

IQWiG Reports – Commission No. A14-32

**Aflibercept (new therapeutic  
indication) –  
Benefit assessment according  
to §35a Social Code Book V<sup>1</sup>**

**Extract**

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<sup>1</sup> Translation of Sections 2.1 to 2.5 of the dossier assessment *Aflibercept (neues Anwendungsgebiet) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11 December 2014). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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<sup>3</sup> Table numbers start with “2” as numbering follows that of the full dossier assessment.

**List of abbreviations**

<b>Abbreviation</b>	<b>Meaning</b>
ACT	appropriate comparator therapy
AE	adverse event
ARR	absolute risk reduction
BCVA	best corrected visual acuity
DMO	diabetic macular oedema
EQ-5D	European Quality of Life-5 Dimensions
ETDRS	Early Treatment Diabetic Retinopathy Study
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IVT	intravitreal
LOCF	last observation carried forward
NEI VFQ-25	National Eye Institute Visual Functioning Questionnaire-25
OR	odds ratio
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
TI	therapeutic indication
VAS	visual analogue scale
VEGF	vascular endothelial growth factor

## 2 Benefit assessment

### 2.1 Executive summary of the benefit assessment

#### Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug aflibercept. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as “the company”). The dossier was sent to IQWiG on 3 September 2014.

#### Research question

The aim of this report was to assess the added benefit of aflibercept in patients with visual impairment due to diabetic macular oedema (DMO).

The G-BA named 2 patient groups in this therapeutic indication and specified an appropriate comparator therapy (ACT) for each of them. This resulted in 2 research questions, which are derived from the 2 patient groups named by the G-BA:

- research question 1: patients with visual impairment due to DMO **with** involvement of the fovea: ranibizumab is the ACT
- research question 2: patients with visual impairment due to DMO **without** involvement of the fovea: focal/grid laser photocoagulation is the ACT

The presence of a clinically significant macular oedema according to the Early Treatment Diabetic Retinopathy Study (ETDRS) criteria is assumed.

The company did not consider the research question on patients with visual impairment due to DMO without involvement of the fovea.

The assessment was conducted based on patient-relevant outcomes and on randomized controlled trials (RCTs) with a minimum duration of 6 months.

#### Results

##### **Research question 1: patients with visual impairment due to DMO with involvement of the fovea**

No direct comparative study was available for the assessment of aflibercept versus ranibizumab. The assessment was conducted on the basis of an adjusted indirect comparison with 2 RCTs on aflibercept and 2 RCTs on ranibizumab. Although the inclusion criteria of the ranibizumab studies RESTORE and REVEAL did not explicitly require including patients with visual impairment with involvement of the fovea, it can be assumed on the basis of the available data that the majority of the patients had foveal involvement.

***Aflibercept studies VISTA and VIVID***

The aflibercept studies VISTA and VIVID were 2 ongoing, randomized, active-controlled, double-blind, multicentre phase 3 studies. Adult patients with visual impairment due to DMO, involving the centre of the macula (fovea centralis) were enrolled. In both studies, patients were randomly assigned to treatment with aflibercept 2 mg (intravitreal [IVT] injection) every 4 weeks (N = 156), aflibercept 2 mg (IVT injection) every 8 weeks following 5 initial injections (N = 154), or laser photocoagulation (N = 156). Treatment with aflibercept 2 mg every 4 weeks does not comply with the approved therapeutic regimen of aflibercept and was therefore not considered in the benefit assessment. Treatment with aflibercept 2 mg following 5 initial monthly injections every 8 weeks in both studies complies with the approved use. After the 5 initial injections, a sham injection was administered (in each case without intraocular penetration) at study visits without active injection. Besides these sham injections, patients also received sham laser treatment at baseline and possibly at 12-week intervals, according to the criteria for active laser photocoagulation. In the control arm, patients received active laser photocoagulation treatment based on the ETDRS recommendations at baseline and then at 12-week intervals. Retreatment was only performed if certain criteria for retreatment were fulfilled. Sham injections were administered at baseline and at every visit.

Starting in week 24, active additional treatments could be given to all patients if certain criteria for additional treatment were met. Patients from the intervention arm could receive active laser photocoagulation, and patients from the control arm could receive additional aflibercept injections. The allocated study treatment was continued. This additional treatment was taken into account in the assessment of the risk of bias.

The primary analysis after 52 weeks was used for the benefit assessment.

***Ranibizumab studies RESTORE and REVEAL***

The ranibizumab studies RESTORE and REVEAL were randomized, active-controlled, double-blind, multicentre phase 3 studies with a study duration of 12 months. The REVEAL study was only conducted in Asian centres. Adult patients with visual impairment due to focal or diffuse DMO were included.

The patients in the 2 studies were randomized to ranibizumab 0.5 mg (IVT injection), ranibizumab 0.5 mg (IVT injection) plus laser photocoagulation, or to laser photocoagulation. The study arm with ranibizumab 0.5 mg alone and the study arm with laser photocoagulation were relevant for the benefit assessment. In the RESTORE study, 116 patients were randomized to ranibizumab, and 111 patients to laser photocoagulation. The corresponding patient numbers in the REVEAL study were 133 and 131. Ranibizumab was administered in compliance with the approval. The patients in the studies initially received 3 consecutive monthly IVT injections with 0.5 mg ranibizumab, followed by further monthly injections according to the criteria for retreatment. Additional sham laser treatments were performed at least at an interval of 12 weeks. Patients in the control arm received active treatment with laser photocoagulation. Retreatment was performed as needed at an interval of at least 12

weeks. The patients also received sham injections analogous to the criteria of the intervention group.

Additional treatments, which were allowed in the aflibercept studies, were not administered in the studies RESTORE and REVEAL.

Analyses were available for the time point 52 weeks.

### ***Similarity of the aflibercept and the ranibizumab studies***

There was mostly similarity of the aflibercept and the ranibizumab studies for study and intervention characteristics of the studies (e.g. study design, treatment duration, interventions, and outcomes). Besides differences in the inclusion criteria (the aflibercept studies specifically included patients with visual impairment due to DMO with involvement of the fovea, whereas the ranibizumab studies did not; but it can be assumed that the majority of the patients in these studies had foveal involvement), there were partly differences in the criteria for retreatment or in the level of detail of the available information. Furthermore, the studies were conducted in different geographical regions (VIVID: partly in Japan, REVEAL: exclusively in Asia). The greater problem appeared to be that only little information on the randomization process was available for the REVEAL study, and that additional treatments could be administered in the aflibercept studies. The resulting differences between the studies were addressed with corresponding methods (sensitivity analyses or last observation carried forward [LOCF] analysis), but uncertainties remained.

Regarding patient characteristics, information for all studies were only available for few characteristics. If there were data, they showed differences in the proportions of men and women included; the patients in the VISTA study on average had a somewhat longer history of diabetes mellitus than the patients in the VIVID and the RESTORE studies. Approximately half of the patients in the studies VISTA, VIVID and RESTORE already had received laser photocoagulation, and some of the patients in the aflibercept studies already had anti-vascular endothelial growth factor (anti-VEGF) treatments, with their proportion being notably higher in the VISTA study than in the VIVID study. Overall, the study, intervention and patient characteristics were considered to be sufficiently similar for an adjusted indirect comparison.

### ***Risk of bias***

The risk of bias at study level was rated as high both for the aflibercept studies VISTA and VIVID and for the ranibizumab study REVEAL because a large proportion of patients in the laser photocoagulation group received additional treatment in the 2 aflibercept studies, and because insufficient information was available on the process of randomization for the REVEAL study. The risk of bias at outcome level was not evaluated in the present assessment because the consistency could not be assessed for the present adjusted indirect comparisons and therefore there was generally low certainty of results. The risk of bias at outcome level was only assessed as additional information if there were important heterogeneous results

between the studies to investigate whether a different risk of bias was a possible explanation of this heterogeneity.

### ***Mortality***

#### *All-cause mortality*

Data on deaths from all 4 studies were available for the adjusted indirect comparison. There was no statistically significant difference between aflibercept and ranibizumab. An added benefit of aflibercept in comparison with ranibizumab is therefore not proven for this outcome.

### ***Morbidity***

#### *Improvement of visual acuity by $\geq 10$ ETDRS letters*

There was an indication of heterogeneity for the aflibercept studies VISTA and VIVID for the outcome “improvement of visual acuity by  $\geq 10$  ETDRS letters” ( $p = 0.13$ ). Possible reasons for the heterogeneity remained unclear. Since there were large effects in the same direction both in the VISTA and in the VIVID study, the studies were still considered jointly for the indirect comparison. There was no statistically significant difference between aflibercept and ranibizumab in the adjusted indirect comparison. An added benefit of aflibercept in comparison with ranibizumab is therefore not proven for this outcome.

#### *Worsening of visual acuity by $\geq 10$ ETDRS letters*

There was no statistically significant difference between aflibercept and ranibizumab for the outcome “worsening of visual acuity by  $\geq 10$  ETDRS letters” in the adjusted indirect comparison. An added benefit of aflibercept in comparison with ranibizumab is therefore not proven for this outcome.

#### *Health status (EQ-5D VAS)*

There were evaluable data for only 3 studies for the outcome “health status”, which was recorded with the visual analogue scale (VAS) of the European Quality of Life-5 Dimensions (EQ-5D). There was no information on variance for the ranibizumab study RESTORE so that this study was not used for the adjusted indirect comparison. There was no statistically significant difference between aflibercept and ranibizumab for the outcome “health status” in the adjusted indirect comparison. An added benefit of aflibercept in comparison with ranibizumab is therefore not proven for this outcome.

#### *Health-related quality of life*

Health-related quality of life was recorded with the National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25). Data were available for all studies except for the ranibizumab study REVEAL. There was no statistically significant difference between aflibercept and ranibizumab for the outcome “health-related quality of life” in the adjusted indirect comparison. An added benefit of aflibercept in comparison with ranibizumab is therefore not proven for this outcome.

