Vadadustat (symptomatic anaemia associated with dialysis-dependent chronic kidney disease)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

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

Medical and scientific advice

- Helmut Ostermann, LMU Clinic

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

Patient and family involvement

The questionnaire on the disease and its treatment was answered by one person.

IQWiG thanks the respondent and the patient organization “Bundesverband Niere e. V.” for participating in the written exchange and for their support. The respondent and the Bundesverband Niere e. V. were not involved in the actual preparation of the dossier assessment.

IQWiG employees involved in the dossier assessment

- Simon Bogner
- Simone Heß
- Florina Kerekes
- Jona Lilienthal
- Regine Potthast
- Daniela Preukschat
- Felix Schwarz
- Carolin Weigel
- Pamela Wronski

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CKD	chronic kidney disease
CTCAE	Common Terminology Criteria for Adverse Events
EMA	European Medicines Agency
EOS	end of study
EOT	end of treatment
ESA	erythropoiesis-stimulating agent
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
Hb	haemoglobin
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MACE	major adverse cardiovascular events
NYHA	New York Heart Association
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SAP	statistical analysis plan
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	Standardized Medical Dictionary for Regulatory Activities Query
SOC	System Organ Class
SPC	Summary of Product Characteristics
TSAT	transferrin saturation

I 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 vadadustat. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 30 May 2024.

Research question

The aim of the present report is to assess the added benefit of vadadustat in comparison with the appropriate comparator therapy (ACT) in symptomatic anaemia associated with chronic kidney disease (CKD) in patients on chronic maintenance dialysis.

The research question presented in Table 2 is derived from the G-BA's specification of the ACT.

Table 2: Research question for the benefit assessment of vadadusta

Therapeutic indication	**ACT**[a, b]
Adult patients with symptomatic anaemia associated with chronic kidney disease (CKD)[c] who are on chronic maintenance dialysis	▪ Darbepoetin alfa or ▪ epoetin alfa or ▪ epoetin beta or ▪ epoetin theta or ▪ epoetin zeta or ▪ methoxy polyethylene glycol-epoetin beta
a. Presented is the ACT specified by the G-BA. b. According to the G-BA, the use of erythropoiesis-stimulating agents (ESAs) requires that other causes of anaemia (in particular iron deficiency) have been ruled out. In addition, the specifications in the respective Summary of Product Characteristics and the specifics of the German health care context must be taken into account. c. In the present therapeutic indication, it is assumed in accordance with the G-BA that guideline- and approval-compliant treatment is ensured in both study arms for any deficiency states that could cause corresponding specific types of anaemia (e.g. iron, water-soluble vitamins). ACT: appropriate comparator therapy; CKD: chronic kidney disease; ESA: erythropoiesis-stimulating agent; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of added benefit.

Study pool and study design

The studies AKB-6548-CI-0016 (CI-0016) and AKB-6548-CI-0017 (CI-0017) were included in the benefit assessment of vadadustat.

The 2 studies were designed jointly, conducted in parallel and have a joint statistical analysis plan (SAP). Both studies together were designed to test the non-inferiority of vadadustat compared with darbepoetin alfa. The study protocols, including the protocol amendments, are identical except for a few specific differences. The differences are listed below in the joint study description.

Both studies are unblinded, multicentre RCTs comparing vadadustat with the erythropoiesis-stimulating agent (ESA) darbepoetin alfa. They included patients with end-stage chronic kidney disease who were receiving maintenance dialysis (either haemodialysis or peritoneal dialysis). Other causes of anaemia – in particular iron and water-soluble vitamin deficiency – had to be ruled out before enrolment. Patients with pre-existing cardiovascular conditions such as severe heart failure or acute coronary syndrome were excluded from both studies.

In the CI-0016 study, a total of 369 patients were randomly assigned in a 1:1 ratio to treatment with vadadustat (N = 181) or darbepoetin alfa (N = 188). Stratification was based on geographic region (United States, Europe, rest of the world), New York Heart Association (NYHA) heart failure class (0 or I versus II or III), and study entry haemoglobin (Hb) level (< 9.5 g/dL; ≥ 9.5 g/dL).

In the CI-0017 study, 3554 patients were randomized in a 1:1 ratio to the intervention arm with vadadustat (N = 1777) or the comparator arm with darbepoetin alfa (N = 1777). Treatment was also stratified by geographic region (United States, Europe, rest of the world), NYHA heart failure class (0 or I versus II or III), and study entry Hb level, but with higher cut-off values (< 10.0 g/dL; ≥ 10.0 g/dL) than in the CI-0016 study.

The CI-0016 study included patients with anaemia who had recently (within 16 weeks) initiated maintenance dialysis. In accordance with the initial study protocol, only patients without pre-existing long-term ESA therapy were initially enrolled, who therefore entered the correction period of anaemia treatment at the start of the study treatment. However, a protocol amendment (from version 3) subsequently allowed the inclusion of patients with prior ESA treatment. The CI-0017 study, in contrast, investigated patients who had been on dialysis for a longer period of time (at least 12 weeks). From the beginning of the study, only patients with pre-existing long-term ESA treatment were included, who were therefore

already in the maintenance period of anaemia treatment at the start of the study treatment. In the intervention arms of both studies, any existing ESA treatment was discontinued in favour of the intervention with vadadustat. A therapeutic indication for this treatment switch was not required.

In line with these differences between the 2 studies, the inclusion criterion for the presence of anaemia in study CI-0016 was defined as a screening Hb < 10.0 g/dL, or between 8.0 and 11.0 g/dL after the described protocol amendment. In the CI-0017 study, Hb levels between 8.0 and 11.0 g/dL were required for inclusion at the US sites, and between 9.0 and 12.0 g/dL at sites outside of the United States.

In both studies, treatment with vadadustat was in compliance with the approval. All patients received a starting dose of 300 mg/day. Treatment with darbepoetin alfa was largely in compliance with the specifications of the Summary of Product Characteristics (SPC). Patients who were already being treated with darbepoetin alfa before the start of the study maintained their existing dosage and frequency. Switching from another ESA to darbepoetin alfa and dose adjustments were to be carried out in compliance with the information provided in the respective SPC. One discrepancy between the protocol and the SPC for darbepoetin alfa concerned the dose adjustment in the event of an Hb increase by more than 2 g/dL within 4 weeks. In this case, the SPC specifies a dose reduction, whereas the study protocol also allowed the dose to be maintained.

The duration of treatment was planned for a minimum of 36 weeks and a maximum of 208 weeks. After discontinuation of treatment, treatment in both study arms was to be continued in accordance with local standards without restrictions (including ESA therapy). It was not planned that patients in the comparator arm switch to the intervention arm treatment. The global study completion was planned for the time at which approx. 631 major adverse cardiovascular events (MACE) had occurred (over both studies) and all included patients had the opportunity to have their Visit 13 (Week 36 +/- 5 days). For the present assessment, it is assumed that the results presented in Module 4 A, in contrast to the information provided by the company, refer to an observation period up to the global study end.

The primary outcomes of studies CI-0016 and CI-0017 were the efficacy outcome “change in Hb between baseline and Weeks 24–36”, and the harm outcome of MACE with the components of death from any cause, non-fatal myocardial infarction, and non-fatal stroke. Patient-relevant secondary outcomes were outcomes on morbidity and adverse events (AEs). Health-related quality of life outcomes and patient-reported morbidity outcomes were not investigated in either study.

Risk of bias

The risk of bias across outcomes was rated as low for both studies. The risk of bias was also rated as low for the outcomes of all-cause mortality, MACE, hospitalization for heart failure, and thromboembolic events. No suitable data are available for the outcome of freedom from transfusion. Therefore, the risk of bias was not assessed for the results of this outcome. The risk of bias for the results of the serious AEs (SAEs) outcome was rated as high. One reason for this is the subjective definition of outcomes in both studies presented. The study stipulated that any other event that the investigator or sponsor judged to be serious was also considered serious. If there was any doubt as to whether the event constituted an AE or an SAE, it was to be treated as an SAE. Another reason is that there is uncertainty in the follow-up observation after treatment discontinuation, as visit schedule and assessments after premature end of treatment were left to the agreement between investigator and patient, which can influence the uniform and complete recording of SAEs. The risk of bias for the results of the outcome of discontinuation due to AEs was rated as high because of lack of blinding in the presence of subjective decision on treatment discontinuation. Analyses for the outcomes of hepatotoxicity and the selected specific AEs were used exclusively at the level of SAEs. The risk of bias for the results of these outcomes was therefore rated as high.

Certainty of conclusions

Overall, there are limitations with regard to the independence of the 2 studies CI-0016 and CI-0017 (including joint study design, parallel conduct and pooled analysis of both studies, in particular with the linking of both studies by a cross-study criterion to define study end, while at the same time the study CI-0016 was small). The confirmation (replication) of results by a second study, which is necessary to derive proof, is therefore generally not given in this situation. The maximum certainty of conclusions achievable by means of a meta-analysis (proof) is therefore reduced in the present situation.

In the meta-analysis of both studies presented, at most an indication, e.g. of an added benefit, can therefore be determined for the outcomes of all-cause mortality, MACE, hospitalization for heart failure, and thromboembolic events. At most hints, e.g. of lesser harm, can be derived for all other outcomes.

Results

Mortality

All-cause mortality

For the outcome of all-cause mortality, the meta-analysis of the studies did not show any statistically significant differences between the treatment arms. There is no hint of added benefit of vadadustat in comparison with the ACT; an added benefit is therefore not proven.

Morbidity

Freedom from transfusion

No suitable data are available for the outcome of freedom from transfusion. There is no hint of added benefit of vadadustat in comparison with the ACT; an added benefit is therefore not proven.

Health-related quality of life

No data were recorded for the outcome of health-related quality of life. There is no hint of added benefit of vadadustat in comparison with the ACT; an added benefit is therefore not proven.

Side effects

SAEs

The meta-analysis of the studies showed a statistically significant difference in favour of vadadustat in comparison with darbepoetin alfa for the outcome of SAEs. There is a hint of lesser harm from vadadustat in comparison with the ACT.

Discontinuation due to AEs

The meta-analysis of the studies showed a statistically significant difference to the disadvantage of vadadustat in comparison with darbepoetin alfa for the outcome of discontinuation due to AEs. There is a hint of greater harm from vadadustat in comparison with the ACT.

MACE, hospitalization for heart failure, and thromboembolic events

The meta-analysis of the studies did not show any statistically significant differences between treatment groups for any of the outcomes of MACE (consisting of the individual components of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke), hospitalization for heart failure, and thromboembolic events (consisting of the individual components of arterial thrombosis, deep vein thrombosis, pulmonary embolism, and vascular access thrombosis). For each of them, there is no hint of greater or lesser harm from vadadustat in comparison with the ACT; greater or lesser harm is therefore not proven.

Hepatotoxicity

For the outcome of hepatotoxicity, the meta-analysis of the studies did not show any statistically significant differences between treatment groups. There is no hint of greater or lesser harm from vadadustat in comparison with the ACT; greater or lesser harm is therefore not proven.

