399, 95% CI 0.194, 0.822)*.	The text has been edited
55	35-36	We do not consider this as an evidence gap as the SmPC clearly states that this was the population studied in RAINBOW. The CHMP assessment report states that limiting the eligibility criteria to performance status 0 and 1 is common practice. For clarity and to be consistent with the CHMP, we would recommend this information be removed from this section.	We are aware that it is a common practice in oncology studies to exclude patients with EGOC PS >1, but as long as it is probable that ramucirumab + paclitaxel could also be used for patients with lower performance status there is in reality a gap in the evidence.
56	5	We would like to clarify that although the safety assessment is restricted as mentioned, this statement does not take into account the rest of the safety evidence and information provided.	No change done.
58	7	We recommend adding a statement to clarify that the reason there are no indirect comparisons for this outcome is due to the lack of available data on comparators for this specific outcome.	Added: due to lack of available data.
59	1	It is unclear which values were used to calculate the study population. We suggest that the values be added to the footnote which already cites the sources.	All numbers presented in Table A9. Actual study participants/events not presented in any of the summary of findings tables.

Page	Line	Comments	Comments from the author
59	7-11	We request that these sentences be removed. Roy et al. reported the number of patients in each arm who discontinued therapy due to adverse events. In both the docetaxel and irinotecan arms, 6 of 44 patients (13.6%) discontinued therapy due to adverse events (page 1570 of Roy publication).	Thank you for pointing this out. Our oversight. Text removed.
61	3	We recommend clarifying that the reason there are no indirect comparisons for this outcome is due to the lack of available data on comparators for this specific outcome. The frequency of SAEs were not presented in comparator studies.	Added: due to lack of available data.
62	3-4	We recommend adding a statement to clarify that the reason there are no indirect comparisons for this outcome is due to the lack of available data on comparators for this specific outcome.	Added: due to lack of available data.
63	2-3	We believe lines this text should be clarified that the events were not reported in RAINBOW and not identified as ADRs. They are listed in the EPAR as warnings and precautions.	Added: as warnings and precautions.
63	22-23	We would like to clarify that the frequency of visits and lab assessments are a potential source of bias. In RAINBOW, patients had weekly assessments and labs which could also lead to a higher number of adverse events, especially hematological events. In part, this could explain the higher frequency of neutropenia in both arms of the RAINBOW study as compared to other studies.	Included in discussion under reporting of adverse events.
63	20-30	We believe this section would benefit by also discussing where no statistical differences were found, the clinical relevance of the toxicities, and the absolute values for these toxicities. For example, although rates of neutropenia and leukopenia may have been higher for ramucirumab plus paclitaxel, there were no differences in febrile neutropenia with a rate of 3.1% for ramucirumab plus paclitaxel. In addition the paragraph should	We tried to keep reporting on a more aggregated level, hence such details are not included. Differences in reporting and available is addressed in the discussion.

Page	Line	Comments	Comments from the author
		also state comparisons with docetaxel were particularly limited by the way that adverse events were reported in COUGAR-02 (at organ level for non-hematological toxicities) so a considerably smaller phase II study was the source for many adverse events. In general, the limitations around the results for any of these indirect comparisons should be stated, along with cautious interpretation.	
64	Table 6.6	We suggest clarifying the last column header of Table 6.6 to read "*Frequency for ramucirumab+paclitaxel*". In addition, we request that alternative wording be used instead of "Not Reported" and would instead recommend that EUnetHTA change "NR" to be "Data Unavailable for Comparisons."	Added footnote for frequency. Changed to not Not available= NA
67	6-11	The conclusion that "One possible interpretation is that the addition of ramucirumab to paclitaxel did not add to the burden of treatment in an unmanageable way" is not consistent with the results nor the interpretation of other data elsewhere in this report. Despite no statistical differences between treatments this conclusion implies doubt, i.e. that there are other possible interpretations of the evidence. We suggest rephrasing this as: The evidence suggests that the addition of ramucirumab to paclitaxel did not add to the burden of treatment in an unmanageable way.	Done.
67	17	Evidence networks were not based on "selected" safety outcomes, but rather on those adverse events reported for comparators. We suggest this sentence be rephrased as: *In addition, they presented evidence networks for all safety outcomes reported for comparators which could analyzed via the network.*	Done.
67	28-32	We request that consideration be given to adding a sentence which states that only RAINBOW was a registration study for	It is a general comment and we would like to keep it as it is.

Page	Line	Comments	Comments from the author
		clarity.	
68	22-23	We would like to clarify that in RAINBOW all investigators were required to report AEs independent of causality.	It is a general comment and we would like to keep it as it is.
68	23-24	We would like to clarify that the frequency of visits and lab assessments are a potential source of bias. In RAINBOW, patients had weekly assessments and labs which could also lead to a higher number of adverse events, especially hematological events. In part, this could explain the higher frequency of neutropenia in both arms of the RAINBOW study as compared to other studies.	Text added based on comment page 63
69	15-18	We do not consider performance status 2 as an evidence gap, and we recommend these lines be removed from this section, especially given the information included in the SmPC. The SmPC clearly states that only performance status 0 and 1 patients were enrolled in RAINBOW. From CHMP assessment report (p 95): The CHMP concluded that although there is some uncertainty on whether similar efficacy and safety results could be observed in patients with poor performance status, it is common for clinical trials to recruit good prognosis patients. Furthermore, in view of the relatively tolerable safety profile, the CHMP considered that this uncertainty raised no major concerns in terms of safety. Thus, in the absence of clear signals against the generalizability of results, the CHMP concluded against a restriction of the indication to patients with good performance status. Although other studies in the indirect analysis included patients with performance status 2, there were no specific evaluations of safety within the performance status 2 subgroup in those studies. Therefore, safety in patients with performance status for these comparators has not been expressly established.	We are aware that it is a common practice in oncology studies to exclude patients with EGOC PS >1, but as long as it is probable that ramucirumab + paclitaxel could also be used for patients with lower performance status there is in reality a gap in the evidence.

Page	Line	Comments	Comments from the author
99	Table A7	Although investigators followed RECIST, risk of bias associated with blinding of assessors for PFS should be rated as high for WJOG and COUGAR-02 since these were open-label studies. The WJOG publication clearly states that no independent review of disease progression was conducted. Furthermore, for COUGAR-02, a 6-week PFS rate was reported in advance of the first scheduled tumor assessment at Week 9. Lack of PFS assessment in the control arm of COUGAR-02 should also be reflected in other aspects of risk of bias.	We have revisited all risk of bias assessments. Updated and clarified for easier overveiw

Input from the WP5 Members on the Editorial Draft Assessment

GENERAL AND SPECIFIC COMMENTS FOR THE AUTHORS

Page	Line	Comments	Comments from the author
Scottish Medicine Consortium, Scotland			
General Comment		Ramucirumab is now authorised in the EU. The figures from the indirect comparison where these have only been reported as the direction of the effect should be added when available.	Thank you very much; we added date of marketing authorisation, 19 December 2014. The authorisation use only the direct evidence. The indirect and network evidence is performed for a wider approach. These data have not been published yet. As described, actual estimates will be presented later.
8	23	Should read .“Ranucirumab is an approved treatment option...	This sentence is now deleted as duplication of the text on page 7.

