IQWiG Reports – Commission No. A20-92

Bempedoic acid (primary hypercholesterolaemia and mixed dyslipidaemia) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Bempedoinsäure (primäre Hypercholesterinämie und gemischte Dyslipidämie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 January 2021). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Table of contents

List of tables[2]

Page

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

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ASCVD	atherosclerotic cardiovascular disease
EMA	European Medicines Agency
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HeFH	heterozygous familial hypercholesterolaemia
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LDL-C	low-density lipoprotein cholesterol
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug bempedoic acid. 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 October 2020.

Research question

The aim of the present report was to assess the added benefit of bempedoic acid as an adjunct to diet and, if appropriate, other lipid-lowering drugs compared with the appropriate comparator therapy (ACT) in adult patients with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia.

The research questions shown in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of bempedoic acid

Research question	Therapeutic indication	ACT[a]
1	Adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in whom drug and dietary options to reduce lipid levels have not been exhausted[b, c]	Maximum tolerated drug treatment specified by the physician under consideration of statins, cholesterol absorption inhibitors and anion exchangers
2	Adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in whom drug (except evolocumab) and dietary options to reduce lipid levels have been exhausted[b, c]	Evolocumab[c] or LDL apheresis (as "last resort" in refractory disease)[d] possibly with concomitant lipid-lowering drug treatment

a. Presentation of the respective ACT specified by the G-BA.
b. Use of bempedoic acid in accordance with the approval as an adjunct to diet in combination with a statin or a statin together with other lipid-lowering therapies in patients who are unable to reach LDL-C goals with the maximum tolerated dose of a statin or as monotherapy or in combination with other lipid-lowering therapies in patients who are statin-intolerant or for whom a statin is contraindicated.
c. The stipulations regarding the limitations of prescription of Appendix III of the Pharmaceutical Directive must be observed.
d. It is a general prerequisite for LDL apheresis that LDL-C cannot be lowered sufficiently with maximum dietary and drug treatment documented for 12 months.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; LDL: low density lipoprotein; LDL-C: low density lipoprotein cholesterol

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

The assessment was 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 12 months were used for the derivation of the added benefit.

Results

Research question 1: patients in whom drug and dietary options to reduce lipid levels have not been exhausted

With its information retrieval, the company identified the RCTs CLEAR HARMONY (hereafter referred to as the HARMONY study), CLEAR WISDOM (hereafter referred to as the WISDOM study) and CLEAR SERENITY (hereafter referred to as the SERENITY study). The company used the studies HARMONY and WISDOM for the derivation of the added benefit. The company presented the SERENITY study only as supplementary information, because, among other things, the study duration of 24 weeks does not adequately represent long-term treatment. The company's approach not to include the SERENITY study in the benefit assessment is appropriate. However, the studies HARMONY and WISDOM included by the company are also unsuitable for the assessment of the added benefit of bempedoic acid.

The studies HARMONY and WISDOM are randomized, double-blind, multicentre studies on the comparison of bempedoic acid with placebo, each in combination with a lipid-lowering background therapy. The studies included adult patients at high cardiovascular risk (defined as atherosclerotic cardiovascular disease [ASCVD] or heterozygous familial hypercholesterolaemia [HeFH]) whose low-density lipoprotein cholesterol (LDL-C) levels were not adequately controlled under ongoing lipid-lowering treatment.

The studies HARMONY and WISDOM are not suitable to draw conclusions on the added benefit of bempedoic acid, as the ACT specified by the G-BA has not been implemented.

While the patients in the intervention arm in both studies received treatment escalation through the administration of bempedoic acid, patients in the comparator arm continued their insufficient lipid-lowering background therapy. Adjustment of the background therapy was only possible from week 24 onwards, provided that defined LDL-C threshold values (> 170 mg/dL and ≥ 25% increase from baseline) were exceeded. Thus, therapy adjustment in the sense of a rescue therapy in the placebo arm was only permitted after about half of the treatment duration had been completed and only in case of worsened LDL-C values that had already been insufficiently controlled at the start of the study. After randomisation, only 9% (WISDOM study) and 10% (HARMONY study) of patients in the comparator arm had their lipid-lowering therapy adjusted.

