Ublituximab (multiple sclerosis)

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

EXTRACT

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[1] Translation of Sections I 1 to I 4 of the dossier assessment *Ublituximab (Multiple Sklerose) – Nutzenbewertung gemäß § 35a SGB V*. 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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Patient and family involvement

The questionnaire on the disease and its treatment was answered by Herbert Temmes.

IQWiG thanks the respondent and the Deutsche Multiple Sklerose Gesellschaft, Bundesverband e. V. for participating in the written exchange about how he experienced the disease and its treatment and about the treatment goals. The respondent was not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AWMF	Association of the Scientific Medical Societies in Germany
EDSS	Expanded Disability Status Scale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GD	gadolinium
IPD	individual patient data
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IRR	infusion-related reactions
MRI	magnetic resonance imaging
PT	Preferred Term
RCT	randomized controlled trial
RMS	relapsing forms of multiple sclerosis
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	magnetic resonance imaging

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug ublituximab. 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 January 2024.

Research question

The aim of the present report is to assess the added benefit of ublituximab in comparison with the appropriate comparator therapy (ACT) in adults with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.

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

Table 2: Research questions of the benefit assessment of ublituximab

Research question	Therapeutic indication[a]	ACT[b]
1	Adults with RMS who have not yet received disease-modifying therapy and show no evidence of a severe course of disease	Dimethyl fumarate or diroximel fumarate or glatiramer acetate or IFN-β1a or IFN-β1b or teriflunomide
2	Adults with RMS who have not yet received disease-modifying therapy and show evidence of a severe course of disease and adults who show an active course of disease despite treatment with a disease-modifying therapy	Individualized therapy[c, d] taking into account the disease activity and prognostic factors[e] choosing from the following drugs: ▪ fingolimod, natalizumab, ocrelizumab, ofatumumab, ozanimod and ponesimod

a. In analogy to the treatment algorithm recommended in the guidelines, a distinction is principally made between the patient populations with regard to previous therapy (treatment-naive or pretreated) and severity of the disease.
b. Presentation of the respective ACT specified by the G-BA.
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. In the present indication, the specified ACT offers the possibility that a single comparator study can also be presented in the benefit assessment and, if applicable, an added benefit can be derived for a part of the therapeutic indication.
d. An unchanged continuation of the prior therapy is not considered an appropriate implementation of the ACT if there is a therapeutic indication to change the disease-modifying therapy.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IFN: interferon; Ig: immunoglobulin; RMS: relapsing multiple sclerosis

In the present benefit assessment, the following terms are used for the research questions:

- Research question 1: treatment-naive patients who show no evidence of a severe course of disease
- Research question 2: treatment-naive patients who show evidence of a severe course of disease and pretreated patients with an active course of disease

The company deviated from the G-BA's specification for differentiating between the different research questions and the respective ACTs. The company refers to the most recent benefit assessment procedures in the present therapeutic indication for the drug ponesimod and describes that the ACT can be derived in analogy to the previous adjudication practice in the therapeutic indication. The company's approach for the distribution of the patient population is not appropriate; the present assessment is based on the research questions defined by the G-BA (populations and associated ACTs).

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 12 months were used for the derivation of the added benefit.

Research question 1: treatment-naive patients who show no evidence of a severe course of disease

Results

The review of the information retrieval identified the studies RMS 301 (hereinafter ULTIMATE I) and RMS 302 (hereinafter ULTIMATE II) for the direct comparison of ublituximab with teriflunomide, each of which contained a relevant subpopulation for research question 1 of the present benefit assessment. Nevertheless, the data on the studies presented by the company are not suitable for drawing conclusions on the added benefit for the relevant population for research question 1 of the present benefit assessment. In the following, the studies are first described and then the lack of suitability of the data presented for the benefit assessment is justified.

Evidence presented by the company – the studies ULTIMATE I and ULTIMATE II

The 2 ULTIMATE studies are double-blind, randomized, active-controlled, multicentre studies comparing ublituximab with teriflunomide. Adults aged 18 to 55 years who had been diagnosed with RMS using the revised 2010 McDonald criteria were included. Moreover, patients had to have an active disease. This was characterized by the presence of at least 2 relapses in the last 2 years before screening or 1 relapse in the last year before screening and/or at least 1 gadolinium (Gd)-enhancing lesion in the magnetic resonance imaging (MRI) for screening. Furthermore, patients were allowed to have an Expanded Disability Status Scale (EDSS) score of no more than 5.5 at the time of screening.

In the ULTIMATE I study, a total of 549 patients were randomized in a 1:1 ratio to the two treatment arms ublituximab (N = 274) and teriflunomide (N = 275). In the ULTIMATE II study, a total of 545 patients were randomized to the treatment arms, ublituximab (N = 272) and teriflunomide (N = 273).

