

IQWiG Reports – Commission No. A13-36

Aflibercept (Eylea, new therapeutic indication) – Benefit assessment according to §35a Social Code Book V¹

Extract

¹ Translation of Sections 2.1 to 2.6 of the dossier assessment *Aflibercept (Eylea, neues Anwendungsgebiet) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 19 December 2013). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:

Institute for Quality and Efficiency in Health Care

Topic:

Aflibercept (Eylea, new therapeutic indication) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:

Federal Joint Committee

Commission awarded on:

24 September 2013

Internal Commission No.:

A13-36

Address of publisher:

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Keywords: aflibercept, retinal vein occlusion, macular edema, benefit assessment

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Table of contents

| | Page |
|---|-----------|
| List of tables..... | iv |
| List of figures | v |
| List of abbreviations..... | vi |
| 2 Benefit assessment | 1 |
| 2.1 Executive summary of the benefit assessment..... | 1 |
| 2.2 Research question | 3 |
| 2.3 Information retrieval and study pool..... | 4 |
| 2.3.1 Information retrieval..... | 4 |
| 2.3.2 Characteristics of the studies and of the interventions of the studies COPERNICUS, GALILEO and CRUISE..... | 4 |
| 2.3.3 Use of aflibercept and ranibizumab not approval-compliant | 10 |
| 2.3.4 Additional comments on the indirect comparison..... | 13 |
| 2.3.5 Summary | 14 |
| 2.4 Results on added benefit..... | 14 |
| 2.5 Extent and probability of added benefit, patient groups with therapeutically important added benefit | 14 |
| 2.6 List of included studies | 15 |
| References for English extract | 15 |

List of tables³

| | Page |
|--|------|
| Table 2: Aflibercept: extent and probability of added benefit | 3 |
| Table 3: Characteristics of the studies included – RCT, indirect comparison: aflibercept vs. ranibizumab | 5 |
| Table 4: Characteristics of the interventions – RCT, indirect comparison: aflibercept vs. ranibizumab | 7 |
| Table 5: Aflibercept: extent and probability of added benefit | 15 |

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

List of figures

| | Page |
|---|-------------|
| Figure 1: Post-hoc analysis: Time to sustained gain in visual acuity of ≥ 15 letters up to week 24 | 12 |

List of abbreviations

| Abbreviation | Meaning |
|--------------|---|
| ACT | appropriate comparator therapy |
| CRVO | central retinal vein occlusion |
| EPAR | European Public Assessment Report |
| 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 |
| RCT | randomized controlled trial |
| SGB | Sozialgesetzbuch (Social Code Book) |
| SPC | Summary of Product Characteristics |

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 abbreviated to “the company”). The dossier was sent to IQWiG on 24 September 2013.

Research question

The aim of this report was to assess the added benefit of aflibercept (Eylea) for the treatment of adults with visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO) in comparison with the appropriate comparator therapy (ACT).

The company chose ranibizumab as ACT. This choice concurred with the G-BA’s specification. The benefit assessment was conducted in comparison with ranibizumab.

The assessment was conducted based on patient-relevant outcomes and on randomized controlled trials (RCTs).

Results

The company presented no relevant data for the assessment of the added benefit of aflibercept versus the ACT.

The study pool of the company contained 3 RCTs in the relevant therapeutic indication, on the basis of which it conducted an indirect comparison between aflibercept (studies COPERNICUS and GALILEO) and ranibizumab (study CRUISE) using the common comparator “sham injection”. However, the indirect comparison was unsuitable to show the added benefit of aflibercept versus ranibizumab. The reason for this is that in the 3 studies used by the company for the indirect comparison, neither aflibercept nor ranibizumab were administered according to the German approval.

Use of aflibercept and ranibizumab not approval-compliant

In studies to investigate the added benefit, aflibercept and ranibizumab must be used in accordance with the German approval for the treatment of visual impairment due to macular oedema secondary to CRVO.