Specific AEs

The meta-analysis of the studies showed a statistically significant difference in favour of vadadustat compared with darbepoetin alfa for each of the outcomes of cardiac disorders (System Organ Class [SOC], SAE), neoplasms benign, malignant and unspecified (SOC, SAE), urinary tract infection (Preferred Term [PT], SAE) and mental status changed (PT, SAE). In each case, there is a hint of lesser harm from vadadustat in comparison with the ACT.

For the outcome of mental status changed (PT, SAE), there is also an effect modification by the characteristic of baseline Hb. For patients with baseline Hb < 10.0 g/dL, a statistically significant difference between treatment groups was shown in favour of vadadustat. For patients with baseline Hb ≥ 10.0 g/dL, in contrast, no statistically significant difference between treatment groups was shown.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the probability and extent of added benefit of the drug vadadustat in comparison with the ACT are assessed as follows:

Overall, there were positive effects for the outcome of SAEs and subcategories of SAEs at SOC and PT level, and a negative effect for the outcome of discontinuation due to AEs for vadadustat compared with the ACT.

No suitable data are available for the morbidity category. Outcomes from the category of health-related quality of life were not recorded. The possibility of evaluating an effect on the benefit side is therefore severely limited in the present assessment.

In summary, there is no proof of an added benefit of vadadustat over the ACT for adult patients with symptomatic anaemia associated with CKD who are on chronic maintenance dialysis.

Table 3 shows a summary of probability and extent of the added benefit of vadadustat.

[3] 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). 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, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Vadadustat – probability and extent of added benefit

Therapeutic indication	**ACT[a, b]**	**Probability and extent of added benefit**
Adult patients with symptomatic anaemia associated with chronic kidney disease (CKD)[c] who are on chronic maintenance dialysis	▪ Darbepoetin alfa or ▪ epoetin alfa or ▪ epoetin beta or ▪ epoetin theta or ▪ epoetin zeta or ▪ methoxy polyethylene glycol-epoetin beta	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, the use of erythropoiesis-stimulating agents (ESAs) requires that other causes of anaemia (in particular iron deficiency) have been ruled out. In addition, the specifications in the respective Summary of Product Characteristics and the specifics of the German health care context must be taken into account.
c. In the present therapeutic indication, it is assumed in accordance with the G-BA that guideline- and approval-compliant treatment is ensured in both study arms for any deficiency states that could cause corresponding specific types of anaemia (e.g. iron, water-soluble vitamins).

ACT: appropriate comparator therapy; CKD: chronic kidney disease; ESA: erythropoiesis-stimulating agent; G-BA: Federal Joint Committee

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

I 2 Research question

The aim of the present report is to assess the added benefit of vadadustat in comparison with the ACT in symptomatic anaemia associated with CKD in patients on chronic maintenance dialysis.

The research question presented in Table 4 is derived from the G-BA's specification of the ACT.

Table 4: Research question for the benefit assessment of vadadustat

Therapeutic indication	**ACT[a, b]**
Adult patients with symptomatic anaemia associated with chronic kidney disease (CKD)[c] who are on chronic maintenance dialysis	▪ Darbepoetin alfa or ▪ epoetin alfa or ▪ epoetin beta or ▪ epoetin theta or ▪ epoetin zeta or ▪ methoxy polyethylene glycol-epoetin beta
a. Presented is the ACT specified by the G-BA. b. According to the G-BA, the use of erythropoiesis-stimulating agents (ESAs) requires that other causes of anaemia (in particular iron deficiency) have been ruled out. In addition, the specifications in the respective Summary of Product Characteristics and the specifics of the German health care context must be taken into account. c. In the present therapeutic indication, it is assumed in accordance with the G-BA that guideline- and approval-compliant treatment is ensured in both study arms for any deficiency states that could cause corresponding specific types of anaemia (e.g. iron, water-soluble vitamins). ACT: appropriate comparator therapy; CKD: chronic kidney disease; ESA: erythropoiesis-stimulating agent; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of added benefit. This concurs with the company's inclusion criteria.

I 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 list on vadadustat (status: 2 April 2024)
- bibliographical literature search on vadadustat (last search on 2 April 2024)
- search in trial registries/trial results databases for studies on vadadustat (last search on 2 April 2024)
- search on the G-BA website for vadadustat (last search on 2 April 2024)

To check the completeness of the study pool:

- search in trial registries for studies on vadadustat (last search on 7 June 2024); for search strategies, see I Appendix A of the full dossier assessment

In addition to the studies AKB-6548-CI-0016 and AKB-6548-CI-0017 (hereinafter referred to as studies CI-0016 and CI-0017) used by the company and included in the present benefit assessment, the check of completeness of the study pool identified 2 further studies as potentially relevant.

Study MT-6548-J03

The MT-6548-J03 study is a double-blind randomized study comparing vadadustat with darbepoetin alfa, which, together with the regulatory dossier, was submitted to the regulatory authority as supportive information, according to the information in Module 4 A [3].

The company identified the MT-6548-J03 study, but excluded it from the study pool, on the one hand, because it was conducted exclusively in Japan so that transferability of the results to the European or German health care context was not guaranteed. The company referred to the differences in sex distribution and body mass index of the patients in comparison with the 2 included studies CI-0016 and CI-0017. On the other hand, the company considered the study to not provide any additional knowledge for the benefit assessment due to the small number of cases.

The MT-6548-J03 study included 323 exclusively Japanese patients with CKD and Hb levels between 9.5 and 12.0 g/dL who had been receiving dialysis for at least 12 weeks before the start of the screening period and ESA therapy for at least 8 weeks. Patients were randomly allocated to treatment with either vadadustat (N = 162) or with darbepoetin alfa (N = 161). Outcomes of this study included Hb-associated measures, other morbidity outcomes, health-related quality of life, and AEs.

According to the inclusion/exclusion criteria, patients with anaemia due to factors other than CKD were to be excluded from the study. Another inclusion criterion was the presence of a serum ferritin level > 100 ng/mL or transferrin saturation (TSAT) > 20% during screening. However, there is uncertainty as to the extent to which the presence of iron deficiency as the cause of symptomatic anaemia can be ruled out before starting treatment. Patients who were diagnosed with iron deficiency at screening received iron supplementation during the screening period. The study protocol did not require a sufficient observation period of the development of Hb levels after iron supplementation. Only the iron parameters were to be checked. At the start of treatment, approx. 40% (39.5% versus 43.5%) of the patients included in the study had ferritin levels below 100 ng/mL, and approx. 20% (19.1% versus 22.4%) had TSAT levels below 20%. It is not clear from the study documents whether it was ensured that the therapeutic indication of symptomatic anaemia persisted even after iron supplementation for detected iron deficiency.

With a total of 323 patients, the study comprises less than 10% of the study population of the 2 included studies CI-0016 and CI-0017 (N = 3923 in total). Even assuming that, after clarification of the uncertainties described, this is a relevant study for the present research question, it can be assumed that the influence on the results of the present benefit assessment is low.

Study AKB-6548-CI-0036

Together with the regulatory dossier, the AKB-6548-CI-0036 study was submitted to the regulatory authority as supportive information, according to the information in Module 4 A [4]. The company identified this study, but excluded it from the study pool because the dosage of vadadustat does not correspond to the information in the SPC.

The AKB-6548-CI-0036 study is an open-label, 3-arm, 1:1:1 randomized study comparing vadadustat given once daily and vadadustat given 3 times weekly with darbepoetin alfa. Administration of vadadustat 3 times a week does not comply with the recommendations of the SPC, which is why the following information relates exclusively to the vadadustat arm with once-daily administration and the darbepoetin alfa arm.

The vadadustat and darbepoetin alfa arms included 105 and 108 patients with CKD and Hb levels between 8.0 and 11 g/dL (centres in the United States) or between 9.0 and 12.0 g/dL (centres in Europe) who had been receiving dialysis for at least 12 weeks before the start of the screening period and ESA therapy for 8 weeks (before Visit 2).

Randomization was stratified with respect to mean weekly darbepoetin alfa dose (or ESA equivalent) before Visit 2 of the screening, with the 2 strata of low-dose darbepoetin alfa group and high-dose darbepoetin alfa group. Outcomes of this study included Hb-associated measures, other morbidity outcomes, health-related quality of life, and AEs.

The daily starting dose of vadadustat was determined based on the average weekly dose of darbepoetin alfa (or ESA equivalent) before the start of the study. The group with low previous dose of darbepoetin alfa received an initial vadadustat dose of 300 mg/day, while the group with high previous dose of darbepoetin alfa received an initial vadadustat dose of 450 mg/day. The dosage of vadadustat was intended to range from 150 mg/day to a maximum of 900 mg/day.

The approval-compliant administration of vadadustat is at a starting dose of 300 mg/day. Accordingly, the subpopulation of patients in both study arms, who were equally allocated to both study arms according to the stratum of the low-dose darbepoetin alfa group, is of potential relevance for the present benefit assessment. These are 80 versus 85 patients (vadadustat versus darbepoetin alfa). For this subpopulation, results on patient-relevant outcomes based on subgroup analyses are available in the study. One uncertainty is that the maximum dosage of 900 mg/day permitted in the vadadustat arm deviates from the approved dosage (600 mg/day). The available information in the study documents suggests that only a small proportion of the patient group with an initial vadadustat dosage of 300 mg/day exceeded the maximum approval-compliant dosage during the course of the study. However, specific data for this patient population is lacking.

With a total of 165 patients, the potentially relevant subpopulation in both study arms comprises about 4% of the study population of the 2 included studies CI-0016 and CI-0017 (N = 3923 in total). The influence on the results of the present benefit assessment is therefore presumably low. The non-inclusion of the results of this study in the present benefit assessment is therefore without consequence.

I 3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: vadadustat vs. darbepoetin alfa

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
AKB-6548-CI-0016 (CI-0016[d])	Yes	Yes[e]	Yes	Yes [5,6]	Yes [7,8]	Yes [9]
AKB-6548-CI-0017 (CI-0017[d])	Yes	Yes[e]	Yes	Yes [6,10]	Yes [11,12]	Yes [9]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to by this acronym.
e. In 2023, the company took over the approval for vadadustat from the study sponsor Akebia Therapeutics.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

This study pool is consistent with that selected by the company.

I 3.2 Study characteristics

Table 6 and Table 7 describe the studies used for the benefit assessment.