### *Adverse events*

There were evaluable data for all 4 studies only for the outcome “serious adverse events (SAEs)”. For the other outcomes on adverse events (AEs) considered, there were no data for the ranibizumab studies REVEAL.

#### *Serious adverse events*

There was an indication of important heterogeneity for the aflibercept studies VISTA and VIVID for the outcome “SAEs” ( $p = 0.134$ ). Possible reasons for the heterogeneity remained unclear. Hence the results of these studies were not pooled in a meta-analysis, but considered separately with the 2 ranibizumab studies RESTORE and REVEAL in an adjusted indirect comparison. There was no statistically significant difference between aflibercept and ranibizumab in any of the analyses. Greater or lesser harm from aflibercept than from ranibizumab is not proven for this outcome.

#### *Discontinuation due to adverse events*

There was no statistically significant difference between aflibercept and ranibizumab for the outcome “discontinuation due to AEs” in the adjusted indirect comparison. Greater or lesser harm from aflibercept than from ranibizumab is not proven for this outcome.

#### *Ocular adverse events, ocular serious adverse events, discontinuation due to ocular adverse events*

There was no statistically significant difference between aflibercept and ranibizumab for the outcomes “ocular AEs”, “ocular SAEs” and “discontinuation due to ocular AEs” in the adjusted indirect comparison. Greater or lesser harm from aflibercept than from ranibizumab is not proven for these outcomes.

No subgroup analyses were considered for the present benefit assessment.

### **Research question 2: patients with visual impairment due to DMO without involvement of the fovea**

Since the company submitted no data for the assessment of the added benefit in the research question on patients with visual impairment due to DMO without involvement of the fovea, an added benefit of aflibercept versus the ACT is not proven for this research question.

### **Extent and probability of added benefit, patient groups with therapeutically important added benefit<sup>4</sup>**

On the basis of the results presented, the extent and probability of the added benefit of the drug aflibercept compared with the ACT is assessed as follows:

#### ***Research question 1: patients with visual impairment due to DMO with involvement of the fovea***

Overall, neither positive nor negative effects remain for aflibercept on the basis of the available results.

In summary, there is no proof of an added benefit of aflibercept versus the ACT ranibizumab for patients with visual impairment due to DMO with involvement of the fovea.

#### ***Research question 2: patients with visual impairment due to DMO without involvement of the fovea***

No data were available for the assessment of the added benefit in the research question on patients with visual impairment due to DMO without involvement of the fovea. An added benefit of aflibercept versus the ACT is not proven for this research question.

Table 2 presents a summary of the extent and probability of the added benefit of aflibercept.

Table 2: Extent and probability of the added benefit of aflibercept

<b>Subindication</b>	<b>ACT</b>	<b>Extent and probability of added benefit</b>
Patients with visual impairment due to DMO <b>with</b> involvement of the fovea <sup>a</sup>	Ranibizumab	Added benefit not proven
Patients with visual impairment due to DMO <b>without</b> involvement of the fovea <sup>a</sup>	Focal/grid laser photocoagulation	Added benefit not proven
a: The presence of a clinically significant macular oedema according to the ETDRS criteria is assumed. ACT: appropriate comparator therapy; DMO: diabetic macular oedema; ETDRS: Early Treatment Diabetic Retinopathy Study		

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

<sup>4</sup> On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data), see [1]. The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit), see [2].

## 2.2 Research question

The aim of this report was to assess the added benefit of aflibercept in patients with visual impairment due to DMO.

2 research questions resulted for the assessment, which are derived from the ACT specified by the G-BA. The G-BA named 2 patient groups and specified an ACT for each of them. Table 3 shows an overview of the research questions for the assessment.

Table 3: Research questions and ACTs for the benefit assessment of aflibercept

Research question	Subindication	ACT
1	Patients with visual impairment due to DMO <b>with</b> involvement of the fovea <sup>a</sup>	Ranibizumab
2	Patients with visual impairment due to DMO <b>without</b> involvement of the fovea <sup>a</sup>	Focal/grid laser photocoagulation

a: The presence of a clinically significant macular oedema according to the ETDRS criteria is assumed.  
ACT: appropriate comparator therapy; DMO: diabetic macular oedema; ETDRS: Early Treatment Diabetic Retinopathy Study

The company deviated from the research questions because it did not consider patients with visual impairment due to DMO **without** involvement of the fovea.

The assessment was conducted based on patient-relevant outcomes and on RCTs with a minimum duration of 6 months. This deviated from the company's approach, which defined no minimum study duration. This deviation had no consequence because the information retrieval only identified relevant studies with a minimum duration of 1 year, i.e. the company included no studies with a duration of less than 6 months.

## 2.3 Research question 1: patients with visual impairment due to DMO with involvement of the fovea

### 2.3.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study lists on aflibercept (studies completed up to 6 August 2014)
- bibliographical literature search on aflibercept (last search on 24 June 2014)
- search in trial registries for studies on aflibercept (last search on 27 June 2014)
- bibliographical literature search on the ACT (last search on 24 June 2014)
- search in trial registries for studies on the ACT (last search on 27 June 2014)

To check the completeness of the study pool:

- bibliographical literature search on aflibercept (last search on 2 October 2014)
- search in trial registries for studies on aflibercept (last search on 2 October 2014)
- bibliographical literature search on the ACT (last search on 2 October 2014)
- search in trial registries for studies on the ACT (last search on 2 October 2014)

One additional potentially relevant study (LUCIDATE) for the adjusted indirect comparison of aflibercept versus ranibizumab with the common comparator (laser photocoagulation) was identified from the check of the completeness of the study pool [3]. The study investigated the comparison of ranibizumab versus laser photocoagulation. The company also identified this study in its literature search, but excluded it from the assessment because of an unsuitable study design (see Module 4 C, Table 4-235 and Table 4-237). The exclusion of this study was not followed. Overall, the study pool of the company was incomplete because of the exclusion of the LUCIDATE study, but the influence of the results of this study on the results of the adjusted indirect comparison was assessed as minor (see Section 2.6.2.3.2 of the full dossier assessment).

### 2.3.1.1 Studies included

The studies listed in the following table were included in the benefit assessment.

Table 4: Study pool – RCT, indirect comparison: aflibercept vs. ranibizumab

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study <sup>a</sup> (yes/no)	Third-party study (yes/no)
<b>Studies with aflibercept</b>			
VISTA	Yes	Yes	No
VIVID	Yes	Yes	No
<b>Studies with ranibizumab</b>			
RESTORE	No	No	Yes
REVEAL	No	No	Yes

a: Study for which the company was sponsor, or in which the company was otherwise financially involved.  
RCT: randomized controlled trial; vs.: versus

The study pool for the benefit assessment of aflibercept concurred with that of the company, but the adjusted indirect comparison based on it was only relevant for research question 1. Although it was not explicit in the inclusion criteria of the ranibizumab studies RESTORE and REVEAL that patients with visual impairment with involvement of the fovea were included, it can be assumed that the majority of the patients had foveal involvement (see Section 2.6.2.5.1 of the full dossier assessment). The ranibizumab study LUCIDATE

additionally identified was not included in the study pool (see Section 2.6.2.3.2 of the full dossier assessment).

Section 2.3.4 contains a reference list for the studies included.

### **2.3.1.2 Study characteristics**

Table 5 and Table 6 describe the studies used for the benefit assessment.

Table 5: Characteristics of the studies included – RCT, indirect comparison: aflibercept vs. ranibizumab

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes <sup>a</sup>
<b>Studies with aflibercept</b>						
VISTA	RCT, double-blind, multicentre	Adult patients with visual impairment (BCVA of 73 to 24 letters according to the ETDRS chart in the study eye) due to DMO with involvement of the centre of the macula	Aflibercept 2Q4 IVT (N = 156) <sup>b</sup> aflibercept 2Q8 IVT (N = 154) laser photocoagulation (N = 156)	Screening phase: day –21 to day –1 Treatment phase: 148 weeks Data cut-off for primary analysis: 52 weeks	54 study centres in the United States 5/2011 – 1/2013 (primary treatment phase) End of study: probably 1/2015	Primary outcome: mean change in BCVA after 52 weeks Secondary outcomes: visual acuity, health status, health-related quality of life, adverse events
VIVID	RCT, double-blind, multicentre	Adult patients with visual impairment (BCVA of 73 to 24 letters according to the ETDRS chart in the study eye) due to DMO with involvement of the centre of the macula	Aflibercept 2Q4 IVT (N = 136) <sup>b</sup> aflibercept 2Q8 IVT (N = 135) laser photocoagulation (N = 135)	Screening phase: day –21 to day –1 Treatment phase: 148 weeks Data cut-off for primary analysis: 52 weeks	73 study centres in Japan, Australia and Europe 5/2011 – 6/2013 (primary treatment phase) End of study: probably in the first quarter of 2015	Primary outcome: mean change in BCVA after 52 weeks Secondary outcomes: visual acuity, health status, health-related quality of life, adverse events

(continued)