Approval of aflibercept and ranibizumab

According to the Summary of Product Characteristics (SPC) for aflibercept, after the initial injection, treatment is given monthly until visual and anatomic outcomes are stable for 3 consecutive monthly assessments (hereinafter referred to as “stable outcome”). Thereafter the need for continued treatment should be reconsidered, according to the SPC. In stable

outcome, treatment may be continued with gradually increasing treatment intervals. Additionally, the SPC for aflibercept describes that continued treatment is not recommended if there is no improvement in visual and anatomic outcomes over the course of the first 3 injections (hereinafter referred to as “treatment failure”).

The SPC for ranibizumab also specifies continued monthly treatment until maximum visual acuity is achieved. In the SPC, maximum visual acuity is defined as the patient’s visual acuity that is stable for 3 consecutive monthly assessments performed while on ranibizumab treatment (hereinafter referred to as “stable outcome”). Thereafter patients should be monitored monthly for visual acuity, according to the SPC. If there is no improvement in visual acuity over the course of the first 3 injections, continued treatment is also not recommended, according to the SPC.

Hence it can be inferred from the specifications of the SPCs cited above that at least 3 injections of aflibercept or ranibizumab are needed. The earliest point in time to determine stable outcome over the course of 3 monthly parallel assessments or treatment failure is after the administration of 3 injections.

Treatment regimen in the studies / implementation in the dossier

In contrast to the administration specified in the SPC, the treatment regimens of the first treatment phase of all 3 studies provided for 6 fixed-planned intravitreal (IVT) injections with the respective study medication up to and including week 20. Continued treatment did not depend on the course of the individual patient outcome in this study phase. Hence, this treatment regimen did not comply with the stipulations of the approvals of aflibercept and ranibizumab.

The assessment that aflibercept and ranibizumab were not administered according to their approval in the 3 studies included by the company concurred with the company’s assessment. The company itself described that, from the third month (week 12), all 3 studies it had included in the assessment of the added benefit deviated from the stipulations defined in their approval. It justified the use of the studies with the consistent continuation of the respective treatment regimen up to the time of analysis of the primary outcome after week 24, i.e. every 4 weeks, in all 3 studies. Moreover, it claimed that the sham injection as control administered in each case served as common comparator. This rationale could not be followed.

However, the company did not justify in its dossier, why it regarded the studies to be usable for the assessment of added benefit using an indirect comparison despite their lack of compliance with the approval. It also did not present in the dossier any analyses on responders (stable outcome for 3 monthly assessments) or non-responders (no improvement over the course of 3 injections) in the course of the studies. Such analyses could facilitate an assessment of how large the proportion of patients in the studies included by the company was for whom monthly administration of the respective drug during the course of the first treatment phase or treatment discontinuation would have been required anyway.

Conclusion

Overall, it remained unclear for all 3 studies, how many patients with stable outcome eventually received unnecessary injections outside the approval because of the fixed-planned 6 injections, or how many patients received continued treatment that did not comply with the approval after treatment failure. This means at the same time that it cannot be determined which proportion of patients as a whole – despite the fixed-planned 6 injections due to unstable course of the individual outcome over the course of all assessments of the first 24 weeks – were treated within the approval.

It is therefore not possible to conclude to what extent the treatment actually administered in the studies deviated from the stipulations of the approval. Hence the indirect comparison conducted by the company on the basis of the 3 studies is unsuitable to assess the added benefit of aflibercept versus ranibizumab.

Extent and probability of added benefit, patient groups with therapeutically important added benefit⁴

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:

Table 2: Aflibercept: extent and probability of added benefit

| Therapeutic indication | ACT ^a | Extent and probability of added benefit |
|--|---|---|
| Treatment of adults with visual impairment due to macular oedema secondary to CRVO | Dexamethasone (intravitreal implant), ranibizumab | Added benefit not proven |

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specifications of the ACT, could choose an ACT from several options, the respective choice of the company is printed in **bold**.

ACT: appropriate comparator therapy; CRVO: central retinal vein occlusion; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

2.2 Research question

The aim of this report was to assess the added benefit of aflibercept (Eylea) for the treatment of adults with visual impairment due to macular oedema secondary to CRVO in comparison with the ACT.

⁴ 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].

The company chose ranibizumab as ACT. This choice concurred with the G-BA's specification. The benefit assessment was conducted in comparison with ranibizumab.