Table 6: Characteristics of the included studies – RCT, direct comparison: vadadustat vs. darbepoetin alfa (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
CI-0016	RCT, open-label, parallel	Adults (≥ 18 years) with anaemia due to end-stage CKD: ▪ who initiated chronic haemodialysis or peritoneal dialysis ≤ 16 weeks prior to screening ▪ with mean screening Hb between 8.0 and 11.0 g/dL[b] ▪ without long-term ESA pretreatment; long-term ESA pretreatment was permitted as of protocol version 3 (8/2017)[c] ▪ with serum ferritin ≥ 100 ng/mL and TSAT ≥ 20% at screening ▪ with folate and vitamin B12 measurements ≥ lower limit of normal at screening	Vadadustat: (N = 181) Darbepoetin alfa (N = 188)	Screening: 8 weeks Treatment: until meeting a discontinuation criterion[d], or until the global study end[e] (minimum 36 weeks, maximum 208 weeks) Observation: up to 4 weeks after the global study end[e], or until lost to follow-up, withdrawal of consent, or death	83 centres in: Argentina, Brazil, Germany, Italy, Korea, Mexico, Poland, Portugal, Russia, Ukraine, United States 7/2016–1/2020	Primary[f]: ▪ Hb value in Weeks 24–36 ▪ MACE (death from any cause, non-fatal myocardial infarction, or non-fatal stroke) Secondary: morbidity, AEs

Table 6: Characteristics of the included studies – RCT, direct comparison: vadadustat vs. darbepoetin alfa (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
CI-0017	RCT, open-label, parallel	Adults (≥ 18 years) with anaemia due to end-stage CKD: ▪ who initiated chronic haemodialysis or peritoneal dialysis ≥ 12 weeks prior to screening ▪ with long-term ESA treatment and administration of at least one dose within 6 weeks before or during screening ▪ with mean screening Hb between 8.0 and 11.0 g/dL in the United States, and between 9.0 and 12.0 g/dL in other countries ▪ with serum ferritin ≥ 100 ng/mL and TSAT ≥ 20% at screening ▪ with folate and vitamin B12 measurements ≥ lower limit of normal at screening	Vadadustat: (N = 1777) Darbepoetin alfa (N = 1777)	Screening: 8 weeks Treatment: until meeting a discontinuation criterion[d], or until the global study end[e] (minimum 36 weeks, maximum 208 weeks) Observation: up to 4 weeks after the global study end[e], or until lost to follow-up, withdrawal of consent, or death	275 centres in: Argentina, Australia, Brazil, Bulgaria, France, Germany, Israel, Italy, Korea, Mexico, Poland, Portugal, Russia, Serbia, Ukraine, United Kingdom, United States 8/2016–1/2020	Primary[f]: ▪ Hb value in Weeks 24–36 ▪ MACE (death from any cause, non-fatal myocardial infarction, or non-fatal stroke) Secondary: morbidity, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. This range was only introduced with protocol version 4 from 1/2018, the previous versions required an Hb value < 10.0 g/dL.
c. In protocol versions 1-2, ESA pretreatment was only permitted as a maximum of 2 doses. As of protocol version 3 (8/2017), long-term ESA pretreatment below the ESA resistance threshold was permitted. This was defined as follows:
- epoetin > 7700 units/dose 3 times per week or > 23 000 units per week;
- darbepoetin alfa > 100 µg/week;
- methoxy polyethylene glycol-epoetin beta > 100 µg every other week or > 200 µg every month.

d. Discontinuation criteria were the following: unacceptable toxicity, investigator or patient decision, withdrawal of consent, pregnancy, kidney transplant, lack of efficacy.
e. Global study completion was planned after accrual of approx. 631 MACE over the studies CI-0016 and CI-0017, but not before all patients have had the opportunity to have their Visit 13 (Week 36 +/- 5 days). In Module 4 A, contrary to the study protocol, the observation period is described as being linked to the treatment duration for all outcomes.
f. The Hb level in Weeks 24–36 was recorded as the primary efficacy outcome, and MACE as the primary harm outcome.

Table 6: Characteristics of the included studies – RCT, direct comparison: vadadustat vs. darbepoetin alfa (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
AE: adverse event; CKD: chronic kidney disease; ESA: erythropoiesis-stimulating agent; Hb: haemoglobin; MACE: major adverse cardiovascular event; N: number of randomized patients; RCT: randomized controlled trial; TSAT: transferrin saturation						

Table 7: Characteristics of the intervention – RCT, direct comparison: vadadustat vs. darbepoetin alfa (multipage table)

Study	Intervention	Comparison
CI-0016	Vadadustat oral ▪ Starting dose: 300 mg/day	Darbepoetin alfa, SC or IV[a] ▪ Starting dose[b]: ▫ Patients without long-term ESA pretreatment: darbepoetin alfa in accordance with local prescribing information (Prescribing Information for the United States, European Summary of Product Characteristics for all other countries) ▫ Patients who were already receiving darbepoetin alfa: continuation of the previous dosing regimen ▫ Patients with an ESA pretreatment other than darbepoetin alfa: switch to darbepoetin alfa according to the local prescribing information
	Dose adjustments: Dose increase or dose reduction depending on target Hb levels (10.0 g/dL to 11.0 g/dL in the United States, and 10.0 g/dL to 12.0 g/dL in other countries)[c]; dose increases were not permitted more frequently than every 4 weeks, dose reductions were permitted more frequently. ▪ Dose options of vadadustat: 150, 300, 450 or 600 mg/day orally, adjustment according to the algorithm in the study protocol	▪ Adjustment of darbepoetin alfa in approx. 25% steps according to the algorithms of the local prescribing information
	Pretreatment ***Allowed*** ▪ ESA pretreatment: see Table 6 ***Disallowed*** ▪ red blood cell transfusion within 8 weeks prior to randomization ▪ investigational medication or participation in an investigational study within 30 days or 5 half-lives of the investigational medication ▪ HIF-PHI other than vadadustat	

Table 7: Characteristics of the intervention – RCT, direct comparison: vadadustat vs. darbepoetin alfa (multipage table)

Study	Intervention	Comparison
	Concomitant treatment ***Disallowed*** ▪ During treatment with study medication: ESAs other than the study medication (exception: rescue therapy or after discontinuation of study treatment, see below) ***Allowed*** ▪ Required: iron supplementation (IV, oral, or intradialytic) to maintain ferritin ≥ 100 ng/mL or TSAT ≥ 20%, or continuation of supplementation prior to study entry; iron containing phosphate binders are allowed ▪ After discontinuation of study treatment: further treatment with standard therapy (including ESA and iron) at the discretion of the investigator ▪ Rescue therapy[d] in accordance with local guidelines ▫ ESA (from Week 6) or ▫ red blood cell transfusion ▫ phlebotomy: optional, if Hb ≥ 14.0 g/dL or the rate of Hb elevation raises concern ▪ Dose restriction for the statins simvastatin (max. 20 mg/day) and rosuvastatin (max. 10 mg/day)	
CI-0017	Vadadustat oral ▪ Starting dose: 300 mg/day	Darbepoetin alfa, SC or IV[a] ▪ Starting dose: ▫ Patients who were already receiving darbepoetin alfa: continuation of the previous dosing regimen ▫ Patients with an ESA pretreatment other than darbepoetin alfa: switch to darbepoetin alfa according to the local prescribing information
	Dose increase or dose reduction: see CI-0016	
	Prior and concomitant treatment: see CI-0016	

a. Intravenous administration for haemodialysis and subcutaneous administration for peritoneal dialysis.
b. The study documents do not contain any specific information on dosage; instead, reference is made to the local product label.
c. The investigator was to consider Hb progression and the response to ESA when adjusting the dose according to the protocol recommendation.
d. ESA rescue therapy in the event of worsening anaemia symptoms and Hb < 9.5 g/dL, or if otherwise indicated by the investigator. Patients in the darbepoetin alfa arm could receive a different ESA as rescue therapy. Study treatment could be continued during the transfusion; in the event of rescue therapy with ESA, study treatment had to be interrupted for 2–14 days. Rescue therapy was to be stopped when Hb was 10 g/dL.

ESA: erythropoiesis-stimulating agent; HIF: hypoxia-inducible factor; HIF-PHI: HIF prolyl-hydroxylase inhibitor; IV: intravenous; RCT: randomized controlled trial; SC: subcutaneous; TSAT: transferrin saturation

Study design

The studies CI-0016 and CI-0017 submitted by the company are part of a global phase 3 study programme of the study sponsor, which comprises a total of 4 studies ($INNO_2VATE$ studies: CI-0016 and CI-0017; PRO_2TECT studies: CI-0014 and CI-0015). The primary objective of these

studies is to investigate the efficacy and cardiovascular safety of vadadustat compared with darbepoetin alfa in the treatment of anaemia in patients with dialysis-dependent ($INNO_2VATE$ studies) or non-dialysis-dependent (PRO_2TECT studies) CKD. The present benefit assessment relates exclusively to the research question of anaemia treatment in patients with dialysis-dependent CKD.

Studies CI-0016 and CI-0017

The studies CI-0016 und CI-0017 were designed jointly, conducted in parallel and have a joint SAP. Both studies together were designed to test the non-inferiority of vadadustat compared with darbepoetin alfa. The study protocols, including the protocol amendments, are identical except for a few specific differences. The differences are listed below in the joint study description.

Both studies are unblinded, multicentre RCTs comparing vadadustat with the ESA darbepoetin alfa. They included patients with end-stage chronic kidney disease who were receiving maintenance dialysis (either haemodialysis or peritoneal dialysis). Other causes of anaemia – in particular iron and water-soluble vitamin deficiency – had to be ruled out before enrolment. Patients with pre-existing cardiovascular conditions such as severe heart failure or acute coronary syndrome were excluded from both studies.

In the CI-0016 study, a total of 369 patients were randomly assigned in a 1:1 ratio to treatment with vadadustat (N = 181) or darbepoetin alfa (N = 188). Stratification was based on geographic region (United States, Europe, rest of the world), NYHA heart failure class (0 or I versus II or III), and study entry Hb level (< 9.5 g/dL; ≥ 9.5 g/dL).

In the CI-0017 study, 3554 patients were randomized in a 1:1 ratio to the intervention arm with vadadustat (N = 1777) or the comparator arm with darbepoetin alfa (N = 1777). Treatment was also stratified by geographic region (United States, Europe, rest of the world), NYHA heart failure class (0 or I versus II or III), and study entry Hb level, but with higher cut-off values (< 10.0 g/dL; ≥ 10.0 g/dL) than in the CI-0016 study.

The CI-0016 study included patients with anaemia who had recently (within 16 weeks) initiated maintenance dialysis. In accordance with the initial study protocol, only patients without pre-existing long-term ESA therapy were initially enrolled, who therefore entered the correction period of anaemia treatment at the start of the study treatment. However, a protocol amendment (from version 3) subsequently allowed the inclusion of patients with prior ESA treatment. The CI-0017 study, in contrast, investigated patients who had been on dialysis for a longer period of time (at least 12 weeks). From the beginning of the study, only patients with pre-existing long-term ESA treatment were included, who were therefore already in the maintenance period of anaemia treatment at the start of the study treatment. In the intervention arms of both studies, any existing ESA treatment was discontinued in

favour of the intervention with vadadustat. A therapeutic indication for this treatment switch was not required.

In line with these differences between the 2 studies, the inclusion criterion for the presence of anaemia in study CI-0016 was defined as a screening Hb < 10.0 g/dL, or between 8.0 and 11.0 g/dL after the protocol amendment described above. In the CI-0017 study, Hb levels between 8.0 and 11.0 g/dL were required for inclusion at the US sites, and between 9.0 and 12.0 g/dL at sites outside of the United States.

