Voclosporin (lupus nephritis)

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

EXTRACT

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IQWiG thanks the medical and scientific advisor for her 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

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

I Table of contents

I List of tables[2]

Page

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

I List of abbreviations

Abbreviation	Meaning
ACR	American College of Rheumatology
ACT	appropriate comparator therapy
EMA	European Medicines Agency
ERA-EDTA	European Renal Association – European Dialysis and Transplant Association
EULAR	European League Against Rheumatism
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GDP	gross domestic product
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IV	intravenous
KDIGO	Kidney Disease Improving Global Outcomes
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SLE	systemic lupus erythematosus
SPC	Summary of Product Characteristics
UPCR	urine protein/creatinine ratio

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 voclosporin (in combination with mycophenolate mofetil). 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 27 February 2023.

Research question

The aim of this report is to assess the added benefit of voclosporin in combination with mycophenolate mofetil (hereafter "voclosporin + mycophenolate mofetil") compared with individualized therapy, taking into account any prior therapy and disease activity, as appropriate comparator therapy (ACT) in adult patients with active class III, IV or V (including mixed class III/V and IV/V) lupus nephritis.

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of voclosporin + mycophenolate mofetil

Therapeutic indication	**ACT[a]**
Adults with active class III, IV or V (including mixed class III/V and IV/V) lupus nephritis[b]	Individualized therapy[c] taking into account any prior therapy and disease activity, choosing from the following drugs: glucocorticoids, azathioprine, cyclophosphamide, hydroxychloroquine, chloroquine, mycophenolate mofetil/mycophenolic acid[d]
a. Presented is the ACT specified by the G-BA. b. Both induction and maintenance therapy are considered in the therapeutic indication of lupus nephritis. Moderate to severe disease activity is assumed. c. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. d. See resolution on an amendment to the AM-RL of Annex VI – off-label use of mycophenolate mofetil/mycophenolenic acid in lupus nephritis. ACT: appropriate comparator therapy; AM-RL: Pharmaceutical Directive; G-BA: Federal Joint Committee	

The company deviated from the G-BA's specification and instead cited belimumab as the ACT. The company justified this approach by stating that the selection of the drugs specified by the G-BA for the individualized therapy cannot be regarded as an adequate and modern lupus nephritis therapy due to their toxicity and lack of efficacy. In its argumentation, the company pointed out, among other things, that although some guidelines recommend basic

immunosuppressive therapy, preferably with mycophenolate mofetil and prednisone or alternatively cyclophosphamide, belimumab is recommended in patients who do not respond to such therapy.

The company's justification for the deviation from the G-BA's ACT is not followed, as no clear recommendation for belimumab in the present therapeutic indication can be derived from any of the guidelines available at the time of the benefit assessment. The present assessment is carried out in comparison with the G-BA's 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 1 year are used for the derivation of the added benefit.

Results

As described above, the company deviated from the G-BA's specification and instead cited belimumab as the ACT. However, as the company did not identify any RCTs for the direct comparison of voclosporin with belimumab in its information retrieval, it aimed at an adjusted indirect comparison, for which it conducted a search for RCTs on voclosporin without restriction regarding the comparator therapy. In this search, the company identified the studies AURA-LV and AURORA-1 as well as its extension study AURORA-2. These studies investigated the comparison of voclosporin with placebo, each in addition to concomitant immunosuppressive therapy, and are thus potentially relevant for the comparison of voclosporin with the ACT. The check for completeness of the company's study pool identified no additional potentially relevant studies on this comparison.

Evidence provided by the company

The company used results from an adjusted indirect comparison of voclosporin with belimumab via the common comparator placebo in combination with basic immunosuppressive therapy for its assessment. As already described above, the indirect comparison presented by the company is not relevant due to the deviation of the company from the ACT of the present benefit assessment.

The data presented by the company on the studies on voclosporin are also not relevant for the present benefit assessment, in particular because it cannot be deduced from the information provided by the company that the ACT of individualized therapy was implemented by means of the concomitant therapy administered in the respective comparator arm of the studies. This is further explained below.

AURA-LV study

The AURA-LV study is a randomized, controlled, double-blind phase 2 study comparing voclosporin with placebo. The study included adult patients aged 18 to 75 years with active

class III, IV or V (including mixed class III/V and IV/V) lupus nephritis and a diagnosis of systemic lupus erythematosus (SLE). In addition, patients had to require treatment with high-dose glucocorticoids and immunosuppressants in the opinion of the investigator.

In the AURA-LV study, a total of 265 patients were randomly assigned in a 2:2:1:1 ratio to either treatment with voclosporin (treatment arm A), high-dose voclosporin (treatment arm B) or one of the corresponding comparator arms with placebo (treatment arms C and D).

In treatment arm A, treatment was with 23.7 mg voclosporin twice a day according to the recommendations of the Summary of Product Characteristics (SPC). To maintain blinding, patients in the comparator arms received placebo, but there was no blinding regarding dose levels. Treatment in the AURA-LV study was given for 48 weeks.

