Dimethyl fumarate (multiple sclerosis in children and adolescents from 13 years of age)

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

EXTRACT

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[1] Translation of Sections I 1 to I 4 of the dossier assessment *Dimethylfumarat (multiple Sklerose bei Kindern und Jugendlichen ab 13 Jahren) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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

Patient and family involvement

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

IQWiG thanks the respondents and the interest group "Selbstbestimmt Leben in Deutschland e. V." (self-determined living in Germany) as well as the German Multiple Sclerosis Society, Federal Association e. V., for participating in the written exchange about how they experienced the disease and its treatment and about the treatment goals. The respondents were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BVMT-R	Brief Visuospatial Memory Test Revised
EDSS	Expanded Disability Status Scale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
INF	Interferon
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
PedsQL	Pediatric Quality of Life Inventory
RCT	randomized controlled trial
RRMS	relapsing remitting multiple sclerosis
SAE	serious adverse event
SDMT	Symbol Digit Modality Test
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug dimethyl fumarate. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 6 July 2023.

Research question

The aim of the present report is to assess the added benefit of dimethyl fumarate in comparison with the appropriate comparator therapy (ACT) in children and adolescents (≥ 13 to < 18 years) with relapsing remitting multiple sclerosis (RRMS).

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

Table 2: Research questions of the benefit assessment of dimethyl fumarate

Therapeutic indication	**ACT**[a]
Children and adolescents (≥ 13 to < 18 years) with RRMS who have not yet received disease-modifying therapy, or children and adolescents pretreated with disease-modifying therapy whose disease is not highly active[b]	**IFN-β1a** or IFN-β1b or glatiramer acetate under consideration of the approval status[c]
a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b. In analogy to the treatment algorithm recommended in the guidelines and the therapeutic indications approved to date for comparable treatment alternatives, a distinction is principally made between the patient populations with regard to previous therapy (treatment-naive or pretreated) and disease activity (not highly active, highly active). According to the G-BA, taking into account the drug properties of dimethyl fumarate, children and adolescents with highly active RRMS despite treatment with disease-modifying therapy are not considered to be the target population of dimethyl fumarate. c. An unchanged continuation of the prior therapy is not considered an appropriate implementation of the ACT if there is a therapeutic indication to change the disease-modifying therapy. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IFN: interferon; RRMS: relapsing remitting multiple sclerosis	

The company followed the G-BA's specification on the ACT and chose interferon (IFN)-β1a from the options named by the G-BA.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 12 months were used for the derivation of the added benefit.

Study pool and study design

The CONNECT study is used for the benefit assessment.

The CONNECT study is a 2-part, open-label study on children and adolescents with RRMS. The randomized, controlled first part of the study, which had already been completed, compared the treatment of children and adolescents with dimethyl fumarate versus treatment with IFN-β 1a. In the second part of the study, which is still ongoing, the children and adolescents could be treated with dimethyl fumarate as part of a single-arm extension.

Children and adolescents (≥ 10 to < 18 years) with ≥ 1 relapse in the past year or ≥ 2 relapses during the past 2 years or ≥ 1 gadolinium-enhancing lesion within the last six weeks before Day 1 of the study and a maximum Expanded Disability Status Scale (EDSS) score of 5.5 were included in the studies. In most cases, pretreatment with disease-modifying drugs prior to the start of the study was not permitted within a certain period of time before the start of the study; children and adolescents pretreated with cladribine and monoclonal antibodies other than natalizumab or rituximab were excluded from the study.

A total of 156 children and adolescents were randomly assigned in a ratio of 1:1 to treatment with dimethyl fumarate or IFN-β1a.

In part 1 of the study, treatment with dimethyl fumarate and IFN-β 1a was carried out over a period of 96 weeks, each in accordance with the Summary of Product Characteristics (SPC). After termination of the randomized treatment phase, the children and adolescents could be treated with dimethyl fumarate as part of the a single-arm extension in part 2 of the study. In Module 4 B of the dossier, the company presents analyses that refer to the randomized controlled 1st part of the study up to week 96. These analyses are relevant for the benefit assessment.

Primary outcome of the study was the proportion of children and adolescents without new or enlarged T2-hyperintense lesions on brain MRI scans at week 96. Patient-relevant outcomes in the categories of mortality, morbidity, health-related quality of life and side effects were also recorded.

The CONNECT study has several uncertainties that are also relevant for the present benefit assessment. This applies in particular to the question of the suitability of the subpopulation presented by the company, the adequate implementation of the intention to treat (ITT) principle for the present analyses and a high number of important protocol violations. These restrictions are explained below.

Suitability of the subpopulation from the CONNECT study presented by the company for the present benefit assessment

The CONNECT study included children and adolescents aged ≥ 10 to < 18 years. However, according to the SPC, dimethyl fumarate is exclusively approved for children and adolescents from 13 years of age. In Module 4 B of the dossier, the company presented analyses on a subpopulation of the study that included children and adolescents aged ≥ 13 years treated with the study medication who received at least 1 dose of the study medication.