The assessment was conducted based on patient-relevant outcomes and on RCTs.

Further information about the research question can be found in Module 3, Section 3.1, and Module 4, Section 4.2.1 of the dossier, and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

2.3 Information retrieval and study pool

2.3.1 Information retrieval

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

Sources of the company in the dossier:

- study list on aflibercept (studies completed up to 29 August 2013)
- bibliographical literature search on aflibercept (last search on 20 August 2013)
- search in trial registries for studies on aflibercept (last search on 29 August 2013)
- bibliographical literature search on the ACT (last search on 20 August 2013)
- search in trial registries for studies on the ACT (last search on 29 August 2013)

The Institute's own search to check the completeness of the study pool:

- search in trial registries for studies on aflibercept (last search on 10 October 2013)
- search in trial registries for studies on the ACT (last search on 10 October 2013)

No study that directly compared aflibercept with ranibizumab in the relevant therapeutic indication was identified from the steps of information retrieval mentioned.

Three RCTs in the relevant therapeutic indication (COPERNICUS [3], GALILEO [4], CRUISE [5,6]) were identified in the check of the company's search for conducting an indirect comparison between aflibercept and ranibizumab using the common comparator "sham injection" used by the company. The 2 studies COPERNICUS and GALILEO compared aflibercept with sham injection, and the CRUISE study compared ranibizumab with sham injection. These studies concurred with the study pool of the company.

However, all 3 studies were unsuitable for the assessment of the added benefit of aflibercept in comparison with the ACT specified by the G-BA.

2.3.2 Characteristics of the studies and of the interventions of the studies COPERNICUS, GALILEO and CRUISE

Table 3 and Table 4 describe the characteristics of the studies and of the interventions of the studies COPERNICUS, GALILEO and CRUISE.

Table 3: 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^a |
|---------------------------------------|---|---|---|---|--|---|
| Aflibercept vs. sham injection | | | | | | |
| COPERNICUS | RCT, double-blind ^b , controlled, parallel | Adult patients with visual impairment due to macular oedema secondary to CRVO | 1) 2 mg aflibercept IVT (N = 115) 2) sham injection (N = 74) | <ul style="list-style-type: none"> ▪ Screening phase: day -21 to day -1 ▪ Treatment phase I: day 0 to week 20 ▪ Treatment phase II: week 24–48 ▪ Extension phase: week 52–100 | Period of study: 8 Jul 2009–4 Apr 2012 Locations of study: India, Israel, Canada, Columbia, USA | Primary outcome: proportion of patients with improvement of the visual acuity by ≥ 15 letters (after 24 weeks) Secondary outcomes: morbidity, health-related quality of life, adverse events |
| GALILEO | RCT, double-blind ^c , controlled, parallel | Adult patients with visual impairment due to macular oedema secondary to CRVO | 1) 2 mg aflibercept IVT (N = 106) 2) sham injection (N = 71) | <ul style="list-style-type: none"> ▪ Screening phase: day -21 to day 0 ▪ Treatment phase I: day 1 to week 20 ▪ Treatment phase II: week 24–48 ▪ Extension phase: week 52–76 | Period of study: 28 Oct 2009–1 Feb 2012 Locations of study: Australia, Germany, France, Italy, Japan, Latvia, Austria, Singapore, South Korea and Hungary | Primary outcome: proportion of patients with improvement of the visual acuity by ≥ 15 letters (after 24 weeks) Secondary outcomes: morbidity, health-related quality of life, adverse events |

(continued)

Table 3: 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^a |
|---------------------------------------|---|---|--|---|--|---|
| Ranibizumab vs. sham injection | | | | | | |
| CRUISE | RCT, double-blind ^d , controlled, parallel | Adult patients with visual impairment due to macular oedema secondary to CRVO | 1) 0.3 mg ranibizumab IVT (N = 132) ^e 2) 0.5 mg ranibizumab IVT (N = 130) 3) sham injection (N = 130) | ▪ Screening phase: day -28 to day -1 ▪ Treatment phase I: day 0 to week 20 ▪ Treatment phase II: week 24–48 | Period of study: Jul 2007–Dec 2009 Location of study: USA | Primary outcome: mean change in BCVA (after 24 weeks) Secondary outcomes: morbidity, health-related quality of life, adverse events |

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes contain exclusively information on relevant available outcomes for the present benefit assessment.

b: Up to week 52.

c: Entire study duration.

d: Up to week 24.

e: The dosage did not concur with the approval and was not relevant for the assessment.