In addition to voclosporin or placebo, patients in all study arms received concomitant immunosuppressive therapy with mycophenolate mofetil and glucocorticoids according to a specific dosing schedule determined in the planning of the study. Patients who were already receiving treatment with mycophenolate mofetil before the start of the study, were to continue this treatment at a stable dose during the study. Patients without treatment or with a different treatment at study start were started on mycophenolate mofetil in the study with a target dose of 2 g/day, which had to be kept stable during the study. Dose adjustments or interruptions were only allowed in case of clearly proven safety concerns. Glucocorticoids were administered according to a weight-dependent dosing schedule, first as intravenous (IV) burst therapy with methylprednisolone and then orally in the form of prednisone. Concomitant antimalarials were to be additionally administered, provided there were no contraindications.

The primary outcome of the AURA-LV study was complete remission. Further patient-relevant outcomes were recorded in the categories of mortality, morbidity, and side effects.

AURORA-1 study

The AURORA-1 study is a randomized, controlled, double-blind phase 3 study comparing voclosporin with placebo, and has many design aspects that are comparable to the AURA-LV study. Like the AURA-LV study, the AURORA-1 study included adult patients aged 18 to 75 years with active class III, IV or V (including mixed class III/V and IV/V) lupus nephritis and a diagnosis of SLE. Analogous to the AURA-LV study, patients also had to require treatment with high-dose glucocorticoids and immunosuppressants in the opinion of the investigator.

In the AURORA-1 study, a total of 357 patients were randomly assigned in a 1:1 ratio to either treatment with voclosporin or placebo.

In the intervention arm, treatment was with 23.7 mg voclosporin twice a day according to the recommendations of the SPC. To maintain blinding, patients in the comparator arm received placebo. Treatment was continued for 52 weeks.

As in the AURA-LV study, patients in the AURORA-1 study also received concomitant immunosuppressive therapy with mycophenolate mofetil and glucocorticoids in addition to voclosporin or placebo. The specifications for the defined dosing schedule as well as for prior and concomitant treatment largely corresponded to those of the AURA-LV study.

After completion of the 52-week treatment in the AURORA-1 study, patients had the option of continuing their therapy (voclosporin or placebo, each in combination with the concomitant medication received in the AURORA-1 study) in the AURORA-2 extension study.

Primary outcome of the AURORA-1 study was renal response. Further patient-relevant outcomes were recorded in the categories of mortality, morbidity, health-related quality of life, and side effects.

AURORA-2 study (extension to the AURORA-1 study)

Patients who had completed 52 weeks of treatment in the AURORA-1 study and in whom continued immunosuppressive therapy was indicated in the opinion of the investigator were eligible to participate in the AURORA-2 extension study. Patients were not re-randomized, but treatment was continued for 24 months according to the allocation in the AURORA-1 study, starting with the treatment regimen administered at the end of treatment in the AURORA-1 study. The specifications for permitted concomitant treatments and dose adjustments for the AURORA-2 study were the same as for the AURORA-1 study.

The AURORA-2 extension study included 216 of the 357 patients randomized in the AURORA-1 study (intervention arm versus comparator arm, n [%]: 116 [65%] versus 100 [56%]). The reduced number is partly due to the fact that some of the patients discontinued the study medication prematurely in the AURORA-1 study (intervention arm versus comparator arm, n [%]: 43 [24%] versus 59 [33%]). In addition, not all patients took the opportunity to participate in the AURORA-2 extension study after the 52 weeks of treatment in the AURORA-1 study. Besides, observations of patients from the AURORA-1 study who did not participate in the extension study were not taken into account by the company in the analyses on the observation period of both studies. Hence, the analyses presented by the company for the AURORA-2 study are not a randomized comparison and are therefore not considered further for the present benefit assessment.

Data presented by the company are unsuitable for the benefit assessment

The studies AURA-LV and AURORA-1 on voclosporin presented by the company are not suitable for comparison with the ACT. This is explained below.

Implementation of the appropriate comparator therapy in the studies AURA-LV and AURORA-1 is unclear

The G-BA specified individualized therapy, taking into account any prior therapy and disease activity, as ACT for adult patients with active class III, IV or V (including mixed class III/V and IV/V) lupus nephritis. Possible therapeutic options are glucocorticoids, azathioprine, cyclophosphamide, hydroxychloroquine, chloroquine, and mycophenolate mofetil/ mycophenolic acid. According to the G-BA, for the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options.

Individualized therapy is not provided for in the AURA-LV and AURORA-1 studies

Patients in the comparator arms of the studies AURA-LV and AURORA-1, in addition to placebo, either continued their pretreatment with mycophenolate mofetil at a stable dose, or initiated treatment with mycophenolate mofetil according to a fixed dosing schedule or were switched to this treatment. In addition, glucocorticoids were administered according to a fixed dosing schedule, as well as antimalarials if clinically necessary or if there were no contraindications. An optimization of the concomitant immunosuppressive therapy or a drug change was not planned in any of the studies. Azathioprine and cyclophosphamide, which are treatment options of individualized therapy within the scope of the ACT, were not allowed in the studies. Thus, a selection of all treatment options specified by the G-BA to permit an individualized treatment decision in the sense of the ACT was not available in the studies.