Page	Line	Comments	Comments from the author
9	27	Full stop missing after cycle	Thank you, correction is made.
9	28	Should read showed a benefit	Thank you, correction is made.
9	33 to 34	Use ‚to' consistently throughout the document for confidence intervals (0.54 to 0.75)	Will use – as that was used the most times
10	2	Bracket missing at start of 95% confidence interval. As above, use to for confidence intervals.	Done
10	3	Specify that a Bucher indirect comparison was performed. This information is not given until much later in the document and it would be helpful to include it in the summary.	Done
10	4	Two full stops after „findings"	Done
10	6	Full stop in middle of sentence before „was"	Done
10	19	Colon missing after CI	Removed to be consistent across the document.
15	12	Should read „progresses"	Done
33	26	This paragraph is a repeat of information given on the previous page (paragraph starting on pge 32, line 32).	Thank you, this paragraph is rewritten now.
41	4	Include a reference(s) to support this sentence.	Thank you, reference is added now.
41	9	It is not clear what is being referred to here as a single agent- perhaps reword to make it clearer.	This paragraph was reworded to raise the clarity of the text, thank you.
42	11	It is not clear if this is prevalence data, or if this is the proportion of patients who have metastatic disease at presentation?	This is the proportion of gastric cancer patients who have metastatic disease.

Page	Line	Comments	Comments from the author
44	8	Should state 4 to 5 cycles	Done
44	15	When describing the studies, it would be helpful to include if they were open-label or blinded.	Done
46	15	Could consider including some further discussion of heteroeneity between the studies (e.g in what respect there were differences e.g. patient population, perfomance status, pre-treament, study outcomes etc).	Since we are not able to present the results of indirect comparisons we described the included studies only briefly. There are more details in discussion part.
47	18	This paragraph may be more appropriate to include in section 6 under safety.	It is removed.
54	34	Include a reference for this information.	Our comment in discussion, unsure what statement they need reference for.
61	9	The numbers for deaths due to an adverse event (n=13 vs n=15) are different from the numbers reported later in the paragraph for patients with an adverse event leading to death (n=39 vs n=51) and it is not clear why these are different.	We present data as submitted. We interpret that the numbers represent different definitions of closely related the adverse event was to cause of death. Note also that the numbers of deaths with causal relationship to a study drug is even lower.
68	13	Delete the word ‚in‘	Done.
FIMEA, Finland			
General comment		General comment: We acted as a dedicated reviewer in this assessment. Overall the report has improved since the previous version.	Thank you
44	11	Please provide further details on the analysis and estimates of the original data for which the indirect estimates are based on. In order to do this, please consider reporting the table 17 (draft submission file; page 71) and consider also providing the image of the network which shows the actual linkage of the studies	See. Deviations from project plan. Not possible for the time being. The MAH indicated that these data are to be submitted for publication and presenting the data in our assessment would prevent acceptance

Page	Line	Comments	Comments from the author
		(draft submission file; figure 6 on page 70).	
Ministry of Health, Czech Republic			
10	23	…irinotoecan…. Typing mistake, correctly: irinotecan	Thank you, correction is made.
10	34	…irinotoecan…. Typing mistake, correctly: irinotecan	Thank you, correction is made.
14	52	Table 5.7 - very poor legibility	Table 5.7 is from EPAR, we do unfortunately not have a higher resolution picture
19	Scope Population	…gastro oesophageal…. Typing mistake, correctly: gastro-oesophageal	Done
44	8	….treatament… Typing mistake, correctly: treatment	Done
Andalusian Agency for Health Technology Assessment (AETSA), Spain			
11,97	1-5,10	The pilot team could consider adjusting the list of planned and ongoing studies to the eligibility criteria of the report. There are listed single-arm trials in others solid tumours and in a different line of therapy, which are not considered in this report, as those issues are out of the scope. Those studies would not be considered for the systematic review if the results were already published. The pilot team could consider deleting the ongoing and completed studies which are indicated below and they could include only planned and ongoing studies that will help to clarify the evidence gaps identified in the assessment of ramucirumab in the current indication and that will facilitate more robust conclusions in the update of this report.	We do see how listing all the trials may be confusing and unnecessary. On the other side, as described in the safety section of the assessment. Information from other study types and patient populations is used to inform the Summary of product characteristics/European public assessment report. Due to the limited evidence at present, we feel that the need to gather experience from similar, even if not identical, setting may add to the evidence base. Hence, we would like to keep information on such potential sources of information.

Page	Line	Comments	Comments from the author
		- NCT02082210: 70 patients in any type solid tumour, not only the one of interest, in combination with an investigational product. The sample size is smaller than in the study included in the assessment and the drug is not administered in monotherapy or in combination with paclitaxel. Thus, in relation to safety, this study will not probably change the uncertainty. - NCT01983878: the drug will be tested in 1st line and in Japanese population. - NCT01253525: is a phase 1, already completed. We suggest keeping only NCT02065765, which might change the uncertainty regarding safety issues and therefore, modify the conclusions. It could be added: “The authors did not identify any planned or ongoing RCT of ramucirumab in combination with paclitaxel against the adequate comparators in the population of interest”.	Text in Summary edited
21		The pilot team could consider dividing the section “method and evidence included“ in 2 sections, and not mixing information under the same heading. First, in the section “Methods”, the Search methods, Data extraction and calculation of estimates and Quality rating of studies could be specified. Later, in the section “Evidence included”, Search results, Unpublished studies found in clinical trials registers, and Table 2.1 could be included.	We have used the REA template. But it is under continuous development, and we will feed your suggestions into upcoming revisions.
21-22		Detailed inclusion and exclusion criteria are not given in the section of methodology. The pilot team could consider adding this information in this section of the report.	Inclusion criteria is presented in the section on search. Exclusion criteria is not stated, but are the negative image of the inclusion criteria.

