IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Ocrelizumab (multiple sclerosis) –

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

Extract

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	Best supportive Care
CI	confidence interval
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EPAR	European public Assessment Report
EQ-5D	European Quality of Life Questionnaire 5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
Gd-T1 lesion	gadolinium-enhancing T1-lesion
IM	intramuscularly
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MCS	Mental Component Summary
MFIS	Modified Fatigue Impact Scale
MMRM	mixed-effects model repeated measures
MS	multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
PCS	Physical Component Summary
POR	Peto Odds Ratio
PPMS	primary progressive multiple sclerosis
RCT	randomized controlled trial
RMS	relapsing multiple sclerosis
SAE	serious adverse event
SC	Subcutaneous
SF-36	Short Form (36) Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug ocrelizumab. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 16 January 2018.

Research question

Aim of the present report was the assessment of the added benefit of ocrelizumab in comparison with the appropriate comparator therapy (ACT) in patients with active relapsing multiple sclerosis (RMS) and in patients with early primary progressive multiple sclerosis (PPMS).

For the benefit assessment of ocrelizumab, the research questions presented in Table 2 resulted from the ACTs specified by the G-BA.

Table 2: Research questions of the benefit assessment of ocrelizumab

Research question	Subindication	ACT[a]
1	Adults with RMS who have not yet received disease-modifying therapy or patients with non-highly active disease pretreated with disease-modifying therapy	**Interferon beta (IFNβ) 1a or 1b** or glatiramer acetate under consideration of the approval
2	Adults with highly active RMS despite treatment with a disease-modifying therapy[b]	Alemtuzumab or fingolimod or natalizumab or, if indicated, change within the basic therapeutics (**IFNβ1a** or IFNβ1b or glatiramer acetate under consideration of the approval)
3	Adults with early PPMS	Best supportive care[c]

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Adequate (pre)treatment usually comprises at least 6 months. Depending on frequency and severity of the relapses as well as on the disability progression, treatment with a disease-modifying therapy might take less than 6 months.
c: Best supportive care (BSC) refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve quality of life.
G-BA: Federal Joint Committee; IFN-β: interferon beta; PPMS: primary progressive multiple sclerosis; RMS: relapsing multiple sclerosis

The company followed the G-BA's specification of the ACTs and chose IFN-β 1a as ACT for research questions 1 and 2, and Best supportive Care (BSC) as ACT for research question 3.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum

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

Results on research question 1: treatment-naive and pretreated patients with non-highly active RMS

The studies OPERA I and II were included in the benefit assessment of ocrelizumab in comparison with IFNβ1a in treatment-naive and pretreated patients with non-highly active RMS (research question 1).

Study design

The design, the inclusion criteria and the statistical analysis plan of the studies OPERA I and II are identical. The meta-analysis of both studies was prespecified in the respective study protocols.

The OPERA studies are randomized, double-blind, actively controlled parallel-group studies on the comparison of ocrelizumab with IFNβ1a (subcutaneous [SC] administration) in patients with RMS. Both studies were conducted worldwide at about the same time and in the same regions.

Adult patients (18 to 55 years) with at least 2 documented relapses during the last 2 years or 1 relapse within the last year before study inclusion and a maximum Expanded Disability Status Scale (EDSS) score of 5.5 were included in the studies.

A total of 1656 patients were randomly assigned to treatment with ocrelizumab (N = 827) or IFNβ1a (N = 829).

The patients were treated in compliance with the recommendations of the respective Summary of Product Characteristics (SPC). Treatment duration in both studies was 96 weeks. Follow-up observation was at least 48 weeks, irrespective of a participation in the extension phase.

Primary outcome of both studies was the annualized relapse rate. Secondary outcomes were outcomes on symptoms, health status, health-related quality of life and side effects.

Subpopulation relevant for research question 1

The subpopulation relevant for research question 1 only included patients who had not yet received disease-modifying therapy for RMS and patients with non-highly active disease pretreated with a disease-modifying therapy. The company presented analyses of the relevant subpopulation. It constituted this subpopulation by excluding patients with high disease activity from its analyses. The company operationalized high disease activity as at least one relapse and/or a gadolinium-enhancing T1-lesion (Gd-T1 lesion) in the year before the start of the study despite adequate treatment. The company defined adequate treatment as continuous, at least 6-month treatment with disease-modifying active substances.

The criteria used by the company are suitable for an adequate representation of the subpopulation relevant for research question 1. However, in its dossier the company chiefly described the total population of the two studies and only presented few patient characteristics of the relevant subpopulation. Since the relevant subpopulation only comprised about 83% of the total population in both studies, the analyses presented by the company were used as sufficient approximation to the population relevant for research question 1, despite the missing information.

Risk of bias

The risk of bias at study level was rated as low for both studies.

The risk of bias was rated as low for all outcomes except for the outcomes "disability severity", "fatigue interference", "health status" and "health-related quality of life". For the mentioned outcomes, the risk of bias was rated as high. Because of the high risk of bias and based on the available data, at most indications can be determined for these outcomes; for all other outcomes there are proofs, e.g. of an added benefit.

Mortality

All-cause mortality

For the outcome "all-cause mortality", there was altogether one event in the IFNβ1a arm of the OPERA I study. Overall, this resulted in no hint of an added benefit of ocrelizumab in comparison with IFNβ1a, an added benefit is therefore not proven.

Morbidity

Relapses (based on EDSS)

There was a statistically significant difference in favour of ocrelizumab in comparison with IFNβ1a for the outcome "relapses". In addition, there was an interaction by the characteristic "age" for this outcome for the total population of the OPERA studies. The meta-analysis showed a statistically significant difference in favour of ocrelizumab for patients both < 40 years and ≥ 40 years. However, for patients ≥ 40 years, the extent was no more than marginal. Thus, this resulted in no hint of an added benefit; an added benefit is therefore not proven. For patients < 40 years, there was proof of an added benefit of ocrelizumab.

Confirmed disability progression (based on EDSS)

There was a statistically significant difference in favour of ocrelizumab in comparison with IFNβ1a for the outcome "confirmed disability progression". The extent was no more than marginal. This resulted in no hint of an added benefit for the outcome "confirmed disability progression"; an added benefit is therefore not proven.

Disability severity (Multiple Sclerosis [MS] Functional Composite [MSFC z-score])

The meta-analysis showed a statistically significant difference in favour of ocrelizumab for the outcome "disability severity" (MSFC z-score). However, the confidence interval (CI) for the

standardized mean difference (Hedges' g) was not fully outside the irrelevance range [−0.2; 0.2]. It can therefore not be inferred that the effect is relevant. This resulted in no hint of an added benefit of ocrelizumab in comparison with IFNβ1a, an added benefit is therefore not proven.

Fatigue interference (Modified Fatigue Impact Scale [MFIS]), health status (visual analogue scale [VAS] European Quality of Life-5 Dimensions [EQ-5D])

The meta-analysis showed no statistically significant difference between the treatment groups for the outcomes "fatigue interference" (MFIS) and "health status" (EQ-5D VAS). This resulted in no hint of an added benefit of ocrelizumab in comparison with IFNβ1a, an added benefit is therefore not proven.

Health-related quality of life

Short Form (36) Health Survey (SF-36)

For the Physical Component Summary (PCS) scale, the meta-analysis showed a statistically significant difference between the treatment groups in favour of ocrelizumab. However, the CI for the standardized mean difference (hedges' g) was not fully outside the irrelevance range [−0.2; 0.2]. It can therefore not be inferred that the effect is relevant. For the Mental Component Summary (MCS) scale, the meta-analysis showed no statistically significant difference between the treatment groups.

Overall, this resulted in no hint of an added benefit of ocrelizumab in comparison with IFNβ1a for the SF-36, an added benefit is therefore not proven.

Side effects

Serious advert events (SAEs)

The meta-analysis showed no statistically significant difference for SAEs between the treatment groups. However, there was an effect modification by the subgroup characteristic "age". A statistically significant difference in favour of ocrelizumab in comparison with IFNβ1a was shown for patients < 40 years. This resulted in proof of lesser harm from ocrelizumab.

For patients ≥ 40 years, in contrast, there was no statistically significant difference between the treatment groups. This resulted in no hint of lesser or greater harm from ocrelizumab, greater or lesser harm is therefore not proven.

Discontinuation due to adverse events (AEs)

The meta-analysis showed a statistically significant difference in favour of ocrelizumab for the outcome "discontinuation due to AEs". The extent was no more than marginal. This resulted in no hint of greater or lesser harm from ocrelizumab in comparison with IFNβ1a for the outcome "discontinuation due to AEs"; greater or lesser harm is therefore not proven.

Specific AEs

Flu-like illness and injection site reactions

The meta-analysis showed a statistically significant difference in favour of ocrelizumab for the outcomes “flu-like illness” and “injection site reactions”. In each case, this resulted in a hint of lesser harm from ocrelizumab in comparison with IFNβ1a.

Reaction associated with an infusion

The meta-analysis showed a statistically significant difference to the disadvantage of ocrelizumab for the outcome “reaction associated with an infusion”. In each case, this resulted in proof of greater harm from ocrelizumab in comparison with IFNβ1a.

Infections and infestations as well as depression

The meta-analysis showed no statistically significant difference between the treatment groups for the outcomes “infections and infestations” and “depression”. This resulted in no hint of lesser or greater harm from ocrelizumab in comparison with IFNβ1a, greater or lesser harm is therefore not proven.

Results on research question 2: pretreated patients with highly active RMS

The studies OPERA I and II were included in the benefit assessment of ocrelizumab in comparison with IFNβ1a in pretreated patients with highly active RMS (research question 2). These are the same studies that had been included for the assessment of ocrelizumab in treatment-naive and pretreated patients with non-highly active RMS (research question 1) (see above)

Study design

The design of the studies OPERA I and II are described under research question 1.

Subpopulation relevant for research question 2

The population relevant for research question 2 comprises patients with highly active RMS despite treatment with a disease-modifying therapy. Consequently, only a subpopulation of the OPERA studies was relevant for the present benefit assessment. Based on the criteria described under research question 1, the company constituted a subpopulation of patients with highly active RMS despite treatment with a disease-modifying therapy. The criteria used by the company are suitable for an adequate representation of the subpopulation relevant for research question 2. Moreover, the company excluded all patients from the subpopulation who, before study inclusion, had received treatment with the comparator therapy IFNβ1a 44 µg SC used in the OPERA studies b, since change had to take place within the basic therapeutic agents according to the G-BA’s specification of the ACT. This approach is accepted with restrictions. The proportion of the relevant subpopulation in the total population amounted to about 13% in both OPERA studies.

As with research question 1, information on the description of patient characteristics of the relevant subpopulation is missing for research question 2. It is therefore unclear to which extent the subpopulation used by the company in its assessment also included patients who did not correspond to the research question or whether all patients of the relevant subpopulation were included. Thus, it cannot be verified whether and to which extent patients pretreated with IFNβ1a 22 µg SC, a dosage that was also approved, were excluded from the subpopulation. Patients with highly active disease pretreated with intramuscularly administered (IM) IFNβ1a, were also included in the subpopulation. For these patients, the company thus interpreted change of the application method from IM to SC as change within the basic therapy.

The company's assessment was not accepted. Although, besides the application method, both the application frequency and the dosage differed between the different IFNβ1a therapies (SC vs. IM), the clinical effects between these therapies were comparable in RMS treatment, and none of the IFNβ1a therapies should be regularly preferred over the other. The G-BA does also not differentiate between the application methods of the ACT (IFNβ1a).

Based on the information on the total population it was estimated that the proportion of patients with highly active disease who had been pretreated with IFNβ1a (IM) probably amounted to < 20% of the total subpopulation relevant for research question 2. The subpopulation presented by the company was thus used as sufficient approximation to the subpopulation relevant for research question 2.

The uncertainties resulting from the missing information were considered in the derivation of the certainty of conclusions of the results (see the following Section).

Risk of bias

As already described in research question 1, the risk of bias of both OPERA studies at study level was rated as low. The risk of bias at outcome level of research question 2 corresponds to that of research question 1 (see above), with the difference that usable data on the harm outcome "depression" are missing for the present research question 2.

Due to the missing information on patient characteristics and the not completely comprehensible composition of the relevant subpopulation, at most indications, e.g. of an added benefit, can be determined for all endpoints on the basis of the available data.

Mortality

All-cause mortality

For the outcome "all cause mortality", there was one event in the ocrelizumab arm and one event in the IFNβ1a arm of the OPERA studies. Overall, this resulted in no hint of an added benefit of ocrelizumab in comparison with IFNβ 1a; an added benefit is therefore not proven.

Morbidity

Relapses (based on EDSS)

There was a statistically significant difference in favour of ocrelizumab in comparison with IFNβ1a for the outcome "relapses". This resulted in an indication of an added benefit of ocrelizumab in comparison with IFNβ1a for the outcome "relapses".

Confirmed disability progression (based on EDSS)

The meta-analysis showed no statistically significant difference between the treatment groups for the outcome "confirmed disability progression". This resulted in no hint of an added benefit of ocrelizumab in comparison with IFNβ1a, an added benefit is therefore not proven.

Disability severity (MSFC z-score)

The meta-analysis showed important unexplained heterogeneity without effects in the same direction for the outcome "disability severity". This resulted in no hint of an added benefit of ocrelizumab in comparison with IFNβ1a, an added benefit is therefore not proven.

Fatigue interference (MFIS) and health status (EQ-5D VAS)

The meta-analysis showed no statistically significant difference between the treatment groups for the outcomes "fatigue interference" (MFIS) and "health status" (EQ-5D VAS). This resulted in no hint of an added benefit of ocrelizumab in comparison with IFNβ1a, an added benefit is therefore not proven.

Health-related quality of life

SF-36

The meta-analysis showed no statistically significant difference for both sum scores of the SF-36 (PCS, MCS). Overall, this resulted in no hint of an added benefit of ocrelizumab in comparison with IFNβ1a for the SF-36, an added benefit is therefore not proven.

Side effects

SAEs and discontinuation due to AEs

The meta-analysis showed no statistically significant difference between the treatment groups for the outcomes "SAEs" and "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from ocrelizumab in comparison with IFNβ1a, greater or lesser harm is therefore not proven.

Specific AEs

Flu-like illness

The meta-analysis showed a statistically significant difference in favour of ocrelizumab for the outcome "flu-like illness". This resulted in an indication of lesser harm from ocrelizumab in comparison with IFNβ1a.

Injection site reactions

The meta-analysis showed no statistically significant difference between the treatment groups for the outcome "injection site reactions". This resulted in no hint of lesser or greater harm of ocrelizumab in comparison with IFNβ1a, greater or lesser harm is therefore not proven.

Reaction associated with an infusion as well as infections and infestations

The meta-analysis showed a statistically significant difference to the disadvantage of ocrelizumab each for the outcomes "reaction associated with an infusion" and "infections and infestations". In each case, this resulted in an indication of greater harm from ocrelizumab in comparison with IFNβ1a.

Depression

The dossier contained no usable data on the outcome "depression" for the relevant subpopulation. This resulted in no hint of lesser or greater harm from ocrelizumab in comparison with IFNβ1a, greater or lesser harm is therefore not proven.

Results on research question 3: Patients with early PPMS

The ORATORIO study was included in the benefit assessment of ocrelizumab in comparison with BSC in patients with early PPMS.

Study design

The ORATORIO study is a randomized, double-blind, placebo-controlled parallel-group study. The study investigated ocrelizumab in comparison with placebo in adults with early PPMS.

Adults (18 to 55 years) with PPMS and an EDSS score of 3 to 6.5 points were included.

In the study, 732 patients were randomly allocated to the study arms ocrelizumab (N = 488) and placebo (N = 244) in a ratio of 2:1. Patients in both study arms also received BSC.

The SPC of ocrelizumab recommends a dosage of 600 mg ocrelizumab as intravenous (IV) infusion at 6-month intervals. Every 6 months, patients in the ORATORIO study received 2 infusions with 300 mg each two weeks apart. However, according to the European Public Assessment Report (EPAR) of the European Medicines Agency (EMA) on ocrelizumab, this changed dosing regimen had no impact on the effect of ocrelizumab.

Treatment duration was at least 120 weeks after inclusion of the last patient, provided that 253 confirmed cases of confirmed disability progression (primary outcome) had been recorded. Otherwise, treatment was continued until the required number of cases had been reached.

Primary outcome of the study was the confirmed disability progression (after 12 weeks). Secondary outcomes are outcomes on "symptoms" and "health-related quality of life", "health status" and "side effects".

Risk of bias

The risk of bias at study level for the ORATORIO study was rated as low. The risk of bias was rated as low for all outcomes for which usable data were available, except for the outcome "disability severity".

On the basis of the available data, at most a hint can be determined for the outcome "disability severity", and for all other outcomes there is at most an indication, e.g. of an added benefit, because of the high risk of bias.

Mortality

All-cause mortality

Four deaths occurred in the ocrelizumab + BSC arm of the study, and 1 death in the BSC arm. There was no statistically significant difference between the treatment groups for the outcome "all-cause mortality". This resulted in no hint of an added benefit of ocrelizumab + BSC in comparison with BSC; an added benefit is therefore not proven.

Morbidity

Confirmed disability progression (based on EDSS)

The outcome "confirmed disability progression" (after 24 weeks) recorded the time from baseline to the occurrence of the first clinically relevant disability progression was confirmed after at least 24 weeks. To replace missing values for confirmation, the company used 2 imputation strategies for patients with initial progression for whom confirmed progression was missing because they had left the study. In imputation strategy 1, patients for whom confirmed disability progression was missing because they had left the study were rated as patients with unconfirmed progressive disability. Whereas in imputation strategy 2 these patients were rated as patients with confirmed progressive disability at the day of treatment discontinuation. In the present situation, none of the two imputation strategies should be preferred unconditionally over the other. Therefore, the results of both analyses were shown for the present research question.

The analysis with imputation strategy 1 showed no statistically significant difference between the treatment groups for the outcome "confirmed (after 24 weeks) disability progression". However, the analysis with imputation strategy 2 shows a statistically significant difference in favour of ocrelizumab. The results are therefore not robust.

To enable better assessment of the results of the disability progression using the EDSS, the results on the disability severity (MSFC z-score) were additionally considered, as also recommended by the EMA.

Neither the change of the mean difference used for the present assessment (see next Section) nor the responder analysis on the MSFC z-score considered by the company in the dossier showed a statistically significant result, which supports the findings of the analysis with

imputation strategy 1. Overall, this resulted in no hint of an added benefit of ocrelizumab + BSC in comparison with BSC for the outcome "relapses", an added benefit is therefore not proven.

Fatigue interference (MFIS) and health status (EQ-5D VAS)

Usable data on the outcomes "fatigue interference" (MFIS) or "health status" (EQ-5D VAS) are not available. This resulted in no hint of an added benefit of ocrelizumab + BSC in comparison with BSC; an added benefit is therefore not proven.

Health-related quality of life

SF-36

No usable data were available for the outcome "health-related quality of life" (recorded with the SF-36). This resulted in no hint of an added benefit of ocrelizumab + BSC in comparison with BSC; an added benefit is therefore not proven.

Side effects

SAEs and discontinuation due to AEs

There was no statistically significant difference between the treatment groups for the outcomes "SAEs" and "discontinuation due to AEs". Hence, there was no hint of greater or lesser harm from ocrelizumab + BSC in comparison with BSC; greater or lesser harm is therefore not proven.

Specific AEs

Reaction associated with an infusion

A statistically significant difference to the disadvantage of ocrelizumab was shown for the outcome "reaction associated with an infusion". This resulted in an indication of greater harm from ocrelizumab + BSC in comparison with BSC.

Infections and infestations

No statistically significant difference was shown for the outcome "infections and infestations". This resulted in no hint of greater or lesser harm from ocrelizumab + BSC in comparison with BSC; greater or lesser harm is therefore not proven.

Depression

A statistically significant difference in favour of ocrelizumab was shown for the outcome "depression". The extent was no more than marginal. This resulted in no hint of greater or lesser harm from ocrelizumab + BSC in comparison with BSC for the outcome "depression"; greater or lesser harm is therefore not proven.

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

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

Research question 1: treatment-naive and pretreated patients with non-highly active RMS

Overall, several positive effects, partly in subgroups, and one negative effect of ocrelizumab in comparison with IFNβ1a were found in the outcome categories "morbidity" and "side effects".

The results showed an effect modification by age for the outcomes "relapses" and "SAEs". This resulted in proof of considerable added benefit or lesser harm each for the outcomes "relapses" and "SAEs" for patients < 40 years.

In the total relevant subpopulation, 2 proofs of lesser harm and one proof of greater harm were shown for the specific AEs, all of them with the extent "considerable".

In summary, this results in a proof of considerable added benefit of ocrelizumab in comparison with IFNβ1a for adult treatment-naive and pretreated patients < 40 years with non-highly active RMS.

After consideration of the specific AEs on the positive and the negative side and in the overall consideration of all results, there is overall a positive effect for patients ≥ 40 years. This resulted in proof of a minor added benefit of ocrelizumab vs. IFNβ1a for adult treatment-naive and pretreated patients ≥ 40 years with non-highly active RMS.

