IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Vedolizumab – Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Assessment module I, Sections I 2.1 to I 2.6, and Assessment module II, Sections II 2.1 to II 2.6, of the dossier assessment *Vedolizumab – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 October 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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Institute for Quality and Efficiency in Health Care
Im Mediapark 8 (KölnTurm)
50670 Cologne
Germany

Tel.: +49 (0)221 – 35685-0
Fax: +49 (0)221 – 35685-1
E-Mail: berichte@iqwig.de
Internet: www.iqwig.de

Vedolizumab

Assessment module I

Ulcerative colitis

Medical and scientific advice:

- Matthias Breidert, Hospitals in the Altmühltal Nature Park, Kösching, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the assessment. However, the advisor was not involved in the actual preparation of the assessment. The responsibility for the contents of the assessment lies solely with IQWiG.

IQWiG employees involved in the assessment[1]:

- Susanne Haag
- Katharina Biester
- Andreas Gerber-Grote
- Ulrich Grouven
- Elke Hausner
- Thomas Kaiser
- Florina Kerekes
- Corinna Kiefer
- Marco Knelangen
- Sarah Mostardt
- Anette ten Haaf
- Min Zhou

Keywords: vedolizumab, colitis – ulcerative, benefit assessment

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

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
N	number of randomized patients
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
TNFα	tumour necrosis factor alpha

I 2 Benefit assessment

I 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 vedolizumab. 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 15 July 2014.

Research question

The drug vedolizumab is approved for several therapeutic indications. The aim of the present assessment module is the assessment of the added benefit of vedolizumab in comparison with the appropriate comparator therapy (ACT) in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a tumour necrosis factor alpha (TNFα) antagonist.

The G-BA derived 2 subpopulations from the therapeutic indication (anti-TNFα-naive patients and patients with anti-TNFα failure), for which it specified a TNFα inhibitor (adalimumab or infliximab) as ACT. It is to be noted that it is possible to switch to a different TNFα inhibitor or to adjust the dose in case of treatment failure with a TNFα inhibitor. According to the approval, treatment with the respective TNFα inhibitor should not be continued or should be carefully reconsidered after a certain type of treatment failure.

The company chose adalimumab as ACT for both subpopulations. For the reasons stated above, this choice does not completely cover the relevant constellations for patients with anti-TNFα failure (patients who were pretreated with adalimumab and are not to be treated anymore with adalimumab according to the approval).

The present benefit assessment was conducted versus adalimumab for anti-TNFα-naive patients, and versus adalimumab or infliximab for patients with anti-TNFα failure.

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

Results

Direct comparison

There were no direct comparative RCTs on vedolizumab versus the ACT.

Indirect comparison

The company presented an adjusted indirect comparison according to Bucher for the derivation of the added benefit of vedolizumab versus adalimumab.

The company identified one RCT that was relevant from the company's point of view in which vedolizumab was compared with placebo (study C13006) and 3 placebo-controlled adalimumab studies for the adjusted indirect comparison (ULTRA 1, ULTRA 2 und M10-447). Hence placebo was the common comparator.

For the following reasons, the adjusted indirect comparison submitted by the company is unsuitable to draw conclusions on the added benefit of vedolizumab:

- The study designs of the studies included by the company in the adjusted indirect comparison and the resulting populations were not sufficiently similar.
- The company presented no adequate analyses on adverse events from the C13006 study.

Study designs and resulting populations were not sufficiently similar

Studies with vedolizumab

The C13006 study with vedolizumab consisted of 2 sequential RCTs, each of them placebo-controlled. The first RCT comprised a comparison in the induction phase, the second RCT a comparison in the maintenance phase. The total treatment duration of the C13006 study was 52 weeks (induction phase: week 0 to 6; maintenance phase: week 6 to 52). The induction phase consisted of 2 cohorts. In cohort 1, the randomized comparison of vedolizumab with placebo was considered. For cohort 2, patients were recruited to have enough patients with clinical response available for the maintenance phase. In the induction phase, they received unblinded vedolizumab treatment.

Patients who had a response in cohort 1 and cohort 2 under vedolizumab treatment within the induction phase were randomized to 3 treatment arms in the maintenance phase (placebo, vedolizumab [every 8 weeks] and vedolizumab [every 4 weeks]. Exclusively selected patients who had responded to vedolizumab in the induction phase were considered in these randomized arms of the maintenance phase, both in the vedolizumab arms and in the placebo arm. Patients who had not responded to vedolizumab in the induction phase received continued unblinded vedolizumab treatment (every 4 weeks) in another study arm in the maintenance phase of the C13006 study. The patients who had been randomized to the placebo arm for the induction phase, continued receiving placebo in the maintenance phase.