Table 5: Characteristics of the studies included – RCT, indirect comparison: aflibercept vs. ranibizumab (continued)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes <sup>a</sup>
<b>Studies with ranibizumab</b>						
RESTORE	RCT, double-blind, multicentre	Adult patients with visual impairment (BCVA of 78 to 39 letters according to the ETDRS chart in the study eye) due to focal or diffuse DMO	Ranibizumab 0.5 mg IVT (N = 116) ranibizumab 0.5 mg IVT + laser photocoagulation (N = 118) <sup>b</sup> laser photocoagulation (N = 111)	Treatment: 12 months Open-label extension study: 24 months	73 centres in Europe, Canada and Australia 5/2008 – 1/2010 (primary treatment phase) End of study: 1/2012	Primary outcome: mean change in BCVA after 52 weeks Secondary outcomes: visual acuity, health status, health-related quality of life, adverse events
REVEAL	RCT, double-blind, multicentre	Adult Asian patients with visual impairment (BCVA of 78 to 39 letters according to the ETDRS chart in the study eye) due to focal or diffuse DMO	Ranibizumab 0.5 mg IVT (N = 133) ranibizumab 0.5 mg IVT + laser photocoagulation (N = 132) <sup>b</sup> laser photocoagulation (N = 131)	Treatment: 12 months	35 study centres in Asia (China, Japan, Singapore, South Korea and Taiwan) 9/2009-8/2011	Primary outcome: mean change in BCVA after 12 months Secondary outcomes: visual acuity, health status, adverse events
<p>a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes exclusively contain information on the relevant available outcomes for this benefit assessment.</p> <p>b: The arm is not relevant for the assessment and is not shown in the next tables.</p> <p>BCVA: best corrected visual acuity; DMO: diabetic macular oedema; ETDRS: Early Treatment Diabetic Retinopathy Study; IVT: intravitreal; N: number of randomized patients; 2Q4: 2.0 mg every 4 weeks; 2Q8: 2.0 mg every 8 weeks; RCT: randomized controlled trial; vs.: versus</p>						

Table 6: Characteristics of the interventions – RCT, indirect comparison: aflibercept vs. ranibizumab

Study	Intervention	Comparison	Concomitant medication
<b>Studies with aflibercept</b>			
VISTA	<p>Aflibercept 2Q8 IVT following 5 initial monthly injections, up to week 144 (from week 20: sham injection at study visits without active injection)</p> <p>+ sham laser photocoagulation (at baseline or starting in week 12 if criteria for laser retreatment<sup>a</sup> are met)</p> <p><b>Additional treatment starting in week 24<sup>b</sup>:</b></p> <ul style="list-style-type: none"> <li>active laser photocoagulation if criteria for additional treatment are met<sup>c, d</sup></li> </ul>	<p>Active laser photocoagulation at baseline, then retreatment if criteria for laser retreatment<sup>a</sup> are met (at a minimum interval of 12 weeks) up to week 144</p> <p>+ sham injection at each study visit (monthly) up to week 96</p> <p><b>Additional treatment starting in week 24<sup>b</sup>:</b></p> <ul style="list-style-type: none"> <li>aflibercept IVT if criteria for additional treatment<sup>c</sup> are met (5 initial monthly injections, then 2Q8 up to week 144)</li> </ul> <p><b>Additional treatment starting in the third year:</b></p> <ul style="list-style-type: none"> <li>patients who do not meet the criteria for additional treatment<sup>c</sup> with aflibercept in the first 2 study years can receive aflibercept IVT as needed if defined criteria are met<sup>e</sup>.</li> </ul>	<p>Study eye:</p> <ul style="list-style-type: none"> <li>any other treatment for DMO besides the study medication was prohibited in the course of the study.</li> </ul>
VIVID	<p>Aflibercept 2Q8 IVT following 5 initial monthly injections, up to week 144 (from week 20: sham injection at study visits without active injection)</p> <p>+ sham laser photocoagulation (at baseline or starting in week 12: sham laser photocoagulation if criteria for laser retreatment<sup>a</sup> are met)</p> <p><b>Additional treatment starting in week 24<sup>b</sup>:</b></p> <ul style="list-style-type: none"> <li>active laser photocoagulation if predefined criteria for additional treatment are met<sup>c, d</sup></li> </ul>	<p>Active laser photocoagulation at baseline, then retreatment if criteria for laser retreatment<sup>a</sup> are met (at a minimum interval of 12 weeks) up to week 144</p> <p>+ sham injection at each study visit (monthly) up to week 96</p> <p><b>Additional treatment starting in week 24<sup>b</sup>:</b></p> <ul style="list-style-type: none"> <li>aflibercept IVT if criteria for additional treatment<sup>c</sup> are met (5 initial monthly injection, then 2Q8 up to week 144)</li> </ul> <p><b>Additional treatment starting in the third year:</b></p> <ul style="list-style-type: none"> <li>patients can receive aflibercept IVT as needed if defined criteria<sup>e</sup> are met.</li> </ul>	<p>Study eye:</p> <ul style="list-style-type: none"> <li>any other treatment for DMO besides the study medication was prohibited in the course of the study.</li> </ul>

(continued)

Table 6: Characteristics of the interventions – RCT, indirect comparison: aflibercept vs. ranibizumab (continued)

Study	Intervention	Comparison	Concomitant medication
<b>Studies with ranibizumab</b>			
RESTORE	Ranibizumab 0.5 mg IVT on day 1, month 1, and month 2, then monthly injections until stable visual acuity is reached (at the investigator's discretion) <sup>f, g</sup> + sham laser photocoagulation according to laser treatment regimen	Active laser photocoagulation on day 1, then as needed, at a minimum interval of 12 weeks + sham injection according to ranibizumab treatment regimen <sup>g</sup>	No data
REVEAL	Ranibizumab 0.5 mg IVT on day 1, month 1, and month 2, then monthly injections until stable visual acuity is reached <sup>h</sup> . If visual acuity was stable, injections were discontinued and re-initiated if needed. + sham laser photocoagulation on day 1, then as needed, at a minimum interval of 12 weeks	Active laser photocoagulation on day 1, then as needed, at a minimum interval of 12 weeks + sham injection according to ranibizumab treatment regimen	No data
<p>a: Criteria for laser retreatment (at least 1 criterion must be met):</p> <ul style="list-style-type: none"> <li>▫ thickening of the retina at or within 500 µm of the centre of the macula</li> <li>▫ hard exudates at or within 500 µm of the centre of the macula, if associated with thickening of adjacent retina</li> <li>▫ a zone or zones of retinal thickening <math>\geq 1</math> disc area, any part of which was within 1 disc diameter of the centre of the macula</li> <li>▫ in the VIVID study, additionally to the 3 criteria mentioned above: patient benefits from laser retreatment in the opinion of the investigator</li> </ul> <p>b: If criteria for additional treatment were met, patients could receive the additional treatment as well as the allocated treatment at the same study visit.</p> <p>c: Criteria for additional treatment:</p> <ul style="list-style-type: none"> <li>▫ loss in visual acuity of <math>\geq 15</math> letters from the best previous test result due to DMO and the patient's current BCVA score is not better than the baseline score</li> <li>▫ loss in visual acuity at 2 consecutive visits at least 7 days apart of <math>\geq 10</math> letters from the best previous test result due to DMO and the patient's current BCVA score is not better than the baseline score</li> </ul> <p>d: Active laser photocoagulation could be conducted until the end of the study at a minimum interval of 12 weeks if the criteria for laser retreatment were met.</p> <p>e: Criteria for additional treatment with aflibercept in the laser arm (year 3, at least 1 had to be met):</p> <ul style="list-style-type: none"> <li>▫ increase in retinal thickness by <math>&gt; 50</math> µm compared with the lowest previous measurement</li> <li>▫ new or persistent cystic retinal changes or sub-retinal fluid or persistent diffuse oedema in the central subfield</li> <li>▫ loss in visual acuity of <math>\geq 5</math> letters compared with the best previous measurement in conjunction with any increase in retinal thickness</li> <li>▫ increase in BCVA between the current and most recent visit of <math>\geq 5</math> letters</li> </ul>			

(continued)

Table 6: Characteristics of the interventions – RCT, indirect comparison: aflibercept vs. ranibizumab (continued)

<p>f: Discontinuation of treatment if any of the following criteria was met:</p> <ul style="list-style-type: none"> <li>▫ no (further) improvement in BCVA could be attributed to IVT injection at the last 2 consecutive visits, in the opinion of the investigator, or</li> <li>▫ BCVA score <math>\geq</math> 84 letters (approximate Snellen equivalent of 20/20) at the last 2 consecutive visits</li> <li>▫ The injections were continued if needed after treatment discontinuation as soon as worsening of visual acuity due to DMO was observed until visual acuity was stable again (at least 2 injections).</li> </ul> <p>g: The (sham) injection was administered at least 30 minutes after (sham) laser photocoagulation.</p> <p>h: Assessed with the BCVA measured with the ETDRS chart and the DMO progression status.</p> <p>BCVA: best corrected visual acuity; DMO: diabetic macular oedema; ETDRS: Early Treatment Diabetic Retinopathy Study; IVT: intravitreal; 2Q8: 2.0 mg every 8 weeks; RCT: randomized controlled trial; vs.: versus</p>
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### Aflibercept studies VISTA and VIVID

The aflibercept studies VISTA and VIVID were 2 ongoing, randomized, active-controlled, double-blind, multicentre phase 3 studies. Adult patients with visual impairment due to DMO, involving the centre of the macula (fovea centralis) were enrolled.

In both studies, patients were randomly assigned to treatment with aflibercept 2 mg (IVT injection) every 4 weeks (N = 156), aflibercept 2 mg (IVT injection) every 8 weeks following 5 initial injections (N = 154), or laser photocoagulation (N = 156). In each case, one eye was defined as the study eye. Randomization was stratified in both studies (VISTA: myocardial infarction and/or cerebrovascular event; VIVID: Japan versus Europe/Australia).

Treatment with aflibercept 2 mg every 4 weeks does not comply with the approved therapeutic regimen of aflibercept and was therefore not considered further in the benefit assessment. Treatment with aflibercept 2 mg following 5 initial monthly injections every 8 weeks in both studies complies with the approved use [4]. After the 5 initial injections, a sham injection was administered at study visits without active injection. The sham injections were given without intraocular penetration. Besides these sham injections, patients also received sham laser treatment at baseline and possibly at 12-week intervals, according to the criteria for active laser photocoagulation described below. Patients in the control arm received active treatment with laser photocoagulation based on the ETDRS recommendations. Treatments were performed at an interval of 12 weeks. Retreatment was only performed if the criteria for retreatment were fulfilled (see Table 6). Sham injections were performed at baseline and at every study visit (or, in the third study year, aflibercept injections if needed).