Research question 2: pretreated patients with highly active RMS

In the overall consideration, there were one negative and two positive effects of ocrelizumab in comparison with IFNβ1a in the outcome categories "morbidity" and "side effects", all of them with considerable extent.

In summary, there is an indication of considerable added benefit of ocrelizumab vs. the ACT IFNβ1a for pretreated patients with highly active RMS.

Research question 3: Patients with early PPMS

Overall, there is a negative effect from the category "non-serious/non-severe side effects".

[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].

herefore, there is an indication of lesser benefit of ocrelizumab + BSC vs. the ACT BSC for patients with early PPMS.

Table 3 presents a summary of the probability and extent of the added benefit of ocrelizumab.

Table 3: Ocrelizumab – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Adults with RMS who had not yet received disease-modifying therapy or patients with non-highly active disease pretreated with disease-modifying therapy	**Interferon beta** (**IFNβ) 1a** or 1b glatiramer acetate under consideration of the approval	Age < 40 years: proof of considerable added benefit
			Age ≥ 40 years: proof of minor added benefit
2	Adults with highly active RMS despite treatment with a disease-modifying therapy[b]	Alemtuzumab or fingolimod or natalizumab or, if indicated, change within the basic therapeutics (**IFN-β 1a** or 1b or glatiramer acetate under consideration of the approval)	Indication of considerable added benefit
3	Adults with early PPMS	Best supportive care[c]	Indication of lesser benefit

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Adequate (pre)treatment usually comprises at least 6 months. Depending on frequency and severity of the relapses as well as on the disability progression, treatment with a disease-modifying therapy might take less than 6 months.
c: Best supportive care (BSC) refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve quality of life.
G-BA: Federal Joint Committee; IFNβ: interferon beta; PPMS: primary progressive multiple sclerosis; RMS: relapsing multiple sclerosis

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

2.2 Research question

Aim of the present report was the assessment of the added benefit of ocrelizumab in comparison with the ACT in patients with active RMS and in patients with early PPMS.

For the benefit assessment of ocrelizumab, the research questions presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of ocrelizumab

Research question	Subindication	ACT[a]
1	Adults with RMS who have not yet received disease-modifying therapy or patients with non-highly active disease pretreated with disease-modifying therapy	**IFNβ1a** or IFNβ1b or glatiramer acetate under consideration of the approval
2	Adults with highly active RMS despite treatment with a disease-modifying therapy[b]	Alemtuzumab or fingolimod or natalizumab or, if indicated, change within the basic therapeutics (**IFNβ1a** or IFNβ1b or glatiramer acetate under consideration of the approval)
3	Adults with early PPMS	Best supportive care[c]

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Adequate (pre)treatment usually comprises at least 6 months. Depending on frequency and severity of the relapses as well as on the disability progression, treatment with a disease-modifying therapy might take less than 6 months.
c: Best supportive care (BSC) refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve quality of life.
G-BA: Federal Joint Committee; IFN-β: interferon beta; PPMS: primary progressive multiple sclerosis; RMS: relapsing multiple sclerosis

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

- Research question 1: Treatment-naive and pretreated patients with non-highly active RMS
- Research question 2: Pretreated patients with highly active RMS
- Research question 3: Patients with early PPMS

The company followed the G-BA's specification of the ACTs and chose IFNβ1a as ACT for research questions 1 and 2, and BSC as ACT for research question 3.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 12 months were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

2.3 Research question 1: treatment-naive and pretreated patients with non-highly active RMS

2.3.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- Study list on ocrelizumab (status: 18 December 2017)

- Bibliographical literature search on ocrelizumab (last search on 14 February 2018)
- search in trial registries for studies on ocrelizumab (last search on 14 February 2018)

To check the completeness of the study pool:

- search in trial registries for studies on ocrelizumab (last search on 29 January 2018)

The check identified no additional relevant study.

2.3.1.1 Studies included

The studies listed in the following Table 5 were included in the benefit assessment of ocrelizumab in comparison with IFNβ1a in treatment-naive and pretreated patients with non-highly active RMS (research question 1).

Table 5.Study pool – RCT, direct comparison: ocrelizumab vs. IFNβ1a

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
WA21092 (OPERA I[b])	Yes	Yes	No
WA21093 (OPERA II[b])	Yes	Yes	No
a: Study sponsored by the company. b: In the following tables, the study is referred to with this abbreviated form. IFNβ: interferon beta; RCT: randomized controlled trial; vs.: versus			

Section 2.3.4 contains a reference list for the studies included.

2.3.1.2 Study characteristics

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

Table 6: Characteristics of the studies included – RCT, direct comparison: ocrelizumab vs. IFNβ1a

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
OPERA I	RCT, double-blind, parallel	Adults (18–55 years) with RMS, at least 2 relapses in the past 2 years or at least 1 relapse in the past year, EDSS 0–5.5	IFNβ1a (N = 411) Ocrelizumab (N = 410) Relevant subpopulation thereof: ▪ for research question 1[b]: ▫ IFNβ1a (N = 336) ▫ Ocrelizumab (N = 346) ▪ research question 2[c]: ▫ IFNβ1a (N = 59) ▫ Ocrelizumab (N = 54)	▪ Screening: 2-8 weeks ▪ Treatment: 96 weeks ▪ Optional extension phase (unblinded) ▪ Follow-up observation: at least 48 weeks also in case of participation in the extension phase	141 study centres in 32 countries in Europe, North and South America, Australia, Asia and Africa Start of the study: 31 August 2011 Data cut-off 02 April 2015	Primary: relapses Secondary: symptoms, health-related quality of life, AEs
OPERA II	RCT, double-blind, parallel	Adults (18–55 years) with RMS, at least 2 relapses in the past 2 years or at least 1 relapse in the past year, EDSS 0–5.5	IFNβ1a (N = 418) Ocrelizumab (N = 417) Relevant subpopulation thereof: ▪ for research question 1[b]: ▫ IFNβ1a (N = 356) ▫ Ocrelizumab (N = 342) ▪ research question 2[c]: ▫ IFNβ1a (N = 47) ▫ Ocrelizumab (N = 57)	▪ Screening: 2-8 weeks ▪ Treatment: 96 weeks ▪ Optional extension phase (unblinded) ▪ Follow-up observation: at least 48 weeks also in case of participation in the extension phase	166 study centres in 24 countries in Europe, North and South America, Australia, Asia and Africa Start of the study: 20 September 2011 Data cut-off: 12 May 2015	Primary: relapses Secondary: symptoms, health-related quality of life, AEs

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes exclusively include information on relevant available outcomes for this benefit assessment.
b: Treatment-naive and pretreated patients with non-highly active RMS.
c: Patients with highly active RMS (patients who had been pretreated with IFNβ1a (SC) were excluded).
AE: adverse event; EDSS: Expanded Disability Status Scale; IFNβ: interferon beta; n: relevant subpopulation; N: number of (included) randomized patients; RMS: relapsing multiple sclerosis; RCT: randomized controlled trial; SC: subcutaneous; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: ocrelizumab vs. IFNβ1a

Study	Intervention	Comparison
OPERA I, II	**Starting dose** Ocrelizumab IV ▪ in weeks 1 and 2: 300 mg each once weekly Placebo SC for IFNβ1a 3 times per week	**Starting dose** IFNβ1a, SC ▪ in weeks 1 and 2: 8.8 µg 3 times per week Placebo IV for ocrelizumab once weekly
	Committed doses Ocrelizumab IV ▪ from week 24–96: 600 mg every 24 weeks Placebo SC for IFNβ1a ▪ from week 3-96: 3 times per week	**Committed doses** IFNβ1a, SC ▪ from week 3-4: 22 µg 3 times per week ▪ from week 5-96: 44 µg 3 times per week Placebo IV for ocrelizumab ▪ from week 24–96: once every 24 weeks
	No dose adjustment planned	Dose reduction to 22 µg 3 times per week was allowed.
	Premedication ▪ 100 mg methylprednisolone IV or an equivalent corticosteroid (e.g. dexamethasone) about 30 minutes before the infusion	
	Prohibited prior and concomitant treatment ▪ Each experimental treatment within 24 weeks before the screening visit ▪ Administration of lymphocyte transport modulators (e.g. natalizumab, fingolimod) within 24 weeks before the screening visit ▪ Immunomodulating therapy within 12 weeks before randomization ▪ Live vaccines within 6 weeks before randomization ▪ Pretreatment with antibiotics (within 2-4 weeks before the baseline visit), immunosuppressants or systemic corticoids (within 4 weeks before the screening) ▪ Other MS drugs or B cell-targeted therapies	
	Allowed concomitant treatment ▪ Analgesics or antipyretics ▪ Antihistamines ▪ Systemic corticosteroids for the treatment of a relapse ▪ Therapies for symptom control	

IFNβ: interferon beta; IV: intravenous; MS: multiple sclerosis; RCT: randomized controlled trial; SC: subcutaneous; vs.: versus

Description of the study design

The design, the inclusion criteria and the statistical analysis plan of the studies OPERA I and II are identical. The meta-analysis of both studies was prespecified in the respective study protocols. Besides the study reports of the individual studies, the company presented a separate study report which pools both studies in a meta-analysis. The OPERA studies are summarized hereinafter.

The OPERA studies are randomized, double-blind, actively controlled parallel-group studies on the comparison of ocrelizumab with IFNβ1a SC administration) in patients with RMS. Both studies were conducted worldwide at about the same time and in the same regions.

Adult patients (18 to 55 years) with at least 2 documented relapses during the last 2 years or 1 relapse within the last year before study inclusion and a maximum EDSS score of 5.5 were included in the studies. The diagnosis of RMS was made using the McDonald criteria revised in 2010 [3].

A total of 1656 patients were randomly assigned to treatment with ocrelizumab (N = 827) or IFNβ1a (N = 829). Randomization was stratified by the factors "EDSS" (< 4 vs. ≥ 4) at the start of the study and "region" (USA vs. others). Blinding was ensured using a double-dummy design.

The patients were treated in compliance with the regimen described in Table 7. In each case, treatment was in compliance with the specifications of the SPCs [4,5]. Treatment duration in both studies was 96 weeks. Patients could then participate in an open-label extension phase on a voluntary basis. Follow-up observation was at least 48 weeks, irrespective of a participation in the extension phase. The present assessment is exclusively based on data from the blinded treatment and follow-up observation phase.

Primary outcome of both studies was the annualized relapse rate. Secondary outcomes were outcomes on symptoms, health status, health-related quality of life and side effects.

Both studies are completed and the assessment is based on the planned analyses at the clinical data cut-offs 2 April 2015 for the OPERA I study or 12 May 2015 for the OPERA II study.

Subpopulation relevant for research question 1

The subpopulation relevant for research question 1 included patients with non-highly active disease who had not yet received disease-modifying therapy for RMS and patients with non-highly active disease who had been pretreated with a disease-modifying therapy. The relevant population therefore included a subpopulation of the total population of the OPERA studies. The company presented analyses of the relevant subpopulation. It constituted this subpopulation by excluding patients with high disease activity from its analyses. The company operationalized high disease activity as at least one relapse and/or a Gd-T1 lesion in the year before the start of the study despite adequate treatment. The company defined adequate treatment as continuous, at least 6-month treatment with disease-modifying active substances. In this case, the entire treatment period must have taken place before the occurrence of the clinical event (relapse or Gd-T1 lesion) and must end at most 2 months before the occurrence of the clinical event.

The criteria used by the company are suitable for an adequate representation of the subpopulation relevant for research question 1. However, in its dossier the company chiefly

described the total population of the two studies and only presented few patient characteristics on the demography of the subpopulation. Information on the description of the disease, the duration and the type of the prior therapies as well as data on the patients of the relevant subpopulation who discontinued treatment or left the study are missing. The exact characteristics of the subpopulation set up by the company can therefore not be completely inferred from the data presented in the dossier and from the available study data.

Since the relevant subpopulation only comprised about 83% of the total population in both studies, the analyses presented by the company were used as sufficient approximation to the population relevant for research question 1, despite the missing information.

Table 8 shows the characteristics of the patients in the total study population and of the relevant subpopulation of the studies included.

Table 8: Characteristics of the study population and the relevant subpopulation (treatment-naive and pretreated patients non-highly active RMS) – RCT, direct comparison: ocrelizumab vs. IFNβ1a

Study Characteristics Category	OPERA I				OPERA II			
	Total population		Relevant subpopulation		Total population		Relevant subpopulation	
	Ocrelizumab	IFNβ1a	Ocrelizumab	IFNβ1a	Ocrelizumab	IFNβ1a	Ocrelizumab	IFNβ1a
	Na = 410	Na = 411	Na = 346	Na = 336	Na = 417	Na = 418	Na = 342	Na = 356
Age [years], mean (SD)	37.1 (9.3)	36.9 (9.3)	37.1 (9.4)	37.1 (9.2)	37.2 (9.1)	37.4 (9.0)	36.9 (9.0)	37.3 (9.0)
Sex [F/M], %	66/34	66/34	66/34	66/34	65/35	67/33	65/35	66/34
Ethnicity, n (%)								
White	375 (91)	375 (91)	316 (91)	306 (91)	368 (88)	382 (91)	307 (90)	327 (92)
Other[b]	35 (9)	36 (9)	30 (9)[c]	30 (9)[c]	49 (12)	36 (9)	35 (10)[c]	29 (8)[c]
EDSS at start of study, n (%)								
< 4	314 (77)	318 (78)	ND		315 (76)	309 (74)	ND	
≥ 4	96 (23)	92 (22)	ND		102 (25)	109 (26)	ND	
Gd-enhancing T1-lesions, n (%)								
0	233 (58)	252 (62)	ND		252 (61)	243 (59)	ND	
≥ 1	172 (42)	155 (38)	ND		161 (39)	172 (41)	ND	
T2 lesions, n (%)								
< 9	28 (7)[c]	29 (7)[c]	ND		35 (8)[c]	35 (8)[c]	ND	
≥ 9	380 (93)	379 (93)	ND		379 (92)	381 (92)	ND	
Time since RMS diagnosis [years], mean (SD)	3.8 (4.8)	3.7 (4.6)	ND		4.2 (5.0)	4.1 (5.1)	ND	
Time since occurrence of MS symptoms [years], mean (SD)	6.7 (6.4)	6.3 (6.0)	ND		6.7 (6.1)	6.7 (6.1)	ND	
Number of relapses in the year before the start of the study, mean (SD)	1.3 (0.7)	1.3 (0.6)	ND		1.3 (0.7)	1.3 (0.7)	ND	
Number of relapses in the last 2 years before the start of the study, mean (SD)	1.8 (0.9)	1.7 (0.9)	ND		1.8 (1.0)	1.8 (0.9)	ND	
Pretreatment with MS therapy, n (%)								
Yes	107 (26)	117 (29)	ND		113 (27)	103 (25)	ND	
No	301 (74)	292 (71)	ND		304 (73)	314 (75)	ND	

(continued)

Table 8: Characteristics of the study population and the relevant subpopulation (treatment-naive and pretreated patients non-highly active RMS) – RCT, direct comparison: ocrelizumab vs. IFNβ1a (continued)

Study Characteristics Category	OPERA I				OPERA II			
	Total population		Relevant subpopulation		Total population		Relevant subpopulation	
	Ocrelizu-mab	IFNβ1a	Ocrelizu-mab	IFNβ1a	Ocrelizu-mab	IFNβ1a	Ocrelizu-mab	IFNβ1a
	N[a] = 410	N[a] = 411	N[a] = 346	N[a] = 336	N[a] = 417	N[a] = 418	N[a] = 342	N[a] = 356
Treatment discontinuation, n (%)	44 (11)	71 (17)	ND		57 (14)	98 (23)	ND	
Study discontinuation, n (%)	32 (7.8)[c]	44 (10.7)[c]	ND		48 (11.5)[c]	77 (18.4)[c]	ND	

a: Number of randomized patients. Data that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Is composed of the ethnicities native American, Asian, black/African American, other ethnicities and multiple answers.
c: Institute's calculation.
EDSS: Expanded Disability Status Scale; F: female; Gd: Gadolinium; IFN-β: interferon beta; M: male; MS: multiple sclerosis; n: number of patients in the category; N: number of randomized (or included) patients; RCT: randomized controlled trial; RMS: relapsing multiple sclerosis; SD: standard deviation; vs.: versus

Based on the available data, there were no noteworthy differences between treatment groups for both the total population and the subpopulation. Also between the studies, the patient characteristics were balanced. The mean age of the patients in the relevant subpopulation was 37 years, about 2 thirds of them were female and over 90% where white.

About 3 quarters of the patients in the total population had an EDSS score of < 4 or had not received prior MS therapy at the start of the study.

Data on study or treatment discontinuations are only available for the respective total populations. Overall, more patients discontinued treatment in the IFNβ1a arm (17% or 23%) than in the ocrelizumab arm (11% or 14%) of the respective studies. In both studies, the main reason for treatment discontinuation was "side effects". In both OPERA studies, more patients in the IFNβ1a arms (11% or 18%) than in the ocrelizumab arms (8% or 12%) discontinued the study.

Risk of bias

Table 9 shows the risk of bias at study level.

Table 9: Risk of bias at study level - RCT, direct comparison: ocrelizumab vs. IFNβ1a (treatment-naive and pretreated patients with non-highly active RMS)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
OPERA I	Yes	Yes	Yes	Yes	Yes	Yes	Low
OPERA II	Yes	Yes	Yes	Yes	Yes	Yes	Low
IFN-β: interferon beta; RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level was rated as low for both studies. This concurs with the company's assessment.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - All-cause mortality
- Morbidity
  - Relapses (based on EDSS)
  - Confirmed disability progression (based on EDSS)
  - Disability severity (based on MSFC)
  - Fatigue interference measured with the MFIS
  - Health status, measured with the EQ-5D VAS
- Health-related quality of life
  - Measured using the SF-36
- Side effects
  - SAEs
  - Discontinuation due to AEs
  - Flu-like illness
  - Injection site reactions

- Reaction associated with an infusion
- Infections and infestations
- Depression
- If applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.7.2.4.3) of the full dossier assessment).

Table 10 shows for which outcomes data were available in the studies included.

Table 10: Matrix of outcomes – RCT, direct comparison: ocrelizumab vs. IFNβ1a (treatment-naive and pretreated patients with non-highly active RMS)

Study	Outcomes													
	All-cause mortality	**Relapses**	**Confirmed disability progression (EDSS)**	**Disability severity (MSFC)**	**Fatigue interference (MFIS)**	**Health status (EQ-5D VAS)**	**Health-related quality of life (SF-36)**	**SAEs**	**Discontinuation due to AEs**	**Flu-like illness (AE, PT)**	**Injection site reactions (AE, PT)**	**Reaction associated with an infusion (AE, PT)**	**Infections and infestations (AE, SOC)**	**Depression (AE, PT)**
OPERA I, II	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes[a]	Yes[b]

a: No data on the SOC "infections and infestations" were available for the relevant subpopulation. The AE data of the category "infections" of Module 4 A of the dossier were used (for reasons, see Section 2.7.2.4.3 of the full dossier assessment).
b: No data on the SOC for the relevant subpopulation, data for the total population were used.
AE: adverse event; EDSS: Expanded Disability Status Scale; EQ-5D: European Quality of Life-5 Dimensions; IFNβ: interferon beta; MFIS: Modified Fatigue Impact Scale; MSFC: Multiple Sclerosis Functional Composite; PT: Preferred Term; RCT: randomized controlled trial; SF-36: Short Form (36) Health Survey; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.3.2.2 Risk of bias

Table 11 shows the risk of bias for the relevant outcomes.

Table 11: Risk of bias at study and outcome level - RCT, direct comparison: ocrelizumab vs. IFNβ1a (treatment-naive and pretreated patients with non-highly active RMS)

Study		Outcomes													
	Study level	All-cause mortality	Relapses	Disability progression (EDSS)	Disability severity (MSFC)	Fatigue interference (MFIS)	Health status (EQ-5D VAS)	Health-related quality of life (SF-36)	SAEs	Discontinuation due to AEs	Flu-like illness (AE, PT)	Injection site reactions (AE, PT)	Reaction associated with an infusion (AE, PT)	Infections and infestations (AE, SOC)	Depression (AE, PT)
OPERA I, II	L	L	L	L	H[a, b]	H[a, b]	H[a, b]	H[a, b]	L	L	L	L	L	L	L

a: High proportion of patients not included in the analysis (> 10%) or because this proportion differed between the treatment groups to a relevant degree (> 5 percentage points).
b: Selective reporting is possible because the analyses presented deviate from the analyses planned a priori.
AE: adverse event; EDSS: Expanded Disability Status Scale; EQ-5D: European Quality of Life-5 Dimensions; H: high; IFNβ: interferon beta; L: low; MFIS: Modified Fatigue Impact Scale; MSFC: Multiple Sclerosis Functional Composite; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SF36: Short Form (36) Health Survey; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

The risk of bias was rated as low for all outcomes except for the outcomes “disability severity”, “fatigue interference”, “health status” and “health-related quality of life”.