Treatment with ublituximab was largely in compliance with the specifications of the Summary of Product Characteristics (SPC). Treatment with teriflunomide was in compliance with the SPC.

The primary outcome of the studies was annualized relapse rate. According to the information in Module 4 A, secondary outcomes comprised outcomes of the categories of morbidity, health-related quality of life and side effects.

Analyses presented on the studies ULTIMATE I and II not suitable for benefit assessment

The studies ULTIMATE I and II each contain a relevant subpopulation for research question 1 of the present benefit assessment. However, the data of the ULTIMATE studies presented by the company are not suitable for deriving conclusions on the added benefit of ublituximab in comparison with the ACT for research question 1 of the present benefit assessment. This is due to the fact that less than 80% of the patients in the studies ULTIMATE I and ULTIMATE II can be assigned to the population relevant for research question 1 of this benefit assessment (treatment-naive and no evidence of a severe course of disease) and no analyses are available for the relevant subpopulation. This is explained below.

Data on the total population of the studies ULTIMATE I and II not suitable for the benefit assessment

Deviating from the patient populations specified by the G-BA for research questions 1 and 2, the company defined the following populations in the dossier (referred to by the company as subpopulations A1 and A2):

- A1: Adults with RMS who have not yet received disease-modifying therapy, or adults with non-highly active disease pretreated with disease-modifying therapy
- A2: Adults with RMS with highly active disease despite treatment with a disease-modifying therapy

The ULTIMATE studies comprise patients from both subpopulations defined by the company. In Module 4 A, the company states that the proportion of patients with highly active disease despite treatment with a disease-modifying therapy (subpopulation A2) in the pooled ULTIMATE studies was 6.4% (ULTIMATE I: 5.5%; ULTIMATE II: 7.4%). Accordingly, subpopulation A1 accounted for 93.6% of all patients in the pooled ULTIMATE studies. Since, according to the company, the inclusion criterion for subpopulation A1 as defined by the company was thus fulfilled in more than 80% of the patients in the studies, the company used

the data of the total population of the respective studies. However, its calculations are not based on the subdivision of the patient populations in accordance with the G-BA's research questions; its approach is therefore not appropriate. For the patient populations of research questions 1 and 2 specified by the G-BA, the proportions of patients of the ULTIMATE studies to be assigned to research questions 1 and 2 rather deviate from the company's calculation. Such an assessment based on the information on pre-treatment and severity of the course of disease available in the dossier is described below.

Estimation of the proportion of ULTIMATE I and II patients corresponding to the population for research question 1 of the present benefit assessment

According to the G-BA, research question 1 includes patients with RMS who have not yet received any disease-modifying therapy and show no evidence of severe disease progression. The company's information on patient numbers for the subgroup characteristic "pre-treatment with disease-modifying therapy (yes; no)" shows that approx. 68% of patients in ULTIMATE I and approx. 65% of patients in ULTIMATE II did not receive any previous treatment with a disease-modifying therapy (= treatment-naive). According to the G-BA's categorization, treatment-naive patients who show no signs of a severe course of disease are to be assigned to research question 1. Treatment-naive patients who show signs of a severe course of disease, on the other hand, are to be assigned to research question 2. Assuming that all treatment-naive patients in the ULTIMATE studies showed no evidence of a severe course of disease, a proportion of approx. 68% of patients in ULTIMATE I and approx. 65% of patients in ULTIMATE II would correspond to the relevant population for research question 1. By assuming that *all* treatment-naive patients in the ULTIMATE studies showed no evidence of a severe course of disease, these proportions are to be understood as upper limits. Accordingly, less than 80% of the patients in the respective ULTIMATE study correspond to the relevant population for research question 1, meaning that the total populations of the studies cannot be used for the benefit assessment.

Results of the subgroup "pre-treatment with disease-modifying therapy - no" not suitable for the present benefit assessment

As described in the previous section, the company presented analyses on the subgroup characteristic "pre-treatment with disease-modifying therapy (yes; no)" in the dossier. It was therefore examined whether the results of the subgroup "pre-treatment with disease-modifying therapy - no" (treatment-naive) could be used as an approximation for the relevant population for research question 1. This would be the case if the proportion of treatment-naive patients with no evidence of a severe course of disease were more than 80% in this subgroup in both ULTIMATE I and II.