Implementation of the appropriate comparator therapy is unclear

Guidelines generally recommend initial intensive immunosuppressive induction therapy followed by less intensive longterm immunosuppressive maintenance therapy for patients in the present therapeutic indication of active class III, IV or V (including mixed class III/V and IV/V) lupus nephritis. The aim of the therapy is to maintain or improve renal function. Response to therapy is generally determined by the decline of proteinuria at 3 or 6 months and the achievement of complete clinical response (urine protein/creatinine ratio [UPCR] < 0.5 to 0.7 mg/mg) at 12 months. Patients with no response or refractory disease are recommended to change the initial induction regimen, for example to cyclophosphamide instead of mycophenolate mofetil (each in combination with glucocorticoids). If there is an adequate response to the initial induction therapy, the patient is switched to longterm maintenance therapy. Both induction and maintenance therapy are generally relevant for the present benefit assessment. On the basis of the available data, however, it remains unclear in which treatment situation or phase the patients included in the studies were and which treatment they therefore needed. According to the inclusion criteria of the AURA-LV and AURORA-1 studies, all patients required treatment with high-dose glucocorticoids and

immunosuppressants in the opinion of the investigator. There were no restrictions regarding disease duration of lupus nephritis since diagnosis, type and/or duration of any prior therapies, or response to prior therapies, according to the inclusion and exclusion criteria, however.

On the one hand, it is possible that newly diagnosed patients were included. In this case, it can be assumed that the patients were either in an early treatment phase (initial induction therapy) at enrolment and had not yet shown a response to their prior therapy, or that they had not yet received any treatment for lupus nephritis and initiated this treatment during the study. On the other hand, it is possible that patients were enrolled who had already received longer (maintenance) therapy for lupus nephritis but had not responded to this therapy or had relapsed after a response.

According to guidelines, mycophenolate mofetil, which was administered in the studies, can be used as both induction and maintenance treatment. For some of the patients, the concomitant mycophenolate mofetil treatment administered in the studies was a change of their prior therapy; for the other part of the patients, the treatment regimen in the studies was the continuation of their prior therapy. The available information shows that a relevant proportion of patients in the comparator arms of the studies AURA-LV (36%) and AURORA-1 (54%) were already taking mycophenolate mofetil at the time of screening and continued this treatment during the studies. However, it is unclear for which proportion of these patients the continuation of treatment with mycophenolate mofetil was adequate or for which proportion a change of therapy would have been indicated.

For patients without mycophenolate mofetil treatment at the time of screening (AURA-LV: 64% in the comparator arm; AURORA-1: 46% in the comparator arm) who were switched to mycophenolate mofetil in the AURA-LV or AURORA-1 studies or who received mycophenolate mofetil for the first time, mycophenolate mofetil may represent a suitable treatment option for the individual patient. Due to a lack of data, the proportion of patients concerned remains unclear, however. Data are available on how many patients had received prior therapy with mycophenolate mofetil (AURA-LV: 44% in the comparator arm; AURORA-1: 62% in the comparator arm). However, these data do not provide any information about the time point at which this medication was administered before study start and whether the patients had an inadequate response to this treatment. In case of insufficient response to prior therapy with mycophenolate mofetil, it is questionable whether (renewed) treatment with mycophenolate mofetil during the studies is a suitable individualized therapy for these patients in the sense of the ACT.

In summary, it cannot be deduced from the information provided by the company that treatment with mycophenolate mofetil in combination with glucocorticoids (as well as any

antimalarials) administered in the comparator arms of the AURA-LV and AURORA-1 studies was an implementation of the ACT of individualized therapy.

Results on added benefit

As no suitable data are available for the benefit assessment of voclosporin + mycophenolate mofetil in adult patients with active class III, IV or V (including mixed class III/V and IV/V) lupus nephritis, there is no hint of an added benefit of voclosporin + mycophenolate mofetil compared 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 voclosporin + mycophenolate mofetil.

Table 3: Voclosporin + mycophenolate mofetil – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adults with active class III, IV or V (including mixed class III/V and IV/V) lupus nephritis[b]	Individualized therapy[c] taking into account any prior therapy and disease activity, choosing from the following drugs: glucocorticoids, azathioprine, cyclophosphamide, hydroxychloroquine, chloroquine, mycophenolate mofetil/mycophenolic acid[d]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Both induction and maintenance therapy are considered in the therapeutic indication of lupus nephritis. Moderate to severe disease activity is assumed.
c. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options.
d. See resolution on an amendment to the AM-RL of Annex VI – off-label use of mycophenolate mofetil/mycophenolenic acid in lupus nephritis.

ACT: appropriate comparator therapy; AM-RL: Pharmaceutical Directive; G-BA: Federal Joint Committee

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].

I 2 Research question

The aim of this report is to assess the added benefit of voclosporin in combination with mycophenolate mofetil (hereafter "voclosporin + mycophenolate mofetil") compared with individualized therapy, taking into account any prior therapy and disease activity, as ACT in adult patients with active class III, IV or V (including mixed class III/V and IV/V) lupus nephritis.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of voclosporin + mycophenolate mofetil

Therapeutic indication	**ACT[a]**
Adults with active class III, IV or V (including mixed class III/V and IV/V) lupus nephritis[b]	Individualized therapy[c] taking into account any prior therapy and disease activity, choosing from the following drugs: glucocorticoids, azathioprine, cyclophosphamide, hydroxychloroquine, chloroquine, mycophenolate mofetil/mycophenolic acid[d]
a. Presented is the ACT specified by the G-BA. b. Both induction and maintenance therapy are considered in the therapeutic indication of lupus nephritis. Moderate to severe disease activity is assumed. c. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. d. See resolution on an amendment to the AM-RL of Annex VI – off-label use of mycophenolate mofetil/mycophenolenic acid in lupus nephritis [3]. ACT: appropriate comparator therapy; AM-RL: Pharmaceutical Directive; G-BA: Federal Joint Committee	