For an adequate comparison with a maximum tolerated drug therapy, it would have been necessary to further optimize the lipid-lowering therapy in the placebo arm on a patient-specific basis at the start of the study medication. Moreover, it would have been necessary to allow adjustments of the insufficient lipid-lowering therapy throughout the entire course of the study. However, such treatment escalation was not carried out in the comparator arms of the studies HARMONY and WISDOM.

Hence, suitable data for the assessment of the added benefit of bempedoic acid in comparison with the ACT were not available. This resulted in no hint of an added benefit of bempedoic acid in comparison with the ACT; an added benefit is therefore not proven.

Research question 2: patients in whom drug (except evolocumab) and dietary options to reduce lipid levels have been exhausted

The company presented no data for the assessment of the added benefit of bempedoic acid in comparison with the ACT in adult patients with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in whom drug (except evolocumab) and dietary lipid-lowering options have been exhausted. This resulted in no hint of an added benefit of bempedoic acid in comparison with the ACT; an added benefit is therefore not proven.

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

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

Table 3: Bempedoic acid – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in whom drug and dietary options to reduce lipid levels have not been exhausted[b, c]	Maximum tolerated drug treatment specified by the physician under consideration of statins, cholesterol absorption inhibitors and anion exchangers	Added benefit not proven
2	Adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in whom drug (except evolocumab) and dietary options to reduce lipid levels have been exhausted[b, c]	Evolocumab[c] or LDL apheresis (as "last resort" in refractory disease)[d] possibly with concomitant lipid-lowering drug treatment	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. Use of bempedoic acid in accordance with the approval as an adjunct to diet in combination with a statin or a statin together with other lipid-lowering therapies in patients who are unable to reach LDL-C goals with the maximum tolerated dose of a statin or as monotherapy or in combination with other lipid-lowering therapies in patients who are statin-intolerant or for whom a statin is contraindicated.
c. The stipulations regarding the limitations of prescription of Appendix III of the Pharmaceutical Directive must be observed.
d. It is a general prerequisite for LDL apheresis that LDL-C cannot be lowered sufficiently with maximum dietary and drug treatment documented for 12 months.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; LDL: low density lipoprotein; LDL-C: low density lipoprotein cholesterol

The G-BA decides on the added benefit.

[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].

2.2 Research question

The aim of the present report was to assess the added benefit of bempedoic acid as an adjunct to diet and, if appropriate, other lipid-lowering drugs compared with the ACT in adult patients with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia.

The research questions shown in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of bempedoic acid

Research question	Therapeutic indication	ACT[a]
1	Adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in whom drug and dietary options to reduce lipid levels have not been exhausted[b, c]	Maximum tolerated drug treatment specified by the physician under consideration of statins, cholesterol absorption inhibitors and anion exchangers
2	Adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in whom drug (except evolocumab) and dietary options to reduce lipid levels have been exhausted[b, c]	Evolocumab[c] or LDL apheresis (as "last resort" in refractory disease)[d] possibly with concomitant lipid-lowering drug treatment

a. Presentation of the respective ACT specified by the G-BA.
b. Use of bempedoic acid in accordance with the approval as an adjunct to diet in combination with a statin or a statin together with other lipid-lowering therapies in patients who are unable to reach LDL-C goals with the maximum tolerated dose of a statin or as monotherapy or in combination with other lipid-lowering therapies in patients who are statin-intolerant or for whom a statin is contraindicated.
c. The stipulations regarding the limitations of prescription of Appendix III of the Pharmaceutical Directive [3] must be observed.
d. It is a general prerequisite for LDL apheresis that LDL-C cannot be lowered sufficiently with maximum dietary and drug treatment documented for 12 months [4].

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; LDL: low density lipoprotein; LDL-C: low density lipoprotein cholesterol

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

The assessment was 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 12 months were used for the derivation of the added benefit. This deviates from inclusion criteria of the company, which specified a minimum study duration of 24 weeks.

2.3 Research question 1: patients in whom drug and dietary options to reduce lipid levels have not been exhausted

2.3.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study lists on bempedoic acid (status: 5 August 2020)
- bibliographical literature search on bempedoic acid (last search on 5 August 2020)
- search in trial registries/trial results databases for studies on bempedoic acid (last search on 5 August 2020)
- search on the G-BA website for bempedoic acid (last search on 5 August 2020)

To check the completeness of the study pool:

- search in trial registries for studies on bempedoic acid (last search on 6 November 2020)

No relevant study was identified from the check.

Study pool of the company

Table 5 shows the studies included by the company.