Page	Line	Comments	Comments from the author
22	8	We do not find the flow chart of study selection in Appendix 1, as it is stated in the sentence.	Updated text. MAH asked that we only present the data as text.
22	22-25	The pilot team could add that for assessing the risk of bias in randomized controlled trials, the authors have followed the recommendations in the EUnetHTA guideline on internal validity of randomized controlled trials. On the other hand, more information about the different domains in the tool could be given for readers who can be unfamiliar with the Cochrane risk of bias tool.	Text updated with reference to guideline. In order to keep the text as short as possible, we will not add extensive information on the tools used. However, for those unfamiliar with them, we do include reference to more information.
25	21-25	The sentence “Ramucirumab is associated with such...and reversible posterior leukoencephalopathy syndrome” could be deleted from the research question B0001, as the safety profile of the drug is assessed in a specific domain. This suggestion could be also taken into account for the lines 20-22 in the discussion in page 34.	Thank you very much. This section is now rewriten according the SmPC. SmPC data should be written in this section.
31-32		The information regarding BSC could be summarized. It is too lengthy.	Thank you, but we think that this text is needed for better understanding problem with BSC.
32	19-23, 24-28	The indication of ramucirumab in the EU appears twice consecutively, as the positive opinion on the drug by CHMP and the approval by the EC.	Thank you very much; we added date of marketing authorisation, 19 December 2014. The text about indications is rewritten also.
32-33	32-35, 1-2, 26-31	The information provided in the last paragraph of page 32, research question A0020 (lines 32-35 and lines 1-2, in page 33) is duplicated. The same information appears in the research question B0003, next to last paragraph in page 33 (lines 26-31). On the other hand, although in both paragraphs the FDA-approved label is indicated, the references provided are different, being the one from the FDA more adequate. The pilot team could consider omitting the redundant information from one of	Thank you, the text is rewritten to avoid duplications.

Page	Line	Comments	Comments from the author
		the research questions to make the report more reader friendly.	
36	12-17	The information regarding risk factors could be replaced in the research question A0003 'What are the known risk factors for the condition?'	We agree with the referee that this would have made sense. However, A0003 was not included in the protocol, but following feedback from dedicated reviewers to previous drafts of the report, we have included a brief paragraph on risk factors in A0003.
40	13-15	Has a systematic review of clinical practice guidelines on the management of advanced gastric cancer been conducted by the company or the authors?. Which electronic databases have been searched for relevant international clinical guidelines? The pilot team could consider adding this information in the section 'Methods'. On the other hand, even though the appropriate comparators for the assessment are identified before the assessment begins, this information regarding the comparators could be provided before, as in page 26 line 7, the comparators considered are listed. It would be useful to have previously the information about the technologies that are reference treatments according to up-to-date high-quality clinical practice guidelines at European or international level with good quality evidence.	Data on Guidelines was provided and literature search was done by Manufacturer; some national guidelines published in 2014 were added by authors, but not through systematic literature search. No quality assessment tool was used for the domains Description and Technical Characteristics of the Technology and Health Problem and Current Use of Technology, but multiple sources were used in order to validate individual, possibly biased, sources. Descriptive analysis was performed on different information sources. So, no quality assessment on guidelines was performed. Some text is added and some is rewritten, please see Method section and text on Comparators in TEC Domain, as well text in A0025, thank you.
40	16-18	The information in the sentence "In Western.... initial surgery" is duplicated. It was provided in the previous page (lines 7-9, page 39, 'in particular….curative').	Thank you, the text is rephrased and duplication was removed.
44		The risk of bias at study level could be reported for each trial and also a reference to the table A6.	The text on this page is to give an overview of the studies. We chose to give reference to the entire appendix 1, as several of the tables presented there add to the information in the overview. We tried to keep the main text as short and simple as possible. We are aware that it is a fine line between the desire to be

Page	Line	Comments	Comments from the author
			readable and the desire for details.
45	1-5	Were the results of the indirect comparisons (for each outcome) performed by the company verified by the pilot team?	No. We assessed the submitted description of methods used, but did not re-enter numbers to re-calculate results.
45	6	The pilot team could consider adding information about the comparisons of patients in treatment arms at baseline in the 4 trials included (in a table regarding RAINBOW study, and in a descriptive way regarding the studies used in the indirect comparisons). Were treatment groups balanced with respect to potential prognostic factors?. A table with baseline characteristics could be included in the clinical effectiveness domain, before the results of the outcomes are explained, or in the Appendix 1.	The included studies were randomised (table A3). Randomisation should balance known and unknown factors across study groups. We have not seen reference to information that the randomisation was unbalanced. A table of baseline characteristics is beyond what we could prioritise with assessments being pressed for time and resources.
45	21	Apart from the quality of the direct evidence for the outcomes according to GRADE, the risk of bias of each outcome described in the research questions could be indicated before the GRADE approach or at least a reference to the table A7.	Risk of bias is part of the GRADE assessment; we therefore do not present this separately in the text here. We acknowledge that it may be easier to see in table A8 (evidence profile) than in the Summary of findings output style used in the main text. However, we chose it as we believe it give easier access to main finding.
47	2-5	In order to know which outcomes are specifically considered in the research question D0005, this could be completed with the following words in quotations below: How does ramucirumab in combination with paclitaxel affect symptoms and findings (severity, frequency) *"in terms of fatigue, pain, physical functioning and objective response rate"* in patients with advanced gastric cancer….?	The text is based on the template and project plan. But it is under continuous development, and we will feed your suggestions into upcoming revisions.
47-48	18-24, 1-3	Please, delete this paragraph. It refers to the number of deaths due to adverse events, and it is misplaced here. The same paragraph appears in the safety domain of the report (research	Done

Page	Line	Comments	Comments from the author
		question C0008d, page 61, lines 9-18).	
48	15	As it appears later in other outcomes evaluated, one of the following sentences regarding the lack of indirect comparisons could be added. "The submission dossier does not present indirect evidence for symptoms such as pain and fatigue" OR "There are no indirect comparisons for symptoms such pain and fatigue".	Done
49	5-9	It is stated that the quality of the evidence reported here is reduced from low to very low. Is it not from moderate to low instead?.	Yes. Updated text.
50	9	The quality of the evidence for indirect comparisons for PFS is not provided.	Added.
53	6	Are any pre-planned subgroup analyses of interest reported in the RCT trial included? Could those analyses be included in the assessment?	We did not specify sub-groups in the aim of this project (project plan).
72	50	A section with the conclusions of the assessment could be added after the last domain. At this moment, the conclusions are only provided in the summary of the report.	Not part of the template as far as we know. We will feed your suggestion into wp5 coordination team for discussion in potential revision of templates.
73		In the second paragraph, the reasons for excluding articles by title/abstract or by full text are not provided. It is only stated "after exclusion of studies that did not meet eligibility criteria", but inclusion and exclusion criteria are not specified.	We refer to the eligibility criteria and state that selection was done base on the focus of this assessment. It is correct that we do not make table or otherwise enhance this information. We will forward this topic to wp5 coordinators to discuss if such tables indeed should be included in an update of the REA template.