The risk of bias was rated as high for the outcomes “disability severity”, “fatigue interference”, health status” and “health-related quality of life” because the proportion of patients who were not considered in the analyses was > 10%, or the difference of the proportions of patients who were not considered was > 5 percentage points between the treatment groups. Moreover, the main analyses (adjusted covariance analyses) presented by the company in the dossier deviated from the analyses defined in the study protocol (mixed-effects model repeated measures [MMRM]) for these outcomes, which enables selective reporting.

Deviating from this, the company rated the risk of bias for the outcomes “fatigue interference”, “health status” and “health-related quality of life” as low. In module 4 A, the company addressed the outcome “disability severity” under the outcome “disability progression”, for which it rated the risk of bias as low.

2.3.2.3 Results

Table 12, Table 13, Table 14 and Table 15 summarize the results on the comparison of ocrelizumab with IFNβ1a in treatment-naive and pretreated patients with non-highly active RMS. Where necessary, calculations conducted by the Institute were provided in addition to the data from the company's dossier. Kaplan-Meier curves for the outcomes "time to first relapse" and "time to first confirmed disability progression" (after 24 weeks) can be found in Appendix A1 of the full dossier assessment. Forest plots of the meta-analyses calculated by the Institute can be found in Appendix A2 of the full dossier assessment. The company's dossier contained no complete lists of the AEs for the relevant subpopulation. Since the subpopulation relevant for research question 1 constituted over 80% of the total population of the OPERA studies, the AEs for the total population of the respective OPERA study were presented for this research question (see Appendix A3).

Table 12: Results (mortality, side effects) – RCT, direct comparison: ocrelizumab vs. IFNβ1a (treatment-naive and pretreated patients with non-highly active RMS)

Outcome category Outcome Study	Ocrelizumab N	Ocrelizumab Patients with event n (%)	IFNβ1a N	IFNβ1a Patients with event n (%)	Ocrelizumab vs. IFNβ1a RR [95% CI]; p-value
Mortality					
All-cause mortality[a]					
OPERA I	345	0 (0.0)	334	1 (0.3)	–[b]
OPERA II	342	0 (0.0)	356	0 (0.0)	–[b]
Total					–[b]
Side effects					
AEs (supplementary information)					
OPERA I	345	269 (78.0)	334	271 (81.1)	-
OPERA II	342	295 (86.3)	356	305 (85.7)	-
SAEs					
OPERA I	345	23 (6.7)	334	22 (6.6)	1.01 [0.58; 1.78]; 0.967[c]
OPERA II	342	24 (7.0)	356	31 (8.7)	0.81 [0.48; 1.34]; 0.409[c]
Total					0.89 [0.61; 1.30]; 0.557[d]
Discontinuation due to AEs					
OPERA I	345	10 (2.9)	334	20 (6.0)	0.48 [0.23; 1.02]; 0.056[c]
OPERA II	342	15 (4.4)	356	23 (6.5)	0.68 [0.36; 1.28]; 0.231[c]
Total					0.59 [0.36; 0.95]; 0.030[d]
Flu-like illness					
OPERA I	345	13 (3.8)	334	70 (21.0)	0.18 [0.10; 0.32]; < 0.001[c]
OPERA II	342	22 (6.4)	356	84 (23.6)	0.27 [0.17; 0.43]; < 0.001[c]
Total					0.23 [0.16; 0.33]; < 0.001[b]

(continued)

Table 12: Results (mortality, side effects) – RCT, direct comparison: ocrelizumab vs. IFNβ1a (treatment-naive and pretreated patients with non-highly active RMS) (continued)

Outcome category Outcome Study	Ocrelizumab N	Ocrelizumab Patients with event n (%)	IFNβ1a N	IFNβ1a Patients with event n (%)	Ocrelizumab vs. IFNβ1a RR [95% CI]; p-value
Injection site reactions					
OPERA I	345	0 (0.0)	334	13 (3.9)	0.04 [0; 0.60]; < 0.001[e]
OPERA II	342	2 (0.6)	356	26 (7.3)	0.08 [0.02; 0.33]; < 0.001[c]
Total					0.05 [0.01; 0.22]; < 0.001[d]
Reaction associated with an infusion					
OPERA I	345	98 (28.4)	334	20 (6.0)	4.74 [3.00; 7.49]; < 0.001[c]
OPERA II	342	128 (37.4)	356	43 (12.1)	3.10 [2.27; 4.23]; < 0.001[c]
Total					3.61 [2.79; 4.67]; < 0.001[d]
Infections and infestations[f]					
OPERA I	345	186 (53.9)	334	175 (52.4)	1.03 [0.89; 1.19]; 0.692[c]
OPERA II	342	200 (58.5)	356	181 (50.8)	1.15 [1.00; 1.32]; 0.043[c]
Total					1.09 [0.99; 1.20]; 0.083[d]
Depression					
OPERA I	408[g]	30 (7.4)	409[g]	24 (5.9)	1.25 [0.75; 2.11][h]; ND
OPERA II	417[g]	34 (8.2)	417[g]	30 (7.2)	1.13 [0.71; 1.82][h]; ND
Total					1.19 [0.84; 1.68]; 0.337[i]

a: Clinical data cut-off: OPERA I (2 April 2015) and OPERA II (12 May 2015).
b: No presentation of effect estimation and CI as these are not informative.
c: Effect estimate 95% CI: generalized linear regression model; p-value: Wald test.
d: Calculation using the IPD meta-analysis.
e: Institute's calculation, unconditional exact test (CSZ method according to [6]).
f: No data on the SOC "infections and infestations" were available for the relevant subpopulation. The AE data of the category "infections" of Module 4 A of the dossier were used (for reasons, see Section 2.7.2.4.3 of the full dossier assessment).
g: The values refer to the total population of the study.
h: Institute's calculation.
i: Institute's calculation using meta-analysis with fixed effect.
CI: confidence interval; IFN-β: interferon beta; IPD: individual patient data; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Table 13: Results (morbidity, relapses) – RCT, direct comparison: ocrelizumab vs. IFNβ1a (treatment-naive and pretreated patients with non-highly active RMS)

Outcome category **Outcome** **Study**	**Ocrelizumab**			**IFNβ1a**			**Ocrelizumab vs. IFNβ1a**
	N	**n/patient years**	**Annualized relapse rate [95% CI][a]**	**N**	**n/patient years**	**Annualized relapse rate [95% CI][a]**	**Rate ratio [95% CI]; p-value[a]**
Morbidity							
Relapses (based on EDSS)							
Annualized relapse rate							
OPERA I	346	77/599.8	0.15 [0.11; 0.20]	336	126/559.9	0.27 [0.21; 0.34];	0.55 [0.40; 0.77]; < 0.001
OPERA II	342	88/578.2	0.18 [0.14; 0.23]	356	142/566.9	0.30 [0.24; 0.38];	0.60 [0.44; 0.82]; 0.001
Total							0.58 [0.46; 0.73]; < 0.001[b]
Annualized relapse rate by severity – moderate/ severe (additional information)							
OPERA I	*346*	*45/599.8*	*0.09 [0.06; 0.12]*	*336*	*73/559.9*	*0.15 [0.11; 0.20]*	*0.56 [0.38; 0.84]; 0.004*
OPERA II	*342*	*50/578.2*	*0.10 [0.07; 0.13]*	*356*	*83/566.9*	*0.16 [0.12; 0.21]*	*0.59 [0.40; 0.86]; 0.006*
Total							*0.58 [0.44; 0.76]; < 0.001[c]*
Annualized relapse rate by severity – severe (additional information)							
OPERA I	*346*	*2/599.8*	*0.004 [0.001; 0.02]*	*336*	*9/559.9*	*0.02 [0.01; 0.04]*	*0.21 [0.05; 0.96]; 0.022*
OPERA II	*342*	*9/578.2*	*0.02 [0.01; 0.04]*	*356*	*12/566.9*	*0.03 [0.01; 0.05]*	*0.73 [0.31; 1.74];*
Total							*0.53 [0.25; 1.12]; 0.097[c]*

a: Adjusted annualized relapse rate, effect measure, CI and p-value: negative binomial model, adjusted for region and EDSS at the start of the study.
b: Calculation using the IPD meta-analysis.
c: Institute's calculation using meta-analysis with fixed effect.
CI: confidence interval; EDSS: Expanded Disability Status Scale; IFN-β: interferon beta; IPD: individual patient data; N: number of analysed patients; n: number of relapses; RCT: randomized controlled trial; vs.: versus

Table 14: Results (morbidity, time to event) – RCT, direct comparison: ocrelizumab vs. IFNβ1a (treatment-naive and pretreated patients with non-highly active RMS)

Outcome category **Outcome** **Study**	**Ocrelizumab** **N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**IFNβ1a** **N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**Ocrelizumab vs. IFNβ1a** **HR [95% CI]; p-value**
Morbidity					
Relapses (based on EDSS) (additional information)					
OPERA I	*346*	*NA* *56 (16.2)*	*336*	*NA* *94 (28.0)*	*0.53 [0.38; 0.74];* *< 0.001*[a]
OPERA II	*342*	*23.7 [NA; NA]* *64 (18.7)*	*356*	*NA* *101 (28.4)*	*0.58 [0.42; 0.79];* *< 0.001*[a]
Total					*0.55 [0.44; 0.70];* *< 0.001*[b]
Confirmed disability progression (based on EDSS)[c]					
OPERA I	346	NA 20 (5.8)	336	NA 29 (8.6)	0.63 [0.35; 1.11]; 0.104[a]
OPERA II	342	NA 26 (7.6)	356	NA 39 (11.0)	0.65 [0.40; 1.07]; 0.089[a]
Total					0.64 [0.44; 0.93]; 0.019[b]

a: Effect measure, 95% CI: Cox proportional hazards model, stratified by region and EDSS at the start of the study; p-value: log-rank test.
b: Calculation using the IPD meta-analysis.
c: Event time analyses with imputation of missing values according to imputation strategy 1 (see Section 2.7.2.4.3 of the full dossier assessment).

CI: confidence interval; EDSS: Expanded Disability Status Scale; HR: hazard ratio; IFN-β: interferon beta; IPD: individual patient data; N: number of analysed patients; n: number of patients with (at least 1) event; NA: not achieved; RCT: randomized controlled trial; vs.: versus

Table 15: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: ocrelizumab vs. IFNβ1a (treatment-naive and pretreated patients with non-highly active RMS)

Outcome category Outcome Study	Ocrelizumab			IFNβ1a			Ocrelizumab vs. IFNβ1a
	N[a]	Values at start of study mean (SD)	Change at week 96 mean[b] (SE)	N[a]	Values at start of study mean (SD)	Change at week 96 mean[b] (SE)	MD [95% CI]; p-value[b]
Morbidity							
Disability severity (MSFC z-score)[c]							
OPERA I	274	-0.02 (0.77)	0.21 (0.04)	254	0.02 (0.64)	0.14 (0.04)	0.07 [-0.02; 0.16]; 0.115
OPERA II	251	0.03 (0.66)	0.26 (0.04)	232	0.0 (0.67)	0.17 (0.04)	0.09 [0.01; 0.16]; 0.028
Total							0.08 [0.02; 0.14]; 0.008[d] Hedges' g: 0.16 [0.04; 0.29][e]
Disability severity Timed 25-Foot Walk[f, g]							
OPERA I	284	-	1.07 [1.01; 1.13][h]	262	-	1.07 [1.02; 1.14][h]	ROM: 0.99 [0.94; 1.06]; ND[i]
OPERA II	262	-	1.06 [1.00; 1.12][h]	241	-	1.14 [1.08; 1.21][h]	ROM: 0.93 [0.87; 0.99]; ND[i]
Total							ROM: 0.96 [0.92; 1.01][d] ND
Disability severity 9-Hole Peg Test[f, g]							
OPERA I	283	-	0.95 [0.93; 0.97][h]	262	-	0.96 [0.94; 0.98][h]	ROM: 0.99 [0.96; 1.02]; ND[i]
OPERA II	259	-	0.94 [0.92; 0.97][h]	243	-	0.98 [0.95; 1.00][h]	ROM: 0.97 [0.94; 1.00]; ND.[i]
Total							ROM: 0.98 [0.96; 1.00][d] ND
Disability severity PASAT[c]							
OPERA I	280	43.01 (12.40)	5.96 (0.59)	258	42.17 (12.35)	4.53 (0.61)	1.43 [0.07; 2.79]; 0.039
OPERA II	257	41.66 (12.74)	7.10 (0.61)	239	41.10 (13.25)	6.46 (0.64)	0.64 [-0.72; 2.01]; 0.357
Total							1.06 [0.10; 2.02]; 0.031[d]

(continued)

Table 15: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: ocrelizumab vs. IFNβ1a (treatment-naive and pretreated patients with non-highly active RMS) (continued)

Outcome category Outcome Study	Ocrelizumab			IFNβ1a			Ocrelizumab vs. IFNβ1a
	N[a]	Values at start of study mean (SD)	Change at week 96 mean[b] (SE)	N[a]	Values at start of study mean (SD)	Change at week 96 mean[b] (SE)	MD [95% CI]; p-value[b]
Fatigue interference							
MFIS total score[g]							
OPERA I	279	31.26 (18.96)	-1.59 (1.05)	249	30.78 (19.63)	1.02 (1.11)	-2.61 [-5.05; -0.16]; 0.037
OPERA II	255	32.03 (20.70)	-1.65 (1.05)	237	33.14 (19.88)	-1.53 (1.09)	-0.12 [-2.49; 2.25]; 0.922
Total							-1.40 [-3.12; 0.31]; 0.108[d]
Fatigue MFIS cognitive[g]							
OPERA I	279	12.80 (9.38)	-0.32 (0.51)	249	12.77 (9.37)	0.59 (0.54)	-0.91 [-2.11; 0.29]; 0.136
OPERA II	255	13.72 (10.19)	-0.37 (0.52)	237	14.17 (9.93)	-1.03 (0.54)	0.66 [-0.51; 1.84]; 0.268
Total							-0.15 [-0.99; 0.70]; 0.735[d]
Fatigue MFIS physical[g]							
OPERA I	279	15.65 (9.29)	-1.01 (0.51)	249	15.28 (9.73)	0.40 (0.54)	-1.41 [-2.60; -0.22]; 0.021
OPERA II	255	15.63 (9.77)	-0.92 (0.53)	237	16.05 (9.54)	-0.22 (0.55)	-0.70 [-1.89; 0.48]; 0.245
Total							-1.07 [-1.91; -0.22]; 0.013[d]
Fatigue MFIS psychosocial[g]							
OPERA I	279	2.81 (2.24)	-0.04 (0.13)	249	2.73 (2.22)	0.20 (0.14)	-0.24 [-0.55; 0.07]; 0.127
OPERA II	255	2.69 (2.27)	-0.13 (0.13)	237	2.91 (2.28)	-0.06 (0.13)	-0.06 [-0.35; 0.23]; 0.670
Total							-0.16 [-0.37; 0.06]; 0.151[d]

(continued)

Table 15: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: ocrelizumab vs. IFNβ1a (treatment-naive and pretreated patients with non-highly active RMS) (continued)

Outcome category Outcome Study	Ocrelizumab			IFNβ1a			Ocrelizumab vs. IFNβ1a
	N[a]	Values at start of study mean (SD)	Change at week 96 mean[b] (SE)	N[a]	Values at start of study mean (SD)	Change at week 96 mean[b] (SE)	MD [95% CI]; p-value[b]
Health status (EQ-5D VAS[c])							
OPERA I	281	72.48 (18.14)	-1.31 (1.11)	249	73.44 (18.35)	-2.41 (1.18)	1.11 [-1.51; 3.72]; 0.407
OPERA II	255	73.29 (17.56)	0.40 (1.14)	237	72.14 (17.55)	-1.88 (1.19)	2.29 [-0.30; 4.88]; 0.083
Total							1.66 [-0.19; 3.50]; 0.079[d]
Health-related quality of life							
SF-36 PCS[c]							
OPERA I	283	45.51 (9.36)	-0.45 (0.53)	253	45.21 (10.04)	-1.93 (0.57)	1.48 [0.26; 2.71]; 0.018
OPERA II	254	44.96 (9.92)	0.32 (0.53)	237	43.69 (9.92)	-0.66 (0.55)	0.99 [-0.19; 2.17]; 0.101
Total							1.25 [0.39; 2.10]; 0.004[d] Hedges' g: 0.18 [0.06; 0.30][e]
SF-36 physical functioning[c]							
OPERA I	283	70.55 (25.98)	-1.81 (1.39)	253	69.56 (27.53)	-4.21 (1.48)	2.39 [-0.76; 5.54]; 0.136
OPERA II	254	70.15 (25.39)	−0.50 (1.30)	237	67.56 (26.52)	-2.38 (1.36)	1.88 [-1.00; 4.76]; 0.201
Total							2.15 [0.02; 4.29]; 0.048[d]
SF-36 physical role functioning[c]							
OPERA I	283	61.65 (27.88)	1.37 (1.54)	253	60.88 (27.69)	-1.66 (1.64)	3.03 [-0.59; 6.65]; 0.101
OPERA II	254	61.78 (28.57)	2.16 (1.63)	237	59.32 (29.19)	1.10 (1.69)	1.05 [-2.61; 4.72]; 0.572
Total							2.07 [−0.50; 4.65]; 0.115[d]

(continued)

Table 15: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: ocrelizumab vs. IFNβ1a (treatment-naive and pretreated patients with non-highly active RMS) (continued)

Outcome category Outcome Study	Ocrelizumab			IFNβ1a			Ocrelizumab vs. IFNβ1a
	N[a]	Values at start of study mean (SD)	Change at week 96 mean[b] (SE)	N[a]	Values at start of study mean (SD)	Change at week 96 mean[b] (SE)	MD [95% CI]; p-value[b]
SF-36 bodily pain[c]							
OPERA I	283	69.09 (25.84)	0.59 (1.59)	253	70.11 (26.95)	-4.59 (1.69)	5.18 [1.45; 8.91]; 0.007
OPERA II	254	70.13 (27.10)	-1.34 (1.61)	237	65.91 (26.28)	−3.42 (1.69)	2.08 [-1.60; 5.77]; 0.267
Total							3.72 [1.10; 6.35]; 0.006[d]
SF-36 general health perception[c]							
OPERA I	283	55.30 (20.07)	−0.37 (1.25)	253	55.37 (20.73)	0.00 (1.34)	-0.37 [-3.34; 2.60]; 0.805
OPERA II	254	54.95 (21.52)	2.53 (1.25)	237	52.61 (19.98)	0.13 (1.30)	2.40 [-0.46; 5.25]; 0.100
Total							0.99 [-1.08; 3.05]; 0.349[d]
SF-36 MCS[c]							
OPERA I	283	43.02 (12.22)	1.56 (0.69)	253	44.07 (11.88)	1.33 (0.73)	0.23 [-1.41; 1.86]; 0.783
OPERA II	254	44.70 (11.46)	1.20 (0.73)	237	44.00 (11.43)	0.98 (0.76)	0.22 [-1.45; 1.89]; 0.795
Total							0.23 [-0.93; 1.40]; 0.697[d]
SF-36 vitality[c]							
OPERA I	283	49.92 (21.73)	1.65 (1.25)	253	51.46 (21.38)	-1.05 (1.32)	2.70 [-0.21; 5.61]; 0.069
OPERA II	254	51.05 (22.90)	4.71 (1.29)	237	49.20 (20.44)	2.22 (1.35)	2.49 [-0.45; 5.42]; 0.097
Total							2.60 [0.54; 4.67]; 0.014[d]

(continued)

Table 15: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: ocrelizumab vs. IFNβ1a (treatment-naive and pretreated patients with non-highly active RMS) (continued)

Outcome category Outcome Study	Ocrelizumab			IFNβ1a			Ocrelizumab vs. IFNβ1a
	N[a]	Values at start of study mean (SD)	Change at week 96 mean[b] (SE)	N[a]	Values at start of study mean (SD)	Change at week 96 mean[b] (SE)	MD [95% CI]; p-value[b]
SF-36 social functioning[c]							
OPERA I	283	66.93 (28.26)	0.70 (1.62)	253	70.35 (26.57)	-2.48 (1.70)	3.18 [-0.61; 6.98]; 0.100
OPERA II	254	68.60 (25.83)	1.30 (1.64)	237	67.37 (27.10)	0.50 (1.71)	0.81 [-2.92; 4.53]; 0.672
Total							2.09 [-0.58; 4.76]; 0.125[d]
SF-36 emotional role functioning[c]							
OPERA I	283	71.14 (26.19)	0.54 (1.55)	253	70.01 (27.96)	1.56 (1.65)	-1.02 [-4.68; 2.65]; 0.586
OPERA II	254	73.73 (26.48)	-2.96 (1.71)	237	71.36 (27.69)	-0.35 (1.79)	-2.61 [-6.52; 1.30]; 0.191
Total							-1.77 [-4.44; 0.90]; 0.193[d]
SF-36 mental wellbeing[c]							
OPERA I	283	63.62 (20.47)	3.28 (1.18)	253	65.84 (19.64)	2.09 (1.25)	1.19 [-1.60; 3.98]; 0.404
OPERA II	254	66.66 (19.35)	3.54 (1.25)	237	65.12 (18.87)	0.93 (1.30)	2.60 [-0.26; 5.47]; 0.075
Total							1.89 [-0.11; 3.88]; 0.064[d]

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: Effect estimate, SE, CI and p-value: ANCOVA analysis adjusted for region and EDSS at the start of the study.
c: A positive change from the start until the end of the study indicates improvement; a positive effect estimate indicates an advantage for ocrelizumab.
d: Calculation using the IPD meta-analysis.
e: Institute's calculation.
f: Presumably ANCOVA analysis adjusted for region and EDSS at the start of the study with adjusted change in relation to the baseline value as outcome variable.
g: A negative change from the start until the end of the study indicates improvement; a negative effect estimate indicates an advantage for ocrelizumab.
h: Presumably adjusted geometric mean; 95% CI.
i: Presumably ratio of the adjusted geometric means.