Any other treatment for DMO besides the respective study medication was prohibited in the course of the study.

Starting in week 24, active additional treatments could be given to all patients. Patients from the intervention arm could receive active laser photocoagulation, and patients from the control arm could receive additional aflibercept injections. Certain criteria had to be fulfilled for this

additional treatment (see Table 6). The allocated study treatment was continued. This additional treatment was taken into account in the assessment of the risk of bias.

The primary outcome for both studies was the mean change in best corrected visual acuity (BCVA) after 52 weeks.

The studies included a treatment phase from day 1 to week 144. Both studies are ongoing and will probably end in the first quarter of 2015. The primary analysis was conducted after 52 weeks. These data were used for the benefit assessment.

### **Ranibizumab studies RESTORE and REVEAL**

The ranibizumab studies RESTORE and REVEAL were randomized, active-controlled, double-blind, multicentre phase 3 studies with a study duration of 12 months. The REVEAL study was only conducted in Asian centres. Adult patients with visual impairment due to focal or diffuse DMO were included.

The patients in the 2 studies were randomized to ranibizumab 0.5 mg (IVT injection), ranibizumab 0.5 mg (IVT injection) plus laser photocoagulation, or to laser photocoagulation. In each case, one eye was defined as the study eye. The study arm with ranibizumab 0.5 mg alone and the study arm with laser photocoagulation were relevant for the benefit assessment and are therefore considered further. In the RESTORE study, 116 patients were randomized to ranibizumab, and 111 patients to laser photocoagulation. The corresponding patient numbers in the REVEAL study were 133 and 131. Only little information was available on the process of randomization for the REVEAL study (see Section 2.6.2.5.2 of the full dossier assessment).

Ranibizumab was administered in compliance with the approval [5]. The patients in the studies initially received 3 consecutive monthly IVT injections with 0.5 mg ranibizumab, followed by further monthly injections according to the criteria for retreatment (see Table 6). Additional sham laser treatments were performed at least at an interval of 12 weeks.

Patients in the control arm received active treatment with laser photocoagulation. Retreatments were performed as needed at an interval of at least 12 weeks. The patients also received sham injections analogous to the criteria of the intervention group. No information on concomitant medication was available.

Additional treatments, which were allowed in the aflibercept studies, were not administered in the studies RESTORE and REVEAL.

The primary outcome in both studies was the mean change in BCVA at week 52.

The randomized phase of the RESTORE study was followed by a 24-month open-label extension phase. All patients received 0.5 mg ranibizumab (IVT injections) if needed at

monthly intervals until visual acuity was stable (no more than 24 injections) and could receive additional laser photocoagulation treatment.

There was no full publication for the REVEAL study, but data from the trial registry “clinicaltrials.gov” (NCT00989989) [6] and an abstract [7].

### **Similarity of the aflibercept and the ranibizumab studies**

The available data on the study and intervention characteristics of the 4 studies VISTA, VIVID, RESTORE and REVEAL showed that the studies are similar (e.g. study design, treatment duration, interventions, outcomes), but that there are also differences. The aflibercept studies specifically included patients with visual impairment due to DMO with involvement of the fovea. This was not the case in the ranibizumab studies, but it can be assumed that the majority of the patients in the RESTORE and REVEAL study had foveal involvement (see Section 2.6.2.5.1 of the full dossier assessment). The interventions appeared to be sufficiently similar; however, there were partly differences in the criteria for retreatment or the information was described at different levels of detail. There were partly differences in geographical regions where the studies were conducted. The VIVID study was also conducted in Japan, and the REVEAL study exclusively in Asia. However, there was no information on whether this influenced the results. The greater problem appeared to be that only little information on the randomization process was available for the REVEAL study, and that additional treatments could be administered in the aflibercept studies, which was not the case in the ranibizumab studies. The resulting differences between the studies were addressed with corresponding methods (sensitivity analyses or LOCF analysis, see Sections 2.6.2.5.2 and 2.6.2.5.3 of the full dossier assessment) so that the studies could be included in the adjusted indirect comparison, but uncertainties remained.

Overall, the study and intervention characteristics were considered to be sufficiently similar for an adjusted indirect comparison.

Table 7 shows the characteristics of the patients in the studies included.

Table 7: Characteristics of the study populations – RCT, indirect comparison: aflibercept vs. ranibizumab

Study	Studies with aflibercept				Studies with ranibizumab			
	VISTA		VIVID		RESTORE		REVEAL	
Characteristics category	Aflibercept N = 151	Laser N = 154	Aflibercept N = 135	Laser N = 132	Ranibizumab N = 116	Laser N = 111	Ranibizumab N = 133	Laser N = 131
Age [years], mean (SD)	63 (9)	62 (9)	64 (8)	64 (9)	63 (9)	64 (9)	61 (9)	62 (10)
Sex [F/M], %	48/52	45/55	35/65	41/59	37/63	48/52	39/61	43/57
Origin, n (%)								
White	125 (82.8)	131 (85.1)	106 (78.5)	106 (80.3)	ND	ND	0 (0)	0 (0)
Black	19 (12.6)	16 (10.4)	1 (0.7)	1 (0.8)	ND	ND	0 (0)	0 (0)
Asian	2 (1.3)	3 (1.9)	27 (20.0)	25 (18.9)	ND	ND	133 (100)	131 (100)
Other/not reported	5 (3.3) <sup>a</sup>	4 (2.6) <sup>a</sup>	1 (0.7)	0 (0)	ND	ND	0 (0)	0 (0)
BMI, mean (SD)	32.0 (7.1)	31.9 (7.3)	28.8 (5.1)	28.7 (5.2)	ND	ND	ND	ND
HbA1c, mean (SD)	7.9 (1.6)	7.6 (1.7)	7.7 (1.4)	7.7 (1.3)	7.2 (1.1)	7.5 (1.1)	ND <sup>b</sup>	ND <sup>b</sup>
Duration of diabetic disease [years], mean (SD)	17.6 (11.5)	17.2 (9.6)	14.1 (8.9) <sup>c</sup>	14.5 (9.8) <sup>c</sup>	15.2 (9.9)	12.9 (9.0)	ND	ND
Type of diabetes, n (%)								
Type 1	10 (6.6)	14 (9.1)	ND	ND	13 (11.2)	13 (11.7)	ND <sup>d</sup>	ND <sup>d</sup>
Type 2	141 (93.4)	140 (90.9)	ND	ND	103 (88.8)	97 (87.4)	ND <sup>d</sup>	ND <sup>d</sup>
insulin-dependent	73 (48.3)	77 (50.0)	ND	ND	ND	ND	ND <sup>d</sup>	ND <sup>d</sup>
non-insulin-dependent	65 (43.0)	60 (39.0)	ND	ND	ND	ND	ND <sup>d</sup>	ND <sup>d</sup>
not recorded	3 (2.0)	3 (1.9)	ND	ND	ND	ND	ND <sup>d</sup>	ND <sup>d</sup>

(continued)

Table 7: Characteristics of the study populations – RCT, indirect comparison: aflibercept vs. ranibizumab (continued)

Study	Studies with aflibercept				Studies with ranibizumab			
	VISTA		VIVID		RESTORE		REVEAL	
Characteristics category	Aflibercept N = 151	Laser N = 154	Aflibercept N = 135	Laser N = 132	Ranibizumab N = 116	Laser N = 111	Ranibizumab N = 133	Laser N = 131
Pretreatment of DMO, n (%)	108 (71.5)	101 (65.6)	ND	ND	ND	ND	ND	ND
IVT anti-VEGF treatment	68 (45)	63 (40.9)	15 (11.1)	13 (9.8)	ND	ND	ND	ND
IVT steroids	42 (27.8)	31 (20.1)	ND	ND	ND	ND	ND	ND
Laser photocoagulation	80 (53.0)	77 (50.0)	83 (61.5)	75 (56.4)	60 (52.2) <sup>a</sup>	47 (42.7) <sup>a</sup>	ND	ND
No pretreatment	43 (28.5)	53 (34.4)	ND	ND	ND	ND	ND	ND
Type of DMO, n (%)								
Focal <sup>e</sup>	ND	ND	ND	ND	64 (55.2)	53 (47.7)	ND	ND
Diffuse <sup>f</sup>	ND	ND	ND	ND	45 (38.8)	52 (46.8)	ND	ND
Not recorded	ND	ND	ND	ND	7 (6.0)	6 (5.4)	ND	ND
BCVA [letters], mean (SD)	59.4 (10.9)	59.7 (11.0)	58.8 (11.2)	60.8 (10.6)	64.8 (10.1)	62.4 (11.1)	ND <sup>g</sup>	ND <sup>g</sup>
CRT [µm], mean (SD)	479.0 (154.0)	483.4 (152.9)	518.4 (147.4)	540.3 (152.4)	426.6 (118.0)	412.4 (124.0)	ND <sup>h</sup>	ND <sup>h</sup>
Treatment discontinuations, n (%)	10 (6.5)	11 (7.1)	15 (11.1)	20 (14.8)	14 (12.1)	13 (11.7)	10 (7.5)	23 (17.6)

(continued)

Table 7: Characteristics of the study populations – RCT, indirect comparison: aflibercept vs. ranibizumab (continued)

a: Institute's calculation.

b: Mean HbA1c for the total population of the study: 7.5%.

c: Data available for 99 aflibercept patients and for 105 laser patients.

d: A total of 98.7% patients with type 2 diabetes were included in all study arms.

e: Focal DMO: More than 67% of the leakage, or 30%-67% of the leakage, was caused by leaking microaneurysms in the total area of the oedema. However, more than 67% of the leakage was caused by microaneurysms in the central subfield.

f: Diffuse DMO: Less than 33% of the leakage was caused by leaking microaneurysms. The rest was caused by diffuse leaking capillaries in the whole area of the oedema, or 30%-67% of the leakage was caused by microaneurysms. However, < 33% of the leakage was caused by microaneurysms in the central subfield.

g: Mean BCVA over all study arms: 58.6 letters.

h: Mean CRT over all study arms: 421.9 µm.