To estimate the proportion of treatment-naive patients with or without evidence of a severe course of disease, the baseline EDSS score was used as a possible approximation for assessing

the severity of disease progression. According to the current guideline of the Association of the Scientific Medical Societies in Germany (AWMF) on the diagnosis and treatment of multiple sclerosis, it can be assumed that treatment-naive patients are likely to have a highly active course of disease if, for example, the EDSS is ≥ 3.0 in the (approx.) first year of the disease. The EDSS scale ranges from 0 to 10 points and increases in 0.5-point increments from an EDSS value of 1.0, with a low score indicating a mild disease severity. The median baseline EDSS score of the patients at was 3.0 in both arms of ULTIMATE I, i.e. a maximum of 50% of the patients in the study had an EDSS score < 3.0 at baseline and therefore showed no evidence of a severe course of disease according to the current guideline. In ULTIMATE II, the median EDSS score of the patients was 2.5 in the intervention arm vs. 3.0 in the comparator arm, i.e. a maximum of 50% of the patients in the comparator arm had a baseline EDSS score < 3.0 and therefore also showed no evidence of a severe course of disease according to the current guideline. Due to the median being 2.5, the upper limit of 50% for the proportion of patients with no evidence of a severe course of disease is not certain within the intervention arm of ULTIMATE II. However, when considering both treatment arms, it can be assumed that this upper limit also applies to the ULTIMATE II study, at least as a good approximation, especially since the mean EDSS score in the intervention arm is 2.8. This means that the criterion "EDSS score at baseline" can be used to estimate a maximum proportion of 74% (ULTIMATE I: 50%/68%) or a maximum of around 77% (ULTIMATE II: 50%/65%) of patients not pre-treated with disease-modifying therapy who show no evidence of a severe course of disease and would therefore approximately correspond to the population for research question 1. In this assessment, too, less than 80% of the patients in the subgroup "Pretreatment with disease-modifying therapy - no" of the respective ULTIMATE study correspond to the relevant population for research question 1, so that the subgroup results of the treatment-naive patients are also unsuitable for addressing research question 1 of the present benefit assessment.

Analyses for the relevant subpopulation of the ULTIMATE studies for research question 1 are to be presented for the benefit assessment

In summary, the studies ULTIMATE I and ULTIMATE II each contain a relevant subpopulation for research question 1 of the present benefit assessment. However, as described, the data of the ULTIMATE studies presented by the company are not suitable for deriving conclusions on the added benefit of ublituximab in comparison with the ACT for research question 1 of the present benefit assessment. The company must present analyses for the relevant subpopulation as part of the commenting procedure.

Results on added benefit

Since no suitable data are available for the present research question, there is no hint of added benefit of ublituximab in comparison with the ACT; an added benefit is therefore not proven.

Research question 2: treatment-naive patients who show evidence of a severe course of disease and pretreated patients with an active course of disease

Results

The check of the information retrieval produced no RCTs on the direct comparison of ublituximab versus the ACT.

Results on added benefit

Since no relevant study is available for the present research question, there is no hint of added benefit of ublituximab over 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 ublituximab.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Ublituximab – probability and extent of added benefit

Research question	Therapeutic indication[a]	ACT[b]	Probability and extent of added benefit
1	Adults with RMS who have not yet received disease-modifying therapy and show no evidence of a severe course of disease	Dimethyl fumarate or diroximel fumarate or glatiramer acetate or IFN-β1a or IFN-β1b or teriflunomide	Added benefit not proven
2	Adults with RMS who have not yet received disease-modifying therapy and show evidence of a severe course of disease and adults who show an active course of disease despite treatment with a disease-modifying therapy	Individualized therapy[c, d] taking into account the disease activity and prognostic factors[e] choosing from the following drugs: ▪ fingolimod, natalizumab, ocrelizumab, ofatumumab, ozanimod and ponesimod	Added benefit not proven

a. In analogy to the treatment algorithm recommended in the guidelines, a distinction is principally made between the patient populations with regard to the previous therapy (treatment-naive or pretreated) and severity of the disease.
b. Presentation of the respective ACT specified by the G-BA.
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. In the present indication, the specified ACT offers the possibility that a single comparator study can also be presented in the benefit assessment and, if applicable, an added benefit can be derived for a part of the therapeutic indication.
d. An unchanged continuation of the prior therapy is not considered an appropriate implementation of the ACT if there is a therapeutic indication to change the disease-modifying therapy.

G-BA: Federal Joint Committee; IFN: interferon; Ig: immunoglobulin; RMS: relapsing multiple sclerosis

The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report is to assess the added benefit of ublituximab in comparison with the ACT in adults with RMS with active disease defined by clinical or imaging features.