In addition, the research question of the present benefit assessment only includes children and adolescents who have not yet received any disease-modifying therapy or children and adolescents who have been pretreated with disease-modifying therapy and whose disease is not highly active. In the subpopulation presented by the company, a total of around 14% of children and adolescents aged ≥ 13 to < 18 years received pretreatment with interferons, glatiramer acetate and/or natalizumab. Since the company provided no information on this in the dossier, it remains unclear how many children and adolescents were included in the subpopulation whose disease is highly active despite treatment with disease-modifying therapy and who therefore do not correspond to the population of the present research question. Although at 14%, this patient group makes up only a small percentage of the subpopulation presented by the company, it remains unclear whether the results for the subpopulation of the CONNECT study can be fully transferred to the target population of treatment-naive and pretreated children and adolescents whose disease is not highly active. This uncertainty is taken into account in the assessment of the certainty of results. The subpopulation presented by the company was used for the benefit assessment.

Adequate implementation of the ITT principle for the analyses presented by the company unclear

It remains unclear whether the ITT principle was adequately implemented the analyses presented by the company. 6 of the children and adolescents included in the CONNECT study discontinued the study after randomization and before the first dose of study medication (5 children and adolescents in the control arm and 1 in the intervention arm). In Module 4 B of the dossier, the company described that this was due to the open-label study design and the type of IFN-β 1a administration. Children and adolescents who discontinued the study immediately after randomization before the 1st dose of study medication were not considered in the company's analyses on the CONNECT study. In the dossier, the company provided no information on how many of the 6 children and adolescents fell into the age group of the subpopulation in question. When estimating the proportion of children and adolescents with missing values for the present analyses, it is therefore generally assumed that, in addition to missing values for other reasons, there are potentially 6 more children and adolescents (5 in the control arm and 1 in the intervention arm). For the benefit assessment, there is

uncertainty regarding the adequate implementation of the ITT principle, which is taken into account in the assessment of the risk of bias.

Study conduct (protocol violations)

It can be inferred from the study documents that at least 1 major protocol deviation occurred in 126 (84%) children and adolescents included in the total study population who received at least 1 dose of the study medication during the course of the study. According to the study documents, important protocol deviations are deviations from the planning according to the study protocol that could affect the integrity of the data or the safety of the children and adolescents. The total number of children and adolescents (≥ 10 to < 18 years) with at least 1 protocol deviation categorized as important is comparable between the study arms, but there are some major differences between the study arms in the individual categories (e.g. regarding the compliance with the study medication). As the dossier provides no detailed information on the extent to which the study design was deviated from and how the deviations affected the data integrity or the safety of the children and adolescents, it remains unclear whether the deviations affected the results of the CONNECT study. This uncertainty was taken into account when assessing the risk of bias of results.

Missing data on treatment and observation periods for the relevant subpopulation

In addition, there was a high number of treatment and study discontinuations in the total population during the course of the CONNECT study, with a difference of around 20% in the proportions between the study arms and 14.3% in the mean duration of exposure to the study medication. Since the observation of the outcomes in the CONNECT study was linked to the duration of treatment in the present data situation, it is assumed that there are similar differences between the study arms for the duration of observation as for the durations of exposure to the study medication. For the relevant subpopulation, the company presented neither data on study and treatment discontinuations nor on the treatment durations or the outcome-specific observation durations of the study arms, which are necessary for the benefit assessment. The relevant subpopulation accounts for 90% of the total study population that received at least 1 dose of the study medication. Based on the available data for the total population, it is therefore assumed for this population that - as in the total population - treatment durations or observation durations are sufficiently comparable. This means that the analyses can be interpreted on the basis of relative risks (RRs) presented by the company for outcomes in the side effects category. However, the extent of the observed effects for these outcomes cannot be quantified due to the remaining uncertainty regarding the outcome-specific observation durations for the relevant subpopulation. Due to the different proportions of treatment discontinuations and the resulting different observation durations, there are also incomplete observations for potentially informative reasons. This is taken into account when assessing the risk of bias.

Risk of bias and assessment of the certainty of conclusions

The risk of bias across outcomes for the CONNECT study is high due to the great number of protocol violations in the study, for which it remains unclear to what extent the study design was deviated from and how the deviations affected the data integrity or the safety of the children and adolescents. In addition to the great number of protocol violations in the study, it also remains unclear whether the relevant subpopulation presented by the company also includes children and adolescents with highly active disease despite appropriate pretreatment with a disease-modifying therapy, in addition to children and adolescents in the present research question. Even if the proportion of this patient group in the subpopulation presented by the company is low at up to 14%, the certainty of the study results for this research question is also reduced for this reason. Based on the CONNECT study, at most hints, e.g. of an added benefit, can be derived for all presented outcomes.

As described above, there are differences in the duration of treatment and observation between the study arms. This results in uncertainty due to incomplete observations for potentially informative reasons, which also contribute to the high risk of bias of the results for the outcomes in the side effects category and the outcomes of all-cause mortality, confirmed relapses and confirmed disability progression. Results on non-serious specific adverse events (AEs) have an additional high risk of bias due to the lack of blinding.

No suitable data are available for further outcomes in the categories “morbidity” and “health-related quality of life”, as there are uncertainties in the proportions of missing values or the proportions of missing values are too high. Hence, the risk of bias of the results is not assessed for these outcomes.