Comparison of the design of the vedolizumab studies versus the design of the adalimumab studies

The design of the 3 placebo-controlled studies with adalimumab was fundamentally different from the one of the C13006 study with vedolizumab. The ULTRA 1 study only comprised an 8-week induction phase. The 2 studies ULTRA 2 and M10-447 both included an induction phase and a maintenance phase. In contrast to the C13006 study however, after the induction phase the patients who had responded to adalimumab were not randomized for the maintenance phase. In case of inadequate response, patients of the ULTRA 2 study could switch to adalimumab after week 12; in the M10-447 study, this was possible after week 8. In

both studies, the data of the patients for whom this treatment switch became necessary were considered as non-responders in the analyses on outcomes (except on adverse events).

Hence the analysis of the studies ULTRA 2 and M10-447 comprised the induction phase and the maintenance phase (week 0 to 52) and the data of all patients (patients who had responded to adalimumab in the induction phase and patients who had not responded to adalimumab).

Overall, the studies on vedolizumab versus placebo and on adalimumab versus placebo identified by the company were unsuitable for an adjusted indirect comparison because of their study designs and the resulting different populations.

No adequate analyses of adverse events in the C13006 study

Besides the fact that the studies on the adjusted indirect comparison were not sufficiently similar, the company also presented no adequate analysis on adverse events. Patients who did not participate in the RCT on the maintenance phase were also included in the analysis of adverse events on the C13006 study.

This means that non-randomized patients from the open-label vedolizumab arm (cohort 2) were also considered in the induction phase. In the maintenance phase, all patients treated with vedolizumab were analysed together and compared with the patients with placebo treatment. Moreover, the patients treated with vedolizumab were also analysed together, irrespective of their dose regimen (vedolizumab every 4 weeks or every 8 weeks) in the maintenance phase.

Because of the analysis of adverse events presented, patients were also considered who were not treated according to the approval, and randomization was also broken. Since there were no analyses on adverse events from a randomized comparison, no balancing of benefit and harm can be conducted.

Summary

There were no relevant data for the benefit assessment of vedolizumab in comparison with adalimumab in patients with ulcerative colitis. An added benefit of vedolizumab over adalimumab is therefore not proven.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[2]

On the basis of the results presented, the extent and probability of the added benefit of the drug vedolizumab compared with the ACT for the therapeutic indication ulcerative colitis is assessed as presented in Table 1.

Table 1: Vedolizumab – extent and probability of added benefit in the therapeutic indication ulcerative colitis

Subpopulation	**ACT**[a]	**Extent and probability of added benefit**
Treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate or no response with, lost response to, or are intolerant to conventional therapy or have a contraindication	TNFα inhibitor (**adalimumab** or infliximab)	Added benefit not proven
Treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate or no response with or lost response to a TNFα inhibitor	TNFα inhibitor[b] (adalimumab or infliximab)	Added benefit not proven

a: Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: It is possible to switch to a different TNFα inhibitor or to adjust the dose in case of treatment failure with a TNFα inhibitor; the respective approval status has to be considered. According to the approval, treatment with adalimumab is not possible for all patients of this patient population.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; TNFα: tumour necrosis factor alpha

The G-BA decides on the added benefit.

[2] 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].

I 2.2 Research question

The drug vedolizumab is approved for several therapeutic indications. The aim of the present assessment module is the assessment of the added benefit of vedolizumab in comparison with the ACT in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a TNFα antagonist.

The G-BA derived 2 subpopulations from the therapeutic indication (anti-TNFα-naive patients and patients with anti-TNFα failure), for which it specified a TNFα inhibitor (adalimumab or infliximab) as ACT. It is to be noted that it is possible to switch to a different TNFα inhibitor or to adjust the dose in case of treatment failure with a TNFα inhibitor. According to the approval, treatment with the respective TNFα inhibitor should not be continued or should be carefully reconsidered after a certain type of treatment failure [3,4].

The company chose adalimumab as ACT for both subpopulations. For the reasons stated above, this choice does not completely cover the relevant constellations for patients with anti-TNFα failure (patients who were pretreated with adalimumab and are not to be treated anymore with adalimumab according to the approval).

The present benefit assessment was conducted versus adalimumab for anti-TNFα-naive patients, and versus adalimumab or infliximab for patients with anti-TNFα failure.

This constitutes a supplementation of the company's choice, which only used adalimumab for the added benefit of vedolizumab. However, this did not have any consequences for the present benefit assessment because for its research question the company presented no suitable data for the derivation of an added benefit of vedolizumab.

The assessment was conducted based on patient-relevant outcomes and on RCTs with a minimum duration of one year. This deviated from the company's approach, which defined no study duration.

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

I 2.3 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 vedolizumab (studies completed up to 21 May 2014)
- bibliographical literature search on vedolizumab (last search on 19 May 2014)
- search in trial registries for studies on vedolizumab (last search on 21 May 2014)
- bibliographical literature search on the ACT (last search on 20 May 2014)

- search in trial registries for studies on the ACT (last search on 21 May 2014)

To check the completeness of the study pool:

- bibliographical literature search on vedolizumab (last search on 23 July 2014)
- search in trial registries for studies on vedolizumab (last search on 24 July 2014)

No additional relevant study was identified from the check.