BCVA: best corrected visual acuity; CRVO: central retinal vein occlusion; IVT: intravitreal; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 4: Characteristics of the interventions – RCT, indirect comparison: aflibercept vs. ranibizumab

| Study | Intervention | Comparison | Concomitant medication |
|---------------------------------------|--|------------|---|
| Aflibercept vs. sham injection | | | |
| COPERNICUS | <p><i>Treatment phase I:</i> day 0–wk 20, recording of outcomes wk 24^a; fixed treatment every 4 wks</p> <ul style="list-style-type: none"> ▪ 2 mg aflibercept IVT ▪ sham injection <p><i>Treatment phase II:</i> wk 24–48, recording of outcomes wk 52^a; study visits every 4 wks</p> <ul style="list-style-type: none"> ▪ unstable outcome (≥ 1 retreatment criterion^b met): 2 mg aflibercept IVT ▪ stable outcome (no retreatment criterion^b met): sham injection ▪ unstable outcome (≥ 1 retreatment criterion^b met): 2 mg aflibercept IVT ▪ stable outcome (no retreatment criterion^b met): sham injection <p><i>Extension phase:</i> wk 52–88, recording of outcomes wk 100^a; study visits every 12 wks (every 4 wks maximum if needed)</p> <ul style="list-style-type: none"> ▪ ≥ 1 retreatment criterion^b met: 2 mg aflibercept IVT ▪ ≥ 1 retreatment criterion^b met: 2 mg aflibercept IVT | | <p>In each study phase: possibility of panretinal photocoagulation if clinically relevant neovascularization developed</p> <p>Not allowed: topical drugs applied to the study eye/non-study eye</p> |
| GALILEO | <p><i>Treatment phase I:</i> day 1–wk 20, recording of outcomes wk 24^a; fixed treatment every 4 wks</p> <ul style="list-style-type: none"> ▪ 2 mg aflibercept IVT ▪ sham injection <p><i>Treatment phase II:</i> wk 24–48, recording of outcomes wk 52^a; study visits every 4 wks</p> <ul style="list-style-type: none"> ▪ deterioration (≥ 1 retreatment criterion of 1–3^b met): 2 mg aflibercept IVT ▪ improvement (retreatment criterion 4^b met): same treatment as the one that caused the improvement ▪ stable outcome (no retreatment criterion^b met): sham injection ▪ sham injection every 4 wks | | <p>In each study phase: possibility of panretinal photocoagulation if clinically relevant neovascularization developed</p> <p>Not allowed: topical drugs applied to the study eye</p> |

(continued)

Table 4: Characteristics of the interventions – RCT, indirect comparison: aflibercept vs. ranibizumab (continued)