The company deviated from the G-BA's specification and instead cited belimumab as the ACT. The company justified this approach by stating that the selection of the drugs specified by the G-BA for the individualized therapy cannot be regarded as an adequate and modern lupus nephritis therapy due to their toxicity and lack of efficacy. In its argumentation, the company pointed out, among other things, that although some guidelines recommend basic immunosuppressive therapy, preferably with mycophenolate mofetil and prednisone or alternatively cyclophosphamide, belimumab is recommended in patients who do not respond to such therapy. The company referred to guidelines by Kidney Disease Improving Global Outcomes (KDIGO) for the management of glomerular diseases [4], by the European League Against Rheumatism (EULAR) for the management of SLE [5], and the American College of Rheumatology (ACR) for the treatment of lupus nephritis [6]. The company pointed out that belimumab had been approved for the treatment of lupus nephritis in 2021, but that targeted therapy with belimumab had already been an important treatment option at the time the guidelines were published (between 2012 and 2021). Even if no current German guideline is

available at the time of the benefit assessment, it can be assumed according to the company that, nowadays, belimumab is preferable also to the other treatment options, such as mycophenolate mofetil, azathioprine and cyclophosphamide, due to its good efficacy.

The company's justification for deviating from the G-BA's ACT is not plausible. None of the guidelines available at the time of the benefit assessment can be used to derive a clear recommendation for belimumab in the present therapeutic indication. This concerns both the guidelines cited by the company [4-6] and the current European guideline by EULAR and the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) for the management of lupus nephritis [7]. The present assessment is carried out in comparison with the G-BA's 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 1 year are used for the derivation of the added benefit.

This corresponds to the inclusion criteria of the company in that the company also considered RCTs, but with a different minimum duration of 24 weeks. However, this is of no consequence for the present assessment, as the company only identified RCTs with a duration of at least 48 weeks for treatment with voclosporin.

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 voclosporin (status: 9 January 2023)
- bibliographical literature search on voclosporin (last search on 9 January 2023)
- search in trial registries/trial results databases for studies on voclosporin (last search on 11 January 2023)
- search on the G-BA website for voclosporin (last search on 23 January 2023)
- bibliographical literature search on belimumab (last search on 9 January 2023)
- search in trial registries/trial results databases for studies on belimumab (last search on 11 January 2023)
- search on the G-BA website for belimumab (last search on 23 January 2023)

To check the completeness of the study pool:

- search in trial registries for studies on voclosporin (last search on 16 March 2023); for search strategies, see I Appendix A of the full dossier assessment

As described in Section I 2, the company deviated from the G-BA's specification and instead cited belimumab as the ACT. However, as the company did not identify any RCTs for the direct comparison of voclosporin with belimumab in its information retrieval, it aimed at an adjusted indirect comparison, for which it conducted a search for RCTs on voclosporin without restriction regarding the comparator therapy. In this search, the company identified the studies AURA-LV [8-11] and AURORA-1 [12-15] as well as its extension study AURORA-2 [16-18]. These studies investigated the comparison of voclosporin with placebo, each in addition to concomitant immunosuppressive therapy, and are thus potentially relevant for the comparison of voclosporin with the ACT. The check for completeness of the company's study pool identified no additional potentially relevant studies on this comparison.

For its assessment, the company also conducted an information retrieval for studies on belimumab for an adjusted indirect comparison using the common comparator placebo in combination with concomitant immunosuppressive therapy. The company identified the BLISS-LN study [19]. However, the indirect comparison of voclosporin versus belimumab presented by the company is not relevant for the present benefit assessment due to the deviation of the company from the ACT of the present assessment (see Section I 2). The completeness of the company's study pool on belimumab was therefore not checked.

The data on the voclosporin studies presented by the company are also unsuitable for the present benefit assessment. This is particularly due to the fact that it cannot be deduced from the information presented by the company that the concomitant treatment administered in the comparator arms of the studies was an implementation of the ACT of individualized therapy (for a detailed reasoning, see sections below).

I 3.1 Evidence provided by the company

The company used results from an adjusted indirect comparison of voclosporin with belimumab via the common comparator placebo in combination with basic immunosuppressive therapy for its assessment. The company conducted 4 types of analyses based on the voclosporin studies AURORA-2 and AURA-LV and AURORA-1 as well as the belimumab study BLISS-LN (one main analysis and 3 sensitivity analyses), in each of which different time points of analysis and outcomes were taken into account (for details, see the following text section on the procedure of the company).

As already described in Section I 3, the indirect comparison of voclosporin versus belimumab presented by the company is not relevant due to the deviation of the company from the ACT of the present benefit assessment. A description of the BLISS-LN study on belimumab is therefore not provided below.

The data presented by the company on the studies on voclosporin are also not relevant for the present benefit assessment, in particular because it cannot be deduced from the information provided by the company that the ACT of individualized therapy was implemented by means of the concomitant therapy administered in the respective comparator arm of the studies. This is further explained below.