Table 5: Study pool of the company – RCT, direct comparison: bempedoic acid + lipid-lowering therapy vs. placebo + lipid-lowering therapy

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])
CLEAR HARMONY, 1002-040 (HARMONY[d])	Yes	No[e]	No	No[f]	Yes [5,6]	Yes [7,8]
CLEAR WISDOM, 1002-047 (WISDOM[d])	Yes	No[e]	No	No[f]	Yes [9,10]	Yes [8,11]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: EPAR.
d. In the following tables, the study is referred to with this abbreviated form.
e. In 2019, Daiichi Sankyo Europe and Esperion Therapeutics entered into a licensing agreement providing for the exclusive commercialization of bempedoic acid by Daiichi Sankyo Europe in the European Economic Area and Switzerland. In June 2020, the marketing authorization holdership was transferred from Esperion Therapeutics to Daiichi Sankyo Europe.
f. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without access to the CSR in Module 5 of the dossier.

CSR: clinical study report; EPAR: European Public Assessment Report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

For the derivation of the added benefit, the company used the RCTs CLEAR HARMONY (hereafter referred to as the HARMONY study) and CLEAR WISDOM (hereafter referred to as the WISDOM study) with patients for whom a statin therapy is generally suitable. Moreover, the company identified the RCT CLEAR SERENITY (hereafter referred to as the SERENITY study) with statin-intolerant patients [12]. However, the company did not use this study to derive the added benefit, but only presented its results as supplementary information.

The company's approach not to include the SERENITY study in the benefit assessment is appropriate (see below). However, the studies HARMONY and WISDOM included by the company are also unsuitable for the assessment of the added benefit of bempedoic acid. The studies are described below and their lack of suitability for the benefit assessment is explained in more detail.

HARMONY and WISDOM studies

Study design

Since the two studies HARMONY and WISDOM have a similar study design, they are described below in summarized form.

The studies HARMONY and WISDOM are randomized, double-blind, multicentre studies on the comparison of bempedoic acid with placebo, each in combination with a lipid-lowering therapy (see Table 11 in Appendix A of the full dossier assessment). The studies included adult patients at high cardiovascular risk (defined as atherosclerotic cardiovascular disease [ASCVD] or heterozygous familial hypercholesterolaemia [HeFH]) whose LDL-C levels were not adequately controlled under ongoing lipid-lowering treatment (≥ 70 mg/dL). ASCVD was defined as existing coronary artery disease (documented history of coronary artery disease: acute or silent myocardial infarction, unstable angina pectoris, coronary revascularization; another diagnosed, clinically relevant coronary heart disease) or other risk equivalents (peripheral arterial occlusive disease, ischaemic stroke and, in the WISDOM study only, carotid endarterectomy, carotid stenting or stenosis > 70% in a carotid artery) and was present in 98% (HARMONY study) or 95% (WISDOM study) of the patients. Only few patients had HeFH (with/without ASCVD) (see Table 13 in Appendix A of the full dossier assessment). According to guidelines [13,14], the vast majority of patients had a very high cardiovascular risk.

The studies HARMONY and WISDOM included a total of 2230 and 779 patients, respectively, who were randomly assigned to treatment with bempedoic acid or placebo in a 2:1 ratio. In both studies, randomization was stratified by the factors "cardiovascular risk (HeFH [with/without ASCVD] versus ASCVD only)" and "statin dose at baseline (low [including no statin] or moderate versus high)".

In a 52-week treatment phase, patients received either 180 mg bempedoic acid or placebo, once daily each, orally as a tablet (see Table 12 in Appendix A of the full dossier assessment). In the studies, the dosage of bempedoic acid complied with the specifications of the approval [15]. To be included in the HARMONY or the WISDOM study, patients also had to have received stable

maximum tolerated lipid-lowering therapy for at least 4 weeks (at least 6 weeks for fibrates) prior to screening, which was to be continued as background therapy. The maximum tolerated lipid-lowering therapy was specified by the investigator based on his/her medical judgement and the available sources, including patient-reported history of lipid-lowering therapy, and comprised a maximum tolerated statin either alone or in combination with other lipid-lowering therapies in both studies. The definition of a maximum tolerated statin therapy also included statin regimens other than daily dosing including those with very low doses (and additionally, only in the WISDOM study, also no dosing). There is no documentation of the investigator's assessment of the maximum tolerated lipid-lowering therapy. 10% of the patients included in the WISDOM study received no treatment with a statin at baseline (see Table 17 of the full dossier assessment). However, for the administration of bempedoic acid in accordance with the approval, it is assumed that the LDL-C target values are not reached with a maximum tolerated statin dose [15]. The available data do not provide any information as to whether a statin therapy was not an option for these patients due to intolerance or contraindication.