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

Table 4: Research questions of the benefit assessment of ublituximab

Research question	Therapeutic indication[a]	ACT[b]
1	Adults with RMS who have not yet received disease-modifying therapy and show no evidence of a severe course of disease	Dimethyl fumarate or diroximel fumarate or glatiramer acetate or IFN-β1a or IFN-β1b or teriflunomide
2	Adults with RMS who have not yet received disease-modifying therapy and show evidence of a severe course of disease and adults who show an active course of disease despite treatment with a disease-modifying therapy	Individualized therapy[c, d] taking into account the disease activity and prognostic factors[e] choosing from the following drugs: ▪ fingolimod, natalizumab, ocrelizumab, ofatumumab, ozanimod and ponesimod

a. In analogy to the treatment algorithm recommended in the guidelines, a distinction is principally made between the patient populations with regard to the previous therapy (treatment-naive or pretreated) and severity of the disease.
b. Presentation of the respective ACT specified by the G-BA.
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. In the present indication, the specified ACT offers the possibility that a single comparator study can also be presented in the benefit assessment and, if applicable, an added benefit can be derived for a part of the therapeutic indication.
d. An unchanged continuation of the prior therapy is not considered an appropriate implementation of the ACT if there is a therapeutic indication to change the disease-modifying therapy.

G-BA: Federal Joint Committee; IFN: interferon; Ig: immunoglobulin; RMS: relapsing multiple sclerosis

In the present benefit assessment, the following terms are used for the research questions:

- Research question 1: treatment-naive patients who show no evidence of a severe course of disease
- Research question 2: treatment-naive patients with indication of a severe course of disease and pretreated patients with an active course of disease

The company deviated from the G-BA's specification for differentiating between the different research questions and the respective ACTs. The company refers to the most recent benefit assessment procedures in the present therapeutic indication for the drug ponesimod [3,4] and describes that the ACT can be derived in analogy to the previous adjudication practice in the therapeutic indication. A consultation with the G-BA did not take place.

According to the company, the patient population for the research question designated by the company as A1 comprises adults with RMS who have not yet received disease-modifying therapy or adults pre-treated with disease-modifying therapy whose disease is not highly active. According to the G-BA's categorization, however, adults who have been pre-treated with disease-modifying therapy and whose disease is not highly active are not covered by research question 1. Rather, research question 1 of the G-BA includes only adults who have not yet received disease-modifying therapy and show no evidence of a severe course of disease.

Moreover, according to the company, the patient population for the research question designated by the company as A2 comprises adults with RMS with highly active disease despite treatment with a disease-modifying therapy. According to the G-BA's categorization, however, research question 2 comprises two different patient groups, firstly adults who have an active course of disease despite treatment with disease-modifying therapy, and secondly adults who have not yet received any disease-modifying therapy and show signs of severe disease progression. The company's approach for the subdivision of the patient population is not appropriate; the assessment is conducted according to the G-BA’s subdivision.

In addition, the company deviated from the respective ACT for both research questions. However, these deviations remain without consequence for the benefit assessment. For its research question A1, the company presented evidence for the assessment of the added benefit of ublituximab compared with the option teriflunomide named by the G-BA. The company presented no data for its research question A2.

The present assessment was conducted on the basis of the research questions specified by the G-BA (populations and corresponding ACTs).

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 12 months were used for the derivation of the added benefit. This concurs with the company’s inclusion criteria.

I 3 Research question 1: treatment-naive patients who show no evidence of a severe course of disease

I 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 list on ublituximab (status: 18 December 2023)
- bibliographical literature search on ublituximab (last search on 04 November 2023)
- search in trial registries/trial results databases for studies on ublituximab (last search on 05 November 2023)
- search on the G-BA website for ublituximab (last search on 01 December 2023)

To check the completeness of the study pool:

- search in trial registries for studies on ublituximab (last search on 15 February 2024); for search strategies, see I Appendix A of the full dossier assessment

The review identified studies RMS 301 (hereafter ULTIMATE I) [5-8] and RMS 302 (hereafter ULTIMATE II) [5,9-11] for the direct comparison of ublituximab versus teriflunomide, each of which contains a relevant subpopulation for research question 1 of the present benefit assessment. The company also identified the studies ULTIMATE I and ULTIMATE II, but considered a patient population that deviated from research question 1 of the G-BA and a different ACT (see Chapter I 2). Even if the studies comprise a subpopulation relevant for research question 1, the data on the studies presented by the company are not suitable for drawing conclusions on the added benefit for the population relevant for research question 1 of the present benefit assessment. In the following, the studies are first described and then the lack of suitability of the data presented for the benefit assessment is justified.

Evidence provided by the company

The company presented a meta-analysis based on individual patient data (IPD) of the studies ULTIMATE I and ULTIMATE II for research question A1 defined by it. Both studies are identical in terms of design and methods, as they are based on identical protocols. The studies are therefore described jointly. The characteristics of the studies are presented as supplementary information in I Appendix B of the full dossier assessment.