BCVA: best corrected visual acuity; BMI: body mass index; CRT: central retinal thickness; DMO: diabetic macular oedema; F: female; HbA1c: haemoglobin A1c; IVT: intravitreal; M: male; N: number of randomized patients, values that are based on other patient numbers are marked in the corresponding column if the deviation is relevant; n: number of patients in the category; ND: no data; RCT: randomized controlled trial; SD: standard deviation; VEGF: vascular endothelial growth factor; vs.: versus

The baseline characteristics of the patients were only available for few characteristics for all studies. The mean age in the studies was between 62 and 64 years. Men and women were included in all studies but their proportions in the studies differed somewhat from one another. Information on origin was available for all studies except for the RESTORE study. As described above, the ranibizumab study REVEAL only included Asians, whereas the aflibercept studies VISTA and VIVID mainly included patients of white origin (in each case over 75%). On average, the patients in the VISTA study had a somewhat longer history of diabetes mellitus than the patients of the studies VIVID and RESTORE (this information was not available for REVEAL). The type of diabetes of the patients was only known for the studies VISTA and RESTORE – the majority of the patients had type 2 diabetes. If pretreatments were known for the studies, approximately half of the patients already had received laser photocoagulation. Patients in the VISTA and VIVID studies already had received anti-VEGF treatments, with the proportion being notably higher in the VISTA study (approximately 45% and 41%) than in the VIVID study (approximately 11% and 10%). Information on the type of DMO (focal or diffuse) was only available for the RESTORE study. Mean visual acuity at baseline was between 59 and 65 letters.

No important differences between the studies could be inferred from the available data. However, some information was missing so that uncertainties regarding the similarity of the studies remain. Despite the uncertainties described, the 4 studies VISTA, VIVID, RESTORE and REVEAL were overall considered to be sufficiently similar so that the assumption of similarity for an adjusted indirect comparison was not rejected.

Table 8 shows the risk of bias at study level.

Table 8: Risk of bias at study level – RCT, indirect comparison: aflibercept vs. ranibizumab

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
<b>Studies with aflibercept</b>							
VISTA	Yes	Yes	Yes	Yes	Yes	No <sup>b</sup>	High
VIVID	Yes	Yes	Yes	Yes	Yes	No <sup>c</sup>	High
<b>Studies with ranibizumab</b>							
RESTORE	Yes	Unclear <sup>a</sup>	Yes	Yes	Yes	Yes	Low
REVEAL	Unclear <sup>a</sup>	Unclear <sup>a</sup>	Yes	Yes	Yes	Yes	High
a: Insufficient information.							
b: 31.2% of the patients in the laser arm received both treatments (0.7% of the patients in the aflibercept arm).							
c: 24.1% of the patients in the laser arm received both treatments (8.1% of the patients in the aflibercept arm).							
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level was rated as high for the aflibercept studies VISTA and VIVID as well as for the ranibizumab study REVEAL. This is justified by the important proportions of patients with additional treatment in the studies VISTA and VIVID. For the REVEAL study, the available information on the process of randomization was insufficient.

The assessment of the risk of bias deviates from the company's assessment, which assessed all 4 studies as having low bias.

### 2.3.2 Results on added benefit

The following patient-relevant outcomes were considered in this assessment (for reasons, see Section 2.6.2.5.3 of the full dossier assessment):

- Mortality
  - All-cause mortality
- Morbidity
  - improvement of visual acuity by  $\geq 10$  ETDRS letters
  - worsening of visual acuity by  $\geq 10$  ETDRS letters
  - health status (EQ-5D VAS)
- Health-related quality of life
  - NEI VFQ-25
- Adverse events
  - SAEs
  - discontinuation due to AEs
  - ocular AEs
  - ocular SAEs
  - discontinuation due to ocular AEs

The choice of patient-relevant outcomes partly deviated from that of the company, which used further outcomes or operationalizations in Module 4 C of the dossier. The outcome “discontinuation due to ocular AEs” was additionally included in the benefit assessment (see Section 2.6.2.5.3 of the full dossier assessment).

Table 9 shows for which outcomes data were available in the studies included.

Table 9: Matrix of outcomes – RCT, indirect comparison: aflibercept vs. ranibizumab

Study	Outcomes									
	All-cause mortality	Improvement of visual acuity by $\geq 10$ ETDRS letters	Worsening of visual acuity by $\geq 10$ ETDRS letters	Health status (EQ-5D VAS)	Health-related quality of life (NEI VFQ-25)	SAEs	Discontinuation due to AEs	Ocular AEs <sup>a</sup>	Ocular SAEs <sup>a</sup>	Discontinuation due to ocular AEs <sup>a</sup>
<b>Studies with aflibercept</b>										
VISTA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
VIVID	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
<b>Studies with ranibizumab</b>										
RESTORE	Yes	Yes	Yes	No <sup>b</sup>	Yes	Yes	Yes	Yes	Yes	Yes
REVEAL	Yes	Yes	Yes	Yes	– <sup>c</sup>	Yes	No <sup>b</sup>	No <sup>b</sup>	No <sup>b</sup>	No <sup>b</sup>
a: Event refers to the study eye. b: No evaluable data (for reasons, see Section 2.6.2.5.3 of the full dossier assessment). c: Outcome not recorded in the study. AE: adverse event; ETDRS: Early Treatment Diabetic Retinopathy Study; NEI VFQ-25: National Eye Institute Visual Functioning Questionnaire-25; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus										

For the ranibizumab study REVEAL, data were not available for all patient-relevant outcomes. The outcome “health-related quality of life” was not recorded. For the REVEAL study, evaluable data regarding AEs were only available for the outcome “SAEs”.

The risk of bias at outcome level was not assessed for this assessment (see Section 2.6.2.5.2 of the full dossier assessment).

### 2.3.2.1 Results

Table 10 to Table 13 contain the results on the comparison of aflibercept with laser photocoagulation and on the comparison of ranibizumab with laser photocoagulation as well as the results on the adjusted indirect comparisons of aflibercept with ranibizumab based on these studies. Where necessary, the data from the company’s dossier were supplemented by the Institute’s calculations.

Due to the limited data availability on the REVEAL study, the results on all outcomes in the adjusted indirect comparison are presented both for the total study pool (with REVEAL) and for the sensitivity analyses (without REVEAL). This concurs with the company’s approach.

In case of the presence of important heterogeneity of the study results, the studies are not pooled. This deviates from the company's approach in the dossier, which investigated the heterogeneity of the pairwise comparisons included in the adjusted indirect comparison, but also pooled the studies in case of identified important heterogeneity.

Table 10: Results on all-cause mortality – RCT, indirect comparison: aflibercept vs. ranibizumab

Outcome category outcome comparison study	Aflibercept or ranibizumab		Laser photocoagulation		Group difference RR [95% CI]; p-value
	N	Patients with event n (%)	N	Patients with event n (%)	
<b>Mortality</b>					
All-cause mortality					
Aflibercept vs. laser					
VISTA	152	0 (0)	154	1 (0.6)	0.34 [0.01; 8.23]; ND
VIVID	135	4 (3.0)	133	1 (0.8)	3.94 [0.45; 34.80]; ND
Total					1.54 [0.15; 15.99]; 0.72 <sup>a</sup>
Ranibizumab vs. laser					
RESTORE	115	2 (1.7)	110	2 (1.8)	0.96 [0.14; 6.67]; ND
REVEAL	133	1 (0.8 <sup>b</sup> ) <sup>c</sup>	131	0 (0)	2.96 [0.12; 71.89] <sup>b</sup> ; NC
Total					1.30 [0.25; 6.82]; 0.758 <sup>a, b</sup>
<b>Adjusted indirect comparison<sup>d</sup>:</b>					
Aflibercept vs. ranibizumab (with REVEAL)					1.18 [0.07; 20.70]; 0.909 <sup>b</sup>
Aflibercept vs. ranibizumab (without REVEAL)					1.61 [0.08; 33.70]; ND
a: Calculated from meta-analysis.					
b: Institute's calculation.					
c: Discrepant data between publication and Module 4 C.					
d: Adjusted indirect comparison according to Bucher [8].					
CI: confidence interval; N: number of analysed patients; n: number of patients with at least one event; NC: not calculated; ND: no data; RCT: randomized controlled trial; RR: relative risk; vs.: versus					

Table 11: Results on morbidity – RCT, indirect comparison: aflibercept vs. ranibizumab

Outcome category outcome comparison study	Aflibercept or ranibizumab		Laser photocoagulation		Group difference RR [95% CI]; p-value
	N	Patients with event n (%)	N	Patients with event n (%)	
<b>Morbidity</b>					
Improvement of visual acuity by $\geq 10$ ETDRS letters					
Aflibercept vs. laser					
VISTA	151	88 (58.3)	154	30 (19.5)	2.99 [2.11; 4.24]; < 0.001 <sup>a</sup>
VIVID	135	72 (53.3)	132	34 (25.8)	2.07 [1.49; 2.88]; < 0.001 <sup>a</sup>
Total					2.48 [1.73; 3.56]; < 0.001 <sup>b</sup>
Ranibizumab vs. laser					
RESTORE	115	43 (37.4)	110	17 (15.5)	2.42 [1.47; 3.98]; < 0.001
REVEAL	133	45 (33.8)	128	17 (13.3)	2.55 [1.54; 4.21]; ND
Total					2.48 [1.74; 3.53]; < 0.001 <sup>b</sup>
<b>Indirect comparison<sup>c</sup>:</b>					
Aflibercept vs. ranibizumab (with REVEAL)					1.00 [0.60; 1.65]; ND
Aflibercept vs. ranibizumab (without REVEAL)					1.02 [0.55; 1.89]; ND
Worsening of visual acuity by $\geq 10$ ETDRS letters					
Aflibercept vs. laser					
VISTA	151	2 (1.3)	154	26 (16.9)	0.08 [0.02; 0.32]; ND
VIVID	135	3 (2.2)	132	21 (15.9)	0.14 [0.04; 0.46]; ND
Total					0.11 [0.04; 0.27]; < 0.001 <sup>b</sup>
Ranibizumab vs. laser					
RESTORE	115	4 (3.5)	110	14 (12.7)	0.27 [0.09; 0.80]; ND
REVEAL	133	4 (3.0)	128	8 (6.3)	0.48 [0.15; 1.56]; ND
Total					0.35 [0.16; 0.78]; 0.01 <sup>b</sup>
<b>Indirect comparison<sup>c</sup>:</b>					
Aflibercept vs. ranibizumab (with REVEAL)					0.31 [0.09; 1.04]; ND
Aflibercept vs. ranibizumab (without REVEAL)					0.40 [0.10; 1.66]; ND