ANCOVA: Analysis of Covariance; CI: confidence interval; EDSS: Expanded Disability Status Scale; EQ-5D: European Quality of Life Questionnaire 5-Dimensions; IFN-β: interferon beta; IPD: individual patient data; MCS: Mental Component Summary scale; MD: mean difference; MFIS: Modified Fatigue Impact Scale; MSFC: Multiple Sclerosis Functional Composite; N: number of analysed patients; PASAT: Paced Auditory Serial Addition Test; PCS: Physical Component Summary scale; ROM: Ratio of Means; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SF-36: Short Form (36) Health Survey; VAS: visual analogue scale; vs.: versus

On the basis of the available data, at most indications can be determined for the outcomes "disability severity", "fatigue interference", "health status" and "health-related quality of life", and for all other outcomes there are proofs, e.g. of an added benefit, because of the high risk of bias (see Section 2.3.2.2).

Mortality

All-cause mortality

For the outcome "all-cause mortality", there was altogether one event in the IFNβ1a arm of the OPERA I study. Overall, this resulted in no hint of an added benefit of ocrelizumab in comparison with IFNβ1a, an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Relapses (based on EDSS)

The annualized relapse rate was considered to be the decisive operationalization for the outcome "relapses". The meta-analysis showed a statistically significant difference in favour of ocrelizumab in comparison with IFNβ1a. In addition, there was an interaction by the characteristic "age" for the outcome "annualized relapse rate" for the total population of the OPERA studies. The meta-analysis showed a statistically significant difference in favour of ocrelizumab both for patients < 40 years and ≥ 40 years. However, for patients ≥ 40 years, the extent for this outcome from the category "non-serious/non-severe symptoms/late complications" was no more than marginal. Thus, this resulted in no hint of an added benefit; an added benefit is therefore not proven. For patients < 40 years, there was proof of an added benefit of ocrelizumab.

This assessment deviates from that of the company. The company did not use subgroup data for the deviation of an added benefit and derived proof of an added benefit of ocrelizumab for the outcome "relapses" for the entire relevant subpopulation.

The operationalizations "relapses by severity grade" (moderate/severe or severe) presented as supplementary information and the time to first confirmed relapse showed less relapses in both the ocrelizumab arm and the IFNβ1a arm of the OPERA studies.

Confirmed disability progression (based on EDSS)

The time to first confirmed disability progression was considered for the outcome "confirmed disability progression". The meta-analysis showed a statistically significant difference in favour of ocrelizumab in comparison with IFNβ1a. The extent for the outcome "time to first disability progression" from the category "non-serious/non-severe symptoms/late complications" was rated as no more than marginal. This resulted in no hint of an added benefit for the outcome "confirmed disability progression", an added benefit is therefore not proven.

This deviates from the company's assessment, which derived proof of an added benefit for ocrelizumab.

Disability severity (MSFC z-score)

The mean difference from the covariance analysis from the start of the study to week 96 was considered for the outcome "disability severity" recorded with the MSFC z-score. The meta-analysis shows a statistically significant difference in favour of ocrelizumab. However, the CI for the standardized mean difference (hedges' g) was not fully outside the irrelevance range [−0.2; 0.2]. It can therefore not be inferred that the effect is relevant. This resulted in no hint of an added benefit of ocrelizumab in comparison with IFNβ1a, an added benefit is therefore not proven.

In the result, this concurs with the company's assessment. The company used responder analyses on the MSFC z-score as well as of the MSFC subscales for the assessment and derived no added benefit on the basis of these analyses.

Fatigue interference (MFIS)

The mean difference from the covariance analysis from the start of the study to week 96 was considered for the outcome "fatigue interference" recorded with the MFIS. The meta-analysis showed no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of ocrelizumab in comparison with IFNβ1a, an added benefit is therefore not proven.

In the result, this also concurs with the company's assessment. However, the company used responder analyses for the assessment of MFIS and derived no added benefit on the basis of these analyses.

Health status (EQ-5D VAS)

The mean difference from the covariance analysis from the start of the study to week 96 was considered for the outcome "health status" recorded with the VAS of the EQ-5D. The meta-analysis showed no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of ocrelizumab for the outcome "health status"; an added benefit is therefore not proven.

This assessment deviates from that of the company. The company used responder analyses on this outcome and derived proof on an added benefit of ocrelizumab on the basis of the results on the response threshold "deterioration by 10 mm".

Health-related quality of life

SF-36

For the SF-36, MCS and the PCS were considered separately. The mean difference of the change from the start of the study until week 96 from the covariance analysis was considered for each summary score. The meta-analysis showed a statistically significant difference in

favour of ocrelizumab between the treatment arms for the PCS. However, the CI for the standardized mean difference (hedges' g) was not fully outside the irrelevance range [−0.2; 0.2]. It can therefore not be inferred that the effect is relevant. The meta-analysis showed no statistically significant difference between the treatment groups for the MCS.

Overall, this resulted in no hint of an added benefit of ocrelizumab in comparison with IFNβ1a for the SF-36, an added benefit is therefore not proven.

This deviates from the company's assessment, which, based on its responder analyses for the PCS, derived proof of an added benefit of ocrelizumab of the SF36.

Side effects

SAEs

The meta-analysis showed no statistically significant difference for SAEs between the treatment groups. However, there was an effect modification by the subgroup characteristic "age". A statistically significant difference in favour of ocrelizumab in comparison with IFNβ1a was shown for patients < 40 years. This resulted in proof of lesser harm from ocrelizumab.

For patients ≥ 40 years, in contrast, there was no statistically significant difference between the treatment groups. This resulted in no hint of lesser or greater harm from ocrelizumab, greater or lesser harm is therefore not proven.

This assessment deviates from that of the company. The company did not use the results of the subgroup analyses for the derivation of an added benefit and derived no added benefit on the basis of the entire relevant subpopulation.

Discontinuation due to AEs

The meta-analysis showed a statistically significant difference in favour of ocrelizumab for the outcome "discontinuation due to AEs". The extent for the outcome "discontinuation due to AEs" from the category "non-serious/non-severe side effects" was rated as no more than marginal. This resulted in no hint of greater or lesser harm from ocrelizumab in comparison with IFNβ1a for the outcome "discontinuation due to AEs"; greater or lesser harm is therefore not proven.

This deviates from the company's assessment, which derived proof of an added benefit of ocrelizumab for this outcome.

Specific AEs

Flu-like illness and injection site reactions

The meta-analysis showed a statistically significant difference in favour of ocrelizumab for the outcomes "flu-like illness" and "injection site reactions". In each case, this resulted in a hint of lesser harm from ocrelizumab in comparison with IFNβ1a.

This concurs with the company's assessment for both outcomes.

Reaction associated with an infusion

The meta-analysis showed a statistically significant difference to the disadvantage of ocrelizumab for the outcome "reaction associated with an infusion". In each case, this resulted in proof of greater harm from ocrelizumab in comparison with IFNβ1a.

The company did not consider subgroup data on this outcome, but also derived proof of greater harm for this outcome for the entire subpopulation.

Infections and infestations as well as depression

The meta-analysis showed no statistically significant difference between the treatment groups for the outcomes "infections and infestations" and "depression". This resulted in no hint of lesser or greater harm from ocrelizumab in comparison with IFNβ1a, greater or lesser harm is therefore not proven.

This concurs with the company's assessment for the outcome "infections and infestations". The company did not assess the outcome "depression" within the context "side effects".

2.3.2.4 Subgroups and other effect modifiers

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

The following potential effect modifiers were considered in the present assessment:

- sex (female versus male)
- age (< 40 years versus ≥ 40 years)
- EDSS at baseline (< 4 vs. ≥ 4)
- region (EU, Switzerland/Norway vs. others)

The company presented complete subgroup data only for the total population of the OPERA studies, the subgroup analyses on the relevant subpopulation were incomplete. As far as available, the subgroup data of the relevant subpopulations were used for the present assessment on research question 1. Otherwise, the analyses on the total population were considered.

Table 16 and Table 17 show the subgroup results of ocrelizumab in comparison with IFNβ1a.

Table 16: Subgroups (morbidity, relapses) – RCT, direct comparison: ocrelizumab vs. IFNβ1a (total population)

Outcome Characteristic	Ocrelizumab			IFNβ1a			Ocrelizumab vs. IFNβ1a
Study Subgroup	N[a]	n/Patient years	Annualized relapse rate [95% CI]	N[a]	n/Patient years	Annualized relapse rate [95% CI]	Rate ratio [95% CI]; p-value
Relapses (based on EDSS)							
annualized relapse rate							
Age							
OPERA I							
< 40 years	244		0.12 [0.09; 0.16]	243		0.26 [0.20; 0.33]	0.45 [0.30; 0.67]; < 0.001[b]
≥ 40 years	166		0.17 [0.12; 0.23]	168		0.24 [0.18; 0.32]	0.69 [0.45; 1.08]; 0.101[b]
OPERA II		ND			ND		
< 40 years	252		0.13 [0.09; 0.17]	241		0.30 [0.24; 0.39]	0.42 [0.29; 0.63]; < 0.001[b]
≥ 40 years	165		0.16 [0.11; 0.21]	177		0.20 [0.15; 0.27]	0.77 [0.50; 1.18]; 0.229[b]
Total						Interaction[c]	p-value = 0.020
< 40 years							0.44 [0.33; 0.58]; < 0.001[d]
≥ 40 years							0.73 [0.53; 0.99]; 0.043[d]

a: The values refer to the total population of the study.
b: Annualized relapse rate, effect measure, CI and p-value: negative binomial model.
c: Likelihood ratio test.
d: Calculation using the IPD meta-analysis.

CI: confidence interval; IFN-β: interferon-beta; IPD: individual patient data; ND: no data; n: number of relapses; N: number of analysed patients; RCT: randomized controlled trial; vs.: versus

Table 17: Subgroups (side effects) – RCT, direct comparison: ocrelizumab vs. IFNβ1a (treatment-naive and pretreated patients with non-highly active RMS)

Outcome Characteristic Study Subgroup	Ocrelizumab L	Ocrelizumab Patients with event n (%)	IFNβ1a N	IFNβ1a Patients with event n (%)	Ocrelizumab vs. IFNβ1a RR [95% CI]	Ocrelizumab vs. IFNβ1a p-value
SAEs						
Age						
OPERA I						
< 40 years	205	8 (3.9)	196	14 (7.1)	0.55 [0.23; 1.27]	0.162[a]
≥ 40 years	140	15 (10.7)	138	8 (5.8)	1.85 [0.81; 4.22]	0.145[a]
OPERA II						
< 40 years	213	9 (4.2)	209	16 (7.7)	0.55 [0.25; 1.22]	0.142[a]
≥ 40 years	129	15 (11.6)	147	15 (10.2)	1.14 [0.58; 2.24]	0.705[a]
Total					Interaction[b]:	0.018
< 40 years					0.55 [0.31; 0.98]	0.043[c]
≥ 40 years					1.39 [0.83; 2.33]	0.210[c]
Reaction associated with an infusion						
Sex						
OPERA I						
Men	116	33 (28.4)	113	4 (3.5)	8.04 [2.94; 21.95]	< 0.001[a]
Women	229	65 (28.4)	221	16 (7.2)	3.92 [2.34; 6.56]	< 0.001[a]
OPERA II						
Men	118	43 (36.4)	121	8 (6.6)	5.51 [2.71; 11.22]	< 0.001[a]
Women	224	85 (37.9)	235	35 (14.9)	2.55 [1.80; 3.61]	< 0.001[a]
Total					Interaction[b]:	0.015
Men					6.34 [3.55; 11.33]	< 0.001[c]
Women					2.96 [2.22; 3.95]	< 0.001[c]

a: Effect estimate 95% CI; generalized linear regression model; p-value: Wald test.
b: Likelihood ratio test.
c: Calculation using the IPD meta-analysis.
CI: confidence interval; IFN-β: interferon beta; IPD: individual patient data; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Relapses (based on EDSS)

There was an interaction by the characteristic "age" for the outcome "annualized relapse rate" for the total population. The meta-analysis showed a statistically significant difference in favour of ocrelizumab both for patients < 40 years and for patients ≥ 40. However, for patients > 40 years, the extent for this outcome from the category "non-serious/non-severe symptoms/late complications" was no more than marginal. Thus, this resulted in no hint of an added benefit; an added benefit is therefore not proven. For patients < 40 years, there was proof of an added benefit of ocrelizumab.

The company presented the results of the subgroup analyses on the total population of the OPERA studies, but did not use them for the derivation of an added benefit.

SAEs

There was an effect modification by the subgroup characteristic "age" for the outcome "SAEs". A statistically significant difference in favour of ocrelizumab in comparison with IFNβ1a was shown for patients < 40 years. This resulted in proof of lesser harm from ocrelizumab.

For patients ≥ 40 years, in contrast, there was no statistically significant difference between the treatment groups. This resulted in no hint of lesser or greater harm from ocrelizumab, greater or lesser harm is therefore not proven.

This assessment deviates from that of the company. The company only presented the results of the subgroup analyses on the total population. However, it did not use subgroup results for the derivation of an added benefit and derived no added benefit on the basis of the total relevant subpopulation.

Reaction associated with an infusion

An interaction by the characteristic "sex" was shown for the outcome "reaction associated with an infusion". The meta-analysis showed a statistically significant difference to the disadvantage of ocrelizumab for both men and women. This resulted in a proof of greater harm from ocrelizumab with the same extent for both sexes. The direction of effect and the extent for both subgroups concurred with the result of the total relevant subpopulation. Hence, this characteristic was not further considered in the overall conclusion on the added benefit.

This assessment deviates from that of the company. The company did not use subgroup results for the derivation of an added benefit and derived proof of lesser benefit for the entire relevant subpopulation.

2.3.3 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below. The various outcome categories and the effect sizes are taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The procedure for deriving an overall conclusion on the added benefit based on the aggregation of the conclusions deduced at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.3.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.3.2.3 (see Table 18). Here, the analyses of the annualized relapse rate were used for the conclusions on the extent for the outcome "relapses".

Determination of the outcome category for the outcomes "symptoms" and "side effects"

In its dossier, the company presented no information that would allow an assessment of the severity category for the outcomes on the relevant subpopulation considered in the present benefit assessment. Therefore, the information on the total population of the OPERA study was used to assess whether an outcome was non-severe/non-serious or severe/serious. The severity classification of relevant outcomes is justified below.

Determination of the outcome category for the outcomes "relapses" and "confirmed disability progression"

"Relapses" and "time to first confirmed disability progression" were recorded with the EDSS or the corresponding functioning systems (see Section 2.7.2.4.3 of the full dossier assessment). The presentation of the relapse rates by severity grade in Table 13 shows that the annual rates of severe relapses were altogether low in the OPERA studies.

In its dossier, the company presented no information that would allow an assessment of the severity of the confirmed disease progression. For instance, data stating how many patients had relatively severe disabilities (EDSS ≥ 4) at the end of the study were missing. Overall, the outcomes "relapses" and "confirmed disease progression" were therefore allocated to the outcome category "non-serious/non-severe symptoms/late complications".

Deviating from this, the company classified the outcome "confirmed disease progression" as "serious/severe symptom/late complications". In its dossier, the company did not state to which outcome category it had allocated the outcome "relapses".

Determination of the outcome category for the outcomes "discontinuation due to adverse events", "flu-like illness", "injection site reactions" and "reaction associated with an infusion"

The severity grades of the outcomes "discontinuation due to AEs", "flu-like illness", "injection site reactions" as well as "reaction associated with an infusion" were assessed based on the proportions of SAEs on the individual outcomes observed in the total population of the OPERA studies.

SAEs for the outcomes "flu-like illness", "injection site reactions" and "reaction associated with an infusion" were at most 0.1%. Both outcomes were therefore allocated to the category "non-serious/non-severe side effects".

The primary AEs resulting in a discontinuation were "flu-like illness", "fatigue" and "injection site reactions". All 3 outcomes were allocated to the category "non-serious/non-severe side effects" due to the low proportion of SAEs; therefore, the outcome "discontinuation due to AEs" is also allocated to this category.

In summary, the outcomes “discontinuation due to AEs”, “flu-like illness”, “injection site reactions” as well as “reaction associated with an infusion” are allocated to the category “non-serious/non-severe side effects”.

In its dossier, the company did not state to which outcome categories it had allocated these outcomes.

Table 18: Extent of added benefit at outcome level: ocrelizumab vs. IFNβ1a (treatment-naive and pretreated patients with non-highly active RMS)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Ocrelizumab vs. IFNβ1a** **Median time to event (months) or proportion of events (%) or MD or annual rate** **Effect estimate [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality	0% vs. 0–0.3% RR: –	Lesser benefit/added benefit not proven
Morbidity		
Relapses Annualized relapse rate Age [years]		
< 40 years	Rate: 0.12–0.13 vs. 0.26–0.30[c] Rate ratio: 0.44 [0.33; 0.58]; p < 0.001 Probability: "proof"	Outcome category "non-serious/non-severe symptoms/late complications" CI_u < 0.80 added benefit; extent: "considerable"
≥ 40 years	Rate: 0.16–0.17 vs. 0.20–0.24[c] Rate ratio: 0.73 [0.53; 0.99]; p = 0.043	Outcome category: "non-serious/non-severe symptoms/late complications" 0.90 ≤ CI_o < 1.00 Lesser benefit/added benefit not proven[d]
Confirmed disability progression		
Time to first confirmed disability progression	Median: NA vs. NA HR: 0.64 [0.44; 0.93] p = 0.019	Outcome category: "non-serious/non-severe symptoms/late complications" 0.90 ≤ CI_o < 1.00 Lesser benefit/added benefit not proven[d]
Disability severity		
MSFC z-score	0.21–0.26 vs. 0.14–0.17[c] MD: 0.08 [0.02; 0.14]; p = 0.008 Hedges' g: 0.16 [0.04; 0.29][e]	Lesser benefit/added benefit not proven
Fatigue interference		
MFIS	–1.65 to 1.59 vs. –1.53 to 1.02[c] MD: –1.40 [–3.12; 0.31]; p = 0.108	Lesser benefit/added benefit not proven
Health status		
EQ-5D VAS	–1.31 to 0.40 vs. –2.41 to –1.88[c] MD: 1.66 [–0.19; 3.50]; p = 0.079	Lesser benefit/added benefit not proven

(continued)

Table 18: Extent of added benefit at outcome level: ocrelizumab vs. IFNβ1a (treatment-naive and pretreated patients with non-highly active RMS) (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Ocrelizumab vs. IFNβ1a** **Median time to event (months) or proportion of events (%) or MD or annual rate** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Health-related quality of life		
SF-36		
PCS	–0.45 to 0.32 vs. –1.93 to –0.66[c] MD: 1.25 [0.39; 2.10]; p = 0.004 Hedges' g: 0.18 [0.06; 0.30][e]	Lesser benefit/added benefit not proven
MCS	1.20–1.56 vs. 0.98–1.33[c] MD: 0.23 [-0.93; 1.40]; p = 0.697	Lesser benefit/added benefit not proven
Side effects		
SAEs Age [years]		
< 40 years	3.9%–4.2% vs. 7.1%-7.7% RR: 0.55 [0.31; 0.98] p = 0.043 probability: "proof"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Lesser harm, extent: "minor"
≥ 40 years	10.7%–11.6% vs. 5.8%–10.2% RR: 1.39 [0.83; 2.33] p = 0.210	Greater/lesser harm not proven
Discontinuation due to AEs	2.9%-4.4% vs. 6.0%-6.5% RR: 0.59 [0.36; 0.95] p = 0.030	Outcome category: non-serious/non-severe side effects $0.90 \leq CI_o < 1.00$ Greater/lesser harm not proven[d]
Flu-like illness	3.8%-6.4% vs. 21.0%–23.6% RR: 0.23 [0.16; 0.33] p < 0.001 probability: "proof"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Lesser harm, extent: "considerable"
Injection site reactions	0.0%-0.6% vs. 3.9%-7.3% RR: 0.05 [0.01; 0.22] p < 0.001 probability: "proof"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Lesser harm, extent: "considerable"