| Study | Intervention | Comparison | Concomitant medication |
|--|--|--|------------------------|
| <i>Extension phase:</i> wk 52-68, recording of outcomes wk 76 ^a ; study visits every 8 wks | | | |
| | <ul style="list-style-type: none"> ▪ deterioration (≥ 1 retreatment criterion of 1–3^b met): 2 mg aflibercept IVT ▪ improvement (retreatment criterion 4^b met): same treatment as the one that caused the improvement ▪ stable outcome (no retreatment criterion^b met): sham injection ▪ or treatment at the investigator's discretion | <ul style="list-style-type: none"> ▪ wk 52: 2 mg aflibercept IVT or sham injection ▪ wk 60 and 68: <ul style="list-style-type: none"> ▪ deterioration (≥ 1 retreatment criterion of 1–3^b met): 2 mg aflibercept IVT ▪ improvement (retreatment criterion 4^b met): same treatment as the one that caused the improvement ▪ stable outcome (no retreatment criterion^b met): sham injection ▪ or treatment at the investigator's discretion | |
| Ranibizumab vs. sham injection | | | |
| CRUISE | <p style="text-align: center;"><i>Treatment phase I:</i> day 0-wk 20, recording of outcomes wk 24^a; fixed treatment every 4 wks</p> <ul style="list-style-type: none"> ▪ first arm: 0.3 mg ranibizumab IVT ▪ second arm: 0.5 mg ranibizumab IVT | | No data |
| | <p style="text-align: center;"><i>Treatment phase II:</i> wk 24–48, recording of outcomes wk 52^a; study visits every 4 wks</p> <ul style="list-style-type: none"> ▪ first arm: ≥ 1 retreatment criterion^c met: 0.3 mg ranibizumab IVT ▪ second arm: ≥ 1 retreatment criterion^c met: 0.5 mg ranibizumab IVT | | |
| <p>a: Refers to the last point in time of treatment; outcomes were recorded at each study visit.</p> <p>b: Retreatment criteria: 1) increase in CRT by $> 50 \mu\text{m}$ compared to the lowest previous measurement as assessed by OCT; 2) new or persistent cystic retinal changes or subretinal fluid as assessed by OCT, or persistent diffuse oedema $\geq 250 \mu\text{m}$ in the central subfield as assessed by OCT; 3) loss of ≥ 5 letters in visual acuity compared to the best previous measurement in conjunction with any increase in CRT as assessed by OCT; 4) improvement of visual acuity by > 5 letters between the current and the last assessment (GALILEO: in the absence of retinal oedema in the central subfield).</p> <p>c: Retreatment criteria: BCVA $\leq 20/40$ on the ETDRS chart or OCT-measured central foveal thickness $\geq 250 \mu\text{m}$.</p> <p>BCVA: best corrected visual acuity; CRT: central retinal thickness; ETDRS: Early Treatment Diabetic Retinopathy Study; IVT: intravitreal; OCT: optical coherence tomography; RCT: randomized controlled trial; vs.: versus; wk: week</p> | | | |

All studies were completed, randomized studies, in which at least the first treatment phase was double-blind. The studies COPERNICUS and GALILEO compared IVT aflibercept injections with sham injections. The CRUISE study compared IVT ranibizumab injections with sham injections.

In all 3 studies, adults with visual impairment due to macular oedema secondary to CRVO were enrolled and randomized to receive treatment with 2 mg aflibercept IVT or sham injection, or to receive treatment with 0.3 mg, 0.5 mg ranibizumab IVT or sham injection. The study arm treated with 0.3 mg ranibizumab is not considered further here because ranibizumab is approved at a dosage of 0.5 mg per injection. Only one eye per patient was designated the study eye.

The studies included by the company consisted of several treatment phases each. The company used the first treatment phase of each study (including the assessment of outcomes at week 24) for an indirect comparison between aflibercept and ranibizumab using the common comparator “sham injection”.

Treatment phase I

In the first treatment phase of the studies COPERNICUS and GALILEO, the patients received either 2 mg aflibercept (IVT) or sham injections at monthly intervals up to and including week 20 according to their randomization.

The same applies to the first treatment phase of the CRUISE study, where the patients also received monthly treatment up to and including week 20 according to their randomization.

In all 3 studies, the analysis of the first treatment phase was conducted in week 24 without administration of treatment prior to the recording of the data.

Treatment phase II

In the second treatment phase, different treatment regimens were used in the studies COPERNICUS and GALILEO. In both studies, 4 retreatment criteria were used at every study visit to decide when treatment was to be continued with aflibercept or sham injection. Except criterion 4, the 4 criteria were identical in the studies (see Table 4). The use of the criteria and the resulting treatment decisions were different in the studies. To receive active treatment with aflibercept, for example, a different combination of criteria was required, or the patients randomized to sham injection could also receive active treatment in the COPERNICUS study in contrast to the GALILEO study.

The patients in the CRUISE study also received an intervention (ranibizumab) depending on retreatment criteria in the second treatment phase. These criteria were not identical with the ones in the 2 aflibercept studies (see Table 4). No further sham injections were conducted.

The study visits with the assessment of outcomes continued to be performed every 4 weeks in all 3 studies.