AURA-LV study

The AURA-LV study is a randomized, controlled, double-blind phase 2 study comparing voclosporin with placebo. The study included adult patients aged 18 to 75 years with active class III, IV or V (including mixed class III/V and IV/V) lupus nephritis. Patients had to have been diagnosed with SLE (according to the 1997 ACR criteria). In addition, class III, IV-segmental (IV-S), IV-global (IV-G) or V lupus nephritis had to have been confirmed by kidney biopsy within 6 months prior to screening. Active lupus nephritis had to be present at screening, defined as follows:

- Class III, IV-S or IV-G: confirmed proteinuria ≥ 1500 mg/24 hours in 24-hour urine collection, and defined as UPCR ≥ 1.5 mg/mg in first morning urine
- Class V (alone or in combination with class III or IV): confirmed proteinuria ≥ 2000 mg/24 hours in 24-hour urine collection, and defined as UPCR ≥ 2 mg/mg in first morning urine

In addition, patients had to require treatment with high-dose glucocorticoids and immunosuppressants in the opinion of the investigator. Patients who were currently requiring renal dialysis or were expected to require dialysis during the study period, as well as patients with a previous kidney transplant or planned transplant within the study period were excluded. Patients with an estimated glomerular filtration rate (eGFR) of ≤ 45 mL/min/1.73 m^2 were also excluded from study participation.

In the AURA-LV study, a total of 265 patients were randomly assigned in a 2:2:1:1 ratio to either treatment with voclosporin (treatment arm A: N = 89), high-dose voclosporin (treatment arm B: N = 88) or one of the corresponding comparator arms with placebo (treatment arms C and D: N = 88 in total). Randomization was stratified by biopsy class (pure class V versus others) and mycophenolate mofetil use at screening (yes versus no).

In treatment arm A, treatment was with 23.7 mg voclosporin twice a day. In treatment arm B, patients received 23.7 mg voclosporin twice a day for 2 weeks, followed by 39.5 mg voclosporin twice a day. To maintain blinding, patients in the respective comparator arms received placebo, but there was no blinding regarding dose levels. Voclosporin treatment in treatment arm A was in compliance with the SPC [20]. In contrast, treatment with high-dose voclosporin in treatment arm B was not in compliance with the recommendations. Treatment in the study was given for 48 weeks.

In addition to voclosporin or placebo, patients in all study arms received concomitant immunosuppressive therapy with mycophenolate mofetil and glucocorticoids according to a specific dosing schedule determined in the planning of the study (for details, see Table 7 in I Appendix B of the full dossier assessment). Patients who were already receiving treatment with mycophenolate mofetil before the start of the study, were to continue this treatment at a stable dose during the study. Patients without treatment or with a different treatment at study start were started on mycophenolate mofetil in the study with a target dose of 2 g/day, which had to be kept stable during the study. Dose adjustments or interruptions were only allowed in case of clearly proven safety concerns. Glucocorticoids were administered according to a weight-dependent dosing schedule, first as IV burst therapy with methylprednisolone and then orally in the form of prednisone. The prednisone dose was gradually reduced from an initial 20 to 25 mg/day to 2.5 mg/day at week 16 according to a fixed schedule. Cyclophosphamide, biologics (e.g. belimumab, rituximab), calcineurin inhibitors (e.g. ciclosporin, tacrolimus), immunoglobulins and other immunosuppressants were not allowed as concomitant medication. Concomitant antimalarials were to be additionally administered, provided there were no contraindications.

The primary outcome of the AURA-LV study was analysed at week 24 and was defined as confirmed UPCR of ≤ 0.5 mg/mg and either eGFR ≥ 60 mL/min/1.73m^2 or no confirmed decrease from baseline in eGFR ≥ 20%. According to the planning of the study, this outcome

was called complete remission. Further patient-relevant outcomes were recorded in the categories of mortality, morbidity, and side effects.

Further information on the AURA-LV study characteristics, the interventions used, and the characteristics and pretreatments of the included patients can be found in I Appendix B of the full dossier assessment.

AURORA-1 study

The AURORA-1 study is a randomized, controlled, double-blind phase 3 study comparing voclosporin with placebo, and has many design aspects that are comparable to the AURA-LV study. Like the AURA-LV study, the AURORA-1 study included adult patients aged 18 to 75 years with active class III, IV or V (including mixed class III/V and IV/V) lupus nephritis and a diagnosis of SLE (according to the 1997 ACR criteria). The specifications for study inclusion regarding histological diagnosis and lupus nephritis activity were slightly different, however. The following criteria had to be met:

- kidney biopsy ≤ 2 years prior to screening indicating class III, IV-S, IV-G (alone or in combination with class V), or class V, with a doubling or greater increase of UPCR within the previous 6 months to a minimum of ≥ 1.5 mg/mg (class III/IV) or to a minimum of ≥ 2 mg/mg for (class V) at screening

  or

- kidney biopsy ≤ 6 months prior to screening indicating class III, class IV-S, class IV-G (alone or in combination with class V), or class V, with a UPCR of ≥1.5 mg/mg (class III, IV-S, or IV-G [alone or in combination with class V]) or UPCR ≥ 2 mg/mg (class V) at screening

Analogous to the AURA-LV study, patients also had to require treatment with high-dose glucocorticoids and immunosuppressants in the opinion of the investigator. The definition of the exclusion criteria regarding dialysis requirement, kidney transplant and eGFR were also analogous to the AURA-LV study.