In both studies, treatment with vadadustat was in compliance with the approval [13]. All patients received a starting dose of 300 mg/day. Treatment with darbepoetin alfa was largely in compliance with the specifications of the SPC [14]. Patients who were already being treated with darbepoetin alfa before the start of the study maintained their existing dosage and frequency. Switching from another ESA to darbepoetin alfa and dose adjustments were to be carried out in compliance with the information provided in the respective SPC. One discrepancy between the protocol and the SPC for darbepoetin alfa concerned the dose adjustment in the event of an Hb increase by more than 2 g/dL within 4 weeks. In this case, the SPC specifies a dose reduction, whereas the study protocol also allowed the dose to be maintained.

The duration of treatment was planned for a minimum of 36 weeks and a maximum of 208 weeks. After discontinuation of treatment, treatment in both study arms was to be continued in accordance with local standards without restrictions (including ESA therapy). It was not planned that patients in the comparator arm switch to the intervention arm treatment. The global study completion was planned for the time at which approx. 631 MACE had occurred (over both studies) and all included patients had the opportunity to have their Visit 13 (Week 36 +/- 5 days).

The primary outcomes of studies CI-0016 and CI-0017 were the efficacy outcome “change in Hb between baseline and Weeks 24–36”, and the harm outcome of MACE with the components of death from any cause, non-fatal myocardial infarction, and non-fatal stroke. Patient-relevant secondary outcomes were outcomes on morbidity and AEs. Health-related quality of life outcomes and patient-reported morbidity outcomes were not investigated in either study.

Further comments on the study design of CI-0016 and CI-0017

Joint consideration of patients with and without ESA pretreatment

As described above, study CI-0016 included patients with ESA pretreatment as well as patients without ESA pretreatment. Both populations are included in the target population of the present benefit assessment, and the G-BA defined only one research question. Both patient populations are therefore considered jointly for the present benefit assessment. Furthermore,

the subgroup analyses of the characteristic of ESA pretreatment presented by the company in Module 4 A do not indicate an effect modification by this characteristic for the patient-relevant outcomes of study CI-0016.

Presence of symptomatic anaemia

In neither study was the presence of symptoms of anaemia required by the approval of vadadustat [13] an explicit inclusion criterion. However, according to the SPCs, ESA treatment of anaemia in CKD is only approved in the presence of symptomatic anaemia [14-16]. Therefore, symptomatic anaemia is assumed to be present in patients in studies CI-0016 and CI-0017 who had been pretreated with ESA.

As described above, study CI-0016 also included patients without ESA pretreatment. These were a total of 192 patients, 89 in the vadadustat arm (49.2% of patients in this arm) and 103 (54.8%) in the darbepoetin alfa arm. A large proportion of these patients can also be assumed to have symptomatic anaemia. According to the Common Terminology Criteria for Adverse Events (CTCAE), anaemia with Hb values of < 10.0 to 8.0 g/dL is classified as grade 2 and therefore as symptomatic and in need of treatment [17]. According to the information in the study documents, the 192 patients without prior ESA treatment had mean Hb levels of 9.07 g/dL (vadadustat arm) and 8.85 g/dL (darbepoetin alfa arm) at the start of treatment. The information in the study documents also shows that at least 144 (75%) of the 192 patients without ESA pretreatment had Hb levels below 10.0 g/dL at the start of treatment. The presence of symptomatic anaemia can therefore potentially be called into question for fewer than 48 patients in the study. When considering studies CI-0016 and CI-0017 together, this corresponds to less than 1.5% of the study population of both studies and is therefore of no consequence for the present benefit assessment.

Differences in target Hb levels between study centres in the United States and Europe/rest of the world in studies CI-0016 and CI-0017

Depending on the location of the study centre (United States or Europe/rest of the world), the 2 studies CI-0016 and CI-0017 had different target Hb levels – to be achieved in the course of the study – for the treatment of renal anaemia under dialysis. These are based on the different specifications in the local prescribing information and guidelines of the United States and Europe/rest of the world [14,18-20].

In accordance with these specifications, target Hb levels in study centres in the United States were 10 to 11 g/dL, and target Hb levels in study centres in Europe/rest of the world were 10 to 12 g/dL. The values for Europe/rest of the world correspond to the recommendations and guidelines for everyday health care in Germany. Despite the high proportion of patients from the United States in the studies (a total of 2375 [61%] patients in both studies), the different target levels do not fundamentally call into question the transferability of the study results to

the German health care context (with the European Hb target level of 10 to 12 g/dL, which is decisive there).

This becomes clear, among other things, in the predefined subgroup analyses conducted in both studies (CI-0016 and CI-0017), and presented by the company in Module 4 A, for the characteristic of target Hb with the 2 subgroups "target Hb 10 to 11 g/dL" and "target Hb 10 to 12 g/dL". They showed only minor differences in Hb levels achieved in the course of the study despite different target levels for both subgroups. In study CI-0017, for example, the mean achieved Hb level was 10.2 versus 10.4 g/dL (vadadustat versus darbepoetin alfa) for the "target Hb 10 to 11 g/dL" subgroup, and 10.7 versus 10.8 g/dL (vadadustat versus darbepoetin alfa) for the "target Hb 10 to 12 g/dL" subgroup.

It should be noted that there is an effect modification for this subgroup characteristic (target Hb) for the outcomes of thromboembolic events and vascular access thrombosis (see I Appendix C of the full dossier assessment). For both outcomes, study CI-0017 showed a disadvantage of vadadustat compared with darbepoetin alfa for the "target Hb 10 to 11 g/dL" subgroup. For the "target Hb 10 to 12 g/dL", however, there was no difference between the 2 treatment groups, however. The disadvantage was therefore only shown in the subgroup with a target Hb that differs slightly from the research question, and there is also no conclusive medical rationale for the pattern of results, because in both arms of the larger CI-0017 study there were fewer thromboembolic events/vascular access thromboses in the subgroup with higher target Hb or higher mean Hb levels.

Protocol amendments

The protocols of both studies were changed several times after the start of the study. These amendments were made simultaneously for both studies, with the exception of an additional amendment for study CI-0016, which permitted prior ESA therapy of the patients as an inclusion criterion. There were thus a total of 6 (CI-0016) and 5 (CI-0017) protocol amendments during the study period of the 2 studies, introduced between 2017 and 2019. The 5 protocol amendments made for both studies, concerned, among other things, the non-inferiority criterion for the primary outcome of Hb level twice, the frequency of follow-up visits after discontinuation of therapy (from 9/2018 in agreement between investigator and patient) and the use of an interactive web response system to guide dose adjustments. The use of this system was discontinued from 1/2018 due to malfunctions. The protocol amendments from 9/2018 also clarified explicitly that the follow-up observation for all outcomes was to take place until global study completion, and corrected the misleading designation of "End of Study Visit" as "End of Treatment Visit".

Deviating information on the planned duration of follow-up observation in Module 4 A

In Module 4 A, the company specified the time from randomization to 4 weeks after the end of the treatment period as the recording period for all outcomes, with the exception of the outcome of freedom from transfusion. This is not consistent with the information in the study documents described above, according to which follow-up observation for all outcomes in studies CI-0016 and C-0017 was planned until global study completion. However, the results presented in Module 4 A for the individual outcomes correspond to the results presented in the study documents. For the present assessment, it is therefore assumed that the data presented in Module 4 A, in contrast to the information provided by the company, refer to an observation period up to the global study end. The particularities of the recording and analysis of the outcome of freedom from transfusion are described in Section I 4.1.

The different presentation in Module 4 may be due to the fact that the study protocol introduced the term “EOT” Visit (end of treatment) for the visit at the end of the study. The study centres were informed of the global study end date approx. 3 months before completion of the study (based on the number of MACE in both studies). Patients who were still receiving the study medication at that time, then had an end of treatment (EOT) visit and a follow-up visit 4 weeks later. The latter was also to be used to record the end of study (EOS) status. Patients who had already terminated the study treatment prematurely were to continue observation after the end of treatment. They had their EOT visit and the subsequent 4-week follow-up according to the initial protocol also at the global study completion (and therefore not directly after treatment discontinuation). Only protocol changes in September 2018 stipulated this EOT visit to be performed directly after discontinuation of treatment. Following the announcement of the global study completion, these patients were then to have an EOS visit, which ended their participation in the study. The frequency of visits from randomization to study end was specified in the initial protocol. With the protocol amendment in September 2018, this scheme only applied to patients under treatment; the frequency of visits after discontinuation of treatment was left to the agreement between treating physician and patient.

Table 8 shows the characteristics of the patients in the studies included.

Table 8: Characteristics of the study populations as well as discontinuation of the study/therapy – RCT, direct comparison: vadadustat vs. darbepoetin alfa (multipage table)

Study	CI-0016		CI-0017	
Characteristic Category	Vadadustat	Darbepoetin alfa	Vadadustat	Darbepoetin alfa
	N[a] = 181	N[a] = 188	N[a] = 1777	N[a] = 1777
Age [years], mean (SD)	57 (15)	56 (15)	58 (14)	58 (14)
Age group, n (%)				
< 65 years	122 (67)	137 (73)	1167 (66)	1161 (65)
≥ 65 years	59 (33)	51 (27)	610 (34)	616 (35)
Sex [F/M], %	41/59	40/60	44/56	44/56
Region, n (%)				
United States	97 (54)	102 (54)	1090 (61)	1086 (61)
EU[b]	26 (14)	16 (9)	254 (14)	281 (16)
Rest of the world[c]	58 (32)	70 (37)	433 (24)	410 (23)
Hb at baseline [g/dL], mean (SD)	9.4 (1.1)	9.2 (1.1)	10.2 (0.9)	10.2 (0.8)
Hb category, n (%)				
< 9.5 g/dL	94 (52)	99 (53)	–	–
≥ 9.5 g/dL	87 (48)	89 (47)	–	–
< 10.0 g/dL	–	–	620 (35)	619 (35)
≥ 10.0 g/dL	–	–	1157 (65)	1158 (65)
ESA pretreatment, n (%)	92 (51[d])	85 (45[d])	1765 (99[d])	1774 (> 99[d])
ESA dosage [IU/kg/week], mean (SD)	154.7 (113.3)	147.5 (115.0)	116.6 (109.4)	111.9 (109.7)
ESA dosage [IU/kg/week], n (%)				
≤ 90	36 (40)	30 (36)	916 (53)	968 (55)
> 90 and < 300	45 (50)	47 (57)	724 (42)	693 (39)
≥ 300	9 (10)	6 (7)	102 (6)	98 (6)
Serum ferritin at baseline [ng/mL], mean (SD)	469.7 (316.9)	527.8 (401.1)	846.8 (562.7)	840.7 (538.5)
TSAT at baseline (%), mean (SD)	31.3 (9.4)	34.2 (12.7)	38.1 (13.4)	37.6 (13.2)
Disease duration: time between CKD diagnosis and randomization [years], mean (SD)	4.8 (7.8)	4.2 (5.9)	6.7 (6.3)	6.9 (6.7)
Years since chronic dialysis initiated, mean (SD)	0.1 (0.1)	0.2 (0.3)	4.0 (4.0)	3.9 (4.0)
CKD aetiology, n (%)				
Diabetes	81 (45)	82 (44)	794 (45)	820 (46)
Hypertension	79 (44)	85 (45)	892 (50)	908 (51)
Autoimmune/glomerulonephritis/vasculitis	24 (13)	29 (15)	175 (10)	185 (10)
Interstitial nephritis/pyelonephritis	11 (6)	11 (6)	85 (5)	71 (4)
Cystic/hereditary/congenital disease	7 (4)	8 (4)	69 (4)	63 (4)
Neoplasms/tumours	0 (0)	1 (< 1)	7 (< 1)	7 (< 1)
Other	16 (9)	24 (13)	195 (11)	205 (12)