However, the data presented by the company were unsuitable to derive conclusions on the added benefit of vedolizumab in adult patients with moderately to severely active ulcerative colitis.

Direct comparison

There were no direct comparative RCTs on vedolizumab versus the ACT.

Indirect comparison

The company presented an adjusted indirect comparison according to Bucher [5] for the derivation of the added benefit of vedolizumab versus adalimumab. Table 2 shows the data presented by the company for the adjusted indirect comparison of vedolizumab with adalimumab and shows for which subpopulation or treatment phase the company used the respective studies.

Table 2: Study pool of the company – RCT, indirect comparison: vedolizumab vs. adalimumab

Comparison study	Subpopulation		Treatment phase	
	Anti-TNFα-naive patients[a]	Patients with anti-TNFα failure[b]	Induction phase	Maintenance phase
Vedolizumab vs. placebo				
C13006	●	●	●	●
Adalimumab vs. placebo				
ULTRA 1	●	–	●	–
ULTRA 2	●	●[c]	●	●
M10-447	●	–	●	●

●: Study was considered by the company for the subpopulation or for the treatment phase in the adjusted indirect comparison.
–: Study was not considered by the company for the subpopulation or for the treatment phase in the adjusted indirect comparison.
a: Patients who have had an inadequate or no response with or lost response to conventional treatment, or are intolerant to the respective treatment.
b: Patients who have had an inadequate or no response with or lost response to a TNFα inhibitor or are intolerant to the respective treatment.
c: Patients with pretreatment with adalimumab were excluded from the study.
RCT: randomized controlled trial; TNFα: tumour necrosis factor alpha; vs.: versus

The company identified one RCT that was relevant from the company's point of view in which vedolizumab was compared with placebo (study C13006 [6,7]). Hence placebo was the common comparator for the company's adjusted indirect comparison.

The company considered 3 placebo-controlled adalimumab studies, which were suitable for the adjusted indirect comparison from the company's point of view (ULTRA 1 [8-10], ULTRA 2 [10-13] and M10-447 [14,15]). The characteristics of the studies included by the company and of the interventions used in the studies can be found in I Appendix A (Table 8 and Table 9) of the full dossier assessment.

The company conducted separate analyses for the induction phase and the maintenance phase. Since a minimum study duration of one year in total is considered to be meaningful for the benefit assessment, the analyses that were only based on the induction phase are not relevant for the benefit assessment, however.

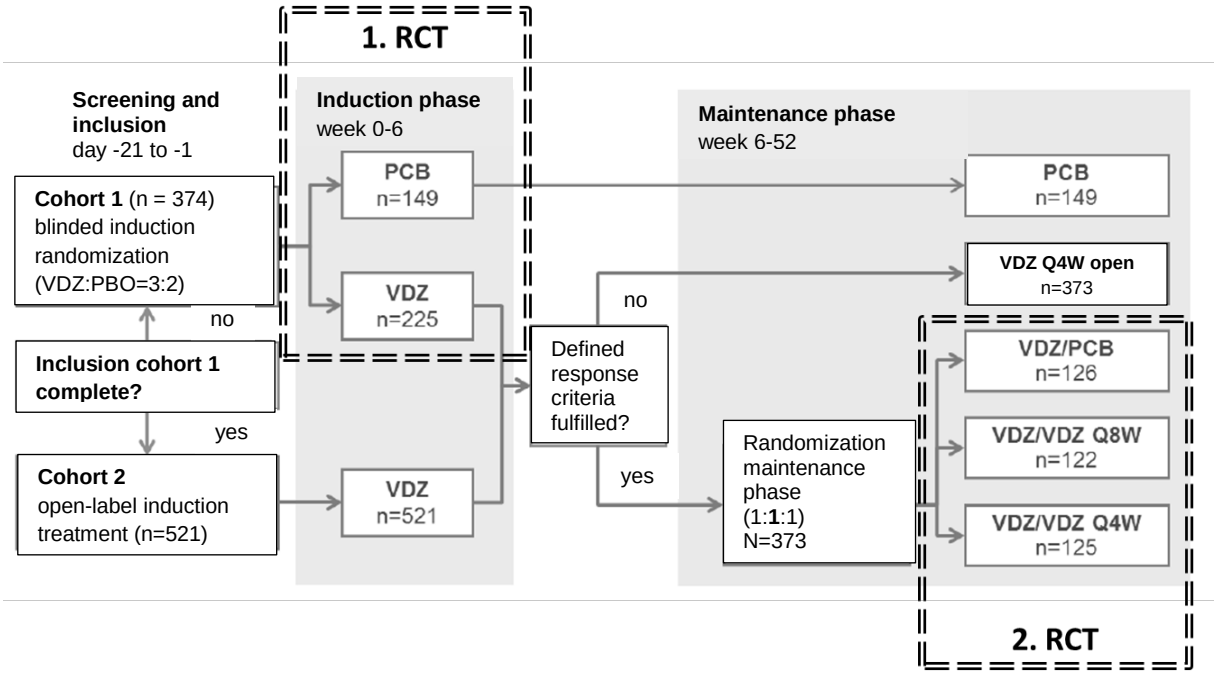
For the following reasons, the adjusted indirect comparison submitted by the company is unsuitable to draw conclusions on the added benefit of vedolizumab:

- The study designs of the studies included by the company in the adjusted indirect comparison and the resulting populations were not sufficiently similar.
- The company presented no adequate analyses on adverse events from the C13006 study.

Study designs and resulting populations were not sufficiently similar

Studies with vedolizumab

The C13006 study with vedolizumab consisted of 2 sequential RCTs, each of them placebo-controlled (see Figure 1). The first RCT comprised a comparison in the induction phase, the second RCT a comparison in the maintenance phase.



In the figure, the randomized study arms of the induction phase and the maintenance phase are framed by a dashed line.

Figure 1: Design of the C13006 vedolizumab study (figure adapted from [16])

The total treatment duration of the C13006 study was 52 weeks and included an induction phase (week 0 to 6) and a maintenance phase (week 6 to 52). The induction phase consisted of 2 cohorts. In cohort 1 the randomized comparison of vedolizumab (N = 225) with placebo (N = 149) was considered. For cohort 2 patients were recruited (n = 521) to have enough patients with clinical response available for the maintenance phase. In the induction phase, they received unblinded vedolizumab treatment. In both cohorts, treatment with vedolizumab was conducted according to the approval for the induction phase [17].

Patients who had a response in cohort 1 and cohort 2 under vedolizumab treatment within the induction phase were randomized to 3 treatment arms in the maintenance phase (placebo, vedolizumab [every 8 weeks] and vedolizumab [every 4 weeks]. Exclusively selected patients who had responded to vedolizumab in the induction phase (hereinafter referred to as “responders”) were considered in these randomized arms of the maintenance phase, both in the vedolizumab arms and in the placebo arm. Patients who had not responded to vedolizumab in the induction phase (hereinafter referred to as “non-responders”) received continued unblinded vedolizumab treatment (every 4 weeks) in another study arm in the maintenance phase of the C13006 study. The patients who had been randomized to the placebo arm for the induction phase, continued receiving placebo in the maintenance phase.

Studies with adalimumab

Figure 2 shows the simplified design of the 3 studies with adalimumab.

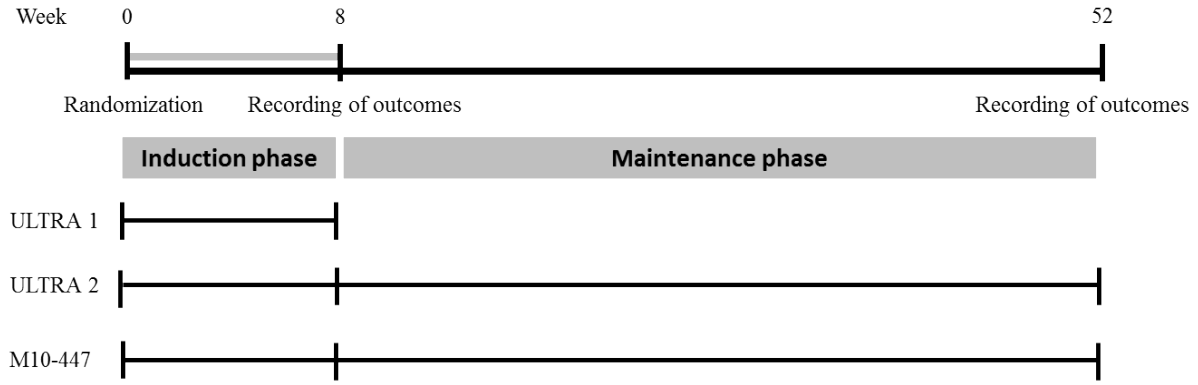


Figure 2: Design of the adalimumab studies (simplified presentation)

Comparison of the design of the vedolizumab studies versus the design of the adalimumab studies