(continued)

Table 11: Results on morbidity – RCT, indirect comparison: aflibercept vs. ranibizumab (continued)

Outcome comparison study	Aflibercept or ranibizumab			Laser photocoagulation			Group difference
	N <sup>e</sup>	Baseline values mean (SD)	Change at end of study mean <sup>f</sup> (SD)	N <sup>e</sup>	Baseline values mean (SD)	Change at end of study mean <sup>f</sup> (SD)	Mean difference [95% CI]; p-value
Health status (EQ-5D VAS)							
Aflibercept vs. laser							
VISTA	151	74.3 (17.1)	-0.3 (17.9)	154	73.5 (18.2)	-2.4 (17.6)	2.1 [-1.88; 6.08]; ND
VIVID	135	68.0 (19.4)	4.3 (16.7)	132	71.3 (19.4)	2.8 (17.2)	1.5 [-2.57; 5.57]; ND
Total <sup>g</sup>							1.81 [-1.04; 4.65] <sup>b</sup> ; ND
Ranibizumab vs. laser							
RESTORE	115	ND	2.6 (ND)	110	ND	2.4 (ND)	ND
REVEAL	129	ND	-1.1 (12.7)	125	ND	1.0 (13.9)	-2.1 [-5.4; 1.2]; ND
Total							ND
<b>Adjusted indirect comparison<sup>c, h</sup>:</b>							
Aflibercept vs. ranibizumab							3.91 [-0.43; 8.25]; ND
<p>a: Institute's calculation, unconditional exact test (CSZ method according to Andrés [9]).</p> <p>b: Calculated from meta-analysis.</p> <p>c: Adjusted indirect comparison according to Bucher [8].</p> <p>d: Institute's calculation.</p> <p>e: Number of patients considered in the analysis for the calculation of the effect estimate; the baseline values study may be based on other patient numbers.</p> <p>f: Unless stated otherwise, LOCF analysis of the FAS population.</p> <p>g: The company calculated the overall estimator from raw changes from baseline, thus deviating from the analyses primarily planned in the studies VISTA and VIVID (ANCOVA models with least square mean differences, see Section 2.6.2.5.3 of the full dossier assessment).</p> <p>h: A sensitivity analysis based on the ANCOVA models with least square mean differences primarily planned in the studies VISTA and VIVID resulted in the same qualitative conclusion (see Section 2.6.2.5.3 of the full dossier assessment).</p> <p>ANCOVA: analysis of covariance; CI: confidence interval; CSZ: convexity, symmetry, z score; ETDRS: Early Treatment Diabetic Retinopathy Study; EQ-5D: European Quality of Life-5 Dimensions; FAS: full analysis set; LOCF: last observation carried forward; N: number of analysed patients; n: number of patients with at least one event; ND: no data; RCT: randomized controlled trial; RR: relative risk; SD: standard deviation; VAS: visual analogue scale; vs.: versus</p>							

Table 12: Results on health-related quality of life – RCT, indirect comparison: aflibercept vs. ranibizumab

Outcome category comparison study	Aflibercept or ranibizumab			Laser photocoagulation			Group difference
	N <sup>a</sup>	Baseline values mean (SD)	Change at end of study mean <sup>b</sup> (SD)	N <sup>a</sup>	Baseline values mean (SD)	Change at end of study mean <sup>b</sup> (SD)	Mean difference [95% CI]; p-value
<b>Health-related quality of life</b>							
NEI VFQ-25 total score							
Aflibercept vs. laser							
VISTA	147	70.5 (17.10)	6.8 (11.92)	151	68.7 (18.06)	4.8 (14.13)	2.0 [-0.97; 4.97]; ND
VIVID	134	71.2 (17.84)	5.3 (10.87)	120	77.4 (15.16)	2.3 (10.06)	3.0 [0.41; 5.59]; ND
Total <sup>c</sup>							2.57 [0.62; 4.52] <sup>d</sup> ; ND
Ranibizumab vs. laser							
RESTORE	114	72.8 (16.9)	5.0 (13.0)	108	73.5 (18.2)	0.6 (12.6)	4.4 [1.0; 7.8]; 0.014
REVEAL		ND	ND		ND	ND	ND
Total							ND
<b>Adjusted indirect comparison<sup>e, f</sup>:</b>							
Aflibercept vs. ranibizumab							-1.83 [-5.73; 2.06]; ND
<p>a: Number of patients considered in the analysis for the calculation of the effect estimate; the baseline values may be based on other patient numbers.</p> <p>b: Unless stated otherwise, LOCF analysis of the FAS population.</p> <p>c: The company calculated the overall estimator from raw changes from baseline, thus deviating from the analyses primarily planned in the studies VISTA and VIVID (ANCOVA models with least square mean differences, see Section 2.6.2.5.3 of the full dossier assessment).</p> <p>d: Calculated from meta-analysis.</p> <p>e: Adjusted indirect comparison according to Bucher [8].</p> <p>f: A sensitivity analysis based on the ANCOVA models with least square mean differences primarily planned in the studies VISTA and VIVID resulted in the same qualitative conclusion.</p> <p>ANCOVA: analysis of covariance; CI: confidence interval; FAS: full analysis set; LOCF: last observation carried forward; N: number of analysed patients; ND: no data; NEI VFQ-25: National Eye Institute Visual Functioning Questionnaire-25; RCT: randomized controlled trial; RR: relative risk; SD: standard deviation; vs.: versus</p>							

Table 13: Results on AEs – RCT, indirect comparison: aflibercept vs. ranibizumab

Outcome category outcome comparison study	Aflibercept or ranibizumab		Laser photocoagulation		Group difference RR [95% CI]; p-value
	N	Patients with at least one event n (%)	N	Patients with at least one event n (%)	
<b>Adverse events</b>					
AEs					
Aflibercept vs. laser					
VISTA	152	139 (91.4)	154	146 (94.8)	
VIVID	135	119 (88.1)	133	112 (84.2)	
Ranibizumab vs. laser					
RESTORE	115	ND	110	ND	
REVEAL	133	ND <sup>a</sup>	128	ND <sup>a</sup>	
SAEs					
Aflibercept vs. laser					
VISTA	152	42 (27.6)	154	54 (35.1)	0.79 [0.56; 1.10]; 0.210 <sup>b</sup>
VIVID	135	30 (22.2)	133	24 (18.0)	1.23 [0.76; 1.99]; 0.498 <sup>b</sup>
Total	heterogeneity: Q = 2.24; df = 1; p = 0.134; I <sup>2</sup> = 55% <sup>c</sup>				
Ranibizumab vs. laser					
RESTORE	115	26 (22.6) <sup>d</sup>	110	17 (15.5)	1.46 [0.84; 2.54] <sup>e</sup> ; NC
REVEAL	133	21 (15.8)	128	19 (14.8)	1.06 [0.60; 1.88]; ND
Total	1.25 [0.84; 1.87]; 0.264 <sup>e, e</sup>				
<b>Adjusted indirect comparison<sup>f</sup>:</b>					
Aflibercept vs. ranibizumab (with REVEAL)					
VISTA vs. RESTORE and REVEAL					0.63 [0.37; 1.07]; 0.088 <sup>e</sup>
VIVID vs. RESTORE and REVEAL					0.98 [0.53; 1.84]; 0.949 <sup>e</sup>
Aflibercept vs. ranibizumab (without REVEAL)					
VISTA vs. RESTORE					0.54 [0.28; 1.03]; 0.064 <sup>e</sup>
VIVID vs. RESTORE					0.84 [0.40; 1.75]; 0.643 <sup>e</sup>

(continued)

Table 13: Results on AEs – RCT, indirect comparison: aflibercept vs. ranibizumab (continued)