Page	Line	Comments	Comments from the author
73		The information in page 73 under the subheading 'Documentation of the search strategies' is exactly the same as the information supplied in page 77. Moreover, the table with the search strategy and its results (numbers) in pages 74-76 is the same one that appears in pages 78-80. On the contrary, MEDLINE search strategy is not in the Appendix.	Updated.
89		The critical appraisal of the included clinical guidelines is not provided. Its quality should be added. On the other hand, the level of evidence of the recommendations is not available in any of the guidelines in the Table.	As stated above, no quality assessment tool was used for the domains Description and Technical Characteristics of the Technology and Health Problem and Current Use of Technology, but multiple sources were used in order to validate individual, possibly biased, sources. There is no standard or approved (till now when ramcuirumab is approved for the 2nd line treatment) in the second line treatment of these patients. Level of evidence and Grade of recommendation were added in the text and Table on clinical guidelines.
92		An oncology guideline published in 2009 (Gastric Carcinoma – Nation-wide guideline) could be considered outdated in 2015, and for that reason, it could be excluded from the Table.	We do not agree; please see text above, thank you.
97	2-8	The pilot team could consider replacing the search methods in clinical trials registries platforms for identification of planned and ongoing studies in the section "Methods" beneath the subheading "Search" after the searches to identify the studies to be included in the systematic review (line 2, page 22).	The pilot team did discuss where to add information on planned or ongoing trials. Considering our response to the similar aspect (your comment to page 11). We feel it most appropriate to keep the information in appendix in this assessment.
99		Typo: "Used in in evidence" instead of "Used in evidence".	Done

Page	Line	Comments	Comments from the author
HAS, France			
7	32	I suggest that we add „patients“ after **5 per 10 000**	Thank you, we added according suggestion.
9	4	Can we please add a reference?	No references used in Summary. References are added in the main methods section.
9	10	In this part on available evidence, I suggest that we • Add for each study, the name and the reference to the publication • Allude there as well to the REGARD study (Ramucirumab monotherapy) as this is discussed later in the report Specify what was defined “active symptom control” and the difference, if any, with BSC	We have tried to keep the summary short and have not used references in this section. The REGARD study is not a part of the summary as it does not comply with our scope.
10	18-19	Could we be more specific with regards to the adverse events grade 3?	We only highlight an overview of the main findings in the summary. Details, such as on specific adverse events, are presented in the main text later.
19	Scope – Comparison	I suggest we add other in the sentence „at present, there are no technologies with marketing authorisation“	Thank you, text is reworded as: At present there are no other technologies (pharmaceuticals) than ramucirumab with marketing authorisation for the intended patient population. The off-label comparators were chosen based on information in published guidelines [ESMO-ESSO-ESTRO, 2013; EUnetHTA, 2013]
22	3	Is it 11071 records or 11056 as stated p73 of the reports?	11056. Changed

Page	Line	Comments	Comments from the author
24	Table 2.1.	Could please add a note after WJOG with „West Japan Oncology Group“?	Added in legend
25	21	I suggest to rephrase for „Ramucirumab is associated with serious adverse effects such as …	Thank you very much, text is revised according SmPC.
27	7	Delete one oft he 2 „weekly“ and add injection (or administration)	Thank you, text was changed according suggestions.
28	10	I suggest we add „administration «after „weeks“.	Thank you, text was changed according suggestions.
30	1	Same as above	Thank you, text was changed according suggestions.
31	19	Could you please describe in 1 sentence the study reported by Kang? (i.e.A Randomized Phase III Trial Comparing Salvage Chemotherapy Plus Best Supportive Care With Best Supportive Care Alone)	Thank you, text was changed according suggestions.
33	32	Can we briefly allude to the Regard study, especially as you are referring to the indication of ramucirumab in monotherapy on p34 line 3	This text is now deleted.
46	Table 5.2.	Could you please use instead of this table the table 17 of the MAH application file (p71)?	Note that tables have changed from the draft submission to the final submission. As noted in deviations form project plan. We have not been able to use those tables.
Evaluation Unit of the Canary Island Health Service (SESCS), Spain			
21	24	The selection criteria (inclusion and exclusion) of studies are scattered throughout Section 2.2. Some is in the search strategy in p21 line24 (design not to be included) and some other in p22 line 6 (design to be included, language). They should be clearly reported and all together in terms of designs, participants,	We refer to the eligibility criteria and state that selection was done base on the focus of this assessment. The section is straight under the scope table.

Page	Line	Comments	Comments from the author
		intervention, comparator, outcomes, languages, etc.)	It is correct that we do not make table or otherwise enhance this information. We will forward this topic to wp5 coordinators to discuss if such tables indeed should be included in an update of the REA template.
21	26	The last phrase of the paragraph starting “They also searched for conference.....“should place better following the list of databases searched	Done
22	3	These data are the result of search but they are in the middle of the methods. In my opinion, if it's not possible to report that in the results section, at least, it should be placed at the end of this section (as the final paragraph).	Moved to last in section as suggested.
22	14	These subsection should be number as 2.3. and subsequently the following “Quality rating of studies“ as 2.4.	No. “Search” and “Data extractrion…” is subheadings/lower level heading.
22	27	What major outcomes mean? Primary ones or, as GRADE proposed, those outcomes that are of importance to patients. This point requires more information	New text: Details of individual GRADE assessments are shown only for clinical effectiveness outcomes and for aggregated safety outcomes of direct evidence.
47	18	I am not expert in cancer research, but I think it is not usual to consider a variable both as an effectiveness and a safety outcome. In page 47 [D0005] the number of deaths due to an adverse event is reported, and the same outcome (and the same paragraph) is reported in the safety section (page 61, line 9) [C008d].	Deleted here and kept in safety domain.
51	7	“Quality of life assessments were performed.....“. In which study or studies?. In my opinion, the explanation of each questionnaire should be placed in the appropriate question: in D0012 Generic questionnaire EQ-5D-3L and in D0013 Disease specific questionnaire EORTC-QLQ-C30.	Done

Page	Line	Comments	Comments from the author
52	7-12	In the text there are not references to tables 5.7. and 5.8.	Added
57	32	In the safety section [C0008a] it is reported that there is a significant difference between groups in the number of AEs of grade 3 or higher. This result is not commented in the discussion (page 67, lin 2).	Text added in discussion.
101	Table A8	To our knowledge, the GRADE system does not offer perfectly objective criterion for assessing imprecision of the estimates. In the case of mortality, the upper limit of the CI is near 1 and the absolute effect ranged from 13 to 139 fewer people in the ramucirumab group. I wonder if it must be considered as a serious risk of bias or not.	We agree that no absolute criteria exist. Given the moderate number of patients, it is uncertain that optimal information size is reached, so to rate down would have been acceptable. We did choose not to rate down because even if the CI is wide, it is all on the benefit side.
105	Table A10	It is commented that “Subgroup analyses have been performed and relative benefit is consistent across regions“. Maybe it would be appropiate to report those data, or at least the regions or countries where the RAINBOW trial was performed.	The applicability table A10 give an overview of the evidence. Due to restricted time and resources in these pilot assessments, we have not prioritised adding subgroup information unless there was reported differences between groups.
Zorginstituut Nederland, the Netherlands			
General comment		Why is there a section about off-label medication? A physician still needs to administer an off-label drug when ramucirumab is administered in combination with paclitaxel?	This text is needed due the questions connected with Checklist for potential ethical, organisational, social and legal aspects. For the future joint work it will be important to have clear explanation or SOP within EUnetHTA how to deal with Checklist in case of „Yes“ answers; to leave answering on raised issue to local (national/regional HTA doers) or try to give answers by Rapid REA team: in this assessment we choose 2nd approach according current Rapid REA Template. In this assessment we used three off-label drugs as comparators. In real life, even now when ramucirumab is approved for 2nd line