Table 8: Characteristics of the study populations as well as discontinuation of the study/therapy – RCT, direct comparison: vadadustat vs. darbepoetin alfa (multipage table)

Study	CI-0016		CI-0017	
Characteristic Category	Vadadustat	Darbepoetin alfa	Vadadustat	Darbepoetin alfa
	N[a] = 181	N[a] = 188	N[a] = 1777	N[a] = 1777
History of cardiovascular disease, n (%)				
Yes	69 (38)	73 (39)	868 (49)	932 (52)
No	112 (62)	115 (61)	909 (51)	845 (48)
History of heart failure, n (%)				
Yes	16 (9[d])	15 (8[d])	361 (20[d])	368 (21[d])
No	54 (30[d])	62 (33[d])	990 (56[d])	985 (55[d])
Unknown	111 (61[d])	111 (59[d])	426 (24[d])	424 (24[d])
Treatment discontinuation, n (%)	60 (33.1)[e]	49 (26.1)[e]	899 (50.6)[f]	653 (36.7)[f]
Study discontinuation, n (%)	21 (11.6)[g]	23 (12.2)[g]	352 (19.8)[h]	356 (20.0)[h]

a. Number of randomized patients. Data in this table that are based on other patient numbers are marked in the corresponding line if the deviation is relevant (> 10%).
b. EU as categorized in the study: Germany, Italy, Poland, Portugal (in study CI-0016), and additionally Bulgaria, France, Serbia and the United Kingdom (in study CI-0017).
c. Rest of the world as categorized in the study: Argentina, Brazil, Mexico, Republic of Korea, Russia, Ukraine (in study CI-0016), and additionally Australia, Canada and Israel (in study CI-0017)
d. Institute's calculation.
e. Frequent reasons for treatment discontinuation in the intervention vs. comparator arm were the following: patient decision (11% vs. 5%), adverse events (8% vs. 3%), investigator decision (6% vs. 1%), kidney transplant (4% vs. 6%), death (1% vs. 6%), other reasons (2% vs. 5%). 2 vs. 2 patients did not receive treatment with the study medication.
f. Frequent reasons for treatment discontinuation in the intervention vs. comparator arm were the following: patient decision (12% vs. 6%), adverse events (6% vs. 3%), investigator decision (5% vs. 2%), kidney transplant (6% vs. 5%), death (8% vs. 10%), other reasons (10% vs. 10%). 9 vs. 8 patients did not receive treatment with the study medication.
g. A common reason for study discontinuation in the intervention vs. comparator arm was death (8% vs. 10%).
h. A common reason for study discontinuation in the intervention vs. comparator arm was death (15% vs. 16%).

CKD: chronic kidney disease; ESA: erythropoiesis-stimulating agent; F: female; Hb: haemoglobin; IU: international units; M: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; TSAT: transferrin saturation

The demographic and clinical characteristics of the patients in both treatment arms were largely similar. The mean age of the patients at study entry was 58 years. The majority of patients in both studies were treated in the United States, fewer than 15% were treated in Europe, and within Europe, 6% were treated in Italy, France, Portugal, Poland, Germany or the United Kingdom. Permanent dialysis was initiated on average 0.2 years before randomization in study CI-0016 and approx. 4 years before randomization in study CI-0017. Mean Hb at the start of study treatment was approx. 9.2 g/dL in study CI-0016 and approx. 10.2 g/dL in study CI-0017.

The proportion of patients who discontinued treatment was notably higher in the intervention arm than in the comparator arm (study CI-0016: 33.1% versus 26.1%; study CI-0017: 50.6% versus 36.7%). The most frequently cited reasons for this in both studies, in descending order, were patient decision, AEs, and investigator decision. Discontinuation of the study for reasons other than death was rare and affected less than 4% of patients in each case.

Table 9 shows the mean and median treatment durations of the patients and information on the observation periods.

Table 9: Information on the course of the study – RCT, direct comparison: vadadustat vs. darbepoetin alfa

Study **Duration of the study phase**	**CI-0016**		**CI-0017**	
	Vadadustat N = 179	Darbepoetin alfa N = 186	Vadadustat N = 1768	Darbepoetin alfa N = 1769
Treatment duration [weeks]				
Median [Q1; Q3]	45.0 [28.0; 73.1]	50.1 [36.0; 80.1]	56.1 [28.9; 85.4]	72.1 [44.9; 98.7]
Mean (SD)	52.8 (34.4)	59.5 (35.6)	60.1 (37.8)	72.5 (36.6)
Observation period [weeks]	ND	ND	ND	ND

N: number of patients with at least one dose of the study medication; ND: no data; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation

The treatment duration showed clear differences between the 2 arms, corresponding to the rate of treatment discontinuation in both studies. In study CI-0016, the median treatment duration in the comparator arm was approx. 11% longer (difference in median treatment duration of 5.1 months); in study CI-0017, the median treatment duration in the comparator arm was approx. 29% longer (difference in median treatment duration of 16.0 months).

No information is available on the observation period of the individual outcomes in Module 4 A. As described above, there is contradictory information on the planned observation period between the study protocol and Module 4 A. In Module 4 A, the observation period is described as being linked to the treatment duration for all outcomes, except for the outcome of freedom from transfusion. In contrast, the study protocol stipulated a fixed planned observation period for all outcomes (until global study completion) regardless of treatment duration. Due to identical results between Module 4 A and the clinical study report, it is assumed for the present benefit assessment that the data in Module 4 A refer to the entire study period.

According to the company's information in Module 4 A, the recording period for the outcome of freedom from transfusion, unlike for all other outcomes, was from Week 0 to Week 52. According to the study protocols of studies CI-0016 and CI-0017, administration of transfusions was indeed to be documented until Week 52. However, it should be noted that,

according to the information in the study documents, only the results up to the patients' discontinuation of treatment were included in the analysis of the outcome. The results presented by the company in Module 4 A are consistent with the results presented in the study documents. It can therefore be assumed that, contrary to the information provided by the company, the data on the outcome of freedom from transfusion in Module 4 A only cover the period up to treatment discontinuation. As shown in Table 9, the duration of treatment was shorter for patients in the vadadustat arm than for patients in the darbepoetin alfa arm. The resulting consequence is described in Section I 4.1.

Meta-analytical summary of studies CI-0016 and CI-0017

Studies CI-0016 and CI-0017 are each relevant with regard to the research question of the present benefit assessment. Both studies were jointly planned by the same company, conducted in parallel during the same period (> 90% of the investigators of study CI-0016 were also investigators of study CI-0017) and analysed according to a common SAP. As described in Section I 3.2, there are few protocol differences between the studies, which affect the patient population included in each case. While the CI-0017 study investigated patients with a longer history of dialysis (more than 12 weeks), the CI-0016 study included patients with anaemia after newly initiated (for a maximum of 16 weeks) maintenance dialysis. These differences are not considered to be so serious as to fundamentally preclude a meta-analytical summary of the 2 studies. However, there are limitations with regard to the independence of the 2 studies. These result in particular from the cross-study statistical planning for the key outcome of MACE, while at the same time the study CI-0016 was small. These limitations are taken into account when assessing the certainty of conclusions (see Section I 4.2).

Risk of bias across outcomes (study level)

Table 10 shows the risk of bias across outcomes (risk of bias at study level).

Table 10: Risk of bias across outcomes (study level) – RCT, direct comparison: vadadustat vs. darbepoetin alfa

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
CI-0016	Yes	Yes	No	No	Yes	Yes	Low
CI-0017	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for both studies.

Limitations resulting from the open-label study design are described in Section I 4.2 under outcome-specific risk of bias.

Transferability of the study results to the German health care context

In the company's view, the results of the studies CI-0016 and CI-0017 are transferable to the German health care context. To estimate the transferability of the average age, sex distribution and distribution of dialysis type, the company used data from the IQTIG Annual Report 2019 on Quality in Dialysis [21]. The company pointed out that this report considered all patients with dialysis-dependent CKD, without making any further restriction to patients with symptomatic anaemia. Due to the high proportion of dialysis-dependent patients of around 83% who receive ESA therapy and must therefore have symptomatic anaemia according to the approval, the company nevertheless considered the data mentioned to be a valid basis for information. According to the company, all considered characteristics sufficiently corresponded to the actual German health care setting.

Besides the study population, the company also considered the medication used in the CI-0016 and CI-0017 studies to be sufficiently transferable to the German health care context. Although the recommendations regarding target Hb and thus also the algorithms for dose adjustment of vadadustat and darbepoetin alfa differed between Europe and the United States, the company considered the studies to fulfil the resulting requirements of the European Medicines Agency (EMA), according to which at least 30 to 40% of patients should be treated in compliance with the SPC. According to the company, 53.9% of patients in study CI-0016 were treated in compliance with the US prescribing information, and 46.1% in compliance with the European SPC; and 61.2% of patients in study CI-0017 were treated in compliance with the US prescribing information, and 38.8% in compliance with the European SPC. As a result, the company considered the study results to be representative for the EU in accordance with EMA requirements. In addition, the company noted that the US target Hb range of 10.0 to 11.0 g/dL is within the European target Hb range of 10.0 to 12.0 g/dL, ruling out, from a European perspective, undertreatment of the study participants treated in compliance with the US prescribing information. In addition, from the company's point of view, the subgroup results by region or target Hb presented in Section 4.3.1.3.2 of Module 4 A show only isolated heterogeneity. The general care situation of the study participants can therefore be considered comparable to the care situation in Europe and Germany, the company concluded.

The company did not provide any further information on the transferability of the study results to the German health care context. For the transferability of the study results, see also above in this section (presentation of the regional differences in target Hb) and Section I 4.1 (comments on the outcome of freedom from transfusion).

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - All-cause mortality
- Morbidity
  - Freedom from transfusion
- Health-related quality of life
- Side effects
  - SAEs
  - Discontinuation due to AEs
  - MACE, composite cardiovascular outcome consisting of the following components:
    - Cardiovascular death
    - Non-fatal myocardial infarction
    - Non-fatal stroke
  - Hospitalization for heart failure
  - Thromboembolic events, composite outcome consisting of the following components:
    - Arterial thrombosis
    - Deep vein thrombosis
    - Pulmonary embolism
    - Vascular access thrombosis
  - Hepatotoxicity (SAEs, Standardized Medical Dictionary for Regulatory Activities Query [SMQ])
  - Other specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4).

Table 11 shows the outcomes for which data were available in the studies included.