Results

Mortality

all-cause mortality

No deaths occurred within the framework of the study. There is no hint of an added benefit of dimethyl fumarate in comparison with IFN-β1a; an added benefit is therefore not proven.

Morbidity

Confirmed relapses

A statistically significant difference between treatment groups in favour of dimethyl fumarate was shown for the outcome of confirmed relapses. There is a hint of added benefit of dimethyl fumarate in comparison with IFN-β 1a.

Confirmed disability progression (EDSS-based)

No statistically significant difference between treatment groups was found for the outcome of confirmed disability progression (EDSS-based). There is no hint of an added benefit of dimethyl fumarate in comparison with IFN-β1a; an added benefit is therefore not proven.

Cognitive functioning (recorded using Brief Visuospatial Memory Test Revised [BVMT-R] or Symbol Digit Modality Test [SDMT])

No suitable data are available for the outcome of cognitive functioning (recorded with BVMT-R or SDMT). There is no hint of an added benefit of dimethyl fumarate in comparison with IFN-β1a; an added benefit is therefore not proven.

Fatigue (recorded using the Pediatric Quality of Life Inventory [PedsQL] Multidimensional Fatigue Scale)

No suitable data were available the outcome "fatigue" (recorded using the PedsQL Multidimensional Fatigue Scale). There is no hint of an added benefit of dimethyl fumarate in comparison with IFN-β1a; an added benefit is therefore not proven.

Health-related quality of life

PedsQL Quality of Life Scale

No suitable data are available for health-related quality of life (recorded using the PedsQL Quality of Life Scale). There is no hint of an added benefit of dimethyl fumarate in comparison with IFN-β1a; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs), discontinuation due to AEs

The analyses on the outcomes "SAEs" and "discontinuations due to AEs" presented by the company consider disease-related events. As a result, the overall rates on "SAEs" and "discontinuations due to AEs" are not suitable for the assessment of the side effects of dimethyl fumarate. However, based on the results on frequent SAEs and discontinuations due to AEs, in view of the low proportion of children and adolescents with events for the outcomes of SAEs and discontinuation due to AEs, no negative effects are expected to an extent that could call into question the added benefit of dimethyl fumarate. For the outcomes, there is no hint of greater or lesser harm from dimethyl fumarate in comparison with IFN-β1a; greater or lesser harm is therefore not proven.

Vascular disorders (AE), gastrointestinal disorders (AE), skin and subcutaneous tissue disorders (AE) and injury, poisoning and procedural complications (AE)

For the outcomes of vascular disorders (AE), gastrointestinal disorders (AE), skin and subcutaneous tissue disorders (AE) and injury, poisoning and procedural complications (AE), there is a statistically significant difference between the treatment groups to the disadvantage

of dimethyl fumarate. There is a hint of greater harm from dimethyl fumarate in comparison with IFN-β 1a.

Flu-like illness (AE)

A statistically significant difference between treatment groups in favour of dimethyl fumarate was shown for the outcome of flu-like illness (AE). There is a hint of lesser harm from dimethyl fumarate in comparison with IFN-β 1a.

Infections and infestations (SAE)

No statistically significant difference between the treatment groups was shown for the outcome "infections and infestations" (SAEs). There is no hint of greater or lesser harm from dimethyl fumarate in comparison with IFN-β1a; 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 added benefit of the drug dimethyl fumarate in comparison with the ACT is assessed as follows:

Overall, there were positive effects of dimethyl fumarate compared to IFN-β 1a with the extent "considerable" or "non-quantifiable" for the outcomes of confirmed relapses and flu-like illness (AE). This was accompanied by several negative effects for the outcomes of side effects. However, the extent of the observed negative effects for these outcomes cannot be quantified due to uncertainties regarding the outcome-specific observation periods for the relevant subpopulation. For the present benefit assessment, it is therefore not possible to estimate whether or to what extent the negative effects raise doubts about the positive effects. However, in the present data situation it is assumed that the positive effects are not completely questioned. In summary, for children and adolescents aged ≥ 13 to < 18 years with RRMS who have not yet received disease-modifying therapy or children and adolescents who have received disease-modifying therapy and whose disease is not highly active, there is a hint of a non-quantifiable added benefit of dimethyl fumarate over IFN-β 1a.

The result of the assessment of the added benefit of dimethyl fumarate in comparison with the ACT is summarized in Table 3.

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

Table 3: Dimethyl fumarate – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Children and adolescents (≥ 13 to < 18 years) with RRMS who have not yet received disease-modifying therapy, or children and adolescents pretreated with disease-modifying therapy whose disease is not highly active[b]	**IFN-β1a** or IFN-β1b or glatiramer acetate under consideration of the approval status[c]	Hint of non-quantifiable added benefit

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. In analogy to the treatment algorithm recommended in the guidelines and the therapeutic indications approved to date for comparable treatment alternatives, a distinction is principally made between the patient populations with regard to previous therapy (treatment-naive or pretreated) and disease activity (not highly active, highly active). According to the G-BA, taking into account the drug properties of dimethyl fumarate, children and adolescents with highly active RRMS despite treatment with disease-modifying therapy are not considered to be the target population of dimethyl fumarate.
c. An unchanged continuation of the prior therapy is not considered an appropriate implementation of the ACT if there is a therapeutic indication to change the disease-modifying therapy.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IFN: interferon; RRMS: relapsing remitting multiple sclerosis

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

I 2 Research question

The aim of the present report is to assess the added benefit of dimethyl fumarate in comparison with the ACT in children and adolescents (≥ 13 to < 18 years) with RRMS.