Page	Line	Comments	Comments from the author
			treatment, could be situation, for example in case of serious ADRs, that off-label drugs should be used further instead of ramucirumab.
7	5-8	What is the rational for only assessing one of the two (newly) approved indications of ramucirumab	We examined the clinical effectiveness and safety of ramucirumab in combination with paclitaxel according the request from the Manufacturer.
7 and 8	21-23 8-10	I do not understand the rational for selecting the comparators. Were these drugs mentioned in a guideline or where they commonly used in clinical practise? Docetaxel is registered as first-line therapy. Is this information not relevant to include? And why was ramucirumab monotherapy not selected as a comparator?	Thank you. For clarification and better understanding, some text is added and some is rewritten, please see text on Comparators in TEC Domain, as well text in A0025, thank you. Data on docetaxel is written in the text and table and we provided already this information.
8	8-10	In this sentence it is stated that improvements in OS and QoL have been shown for second-line chemotherapy. However, from the data on page 27-30, I understand there was only a minimal effect (in particular for paclitaxel). Could you please clarify?	In patients of adequate performance status, second-line chemotherapy is associated with improvements in overall survival and quality of life compared with best supportive care, with treatment options including irinotecan, docetaxel, or paclitaxel. Paclitaxel have less ADR than other chemotherapeutics. Minimal effect is statistically proven.
8	10-11	I do not understand the meaning of the sentence: “Additionally …..in appropriate clinical trials”.	This sentence is deleted now from Summary; more details could be found in Health Problem and Current Use of the Technology.
7 and 8		Some information seems to be duplicated (e.g., ramucirumab is the only approved treatment option)	Text is rewritten and duplications were removed, thank you.
8	29-34	Could the search-terms be included in this section?	We can not add all details in summary or even in main text. We did update text to be the same as page 21.

Page	Line	Comments	Comments from the author
10	3-11	Please check whether this is proper English? (E.g., by checking the canagliflozin report?)?	Medical editing have been used.
12 and 13		I find the table difficult to read. It is possible to make a table for the direct and indirect comparisons? Is it also possible to add the events (or median survival time) in each of the treatment-arms? Why were three type of (TE)AE shown? What was the rational for the selection? Furthermore, if there is subgroup analysis and the results are consistent within these subgroups, is it necessary to downgrade on consistency? And why did the authors did not evaluated whether the results was clinically important (column imprecision)	The table is part of the REA template. We show only the main, or more overall/higher level, outcomes here. For safety/harm, we chose the three different presentations of adverse events instead of randomly selecting specific types of adverse events. The help module in grade (gdt) state the following "Inconsistency refers to an unexplained heterogeneity of results. True differences in the underlying treatment effect may be likely when there are widely differing estimates of the treatment effect (i.e. heterogeneity or variability in results) across studies." Even if subgroups are similar, we still only have one included study and do not know it results are consistent across studies – even if they are reproducible or not. What is deemed clinical important is to some extent based on experience and individual preference. We included some information on this is the discussion sections. However, we believe that should ultimately be up to the decision makers using this report.
15	10-13	Please check this sentence.	Progress -> progesses
15	13-20	I believe this statement is only correct for the first cycle. In the EPAR there was data after different cycles Please check the	The text has been edited

Page	Line	Comments	Comments from the author
		data. I also thought the QoL data was really limited. Do the (co-)authors think there is sufficient data on QoL?	
15	21	Is it direct and/or indirect comparisons that were limited by the number of studies?	Both.
15 and 16		I miss in the discussion section information about the rational for the choice of the MAH to combine the new drug with an (off-label) drug, namely paclitaxel. Do the (co-)authors know the rational for this choice?	We do not have insight in MAH developing program. We assume paclitaxel was the most commonly used treatment.
16	15-16	Did the (co-)authors mean the overall result is clinically relevant or the average difference? In OS the upper 95% CI was very close to 1.	As discussed in 5.3 “So far there are no published recommendations for what effect size on OS or PFS is acceptable as clinically meaningful for this particular patient population”
19		Why was the population smaller than the approved indication? Most countries need to assess the therapeutic value of the drug among patients with the registered indication.	Decided in dialogue with marketing authorisation holder, their wish.
19		Can the (co-)authors put the comparators in the order that they are most commonly used in Europe? I also would like to see ramucirumab added to the list of comparators.	Please see answers above.
21	21-28	Please add the search-terms to this section.	We believe it will be too detailed to add all search terms here. We include reference to full search strategy in appendix 1.
21 and 22		Please add a flow-chart (paragraph search)	Text updated. Will not be able to add flow chart, based on dialogue with manufacturer. A text description of the selection flow is part of Appendix 1.

Page	Line	Comments	Comments from the author
22	26-28	I do not understand the last part of the sentence	New text: Details of individual GRADE assessments are shown only for clinical effectiveness outcomes and for aggregated safety outcomes of direct evidence
23	24-29	I can not find the section that explains why only three studies were selected for he indirect comparison. Could this be added?	It is in the second to last paragraph of search section and Appendix 1. Those were the only studies meeting the scope of this REA.
31 and 32		There seems to be some overlap in the information in paragraph BSC. Can the (co-)authors maybe shorten this section?	Thank you, but we think that this text is needed for better understanding the problem with BSC.
33	21-23	Can you please provide the source of this claim.	This paragraph is deleted now.
34	13-25	Is a discussion section really needed here? If yes, please provide the rational for not selecting ramucirumab (monotherapy) as a comparator.	Discussion section is included in the current Format, it could be discussed further in EUnetHTA do we need Discussion section for the first two Domains.
36	21-36	I miss in this section the average median survival time (EPAR page 8) Could this information be added?	The text is added: Although there has been some progress in the treatment of gastric cancer, the prognosis still remains poor, in particular in Western countries; for patient diagnosed with advanced gastric cancer is approximately 1 year median survival [51].
37-39		Why are the tables not included in the appendix?	We discussed about this issue and decided to leave them as such.
40-41		I find this section difficult to read. Were these comparators mentioned in the ESMO guideline or where they commonly used in clinical practise? It the latter, please provide the source. I also wonder which of these agents is most commonly used? Furthermore, why is the combination of paclitaxel and FOLFOX not included as a comparator (see line 11-12)?	Text is rewritten to raise clarity. Please see also explanation on comparator already given above, thank you.