In the AURORA-1 study, a total of 357 patients were randomly assigned in a 1:1 ratio to either treatment with voclosporin (N = 179) or placebo (N = 178). As for the AURA-LV study, randomization was stratified by biopsy class (pure class V versus others) and mycophenolate mofetil use at screening (yes versus no).

In the intervention arm, treatment was with 23.7 mg voclosporin twice a day. To maintain blinding, patients in the comparator arm received placebo. Voclosporin treatment was in compliance with the SPC [20]. Treatment was continued for 52 weeks.

As in the AURA-LV study, patients in the AURORA-1 study also received concomitant immunosuppressive therapy with mycophenolate mofetil and glucocorticoids in addition to voclosporin or placebo. The specifications for the defined dosing schedule as well as for prior and concomitant treatment largely corresponded to those of the AURA-LV study (for details, see Table 7 in I Appendix B of the full dossier assessment). The dosage of mycophenolate mofetil also had to remain stable during the study with a target dose of 2 g/day, and glucocorticoids were reduced to 2.5 mg/day by week 16 according to a fixed schedule in the course of the study.

After completion of the 52-week treatment in the AURORA-1 study, patients had the option of continuing their therapy (voclosporin or placebo, each in combination with the concomitant medication received in the AURORA-1 study) in the AURORA-2 extension study.

The primary outcome of the AURORA-1 study was analysed at week 52 and was defined as UPCR of ≤ 0.5 mg/mg and either eGFR ≥ 60 mL/min/1.73 m^2 or no confirmed decrease from baseline in eGFR > 20%. In contrast to the AURA-LV study, this outcome was not called complete remission but renal response, according to the planning of the study. Further patient-relevant outcomes were recorded in the categories of mortality, morbidity, health-related quality of life, and side effects.

Further information on the AURORA-1 study characteristics, the interventions used, and the characteristics and pretreatments of the included patients can be found in I Appendix B of the full dossier assessment.

AURORA-2 study (extension to the AURORA-1 study)

The AURORA-2 study is a controlled, double-blind extension study of the RCT AURORA-1. Patients who had completed 52 weeks of treatment in the AURORA-1 study and in whom continued immunosuppressive therapy was indicated in the opinion of the investigator were eligible to participate in the AURORA-2 study. Patients were not re-randomized, but treatment was continued for 24 months according to the allocation in the AURORA-1 study, starting with the treatment regimen administered at the end of treatment in the AURORA-1 study. The specifications for permitted concomitant treatments and dose adjustments for the AURORA-2 study were the same as for the AURORA-1 study.

The AURORA-2 extension study included 216 of the 357 patients randomized in the AURORA-1 study (intervention arm versus comparator arm, n [%]: 116 [65%] versus 100 [56%]). The reduced number is partly due to the fact that some of the patients discontinued the study medication prematurely in the AURORA-1 study (intervention arm versus comparator arm, n [%]: 43 [24%] versus 59 [33%]). In addition, not all patients took the opportunity to participate in the AURORA-2 extension study after the 52 weeks of treatment in the AURORA-1 study. Besides, observations of patients from the AURORA-1 study who did not

participate in the extension study were not taken into account by the company in the analyses on the observation period of both studies. Hence, the analyses presented by the company for the AURORA-2 study are not a randomized comparison and are therefore not considered further for the present benefit assessment.

Detailed information on the AURORA-2 study characteristics and the intervention used in the study can be found in I Appendix B of the full dossier assessment.

Approach of the company

The company used results from an adjusted indirect comparison of voclosporin with belimumab via the common comparator placebo in combination with concomitant immunosuppressive therapy for its assessment. The company conducted 4 types of analyses based on the voclosporin studies AURORA-2 and AURA-LV and AURORA-1 as well as the belimumab study BLISS-LN (one main analysis and 3 sensitivity analyses), in each of which different time points of analysis and outcomes were taken into account.

For its main analysis, the company used results at the end of the AURORA-2 study for the intervention (treatment duration of 3 years in total [including the treatment in the AURORA-1 study]), and results at the end of the BLISS-LN study for the comparator therapy (treatment duration of 2 years). The company presented these analyses for selected outcomes in the categories of mortality, morbidity and side effects.

In addition, the company carried out 3 sensitivity analyses. For one of these analysis, the company used results of the AURORA-2 study at the time point of 12 months for the intervention (treatment duration of 2 years in total [including the treatment in the AURORA-1 study]), and results at the end of the BLISS-LN study for the comparator therapy (treatment duration of 2 years). The company presented these analyses for selected outcomes in the categories of morbidity and side effects. A further sensitivity analysis is based on a meta-analytical summary of the results from the AURORA-1 and AURA-LV studies at the end of each study (treatment duration of 1 year) for the intervention, and on results at the end of the BLISS-LN study (treatment duration of 2 years) for the comparator therapy. The company presented this analysis for selected outcomes in the category of morbidity. For the outcome of renal response, the company also presented a sensitivity analysis based on the same analyses for the intervention pooled in a meta-analysis, and for the comparator therapy on results of the BLISS-LN study after 1 year of treatment.