Outcome category outcome comparison study	Aflibercept or ranibizumab		Laser photocoagulation		Group difference RR [95% CI]; p-value
	N	Patients with at least one event n (%)	N	Patients with at least one event n (%)	
Discontinuation due to AEs					
Aflibercept vs. laser					
VISTA	152	3 (2.0)	154	4 (2.6)	0.76 [0.17; 3.34]; ND
VIVID	135	4 (3.0) <sup>g</sup>	133	8 (6.0)	0.49 [0.15; 1.60] <sup>e</sup> ; NC
Total					0.58 [0.23; 1.46]; 0.250 <sup>c, e</sup>
Ranibizumab vs. laser					
RESTORE	115	7 (6.1)	110	6 (5.5)	1.12 [0.39; 3.22]; 0.860 <sup>b, e</sup>
REVEAL	133	ND	128	ND	ND
Total					ND
<b>Adjusted indirect comparison<sup>f</sup>:</b>					
Aflibercept vs. ranibizumab					0.52 [0.13; 2.11] <sup>e</sup> ; 0.358
Ocular AEs <sup>h</sup>					
Aflibercept vs. laser					
VISTA	152	87 (57.2)	154	103 (66.9)	0.86 [0.72; 1.02]; ND
VIVID	135	80 (59.3)	133	82 (61.7)	0.96 [0.79; 1.17]; ND
Total					0.90 [0.79; 1.03]; 0.12 <sup>c</sup>
Ranibizumab vs. laser					
RESTORE	115	49 (42.6)	110	43 (39.1)	1.09 [0.80; 1.49]; ND
REVEAL	133	ND	128	ND	ND
Total					ND
<b>Adjusted indirect comparison<sup>f</sup>:</b>					
Aflibercept vs. ranibizumab					0.83 [0.59; 1.16]; ND
Ocular SAEs <sup>h</sup>					
Aflibercept vs. laser					
VISTA	152	2 (1.3)	154	6 (3.9)	0.34 [0.07; 1.65]; ND
VIVID	135	3 (2.2)	133	6 (4.5)	0.49 [0.13; 1.93]; ND
Total					0.42 [0.15; 1.18]; 0.10 <sup>c</sup>
Ranibizumab vs. laser					
RESTORE	115	0 (0)	110	2 (1.8)	0.19 [0.01; 3.94]; ND
REVEAL	133	ND	128	ND	ND
Total					ND
<b>Adjusted indirect comparison<sup>f</sup>:</b>					
Aflibercept vs. ranibizumab					2.19 [0.09; 53.62]; ND

(continued)

Table 13: Results on AEs – RCT, indirect comparison: aflibercept vs. ranibizumab (continued)

Outcome category outcome comparison study	Aflibercept or ranibizumab		Laser photocoagulation		Group difference RR [95% CI]; p-value
	N	Patients with at least one event n (%)	N	Patients with at least one event n (%)	
Discontinuation due to ocular AEs <sup>h</sup>					
Aflibercept vs. laser					
VISTA	152	0 (0)	154	0 (0)	ND
VIVID	135	0 (0)	133	4 (3.0)	0.11 [0.01; 2.01] <sup>c</sup> ; 0.044 <sup>b</sup>
Total					ND
Ranibizumab vs. laser					
RESTORE	115	0 (0)	110	3 (2.7)	0.14 [0.01; 2.62] <sup>c</sup> ; 0.079 <sup>b</sup>
REVEAL		ND		ND	ND
Total					ND
<b>Adjusted indirect comparison<sup>f</sup>:</b>					
Aflibercept vs. ranibizumab					0.79 [0.02; 36.73]; 0.902 <sup>e</sup>
a: The source documents (publication, registry report) available for this study contained no SAEs in the overall rate of AEs.					
b: Institute's calculation, unconditional exact test (CSZ method according to Andrés [9]).					
c: Calculated from meta-analysis.					
d: Discrepant data between registry report and Module 4 C.					
e: Institute's calculation.					
f: Adjusted indirect comparison according to Bucher [8].					
g: Discrepant data between CSR and Module 4 C.					
h: Event refers to the study eye.					
AE: adverse event; CI: confidence interval; CSR: clinical study report; CSZ: convexity, symmetry, z score; N: number of analysed patients; n: number of patients with at least one event; NC: not calculated; ND: no data; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus					

## Mortality

### All-cause mortality

Data on deaths from all 4 studies were available for the adjusted indirect comparison. There was no statistically significant difference between aflibercept and ranibizumab for the total study pool (with REVEAL) or in the sensitivity analysis (without REVEAL). An added benefit of aflibercept in comparison with ranibizumab is therefore not proven for this outcome.

This concurs with the company's assessment. However, the company described that no data on deaths were described for the ranibizumab study REVEAL.

**Morbidity*****Improvement of visual acuity by  $\geq 10$  ETDRS letters***

There was an indication of heterogeneity for the aflibercept studies VISTA and VIVID for the outcome “improvement of visual acuity by  $\geq 10$  ETDRS letters” ( $Q = 2.27$ ;  $df = 1$ ;  $p = 0.13$ ;  $I^2 = 56\%$ , calculated from meta-analysis). Possible reasons for the heterogeneity remained unclear. Since there were large effects in the same direction both in the VISTA and in the VIVID study, the studies were still considered jointly for the indirect comparison. There was no statistically significant difference in the adjusted indirect comparison between aflibercept and ranibizumab for the total study pool (with REVEAL) or in the sensitivity analysis (without REVEAL) for the outcome “improvement of visual acuity by  $\geq 10$  ETDRS letters”. An added benefit of aflibercept in comparison with ranibizumab is therefore not proven for this outcome.

This concurs with the company’s assessment.

***Worsening of visual acuity by  $\geq 10$  ETDRS letters***

There was no statistically significant difference between aflibercept and ranibizumab both for the total study pool and in the sensitivity analysis (without REVEAL) for the outcome “worsening of visual acuity by  $\geq 10$  ETDRS letters” in the adjusted indirect comparison. An added benefit of aflibercept in comparison with ranibizumab is therefore not proven for this outcome.

This assessment deviates from the company, which derived an indication of a non-quantifiable added benefit for this outcome. The company found a statistically significant difference in favour of aflibercept in the adjusted indirect comparison for the total study pool (with REVEAL) for the odds ratio (OR) and absolute risk reduction (ARR), but not for the relative risk (RR). It no longer found statistically significant differences in its sensitivity analysis, in which it excluded the REVEAL study to examine the robustness of the results – neither for the OR nor for the ARR (also not for the RR).

***Health status (EQ-5D VAS)***

There were evaluable data for only 3 studies for the outcome “health status”, which was recorded with the VAS of the EQ-5D. There was no information on variance for the ranibizumab study RESTORE so that this study was not used for the adjusted indirect comparison. There was no statistically significant difference between aflibercept and ranibizumab for the outcome “health status” in the adjusted indirect comparison. An added benefit of aflibercept in comparison with ranibizumab is therefore not proven for this outcome.

This concurs with the company’s assessment. However, the company considered the EQ-5D VAS for health-related quality of life.

**Health-related quality of life**

Health-related quality of life was recorded with the NEI VFQ-25. Data were available for all studies except for the ranibizumab study REVEAL. There was no statistically significant difference between aflibercept and ranibizumab for the outcome “health-related quality of life” in the adjusted indirect comparison. An added benefit of aflibercept in comparison with ranibizumab is therefore not proven for this outcome.

This concurs with the company’s assessment. However, besides the NEI VFQ-25 total score, the company also selectively considered 2 NEI VFQ-25 subscales (Near Activities and Distance Activities) as well as the VAS of the EQ-5D for the outcome “health-related quality of life”.

**Adverse events**

There were evaluable data for all 4 studies only for the outcome “SAEs”. For the other outcomes on AEs considered, there were no data for the ranibizumab studies REVEAL.

***Serious adverse events***

There was an indication of important heterogeneity for the aflibercept studies VISTA and VIVID for the outcome “SAEs” ( $p = 0.134$ ). Possible reasons for the heterogeneity remained unclear. Hence the results of these studies were not pooled in a meta-analysis, but considered separately with the 2 ranibizumab studies RESTORE and REVEAL in an adjusted indirect comparison (an analogous approach was used for the sensitivity analysis without REVEAL). There was no statistically significant difference between aflibercept and ranibizumab in any of the analyses. Greater or lesser harm from aflibercept than from ranibizumab is not proven for this outcome.

This concurs with the company’s assessment. However, the company pooled the studies VISTA and VIVID in a meta-analysis despite the presence of heterogeneity and conducted the adjusted indirect comparison on the basis of the total study pool.

***Discontinuation due to adverse events***

There was no statistically significant difference between aflibercept and ranibizumab for the outcome “discontinuation due to AEs” in the adjusted indirect comparison. Greater or lesser harm from aflibercept than from ranibizumab is not proven for this outcome.

The deviation regarding the outcome “discontinuation due to AEs” deviates from the company, which described that no data on the outcome “discontinuation due to AEs” were available for the 2 ranibizumab studies and that the corresponding adjusted indirect comparison could not be conducted.

***Ocular adverse events, ocular serious adverse events, discontinuation due to ocular adverse events***

There was no statistically significant difference between aflibercept and ranibizumab for the outcomes “ocular AEs”, “ocular SAEs” and “discontinuation due to ocular AEs” in the adjusted indirect comparison. Greater or lesser harm from aflibercept than from ranibizumab is not proven for these outcomes.

This concurs with the company’s assessment. However, the company did not consider the outcome “discontinuation due to ocular AEs”.

**2.3.2.2 Subgroups and other effect modifiers**

No subgroup analyses were considered for the present benefit assessment of aflibercept (see Section 2.6.2.5.2 of the full dossier assessment). This deviates from the company, which presented subgroup analyses for the outcome “health-related quality of life”. However, it did not derive any conclusions on added benefit based on subgroups.

**2.3.3 Extent and probability of added benefit**

The derivation of extent and probability of added benefit for research question 1 at outcome level is shown below, taking into account the various outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

**2.3.3.1 Assessment of added benefit at outcome level**

The data presented in Section 2.3.2 resulted neither in proof of an added benefit nor in proof of lesser or greater harm from aflibercept in comparison with ranibizumab for patients with visual impairment due to DMO with involvement of the fovea.

Table 14 provides an overview of the results on added benefit at outcome level.