Page	Line	Comments	Comments from the author
42		Is the discussion section really needed?	Discussion section is included in the current Format, it could be discussed further in EUnetHTA do we need Discussion section for the first two Domains.
44	12-36	Could the (co-)authors add information on the dose (and schedule) to this section. Why did the (co-authors) included a study that was stopped earlier than planned? Should this study have been excluded?	The text here is to give an overview of the studies. We chose to give reference to the entire appendix 1, as several of the tables presented there add to the information in the overview. We tried to keep the main text as short and simple as possible. We are aware that it is a fine line between the desire to be readable and the desire for details. Even if the study was stopped early, it may add to the evidence base and be included. However, as indicated in e.g table A6, the conduct impact on the risk of bias assessment.
45	19	It is an increase in *median* survival time.	We added median
49		What was the rational for the order of the questions/elements? Is data on PFS not more important than on symptoms?	The is part of the REA template.
51	24-28	Can you please provide the average difference and the number of patients that completed the questionnaire? If this data is not available, is it not better to decide not to include this data?	Full QoL data not published yet. However, we present the available results according to our scope.
52	14	Why is there a column no data provided? Does this not bias your results? I would prefer to see this column removed and the data recalculated. Also include info on the number of patients that answered the questionnaire. Is the data in Table 5.8 correct?	Table 5.7 is as presented in the suggested EPAR submitted to us.
53	12-14	Is 50% relatively few?	We consider that only 15-50% of those treated in first line is relatively few.

Page	Line	Comments	Comments from the author
53-55		Could the (co-)authors add the results of the subgroup analyses to this section? Can the authors address here the question: whether there is sufficient data on QoL?	Subgroups was not part of our scope
56		Could the authors include information on the average dose, average duration of use, dose intensity, etc	Some information on dosing is part of table A3
56-72		Could the (co-)authors check whether the provided data on AE or TEAE? (This will also need to be checked in the graphs	They are treatment-emergent. P57 line 26
56-72		Most information provided here deals with the event rate, etc. I am missing data on the most common adverse events and the EMA adverse events of special interest. Could this be added (also in the discussion section)?	We aim not to duplicate information already addressed by EMA. Time and resources are limited, so unless we are able to copy information easily, it may be not the highest priority. We see that it may reduce the readability not having all information in the same document. We will forward this issue to the wp5 coordinators and discuss it for coming pilots.
72+		I miss a conclusion. There is one in the summary. Could we add this section?	We do not understand this question. Ethical and organisational issues do not have a conclusion in the summary section.
88		Why was this figure added if most of the studies are not used in the network-analyses?	We show the complete network to allow everyone the full picture. As discussed, we included the comparators in most clinical use and according to guidelines. However, if anyone should be interested in other alternatives. It will be apparent here.
89 to 92		Were these guidelines mentioned in the text of the report? If no, why was this information added in the appendix?	There is no sense to write and duplicate all specific data from these guidelines through the text and table, an overview was presented and more specific data are listed in Table A3 in Appendix 1. These data are important for understanding the choice of off-label comparators, please see explanations already

Page	Line	Comments	Comments from the author
			written above.
95		Is the title of the table correct?	RAINBOW is also used for the indirect comparisons, but we added direct – to be direct and indirect perhaps more in line with rest of the report.
101 and 102		Could you please take another look at the headers in the table? (E.g. is it mortality or overall survival)? In addition, why is there a row named median survival (which only include data on ramucirumab)? Why was no data available included in the calculations of the RR of QoL?	Done Median survival is a continuous variable, output style only show only absolute effects. That column for all outcomes refer to ramucirumab+paclitaxel compared to paxlitaxel The table show patients with stable or improved QoL.
AIFA, Italy			
22	3	Please specify the inclusion/exclusion criteria in the screening process for the identification of the pertinent clinical studies (i.e. PRISMA diagram).	Text edited. The MAH used the scope to screen publications. We were not able to use the flow chart, but it is described in text in appendix
22	11-13	The search for ongoing trials was performed only in the WHO International Clinical Trials Registry Platform (ICTRP). Other international clinical trial registers could be also searched: EU Clinical Trials Register, ClinicalTrials.gov, and the International Standard Randomized Controlled Trial Number Register (ISRCTN).	The WHO platform search other sites, every week or every 4 weeks depending on source, so that we do not need to search each site separately. http://apps.who.int/trialsearch/Default.aspx
22	13	It could be useful to report the search strategy for clinical guidelines and the quality assessment of those selected (through AGREE instrument).	Thank you for your comment. Data on Guidelines was provided and literature search was done by Manufacturer; some national guidelines published in 2014 were added by authors, but not through systematic literature

Page	Line	Comments	Comments from the author
			search. No quality assessment tool was used for the domains Description and Technical Characteristics of the Technology and Health Problem and Current Use of Technology, but multiple sources were used in order to validate individual, possibly biased, sources. Descriptive analysis was performed on different information sources. No quality assessment on guidelines was performed.
21-22,73		The point-list of the searched databases needs to be re-formatted since HTA database is included in Cochrane Library. There is also inconsistency with what is reported at pag. 21-22.	This is presented as described in the submitted documents. They may have search main sources in addition to aggregated ones. Inconsistency in number updated
77-80		These pages are duplicates of pages 73-76.	Changed
73-87		The search strategy for the Cochrane Library is missing.	Cochrane Library is listed among others in the second search table
89-93		The level of evidence of each guidelines is missing.	Level of evidence and Grade of recommendation were added in the text and Table on clinical guidelines.
98	1-10	As commented for page 22, lines 11-13.	See above
101-104		It seems that only one study was evaluated (see column No of studies). In our opinion thse assessment of the overall quality of evidence should be conducted when multiple studies are considered.	Table A8 is for direct evidence and that was only one trial.

eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

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ADDITIONAL APPENDIX TO THE ASSESSMENT OF: RAMUCIRUMAB IN COMBINATION WITH PACLITAXEL AS SECOND-LINE TREATMENT FOR ADULT PATIENTS WITH ADVANCED GASTRIC OR GASTRO-OESOPHAGEAL JUNCTION ADENOCARCINOMA

LIST OF TABLES

Table A.A.1. Indirect Comparison - Results for base-case - Overall Survival for comparisons of treatment ramucirumab plus paclitaxel vs. paclitaxel, irinotecan, docetaxel and placebo/best supportive care.