(continued)

Table 18: Extent of added benefit at outcome level: ocrelizumab vs. IFNβ1a (treatment-naive and pretreated patients with non-highly active RMS) (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Ocrelizumab vs. IFNβ1a** **Median time to event (months) or proportion of events (%) or MD or annual rate** **Effect estimate [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Reaction associated with an infusion		
Sex		
Male	28.4%–36.4% vs. 3.5–6.6% RR: 6.34 [3.55; 11.33]; p = < 0.001 RR: 0.16 [0.09; 0.28][f] probability: "proof"	Outcome category "non-serious/non-severe AEs" CI_u < 0.80 greater harm, extent: "considerable"
Female	28.4-37.9% vs. 7.2-14.9% RR: 2.96 [2.22; 3.95]; < 0.001 RR: 0.34 [0.25; 0.45][f] probability: "proof"	Outcome category "non-serious/non-severe AEs" CI_u < 0.80 greater harm, extent: "considerable"
Infections and infestations	53.9–58.5% vs. 52.4-50.8% RR: 1.09 [0.99; 1.20] p = 0.083	Greater/lesser harm not proven
Depression	7.4-8.2% vs. 5.9-7.2% RR: 1.19 [0.84; 1.68] p = 0.337	Greater/lesser harm not proven

a: Probability provided if statistically significant differences are present.
b: Estimations of effect size were made depending on the outcome category with different limits based on the CI_u.
c: Minimum and maximum change at week 96 or annual rate per treatment arm in the studies included.
d: The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
e: If the CI of Hedges' g is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived.
f: Institute's calculation: reversed direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CI: confidence interval; IFN-β: interferon beta; CIu: upper limit of confidence interval; MCS: Mental Component Summary; MD: mean difference; MFIS: Modified Fatigue Impact Scale; MSFC: Multiple Sclerosis Functional Composite; NA: not achieved; PASAT: Paced Auditory Serial Addition Test; PCS: Physical Component Summary scale; RR: relative risk; SF 36: Short Form (36) Health Survey; SAE: serious adverse event; vs.: versus

2.3.3.2 Overall conclusion on added benefit

Table 19 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 19: Positive and negative effects from the assessment of ocrelizumab in comparison with IFNβ1a (treatment-naive and pretreated patients with non-highly active RMS)

Positive effects	**Negative effects**
Non-serious/non-severe symptoms/late complications ▪ Relapses: ▫ < 40 years: proof of an added benefit – extent: "considerable"	
Outcome category: serious/severe side effects ▪ SAEs: ▫ < 40 years: proof of lesser harm – extent: "minor"	
Outcome category: non-serious/non-severe side effects ▪ Specific AEs (flu-like illness, injection site reactions): proof of lesser harm – extent: "considerable"	Outcome category: non-serious/non-severe side effects ▪ Specific AEs (reaction associated with an infusion): proof of greater harm - extent "considerable"
AE: adverse event; IFN-β: interferon beta; SAE: serious adverse event	

Overall, there were several positive effects, partially in subgroups, and one negative effect of ocrelizumab in comparison with IFNβ1a in the outcome categories "morbidity" and "side effects".

The results showed an effect modification by age for the outcomes "relapses" and "SAEs". This resulted in one proof of a considerable added benefit or lesser harm each for the outcomes "relapses" and "SAEs" for patients < 40 years.

In the total relevant subpopulation, 2 proofs of lesser harm and one proof of greater harm were shown for the specific AEs, all of them with the extent "considerable".

In summary, this results in a proof of considerable added benefit of ocrelizumab in comparison with IFNβ1a for adult treatment-naive and pretreated patients with non-highly active RMS and patients < 40 years.

After consideration of the specific AEs on the positive and the negative side and in the overall consideration of all results, there is overall a positive effect for patients ≥ 40 years. This results in a proof of minor added benefit of ocrelizumab vs. IFNβ1a for adult treatment-naive and pretreated patients ≥ 40 years with non-highly active RMS.

2.3.4 List of included studies

OPERA I

F. Hoffmann-La Roche. A randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon beta-1a (Rebif) in patients with relapsing multiple sclerosis: clinical trial results [online]. In: EU Clinical Trials Register. 03.06.2016 [Accessed: 06.02.2018]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-020337-99/results.

F. Hoffmann-La Roche. A randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon beta-1a (Rebif) in patients with relapsing multiple sclerosis [online]. In: EU Clinical Trials Register. [Accessed: 06.02.2018]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2010-020337-99.

F. Hoffmann-La Roche. A randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon beta-1a (Rebif) in patients with relapsing multiple sclerosis [online]. In: Clinical Trials Perurian Registry. [Accessed: 06.02.2018]. URL: http://www.ins.gob.pe/ensayosclinicos/rpec/recuperarECPBNuevoEN.asp?numec=024-14.

F. Hoffmann-La Roche. A randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon beta-1a (Rebif) in patients with relapsing multiple sclerosis: study WA21092; primary clinical study report; report no. 1062034 [unpublished]. 2016.

Hoffmann-La Roche. A study of ocrelizumab in comparison with interferon beta-1a (Rebif) in participants with relapsing multiple sclerosis: study results [online]. In: ClinicalTrials.gov. 25.01.2018 [Accessed: 06.02.2018]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01247324.

Hoffmann-La Roche. A study of ocrelizumab in comparison with interferon beta-1a (Rebif) in participants with relapsing multiple sclerosis: study details [online]. In: ClinicalTrials.gov. 25.01.2018 [Accessed: 06.02.2018]. URL: https://ClinicalTrials.gov/show/NCT01247324.

OPERA II

F. Hoffmann-La Roche. A randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon beta-1a (Rebif) in patients with relapsing multiple sclerosis: clinical trial results [online]. In: EU Clinical Trials Register. 03.06.2016 [Accessed: 06.02.2018]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-020315-36/results.

F. Hoffmann-La Roche. A randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon beta-1a (Rebif) in patients with relapsing multiple sclerosis [online]. In: EU Clinical Trials Register. [Accessed: 06.02.2018]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2010-020315-36.

F. Hoffmann-La Roche. A randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon beta-1a (Rebif) in patients with relapsing multiple sclerosis [online]. In: Clinical Trials Perurian Registry. [Accessed: 06.02.2018]. URL: http://www.ins.gob.pe/ensayosclinicos/rpec/recuperarECPBNuevoEN.asp?numec=128-11.

F. Hoffmann-La Roche. A randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon beta-1a (Rebif) in patients with relapsing multiple sclerosis: study WA21093; primary clinical study report; report no. 1062035 [unpublished]. 2016.

Hoffmann-La Roche. A study of ocrelizumab in comparison with interferon beta-1a (Rebif) in participants with relapsing multiple sclerosis: study results [online]. In: ClinicalTrials.gov. 25.01.2018 [Accessed: 06.02.2018]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01412333.

Hoffmann-La Roche. A study of ocrelizumab in comparison with interferon beta-1a (Rebif) in participants with relapsing multiple sclerosis: study details [online]. In: ClinicalTrials.gov. 25.01.2018 [Accessed: 06.02.2018]. URL: https://ClinicalTrials.gov/show/NCT01412333.

OPERA I + II

F. Hoffmann-La Roche. Randomized, double-blind, double-dummy, parallel-group studies to evaluate the efficacy and safety of ocrelizumab in comparison to interferon beta-1a (Rebif) in patients with relapsing multiple sclerosis: study WA21092 and WA21093; pooled analysis report; report no. 1062982 [unpublished]. 2016.

F. Hoffmann-La Roche. Randomized, double-blind, double-dummy, parallel-group studies to evaluate the efficacy and safety of ocrelizumab in comparison to interferon beta-1a (Rebif) in patients with relapsing multiple sclerosis; study WA21092 and WA21093; pooled analysis report; report no. 1062982; Zusatzanalysen [unpublished]. 2017.

Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung HP, Hemmer B et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. N Engl J Med 2017; 376(3): 221-234.

2.4 Research question 2: pretreated patients with highly active RMS

2.4.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on ocrelizumab (status: 18 December 2017)
- bibliographical literature search on ocrelizumab (last search on 14 February 2018)
- search in trial registries for studies on ocrelizumab (last search on 14 February 2018)

To check the completeness of the study pool:

- search in trial registries for studies on ocrelizumab (last search on 29 January 2018)

The check identified no additional relevant study.

2.4.1.1 Studies included

The studies OPERA I and II were included in the benefit assessment of ocrelizumab in comparison with IFNβ1a in pretreated patients with highly active RMS (research question 2). These are the same studies that had been included in the assessment of ocrelizumab in treatment-naive and pretreated patients with non-highly active RMS (research question 1) (see Table 5).

Section 2.3.4 contains a reference list for the studies included.

2.4.1.2 Study characteristics and study design

Table 6 and Table 7 show the study characteristics as well as the interventions of the OPERA studies. The design of the studies is described in Section 2.3.1.2

Subpopulation relevant for research question 2

The population relevant for research question 2 comprises patients with highly active RMS despite treatment with a disease-modifying therapy. Consequently, only a subpopulation of the OPERA I and OPERA II studies was relevant for the present research question. Based on the criteria described in Section 2.3.1.2, the company built a subpopulation of patients with highly active RMS despite treatment with a disease-modifying therapy. The criteria used by the company are suitable to adequately represent the subpopulation relevant for research question 2. Moreover, the company excluded all patients from the subpopulation who, before study inclusion, had received treatment with the comparator therapy IFNβ1a 44 µg SC used in the OPERA studies b, since change had to take place within the basic therapeutic agents according to the G-BA's specification of the ACT. This approach is accepted with restrictions. The proportion of the relevant subpopulation in the total population amounted to about 13% in both OPERA studies.

As with research question 1, information for the description of disease, duration and type of prior therapies of the relevant subpopulation is also missing for research question 2. It is therefore unclear to which extent the subpopulation used by the company in its assessment also included patients who did not correspond to the research question or whether all patients of the relevant subpopulation were included.

Thus, it cannot be verified whether and to which extent patients pretreated with IFNβ1a 22 µg SC, a dosage that was also approved, were excluded from the subpopulation. Patients with highly active RMS pretreated with intramusculary (IM) administered IFNβ1a were also

included in the subpopulation. The company thus interpreted change of the application form from IM to SC as change within the basic therapy for these patients.

The company's assessment was not accepted. Although, besides the application method, both the application frequency and the dosage differed between the different IFNβ1a therapies (SC vs. IM), the clinical effects between these RMS therapies were comparable, and none of the IFNβ1a therapies should be regularly preferred over the other one [5,7,8]. Therefore, the G-BA also rated a differentiation between the application methods of the ACT (IFNβ1a) as inadequate [9].

Due to missing information, the proportion of patients pretreated with IFNβ 1a (IM) with highly active RMS had to be estimated on the basis of the data available for the total population. For this purpose, it was assumed that the ratio between the patients pretreated with IFNβ1a (IM) and those pretreated with IFNβ1a (SC) in the total study corresponded to that of the subpopulation for research question 2. It was estimated that the proportion of patients with highly active disease who had been pretreated with IFNβ1a (IM) probably amounted to < 20% of the total subpopulation relevant for research question 2. The subpopulation presented by the company was thus used as sufficient approximation to the subpopulation relevant for research question 2.

The uncertainties resulting from the missing information were considered in the derivation of the certainty of conclusions of the results (see Section 2.4.2.2).

Table 20 shows the characteristics of the patients of the relevant subpopulation. For information on the total study population of the studies OPERA I and II (please refer to Table 8).

Table 20: Characteristics of the relevant subpopulation – RCT, direct comparison: ocrelizumab vs. IFNβ1a (pretreated patients with highly active RMS)

Study	**OPERA I**		**OPERA II**	
Characteristics Category	**Ocrelizumab**	**IFNβ1a**	**Ocrelizumab**	**IFNβ1a**
	N[a] = 54	**N[a] = 59**	**N[a] = 57**	**N[a] = 47**
Age [years], mean (SD)	37.0 (9.4)	35.2 (9.7)	37.6 (8.7)	37.9 (9.1)
Sex [F/M],%	59/41	71/29	61/39	72/28
Ethnicity, n (%)				
White	50 (93)	54 (92)	46 (81)	44 (94)
Other[c]	4 (7)[b]	5 (8)[b]	11 (19)[b]	3 (6)[b]
EDSS at the start of the study, n (%)				
< 4	ND		ND	
≥ 4	ND		ND	
Gd-enhancing lesions, n (%)				
0	ND		ND	
≥ 1	ND		ND	
T2 lesions, n (%)				
< 9	ND		ND	
≥ 9	ND		ND	
Time since RMS diagnosis [years], mean (SD)	ND		ND	
Time since occurrence of MS symptoms [years], mean (SD)	ND		ND	
Number of relapses in the year before the start of the study, mean (SD)	ND		ND	
Number of relapses in the last 2 years before the start of the study, mean (SD)	ND		ND	
Pretreatment with MS therapy, n (%)				
Yes	ND		ND	
No	ND		ND	
Treatment discontinuation, n (%)	ND		ND	
Study discontinuation, n (%)	ND		ND	

a: Number of randomized patients. Data that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Institute's calculation.
c: Is composed of the ethnicities native American, Asian, black/African American, other ethnicities and multiple answers.
EDSS: Expanded Disability Status Scale; F: female; Gd: Gadolinium; IFN-β: interferon beta; M: male; MS: multiple sclerosis; n: number of patients in the category; N: number of randomized (or included) patients; RCT: randomized controlled trial; RMS: relapsing multiple sclerosis; SD: standard deviation; vs.: versus

The few available demographic characteristics of the patients in this subpopulation were largely balanced both between the individual study arms and between the studies. The mean age of the

patients of the relevant subpopulation was about 37 years, about 2 thirds of them were female and about 90% where white. There are slight imbalances between the treatment groups regarding the characteristics “sex” and “ethnicity”. The share of women in den IFNβ1a arms of the studies was higher than in the ocrelizumab arms. Moreover, the ocrelizumab arm of the OPERA II study had a higher share of other ethnicities than the other study arms.

Information on study and treatment discontinuations is only available for the respective total populations. They are described in research question 1 (see Section 2.3.1.2).

As already described in research question 1, the risk of bias of both OPERA studies at study level was rated as low. This concurs with the company’s assessment (see Table 9 in Section 2.3.1.2).

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment).

- Mortality
  - All-cause mortality
- Morbidity
  - Relapses (based on EDSS)
  - Confirmed disability progression (based on EDSS)
  - Disability severity (based on MSFC)
  - Fatigue interference measured with the MFIS
  - Health status, measured using the EQ-5D VAS
- Health-related quality of life
  - Measured using the SF-36.
- Side effects
  - SAEs
  - Discontinuation due to AEs
  - Flu-like illness
  - Injection site reactions
  - Reaction associated with an infusion
  - Infections and infestations
  - Depression

- If applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4) (see Section 2.7.2.4.3 of the full dossier assessment).

Table 21 shows for which outcomes data were available in the studies included.

Table 21: Matrix of the outcomes– RCT, direct comparison: ocrelizumab vs. IFNβ1a (pretreated patients with highly active RMS)

Study	Outcomes													
	All-cause mortality	Relapses	Disability progression (EDSS)	Disability severity (MSFC)	Fatigue interference (MFIS)	Health status (EQ-5D VAS)	Health-related quality of life (SF-36)	SAEs	Discontinuation due to AEs	Flu-like illness (AE, PT)	Injection site reactions (AE, PT)	Reaction associated with an infusion (AE, PT)	Infections and infestations (AE, SOC)	Depression (AE, PT)
OPERA I, II	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes[a]	No[b]

a: No data on the SOC "infections and infestations" were available for the relevant subpopulation. The data of the adverse event "infections" of Module 4 A of the dossier were used (for reasons, see Section 2.7.2.4.3 of the full dossier assessment).
b: No data available for the relevant subpopulation.

AE: adverse event; EDSS: Expanded Disability Status Scale; EQ-5D: European Quality of Life-5 Dimensions; IFNβ: interferon beta; MFIS: Modified Fatigue Impact Scale; MSFC: Multiple Sclerosis Functional Composite; PT: Preferred Term; RCT: randomized controlled trial; SF-36: Short Form (36) Health Survey; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.4.2.2 Risk of bias

Table 22 shows the risk of bias for the relevant outcomes.

Table 22: Risk of bias at study and outcome level - RCT, direct comparison: ocrelizumab vs. IFNβ1a (pretreated patients with highly active RMS)

Study		Outcomes													
	Study level	All-cause mortality	Relapses	Disability progression (EDSS)	Disability severity (MSFC)	Fatigue interference (MFIS)	Health status (EQ-5D VAS)	Health-related quality of life (SF-36)	SAEs	Discontinuation due to AEs	Flu-like illness (AE, PT)	Injection site reactions (AE, PT)	Reaction associated with an infusion (AE, PT)	Infections and infestations (AE, SOC)	Depression (AE, PT)
OPERA I, II	L	L	L	L	H[a, b]	H[a, b]	H[a, b]	H[a, b]	L	L	L	L	L	L	-[c]

a: High proportion of patients not included in the analysis (> 10%) or because this proportion differed between the treatment groups to a relevant degree (> 5 percentage points).
b: Selective reporting is possible because the analyses presented deviate from the analyses planned a priori.
c: No data available for the relevant subpopulation.
AE: adverse event; EDSS: Expanded Disability Status Scale; EQ-5D: European Quality of Life-5 Dimensions; H: high; IFNβ: interferon beta; L: low; MFIS: Modified Fatigue Impact Scale; MSFC: Multiple Sclerosis Functional Composite; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SF36: Short Form (36) Health Survey; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

The risk of bias at outcome level on research question 2 corresponds to that of research question 1 (see Section 2.3.2.2), with the difference that usable data on the harm outcome "depression" for the present research question 2 are missing.

Overall assessment of the certainty of conclusions

Due to the missing information on patient characteristics (data on disease, prior therapies etc.), subgroup data and AEs for the relevant subpopulation, and because the composition of the relevant subpopulation was not completely comprehensible, at most indications, e.g. of an added benefit, can be determined on the basis of the available data.

Additionally, there was a high risk of bias at outcome level for the outcomes "disability severity", "fatigue interference", "health status" and "health-related quality of life" because the proportion of patients who were not considered in the relevant analyses was high or the proportion of patients who were not considered differed significantly between the treatment groups (> 5 percentage points). Moreover, these outcomes might have been subject to selective reporting, since the analyses on these outcomes presented in Module 4 A (adjusted covariance analyses) do not correspond to the predefined analyses in the study protocol (MMRM).

2.4.2.3 Results

Table 23 to Table 24, Table 25 and Table 26 summarize the results on the comparison of ocrelizumab with IFNβ1a in pretreated patients with highly active RMS. Where necessary, calculations conducted by the Institute were provided in addition to the data from the company's dossier. Kaplan-Meier curves for the outcomes "time to first relapse" and "time to first confirmed disability progression" (after 24 weeks) can be found in Appendix B.1 of the full dossier assessment. The forest plots of the meta-analyses calculated by the Institute can be found in Appendix B.2 of the full dossier assessment. The company's dossier contained no complete lists of the AEs for the relevant subpopulation. Therefore, common AEs were not presented for research question 2. The choice of specific AEs on the basis of the frequency was thus impossible.

MMRM analyses on the continuous data were predefined in the statistical analysis plan. However, the dossier only includes analyses from covariance analyses. In the present benefit assessment, the respective covariance analyses were used for the analyses of continuous data on the outcomes "disability severity", "fatigue interference", "health status" and "health-related quality of life".