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

Table 4: Research questions of the benefit assessment of dimethyl fumarate

Therapeutic indication	**ACT**[a]
Children and adolescents (≥ 13 to < 18 years) with RRMS who have not yet received disease-modifying therapy, or children and adolescents pretreated with disease-modifying therapy whose disease is not highly active[b]	**IFN-β1a** or IFN-β1b or glatiramer acetate under consideration of the approval status[c]
a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b. In analogy to the treatment algorithm recommended in the guidelines and the therapeutic indications approved to date for comparable treatment alternatives, a distinction is principally made between the patient populations with regard to previous therapy (treatment-naive or pretreated) and disease activity (not highly active, highly active). According to the G-BA, taking into account the drug properties of dimethyl fumarate, children and adolescents with highly active RRMS despite treatment with disease-modifying therapy are not considered to be the target population of dimethyl fumarate. c. An unchanged continuation of the prior therapy is not considered an appropriate implementation of the ACT if there is a therapeutic indication to change the disease-modifying therapy. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IFN: interferon; RRMS: relapsing remitting multiple sclerosis	

The company followed the G-BA's specification on the ACT and chose IFN-β1a from the options named by the G-BA.

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

I 3 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 dimethyl fumarate (status: 19 April 2022)
- bibliographical literature search on dimethyl fumarate (last search on 19 April 2022)
- search in trial registries/trial results databases for studies on dimethyl fumarate (last search on 19 April 2022)
- search on the G-BA website for dimethyl fumarate (last search on 19 April 2022)

To check the completeness of the study pool:

- search in trial registries for studies on dimethyl fumarate (last search on 25 July 2023); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

Due to the course of the present procedure, the status of the company's information retrieval was more than 3 months before IQWiG was commissioned with the benefit assessment of the drug dimethyl fumarate by the G-BA (for explanation, see Section I 2). However, this has no consequence for the present benefit assessment, as the check of completeness of the study pool identified no other relevant study.

I 3.1 Studies included

The study presented in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: dimethyl fumarate vs. IFN-β1a

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical Study Report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
109MS306 (CONNECT[c])	Yes	Yes	No	Yes [3]	Yes [4,5]	Yes [6]

a. Study for which the company was sponsor.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.
IFN: interferon; RCT: randomized controlled trial

The CONNECT study is used for the benefit assessment. The study pool concurs with that of the company. The study is described in the following section.

I 3.2 Study characteristics

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

Table 6: Characteristics of the studies included – RCT, direct comparison: dimethyl fumarate vs. IFN-β1a

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
CONNECT	RCT, open-label, parallel[b]	Paediatric patients (≥ 10 to < 18 years) with RRMS: ▪ EDSS score = 0-5.5 ▪ with at least one of the following: ▫ ≥ 1 relapse in the past year and MS-typical lesions (MRI) or ▫ ≥ 2 relapses in the past 2 years and MS-typical lesions (MRI) ▫ ≥ 1 GD-enhancing lesion within the past 6 weeks before Day 1	Dimethyl fumarate (N = 79) IFN-β1a (N = 77)[c] relevant subpopulation thereof[d]: dimethyl fumarate (n = 71) IFN-β1a (n = 64)	Screening: ≤ 6 weeks treatment: 96 weeks[e] observation: until approx. 4 days after the end of the treatment phase[f]	63 study sites in Belgium, Bulgaria, Canada, Czech Republic, Denmark, France, Germany, Hungary, Israel, Italy, Kuwait, Poland, Serbia, Spain, Sweden, Turkey, United Kingdom, and United States 08/2014-11/2020[g]	Primary: proportion of patients without new or enlarged T2-hyperintense lesions on brain MRI scans at Week 96 secondary: mortality, morbidity, health-related quality of life, AEs

a. Primary outcomes include information without taking into account relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Information only refers to part 1 of the CONNECT study. Part 2 represents an optional, single-arm extension in which all patients received dimethyl fumarate. This part of the study is not subject of the present assessment.
c. 6 patients discontinued the study after randomization and before the 1st dose. The company only presented analyses on patients who had received at least 1 dose (78 dimethyl fumarate vs. 72 IFN-β1a).
d. The subpopulation relevant for the present assessment includes patients aged ≥ 13 to < 18 years.
e. After completion of randomized treatment in part 1 of the study, patients could participate in a single-arm extension in part 2 of the study.
f. Patients who did not participate in part 2 of the study or those who discontinued treatment prematurely in part 1 of the study were followed up until approx. 4 weeks after the last dose of the study medication.
g. Refers to part 1 of the study; part 2 of the study is still ongoing at the time of report production (planned end: 8 September 2025).