Study design and study medication

The 2 ULTIMATE studies are double-blind, randomized, active-controlled, multicentre studies comparing ublituximab with teriflunomide (see also Table 6 of the full dossier assessment). Adults aged 18 to 55 years who had been diagnosed with RMS using the revised 2010

McDonald criteria [12] were included. Moreover, patients had to have an active disease. This was characterized by the presence of at least 2 relapses in the last 2 years before screening or 1 relapse in the last year before screening and/or at least 1 Gd-enhancing lesion in the MRI for screening. Furthermore, patients were allowed to have an EDSS score of no more than 5.5 at the time of screening.

In the ULTIMATE I study, a total of 549 patients were randomized in a 1:1 ratio to the two treatment arms ublituximab (N = 274) and teriflunomide (N = 275). In the ULTIMATE II study, a total of 545 patients were randomized to the treatment arms, ublituximab (N = 272) and teriflunomide (N = 273). Randomization was not stratified.

The patients were treated in compliance with the regimen described in Table 7 of the full dossier assessment over a period of 96 weeks. Treatment with ublituximab was largely in accordance with the SPC [13]. According to the study protocol, the treatment interval between two consecutive ublituximab infusions should be at least 16 weeks if the infusion is postponed. In contrast, the SPC for ublituximab specifies a minimum interval of 5 months between two consecutive infusions. The dossier contains no information on the mean interval between ublituximab infusions, nor on how many patients deviated from the minimum interval of 5 months stated in the SPC. Treatment with teriflunomide was in compliance with the SPC [14].

The primary outcome of the studies was annualized relapse rate. According to the information in Module 4 A, secondary outcomes comprised outcomes of the categories of morbidity, health-related quality of life and side effects.

Assessment of the evidence presented by the company

The studies ULTIMATE I and II each contain a relevant subpopulation for research question 1 of the present benefit assessment. However, the data of the ULTIMATE studies presented by the company are not suitable for deriving conclusions on the added benefit of ublituximab in comparison with the ACT for research question 1 of the present benefit assessment. This is due to the fact that less than 80% of the patients in the studies ULTIMATE I and ULTIMATE II can be assigned to the population relevant for research question 1 of this benefit assessment (treatment-naive and no evidence of a severe course of disease). This is explained below.

Data on the total population of ULTIMATE I and ULTIMATE II not suitable for the present benefit assessment

Deviating from the patient populations specified by the G-BA for research questions 1 and 2, the company defined the following populations in the dossier (referred to by the company as subpopulations A1 and A2, see also Chapter I 2):

- A1: Adults with RMS who have not yet received disease-modifying therapy, or adults with non-highly active disease pretreated with disease-modifying therapy
- A2: Adults with RMS with highly active disease despite treatment with a disease-modifying therapy

The ULTIMATE studies comprise patients from both subpopulations defined by the company. In Module 4 A, the company states that the proportion of patients with highly active disease despite treatment with a disease-modifying therapy (subpopulation A2) in the pooled ULTIMATE studies was 6.4% (ULTIMATE I: 5.5%; ULTIMATE II: 7.4%). Accordingly, subpopulation A1 accounted for 93.6% of all patients in the pooled ULTIMATE studies. Since, according to the company, the inclusion criterion for subpopulation A1 as defined by the company was thus fulfilled in more than 80% of the patients in the studies, the company used the data of the total population of the respective studies. However, its calculations are not based on the subdivision of the patient populations in accordance with the G-BA's research questions; its approach is therefore not appropriate. For the patient populations of research questions 1 and 2 specified by the G-BA, the proportions of patients of the ULTIMATE studies to be assigned to research questions 1 and 2 rather deviate from the company's calculation. Such an assessment based on the information on pre-treatment and severity of the course of disease (see Table 8 of the full dossier assessment) available in the dossier is described below.

Estimation of the proportion of ULTIMATE I and II patients corresponding to the population for research question 1 of the present benefit assessment

According to the G-BA, research question 1 includes patients with RMS who have not yet received any disease-modifying therapy and show no evidence of severe disease progression. The company's information on patient numbers for the subgroup characteristic "pre-treatment with disease-modifying therapy (yes; no)" shows that approx. 68% of patients in ULTIMATE I and approx. 65% of patients in ULTIMATE II did not receive any previous treatment with a disease-modifying therapy (= treatment-naive) (see Table 8 of the full dossier assessment). According to the G-BA's categorization, treatment-naive patients who show no signs of a severe course of disease are to be assigned to research question 1. Treatment-naive patients who show signs of a severe course of disease, on the other hand, are to be assigned to research question 2. Assuming that all treatment-naive patients in the ULTIMATE studies showed no evidence of a severe course of disease, a proportion of approx. 68% of patients in ULTIMATE I and approx. 65% of patients in ULTIMATE II would correspond to the population relevant for research question 1. By assuming that *all* treatment-naive patients in the ULTIMATE studies showed no evidence of a severe course of disease, these proportions are to be understood as upper limits. Accordingly, less than 80% of the patients in the respective ULTIMATE study correspond to the population relevant for research question 1, meaning that the total population of the studies cannot be used for the benefit assessment.