The company used the total population of the respective studies for all analyses. For the AURA-LV study, the company only took into account the intervention arm, in which voclosporin was administered at 23.7 mg in accordance with the SPC [20].

All analyses presented by the company investigate the comparison of voclosporin versus belimumab. As already described in Section I 2, the data presented by the company on the indirect comparison of voclosporin versus belimumab are not relevant for the present benefit assessment due to the deviation of the company from the ACT. In the dossier, the company did not provide any data for a comparison of voclosporin with the ACT of the present assessment.

I 3.2 Assessment of the evidence presented by the company

The studies AURA-LV and AURORA-1 on voclosporin presented by the company are not suitable for comparison with the ACT. This is due to the fact that it cannot be deduced from the information presented by the company that the concomitant treatment administered in the comparator arms of the studies was an implementation of the ACT of individualized therapy. This is explained below.

Implementation of the appropriate comparator therapy in the studies AURA-LV and AURORA-1 is unclear

The G-BA specified individualized therapy, taking into account any prior therapy and disease activity, as ACT for adult patients with active class III, IV or V (including mixed class III/V and IV/V) lupus nephritis. Possible therapeutic options are glucocorticoids, azathioprine, cyclophosphamide, hydroxychloroquine, chloroquine, and mycophenolate mofetil/ mycophenolic acid. According to the G-BA, for the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options.

Individualized therapy is not provided for in the AURA-LV and AURORA-1 studies

Patients in the comparator arms of the studies AURA-LV and AURORA-1, in addition to placebo, either continued their pretreatment with mycophenolate mofetil at a stable dose, or initiated treatment with mycophenolate mofetil according to a fixed dosing schedule or were switched to this treatment. In addition, glucocorticoids were administered according to a fixed dosing schedule, as well as antimalarials if clinically necessary or if there were no contraindications. An optimization of the concomitant immunosuppressive therapy or a drug change was not planned in any of the studies. Azathioprine and cyclophosphamide, which are treatment options of individualized therapy within the scope of the ACT, were not allowed in the studies. Thus, a selection of all treatment options specified by the G-BA to permit an individualized treatment decision in the sense of the ACT was not available in the studies.

Implementation of the appropriate comparator therapy is unclear

As described in Section I 3.1, the company only used analyses on the comparison of voclosporin with belimumab for its assessment. In the dossier, the company did not discuss the extent to which the therapy administered in the AURA-LV and AURORA-1 studies can be regarded as an adequate implementation of the ACT of the present benefit assessment for the patients.

Guidelines [4,7] generally recommend initial intensive immunosuppressive induction therapy followed by less intensive longterm immunosuppressive maintenance therapy for patients in the present therapeutic indication of active class III, IV or V (including mixed class III/V and IV/V) lupus nephritis. The aim of the therapy is to maintain or improve renal function. Response to therapy is generally determined by the decline of proteinuria at 3 or 6 months and the achievement of complete clinical response (UPCR < 0.5 to 0.7 mg/mg) at 12 months. Patients with no response or refractory disease are recommended to change the initial induction regimen [7], for example to cyclophosphamide instead of mycophenolate mofetil (each in combination with glucocorticoids). If there is an adequate response to the initial induction therapy, the patient is switched to longterm maintenance therapy. Both induction and maintenance therapy are generally relevant for the present benefit assessment. On the basis of the available data, however, it remains unclear in which treatment situation or phase the patients included in the studies were and which treatment they therefore needed. According to the inclusion criteria of the AURA-LV and AURORA-1 studies, all patients required treatment with high-dose glucocorticoids and immunosuppressants in the opinion of the investigator. There were no restrictions regarding disease duration of lupus nephritis since diagnosis, type and/or duration of any prior therapies, or response to prior therapies, according to the inclusion and exclusion criteria, however.

On the one hand, it is possible that newly diagnosed patients were included. In this case, it can be assumed that the patients were either in an early treatment phase (initial induction therapy) at enrolment and had not yet shown a response to their prior therapy, or that they had not yet received any treatment for lupus nephritis and initiated this treatment during the study. On the other hand, it is possible that patients were enrolled who had already received longer (maintenance) therapy for lupus nephritis but had not responded to this therapy or had relapsed after a response.

According to guidelines, mycophenolate mofetil, which was administered in the studies, can be used as both induction and maintenance treatment [7]. For some of the patients, the concomitant mycophenolate mofetil treatment administered in the studies was a change of their prior therapy; for the other part of the patients, the treatment regimen in the studies was the continuation of their prior therapy. The available information shows that a relevant proportion of patients in the comparator arms of the studies AURA-LV (36%) and AURORA-1

(54%) were already taking mycophenolate mofetil at the time of screening and continued this treatment during the studies (see Table 9 in I Appendix B of the full dossier assessment). However, it is unclear for which proportion of these patients the continuation of treatment with mycophenolate mofetil was adequate or for which proportion a change of therapy would have been indicated.