AE: adverse event; EDSS: Expanded Disability Status Scale; Gd: gadolinium; IFN: interferon; MRI: magnetic resonance imaging; MS: multiple sclerosis; n: subpopulation analysed by the company; N: number of randomized (included) patients; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis

Table 7: Characteristics of the intervention – RCT, direct comparison: dimethyl fumarate vs. IFN-β1a

Study	Intervention	Comparison
CONNECT	Dimethyl fumarate, orally, twice daily initial dose (Days 1 to 7): 120 mg twice daily maintenance phase (from Day 8): 240 mg twice daily	IFN-β 1a[a], IM injection, once weekly titration phase: Week 1: 7.5 µg Week 2: 15 µg Week 3: 22.5 µg maintenance phase (from week 4): 30 µg
	Prohibited prior and concomitant treatment ▪ at any time prior to the start of the study: fumaric acid esters, dimethyl fumarate, total lymphoid radiation, cladribine, T-cell or T-cell receptor vaccinations as well as monoclonal antibodies other than rituximab and natalizumab ▪ ≤ 12 months prior to study start: mitoxantrone, cyclophosphamide, rituximab ▪ ≤ 6 months prior to study start: fingolimod, teriflunomide, natalizumab, cyclosporin, azathioprine, methotrexate, mycophenolate mofetil, laquinimod, immunoglobulin (IV), plasmapheresis or cytapheresis ▪ ≤ 30 prior to study start: steroids (IV or oral corticosteroids, including drugs that may act via the corticosteroid pathway [e. g. low-dose naltrexone]); 4-aminopyredine or similar products[b] ▪ during the study: any alternative therapy for the treatment of MS; systemic steroid therapy with the exception of the treatment of relapses[c] **allowed concomitant treatment** ▪ symptomatic treatment, e. g. for the treatment of spasticity, depression or fatigue[d] ▪ steroids that are not administered systemically (e. g. topically, by inhalation) ▪ treatment of relapses[c]	

a. IFN-β 1a was administered in the form of the product "Avonex".
b. Except fampridine in a stable dose for 3 months.
c. According to the study protocol, methylprednisolone with up to 1000 mg/day IV for 3-5 days for the treatment of relapses was allowed.
d. Should be optimized at screening to maintain consistent treatment during the entire study duration.
IFN: interferon; IV: intravenous; MS: multiple sclerosis; RCT: randomized controlled trial

Study design

The CONNECT study is a 2-part, open-label study on children and adolescents with RRMS. The randomized, controlled first part of the study, which had already been completed, compared the treatment of children and adolescents with dimethyl fumarate versus treatment with IFN-β 1a. In the second part of the study, which is still ongoing, the children and adolescents could be treated with dimethyl fumarate as part of a single-arm extension.

Children and adolescents (≥ 10 to < 18 years) with ≥ 1 relapse in the past year or ≥ 2 relapses during the past 2 years or ≥ 1 gadolinium-enhancing lesion within the last six weeks before Day 1 of the study and a maximum EDSS score of 5.5 were included in the studies. Included

were children and adolescents with a minimum body weight of 30 kg who showed no signs of relapses within 50 days before the start of the study. In most cases, pretreatment with disease-modifying drugs prior to the start of the study was not permitted within a certain period of time before the start of the study (see Table 7 for details); children and adolescents pretreated with cladribine and monoclonal antibodies other than natalizumab or rituximab were excluded from the study.

A total of 156 children and adolescents were randomly assigned in a ratio of 1:1 to treatment with dimethyl fumarate (N = 79) or IFN-β1a (N = 77). Randomization was stratified by age groups (10 to < 13 years, 13 to < 15 years, 15 to < 18 years). In addition, as of protocol version 5 from 25 July 2017, patients were stratified according to whether they had received treatment with IFN-β 1a or glatiramer acetate within 4 weeks prior to the start of the study. However, it is clear from the study documents that for the majority of children and adolescents who were already participating in the study when this protocol version was implemented, no information on pretreatment with IFN-β 1a or glatiramer acetate within 4 weeks before the start of the study was recorded at the time of randomization. Taking into account the available data, only 4 children and adolescents fulfilled the relevant criterion, so that this stratification factor was ultimately not considered in the analyses of the study.

In part 1 of the study, treatment with dimethyl fumarate and IFN-β 1a was carried out over a period of 96 weeks, each in accordance with the SPC [7,8]. After termination of the randomized treatment phase, the children and adolescents could be treated with dimethyl fumarate as part of the a single-arm extension in part 2 of the study. In Module 4 B of the dossier, the company presents analyses that refer to the randomized controlled 1st part of the study up to week 96. These analyses are relevant for the benefit assessment.

Primary outcome of the study was the proportion of children and adolescents without new or enlarged T2-hyperintense lesions on brain MRI scans at week 96. Patient-relevant outcomes in the categories of mortality, morbidity, health-related quality of life and side effects were also recorded.

The CONNECT study has several uncertainties that are also relevant for the present benefit assessment. This applies in particular to the question of the suitability of the subpopulation presented by the company, the adequate implementation of the ITT principle for the present analyses and a high number of important protocol violations. These topics are discussed in detail below.