Results of the subgroup "pre-treatment with disease-modifying therapy - no" not suitable for the present benefit assessment

As described in the previous section, the company presented analyses on the subgroup characteristic "pre-treatment with disease-modifying therapy (yes; no)" in the dossier. It was therefore examined whether the results of the subgroup "pre-treatment with disease-modifying therapy - no" (treatment-naive) could be used as an approximation for the relevant population for research question 1. This would be the case if the proportion of treatment-naive patients with no evidence of a severe course of disease were more than 80% in this subgroup in both ULTIMATE I and II.

To estimate the proportion of treatment-naive patients with or without evidence of a severe course of disease, the baseline EDSS score was used as a possible approximation for assessing the severity of disease progression. According to the current guideline of the AWMF on the diagnosis and treatment of multiple sclerosis [15], it can be assumed that treatment-naive patients are likely to have a highly active course of disease if, for example, the EDSS is ≥ 3.0 in the (approx.) first year of the disease. The EDSS scale ranges from 0 to 10 points and increases in 0.5-point increments from an EDSS value of 1.0, with a low score indicating a mild disease severity. The median baseline EDSS score of the patients was 3.0 in both arms of ULTIMATE I (see Table 8 of the full dossier assessment), i.e. a maximum of 50% of the patients in the study had an EDSS score < 3.0 at baseline and therefore showed no evidence of a severe course of disease according to the current guideline. In ULTIMATE II, the median EDSS score of the patients was 2.5 in the intervention arm vs. 3.0 in the comparator arm (see Table 8 of the full dossier assessment), i.e. a maximum of 50% of the patients in the comparator arm had a baseline EDSS score < 3.0 and therefore also showed no evidence of a severe course of disease according to the current guideline. Due to the median being 2.5, the upper limit of 50% for the proportion of patients with no evidence of a severe course of disease is not certain within the intervention arm of ULTIMATE II. However, when considering both treatment arms, it can be assumed that this upper limit also applies to the ULTIMATE II study, at least as a good approximation, especially since the mean EDSS score in the intervention arm is 2.8. This means that the criterion "EDSS score at baseline" can be used to estimate a maximum proportion of 74% (ULTIMATE I: 50%/68%) or a maximum of around 77% (ULTIMATE II: 50%/65%) of patients not pre-treated with disease-modifying therapy who show no evidence of a severe course of disease and would therefore approximately correspond to the population for research question 1. In this assessment, too, less than 80% of the patients in the subgroup "Pretreatment with disease-modifying therapy - no" of the respective ULTIMATE study correspond to the relevant population for research question 1, so that the subgroup results of the treatment-naive patients are also unsuitable for addressing research question 1 of the present benefit assessment.

In the estimation described above, it should also be noted that the used criterion "EDSS value at baseline" does not exactly reflect the criterion of the AWMF guideline, which specifies the EDSS score in relation to the first year of the disease as a possible criterion for the severity or activity of the course of the disease in treatment-naive patients. According to the AWMF guideline [15], there are also further or additional criteria for categorizing the course of the disease as severe or probably highly active in treatment-naive patients: If a relapse has led to a severe deficit relevant to everyday life after relapse therapy has been exhausted and/or in the event of poor recovery from the first two relapses and/or a high relapse frequency (≥ 3 in the first 2 [approx.] years or ≥ 2 in the 1st [approx.] year) after disease onset and/or with pyramidal tract involvement in the first year of the disease and/or if there are ≥ 2 contrast agent-absorbing lesions and a high T2 lesion load with special weighting of spinal or infratentorial lesions in the MRI findings at the time of diagnosis). Since the dossier contains no information on the proportion of patients in the ULTIMATE studies to whom one or more of the criteria mentioned apply or do not apply, only an approximate estimate of a relevant subpopulation for research question 1 could be made here. As described above, this was carried out on the basis of the information on patient numbers for the pretreatment with disease-modifying therapy and the criterion "EDSS score at baseline".

Analyses for the relevant subpopulation of the ULTIMATE studies for research question 1 are to be presented for the benefit assessment

In summary, the studies ULTIMATE I and ULTIMATE II each contain a relevant subpopulation for research question 1 of the present benefit assessment. However, as described, the data of the ULTIMATE studies presented by the company are not suitable for deriving conclusions on the added benefit of ublituximab in comparison with the ACT for research question 1 of the present benefit assessment. The company must present analyses for the relevant subpopulation as part of the commenting procedure.