Comparator→ Intervention↓	Paclitaxel	Irinotecan	Docetaxel	Placebo/BSC
Ramucirumab+ Paclitaxel	0.81 (0.68-0.96)*	0.72 (0.52 – 0.99)	0.51 (0.23 – 1.13)	0.34 (0.17-0.71)

All estimates are hazard ratio and 95% confidence intervals. Grey cells = direct evidence.
* adjusted HR

Results from direct comparisons used to make indirect comparisons and networks:

RAINBOW [1] HR 0.82 (0.69-0.98), COUGAR-02 [2] HR 0.67 (0.49-0.92), WJOG [3] HR 1.13 (0.86-1.49), Roy 2013 [4] HR 0.96 (0.60-1.53) and Thuss-Patience 2011 [5] HR 0.48 (0.25-0.92)

Table A.A.2. Indirect Comparison for ORR (evaluable population). Comparisons of treatment: ramucirumab plus paclitaxel vs. paclitaxel, irinotecan and docetaxel.

Comparator→ Intervention↓	Paclitaxel	Irinotecan	Docetaxel	Placebo/BSC
Ramucirumab+ Paclitaxel	2.01 (1.38-2.93)	3.36 (1.40-8.08)	1.30 (0.24-6.92)	Not available

All estimates are odds ratio and 95% confidence intervals. Grey cells = direct evidence

Results from direct comparisons used to make indirect comparisons and networks:

RAINBOW [1] OR 2.01 (1.38-2.93), WJOG [3] OR 0.60 (0.27-1.32) and Roy 2013 [4] OR 0.39 (0.09-1.61)

Table A.A.3. Indirect comparisons for PFS

Comparator→ Intervention↓	Paclitaxel	Irinotecan	Docetaxel	Placebo/BSC
Ramucirumab + paclitaxel	0.64 (0.54-0.75)*	0.56 (0.41-0.76)	0.70 (0.46-1.07)	Not available

All estimates are hazard ratio and 95% confidence intervals. Grey cells = direct evidence.
* adjusted HR

Results from direct comparisons used to make indirect comparisons and networks:

RAINBOW [1] HR 0.64 (0.54-0.76), WJOG [3] HR 1.14 (0.88-1.49) and Roy 2013 [4] HR 1.26 (0.94-1.68)

Table A.A.4. Treatment withdrawal due to adverse events – from evidence network

Comparator→ Intervention↓	Paclitaxel	Irinotecan	Docetaxel	Placebo/BSC
Ramucirumab+ Paclitaxel	1.05 (0.65-1.68)	0.62 (0.20-1.97)	0.62 (0.12-3.33)	33.49 (1.26-893.60)

All estimates are odds ratio and 95% confidence intervals. Grey cells = direct evidence

Results from direct comparisons used to make indirect comparisons and networks:

RAINBOW [1] OR 1.05 (0.65-1.68), COUGAR-02 [2] OR 53.81 (3.19-906.64), WJOG [3] OR 1.68 (0.59-4.80) and Roy 2013 [4] OR 1.00 (0.30-3.38).

Table A.A.5. Summary of comparative safety estimates for specific adverse events

Ramucirumab +paclitaxel vs.: → Adverse event↓	Paclitaxel	Irinotecan	Docetaxel	BSC	Frequency#
Blood and lymphatic system disorders					
All grade anemia	0.94 (0.69-1.30)	0.52 (0.26-0.57)	NR	NR	34.5%
Grade 3+4*	0.88 (0.52-1.47)	0.55 (0.25-1.24)	0.36 (0.05-2.68)	0.41 (0.04-4.67)	9.2%
All grade bleeding	NR	NR	NR	NR	
All grade neutropenia	2.66 (1.93-3.66)	4.21 (2.11-8.42)	NR	NR	54.4%
Grade 3+4*	2.95 (2.07-4.20)	1.88 (0.96-3.66)	7.47 (1.28-43.55)	200.23 (7.04-5694.37)	40.7%
All grade leukocytopenia	1.94 (1.36-2.75)	3.81 (1.85-7.85)	NR	NR	33.9%
Grade 3+4*	2.95 (1.75-4.95)	3.19 (1.37-7.44)	NR	NR	17.4%
All grade thrompcytopenia	2.34 (1.34-4.07)	0.87 (0.28-2.70)	NR	NR	13.1%
Grade 3+4*	0.84 (0.25-2.77)	0.42 (0.03-6.25)	1.30 (0.02-86.85)	NR	1.5%
All grade febrile neutropenia	1.27 (0.49-3.25)	0.36 (0.07-1.83)	NR	NR	3.1%

Ramucirumab +paclitaxel vs.: → Adverse event↓	Paclitaxel	Irinotecan	Docetaxel	BSC	Frequency#
Grade 3+4*	1.27 (0.49-3.25)	0.36 (0.07-1.83)	0.97 (0.09-10.18)	12.49 (0.30-518.56)	3.1%
Gastrointestinal disorders					
All grade vomiting	1.41 (0.98-2.03)	0.63 (0.31-1.28)	NR	NR	26.9%
Grade 3+4*	0.83 (0.35-1.96)	2.60 (0.23-29.59)	5.60 (0.33-95.39)	NR	3.1%
All grade diarrhoea	1.60 (1.13-2.26)	2.55 (1.56-4.16)	NR	NR	32.4%
Grade 3+4*	2.47 (0.86-7.09)	0.48 (0.04-5.38)	4.63 (0.19-114.87)	NR	3.7%
All grade nausea	1.11 (0.80-1.53)	0.39 (0.21-0.75)	NR	NR	35.2%
Grade 3+4*	0.75 (0.26-2.19)	0.30 (0.04-2.14)	1.56 (0.04-59.75)	NR	1.8%
All grade anorexia	1.43 (1.03-1.96)	0.50 (0.26-0.96)	NR	NR	40.1%
Grade 3+4*	0.77 (0.33-1.77)	0.29 (0.09-0.99)	2.21 (0.09-55.76)	NR	3.1%
Nervous system disorders					
All grade peripheral sensory neuropathy	1.72 (1.10-2.69)	125.06 (27.42-570.45)	NR	NR	17.4%
Grade 3+4	2.03 (0.50-8.19)	37.98 (1.57-919.21)	NR	NR	1.8%
All grade neuropathy	1.50 (0.09-2.04)	108.85 (24.70-479.67)	NR	NR	45.9%
Grade 3+4	1.88 (0.98-3.61)	35.23 (1.87-665.10)	NR	NR	8.3%
Investigations					
All grade increased bilirubin	1.01 (0.35-2.90)	0.44 (0.11-1.65)	NR	NR	2.1%
Grade 3+4	0.50 (0.05-	0.38 (0.02-	NR	NR	0.3%