Extension phase

In the studies COPERNICUS and GALILEO, the second treatment phase was followed by an extension phase in which the continued treatment was also decided upon on the basis of retreatment criteria. The extension phases of the 2 studies differed in duration, number of study visits and use of retreatment criteria.

No extension phase was envisaged in the CRUISE study. After completion of the second treatment phase, patients could be enrolled in the extension study HORIZON [7].

Conclusion

The company described in Module 4, Section 4.3.2.1.3, that there was no common comparator in the 3 studies COPERNICUS, GALILEO and CRUISE from the second treatment phase onwards. This statement was accepted.

The company used the first treatment phase of the 3 studies for an indirect comparison between aflibercept and ranibizumab to present the added benefit of aflibercept. The company then claimed in Module 4, Section 4.5.1, that the studies COPERNICUS, GALILEO and CRUISE in the time to week 24 were suitable for an indirect comparison because of the common design of the first treatment phase of all 3 studies and the common comparator “sham injection”. However, neither aflibercept nor ranibizumab were used in accordance with the German approval in the 3 studies (for reasons, see below). Because of this, none of the 3 studies was suitable for an adequate indirect comparison for answering the present research question. Hence the indirect comparison was inadequate.

2.3.3 Use of aflibercept and ranibizumab not approval-compliant

In studies to investigate the added benefit, aflibercept and ranibizumab must be used in accordance with the German approval for the treatment of visual impairment due to macular oedema secondary to CRVO.

Approval of aflibercept and ranibizumab

According to the SPC for aflibercept [8], after the initial injection, treatment is given monthly until visual and anatomic outcomes are stable for 3 monthly assessments (hereinafter referred to as “stable outcome”). Thereafter the need for continued treatment should be reconsidered, according to the SPC. In stable outcome, treatment may be continued with gradually increasing treatment intervals. Additionally, the SPC for aflibercept describes that continued treatment is not recommended if there is no improvement in visual and anatomic outcomes over the course of the first 3 injections (hereinafter referred to as “treatment failure”).

The SPC for ranibizumab [9] also specifies continued monthly treatment until maximum visual acuity is achieved. In the SPC, maximum visual acuity is defined as the patient’s visual acuity that is stable for 3 consecutive monthly assessments performed while on ranibizumab treatment (hereinafter referred to as “stable outcome”). If there is no improvement in visual

acuity over the course of the first 3 injections, continued treatment is also not recommended, according to the SPC. Thereafter patients should be monitored monthly for visual acuity, according to the SPC.

Hence it can be inferred from the specifications of the SPCs cited above that at least 3 injections of aflibercept or ranibizumab are needed. The earliest point in time to determine stable outcome over the course of 3 monthly parallel assessments or treatment failure is after the administration of 3 injections.

Treatment regimen in the studies / implementation in the dossier

In contrast to the administration specified in the SPC, the treatment regimens of the first treatment phase of all 3 studies provided for 6 fixed-planned IVT injections with the respective study medication up to and including week 20. Continued treatment did not depend on the course of the individual patient outcome in this study phase. Hence, this treatment regimen did not comply with the stipulations of the approvals of aflibercept and ranibizumab.

The assessment that aflibercept and ranibizumab were not administered according to their approval in the 3 studies included by the company concurred with the company's assessment. The company itself already described in Module 4, Sections 4.2.1 and 4.5.1, that, from the third month (week 12), all 3 studies it had included in the assessment of the added benefit deviated from the stipulations defined in their approval. It justified the use of the studies with the consistent continuation of the respective treatment regimen up to the time of analysis of the primary outcome after week 24, i.e. every 4 weeks, in all 3 studies. Moreover, it claimed that the sham injection as control administered in each case served as common comparator. This rationale could not be followed.

However, the company did not justify in its dossier, why it regarded the studies to be usable for the assessment of added benefit using an indirect comparison despite their lack of compliance with the approval. It also did not present in the dossier any analyses on responders (stable outcome for 3 monthly assessments) or non-responders (no improvement over the course of 3 injections) in the course of the studies. Such analyses could facilitate an assessment of how large the proportion of patients in the studies included by the company was for whom monthly administration of the respective drug during the course of the first treatment phase or treatment discontinuation would have been required anyway. Depending on the size of the proportions of these patients, the study results then might be transferable to the approved treatment regimen and suitable for conducting an indirect comparison for assessing the added benefit.