Table 23: Results (mortality, side effects) – RCT, direct comparison: ocrelizumab vs. IFNβ1a (pretreated patients with highly active RMS)

Outcome category Outcome Study	Ocrelizumab N	Ocrelizumab Patients with event n (%)	IFNβ1a N	IFNβ1a Patients with event n (%)	Ocrelizumab vs. IFNβ1a RR [95% CI]; p-value
Mortality					
All-cause mortality[a]					
OPERA I	53	0 (0)	59	0 (0)	-[b]
OPERA II	57	1 (1.8)	46	1 (2.2)	0.81 [0.05; 12.55]; 0.878
Total					0.81 [0.05; 12.55]; 0.878
Side effects					
AEs (supplementary information)					
OPERA I	53	49 (92.5)	59	48 (81.4)	-
OPERA II	57	50 (87.7)	46	38 (82.6)	-
SAEs					
OPERA I	53	4 (7.5)	59	6 (10.2)	0.74 [0.22; 2.49]; 0.629[c]
OPERA II	57	4 (7.0)	46	4 (8.7)	0.81 [0.21; 3.05]; 0.752[c]
Total					0.77 [0.32; 1.88]; 0.568[d]
Discontinuation due to AEs					
OPERA I	53	2 (3.8)	59	4 (6.8)	0.56 [0.11; 2.92]; 0.488[c]
OPERA II	57	1 (1.8)	46	1 (2.2)	0.81 [0.05; 12.55]; 0.878[c]
Total					0.61 [0.15; 2.50]; 0.496[d]
Flu-like illness					
OPERA I	53	2 (3.8)	59	14 (23.7)	0.16 [0.04; 0.67]; 0.012[c]
OPERA II	57	1 (1.8)	46	7 (15.2)	0.12 [0.01; 0.90]; 0.040[c]
Total					0.14 [0.04; 0.46]; 0.001[d]

(continued)

Table 23: Results (mortality, side effects) – RCT, direct comparison: ocrelizumab vs. IFNβ1a (pretreated patients with highly active RMS) (continued)

Outcome category Outcome Study	Ocrelizumab N	Ocrelizumab Patients with event n (%)	IFNβ1a N	IFNβ1a Patients with event n (%)	Ocrelizumab vs. IFNβ1a RR [95% CI]; p-value
Injection site reactions					
OPERA I	53	0 (0)	59	3 (5.1)	0.16 [0.01; 3.00][e]; ND
OPERA II	57	0 (0)	46	2 (4.3)	0.16 [0.01; 3.29][e]; ND
Total					0.16 [0.02; 1.32]; 0.089[f]
Reaction associated with an infusion					
OPERA I	53	23 (43.4)	59	6 (10.2)	4.27 [1.88; 9.67]; < 0.001[c]
OPERA II	57	22 (38.6)	46	5 (10.9)	3.55 [1.46; 8.65]; 0.005[c]
Total					3.94 [2.15; 7.20]; < 0.001[d]
Infections and infestations[g]					
OPERA I	53	39 (73.6)	59	33 (55.9)	1.32 [1.00; 1.74]; 0.053[c]
OPERA II	57	38 (66.7)	46	27 (58.7)	1.14 [0.84; 1.54]; 0.412[c]
Total					1.23 [1.00; 1.52]; 0.047[d]
Depression	No usable data[h]				

a: Clinical data cut-off: OPERA I (2 April 2015) and OPERA II (12 May 2015).
b: No presentation of effect estimation and CI as these are not informative.
c: Effect estimate 95% CI: generalized linear regression model; p-value: Wald test.
d: Calculation using the IPD meta-analysis.
e: Institute's calculation.
f: Institute's calculation using meta-analysis with fixed effect.
g: No data on the SOC "infections and infestations" were available for the relevant subpopulation. The AE data of the category "infections" of Module 4 A of the dossier were used (for reasons, see Section 2.7.2.4.3 of the full dossier assessment).
h: No data available for the relevant subpopulation.
CI: confidence interval; IFN-β: interferon beta; IPD: individual patient data; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RMS: relapsing multiple sclerosis; RR: relative risk; vs.: versus

Table 24: Results (morbidity, annualized relapse rate) – RCT, direct comparison: ocrelizumab vs. IFNβ1a (pretreated patients with highly active RMS)

Outcome category Outcome Study	Ocrelizumab			IFNβ1a			Ocrelizumab vs. IFNβ1a
	N	n/Patient years	Annualized relapse rate [95% CI][a]	N	n/Patient years	Annualized relapse rate [95% CI][a]	Rate ratio [95% CI]; p-value[a]
Morbidity							
Relapses (based on EDSS)							
Annualized relapse rate							
OPERA I	54	16/91.1	0.20 [0.11; 0.35]	59	35/93.0	0.47 [0.29; 0.77]	0.42 [0.20; 0.86]; 0.016
OPERA II	57	7/100.8	0.07 [0.03; 0.16]	47	19/73.2	0.25 [0.12; 0.51]	0.26 [0.09; 0.74]; 0.011
Total							0.36 [0.20; 0.65]; < 0.001[b]
Annualized relapse rate by severity – moderate/ severe (additional information)							
OPERA I	*54*	*8/91.1*	*0.10 [0.05; 0.22]*	*59*	*19/93.0*	*0.25 [0.14; 0.46]*	*0.40 [0.16; 1.03]; 0.053*
OPERA II	*57*	*3/100.8*	*0.02 [0.003; 0.08]*	*47*	*11/73.2*	*0.08 [0.02; 0.27]*	*0.21 [0.05; 0.92]; 0.035*
Total							*0.32 [0.14; 0.72]; 0.005[b]*
annualized relapse rate by severity – severe (additional information)							
OPERA I	*54*	*2/91.1*	*0.02 [0.01; 0.10]*	*59*	*4/93.0*	*0.06 [0.02; 0.16]*	*-[c]*
OPERA II	*57*	*0/100.8*	*-[c]*	*47*	*1/73.2*	*-[c]*	*-[c]*
Total							*0.36 [0.07; 1.91]; 0.208[b]*

a: Adjusted annualized relapse rate, effect measure, CI and p-value from negative binomial model, adjusted for region and EDSS at the start of the study.
b: Calculation using the IPD meta-analysis.
c: No presentation of effect estimation and CI as these are not informative.

CI: confidence interval; EDSS: Expanded Disability Status Scale; IFN-β: interferon beta; IPD: individual patient data; n: number of relapses; N: number of analysed patients; RCT: randomized controlled trial; vs.: versus

Table 25: Results (morbidity, time to event) – RCT, direct comparison: ocrelizumab vs. IFNβ1a (pretreated patients with highly active RMS)

Outcome category Outcome Study	Ocrelizumab N	Ocrelizumab Median time to event in months [95% CI] Patients with event n (%)	IFNβ1a N	IFNβ1a Median time to event in months [95% CI] Patients with event n (%)	Ocrelizumab vs. IFNβ1a HR [95% CI]; p-value
Morbidity					
Relapses (based on EDSS) (additional information)					
OPERA I	*54*	*NA* *12 (22.2)*	*59*	*NA [19.0; NA]* *22 (37.3)*	*0.44 [0.22; 0.91];* *0.022*[a]
OPERA II	*57*	*NA* *7 (12.3)*	*47*	*NA* *11 (23.4)*	*0.45 [0.17; 1.15];* *0.087*[a]
Total					*0.44 [0.25; 0.79];* *0.004*[b]
Confirmed disability progression (based on EDSS)[c]					
OPERA I	54	NA 3 (5.6)	59	NA 8 (13.6)	0.38 [0.10; 1.45]; 0.144[a]
OPERA II	57	NA 6 (10.5)	47	NA 6 (12.8)	0.72 [0.23; 2.23]; 0.568[a]
Total					0.54 [0.23; 1.27]; 0.154[b]

a: Effect measure and 95% CI from Cox proportional hazards model, stratified by region and EDSS at the start of the study; p-value: log-rank test.
b: Calculation using the IPD meta-analysis.
c: Event time analyses with imputation of missing values according to imputation strategy 1 (see Section 2.7.2.4.3 of the full dossier assessment).

CI: confidence interval; EDSS: Expanded Disability Status Scale; HR: hazard ratio; IFN-β: interferon beta; IPD: individual patient data; n: number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial; vs.: versus

Table 26: Results (morbidity, continuous) – RCT, direct comparison: ocrelizumab vs. IFNβ1a (pretreated patients with highly active RMS)

Outcome category Outcome Study	Ocrelizumab			IFNβ1a			Ocrelizumab vs. IFNβ1a
	N[a]	Values at start of study mean (SD)	Change at week 96 mean (SE)[b]	N[a]	Values at start of study mean (SD)	Change at week 96 mean (SE)[b]	MD [95% CI]; p-value[b]
Morbidity							
Disability severity (MSFC z-score)[c]							
OPERA I	41	-0.05 (0.74)	0.26 (0.09)	44	0.14 (0.60)	0.26 (0.09)	0.00 [-0.22; 0.23]; 0.978
OPERA II	43	-0.03 (0.50)	0.41 (0.06)	30	-0.05 (0.66)	0.10 (0.07)	0.32 [0.15; 0.48]; < 0.001 Hedges' g: 0.89 [0.41; 1.38][d]
Total	Heterogeneity: Q = 5.05; df = 1; p = 0.025; I^2 = 80.2%[e]						
Disability severity Timed 25-Foot Walk[f, g]							
OPERA I	43	-	0.96 [0.85; 1.08][h]	45	-	1.04 [0.92; 1.19][h]	ROM: 0.92 [0.78; 1.08]; ND.[j]
OPERA II	45	-	0.89 [0.79; 1.01][h]	34	-	1.12 [0.97; 1.30][h]	ROM: 0.79 [0.66; 0.96]; ND.[j]
Total							ROM: 0.85 [0.75; 0.95]; ND.[i]
Disability severity 9-Hole Peg Test[f, g]							
OPERA I	42	-	0.93 [0.89; 0.97][h]	47	-	0.93 [0.89; 0.97][h]	ROM: 1.00 [0.95; 1.06]; ND.[j]
OPERA II	48	-	0.89 [0.85; 0.94][h]	35	-	1.00 [0.94; 1.06][h]	ROM: 0.89 [0.83; 0.96]; ND.[j]
Total	Heterogeneity: Q = 6.29; df=1; p = 0.012; I^2 = 84.1%[e]						
Disability severity PASAT[c]							
OPERA I	43	45.38 (10.87)	4.19 (1.49)	45	44.39 (12.04)	6.64 (1.58)	-2.45 [-6.29; 1.39]; 0.208
OPERA II	46	40.19 (12.12)	8.77 (1.31)	31	39.44 (12.75)	5.96 (1.59)	2.82 [-1.07; 6.70]; 0.153
Total							-0.12 [-2.85; 2.60]; 0.928[i]

(continued)

Table 26: Results (morbidity, continuous) – RCT, direct comparison: ocrelizumab vs. IFNβ1a (pretreated patients with highly active RMS) (continued)

Fatigue interference							
MFIS total score[f]							
OPERA I	41	38.88 (20.52)	-3.13 (2.24)	45	35.79 (20.07)	-8.90 (2.44)	5.77 [0.00; 11.54]; 0.0499
OPERA II	44	39.31 (20.74)	-4.08 (2.54)	30	35.09 (19.50)	-3.22 (2.98)	-0.86 [-8.32; 6.60]; 0.819
Total							2.27 [-2.36; 6.90]; 0.334[i]
Outcome category	**Ocrelizumab**			**IFNβ1a**			**Ocrelizumab vs. IFNβ1a**
Outcome							
Study	**N[a]**	**Values at start of study mean (SD)**	**Change at week 96 mean (SE)[b]**	**N[a]**	**Values at start of study mean (SD)**	**Change at week 96 mean (SE)[b]**	**MD [95% CI]; p-value[b]**
Fatigue MFIS cognitive[f]							
OPERA I	41	16.62 (10.15)	-0.82 (1.02)	45	15.45 (9.41)	-3.00 (1.12)	2.18 [-0.48; 4.83]; 0.106
OPERA II	44	16.17 (10.61)	-0.80 (1.23)	30	14.63 (9.06)	-0.80 (1.44)	0.00 [-3.63; 3.62]; 0.998
Total							0.94 [-1.24; 3.11]; 0.396[i]
Fatigue MFIS physical[f]							
OPERA I	41	19.24 (10.06)	-2.17 (1.19)	45	17.16 (10.04)	-4.77 (1.29)	2.61 [-0.43; 5.65]; 0.092
OPERA II	44	19.61 (9.59)	-2.94 (1.20)	30	17.22 (9.70)	-2.43 (1.41)	-0.51 [-4.04; 3.01]; 0.772
Total							1.06 [-1.24; 3.35]; 0.365[i]
Fatigue MFIS psychosocial[f]							
OPERA I	41	3.02 (2.25)	0.08 (0.29)	45	3.18 (2.36)	-0.87 (0.32)	0.95 [0.18; 1.72]; 0.016
OPERA II	44	3.54 (2.30)	-0.35 (0.28)	30	3.24 (2.19)	-0.02 (0.34)	-0.33 [-1.16; 0.51]; 0.442
Total	Heterogeneity: Q = 4.88; df = 1; p = 0.027; I^2 = 79.5%[e]						
Health status (EQ-5D VAS[c])							
OPERA I	41	69.78 (18.69)	-1.89 (2.43)	46	70.27 (17.38)	4.17 (2.61)	-6.06 [-12.27; 0.16]; 0.056
OPERA II	44	66.56 (19.97)	7.87 (2.68)	30	73.11 (16.73)	5.52 (3.17)	2.34 [-5.66; 10.35]; 0.561
Total							-1.90 [-6.81; 3.01]; 0.446[i]

(continued)

Table 26: Results (morbidity, continuous) – RCT, direct comparison: ocrelizumab vs. IFNβ1a (pretreated patients with highly active RMS) (continued) (continued)

Health-related quality of life							
SF-36 PCS[c]							
OPERA I	42	41.57 (10.19)	-0.01 (1.25)	46	44.84 (8.37)	2.40 (1.30)	-2.41 [-5.53; 0.71]; 0.128
OPERA II	47	40.99 (10.98)	2.29 (1.18)	30	44.30 (9.65)	1.07 (1.42)	1.22 [-2.30; 4.75]; 0.491
Total							-0.72 [-3.07; 1.63]; 0.544[i]
Outcome category **Outcome**	**Ocrelizumab**			**IFNβ1a**			**Ocrelizumab vs. IFNβ1a**
Study	**N[a]**	**Values at start of study mean (SD)**	**Change at week 96 mean (SE)[b]**	**N[a]**	**Values at start of study mean (SD)**	**Change at week 96 mean (SE)[b]**	**MD [95% CI]; p-value[b]**
SF-36 physical functioning[c]							
OPERA I	42	64.81 (25.22)	-3.65 (3.14)	46	70.71 (24.05)	3.07 (3.32)	-6.72 [-14.48; 1.04]; 0.089
OPERA II	47	59.29 (27.33)	8.20 (2.83)	30	64.02 (28.36)	3.98 (3.48)	4.22 [-4.28; 12.72]; 0.325
Total							-1.60 [-7.30; 4.11]; 0.582[i]
SF-36 physical role functioning[c]							
OPERA I	42	56.49 (30.32)	2.40 (3.63)	46	60.38 (25.12)	7.12 (3.89)	-4.72 [-13.98; 4.54]; 0.314
OPERA II	47	50.33 (33.74)	10.15 (3.24)	30	58.83 (28.52)	8.21 (3.97)	1.94 [-7.84; 11.72]; 0.694
Total							-1.52 [-8.17; 5.14]; 0.653[i]
SF-36 bodily pain[c]							
OPERA I	42	62.69 (29.63)	−1.61 (3.69)	46	66.64 (24.87)	2.67 (3.96)	-4.28 [-13.82; 5.27]; 0.375
OPERA II	47	62.09 (25.81)	3.55 (3.32)	30	69.76 (24.43)	-1.03 (4.08)	4.58 [-5.59; 14.75]; 0.372
Total							0.67 [-6.26; 7.60]; 0.849[i]
SF-36 general health perception[c]							
OPERA I	42	47.81 (20.94)	6.03 (2.62)	46	50.36 (19.11)	8.48 (2.80)	-2.44 [-9.15; 4.26]; 0.471
OPERA II	47	51.34 (22.72)	8.72 (2.47)	30	55.13 (17.86)	3.55 (3.05)	5.17 [-2.43; 12.78]; 0.180
Total							0.84 [-4.13; 5.81]; 0.739[i]

(continued)

Table 26: Results (morbidity, continuous) – RCT, direct comparison: ocrelizumab vs. IFNβ1a (pretreated patients with highly active RMS) (continued) (continued)

SF-36 MCS[c]							
OPERA I	42	44.67 (12.34)	2.89 (1.59)	46	41.31 (11.30)	2.79 (1.72)	0.10 [-4.10; 4.30]; 0.962
OPERA II	47	42.43 (14.01)	5.67 (1.38)	30	42.48 (11.86)	2.85 (1.73)	2.82 [-1.44; 7.08]; 0.191
Total							1.82 [-1.10; 4.74]; 0.220[i]
Outcome category **Outcome**	**Ocrelizumab**			**IFNβ1a**			**Ocrelizumab vs. IFNβ1a**
Study	**N[a]**	**Values at start of study mean (SD)**	**Change at week 96 mean (SE)[b]**	**N[a]**	**Values at start of study mean (SD)**	**Change at week 96 mean (SE)[b]**	**MD [95% CI]; p-value[b]**
SF-36 vitality[c]							
OPERA I	42	47.00 (23.10)	2.10 (2.84)	46	43.30 (21.35)	10.18 (3.12)	-8.08 [-15.54; -0.63]; 0.034
OPERA II	47	44.64 (25.41)	10.29 (2.84)	30	46.88 (21.15)	4.00 (3.53)	6.29 [-2.43; 15.01]; 0.155
Total	Heterogeneity: Q = 6.03; df = 1; p = 0.014; I^2 = 83.4%[e]						
SF-36 social functioning[c]							
OPERA I	42	66.59 (28.94)	4.31 (3.52)	46	66.52 (25.13)	5.08 (3.82)	-0.77 [-9.89; 8.36]; 0.868
OPERA II	47	60.27 (28.42)	7.14 (3.76)	30	64.95 (25.09)	3.62 (4.67)	3.52 [-8.05; 15.09]; 0.546
Total							1.95 [-5.21; 9.10]; 0.592[i]
SF-36 emotional role functioning[c]							
OPERA I	42	71.96 (27.27)	1.81 (3.34)	46	67.71 (25.72)	2.42 (3.61)	-0.61 [-9.33; 8.10]; 0.889
OPERA II	47	66.37 (31.50)	8.82 (3.09)	30	68.48 (26.52)	7.30 (3.85)	1.52 [-7.95; 11.00]; 0.749
Total							1.17 [-5.16; 7.51]; 0.715[i]
SF-36 mental wellbeing[c]							
OPERA I	42	66.35 (20.80)	5.64 (2.71)	46	62.23 (19.68)	4.12 (2.96)	1.52 [-5.66; 8.70]; 0.675
OPERA II	47	62.95 (23.58)	11.49 (2.29)	30	63.04 (21.28)	4.15 (2.87)	7.34 [0.27; 14.41]; 0.042
Total							4.38 [-0.52; 9.29]; 0.080[i]

(continued)

Table 26: Results (morbidity, continuous) – RCT, direct comparison: ocrelizumab vs. IFNβ1a (pretreated patients with highly active RMS) (continued)

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: Effect estimate, CI and p-value from ANCOVA analysis adjusted for region and EDSS at the start of the study.
c: A positive change from the start until the end of the study indicates improvement; a positive effect estimate indicates an advantage for ocrelizumab.
d: Institute's calculation.
e: Institute's calculation using meta-analysis with fixed effect.
f: A negative change from the start until the end of the study indicates improvement; a negative effect estimate indicates an advantage of ocrelizumab.
g: Presumably ANCOVA analysis adjusted for region and EDSS at the start of the study with adjusted change in relation to the baseline value as outcome variable.
h: Presumably adjusted geometric mean; 95% CI.
i: Calculation using the IPD meta-analysis.
j: Presumably ratio of the adjusted geometric means.
ANCOVA: Analysis of Covariance; CI: confidence interval; EDSS: Expanded Disability Status Scale; EQ-5D: European Quality of Life Questionnaire 5-Dimensions; IFN-β: interferon beta; IPD: individual patient data; MCS: Mental Component Summary scale; MD: mean difference; MFIS: Modified Fatigue Impact Scale; MSFC: Multiple Sclerosis Functional Composite; N: number of analysed patients; PASAT: Paced Auditory Serial Addition Test; PCS: Physical Component Summary scale; RCT: randomized controlled trial; ROM: Ratio of Means; SD: standard deviation; SE: standard error; SF-36: Short Form (36) Health Survey; VAS: visual analogue scale; vs.: versus

As shown in Section 2.4.2.2, the certainty of conclusions of the results on the basis of the available data was reduced. Hence, at most indications, e.g. of an added benefit, can be determined for the outcomes. This deviates from the approach of the company, which rated the certainty of conclusions as proven for all outcomes.

Mortality

All-cause mortality

On the outcome "all-cause mortality" there was altogether one event in the ocrelizumab arm and one event in the IFNβ1a arm of the OPERA studies. Overall, this resulted in no hint of an added benefit of ocrelizumab in comparison with IFNβ 1a; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Relapses (based on EDSS)

The annualized relapse rate was considered to be the decisive operationalization for the outcome "relapses". The meta-analysis showed a statistically significant difference in favour of ocrelizumab in comparison with IFNβ1a. This resulted in an indication of an added benefit of ocrelizumab in comparison with IFNβ1a for the outcome "relapses".

This concurs with the company's assessment.

The operationalizations “relapses by severity grade” (moderate/severe or severe) presented as supplementary information, and the “time to first confirmed relapse” showed less relapses in the ocrelizumab arm than in the IFNβ1a arm of the OPERA studies.

Confirmed disability progression (based on EDSS)

The time to first disability progression is used for the outcome “confirmed disability progression”. The meta-analysis showed no statistically significant difference between the treatment groups for the outcome “confirmed disability progression”. This resulted in no hint of an added benefit of ocrelizumab in comparison with IFNβ1a, an added benefit is therefore not proven.