Further notes on the data presented by the company

Irrespective of the fact that the analyses on the studies ULTIMATE I and ULTIMATE II presented by the company are not suitable for the benefit assessment for the reasons described above, there are the following uncertainties regarding the AESIs:

Prespecification of AESIs unclear

In Module 4 A, the company presented analyses on the following AESIs: Cytopenia, hepatic dysfunction, hypogammaglobulinaemia, infusion-related reactions (IRR), malignant diseases and serious infections. In Module 4 A, the company states that the AESIs were pre-specified. However, versions 1 to 4 of the study protocol define AESIs that differ from Module 4 A. In the latest version 5 of the study protocol [8,11] of 04 September 2020, not a single AESI is explicitly named. Instead, the protocol refers to the "Ublituximab Investigator Brochure", which is not comprised in the company's dossier. Based on the available study documents, it therefore

remains unclear whether the AESIs analysed in Module 4 A and the System Organ Classes (SOCs) and preferred terms (PTs) on which the analyses were based were pre-specified.

Recording of PT events of the outcome "IRR" as part of the general AE analysis of Treatment-Emergent Adverse Events (TEAE) unclear

In Module 4 A of the dossier, the company presents analyses on the outcome "IRR" based on the events of a PT list, for which, however, it is unclear whether this was pre-specified, as described above. According to the information in the study protocol, events that occurred during the infusion or up to 24 hours after the end of the infusion were documented as IRR. It is not clear from the information in the dossier whether the PT events underlying the outcome of IRR were also included in the general AE analysis of the Treatment-Emergent AEs (TEAEs) . In case that the PT events were not recorded in the general AE analysis of the TEAE, the interpretability of the common PTs/SOCs might be limited (see A21-60 [16]). In this case, the events under the symptoms concerned (e.g. the PT chills) would not be fully recorded in the analyses on PT/SOC presented by the company in Module 4 A.

I 3.2 Results on added benefit

No suitable data are available to assess the added benefit of ublituximab in comparison with the ACT for the treatment of adults with RMS who have not yet received disease-modifying therapy and show no evidence of a severe course of disease. There is no hint of an added benefit of ublituximab over the ACT; an added benefit is therefore not proven.

I 3.3 Probability and extent of added benefit

No suitable data are available to assess the added benefit of ublituximab in comparison with the ACT in adults with RMS who have not yet received disease-modifying therapy and show no evidence of a severe course of disease. An added benefit of ublituximab in comparison with the ACT is therefore not proven for these patients.

This deviates from the company's assessment, which derives proof of a considerable added benefit over teriflunomide as an ACT for the patient population of adults with RMS defined by it who have not yet received any disease-modifying therapy or adults who have been pre-treated with disease-modifying therapy and whose disease is not highly active (patient population deviating from research question 1 of the G-BA) on the basis of the IPD meta-analysis of the studies ULTIMATE I and ULTIMATE II.

I 4 Research question 2: treatment-naive patients who show evidence of a severe course of disease and pretreated patients with an active course of disease

I 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 list on ublituximab (status: 18 December 2023)
- bibliographical literature search on ublituximab (last search on 04 November 2023)
- search in trial registries/trial results databases for studies on ublituximab (last search on 05 November 2023)
- search on the G-BA website for ublituximab (last search on 01 December 2023)

To check the completeness of the study pool:

- search in trial registries for studies on ublituximab (last search on 15 February 2024); for search strategies, see I Appendix A of the full dossier assessment

The check produced no RCTs on the direct comparison of ublituximab versus the ACT. The company also identified no relevant RCTs for the direct comparison of ublituximab versus the ACT; however, in its search the company took into account a patient population that deviated from research question 2 of the G-BA, and a different ACT (see Chapter I 2).

I 4.2 Results on added benefit

No data are available for the assessment of the added benefit of ublituximab compared to the ACT for the treatment of adults with RMS who have not yet received disease-modifying therapy and show evidence of a severe course of disease, as well as adults who show active disease progression despite treatment with disease-modifying therapy. There is no hint of an added benefit of ublituximab over the ACT; an added benefit is therefore not proven.

I 4.3 Probability and extent of added benefit

No data are available for the assessment of the added benefit of ublituximab compared to the ACT in adults with RMS who have not yet received disease-modifying therapy and show evidence of a severe course of disease, as well as adults who show active disease progression despite treatment with disease-modifying therapy. An added benefit of ublituximab in comparison with the ACT is therefore not proven for these patients.

This is in line with the company’s assessment, which also derived no any added benefit for the deviating patient population defined by it.

I 5 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of ublituximab in comparison with the ACT is summarized in Table 5.