The design of the 3 placebo-controlled studies with adalimumab was fundamentally different from the one of the C13006 study with vedolizumab. The ULTRA 1 study only comprised an 8-week induction phase. The 2 studies ULTRA 2 and M10-447 both included an induction phase and a maintenance phase. In contrast to the C13006 study however, after the induction phase the patients who had responded to adalimumab (hereinafter also referred to as "responders") were not randomized for the maintenance phase. All non-responders of the ULTRA 2 study and of the M10-447 study had the possibility to receive adalimumab treatment from week 12, or from week 8 respectively, in case of inadequate response. In ULTRA 2, the patients who switched treatment were unblinded at this time point and continued treatment with adalimumab 40 mg every 2 weeks. In the M10-447 study, the patients who switched treatment from the placebo arm in the first 4 weeks received blinded 160 mg or 80 mg adalimumab at intervals of 2 weeks, followed by open-label treatment with 40 mg adalimumab (every 2 weeks). Patients switching treatment who had been randomized to adalimumab received blinded 40 mg adalimumab at intervals of 2 weeks in the first 4 weeks, followed by open-label treatment with 40 mg adalimumab (every 2 weeks). Dose increase to 80 mg adalimumab (every 2 weeks) was possible in case of continued inadequate response after this treatment switch. In both studies, the data of the patients for whom this treatment switch became necessary were considered as non-responders in the outcome analyses (except on adverse events).

Hence the analysis of the studies ULTRA 2 and M10-447 comprised the induction phase and the maintenance phase (week 0 to 52) and the data of all patients (responders and patients who had not responded to adalimumab in the induction phase [hereinafter also referred to as "non-responders"]).

Different populations for the maintenance phase also resulted from the different study designs. However, sufficient similarity of the included populations is a basic prerequisite for conducting an adjusted indirect comparison [18].

The company also saw the problem that in the maintenance phase the populations of the vedolizumab study only consisted of responders, and in the adalimumab studies both of responders and non-responders. It tried to account for this problem and noted that, partially, separate data were available for patients who showed response to adalimumab in the induction phase, and that it wanted to preferentially use these data for the adjusted indirect comparison.

However, this cannot solve the problem of the different populations. Corresponding results (responders on the adalimumab side) were only available for patients in the adalimumab arms. The population of the placebo arm of the adalimumab studies, which served as common comparator, still consisted of responders and non-responders and therefore did not correspond to the population of the placebo arm of the vedolizumab study. This consisted exclusively of responders so that the population of the common comparator is not comparable. Moreover, randomization was broken by the fact that a certain population (here: responders under adalimumab) was only used from one study arm of one RCT. In summary, the limitation to responders therefore broke the randomization in the studies with adalimumab without sufficient similarity of the populations being guaranteed.

Overall, the studies on vedolizumab versus placebo and on adalimumab versus placebo identified by the company were unsuitable for an adjusted indirect comparison because of their study designs and the resulting different populations.

No adequate analyses of adverse events in the C13006 study

Besides the fact that the studies on the adjusted indirect comparison were not sufficiently similar, the company also presented no adequate analysis on adverse events. Patients who did not participate in the RCT on the maintenance phase were also included in the analysis of adverse events on the C13006 study (see Figure 3).