Information from the approval documents

The European approval documents provide useful information for an approximation of the extent to which the treatment actually administered in the studies deviated from the stipulations of the approval. The *European Public Assessment Report* (EPAR) [10] of aflibercept describes the results of post-hoc analyses conducted in the framework of the

approval process. These showed that individual and pooled analyses of the studies COPERNICUS and GALILEO showed that the plateau of the effect of the response was already achieved at around month 3, and that only 15% of patients benefited from subsequent monthly treatment with aflibercept. This indicates that, in the first treatment phase of the studies COPERNICUS and GALILEO, a possibly considerable proportion of patients received treatment unnecessarily despite stable outcome and thus outside the approval. There was no information on non-responders in the EPAR.

Information in the unpublished European approval documents [11] supports the assumption that a considerable proportion of patients in the aflibercept studies might have been treated outside the approval and received too many injections. In the framework of the approval, the company conducted an analysis according to Kaplan and Meier on the patients who gained ≥ 15 letters in visual acuity during the first treatment phase (up to week 24) of the studies COPERNICUS and GALILEO and maintained that gain until the end of this treatment phase (hereinafter referred to as “sustained gain”, see Figure 1). The European approval documents describe that, according to this analysis, 57% of the patients had achieved a sustained gain of ≥ 15 letters by the end of the first treatment phase, and that this was already the case after the third injection in 45%. In the studies, the outcomes of an injection were always assessed during the assessments at monthly intervals. According to the approval, if sustained gain was determined after the third injection (which took place in week 8), and subject to the condition of a stable anatomic outcome for these patients, continued treatment should have been clarified in week 12 already, instead of having a new injection administered without prior clarification. The European approval documents did not contain any information on the development of the anatomic outcome. Moreover, it was also not reported how many patients did not achieve improvement in visual acuity after the third injection and hence had treatment failure (= non-responders), which would have required treatment discontinuation according to the approval.

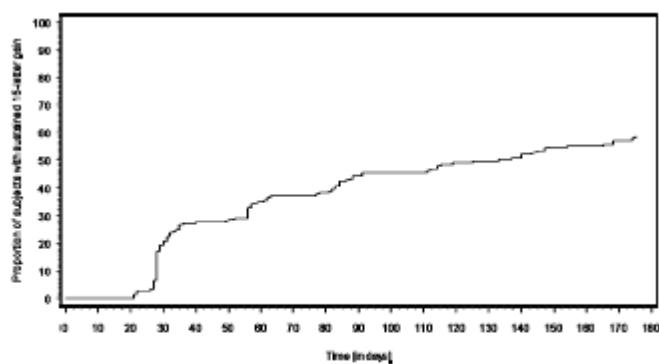


Figure 5: Time to sustained gain ≥ 15 letters GALILEO and COPERNICUS Integrated analysis

Figure 1: Post-hoc analysis: Time to sustained gain in visual acuity of ≥ 15 letters up to week 24, integrated analysis of the studies COPERNICUS and GALILEO [11]

No information of the type described above was available for the ranibizumab study CRUISE.

Conclusion

Overall, it remained unclear for all 3 studies, how many patients with stable outcome eventually received unnecessary injections outside the approval because of the fixed-planned 6 injections, or how many patients received continued treatment that did not comply with the approval after treatment failure. This means at the same time that it cannot be determined which proportion of patients as a whole – despite the fixed-planned 6 injections due to unstable course of the individual outcome over the course of all assessments of the first 24 weeks – were treated within the approval.

It is therefore not possible to conclude to what extent the treatment actually administered in the studies deviated from the stipulations of the approval. Hence the indirect comparison conducted by the company on the basis of the 3 studies is unsuitable to assess the added benefit of aflibercept versus ranibizumab.

2.3.4 Additional comments on the indirect comparison

The company presented an indirect comparison of aflibercept with the ACT ranibizumab using the common comparator “sham injection”.