For patients without mycophenolate mofetil treatment at the time of screening (AURA-LV: 64% in the comparator arm; AURORA-1: 46% in the comparator arm) who were switched to mycophenolate mofetil in the AURA-LV or AURORA-1 studies or who received mycophenolate mofetil for the first time, mycophenolate mofetil may represent a suitable treatment option for the individual patient. Due to a lack of data, the proportion of patients concerned remains unclear, however. Data are available on how many patients had received prior therapy with mycophenolate mofetil (AURA-LV: 44% in the comparator arm; AURORA-1: 62% in the comparator arm, see Table 9 in I Appendix B of the full dossier assessment). However, these data do not provide any information about the time point at which this medication was administered before study start and whether the patients had an inadequate response to this treatment. In case of insufficient response to prior therapy with mycophenolate mofetil, it is questionable whether (renewed) treatment with mycophenolate mofetil during the studies is a suitable individualized therapy for these patients in the sense of the ACT.

In the context of the approval procedure for voclosporin, the European Medicines Agency (EMA) also described that the treatment situation the patients in the AURA-LV and AURORA-1 studies were in was unclear [21,22]. It can be inferred from information provided by the company as part of the approval procedure [22] that a total of 251 patients (47%) in the 2 studies were diagnosed within 12 months before randomization and 117 patients (22%) were assessed as refractory (defined as starting treatment with azathioprine, mycophenolate mofetil or cyclophosphamide > 6 months before randomization and UPCR > 1.5 mg/mg). In addition, only a few treatment-naïve patients were included [21]. Overall, however, the information provided by the company in the context of the approval procedure also does not allow any conclusions to be drawn as to whether the patients had shown a response to their respective therapy before the start of the study. Therefore, it remains unclear whether the concomitant treatment administered in the studies was appropriate for the patients included in each case or whether an optimization of the treatment would have been necessary.

In summary, it cannot be deduced from the information provided by the company that treatment with mycophenolate mofetil in combination with glucocorticoids (as well as any antimalarials) administered in the comparator arms of the AURA-LV and AURORA-1 studies was an implementation of the ACT of individualized therapy.

Potential limitations to the validity of the results from the AURA-LV study

Irrespective of the question of the implementation of the ACT, the EMA describes irregularities regarding the randomization in the AURA-LV study, which potentially affect the validity of the study results. According to the EMA [21], there was a local imbalance in randomization with patients from low gross domestic product (GDP) countries (Bangladesh, Sri Lanka, Philippines) over-represented in treatment arm A (voclosporin in compliance with the SPC) (47% compared with 32% under placebo and 38% in treatment arm B [high-dose voclosporin]). Patients in treatment arm A also had longer disease duration, more severe kidney disease and more haematological SLE involvement at baseline, according to the EMA assessment report [21]. According to the EMA, the imbalance in the distribution of patients from low GDP countries could explain, on the one hand, the observed differences in patient characteristics and, on the other, the discrepancies in the frequency of deaths seen between the study arms (treatment arm A: 10 deaths, compared with placebo: 1 death, and treatment arm B: 2 deaths). The company did not address this issue in Module 4 A of the dossier.

Further limitations of the analyses presented by the company

Irrespective of the fact that the implementation of the ACT cannot be deduced from the available data, the analyses used by the company for the adjusted indirect comparison of voclosporin with belimumab are also not suitable for the following reasons:

The company based its main analysis and one of its sensitivity analyses on the intervention side on the AURORA-2 study (see Section I 3.1). However, as described in Section I 3.1, the analyses of the AURORA-2 study are not suitable for the benefit assessment because there was no randomized comparison.

The other sensitivity analyses of the company (see Section I 3.1) for voclosporin were not based on the AURORA-2 study, but on a meta-analytical summary of the results of the AURA-LV and AURORA-1 studies. In one analysis, the company used notably different analysis dates for voclosporin and belimumab, however (AURORA-1 and AURA-LV: 1 year; BLISS-LN: 2 years under treatment). In addition, the company presented these analyses only for individual outcomes. The other sensitivity analysis was based on the same analysis date (1 year under treatment) on both sides of the comparison, but the company only presented analyses for the outcome of renal response.

I 4 Results on added benefit

No suitable data are available to assess the added benefit of voclosporin + mycophenolate mofetil compared with the ACT in adult patients with active class III, IV or V (including mixed class III/V and IV/V) lupus nephritis. There is no hint of an added benefit of voclosporin + mycophenolate mofetil in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of added benefit for voclosporin + mycophenolate mofetil in comparison with the ACT.

Table 5: Voclosporin + mycophenolate mofetil – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with active class III, IV or V (including mixed class III/V and IV/V) lupus nephritis[b]	Individualized therapy[c] taking into account any prior therapy and disease activity, choosing from the following drugs: glucocorticoids, azathioprine, cyclophosphamide, hydroxychloroquine, chloroquine, mycophenolate mofetil/mycophenolic acid[d]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Both induction and maintenance therapy are considered in the therapeutic indication of lupus nephritis. Moderate to severe disease activity is assumed.
c. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options.
d. See resolution on an amendment to the AM-RL of Annex VI – off-label use of mycophenolate mofetil/mycophenolenic acid in lupus nephritis [3].

ACT: appropriate comparator therapy; AM-RL: Pharmaceutical Directive; G-BA: Federal Joint Committee

The assessment described above corresponds to the assessment of the company in that the company also concluded that an added benefit of voclosporin is not proven. However, the company based this conclusion on the comparison of voclosporin versus belimumab (in deviation from the G-BA named as ACT by the company).

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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