Ramucirumab +paclitaxel vs.: → Adverse event↓	Paclitaxel	Irinotecan	Docetaxel	BSC	Frequency#
	5.56)	6.54)			
All grade increased AST	1.65 (0.88-3.09)	1.13 (0.48-2.62)	NR	NR	8.3%
Grade 3+4	1.21 (0.37-4.01)	0.52 (0.10-2.87)	NR	NR	1.8%
All grade increased ALT	1.13 (0.58-2.17)	0.54 (0.22-1.31)	NR	NR	6.1%
Grade 3+4	1.35 (0.30-60.6)	1.37 (0.15-12.54)	NR	NR	1.2%
All grade hyponatremia	2.19 (0.98-4.92)	1.13 (0.41-3.15)	NR	NR	5.8%
Grade 3+4	2.83 (0.89-8.98)	0.60 (0.12-2.98)	NR	NR	3.4%

All estimates are odds ratio and 95% confidence intervals. Grey cells = direct evidence *: Results are consistent with sensitivity analyses using the ITT analysis instead of the safety population. # Frequency of the specific adverse events in the ramucirumab plus paclitaxel group to illustrate actual frequencies (based on the RAINBOW trial). Definition of severity from [6] **Grade 3**: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care Activities of Daily Living. **Grade 4**: Life-threatening consequences; urgent intervention indicated.

Results from direct comparisons used to make indirect comparisons and networks:

All grade anemia: RAINBOW [1] OR 0.94 (0.69-1.30), COUGAR-02 [2] OR 1.33 (0.64-2.75) and WJOG [3] OR 1.83 (1.01-3.29). Grade 3 or 4 anemia: RAINBOW [1] OR 0.88 (0.52-1.47), COUGAR-02 [2] OR 1.15 (0.30-4.46), WJOG [3] OR 1.58 (0.86-2.93) and Roy 2013 [4] OR 0.65 (0.10-4.10).

All grade neutropenia: RAINBOW [1] OR 2.66 (1.93-3.66), COUGAR-02 [2] OR 29.38 (1.71-503.84) and WJOG [3] OR 0.63 (0.34-1.17). Grade 3 or 4 neutropenia: RAINBOW [1] OR 2.95 (2.07-4.20), COUGAR-02 [2] OR 26.81 (1.56-461.53), WJOG [3] OR 1.57 (0.89-2.76) and Roy 2013 [4] OR 3.97 (0.78-20.33).

All grade leukocytopenia: RAINBOW [1] OR 1.94 (1.36-2.75) and WJOG [3] OR 0.51 (0.27-0.96). Grade 3 or 4 leukocytopenia: RAINBOW [1] OR 2.95 (1.75-4.95) and WJOG [3] OR 0.92 (0.47-1.80)

All grade thrombocytopenia: RAINBOW [1] OR 2.34 (1.34-4.07) and WJOG [3] OR 2.68 (0.999-7.20). Grade 3 or 4 thrombocytopenia: RAINBOW [1] OR 0.84 (0.25-2.77), WJOG [3] OR 1.98 (0.18-22.18) and Roy 2013 [4] OR 3.07 (0.12-77.46).

All grade febrile neutropenia: RAINBOW [1] OR 1.27 (0.49-3.25), COUGAR-02 [2] OR 12.83 (0.71-231.80) and WJOG [3] OR 3.50 (0.94-13.09). Grade 3 or 4 febrile neutropenia: RAINBOW [1] OR 1.27 (0.49-3.25), COUGAR-02 [2] OR 12.83 (0.71-231.80), WJOG [3] OR 3.50 (0.94-13.09) and Roy 2013 [4] OR 2.69 (0.49-14.69).

All grade vomiting: RAINBOW [1] OR 1.41 (0.98-2.03) and WJOG [3] OR 2.23 (1.22-4.10). Grade 3 or 4 vomiting. RAINBOW [1] OR 0.83 (0.36-1.96), WJOG [3] OR 0.32 (0.03-3.14) and Roy 2013 [4] OR 2.16 (0.50-9.24).

All grade diarrhoea: RAINBOW [1] OR 1.60 (1.13-2.26) and WJOG [3] OR 0.63 (0.44-0.88). Grade 3 or 4 diarrhoea: RAINBOW [1] OR 2.47 (0.86-7.09), WJOG [3] OR 5.10 (0.59-44.35) and Roy 2013 [4] OR 9.56 (1.14-80.05).

All grade nausea: RAINBOW [1] OR 1.11 (0.80-1.53) and WJOG [3] OR 2.83 (1.62-4.93). Grade 3 or 4 nausea: RAINBOW [1] OR 0.75 (0.26-2.19), WJOG [3] OR 2.52 (0.48-13.30) and Roy 2013 [4] OR 5.24 (0.24-112.36).

All grade anorexia: RAINBOW [1] OR 1.43 (1.03-1.96) and WJOG [3] OR 2.83 (1.62-4.94). Grade 3 or 4 anorexia: RAINBOW [1] OR 0.77 (0.33-1.77), WJOG [3] OR 2.61 (1.09-6.25) and Roy 2013 [4] OR 7.50 (0.38-149.93).

All grade peripheral sensory neuropathy: RAINBOW [1] OR 1.72 (1.10-2.69) and WJOG [3] OR 0.01 (<0.01-0.06). Grade 3 or 4 peripheral sensory neuropathy: RAINBOW [1] OR 2.03 (0.50-8.19) and WJOG [3] OR 0.05 (<0.01-0.90).

All grade neuropathy: RAINBOW [1] OR 1.50 81.09-2.04) and WJOG [3] OR 0.01 (<0.01-0.06). Grade 3 or 4 neuropathy: RAINBOW [1] OR 1.88 (0.98-3.6) and WJOG [3] OR 0.05 (<0.01-0.94).

All grade increased bilirubin: RAINBOW [1] OR 1.01 (0.35-2.90) and WJOG [3] OR 2.31 (1.03-5.18). Grade 3 or 4 increased bilirubin: RAINBOW [1] OR 0.50 (0.05-5.56) and WJOG [3] OR 1.32 (0.29-6.05).

All grade increased AST: RAINBOW [1] OR 1.65 (0.88-3.09) and WJOG [3] OR 1.47 (0.83-2.58). Grade 3 or 4 increased AST: RAINBOW [1] OR 1.21 (0.37-4.01) and WJOG [3] OR 2.32 (0.69-7.76).

All grade increased ALT: RAINBOW [1] OR 1.13 (0.58-2.17) and WJOG [3] OR 2.08 (1.15-3.77). Grade 3 or 4 increased ALT: RAINBOW [1] OR 1.35 (0.30-6.06) and WJOG [3] OR 0.98 (0.19-4.97).

All grade hyponatremia: RAINBOW [1] OR 2.19 (0.98-4.92) and WJOG [3] OR 1.93 (1.04-3.60). Grade 3 or 4 hyponatremia: RAINBOW [1] OR 2.83 (0.89-8.98) and WJOG [3] OR 4.75 (1.54-14.63).

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