Table 14: Extent of added benefit at outcome level: aflibercept vs. ranibizumab

<b>Outcome category outcome comparison study</b>	<b>Aflibercept vs. ranibizumab effect estimate [95% CI] p-value probability<sup>a</sup></b>	<b>Derivation of extent<sup>b</sup></b>
<b>Mortality</b>		
All-cause mortality	RR: 1.18 [0.07; 20.70] <sup>c</sup> p = 0.909	Added benefit not proven
<b>Morbidity</b>		
Improvement of visual acuity by ≥ 10 ETDRS letters	RR: 1.21 [0.73; 1.98] <sup>c, d</sup> p = 0.454	Added benefit not proven
	RR: 0.83 [0.51; 1.35] <sup>c, e</sup> p = 0.453	
Worsening of visual acuity by ≥ 10 ETDRS letters	RR: 0.31 [0.09; 1.04] p = ND	Added benefit not proven
Health status (EQ-5D VAS)	RR: 3.91 [-0.43; 8.25] p = ND	Added benefit not proven
<b>Health-related quality of life</b>		
NEI VFQ-25 total score	RR: -1.83 [-5.73; 2.06] p = ND	Added benefit not proven
<b>Adverse events</b>		
SAEs	RR: 0.63 [0.37; 1.07] <sup>c, d</sup> p = 0.088	Greater/lesser harm not proven
	RR: 0.98 [0.53; 1.84] <sup>c, e</sup> p = 0.949	
Discontinuation due to AEs	RR: 0.52 [0.13; 2.11] <sup>c</sup> p = 0.358	Greater/lesser harm not proven
Ocular AEs <sup>f</sup>	RR: 0.83 [0.59; 1.16] p = ND	Greater/lesser harm not proven
Ocular SAEs <sup>f</sup>	RR: 2.19 [0.09; 53.62] p = ND	Greater/lesser harm not proven
Discontinuation due to ocular AEs <sup>f</sup>	RR: 0.79 [0.02; 36.73] <sup>c</sup> p = 0.902	Greater/lesser harm not proven
<p>a: Probability provided if statistically significant differences were present.  b: Estimations of effect size are made depending on the outcome category with different limits based on the CI<sub>u</sub>.  c: Institute's calculation.  d: Separate consideration of the studies because of heterogeneous results between the aflibercept studies: effect estimate applies to VISTA vs. ranibizumab.  e: Separate consideration of the studies because of heterogeneous results between the aflibercept studies: effect estimate applies to VIVID vs. ranibizumab.  f: Result refers to the study eye.  AE: adverse event; CI: confidence interval; CI<sub>u</sub>: upper limit of CI; EQ-5D: European Quality of Life-5 Dimensions; ETDRS: Early Treatment Diabetic Retinopathy Study; ND: no data; NEI VFQ-25: National Eye Institute Visual Functioning Questionnaire-25; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus</p>		

### 2.3.3.2 Overall conclusion on added benefit

Overall, neither positive nor negative effects remain for aflibercept on the basis of the available results.

In summary, there is no proof of an added benefit of aflibercept versus the ACT ranibizumab for patients with visual impairment due to DMO with involvement of the fovea.

This deviates from the company's approach, which derived an indication of non-quantifiable added benefit.

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

### 2.3.4 List of included studies

First the sources are presented that only refer to the respective study included, then the sources are presented that refer to several of the studies included.

#### VISTA

Bayer HealthCare. A double-masked, randomized, active-controlled, phase 3 study of the efficacy and safety of intravitreal administration of VEGF Trap-Eye in patients with diabetic macular edema: study 14299; clinical study report [unpublished]. 2013.

Regeneron Pharmaceuticals. A double-masked, randomized, active-controlled, phase 3 study of the efficacy and safety of intravitreal administration of VEGF trap-eye in patients with diabetic macular edema: study VGFT-OD-1009.03; statistical analysis plan; final [unpublished]. 2013.

Regeneron Pharmaceuticals. A double-masked, randomized, active-controlled, phase 3 study of the efficacy and safety of intravitreal administration of VEGF Trap-Eye in patients with diabetic macular edema: study VGFT-OD-1009; clinical study protocol [unpublished]. 2013.

Regeneron Pharmaceuticals. Study of intravitreal administration of VEGF Trap-Eye (BAY86-5321) in patients with diabetic macular edema (VISTA DME): full text view [online]. In: Clinicaltrials.gov. 11 February 2014 [accessed: 19 August 2014]. URL: <http://www.clinicaltrials.gov/ct2/show/NCT01363440>.

#### VIVID

Bayer. VEGF Trap-Eye in vision impairment due to DME (VIVID-DME) [online]. In: Clinicaltrials.gov. 30 April 2014 [accessed: 20 May 2014]. URL: <http://www.clinicaltrials.gov/ct2/show/NCT01331681>.

Bayer HealthCare. A randomized, double masked, active controlled, phase III study of the efficacy and safety of repeated doses of intravitreal VEGF Trap-Eye in subjects with diabetic macular edema: study 91745; clinical study report [unpublished]. 2013.

Bayer HealthCare. A randomized, double masked, active controlled, phase III study of the efficacy and safety of repeated doses of intravitreal VEGF Trap-Eye in subjects with diabetic macular edema: study 91745; documentation of statistical methods [unpublished]. 2013.

Bayer HealthCare. A randomized, double masked, active controlled, phase III study of the efficacy and safety of repeated doses of intravitreal VEGF Trap-Eye in subjects with diabetic macular edema: study 91745; final protocol, including any amendments [unpublished]. 2013.

## **RESTORE**

Mitchell P, Bandello F, Schmidt-Erfurth U, Lang GE, Massin P, Schlingemann RO et al. Supplemental material for "The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmology* 2011; 118(4): 615-25": appendix 1-4 [online]. 2011 [accessed: 7 November 2014]. URL: <http://www.aaojournal.org/cms/attachment/2020137131/2039955369/mmc8.pdf>.

Mitchell P, Bressler N, Tolley K, Gallagher M, Petrillo J, Ferreira A et al. Patient-reported visual function outcomes improve after ranibizumab treatment in patients with vision impairment due to diabetic macular edema: randomized clinical trial. *JAMA Ophthalmol* 2013; 131(10): 1339-1347.

Mitchell P, Bressler N, Tolley K, Gallagher M, Petrillo J, Ferreira A et al. Supplementary online content for "Patient-reported visual function outcomes after ranibizumab treatment. *JAMA Ophthalmol* 2013; 131(10): 1339-1347" [online]. 2013 [accessed: 7 November 2014]. URL: [http://archophth.jamanetwork.com/data/Journals/OPHTH/927866/EOI130142suppl1\\_prod.pdf](http://archophth.jamanetwork.com/data/Journals/OPHTH/927866/EOI130142suppl1_prod.pdf).

Novartis. A 12 month core study to assess the efficacy and safety of ranibizumab (intravitreal injections) in patients with visual impairment due to diabetic macular edema and a 24 month open-label extension study (RESTORE): full text view [online]. In: *Clinicaltrials.gov*. 26 March 2013 [accessed: 25 February 2014]. URL: <http://www.clinicaltrials.gov/ct2/show/study/NCT00687804>.

Novartis. An open-label, multi-center, 24-month extension study to evaluate the safety of ranibizumab as symptomatic treatment for visual impairment due to diabetic macular edema in patients who have completed the RESTORE trial [online]. In: *Novartis Clinical Trial Results Database*. 17 January 2013 [accessed: 18 November 2014]. URL: <http://www.novctrd.com/ctrdWebApp/clinicaltrialrepository/displayFile.do?trialResult=7803>.

Novartis Pharma. A 12 month core study to assess the efficacy and safety of ranibizumab (intravitreal injections) in patients with visual impairment due to diabetic macular edema and a 24 month open-label extension study (RESTORE): study results [online]. In: *Clinicaltrials.gov*. 26 March 2013 [accessed: 25 June 2014]. URL: <http://www.clinicaltrials.gov/ct2/show/results/NCT00687804>.

## **REVEAL**

Fong AH, Lai TY. Long-term effectiveness of ranibizumab for age-related macular degeneration and diabetic macular edema. *Clin Interv Aging* 2013; 8: 467-483.

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## 2.4 Research question 2: patients with visual impairment due to DMO without involvement of the fovea

### 2.4.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study lists on aflibercept (studies completed up to 6 August 2014)
- bibliographical literature search on aflibercept (last search on 24 June 2014)
- search in trial registries for studies on aflibercept (last search on 27 June 2014)
- bibliographical literature search on the ACT (last search on 24 June 2014)
- search in trial registries for studies on the ACT (last search on 27 June 2014)

To check the completeness of the study pool:

- bibliographical literature search on aflibercept (last search on 2 October 2014)
- search in trial registries for studies on aflibercept (last search on 2 October 2014)
- bibliographical literature search on the ACT (last search on 2 October 2014)
- search in trial registries for studies on the ACT (last search on 2 October 2014)

No additional relevant study was identified from the check.

### 2.4.2 Results on added benefit

The company presented no data for the assessment of the added benefit in the research question on patients with visual impairment due to DMO **without** involvement of the fovea.

### 2.4.3 Extent and probability of added benefit

Since the company submitted no data for patients with visual impairment due to DMO **without** involvement of the fovea, an added benefit of aflibercept versus the ACT is not proven for this research question.

This deviates from the company's approach, which did not consider the patient group with visual impairment due to DMO **without** involvement of the fovea.

The G-BA decides on the added benefit.

## 2.5 Extent and probability of added benefit – summary

The result of the benefit assessment of aflibercept in comparison with the ACT is shown in Table 15.

Table 15: Extent and probability of the added benefit of aflibercept

Subindication	ACT	Extent and probability of added benefit
Patients with visual impairment due to DMO <b>with</b> involvement of the fovea <sup>a</sup>	Ranibizumab	Added benefit not proven
Patients with visual impairment due to DMO <b>without</b> involvement of the fovea <sup>a</sup>	Focal/grid laser photocoagulation	Added benefit not proven
a: The presence of a clinically significant macular oedema according to the ETDRS criteria is assumed. ACT: appropriate comparator therapy; DMO: diabetic macular oedema; ETDRS: Early Treatment Diabetic Retinopathy Study		

The conclusion on added benefit deviates from that of the company, which derived an indication of non-quantifiable added benefit for patients with visual impairment due to DMO **with** involvement of the fovea, and which did not consider patients with visual impairment due to DMO **without** involvement of the fovea.

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Please see full dossier assessment for full reference list.

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