Suitability of the subpopulation from the CONNECT study presented by the company for the present benefit assessment

The CONNECT study included children and adolescents aged ≥ 10 to < 18 years. However, according to the SPC, dimethyl fumarate is exclusively approved for children and adolescents

from 13 years of age [7]. This age group included 90% of the children and adolescents who received at least 1 dose of the study medication. In Module 4 B of the dossier, the company presented analyses on a subpopulation of the study that included children and adolescents aged ≥ 13 years treated with the study medication.

Some of the children and adolescents included in the CONNECT study had not yet received disease-modifying therapies, while others had been pretreated with interferons, glatiramer acetate, or natalizumab. The research question of the present benefit assessment only includes children and adolescents who have not yet received any disease-modifying therapy or children and adolescents who have been pretreated with disease-modifying therapy and whose disease is not highly active (see Chapter I 2). In the dossier, the company does not address the disease activity of the children and adolescents who were considered in the analyses it presented on the subpopulation. In the subpopulation, a total of around 14% of children and adolescents aged ≥ 13 to < 18 years received pretreatment with interferons, glatiramer acetate and/or natalizumab (see Table 8). Since the company provided no information on this in the dossier, it remains unclear how many children and adolescents were included in the subpopulation whose disease is highly active despite treatment with disease-modifying therapy and who therefore do not correspond to the population of the present research question.

Although at 14%, this patient group makes up only a small percentage of the subpopulation presented by the company, it remains unclear whether the results for the subpopulation of the CONNECT study can be fully transferred to the target population of treatment-naive and pretreated children and adolescents whose disease is not highly active. This uncertainty is taken into account when assessing the certainty of conclusions (see Section I 4.2). The subpopulation presented by the company was used for the benefit assessment.

Adequate implementation of the ITT principle for the analyses presented by the company unclear

It remains unclear whether the ITT principle was adequately implemented the analyses presented by the company. 6 of the children and adolescents included in the CONNECT study discontinued the study after randomization and before the first dose of study medication (5 children and adolescents in the control arm and 1 in the intervention arm). In Module 4 B of the dossier, the company described that this was due to the open-label study design and the type of IFN-β 1a administration. Children and adolescents who discontinued the study immediately after randomization before the 1st dose of study medication were not considered in the company's analyses on the CONNECT study. This applies both to the analyses on the total population of the study provided in Module 5 of the dossier and to the analyses on the subpopulation of children and adolescents aged ≥ 13 to < 18 years provided in Module 4 B of the dossier. In the dossier, the company provided no information on how many of the

6 children and adolescents fell into this age group. When estimating the proportion of children and adolescents with missing values for the present analyses, it is therefore generally assumed that, in addition to missing values for other reasons, there are potentially 6 more children and adolescents (5 in the control arm and 1 in the intervention arm). For the benefit assessment, there is uncertainty regarding the adequate implementation of the ITT principle, which is taken into account in the assessment of the risk of bias (see Section I 4.2).

Implementation of the ACT

In individual cases, children and adolescents who had already received prior treatment with IFN-β 1a as a disease-modifying therapy were also included in the CONNECT study. For the age group of ≥ 13 to < 18-year-olds, this applies to 8 children and adolescents in the intervention arm and 3 in the control arm. In the dossier, the company provides no information on whether pretreatment with IFN-β1a of the 3 affected children and adolescents in the control arm was continued within the framework of the study. An unchanged continuation of the prior therapy is not considered an appropriate implementation of the ACT if there is a therapeutic indication to change the disease-modifying therapy. Based on the information available, it remains unclear whether the pretreatment was continued without any changes. For the present benefit assessment, it is overall assumed that the ACT was adequately implemented in the control arm, since only individual children and adolescents received pretreatment with IFN-β1a.

Study conduct (protocol violations)

It can be inferred from the study documents that at least 1 major protocol deviation occurred in 126 (84%) children and adolescents included in the total study population who received at least 1 dose of the study medication during the course of the study. According to the study documents, important protocol deviations are deviations from the planning according to the study protocol that could affect the integrity of the data or the safety of the children and adolescents. The total number of children and adolescents with at least 1 protocol deviation categorized as important is comparable between the study arms, but there are some major differences between the study arms in the individual categories (see Table 18 in I Appendix B). For example, large differences were observed between the study arms, particularly with regard to compliance with the study medication. The dossier provides no detailed information on the extent to which the study design was deviated from and how the deviations affected the data integrity or the safety of the children and adolescents. The study documents in Module 5 of the dossier only contain a general statement that there were no important protocol deviations that would have had a substantial impact on the study results or conclusions. In Module 4 B of the dossier, the company does not address the high number of important protocol deviations. The company does not provide information on the proportion of children and adolescents affected in the relevant subpopulation (≥ 13 to < 18 years). Overall, it therefore remains unclear whether the deviations affect the analyses of the

CONNECT study presented by the company in Module 4 B of the dossier. This uncertainty has been taken into account in the assessment of the risk of bias of results (see Section I 4.2).

Patient characteristics

Table 8 shows the characteristics of the children and adolescents ≥ 13 to < 18 years in the study included.