This concurs with the company’s assessment.

Disability severity (MSFC z-score)

The mean difference from the covariance analysis from the start of the study to week 96 was considered for the outcome “disability severity” recorded with the MSFC z-score. The meta-analysis showed important unexplained heterogeneity without effects in the same direction. This resulted in no hint of an added benefit of ocrelizumab in comparison with IFNβ1a, an added benefit is therefore not proven.

In the result, this concurs with the company’s assessment. The company assessed this outcome under the outcome “disability progression” and used responder analyses on the MSFC z-score as well as on the MSFC subscales for the assessment, but derived no added benefit on the basis of these analyses.

Fatigue interference (MFIS)

The mean difference from the covariance analysis from the start of the study to week 96 was considered for the outcome “fatigue interference” recorded with the MFIS. The meta-analysis showed no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of ocrelizumab in comparison with IFNβ1a, an added benefit is therefore not proven.

In the result, this concurs with the company’s assessment. However, the company used responder analyses for the assessment of MFIS and derived no added benefit.

Health status (EQ-5D VAS)

The mean difference from the covariance analysis from the start of the study to week 96 was considered for the outcome “health status” recorded with the EQ-5D VAS. The meta-analysis showed no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of ocrelizumab in comparison with IFNβ1a, an added benefit is therefore not proven.

In the result, this concurs with the company's assessment, which, however, uses responder analyses for its assessment.

Health-related quality of life

SF-36

For the SF-36, the PCS and MCS were considered separately. The mean difference from the start of the study until week 96 from the covariance analysis was considered for each summary score. However, the meta-analysis showed no statistically significant difference for both sum scores. Overall, this resulted in no hint of an added benefit of ocrelizumab in comparison with IFNβ1a for the SF-36, an added benefit is therefore not proven.

In the result, this concurs with the company's assessment, which, however, considered responder analyses for this outcome.

Side effects

SAEs and discontinuation due to AEs

The meta-analysis showed no statistically significant difference between the treatment groups for the outcomes "SAEs" and "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from ocrelizumab in comparison with IFNβ1a, greater or lesser harm is therefore not proven.

This concurs with the company's assessment for both outcomes.

Specific AEs

Flu-like illness

The meta-analysis showed a statistically significant difference in favour of ocrelizumab for the outcome "flu-like illness". This resulted in an indication of lesser harm from ocrelizumab in comparison with IFNβ1a.

This concurs with the company's assessment.

Injection site reactions

The meta-analysis showed no statistically significant difference between the treatment groups for the outcome "injection site reactions". This resulted in no hint of lesser or greater harm from ocrelizumab in comparison with IFNβ1a, greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Reaction associated with an infusion as well as infections and infestations

The meta-analysis showed a statistically significant difference to the disadvantage of ocrelizumab each for the outcomes "reaction associated with an infusion" and "infections and infestations". In each case, this resulted in an indication of greater harm from ocrelizumab in comparison with IFNβ1a.

This concurs with the company's assessment.

Depression

The dossier contained no usable data on the outcome "depression" for the relevant subpopulation. This resulted in no hint of lesser or greater harm from ocrelizumab in comparison with IFNβ1a, greater or lesser harm is therefore not proven.

The company does not assess the outcome "depression" in the context of the side effects.

2.4.2.4 Subgroups and other effect modifiers

The company presented subgroup analyses for the relevant subpopulation, i.e. pretreated patients with highly active RMS, only for outcomes on side effects. For all other outcomes, the company's dossier only includes subgroup analyses on the basis of the total populations of the OPERA I and II studies. However, these subgroup analyses cannot be used for the present research question.

2.4.3 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below. The various outcome categories and the effect sizes are taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The procedure for deriving an overall conclusion on the added benefit based on the aggregation of the conclusions deduced at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.4.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4.2.3 (see Table 27).

Determination of the outcome category for the outcomes "symptoms" and "side effects"

In its dossier, the company presented no information that would allow an assessment of the severity category for the outcomes on the relevant subpopulation considered in the present benefit assessment. The relevant outcomes "relapses", "flu-like illness", "reaction associated with an infusion and infections and infestations" are therefore allocated to the category non-serious/non-severe symptoms/late complications" or "side effects".

Table 27: Extent of added benefit at outcome level: ocrelizumab vs. IFNβ1a (pretreated patients with highly active RMS)

Outcome category **Outcome**	**Ocrelizumab vs. IFNβ1a** **Median time to event (months) or proportion of events (%) or MD or annual rate** **Effect estimate [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality	0-1.8% vs. 0-2.2% RR: 0.81 [0.05; 12.55] p = 0.878	Lesser benefit/added benefit not proven
Morbidity		
Relapses		
annualized relapse rate	Rate: 0.07-0.20 vs. 0.25 -0.47[c] Rate ratio: 0.36 [0.20; 0.65]; p = 0.001 Probability: "indication"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
Confirmed disability progression		
time to first confirmed disability progression	Median: NA vs. NA HR: 0.54 [0.23; 1.27] p = 0.154	Lesser benefit/added benefit not proven
Disability severity		
Multiple Sclerosis Functional Composite (MSFC) z-score	Heterogeneous results without effects in the same direction[d]	Lesser benefit/added benefit not proven
Fatigue interference		
MFIS	-4.08 to 3.13 vs. -8.90 to -3.22[c] MD: 2.27 [-2.36; 6.90]; p = 0.334	Lesser benefit/added benefit not proven
Health status		
EQ-5D VAS	-1.89 to 7.87 vs. 4.17 to 5.52[c] MD: -1.90 [-6.81; 3.01]; p = 0.446	Lesser benefit/added benefit not proven
Health-related quality of life		
SF-36		
PCS	-0.01 to 2.29 vs. 1.07 to 2.40[c] MD: -0.72 [-3.07; 1.63]; p = 0.544	Lesser benefit/added benefit not proven
MCS	2.89–5.67 vs. 2.79–2.85[c] MD: 1.82 [-1.10; 4.74]; p = 0.220	Lesser benefit/added benefit not proven

(continued)

Table 27: Extent of added benefit at outcome level: ocrelizumab vs. IFNβ1a (pretreated patients with highly active RMS) (continued)

Outcome category **Outcome**	**Ocrelizumab vs. IFNβ1a** **Median time to event (months) or proportion of events (%) or MD or annual rate** **Effect estimate [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Side effects		
SAEs	7.0-7.5% vs. 8.7-10.2% RR: 0.77 [0.32; 1.88] p = 0.568	Greater/lesser harm not proven
Discontinuation due to AEs	1.8-3.8% vs. 2.2-6.8% RR: 0.61 [0.15; 2.50] p = 0.496	Greater/lesser harm not proven
Flu-like illness	1.8–3.8% vs. 15.2–23.7% RR: 0.14 [0.04; 0.46] p = 0.001 probability: "indication"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Injection site reactions	0% vs. 4.3–5.1% RR: 0.16 [0.02; 1.32] p = 0.089	Greater/lesser harm not proven
Reaction associated with an infusion	38.6-43.4% vs. 10.2-10.9% RR: 3.94 [2.15; 7.20]; p < 0.001 RR: 0.25 [0.14; 0.47][e] probability: "indication"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm, extent: "considerable"
Infections and infestations	66.7-73.6% vs. 55.9-58.7% RR: 1.23 [1.00; 1.52] p = 0.047 RR: 0.81 [0.66; 1.00]	Outcome category: "non-serious/non-severe symptoms/late complications" $0.90 \leq CI_u < 1.00$ greater/lesser harm not proven[f]
Depression	No usable data	Greater/lesser harm not proven

a: Probability provided if statistically significant differences are present.
b: Estimations of effect size were made depending on the outcome category with different limits based on the CI_u.
c: Minimum and maximum change at week 96 or annual rate per treatment arm in the studies included.
d: Provision of a common effect estimate is not meaningful due to heterogeneous data.
e: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
f: The extent of the effect in this non-serious/non-severe outcome was no more than marginal.

AE: adverse event; CI: confidence interval; IFN-β: interferon beta; CIu: upper limit of confidence interval; MCS: Mental Component Summary; MD: mean difference; MFIS: Modified Fatigue Impact Scale; MSFC: Multiple Sclerosis Functional Composite; NA: not achieved; PASAT: Paced Auditory Serial Addition Test; PCS: Physical Component Summary scale; RR: relative risk; SF 36: SF-36: Short Form (36) Health Survey; SAE: serious adverse event; vs.: versus

2.4.3.2 Overall conclusion on added benefit

Table 28 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 28: Positive and negative effects from the assessment of ocrelizumab in comparison with IFNβ1a (pretreated patients with highly active RMS)

Positive effects	Negative effects
Non-serious/non-severe symptoms/late complications ▪ Relapses: indication of an added benefit – extent: "considerable"	
Outcome category: non-serious/non-severe side effects ▪ Specific AE (flu-like illness): indication of lesser harm – extent: "considerable"	Outcome category: non-serious/non-severe side effects ▪ Specific adverse event (AE) (reaction associated with an infusion): indication of greater harm extent "considerable"
AE: adverse event; IFN-β: interferon beta	

In the overall consideration, there were two positive effects and one negative effect of ocrelizumab in comparison with IFNβ1a in the outcome categories "morbidity" and "side effects", all of them with considerable extent.

In summary, there is an indication of considerable added benefit of ocrelizumab vs. the ACT IFNβ1a for pretreated patients with highly active RMS.

2.4.4 List of included studies

The list of the studies included on research question 2 corresponds to the one of research question 1 (see Section 2.3.4).

2.5 Research question 3: Patients with early PPMS

2.5.1 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 ocrelizumab (status: 18 October 2017)
- bibliographical literature search on ocrelizumab (last search on 14 February 2018)
- search in trial registries for studies on ocrelizumab (last search on 14 February 2018)

To check the completeness of the study pool:

- search in trial registries for studies on ocrelizumab (last search on 29 January 2018)

The check identified no additional relevant study.

2.5.1.1 Studies included

The study shown in the following table is included in the benefit assessment of ocrelizumab in comparison with BSC in patients with early PPMS.

Table 29: Study pool – RCT, direct comparison: ocrelizumab + BSC vs. placebo + BSC

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
WA25046 (ORATORIO[b])	Yes	Yes	No

a: Study sponsored by the company.
b: In the following tables, the study is referred to with this abbreviated form.
BSC: best supportive care; RCT: randomized controlled trial; vs.: versus

Section 2.5.4 contains a reference list for the studies included.

2.5.1.2 Study characteristics

Table 30 and Table 31 describe the studies used for the benefit assessment.

Table 30: Characteristics of the study included – RCT, direct comparison: ocrelizumab + BSC vs. placebo + BSC

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ORATORIO	RCT, double-blind, parallel	Adults (18–55 years) with early PPMS, EDSS 3.0–6.5, disease duration since first occurrence of MS symptoms: < 15 years, when EDSS > 5.0 and < 10 years, when EDSS ≥ 5.0	ocrelizumab + BSC (N = 488) placebo + BSC (N = 244)	Screening: 4-8 weeks Treatment: at least 120 weeks and until occurrence of 253 confirmed cases of disability progression ▪ Optional extension phase (unblinded) of at most 4 years[b] Follow up observation: at least 48 weeks after the last administration of the study medication, also in case of participation in the extension phase	182 study centres in 29 countries in Europe, North and South America, Australia and Asia. Start of the study: 3 March 2011 Data cut-off 24 July 2015	Primary: disability progression Secondary: symptoms, health-related quality of life, AEs

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes exclusively include information on relevant available outcomes for this benefit assessment.
b: The optional extension phase had not yet started at the time point of the data cut-off.
AE: adverse event; BSC: Best supportive Care; EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; N: number of (included) randomized patients ; PPMS: primary progressive multiple sclerosis; RCT: randomized controlled trial; vs.: versus

Table 31: Characteristics of the interventions – RCT, direct comparison: ocrelizumab + BSC vs. placebo + BSC

Study	Intervention	Comparison
ORATORIO	Ocrelizumab ▪ 600 mg IV every 24 weeks administered as 2 doses of 300 mg each at 2-week intervals No dose adjustment planned, treatment interruption was allowed	Placebo for ocrelizumab ▪ Administered IV every 24 weeks two times each at 2-week intervals No dose adjustment planned, treatment interruption was allowed
	Premedication 100 mg methylprednisolone IV or an equivalent corticosteroid (e.g. dexamethasone) about 30 minutes before the infusion **Prohibited prior and concomitant treatment** ▪ Each experimental treatment within 24 weeks before the screening visit ▪ Immunomodulating therapy within 12 weeks before randomization ▪ Live vaccines within 6 weeks before randomization ▪ Pretreatment with immunosuppressants or systemic corticosteroids (within 4 weeks before screening) ▪ Other MS drugs or B cell-targeted therapies ▪ Administration of lymphocyte transport modulators (e.g. natalizumab, fingolimod) ▪ After treatment discontinuation as long as the number of B cells is reduced: any administration of immunosuppressants or lymphocyte-depleting drugs or lymphocyte transport modulators **Allowed concomitant treatment** ▪ Analgesics or antipyretics ▪ Antihistamines ▪ Systemic corticosteroids for the treatment of a relapse ▪ Therapies for symptom control	

BSC: best supportive care; IV: intravenous; MS: multiple sclerosis; RCT: randomized controlled trial; vs.: versus

Description of the study design

The ORATORIO study is a randomized, double-blind, placebo-controlled parallel-group study, which was conducted worldwide in 29 countries. The study investigated ocrelizumab in comparison with placebo in adults with early PPMS.

Adults (18 to 55 years) with PPMS according to the McDonald criteria of 2005 and an EDSS score of 3 to 6.5 points were included [10]. The total duration of the disease had to be < 15 years (for patients with an EDSS score of > 5 at the start of the study) or < 10 years (for patients with an EDSS score of ≤ 5 at the start of the study).

In the study, 732 patients were randomly allocated to the study arms ocrelizumab (N = 488) and placebo (N = 244) in a ratio of 2:1. Randomization was stratified by the factors “region” (USA vs. others) and “age” (≤ 45 years vs. > 45 years).

Treatment with ocrelizumab or placebo followed the regimen described in Table 31. Patients in both study arms also received BSC. The SPC of ocrelizumab recommends a dosage of 600 mg ocrelizumab as intravenous (IV) infusion every 6 months [4]. The initial dosage were to be administered in 2 infusions with 300 mg each at 2-week intervals. Regarding the dosage of the subsequent injections, the dosage in the ORATORIO study deviates from the SPC. Every 6 months, patients in the ORATORIO study received 2 infusions with 300 mg each at 2-week intervals. However, according to the EPAR of EMA on ocrelizumab, this changed dosing regimen has no impact on the effect of ocrelizumab [11]. It is therefore assumed that this deviation of the ocrelizumab dosage had no relevant influence on the study results.

The ACT BSC specified by the G-BA was adequately implemented in the ORATORIO study. According to the study protocol, the investigators had been instructed to provide the patients with individual supportive therapies (drug and non-drug treatments) to alleviate symptoms. The documentation of the concomitant medication in the study report confirms that these patient received BSC, which was comparable in both study arms.

Treatment duration was at least 120 weeks after inclusion of the last patient, provided that 253 confirmed cases of a confirmed disability progression (primary outcome) were available. Otherwise, treatment was continued until the required number of cases had been reached. Patients could then participate in an open-label extension phase for at most 4 years on a voluntary basis. Follow-up observation was at least 48 weeks, irrespective of a participation in the extension phase. The present assessment is exclusively based on data from the treatment and the follow-up observation phase.

Primary outcome of the study was the confirmed disability progression (after 12 weeks). Secondary outcomes are outcomes on “symptoms” and “health-related quality of life”, “health status” and “side effects”.

Description of the study population

Table 32 shows the characteristics of the patients in the study included.

Table 32: Characteristics of the study populations - RCT, direct comparison: ocrelizumab + BSC vs. placebo + BSC (patients with early PPMS)

Study Characteristics Category	**Ocrelizumab + BSC**	**Placebo + BSC**
ORATORIO	N[a] = 488	N[a] = 244
Age [years], mean (SD)	44.7 (7.9)	44.4 (8.3)
Sex [F/M],%	49/51	51/49
Ethnicity, n (%)		
White	454 (93.0)	235 (96.3)
Other	32 (6.6[c])	9 (3.7[c])
Unknown	2 (0.4)	0
EDSS at the start of the study, mean (SD)	4.7 (1.2)	4.7 (1.2)
Gd-enhancing T1-lesions, n (%)		
0	351 (73)	183 (75)
> 0	133 (27)	60 (25)
T2 lesions, n (%)		
0-5	50 (10)	29 (12)
6-9	11 (2)	6 (3)
> 9	425 (87)	208 (86)
Pretreatment with MS-modifying therapy, n (%)		
Yes	55 (11)	30 (12)
No	433 (89)	214 (88)
Time since occurrence of MS symptoms [years], mean (SD)	6.7 (4.0)	6.1 (3.6)
Time since PPMS diagnosis [years], mean (SD)	2.9 (3.2)	2.8 (3.3)
Treatment discontinuation, n (%)	101 (21[c])	82 (34[c])
Study discontinuation, n (%)	64 (13)[c]	48 (20)[c]

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Is composed of the ethnicities native American, black/African American and other ethnicities.
c: Institute's calculation.
BSC: best supportive care; EDSS: Expanded Disability Status Scale; F: female; Gd: Gadolinium; M: male; MS: multiple sclerosis; n: number of patients in the category; N: number of randomized (or included) patients; RCT: randomized controlled trial; PPMS: primary progressive multiple sclerosis; SD: standard deviation; vs.: versus

The patient characteristics were sufficiently balanced between the treatment groups of the ORATORIO study. The mean age of the patients was about 45 years, about half of them were female and about 95% where white. At the start of the study, the mean EDSS was 4.7, and almost 90% of the patients had not yet received disease-modifying pre-treatment. As already described on the inclusion criteria, the study included patients with early PPMS, which is also reflected by the patient characteristics. For instance, the mean total disease duration of the patients was about 6 years. On average, PPMS had been diagnosed nearly 3 years ago.

Overall, more patients discontinued treatment in the placebo + BSC arm (34%) than in the ocrelizumab + BSC arm (21%) of the study. The main reason for treatment discontinuation in the placebo + BSC arm was the lack of effectiveness (11.1%) withdrawal of informed consent (8.6%). Reasons for treatment discontinuation in the ocrelizumab + BSC arm was the lack of effectiveness (4.3%) or the withdrawal of the informed consent (4.5%). Reasons for a withdrawal of the informed consent were lack of effectiveness, disease progression, personal reasons, wish for another treatment, move or the desire to have children. The proportion of patients who discontinued the study was also higher in the placebo + BSC arm (20%) than in the ocrelizumab + BSC arm (13%) of the study.

Risk of bias

Table 33 shows the risk of bias at study level.

Table 33: Risk of bias at study level - RCT, direct comparison: ocrelizumab + BSC vs. placebo + BSC (patients with early PPMS)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
ORATORIO	Yes	Yes	Yes	Yes	Yes	Yes	Low
BSC: best supportive care; RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level for the ORATORIO study was rated as low. This concurs with the company's assessment.

2.5.2 Results on added benefit

2.5.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - All-cause mortality
- Morbidity
  - Confirmed disability progression (based on EDSS)
  - Disability severity (based on MSFC)
  - Fatigue interference measured with the MFIS

- Health status, measured using the EQ-5D VAS

- Health-related quality of life
  - Measured using the SF-36.

- Side effects
  - SAEs
  - Discontinuation due to AEs
  - Reaction associated with an infusion
  - Infections and infestations
  - Depression
  - If applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4) (see Section 2.7.2.4.3 of the full dossier assessment).

Table 34 shows for which outcomes data were available in the studies included.

Table 34: Matrix of the outcomes - RCT, direct comparison: ocrelizumab + BSC vs. placebo + BSC (patients with early PPMS)

Study	Outcomes										
	All-cause mortality	**Confirmed disability progression (EDSS)**	**Disability severity (MSFC)**	**Fatigue interference (MFIS)**	**Health status (EQ-5D VAS)**	**Health-related quality of life (SF-36)**	**SAEs**	**Discontinuation due to AEs**	**Reaction associated with an infusion (AE, PT)**	**Infections and infestations (AE, SOC)**	**Depression (AE, PT)**
ORATORIO	Yes	Yes	Yes	No[a]	No[a]	No[a]	Yes	Yes	Yes	Yes	Yes

a: No usable data were available for the relevant operationalization; proportion of patients not considered in the analysis was too large, for reasons see Section 2.7.2.4.2 and Section 2.7.2.4.3 of the present dossier assessment.

AE: adverse event; BSC: best supportive care; EDSS: Expanded Disability Status Scale; EQ-5D: European Quality of Life-5 Dimensions; MFIS: Modified Fatigue Impact Scale; MSFC: Multiple Sclerosis Functional Composite; PT: Preferred Term; RCT: randomized controlled trial; SF-36: Short Form (36) Health Survey; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.5.2.2 Risk of bias

Table 35 shows the risk of bias for the relevant outcomes.