In the studies HARMONY and WISDOM, the term "maximum tolerated lipid-lowering therapy at baseline" should not be understood to mean that all treatment options had already been exhausted at baseline. Lipid-lowering therapy at any time before or at baseline was mainly statins without other lipid-modifying agents (see Tables 14 to 17 in Appendix A of the full dossier assessment). Other lipid-lowering therapies (e.g. fibrates, cholesterol absorption inhibitors, bile acid sequestrants) alone or in combination with statins were hardly used in patients. 6% of patients in the WISDOM study received no lipid-modifying therapy at baseline. The available data do not provide any information as to whether all available lipid-lowering treatment options for these patients had been exhausted due to intolerance or contraindication. However, for the vast majority of patients covered by question 1 of the present benefit assessment included in the studies HARMONY and WISDOM, the lipid-lowering treatment options in the sense of the G-BA's ACT (see Table 4) had not been exhausted.

Adjustment of the background therapy (dose adjustment or addition of new drugs) in the sense of a rescue therapy was permitted from week 24 onwards if defined LDL-C threshold values were exceeded (> 170 mg/dL and ≥ 25% increase from baseline). However, information on dosages and administered drug combinations is missing in the available sources.

The primary outcome of the HARMONY study was "general safety" and included adverse events (AEs), clinical safety laboratory parameters, physical examination, vital signs and electrocardiogram. Primary outcome in the WISDOM study was the change in LDL-C at week 12. Other patient-relevant secondary outcomes in both studies were "mortality", "cardiovascular events" and "AEs" (WISDOM only).

Further details on the characteristics of the studies, interventions and patients included can be found in Appendix A.

Missing implementation of the appropriate comparator therapy

The G-BA specified a maximum tolerated drug treatment of physician's choice under consideration of statins, cholesterol absorption inhibitors and anion exchangers (in addition to diet) as ACT for adult patients in whom drug and dietary options to reduce lipid levels have not been exhausted. An adequate implementation of the G-BA's ACT requires an escalation of the ongoing lipid-lowering therapy. However, such treatment escalation was not carried out in the comparator arms of the studies HARMONY and WISDOM.

While the patients in the intervention arm in both studies received treatment escalation through the administration of bempedoic acid, patients in the comparator arm continued their insufficient lipid-lowering background therapy. Adjustment of the background therapy was only possible from week 24 onwards, provided that defined LDL-C threshold values (> 170 mg/dL and ≥ 25% increase from baseline) were exceeded. Thus, therapy adjustment in the sense of a rescue therapy in the placebo arm was only permitted after about half of the treatment duration had been completed and only in case of worsened LDL-C values that had already been insufficiently controlled at the start of the study.

Following randomisation, only 9% (WISDOM study) and 10% (HARMONY study) of patients in the comparator arm received rescue therapy (see Table 18 and Table 19 in Appendix A of the full dossier assessment). Statins were used in the majority of cases. Only < 1% of the patients additionally received cholesterol absorption inhibitors, fibrates or bile acid sequestrants. However, information on dosages and administered drug combinations is missing in the available sources. Moreover, no information is available on whether a dose escalation or a change or addition of a drug took place. The study results on the time course of the mean LDL-C values after randomization presented in Figure 1 and Figure 2 also confirm that hardly any further drug interventions were carried out in the placebo arm.