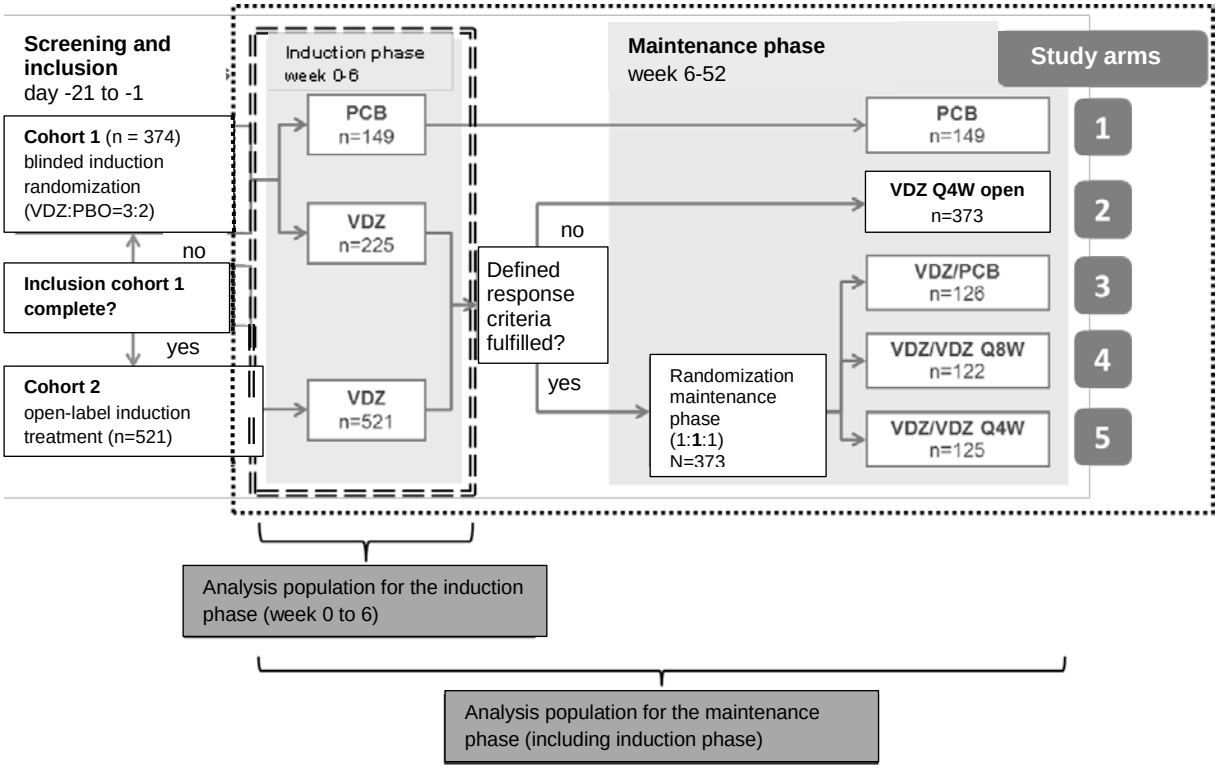


Figure 3: Analysis populations of the company for the assessment of adverse events in the C13006 study (figure adapted according to [16])

This means that non-randomized patients from the open-label vedolizumab arm (cohort 2) were also considered in the induction phase. In the maintenance phase, all patients treated with vedolizumab (study arms 2, 4 and 5 in Figure 3) were analysed together and compared with the patients with placebo treatment (study arms 1 and 3 in Figure 3). Moreover, the patients treated with vedolizumab were also analysed together in the maintenance phase, irrespective of their dose regimen (vedolizumab every 4 weeks [see study arms 2 and 5 in Figure 3] or every 8 weeks [see study arm 4 in Figure 3]).

Because of the analysis of adverse events presented, patients were also considered who were not treated according to the approval, and randomization was also broken. The company's justification for this approach was not accepted (see Section I 2.7.2.5 of the full dossier assessment). Since there were no analyses on adverse events from a randomized comparison, no balancing of benefit and harm can be conducted. Hence there are no suitable data for a derivation of an added benefit of vedolizumab.

Summary

There were no direct comparative RCTs on vedolizumab versus the ACT.

The adjusted indirect comparison presented by the company was unsuitable because the studies with vedolizumab and adalimumab were not sufficiently similar and the company

presented no adequate analysis on adverse events. Overall there were therefore no suitable data for the assessment of the added benefit of vedolizumab.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4 A, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections I 2.7.2.1 and I 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 A, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier, and in Sections I 2.7.2.3.1 and I 2.7.2.3.2 of the full dossier assessment.

I 2.4 Results on added benefit

The company presented no suitable data for the assessment of the added benefit of vedolizumab. Hence the added benefit of vedolizumab in the therapeutic indication ulcerative colitis versus the ACT is not proven.

This result deviates from that of the company, which derived a hint of a considerable added benefit for anti-TNFα-naive patients and a hint of a non-quantifiable added benefit for patients with anti-TNFα failure.

Further information about the results on added benefit can be found in Module 4 A, Sections 4.3.1.3 and 4.3.2.1.3 of the dossier and in Sections I 2.7.2.4 and I 2.7.2.5 of the full dossier assessment.

I 2.5 Extent and probability of added benefit

The result of the assessment of the added benefit of vedolizumab in comparison with the ACT is summarized in Table 3.

Table 3: Vedolizumab – extent and probability of added benefit in the therapeutic indication ulcerative colitis

Subpopulation	**ACT**[a]	**Extent and probability of added benefit**
Treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate or no response with, lost response to, or are intolerant to conventional therapy or have a contraindication	TNFα inhibitor (**adalimumab** or infliximab)	Added benefit not proven
Treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate or no response with or lost response to a TNFα inhibitor	TNFα inhibitor[b] (adalimumab or infliximab)	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b: It is possible to switch to a different TNFα inhibitor or to adjust the dose in case of treatment failure with a TNFα inhibitor; the respective approval status has to be considered. According to the approval, treatment with adalimumab is not possible for all patients of this patient population. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; TNFα: tumour necrosis factor alpha		

This result deviates from that of the company, which derived a hint of a considerable added benefit for anti-TNFα-naive patients and a hint of a non-quantifiable added benefit for patients with anti-TNFα failure.

The G-BA decides on the added benefit.

I 2.6 List of included studies

The information usually provided here is not applicable as the studies included by the company were unsuitable for the assessment of the added benefit of vedolizumab for the reasons stated above.

References for English extract

Please see full assessment for full reference list.

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Vedolizumab

Assessment module II

Crohn disease

Medical and scientific advice:

- Matthias Breidert, Hospitals in the Altmühltal Nature Park, Kösching, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the assessment. However, the advisor was not involved in the actual preparation of the assessment. The responsibility for the contents of the assessment lies solely with IQWiG.