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: dimethyl fumarate vs. IFN-β1a (multipage table)

Study characteristic category	Dimethyl fumarate N[a] = 71	IFN-β1a N[a] = 64
CONNECT study		
Age [years], mean (SD)	15.2 (1.3)	15.4 (1.1)
Age category, n (%)		
13–14 years	18 (25)	14 (22)
15–17 years	53 (75)	50 (78)
Sex [f/m], %	70/30	72/28
Family origin, n (%)		
White	9 (13)	13 (20)
Asian	1 (1)	1 (2)
Not reported due to confidentiality rules	25 (35)	24 (38)
Other	3 (4)	0 (0)
Not known/missing	33 (46)	26 (41)
Region, n (%)		
Europe	59 (83)	61 (95)
Non-Europe	12 (17)	3 (5)
Body weight [kg], mean (SD)	65.6 (14.8)	65.4 (12.9)
Time since occurrence of first MS symptoms [years], mean (SD)	1.6 (1.6)	1.2 (1.3)
Time since MS diagnosis (years), mean (SD)	0.8 (1.2)	0.5 (0.7)
Number of relapses in the past 12 months, n (%)		
0	0 (0)	2 (3)
1	40 (56)	33 (52)
2	17 (24)	23 (36)
3	10 (14)	6 (9)
≥ 4	3 (4)	0 (0)

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: dimethyl fumarate vs. IFN-β1a (multipage table)

Study characteristic category	**Dimethyl fumarate N[a] = 71**	**IFN-β1a N[a] = 64**
Number of relapses in the past 2 years, n (%)		
0	0 (0)	2 (3)
1	24 (34)	21 (33)
2	32 (45)	31 (48)
3	10 (14)	8 (13)
≥ 4	4 (6)	2 (3)
Time since the last relapse before the study (months), mean (SD)	4.9 (2.8)	4.7 (2.9)
GD-enhancing lesions at baseline, median [Q1; Q3][b]	1.0 [0.0; 3.0]	1.0 [0.0; 3.0]
EDSS at baseline, median [Q1; Q3]	1.0 [0.0; 2.0]	1.0 [0.0; 1.5]
Pretreatment with disease-modifying therapy, n (%)	12 (17)	7 (11)
IFN-β1a	8 (11)	3 (5)
Glatiramer acetate	3 (4)	3 (5)
IFN-β1b	3 (4)	2 (3)
Natalizumab	2 (3)	0 (0)
Treatment discontinuation, n (%)[c]	ND	ND
Study discontinuation, n (%)[d]	ND	ND

a. Number of patients aged ≥ 13 to < 18 years who received at least 1 dose of the study medication. Values which are based on different patient numbers are marked in the corresponding line if the deviation is relevant.

b Data refer to patients aged ≥ 10 to < 18 years who received at least 1 dose of study medication (78 for dimethyl fumarate vs. 72 for IFN-β1a, 150 in total).

c. Of the patients aged ≥ 10 to < 18 years who received at least 1 dose of the study medication (150 in total), 22% in the intervention arm vs. 42% in the control arm (17 vs. 30) discontinued treatment. a. Common reasons for treatment discontinuation in the intervention vs. the control arm were: discontinuation due to AEs (8% vs. 11%), withdrawal of consent (5% vs. 15%), investigator's decision (5% vs. 13 %). In addition, 1 vs. 5 of the randomized patients in this age group (156 in total) did not receive a dose of the study medication.

d. Of the patients aged ≥ 10 to < 18 years who received at least 1 dose of the study medication (150 in total), 21% in the intervention arm vs. 42% in the control arm (16 vs. 30) discontinued the study. a. Common reasons for study discontinuation in the intervention vs. the control arm were: discontinuation due to AEs (6% vs. 11%), withdrawal of consent (5% vs. 15%), investigator's decision (5% vs. 13 %). In addition, 1 vs. 5 of the randomized patients in this age group (156 in total) did not receive a dose of the study medication. In Module 4 B of the dossier, the company states that these people left the study.

Gd: gadolinium; F: female; M: male; n: number of patients in the category; N: number of patients aged ≥ 13 to < 18 years who received at least one dose of the study medication; ND: no data; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; SD: standard deviation

The patient characteristics are largely comparable between the treatment arms. The mean age of the children and adolescents in the relevant subpopulation was 15 to 16 years; more than two thirds were female. In both study arms, the majority of children and adolescents

came from Europe, with a higher proportion from this region (96%) in the control arm than in the intervention arm (85%). Overall, the number of relapses before start of the study were sufficiently comparable between the study arms. Slightly more than half of the population had 1 relapse in the last year prior to the start of the study. Children and adolescents in the intervention arm tended to have more than 2 relapses in the last year before the start of the study slightly more frequently than those in the control arm (18% versus 9%). Within 2 years prior to study start, nearly one third of the children and adolescents had 1 relapse, slightly less than half of them had 2 relapses, and about 18% had ≥ 3 relapses.

At the start of the study, most of the children and adolescents had no severe physical limitations with a median EDSS score of 1.0. The diagnosis of multiple sclerosis (MS) was made on average 0.5 to 0.8 years before randomization and the first symptoms of the disease had occurred 1.2 to 1.6 years ago.