Table 35: Risk of bias at study and outcome level - RCT, direct comparison: ocrelizumab + BSC vs. placebo + BSC (patients with early PPMS)

Study	Study level	Outcomes										
		All-cause mortality	Disability progression (EDSS)	Disability severity (MSFC)	Fatigue interference (MFIS)	Health status (EQ-5D VAS)	Health-related quality of life (SF-36)	SAEs	Discontinuation due to AEs	Reaction associated with an infusion (AE, PT)	Infections and infestations (AE, SOC)	Depression (AE, PT)
ORATORIO	L	L	L	H[a]	–[b]	–[b]	–[b]	L	L	L	L	L

a: High proportion of patients (> 10%) as well as large difference between the treatment groups (> 5 percentage points) regarding the proportion of patients who were not considered in the analysis.
b: Because the proportion of patients who were not considered in the respective relevant analysis was > 30%, the data were not presented.

AE: adverse event; BSC: best supportive care; EDSS: Expanded Disability Status Scale; EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; MFIS: Modified Fatigue Impact Scale; MSFC: Multiple Sclerosis Functional Composite; PT: Preferred Term; RCT: randomized controlled trial; SF-36: Short Form (36) Health Survey; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

The risk of bias was rated as low for all outcomes for which usable data were available, except for the outcome “disability severity”.

Usable data on the outcomes “fatigue interference” (MFIS), “health status” (EQ-5D VAS) and “health-related quality of life” (SF-36) are not available because the proportion of patients who were not considered in the relevant analyses was > 10%, or the difference of the proportions of patients who were not considered in the relevant analyses was > 30%.

For the outcome “disability severity” (MSFC), the company left > 10% of the randomized patients unconsidered in the relevant analyses, or this proportion differed between the treatment arms by > 5 percentage points. Therefore, the risk of bias for this outcome was rated as high.

Deviating from this, the company rated the risk of bias for the outcomes “fatigue interference”, “health status” and “health-related quality of life” as low. In module 4 B, the company addresses the outcome “disability severity” under the outcome “disability progression”, it rated the related risk of bias as low.

2.5.2.3 Results

Table 36, Table 37 and Table 38 summarize the results on the comparison of ocrelizumab + BSC with BSC in patients with early PPMS. Where necessary, calculations conducted by the Institute were provided in addition to the data from the company’s dossier. Appendix C.1 shows the Kaplan-Meier curves on the outcome “time to first confirmed disability progression”. Common AEs are listed in Annex C.2.

The Peto odds ratio (POR) offers a good approximation of the relative risk (RR) in certain situations (see Section 2.7.2.2 of the full dossier assessment). Hence, in these situations the POR was calculated as estimator for the RR and used for the assessment.

Table 36: Results (mortality, side effects) - RCT, direct comparison: ocrelizumab + BSC vs. placebo + BSC (patients with early PPMS)

Study Outcome category Outcome	Ocrelizumab + BSC N	 Patients with event n (%)	Placebo + BSC N	 Patients with event n (%)	Ocrelizumab + BSC vs. placebo + BSC RR [95% CI]; p-value
ORATORIO					
Mortality					
All-cause mortality (27 July 2015)	486	4 (0.8)	239	1 (0.4)	POR: 1.80 [0.28; 11.70][a] 0.618[b]
Side effects					
AEs (supplementary information)	486	462 (95.1)	239	215 (90.0)	-
SAEs	486	99 (20.4)	239	53 (22.2)	0.92 [0.68; 1.23]; 0.618[b]
Discontinuation due to AEs	486	20 (4.1)	239	8 (3.3)	1.23 [0.55; 2.75]; 0.735[b]
Reaction associated with an infusion	486	194 (39.9)	239	61 (25.5)	1.56 [1.23; 1.99]; < 0.001[b]
Infections and infestations	486	339 (69.8)	239	162 (67.8)	1.03 [0.93; 1.14][a] 0.625[b]
Depression	486	37 (7.6)	239	30 (12.6)	0.61 [0.38; 0.96]; 0.033[b]

a: Institute's calculation, asymptotic.
b: Institute's calculation, unconditional exact test (CSZ method according to [6]).
AE: adverse event; BSC: Best supportive Care; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; n: number of patients with (at least one) event; N: number of analysed patients; POR: Peto Odds Ratio; RCT: randomized controlled trial; PPMS: primary progressive multiple sclerosis; RR: relative risk; SAE: serious adverse event; vs.: versus

Table 37: Results (morbidity, time to event) - RCT, direct comparison: ocrelizumab + BSC vs. placebo + BSC (patients with early PPMS)

Study Outcome category Outcome	Ocrelizumab + BSC N	Ocrelizumab + BSC Median time to event in months [95% CI] Patients with event n (%)	Placebo + BSC N	Placebo + BSC Median time to event in months [95% CI] Patients with event n (%)	Ocrelizumab + BSC vs. placebo + BSC HR [95% CI][a]; p-value[b]
ORATORIO					
Morbidity					
Confirmed disability progression (based on EDSS)					
Imputation strategy 1[c]	487	NA 128 (26.3)	244	NA 71 (29.1)	0.82 [0.62; 1.10]; 0.188
Imputation strategy 2[d]	487	NA 144 (29.6)	244	NA 87 (35.7)	0.75 [0.58; 0.98]; 0.037

a: HR, 95% CI: Cox proportional hazards model stratified by region and age.
b: P-value: log-rank test.
c: Patients for whom confirmed disability progression was missing because they had left the study were rated as patients with unconfirmed progressive disability at the day of treatment discontinuation. This imputation strategy is referred to as "without imputation" in the company's dossier (see Section 2.7.2.4.3).
d: For patients for whom confirmed disability progression after 24 weeks was missing because they had left the study, confirmed EDSS progression was imputed at the day of treatment discontinuation. In the company's dossier, this imputation strategy is referred to as "with imputation" (see Section 2.7.2.4.3).

BSC: best supportive care; CI: confidence interval; EDSS: Expanded Disability Status Scale; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; PPMS: primary progressive multiple sclerosis; RCT: randomized controlled trial; vs.: versus

Table 38: Results (morbidity, continuous) - RCT, direct comparison: ocrelizumab + BSC vs. placebo + BSC (patients with early PPMS)

Study Outcome category Outcome	Ocrelizumab + BSC			Placebo + BSC			Ocrelizumab + BSC vs. placebo + BSC
	N[a]	Values at start of study mean (SD)	Change at week 120 mean (SE)	N[a]	Values at start of study mean (SD)	Change at week 120 mean (SE)	MD [95% CI]; p-value
ORATORIO							
Morbidity							
Disability severity (MSFC z-score)[b]	383	0.00 (0.73)	-0.13 (0.04)	170	0.02 (0.67)	-0.21 (0.06)	0.09 [-0.05; 0.22]; 0.217[c]
Disability severity Timed 25-Foot Walk[d, e]	397	-	1.31 [1.20; 1.42][f]	174	-	1.39 [1.24; 1.56][f]	0.94 [0.84; 1.05] ND[g]
Disability severity 9-Hole Peg Test[d, e]	400	-	1.04 [1.01; 1.07][f]	172	-	1.08 [1.04; 1.13][f]	0.96 [0.92; 1.00] ND[g]
Disability severity PASAT[b]	386	40.84 (13.92)	4.74 (0.49)	172	40.07 (14.06)	4.72 (0.66)	0.02 [-1.45; 1.49]; 0.979[c]
Fatigue interference (MFIS)	No usable data[h]						
Health status (EQ-5D VAS)	No usable data[h]						
Health-related quality of life							
SF-36	No usable data[h]						

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study (possibly at other time points) may be based on other patient numbers.
b: Positive change indicates improvement.
c: Effect, CI and p-value: mixed-effects model repeated measures (MMRM).
d: Negative change indicates improvement.
e: Presumably ANCOVA analysis adjusted for region and EDSS at the start of the study with adjusted change in relation to the baseline value.
f: Presumably adjusted geometric mean; 95% CI.
g: Presumably ratio of the adjusted geometric means.
h: The data were not presented because the proportion of patients who were not considered in the respective relevant analysis was > 30%.

ANCOVA: Analysis of Covariance; BSC: Best supportive Care; CI: confidence interval; EDSS: Expanded Disability Status Scale; EQ-5D: European Quality of Life Questionnaire 5-Dimensions; MCS: Mental Component Summary scale; MD: mean difference; MFIS: Modified Fatigue Impact Scale; MMRM: mixed-effects model repeated measures; MSFC: Multiple Sclerosis Functional Composite; N: number of analysed patients; NA: not achieved; PASAT: Paced Auditory Serial Addition Test; PCS: Physical Component Summary scale; PPMS: primary progressive multiple sclerosis; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SF-36: Short Form (36) Health Survey; VAS: visual analogue scale; vs.: versus

Because of the high risk of bias, at most a hint, e.g. of an added benefit, can be determined for the outcome “disability severity”, and at most an indication, e.g. of an added benefit, can be determined for all other outcomes on the basis of the available data.

Mortality

All-cause mortality

Four deaths occurred in the ocrelizumab + BSC arm of the study, and 1 death in the BSC arm. There was no statistically significant difference between the treatment groups for the outcome "all-cause mortality". Hence, there was no hint of an added benefit of ocrelizumab + BSC in comparison with BSC; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Confirmed disability progression (based on EDSS)

The outcome "confirmed disability progression" (after 24 weeks) recorded the time from baseline to the occurrence of the first clinically relevant disability progression that was confirmed after at least 24 weeks. To replace missing values for confirmation, the company used 2 imputation strategies for patients with initial progression for whom confirmed progression was missing because they had left the study (N = 16 [3.3%] in the ocrelizumab + BSC arm and N = 16 [6.6%] in the BSC arm). In imputation strategy 1, patients for whom confirmed disability progression was missing because they had left the study were rated as patients with unconfirmed progressive disability. In imputation strategy 2, however, these patients were rated as patients with confirmed progressive disability at the day of treatment discontinuation (see Section 2.7.2.4.3). In the present situation, none of the two imputation strategies should be preferred unconditionally over the other. Therefore, the results of both analyses were shown for the present research question (see Section 2.7.2.4.3).

The analysis with imputation strategy 1 showed no statistically significant difference between the treatment groups for the outcome "confirmed disability progression" (after 24 weeks). However, the analysis with imputation strategy 2 shows a statistically significant difference in favour of ocrelizumab. The results are therefore not robust.

To enable better assessment of the results of the disability progression using the EDSS, the results on the disability severity (MSFC z-score) are additionally considered, as also recommended by the European Medicines Agency (EMA) [12].

Neither the change of the mean difference used for the present assessment (see next Section) nor the responder analysis on the MSFC z-score considered by the company in the dossier showed a statistically significant result, which supports the findings of the analysis with imputation strategy 1. Overall, this resulted in no hint of an added benefit of ocrelizumab + BSC in comparison with BSC for the outcome "relapses", an added benefit is therefore not proven.

For its assessment, the company used analyses "with imputation" (imputation strategy 2) and derived proof of minor added benefit from this.

Disability severity (MSFC z-score)

The mean difference from the MMRM analysis from the start of the study to week 120 was considered for the outcome "disability severity" (recorded with the MSFC z-score). There was no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of ocrelizumab + BSC in comparison with BSC; an added benefit is therefore not proven.

This concurs with the company's assessment, which based its assessment on responder analyses and considered this outcome under the outcome "disease progression".

Fatigue interference (MFIS)

The mean difference from the MMRM analysis from the start of the study to week 120 was considered for the outcome "fatigue interference". However, > 30% of the randomized patients were not considered in this analysis. Hence, no usable data were available for the relevant analysis. This resulted in no hint of an added benefit of ocrelizumab + BSC in comparison with BSC; an added benefit is therefore not proven.

For its assessment, the company used responder analyses and derived proof of considerable added benefit from this.

Health status (EQ-5D VAS)

The mean difference from the covariance analysis from the start of the study to week 120 was considered for the outcome "health status" recorded with the EQ-5D VAS. However, > 30% of the randomized patients were not considered in this analysis. Hence, no usable data were available for the relevant operationalization. This resulted in no hint of an added benefit of ocrelizumab + BSC in comparison with BSC; an added benefit is therefore not proven.

For its assessment, the company used responder analyses and also derived no proof of an added benefit from it.

Health-related quality of life

SF-36

The mean difference from the MMRM analysis from the start of the study to week 120 was considered for the outcome "health-related quality of life" (recorded with the SF-36). However, > 30% of the randomized patients were not considered in this analysis. Hence, no usable data were available for the relevant analysis. This resulted in no hint of an added benefit of ocrelizumab + BSC in comparison with BSC; an added benefit is therefore not proven.

For its assessment, the company used responder analyses and also derived no proof of an added benefit.

Side effects

SAEs and discontinuation due to AEs

There was no statistically significant difference between the treatment groups for the outcomes "SAEs" and "discontinuation due to AEs". Hence, there was no hint of greater or lesser harm from ocrelizumab + BSC in comparison with BSC; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Specific AEs

Reaction associated with an infusion

A statistically significant difference to the disadvantage of ocrelizumab was shown for the outcome "reaction associated with an infusion". This resulted in an indication of greater harm from ocrelizumab + BSC in comparison with BSC.

This concurs with the company's assessment.

Infections and infestations

No statistically significant difference was shown for the outcome "infections and infestations". This resulted in no hint of greater or lesser harm from ocrelizumab + BSC in comparison with BSC; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Depression

A statistically significant difference in favour of ocrelizumab was shown for the outcome "depression". The extent for the outcome "depression" from the category "non-serious/non-severe side effects" was rated as no more than marginal. This resulted in no hint of greater or lesser harm from ocrelizumab + BSC in comparison with BSC for the outcome "depression"; greater or lesser harm is therefore not proven.

This deviates from the company's assessment, which assigned this outcome to another severity category and derived proof of an added benefit.

2.5.2.4 Subgroups and other effect modifiers

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

The following potential effect modifiers were considered in the present assessment:

- sex (female versus male)

- age (≤ 45 years versus > 45 years)
- EDSS at baseline (≤ 5.5 vs. > 5.5)
- region (EU, Switzerland/Norway vs. others)
- previous MS therapy (yes vs. no)

All subgroup characteristics were predefined, except for the characteristic "region". In accordance with the methods described above, no relevant effect modification was identified for the present research question. This concurs with the company's assessment.

2.5.3 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below. The various outcome categories and the effect sizes are taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The procedure for deriving an overall conclusion on the added benefit based on the aggregation of the conclusions deduced at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.3.2 (see Table 39).

Determination of the outcome category for the outcomes on AEs

Not for all outcomes considered in the present benefit assessment did the dossier indicate whether they were non-severe/non-serious or severe/serious. The classification of these outcomes is justified below.

Determination of the outcome category for the outcomes "reaction associated with an infusion" and "depression"

The severity grades of the outcomes "reaction associated with an infusion" and "depression" were assessed based on the proportions of SAEs on the individual outcomes observed in the ORATORIO study. In the ocrelizumab arm, SAEs accounted for 2.6% of the AEs on the outcome "reaction associated with an infusion". In the comparator arm, SAEs did not contribute at all to this outcome. SAEs on the outcome "depression" were not detected.

Both outcomes were therefore allocated to the category of non-serious/non-severe side effects.

Table 39: Extent of added benefit at outcome level: ocrelizumab + BSC vs. BSC (patients with early PPMS)

Outcome category **Outcome**	**Ocrelizumab vs. IFNβ1a** **Median time to event (months) or proportion of events (%) or MD** **Effect estimate [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality	0.8% vs. 0.4% POR: 1.80 [0.28; 11.70] p = 0.618	Lesser benefit/added benefit not proven
Morbidity		
Confirmed disability progression		
Imputation strategy 1	Median: NA vs. NA HR: 0.82 [0.62; 1.10] p = 0.188	Lesser benefit/added benefit not proven[c]
Imputation strategy 2	Median: NA vs. NA HR: 0.75 [0.58; 0.98] p = 0.037	
disability severity		
MSFC z-score	-0.13 vs. -0.21[d] MD: 0.09 [-0.05; 0.22] p = 0.217	Lesser benefit/added benefit not proven
Fatigue interference		
MFIS	No usable data	Lesser benefit/added benefit not proven
Health status		
EQ-5D VAS	No usable data	Lesser benefit/added benefit not proven
Health-related quality of life		
SF-36	No usable data	Lesser benefit/added benefit not proven

(continued)

Table 39: Extent of added benefit at outcome level: ocrelizumab + BSC vs. BSC (patients with early PPMS) (continued)

Outcome category **Outcome**	**Ocrelizumab vs. IFNβ1a** **Median time to event (months) or proportion of events (%) or MD** **Effect estimate [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Side effects		
SAEs	20.4% vs. 22.2% RR: 0.92 [0.68; 1.23] p = 0.618	Greater/lesser harm not proven
Discontinuation due to AEs	4.1% vs. 3.3% RR: 1.23 [0.55; 2.75] p = 0.735	Greater/lesser harm not proven
Reaction associated with an infusion	39.9% vs. 25.5% RR: 1.56 [1.23; 1.99]; p < 0.001 RR: 0.64 [0.50; 0.81][e] probability: "hint"	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ Greater harm, extent: "minor"
Infections and infestations	69.8% vs. 67.8% RR: 1.03 [0.93; 1.14] p = 0.625	Greater/lesser harm not proven
Depression	7.6% vs. 12.6% RR: 0.61 [0.38; 0.96] p = 0.033	Outcome category: non-serious/non-severe side effects $0.90 \leq CI_u < 1$ Greater/lesser harm not proven[f]

a: Probability provided if statistically significant differences are present.
b: Estimations of effect size were made depending on the outcome category with different limits based on the CI_u.
c: In the derivation of the extent, imputed and non-imputed analyses were jointly considered.
d: Change from start of the study to week 120.
e: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
f: The extent of the effect in this non-serious/non-severe outcome was no more than marginal.

AE: adverse event; BSC: Best supportive Care; CI: confidence interval; CI_u: upper limit of confidence interval; EDSS: Expanded Disability Status Scale; EQ-5D: European Quality of Life Questionnaire 5-Dimensions; HR: Hazard Ratio; MCS: Mental Component Summary scale; MD: mean difference; MFIS: Modified Fatigue Impact Scale; MSFC: Multiple Sclerosis Functional Composite; POR: Peto Odds Ratio; PPMS: primary progressive multiple sclerosis; RR: relative risk; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; VAS: visual analogue scale; vs.: versus

2.5.3.2 Overall conclusion on added benefit

Table 40 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 40: Positive and negative effects from the assessment of ocrelizumab in comparison with BSC (patients with early PPMS)

Positive effects	**Negative effects**
–	Non-serious/non-severe side effects ▪ Specific AE (“reaction associated with an infusion”): indication of greater harm - extent “minor”
Usable data for the outcomes MFIS, EQ-5D VAS and SF-36 are not available for the relevant analyses.	
AE: adverse event; BSC: Best supportive Care; EQ-5D: European Quality of Life Questionnaire 5-Dimensions; MFIS: Modified Fatigue Impact Scale; PPMS: primary progressive multiple sclerosis; SF-36: Short Form (36) Health Survey; VAS: visual analogue scale;	

Overall, there is a negative effect from the category “non-serious/non-severe side effects”.

Therefore, there is an indication of lesser benefit of ocrelizumab + BSC vs. the ACT BSC for patients with early PPMS.

This deviates from the company’s assessment, which overall derived proof of an at least minor added benefit.

2.5.4 List of included studies

2.6 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of ocrelizumab in comparison with the ACT is summarized in Table 41.

Table 41: Ocrelizumab – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Adults with RMS who have not yet received disease-modifying therapy or patients with non-highly active disease pretreated with disease-modifying therapy	**IFNβ1a** or IFNß1b or glatiramer acetate under consideration of the approval	Age < 40 years: proof of considerable added benefit
			Age ≥ 40 years: proof of minor added benefit
2	Adults with highly active RMS despite treatment with a disease-modifying therapy[b]	Alemtuzumab or fingolimod or natalizumab or, if indicated, change within the basic therapeutic agents (**IFNβ 1a** or IFNβ1b or glatiramer acetate under consideration of the approval)	Indication of considerable added benefit
3	Adults with early PPMS	Best supportive care[c]	Indication of lesser benefit

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Adequate (pre)treatment usually comprises at least 6 months. Depending on frequency and severity of the relapses as well as on the disability progression, treatment with a disease-modifying therapy might take less than 6 months.
c: Best supportive care (BSC) refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve quality of life.
G-BA: Federal Joint Committee; IFNβ: interferon beta; PPMS: primary progressive multiple sclerosis; RMS: relapsing multiple sclerosis

The assessment described above deviates from that of the company, which derived proof of considerable added benefit both for treatment-naive and pretreated patients with non-highly active disease (research question 1) and pretreated patients with highly active disease (research question 2). For patients with early PPMS, the company derived proof of an at least minor added benefit.

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

References for English extract

Please see full dossier assessment for full reference list.

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

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