IQWiG employees involved in the assessment[1]:

- Anette ten Haaf
- Katharina Biester
- Andreas Gerber-Grote
- Ulrich Grouven
- Susanne Haag
- Elke Hausner
- Thomas Kaiser
- Florina Kerekes
- Corinna Kiefer
- Marco Knelangen
- Sarah Mostardt
- Min Zhou

Keywords: vedolizumab, Crohn disease, benefit assessment

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

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Abbreviation	Meaning
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
TNFα	tumour necrosis factor alpha

II 2 Benefit assessment

II 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 vedolizumab. 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 15 July 2014.

Research question

The drug vedolizumab is approved for several therapeutic indications. The aim of the present assessment module is the assessment of the added benefit of vedolizumab in comparison with the appropriate comparator therapy (ACT) in adult patients with moderately to severely active Crohn disease who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a tumour necrosis factor alpha (TNFα) antagonist.

The G-BA derived 2 subpopulations from the therapeutic indication (anti-TNFα-naive patients and patients with anti-TNFα failure), for which it specified TNFα inhibitors (adalimumab or infliximab) as ACT. It is to be noted that it is possible to switch to a different TNFα inhibitor or to adjust the dose in case of treatment failure with a TNFα inhibitor. According to the approval, treatment with the respective TNFα inhibitor should be carefully reconsidered after a certain type of treatment failure.

The company chose adalimumab as ACT for both subpopulations. For the reasons stated above, this choice does not completely cover the relevant constellations for patients with anti-TNFα failure (patients who were pretreated with adalimumab and who are no longer eligible for treatment with adalimumab).

The present benefit assessment was conducted versus adalimumab for anti-TNFα-naive patients, and versus adalimumab or infliximab for patients with anti-TNFα failure.

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

Results

Direct comparison

The company identified no direct comparative RCTs on vedolizumab versus the ACT.

Indirect comparison

No indirect comparisons on the basis of RCTs were conducted in the dossier to describe the added benefit of vedolizumab. The company conducted a search for studies for an indirect comparison, and also identified studies that were relevant from the company's point of view.

It argued, however, that an indirect comparison was not feasible and that the results of an indirect comparison could not be interpreted in a meaningful way.

Summary

There were no relevant data for the benefit assessment of vedolizumab in comparison with adalimumab in patients with Crohn disease. An added benefit of vedolizumab over adalimumab is therefore not proven.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[2]

On the basis of the results presented, the extent and probability of the added benefit of the drug vedolizumab compared with the ACT for the therapeutic indication Crohn disease is assessed as presented in Table 1.

Table 1: Vedolizumab – extent and probability of added benefit in the therapeutic indication Crohn disease

Subpopulation	**ACT**[a]	**Extent and probability of added benefit**
Treatment of adult patients with moderately to severely active Crohn disease who have had an inadequate or no response with, lost response to, or are intolerant to conventional therapy or have a contraindication	TNFα inhibitor (**adalimumab** or infliximab)	Added benefit not proven
Treatment of adult patients with moderately to severely active Crohn disease who have had an inadequate or no response with or lost response to a TNFα inhibitor	TNFα inhibitor[b] (adalimumab or infliximab)	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b: It is possible to switch to a different TNFα inhibitor or to adjust the dose in case of treatment failure with a TNFα inhibitor; the respective approval status has to be considered. According to the approval, treatment with adalimumab is not meaningful for all patients of this patient population. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; TNFα: tumour necrosis factor alpha		

The G-BA decides on the added benefit.

[2] 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].

II 2.2 Research question

The drug vedolizumab is approved for several therapeutic indications. The aim of the present assessment module is the assessment of the added benefit of vedolizumab in comparison with the ACT in adult patients with moderately to severely active Crohn disease who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a TNFα antagonist.

The G-BA derived 2 subpopulations from the therapeutic indication (anti-TNFα-naive patients and patients with anti-TNFα failure), for which it specified a TNFα inhibitor (adalimumab or infliximab) as ACT. It is to be noted that it is possible to switch to a different TNFα inhibitor or to adjust the dose in case of treatment failure with a TNFα inhibitor. According to the approval, treatment with the respective TNFα inhibitor should be carefully reconsidered after a certain type of treatment failure.

The company chose adalimumab as ACT for both subpopulations. For the reasons stated above, this choice does not completely cover the relevant constellations for patients with anti-TNFα failure (patients who were pretreated with adalimumab and who are no longer eligible for treatment with adalimumab).

The present benefit assessment was conducted versus adalimumab for anti-TNFα-naive patients, and versus adalimumab or infliximab for patients with anti-TNFα failure.

This constitutes a supplementation of the company's choice, which only used adalimumab for the added benefit of vedolizumab. However, this did not have any consequences for the present benefit assessment because for its research question the company presented no suitable data for the derivation of an added benefit of vedolizumab.