In the indirect comparison, the company exclusively investigated beneficial outcomes of the first treatment phase (up to week 24) of each of the studies COPERNICUS, GALILEO and CRUISE. It did not investigate adverse events in the indirect comparison. In its description of the incidence of adverse events of the CRUISE study in Module 4, Section 4.3.1.3.1.4, the company argued that selected adverse events according to Preferred Terms and System Organ Classes were presented for this study, but that there was no overall summary of the safety data after 24 and 52 weeks. The company claimed that these data could not be compared with the results of the studies COPERNICUS and GALILEO without information on the overall profile of adverse events.

In principle, the investigation of harm forms part of an adequate indirect comparison. Only this makes it possible to balance benefit and harm of an intervention to be able to draw an overall conclusion on the added benefit. The company’s statement that no information on the overall rates of adverse events can be inferred from the publication on CRUISE at 24 weeks [5] is comprehensible at first. However, in Module 4, Section 4.3.1.3.1.4, the company defined ocular adverse events to be of interest. These include arterial thromboembolic events and retinal pigment epithelium tear, which were also documented in the publication on CRUISE mentioned above. In the integrated analysis of the studies COPERNICUS and GALILEO on the incidence of ocular adverse events of interest, the company named the Preferred Term “retinal tear”. It remained unclear why it did not consider this adverse event in the indirect comparison. The company did not justify its approach. The approach of the company was not accepted.

2.3.5 Summary

The studies COPERNICUS, GALILEO and CRUISE included by the company were unsuitable for performing an adequate indirect comparison for the investigation of the added benefit of aflibercept versus the ACT. The treatment regimens of the first study phase (up to week 24) of all 3 studies envisaged 6 fixed-planned injections and thus a treatment that did not comply with the approval and that did not consider the individual course of the visual and anatomic outcomes of the patients or treatment failure. Moreover, it could not be derived from the available data which proportion of patients nonetheless received approval-compliant treatment with the planned treatment of 6 injections because of the courses that actually occurred in the studies, and for which proportion of patients the treatment did not comply with the approval.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment. Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier and in Sections 2.7.2.3.1 and 2.7.2.3.2 of the full dossier assessment. Further information about the study design and the study populations can be found in Module 4, Sections 4.3.1.2.1 and 4.3.2.1.2 of the dossier, and in Section 2.7.2.3.2 of the full dossier assessment.

2.4 Results on added benefit

In its dossier, the company presented no assessment of aflibercept versus the ACT specified by the G-BA. The study pool of the company contained no study that was suitable for comparing aflibercept and ranibizumab. The indirect comparison conducted by the company on the basis of unsuitable studies was inadequate. Since no relevant data for the benefit assessment were presented, there is no proof of an added benefit of aflibercept in comparison with the ACT specified by the G-BA.

This result deviates from that of the company, which derived an added benefit from the studies it included.

Further information about the results on added benefit can be found in Module 4, Section 4.3.1.3 of the dossier, and in Section 2.7.2.4 of the full dossier assessment.

2.5 Extent and probability of added benefit, patient groups with therapeutically important added benefit

The result of the assessment of the added benefit of aflibercept in comparison with the ACT is shown in Table 5.

Table 5: Aflibercept: extent and probability of added benefit

| Therapeutic indication | ACT ^a | Extent and probability of added benefit |
|--|--|---|
| Treatment of adults with visual impairment due to macular oedema secondary to CRVO | Dexamethasone (intravitreal implant), ranibizumab | Added benefit not proven |

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specifications of the ACT, could choose an ACT from several options, the respective choice of the company is printed in **bold**.

ACT: appropriate comparator therapy; CRVO: central retinal vein occlusion; G-BA: Federal Joint Committee

This assessment deviates from that of the company, which derived an indication of a non-quantifiable added benefit of aflibercept.

The G-BA decides on the added benefit.

2.6 List of included studies

The information usually provided here is not applicable as the company did not include any relevant studies for the assessment of the added benefit of aflibercept versus the ACT specified by the G-BA in its assessment.

References for English extract

Please see full dossier assessment for full reference list.

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