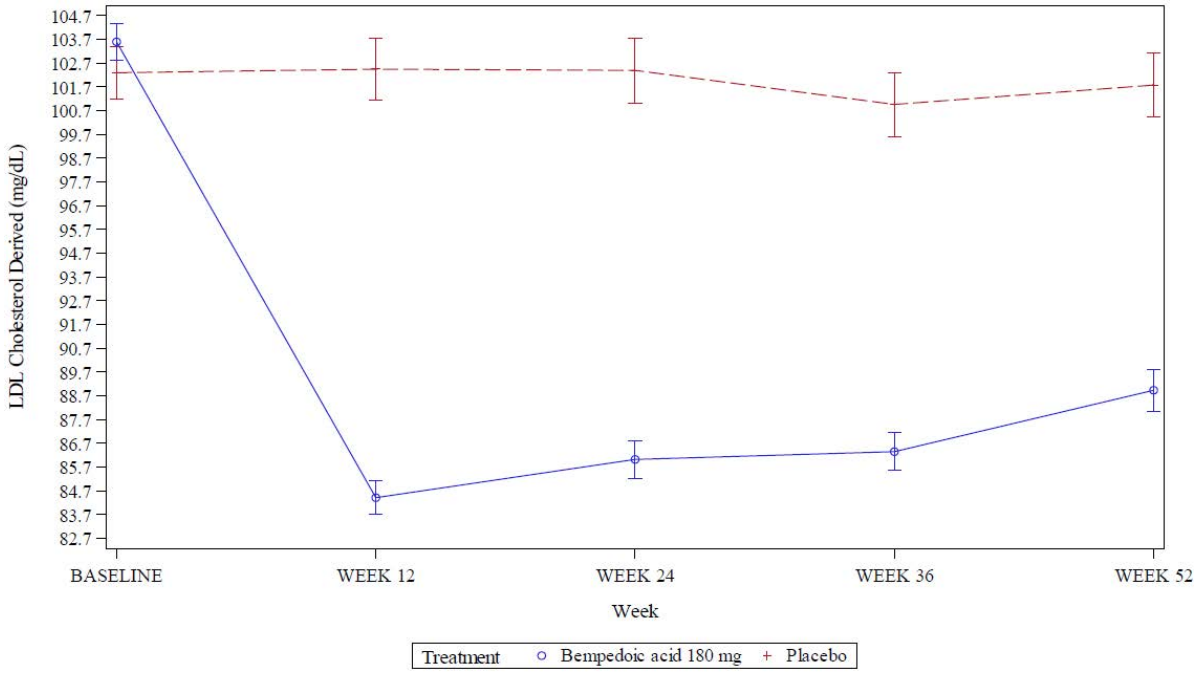

Figure 1: Mean LDL-C level in mg/dL depending on study visit and treatment in the HARMONY study (full analysis set)

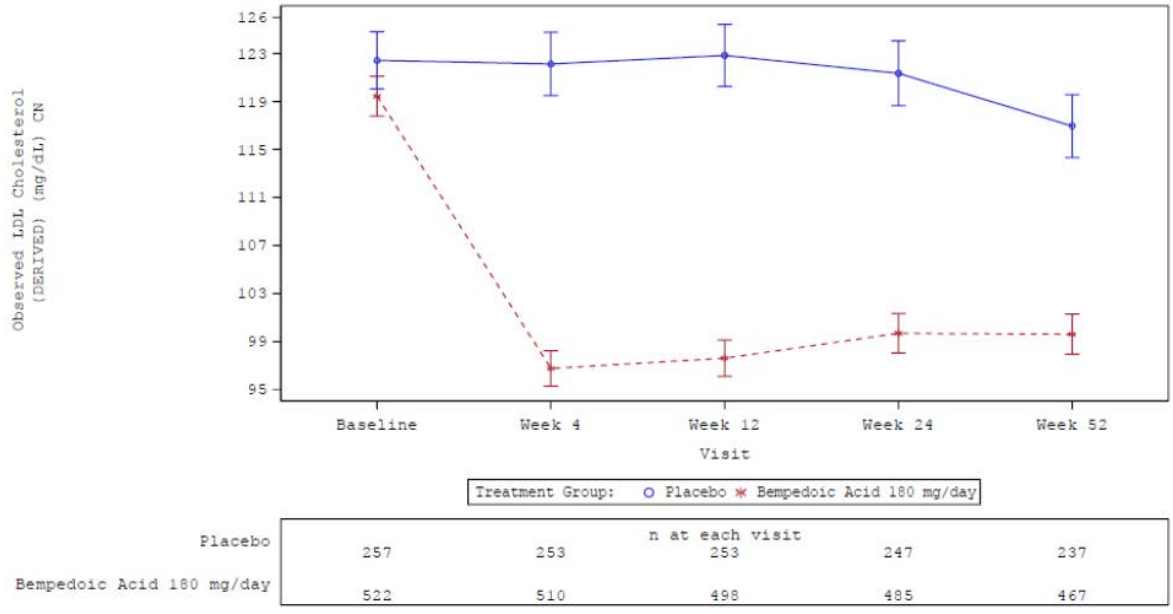

Figure 2: Mean LDL-C level in mg/dL depending on study visit and treatment in the WISDOM study (Full Analysis Set)