The assessment was conducted based on patient-relevant outcomes and on RCTs with a minimum duration of one year. This deviated from the company's approach, which defined no minimum study duration.

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

II 2.3 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 vedolizumab (studies completed up to 21 May 2014)
- bibliographical literature search on vedolizumab (last search on 19 May 2014)
- search in trial registries for studies on vedolizumab (last search on 21 May 2014)
- bibliographical literature search on the ACT (last search on 20 May 2014)

- search in trial registries for studies on the ACT (last search on 21 May 2014)

The company presented no relevant data in Module 4 B to derive conclusions on the added benefit of vedolizumab versus the ACT in adult patients with moderately to severely active Crohn disease.

Direct comparison

The company identified no direct comparative RCTs on vedolizumab versus the ACT.

Indirect comparison

No indirect comparisons on the basis of RCTs were conducted in the dossier to describe the added benefit of vedolizumab.

The company presented placebo-controlled RCTs on vedolizumab and adalimumab, but conducted no adjusted indirect comparisons.

In the information retrieval, the company identified studies that, from the company's point view, were relevant for an adjusted indirect comparison. The company identified 2 RCTs in which vedolizumab was compared with placebo (studies C13007 [3,4] and C13011 [5]) und 4 studies in which adalimumab was compared with placebo (CHARM [6-15], CLASSIC I [16,17], CLASSIC II [18,19] and M04-729 [20,21].

The company argued that an indirect comparison was not feasible and that the results of an indirect comparison could not be interpreted in a meaningful way, and provided the following reasons:

1) lower certainty of results of indirect comparisons, particularly in the therapeutic indication Crohn disease
2) lower power of the reanalysis of study data based on subpopulations

According to the company, these reasons overall resulted in a "low reliability of the conclusions", which would not allow a meaningful interpretation of results from an indirect comparison.

The company's reasons are insufficient and inadequate to justify the "non-feasibility" of an adjusted indirect comparison (for reasons, see Section II 2.7.2.5 of the full dossier assessment).

The completeness of the study pool was not examined further because the company conducted no adjusted indirect comparison with the placebo-controlled studies on vedolizumab and the ACT it had identified and because there were also no data from direct comparative RCTs on vedolizumab for the research question. It was also not examined whether the studies the company had identified as relevant would have been suitable for the adjusted indirect comparison with regard to content.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4 B, Sections 4.2.2 and 4.2.3, of the dossier, and in Sections II 2.7.2.1 and II 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 B, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier, and in Sections II 2.7.2.3.1 and II 2.7.2.3.2 of the full dossier assessment.

II 2.4 Results on added benefit

In Module 4 B, the company presented no relevant data for assessing the added benefit of vedolizumab, neither for a direct comparison nor for an indirect comparison based on RCTs. Hence the added benefit of vedolizumab in the therapeutic indication Crohn disease versus the ACT is not proven.

This result deviates from the company's assessment, which derived a hint of a non-quantifiable added benefit for the subpopulation of patients with anti-TNFα failure without presenting any corresponding studies.

Further information about the results on added benefit can be found in Module 4 B, Sections 4.3.1.3 and 4.3.2.1.3 of the dossier and in Sections II 2.7.2.4 and II 2.7.2.5 of the full dossier assessment.

II 2.5 Extent and probability of added benefit

The result of the assessment of the added benefit of vedolizumab in comparison with the ACT is summarized in Table 2.

Table 2: Vedolizumab – extent and probability of added benefit in the therapeutic indication Crohn disease

Subpopulation	**ACT**[a]	**Extent and probability of added benefit**
Treatment of adult patients with moderately to severely active Crohn disease who have had an inadequate or no response with, lost response to, or are intolerant to conventional therapy or have a contraindication	TNFα inhibitor (**adalimumab** or infliximab)	Added benefit not proven
Treatment of adult patients with moderately to severely active Crohn disease who have had an inadequate or no response with or lost response to a TNFα inhibitor	TNFα inhibitor[b] (adalimumab or infliximab)	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b: It is possible to switch to a different TNFα inhibitor or to adjust the dose in case of treatment failure with a TNFα inhibitor; the respective approval status has to be considered. According to the approval, treatment with adalimumab is not meaningful for all patients of this patient population. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; TNFα: tumour necrosis factor alpha		

This result deviates from the assessment of the company. The company also regarded an added benefit as not proven for anti-TNFα-naive patients, but derived a hint of a non-quantifiable added benefit of vedolizumab for patients with anti-TNFα failure without presenting any corresponding studies.

The G-BA decides on the added benefit.

Further information on the extent and probability of the added benefit can be found in Module 4 B, Section 4.4 of the dossier, and in Section II 2.7.2.8 of the full dossier assessment.

II 2.6 List of included studies

Not applicable as no studies were included in the benefit assessment.

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Please see full assessment for full reference list.

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