Table 11: Matrix of outcomes – RCT, direct comparison: vadadustat vs. darbepoetin alfa

Study	Outcomes									
	All-cause mortality[a]	Freedom from transfusion[b]	Health-related quality of life	SAEs[c]	Discontinuation due to AEs	MACE[d]	Hospitalization for heart failure	Thromboembolic events[e]	Hepatotoxicity (SAEs, SMQ[f])	Further specific AEs[g]
CI-0016	Yes	No[h]	No[i]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CI-0017	Yes	No[h]	No[i]	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Mortality was recorded in the context of the safety analysis, as part of the composite MACE outcome.
b. The protocol defined the outcome as freedom from transfusion from baseline to Week 52, but only the period up to treatment discontinuation was included in the analyses.
c. Worsening anaemia was not rated as AE in the studies unless the worsening anaemia was due to a cause other than CKD.
d. Composite cardiovascular outcome consisting of the following components: cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke; after review by the outcome adjudication committee.
e. Consisting of the following individual events: arterial thrombosis, deep vein thrombosis, pulmonary embolism, and vascular access thrombosis; after review by the outcome adjudication committee.
f. Operationalized as Comprehensive SMQ broad.
g. The following events are considered (coded according to MedDRA): cardiac disorders (SOC, SAE), neoplasms benign, malignant and unspecified (SOC, SAE), urinary tract infection (PT, SAE), and mental status changed (PT, SAE).
h. No suitable data available; for reasons, see the following text section.
i. No outcomes in the category of health-related quality of life were recorded.

AE: adverse event; CKD: chronic kidney disease; MACE: major adverse cardiovascular event; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class

Notes on the outcomes

Analyses of the outcome of freedom from transfusion

In the present therapeutic indication, long-term or sustainable independence of transfusions while maintaining a defined minimum Hb level is a primary treatment goal, with the aim of controlling anaemia and anaemia-related symptoms while at the same time avoiding transfusions. Long-term complications resulting from transfusions, in particular the symptoms of chronic iron overload, cannot usually be recorded within the usual study duration. Due to the importance of these late complications, the avoidance of transfusions is considered patient relevant. In the present therapeutic indication, transfusions can also lead to the formation of alloantibodies, which make a frequently indicated kidney transplant more difficult. In contrast, aspects of (anaemia-related) symptoms (e.g. fatigue) and quality of life,

as well as psychosocial aspects (burden from transfusion therapy), can and should be represented directly via patient-reported outcomes in clinical trials.

Investigators in studies CI-0016 and CI-0017 were to use their local institution's transfusion guidelines when determining whether to transfuse a study participant. In general, in the event of an acute or severe loss of blood, a red blood cell transfusion was to be administered as clinically indicated. In less severe instances but where there was worsening of anaemia or moderate to severe symptoms of anaemia, red blood cell transfusions were permitted at the discretion of the investigator given medical necessity. The reasons for a red blood cell transfusion had to be recorded in the corresponding case report form. It is not clear from the study documents whether standardized instructions with criteria (e.g. for laboratory parameters or symptoms) were available. The absence of criteria for the administration of transfusions results in an uncertainty regarding the extent to which different study centres administered transfusions under comparable conditions and whether their practices are in line with the German health care context.

In Module 4 A, the company presented analyses for the outcome of freedom from transfusion, which, according to the company, includes the proportion of patients who did not receive red blood cell transfusion between baseline and Week 52.

As described above, it can be inferred from the study protocol that packed red blood cell transfusions were recorded until the end of the study, regardless of the time of treatment discontinuation. However, only transfusions until Week 52 were considered in the predefined analyses. In addition, the analyses presented in the study documents include only packed red blood cell transfusions until treatment discontinuation. This means that patients who received a transfusion after discontinuing treatment were still counted as transfusion-free, but a connection between discontinuation and subsequent transfusion cannot be ruled out. This approach is not appropriate. In addition, the observation period of the outcome was notably shorter in the vadadustat arm than in the darbepoetin alfa arm (see Table 9), so that a higher proportion of patients in the vadadustat arm had the opportunity to achieve freedom from transfusion over the shorter observation period than in the darbepoetin alfa arm. Analyses of the proportion of patients with freedom from transfusion are required that include complete observation also after discontinuation of treatment. A complete analysis of the data recorded for the outcome of freedom from transfusion is particularly necessary because, based on the time-to-event analyses for the counter-event (time to first transfusion) reported in the study documents for this outcome, it cannot be ruled out that a disadvantage could arise for the intervention arm when considering the entire study period. The analyses submitted by the company for the outcome of transfusion avoidance are therefore disregarded in the benefit assessment. In addition to the complete analysis, the benefit assessment also requires data

on the observation period per arm, as it is unclear to what extent different observation periods exist and whether time-to-event analyses may therefore be necessary (see Section I 3.2).

Health-related quality of life

Data on outcomes in the category of health-related quality of life were not recorded in the studies CI-0016 and CI-0017.

Subjective component of the definition of SAEs in the study protocols

In the operationalization of the outcome of SAEs, the company listed all qualifying events of the standardized definition of the International Conference on Harmonisation [22] in the protocols for both studies submitted, supplementing them in particular with the following aspect. The study stipulated that any other event that the investigator or sponsor judged to be serious was also considered serious. If there was any doubt as to whether the event constituted an AE or an SAE, it was to be treated as an SAE. This point allows a subjective categorization of an AE as an SAE by both the investigator and the sponsor. The specification "Other", which included this subjective component, could be marked in the case report form when stating the reason for the classification of an AE as an SAE. It is not clear from the dossier how many events these were. The uncertainty that arises for the interpretation of the results due to the definition of SAEs in the study is described in the assessment of the risk of bias for the results of these outcomes (Section I 4.2).

Further uncertainty regarding the recording of AEs overall is due to the specifications in the protocol for the follow-up observation of the outcomes after treatment discontinuation. The original protocol stipulated that all planned visits should be attended even after the premature end of treatment. With protocol amendments in September 2018, visit schedule and assessments after premature end of treatment were left to the agreement between investigator and patient. The End of Study (EOS) visit was still scheduled for all patients. The described specifications after the protocol amendment did not reliably guarantee uniform and complete recording of AEs in both arms.

MACE, thromboembolic events, and hospitalization for heart failure

The outcomes summarized as MACE outcomes in the 2 studies CI-0016 and CI-0017 serve to record the specific cardiovascular risk profile of the study medication in the intervention and comparator arms. All events for these outcomes and components were adjudicated by a blinded committee (Endpoint Adjudication Committee).

The MACE outcomes in the 2 studies CI-0016 and CI-0017 were defined as composite outcomes with various individual components. The 3-component MACE with the components of death from any cause, non-fatal myocardial infarction and non-fatal stroke was a primary outcome of the studies, where it was referred to as "MACE" for short. "Cardiovascular MACE"

was another 3-component outcome, which included death due to a cardiovascular event, non-fatal myocardial infarction and non-fatal stroke.

Both studies also recorded an extended 5-component MACE, in which the 2 components of hospitalization for heart failure and thromboembolic events were considered in addition to the components of death from any cause, non-fatal myocardial infarction and non-fatal stroke.

The thromboembolic events were composed of the subcomponents of arterial thromboses, deep vein thromboses, pulmonary embolisms and vascular access thromboses.

For the present benefit assessment, cardiovascular MACE (death due to cardiovascular events, non-fatal myocardial infarction and non-fatal stroke) is used to represent cardiovascular events and is referred to as “MACE” for short. Thromboembolic events and hospitalization for heart failure are also included and considered separately.

Hepatotoxicity

Monitoring of hepatotoxicity was mandated in the EMA Risk Management Plan for vadadustat as part of the European approval. In the studies presented, the outcome of hepatotoxicity was operationalized using a Comprehensive SMQ specified in the SAP.

Other specific AEs

The above comments on SAEs also apply to outcomes in the category of other specific AEs, depending on their severity.

I 4.2 Risk of bias

Table 12 describes the risk of bias for the results of the relevant outcomes.

Table 12: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: vadadustat vs. darbepoetin alfa

Study	Study level	Outcomes									
		All-cause mortality[a]	Freedom from transfusion[b]	Health-related quality of life	SAEs[c]	Discontinuation due to AEs	MACE[d]	Hospitalization for heart failure	Thromboembolic events[e]	Hepatotoxicity (SAEs, SMQ[f])	Further specific AEs[g]
CI-0016	L	L	–[h]	–[i]	H[j]	H[k]	L	L	L	H[j]	H[j]
CI-0017	L	L	–[h]	–[i]	H[j]	H[k]	L	L	L	H[j]	H[j]

a. Mortality was recorded in the context of the safety analysis, as part of the composite MACE outcome.
b. The protocol defined the outcome as freedom from transfusion from baseline to Week 52, but only the period up to treatment discontinuation was included in the analyses.
c. Worsening anaemia was not rated as AE in the studies unless the worsening anaemia was due to a cause other than CKD.
d. Composite cardiovascular outcome consisting of the following components: cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke; after review by the outcome adjudication committee.
e. Consisting of the following individual events: arterial thrombosis, deep vein thrombosis, pulmonary embolism, and vascular access thrombosis; after review by the outcome adjudication committee.
f. Operationalized as Comprehensive SMQ broad.
g. The following events are considered (coded according to MedDRA): cardiac disorders (SOC, SAEs), neoplasms benign, malignant and unspecified (SOC, SAEs), urinary tract infection (PT, SAEs), and mental status changed (PT, SAEs).
h. No suitable data available. See Section I 4.1 for reasons.
i. No outcomes in the category of health-related quality of life were recorded.
j. Lack of blinding in subjective recording of outcomes or subjective categorization as SAE (see Section I 4.1) and uncertainties regarding follow-up observation.
k. Lack of blinding in the presence of subjective decision on treatment discontinuation.

AE: adverse event; CKD: chronic kidney disease; H: high; L: low; MACE: major adverse cardiovascular event; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class

The risk of bias was rated as low for the outcomes of all-cause mortality, MACE, hospitalization for heart failure, and thromboembolic events.

No suitable data are available for the outcome of freedom from transfusion. Therefore, the risk of bias was not assessed for the results of this outcome.

The risk of bias of the results of the outcome of SAEs was rated as high. The reason for this is, on the one hand, the subjective outcome definition used in both studies presented and, on

the other, the uncertainty in follow-up observation after treatment discontinuation described in Section I 4.1, which can also influence the recording of SAEs.

The risk of bias for the results of the outcome of discontinuation due to AEs was rated as high because of lack of blinding in the presence of subjective decision on treatment discontinuation.

Analyses for the outcomes of hepatotoxicity and the selected specific AEs were used exclusively at the level of SAEs. The risk of bias for these outcomes was therefore rated as high.

Certainty of conclusions

As described in Section I 3.2, there are limitations with regard to the independence of the 2 studies (joint study design, parallel conduct and pooled analysis of both studies, in particular with the linking of both studies by a cross-study criterion to define study end, while at the same time the study CI-0016 was small). The confirmation (replication) of results by a second study, which is necessary to derive proof, is therefore generally not given in this situation. The certainty of conclusions achievable by means of a meta-analysis (proof) is therefore reduced in the present situation.