Table 5: Ublituximab – probability and extent of added benefit

Research question	Therapeutic indication[a]	ACT[b]	Probability and extent of added benefit
1	Adults with RMS who have not yet received disease-modifying therapy and show no evidence of a severe course of disease	Dimethyl fumarate or diroximel fumarate or glatiramer acetate or IFN-β1a or IFN-β1b or teriflunomide	Added benefit not proven
2	Adults with RMS who have not yet received disease-modifying therapy and show evidence of a severe course of disease and adults who show an active course of disease despite treatment with a disease-modifying therapy	Individualized therapy[c, d] taking into account the disease activity and prognostic factors[e] choosing from the following drugs: ▪ fingolimod, natalizumab, ocrelizumab, ofatumumab, ozanimod and ponesimod	Added benefit not proven

a. In analogy to the treatment algorithm recommended in the guidelines, a distinction is principally made between the patient populations with regard to the previous therapy (treatment-naive or pretreated) and severity of the disease.
b. Presentation of the respective ACT specified by the G-BA.
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. In the present indication, the specified ACT offers the possibility that a single comparator study can also be presented in the benefit assessment and, if applicable, an added benefit can be derived for a part of the therapeutic indication.
d. An unchanged continuation of the prior therapy is not considered an appropriate implementation of the ACT if there is a therapeutic indication to change the disease-modifying therapy.

G-BA: Federal Joint Committee; IFN: interferon; Ig: immunoglobulin; RMS: relapsing multiple sclerosis

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.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 06.10.2023]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://doi.org/10.1002/bimj.201300274.

3. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Ponesimod (Schubförmige Multiple Sklerose) [online]. 2021 [Accessed: 12.03.2024]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/706/.

4. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Ponesimod (Schubförmige Multiple Sklerose) [online]. 2022 [Accessed: 12.03.2024]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/768/.

5. Steinman L, Fox E, Hartung HP et al. Ublituximab versus Teriflunomide in Relapsing Multiple Sclerosis. N Engl J Med 2022; 387(8): 704-714. https://doi.org/10.1056/NEJMoa2201904.

6. TG Therapeutics. Study to Assess the Efficacy and Safety of Ublituximab in Participants With Relapsing Forms of Multiple Sclerosis (RMS) (ULTIMATE 1) (ULTIMATE 1) [online]. 2021 [Accessed: 21.02.2024]. URL: https://clinicaltrials.gov/study/NCT03277261.

7. TG Therapeutics. Phase III; UbLiTuximab In Multiple Sclerosis Treatment Effects (ULTIMATE I STUDY) [online]. [Accessed: 21.02.2024]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2017-000638-75.

8. TG Therapeutics. TG1101-RMS301 Clinical Study Report [unpublished]. 2021.

9. TG Therapeutics. Study to Assess the Efficacy and Safety of Ublituximab in Participants With Relapsing Forms of Multiple Sclerosis (RMS) (ULTIMATE II) [online]. 2021 [Accessed: 21.02.2024]. URL: https://clinicaltrials.gov/study/NCT03277248.

10. TG Therapeutics. Phase III; UbliTuximab In Multiple Sclerosis Treatment Effects (ULTIMATE II STUDY) [online]. [Accessed: 21.02.2024]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2017-000639-15.

11. TG Therapeutics. TG1101-RMS302 Clinical Study Report. 2021.

12. Polman CH, Reingold SC, Banwell B et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011; 69(2): 292-302. https://doi.org/10.1002/ana.22366.

13. Neuraxpharm. Briumvi 150 mg Konzentrat zur Herstellung einer Infusionslösung [online]. 2024 [Accessed: 02.04.2024]. URL: https://www.fachinfo.de/.

14. Sanofi. AUBAGIO 7 mg Filmtabletten; AUBAGIO 14 mg Filmtabletten [online]. 2022 [Accessed: 01.02.2024]. URL: https://www.fachinfo.de/.

15. Hemmer B. Diagnose und Therapie der Multiplen Sklerose, Neuromyelitis-optica-Spektrum-Erkrankungen und MOG-IgG-assoziierten Erkrankungen; S2k-Leitlinie [online]. 2023 [Accessed: 01.02.2024]. URL: https://register.awmf.org/assets/guidelines/030-050l_S2k_Diagnose-Therapie-Multiple-Sklerose-Neuromyelitis-Optica-Spektrum-MOG-IgG-assoziierte-Erkrankungen_2024-01.pdf.

16. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Isatuximab (multiples Myelom, nach ≥ 1 Vortherapie) – Nutzenbewertung gemäß § 35a SGB V (frühe Nutzenbewertung); Dossierbewertung [online]. 2021 [Accessed: 11.07.2023]. URL: https://www.iqwig.de/download/a21-60_isatuximab_nutzenbewertung-35a-sgb-v_v1-0.pdf.

The full report (German version) is published under https://www.iqwig.de/en/projects/a24-13.html.