For an adequate comparison with a maximum tolerated drug treatment, it would have been necessary to further optimize the lipid-lowering therapy for the individual patient in the placebo arms of the studies HARMONY and WISDOM at the start of the study medication, for instance, by adjusting the dose, by adding another lipid-lowering drug, or by switching to another lipid-

lowering therapy. Moreover, it would have been necessary to allow adjustments of the insufficient lipid-lowering therapy throughout the entire course of the study.

Overall, treatment in the comparator arm of the studies HARMONY and WISDOM did therefore not concur with the G-BA's ACT of a maximum tolerated drug treatment to reduce lipid levels. The studies HARMONY and WISDOM were thus unsuitable for the assessment of the added benefit of bempedoic acid versus the ACT.

SERENITY study

Study design

The SERENITY study included a total of 345 adult patients who required primary prevention (at least one history of need for lipid-modifying therapy based on local guidelines) or secondary prevention (history of coronary artery disease, symptomatic peripheral arterial occlusive disease and/or cerebrovascular atherosclerotic disease) of cardiovascular events and/or had HeFH. Moreover, an LDL-C level of ≥ 130 mg/dL (primary prevention) or ≥ 100 mg/dL (secondary prevention and/or HeFH) at screening and statin intolerance had to be present. This was recorded on a patient-reported basis (confirmed by medical records if available) and was defined as intolerance to ≥ 2 statins (1 low-dose statin) due to an AE that started or worsened during statin therapy and disappeared or improved after discontinuation of the statin therapy. Treatment with very low-dose statins was allowed. 29 patients (8%) in the SERENITY study received statins at baseline.

The patients were randomly assigned to 24-week treatment with either 180 mg bempedoic acid or placebo in a 2:1 ratio. Moreover, patients could continue an ongoing lipid-lowering therapy, provided that the agents and dosages administered had been stable for 4 weeks (at least 6 weeks for fibrates) prior to screening. 58% of the patients had not received any lipid-lowering therapy at baseline. Since almost all patients only received statins and no (additional) other lipid-lowering therapy as pretreatment, not all treatment options were exhausted. Accordingly, the patient population of the SERENITY study includes patients according to research question 1.

Primary outcome of the study was the change in the LDL-C value at week 12.

Concurring with the company, the SERENITY study is not relevant for the benefit assessment

The company did not use the SERENITY study to derive the added benefit, but only presented its results as supplementary information. The company gave the following reasons for not including the study: firstly, the majority of the patients included had received bempedoic acid for primary prevention and therefore the patient population did not meet the requirements of Appendix III of the Pharmaceutical Directive regarding the limitations of prescription for lipid-lowering agents [3], and secondly, the study duration of 24 weeks did not adequately represent long-term treatment.

The first argument put forward by the company is not valid, as the study also included patients with secondary prevention (39%) and/or HeFH (2%), who, depending on the underlying disease or cardiovascular risk, may have met the requirements of the Drug Guideline Annex III. However, this has no consequences, as the SERENITY study is not relevant for the benefit assessment for the following reasons:

The company's assessment that the SERENITY study is too short with a treatment duration of 24 weeks is appropriate, however, the argumentation of the company is inconsistent: The company specified a minimum study duration of 24 weeks in its inclusion criteria with reference to the guideline of the European Medicines Agency (EMA) on clinical investigation of medicinal products in the treatment of lipid disorders [16]. However, the company subsequently described in its dossier that a study duration of 24 weeks does not adequately represent long-term treatment and that the SERENITY study is therefore presented as supplementary information. Moreover, a minimum study duration of 24 weeks cannot be explicitly derived from the EMA guideline; rather, a minimum study duration of 3 months is considered sufficient for the investigation of drugs with known mechanisms of action, whereas, depending on the objective, a study duration of up to 12 months is recommended for other mechanisms of action [16]. Treatment with bempedoic acid corresponds to the long-term treatment of chronic diseases with the primary goal of lowering the LDL-C value to reduce the cardiovascular risks. Therefore, a study duration of at least 12 months is considered reasonable for the assessment of long-term effects of bempedoic acid on patient-relevant outcomes, particularly on cardiovascular events, in the present therapeutic indication. This is consistent with the approach taken in previous dossier assessments on substances also used for lipid lowering (alirocumab [17,18], evolocumab [19,20] and lomitapide [21]).