In the meta-analysis of both studies presented, at most an indication, e.g. of an added benefit, can therefore be determined for the outcomes of all-cause mortality, MACE, hospitalization for heart failure, and thromboembolic events. At most hints, e.g. of lesser harm, can be derived for all other outcomes.

I 4.3 Results

Table 13 and Table 14 summarize the results from the comparison of vadadustat with darbepoetin alfa in symptomatic anaemia associated with CKD in patients on chronic maintenance dialysis. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier. The Kaplan-Meier curves for all-cause mortality are presented in I Appendix B of the full dossier assessment. The results on common AEs, SAEs and discontinuations due to AEs are presented in I Appendix D of the full dossier assessment.

Table 13: Results (side effects, time to event) – RCT, direct comparison: vadadustat vs. darbepoetin alfa

Outcome category Outcome Study	Vadadustat N	Vadadustat Median time to event in weeks [95% CI] Patients with event n (%)	Darbepoetin alfa N	Darbepoetin alfa Median time to event in weeks [95% CI] Patients with event n (%)	Vadadustat vs. darbepoetin alfa HR [95% CI]; p-value[a]
Mortality					
All-cause mortality					
CI-0016	179	NA 15 (8.4)	186	NA 20 (10.8)	0.78 [0.39; 1.56]; 0.512
CI-0017	1768	NA 276 (15.6)	1769	NA 290 (16.4)	0.96 [0.82; 1.14]; 0.581
Total					0.95 [0.81; 1.12]; 0.488[b]

a. HR and 95% CI from Cox regression model, p-value from log-rank test. The analyses are each stratified by geographic region (United States/Europe/rest of the world), NYHA heart failure class (0 or I / II or III), baseline Hb, sex (male/female), age (> 65/≤ 65 years), family origin (white/other), history of cardiovascular disease (yes/no), and presence of diabetes mellitus (yes/no).

a. IPD meta-analysis: HR and 95% CI from Cox regression model, p-value from log-rank test. Stratification factors: as for the individual studies, additionally stratified by study.

CI: confidence interval; EU: European Union; Hb: haemoglobin; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; NYHA: New York Heart Association; RCT: randomized controlled trial

Table 14: Results (morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: vadadustat vs. darbepoetin alfa (multipage table)

Outcome category Outcome Study	Vadadustat N	Vadadustat Patients with event n (%)	Darbepoetin alfa N	Darbepoetin alfa Patients with event n (%)	Vadadustat vs. darbepoetin alfa RR [95% CI]; p-value[a]
Morbidity					
Freedom from transfusion	No suitable data[b]				
Health-related quality of life	No outcomes in the category of health-related quality of life were recorded				
Side effects					
AEs (supplementary information)					
CI-0016	179	150 (83.8)	186	159 (85.5)	–
CI-0017	1768	1562 (88.3)	1769	1580 (89.3)	–
SAEs					
CI-0016	179	89 (49.7)	186	105 (56.5)	0.87 [0.71; 1.05]; 0.151[c]
CI-0017	1768	973 (55.0)	1769	1032 (58.3)	0.94 [0.89; 0.99]; 0.029[c]
Total					0.93 [0.89; 0.99]; 0.013[d]
Discontinuation due to AEs					
CI-0016	179	5 (2.8)	186	2 (1.1)	2.60 [0.50; 13.60]; 0.242[c]
CI-0017	1768	91 (5.2)	1769	20 (1.1)	4.50 [2.79; 7.26]; < 0.001[c]
Total					4.31 [2.72; 6.83]; < 0.001[d]
MACE[e]					
CI-0016	179	16 (8.9)	186	14 (7.5)	1.19 [0.60; 2.36]; 0.712
CI-0017	1768	209 (11.8)	1769	228 (12.9)	0.92 [0.77; 1.09]; 0.530
Total					0.93 [0.79; 1.11]; 0.421[f]
Cardiovascular mortality[g]					
CI-0016	179	9 (5.0)	186	10 (5.4)	0.94 [0.39; 2.25]; 0.897
CI-0017	1768	141 (8.0)	1769	150 (8.5)	0.94 [0.75; 1.17]; 0.683
Total					0.94 [0.76; 1.16]; 0.572[f]
Non-fatal myocardial infarction[g]					
CI-0016	179	5 (2.8)	186	3 (1.6)	1.73 [0.42; 7.14]; 0.533
CI-0017	1768	77 (4.4)	1769	85 (4.8)	0.91 [0.67; 1.23]; 0.533
Total					0.93 [0.70; 1.25]; 0.649[f]
Non-fatal stroke[g]					
CI-0016	179	4 (2.2)	186	3 (1.6)	1.39 [0.31; 6.10]; 0.720
CI-0017	1768	28 (1.6)	1769	40 (2.3)	0.70 [0.43; 1.13]; 0.147
Total					0.75 [0.48; 1.18]; 0.208[f]

Table 14: Results (morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: vadadustat vs. darbepoetin alfa (multipage table)

Outcome category Outcome Study	Vadadustat		Darbepoetin alfa		Vadadustat vs. darbepoetin alfa
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
Hospitalization for heart failure					
CI-0016	179	11 (6.1)	186	7 (3.8)	1.63 [0.65; 4.12]; 0.310
CI-0017	1768	73 (4.1)	1769	82 (4.6)	0.89 [0.65; 1.21]; 0.533
Total					0.95 [0.71; 1.27]; 0.720[f]
Thromboembolic events[h]					
CI-0016	179	7 (3.9)	186	13 (7.0)	0.56 [0.23; 1.37]; 0.247
CI-0017	1768	162 (9.2)	1769	135 (7.6)	1.20 [0.96; 1.49]; 0.103
Total					1.15 [0.93; 1.42]; 0.209[f]
Arterial thrombosis					
CI-0016	179	0 (0)	186	0 (0)	–
CI-0017	1768	7 (0.4)	1769	4 (0.2)	1.75 [0.51; 5.97]; 0.530
Deep vein thrombosis					
CI-0016	179	0 (0)	186	3 (1.6)	0.15 [0.01; 2.85]; 0.097
CI-0017	1768	15 (0.8)	1769	17 (1.0)	0.88 [0.44; 1.76]; 0.794
Total					0.76 [0.39; 1.47]; 0.412[f]
Pulmonary embolism					
CI-0016	179	0 (0)	186	1 (0.5)	0.35 [0.01; 8.45]; 0.515
CI-0017	1768	5 (0.3)	1769	8 (0.5)	0.63 [0.20; 1.91]; 0.530
Total					0.58 [0.20; 1.66]; 0.312[f]
Vascular access thrombosis					
CI-0016	179	7 (3.9)	186	9 (4.8)	0.81 [0.31; 2.12]; 0.712
CI-0017	1768	139 (7.9)	1769	111 (6.3)	1.25 [0.98; 1.59]; 0.071
Total					1.22 [0.97; 1.54]; 0.094[f]
Hepatoxicity (SMQ, SAE)[i]					
CI-0016	179	5 (2.8)	186	6 (3.2)	0.94 [0.27; 3.30]; 0.926[c]
CI-0017	1768	45 (2.5)	1769	46 (2.6)	0.98 [0.65; 1.46]; 0.906[c]
Total					0.97 [0.66; 1.43]; 0.888[d]
Cardiac disorders (SOC, AE)					
CI-0016	179	23 (12.8)	186	25 (13.4)	0.96 [0.56; 1.62]; 0.878[j]
CI-0017	1768	296 (16.7)	1769	353 (20.0)	0.84 [0.73; 0.96]; 0.015[j]
Total					0.85 [0.74; 0.97]; 0.015[d]

Table 14: Results (morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: vadadustat vs. darbepoetin alfa (multipage table)

Outcome category Outcome Study	Vadadustat		Darbepoetin alfa		Vadadustat vs. darbepoetin alfa
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
Neoplasms benign, malignant and unspecified (SOC, SAE)					
CI-0016	179	2 (1.1)	186	4 (2.2)	0.52 [0.10; 2.80]; 0.533
CI-0017	1768	38 (2.1)	1769	58 (3.3)	0.66 [0.44; 0.98]; 0.049[j]
Total					0.65 [0.44; 0.96]; 0.030[d]
Urinary tract infection (PT, SAE)					
CI-0016	179	2 (1.1)	186	1 (0.5)	2.08 [0.19; 22.72]; 0.600
CI-0017	1768	15 (0.8)	1769	32 (1.8)	0.47 [0.25; 0.86]; 0.018[j]
Total					0.51 [0.28; 0.93]; 0.027[d]
Mental status changed (PT, SAE)					
CI-0016	179	0 (0)	186	2 (1.1)	0.21 [0.01; 4.30]; 0.225
CI-0017	1768	11 (0.6)	1769	23 (1.3)	0.48 [0.23; 0.98]; 0.056[j]
Total					0.46 [0.23; 0.92]; 0.028[d]

a. Unless stated otherwise: Institute's calculation of effect, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [23]). In case of zero events in one study arm, the correction factor 0.5 was used for the calculation of effect and CI in both study arms.
b. No suitable data available; see Section I 4.1 for reasons.
c. RR: stratified by geographic region (United States/Europe/rest of the world), NYHA heart failure class (0 or I / II or III), baseline Hb (< 9.5/≥ 9.5 g/dL in study CI-0016 and < 10.0/≥ 10.0 g/dL in study CI-0017), CI: normal distribution approximation, p-Wert: Cochran-Mantel-Haenszel test.
d. Meta-analysis with fixed effects (inverse variance), CI and p-value via normal distribution approximation.
e. Composite cardiovascular outcome consisting of the following components: cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke; after review by the outcome adjudication committee.
f. Institute's calculation: meta-analysis with fixed effect (Mantel-Haenszel method).
g. The first event in this outcome was taken into account regardless of whether it was also the first event in the composite MACE outcome.
h. Consisting of the following components: arterial thrombosis, deep vein thrombosis, pulmonary embolism, and vascular access thrombosis; after review by the outcome adjudication committee.
i. Operationalized as Comprehensive SMQ broad.
j. RR: unstratified, CI: normal distribution approximation, p-value: Fisher test.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; Hb: haemoglobin; MACE: major adverse cardiovascular event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; NYHA: New York Heart Association; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class

Based on the available information, at most indications, e.g. of an added benefit, can be determined for the outcomes of all-cause mortality, MACE, hospitalization for heart failure, and thromboembolic events, and at most hints for all other outcomes.

Mortality

All-cause mortality

For the outcome of all-cause mortality, the meta-analysis of the studies did not show any statistically significant differences between the treatment arms. There is no hint of added benefit of vadadustat in comparison with the ACT; an added benefit is therefore not proven.

Morbidity

Freedom from transfusion

No suitable data are available for the outcome of freedom from transfusion. There is no hint of added benefit of vadadustat in comparison with the ACT; an added benefit is therefore not proven.

Health-related quality of life

No data were recorded for the outcome of health-related quality of life. There is no hint of added benefit of vadadustat in comparison with the ACT; an added benefit is therefore not proven.