Moreover, the ACT for research question 1 of the present benefit assessment was not implemented in the SERENITY study: The lipid-lowering therapy, which had been stable for at least 4 weeks before the start of the study, could only be adjusted from week 4 onwards if a triglyceride threshold value (> 1000 mg/dL) was exceeded in the sense of a deterioration compared to baseline. Therapy adjustment depending on LDL-C values was not planned. However, the patients already had inadequately controlled LDL-C levels at baseline and thus required an escalation of the ongoing lipid-lowering therapy. In the intervention arm, treatment was escalated by administering bempedoic acid with the start of the study medication. In the comparator arm, treatment escalation of the ongoing LDL-C-lowering therapy was neither mandated nor carried out.

Overall, the SERENITY study was thus unsuitable for the assessment of the added benefit of bempedoic acid versus the ACT.

2.3.2 Results on added benefit

The company presented no suitable data for the assessment of the added benefit of bempedoic acid in comparison with the ACT in adult patients with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in whom drug and dietary

lipid-lowering options have been exhausted. This resulted in no hint of an added benefit of bempedoic acid in comparison with the ACT; an added benefit is therefore not proven.

2.3.3 Probability and extent of added benefit

The company presented no suitable data for the assessment of the added benefit of bempedoic acid in comparison with the ACT for adult patients with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in whom drug and dietary lipid-lowering options have not been exhausted. An added benefit is therefore not proven.

This deviates from the company's assessment, which derived proof of considerable added benefit under consideration of results of the studies HARMONY and WISDOM summarized in a meta-analysis. According to the company, the added benefit is supported by the results of the SERENITY study presented as supplementary information.

2.4 Research question 2: patients in whom drug (except evolocumab) and dietary options to reduce lipid levels have been exhausted

2.4.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study lists on bempedoic acid (status: 5 August 2020)
- bibliographical literature search on bempedoic acid (last search on 5 August 2020)
- search in trial registries/trial results databases for studies on bempedoic acid (last search on 5 August 2020)
- search on the G-BA website for bempedoic acid (last search on 5 August 2020)

To check the completeness of the study pool:

- search in trial registries for studies on bempedoic acid (last search on 6 November 2020)

No relevant study was identified from the check.

2.4.2 Results on added benefit

The company presented no data for the assessment of the added benefit of bempedoic acid in comparison with the ACT in adult patients with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in whom drug (except evolocumab) and dietary lipid-lowering options have been exhausted. This resulted in no hint of an added benefit of bempedoic acid in comparison with the ACT; an added benefit is therefore not proven.

2.4.3 Probability and extent of added benefit

The company presented no data for the assessment of the added benefit of bempedoic acid in comparison with the ACT for adult patients with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in whom drug (except evolocumab) and dietary lipid-lowering options have been exhausted. An added benefit of bempedoic acid is therefore not proven.

This concurs with the company's assessment.

2.5 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of bempedoic acid in comparison with the ACT is summarized in Table 6.

Table 6: Bempedoic acid – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in whom drug and dietary options to reduce lipid levels have not been exhausted[b, c]	Maximum tolerated drug treatment specified by the physician under consideration of statins, cholesterol absorption inhibitors and anion exchangers	Added benefit not proven
2	Adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in whom drug (except evolocumab) and dietary options to reduce lipid levels have been exhausted[b, c]	Evolocumab[c] or LDL apheresis (as "last resort" in refractory disease)[d] possibly with concomitant lipid-lowering drug treatment	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. Use of bempedoic acid in accordance with the approval as an adjunct to diet in combination with a statin or a statin together with other lipid-lowering therapies in patients who are unable to reach LDL-C goals with the maximum tolerated dose of a statin or as monotherapy or in combination with other lipid-lowering therapies in patients who are statin-intolerant or for whom a statin is contraindicated.
c. The stipulations regarding the limitations of prescription of Appendix III of the Pharmaceutical Directive [3] must be observed.
d. It is a general prerequisite for LDL apheresis that LDL-C cannot be lowered sufficiently with maximum dietary and drug treatment documented for 12 months [4].

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; LDL: low density lipoprotein; LDL-C: low density lipoprotein cholesterol

The G-BA decides on the added benefit.

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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