Side effects

SAEs

The meta-analysis of the studies showed a statistically significant difference in favour of vadadustat in comparison with darbepoetin alfa for the outcome of SAEs. There is a hint of lesser harm from vadadustat in comparison with the ACT.

Discontinuation due to AEs

The meta-analysis of the studies showed a statistically significant difference to the disadvantage of vadadustat in comparison with darbepoetin alfa for the outcome of discontinuation due to AEs. There is a hint of greater harm from vadadustat in comparison with the ACT.

MACE, hospitalization for heart failure, and thromboembolic events

The meta-analysis of the studies did not show any statistically significant differences between treatment groups for any of the outcomes of MACE (consisting of the individual components of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke), hospitalization for heart failure, and thromboembolic events (consisting of the individual components of arterial thrombosis, deep vein thrombosis, pulmonary embolism, and vascular access thrombosis). For each of them, there is no hint of greater or lesser harm from vadadustat in comparison with the ACT; greater or lesser harm is therefore not proven.

Hepatotoxicity

For the outcome of hepatotoxicity, the meta-analysis of the studies did not show any statistically significant differences between treatment groups. There is no hint of greater or lesser harm from vadadustat in comparison with the ACT; greater or lesser harm is therefore not proven.

Specific AEs

The meta-analysis of the studies showed a statistically significant difference in favour of vadadustat compared with darbepoetin alfa for each of the outcomes of cardiac disorders (SOC, SAE), neoplasms benign, malignant and unspecified (SOC, SAE), urinary tract infection (PT, SAE) and mental status changed (PT, SAE). In each case, there is a hint of lesser harm from vadadustat in comparison with the ACT.

For the outcome of mental status changed (PT, SAEs), there is also an effect modification by the characteristic of baseline Hb. For patients with baseline Hb < 10.0 g/dL, a statistically significant difference between treatment groups was shown in favour of vadadustat. For patients with baseline Hb ≥ 10.0 g/dL, in contrast, no statistically significant difference between treatment groups was shown, see Section I 4.4 (Table 15).

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account for the present benefit assessment:

- age (< 65 years versus ≥ 65 years)
- sex (female versus male)
- baseline Hb (< 10.0 g/dL versus ≥ 10.0 g/dL)

In addition to the subgroup characteristics of age and sex, the characteristic of baseline Hb was also used. According to the CTCAE [17], Hb values below the threshold of < 10.0 g/dL are classified as symptomatic and in need of treatment, which is why this characteristic was used as an approximate representation of disease severity.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

The results are presented in Table 15.

Table 15: Subgroups (side effects, dichotomous) – RCT, direct comparison: vadadustat vs. darbepoetin alfa

Outcome Characteristic Study Subgroup	Vadadustat N	Vadadustat Patients with event n (%)	Darbepoetin alfa N	Darbepoetin alfa Patients with event n (%)	Vadadustat vs. darbepoetin alfa RR [95% CI][a]	Vadadustat vs. darbepoetin alfa p-value[a]
Side effects						
Mental status changed (PT, SAE)						
Baseline Hb						
Total						
< 10.0 g/dL	742	0 (0)	758	14 (1.8)	0.10 [0.01; 0.84]	0.034
≥ 10.0 g/dL	1205	11 (0.9)	1197	11 (0.9)	1.00 [0.44; 2.29]	0.991
					Interaction:	0.048[b]

a. Meta-analysis with fixed effects (inverse variance), CI and p-value via normal distribution approximation.
b. No information on the methods in the study documents; presumably Cochran Q-test.

CI: confidence interval; Hb: haemoglobin; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

Side effects

Mental status changed (PT, SAE)

For the outcome of mental status changed (PT, SAE), there is an effect modification by the characteristic of baseline Hb. For patients with baseline Hb < 10.0 g/dL, a statistically significant difference between treatment groups was shown in favour of vadadustat. For patients with baseline Hb ≥ 10.0 g/dL, in contrast, no statistically significant difference between treatment groups was shown. For patients with baseline Hb < 10.0 g/dL, there is a hint of lesser harm from vadadustat compared with the ACT.

I 5 Probability and extent of added benefit

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

The approach for deriving an overall conclusion on the 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.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Chapter I 4 (see Table 16).

Determination of the outcome category for the outcomes on side effects

It cannot be inferred from the dossier for all outcomes considered in the present benefit assessment whether they are serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

Discontinuation due to AEs

Due to the lack of valid grading, it is not possible to categorize the severity of the AEs that led to discontinuation. The company allocated the outcome to the category of non-serious/non-severe side effects. The clinical study report shows that < 40% of the AEs that led to discontinuation were assessed as serious by the company. For the present assessment, the outcome of discontinuation due to AEs is allocated to the category of non-serious/non-severe side effects.

Table 16: Extent of added benefit at outcome level: vadadustat vs. darbepoetin alfa (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Intervention vs. comparator** **Quantile of time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	Median: NA vs. NA HR: 0.95 [0.81; 1.12] p = 0.488	Lesser/added benefit not proven
Morbidity		
Freedom from transfusion	No suitable data	Lesser/added benefit not proven
Health-related quality of life		
No outcomes recorded		
Side effects		
SAEs	49.7%–55.0% vs. 56.5%–58.3% RR: 0.93 [0.89; 0.99] p = 0.013 Probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Lesser harm, extent: "minor"
Discontinuation due to AEs	2.8%–5.2% vs. 1.1%–1.1% RR: 4.31 [2.72; 6.83] RR: 0.23 [0.15; 0.37][c] p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm; extent: "considerable"
MACE[d]	8.9%–11.8% vs. 7.5%–12.9% RR: 0.93 [0.79; 1.11] p = 0.421	Lesser/added benefit not proven
Hospitalization for heart failure	4.1%–6.1% vs. 3.8%–4.6% RR: 0.95 [0.71; 1.27] p = 0.720	Lesser/added benefit not proven
Thromboembolic events[f]	3.9%–9.2% vs. 7.0%–7.6% RR: 1.15 [0.93; 1.42] p = 0.209	Lesser/added benefit not proven
Hepatotoxicity (SMQ, SAE)	2.5%–2.8% vs. 2.6%–3.2% RR: 0.97 [0.66; 1.43] p = 0.888	Lesser/added benefit not proven
Cardiac disorders (SOC, AE)	12.8%–16.7% vs. 13.4%–20.0% RR: 0.85 [0.74; 0.97] p = 0.015 Probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Lesser harm, extent: "minor"

Table 16: Extent of added benefit at outcome level: vadadustat vs. darbepoetin alfa (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Intervention vs. comparator** **Quantile of time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Neoplasms benign, malignant and unspecified (SOC, SAE)	1.1%–2.1% vs. 2.2%–3.3% RR: 0.65 [0.44; 0.96] p = 0.030 Probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Lesser harm, extent: "minor"
Urinary tract infection (PT, SAE)	0.8%–1.1% vs. 0.5%–1.8% RR: 0.51 [0.28; 0.93] p = 0.027 Probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Lesser harm, extent: "minor"
Mental status changed (PT, SAE)		
Baseline Hb[g]		
< 10.0 g/dL	0% vs. 1.8% RR: 0.10 [0.01; 0.84] p = 0.034 Probability: "hint"	Outcome category: serious/severe side effects $0.80 \leq CI_u < 0.90$ Lesser harm, extent: "considerable"
≥ 10.0 g/dL	0.9% vs. 0.9% RR: 1.00 [0.44; 2.29] p = 0.991	Lesser/added benefit not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
d. Composite cardiovascular outcome consisting of the following components: cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke; after review by the outcome adjudication committee.
e. The first event in this outcome was taken into account regardless of whether it was also the first event in the composite MACE outcome.
f. Consisting of the following components: arterial thrombosis, deep vein thrombosis, pulmonary embolism, and vascular access thrombosis; after review by the outcome adjudication committee.
g. The subgroup characteristic of baseline Hb with the cut-off value of 10 g/dL was only analysed for the pooled data of the patients in both studies, but not separately for each study.

CI: confidence interval; CI_u: upper limit of the confidence interval; Hb: haemoglobin; HR: hazard ratio; MACE: major adverse cardiovascular event; MedDRA: Medical Dictionary for Regulatory Activities; NA: not achieved; PT: Preferred Term; RR: relative risk; SAE: serious adverse event; SMQ: Standardized Medical Dictionary for Regulatory Activities Query; SOC: System Organ Class

I 5.2 Overall conclusion on added benefit

Table 17 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 17: Positive and negative effects from the assessment of vadadustat in comparison with the ACT

Positive effects	**Negative effects**
Serious/severe side effects ▪ SAEs: hint of lesser harm – extent: “minor” ▫ Specific AEs (SAEs): - Cardiac disorders: hint of lesser harm – extent: “minor” - Neoplasms benign, malignant and unspecified (incl cysts and polyps): hint of lesser harm – extent “minor” - Urinary tract infection: hint of lesser harm – extent: “minor” - Mental status changed: Baseline Hb < 10.0 g/dL: hint of lesser harm – extent: “considerable”	–
–	Non-serious/non-severe side effects ▪ Discontinuation due to AEs: hint of greater harm – extent: “considerable”
No suitable data are available for the morbidity category; no data were recorded for the health-related quality of life category.	
AE: adverse event; Hb: haemoglobin; SAE: serious adverse event	

Overall, there were positive effects for the outcome of SAEs and subcategories of SAEs at SOC and PT level, and a negative effect for the outcome of discontinuation due to AEs for vadadustat compared with the ACT.

No suitable data are available for the morbidity category. Outcomes from the category of health-related quality of life were not recorded. The possibility of evaluating an effect on the benefit side is therefore severely limited in the present assessment.

In summary, there is no proof of an added benefit of vadadustat over the ACT for adult patients with symptomatic anaemia associated with CKD who are on chronic maintenance dialysis.

Table 18 summarizes the result of the assessment of the added benefit of vadadustat in comparison with the ACT.

Table 18: Vadadustat – probability and extent of added benefit

Therapeutic indication	**ACT[a, b]**	**Probability and extent of added benefit**
Adult patients with symptomatic anaemia associated with chronic kidney disease (CKD)[c] who are on chronic maintenance dialysis	▪ Darbepoetin alfa or ▪ epoetin alfa or ▪ epoetin beta or ▪ epoetin theta or ▪ epoetin zeta or ▪ methoxy polyethylene glycol-epoetin beta	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, the use of erythropoiesis-stimulating agents (ESAs) requires that other causes of anaemia (in particular iron deficiency) have been ruled out. In addition, the specifications in the respective Summary of Product Characteristics and the specifics of the German health care context must be taken into account.
c. In the present therapeutic indication, it is assumed in accordance with the G-BA that guideline- and approval-compliant treatment is ensured in both study arms for any deficiency states that could cause corresponding specific types of anaemia (e.g. iron, water-soluble vitamins).

ACT: appropriate comparator therapy; CKD: chronic kidney disease; ESA: erythropoiesis-stimulating agent; G-BA: Federal Joint Committee

The assessment described above deviates from that of the company, which determined proof of minor added benefit.

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

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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