Prior to study inclusion, approx. 11 to 17% of the children and adolescents had received prior disease-modifying therapies. The majority of them had already received treatment with beta-interferons (IFNβ1a or 1b).

For the relevant subpopulation, the company did not provide any information on study or treatment discontinuations. In the total population of the study with at least 1 dose of the study medication, the proportion of treatment discontinuations was clearly higher in the control arm (30 children and adolescents [42%]) than in the intervention arm (17 children and adolescents [22%]). Except for 1 patient in the control arm, the children and adolescents not only discontinued treatment, but also participation in the study. In addition, 5 children and adolescents in the control arm and 1 in the intervention arm withdrew their consent to participate after learning of their allocation before receiving the first dose of study medication. Overall, 45% of the randomized children and adolescents in the control arm and 23% in the intervention arm discontinued treatment. The most common reason for treatment or study discontinuation was discontinuation due to AEs in the intervention arm and withdrawal of consent in the control arm. For the relevant subpopulation, the company does not provide any information on treatment and study discontinuations, but since the relevant subpopulation comprised 87% of the randomized children and adolescents or 90% of the total population of the study who received at least 1 dose of the study medication, it can be assumed that there are similarly high proportions of discontinuations.

The high proportion of children and adolescents who discontinued treatment or the study, with differentially varying proportions between the study arms (around 20% more discontinuations for the total population in the control arm), may result in outcome-specific differences in the observation periods. In the dossier, the company does not provide any information on observation durations per outcome, so that it remains unclear whether the differences in discontinuations lead to different observation durations. For the total

population of the study with at least 1 dose of the study medication, the study documents show that 28% of children and adolescents in the control arm and 12% in the intervention arm received the study medication for less than half of the planned treatment duration, i.e. for a maximum of 48 out of 96 weeks. On average, the study medication was administered for 84.4 weeks in the intervention arm and for 72.3 weeks in the control arm. The difference between the study arms in the mean duration of exposure to the study medication was therefore 14.3%.

According to the study design, the outcomes in the CONNECT study were also to be recorded after discontinuation of treatment, provided that the children and adolescents continued to participate in the study. However, except for 1 patient in the control arm, the children and adolescents included in the study not only discontinued treatment, but also participation in the study. After study discontinuation, a follow-up of up to 4 weeks was planned for AEs only. The observation of the outcomes in the CONNECT study was thus linked to the duration of treatment in the present data situation. It is therefore assumed that there will be similar differences between the study arms for the duration of observation as for the duration of exposure to the study medication.

For the relevant subpopulation, the company presented neither data on study and treatment discontinuations nor on the treatment durations or the outcome-specific observation durations of the study arms, which are necessary for the benefit assessment. The relevant subpopulation accounts for 90% of the total study population that received at least 1 dose of the study medication. Based on the available data for the total population, it is therefore assumed for this population that - as in the total population - treatment durations or observation durations are sufficiently comparable.

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: dimethyl fumarate vs. IFN-β1a

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			
CONNECT	Yes	Yes	No	No	Yes	No[a]	High

a. During the course of the study, a high proportion of children and adolescents in the total study population experienced ≥ 1 major protocol violation, with sometimes large differences between the study arms for the individual categories (see Table 18 in I Appendix B). Since it remains unclear to what extent the study design was deviated from and how the deviations affected the data integrity or the safety of the children and adolescents, there is a high risk of bias at study level.

IFN: interferon; RCT: randomized controlled trial

The risk of bias across outcomes was rated as high for the CONNECT study. The reason for this is the high number of protocol violations in the study, for which it remains unclear to what extent the study design was deviated from and how the deviations affected the data integrity or the safety of the children and adolescents (for a detailed explanation, see the text section Study conduct [protocol violations] in this section above).

Furthermore, it remains unclear whether the ITT principle was adequately implemented for the analyses of the CONNECT study presented by the company, as children and adolescents who discontinued the study immediately after randomization before the first dose of study medication were not considered (in the total population, 5 children and adolescents in the control arm and 1 in the intervention arm). It remains unclear which proportion of the relevant subpopulation is affected. When assessing the proportion of children and adolescents with missing values, it is therefore generally assumed that there are potentially 6 additional children and adolescents with missing values (5 in the control arm and 1 in the intervention arm, see Section I 4.2). Further limitations resulting from the open-label study design are described in Section I 4.2 with the outcome-specific risk of bias.

Transferability of the study results to the German health care context

In the company's view, the results of the CONNECT study are suitable for transfer to the German healthcare context. According to the company, the majority of the paediatric patients of the CONNECT study comes from Europe, and - among others - the study was also conducted in 3 German study centres. According to the company, the operationalizations of the outcomes recorded in the study (e.g. relapses and disability progression) correspond to the usual operationalizations in Germany. According to the company, it compared the patient

characteristics of sex and age of the study with published data from Germany and supporting international data on female and male MS patients. The company referred to [9,10]. From the comparison, the company concludes that the age distribution given in the study corresponds to epidemiological studies, according to which the occurrence of MS symptoms and the associated diagnosis is very rare before adolescence and increases sharply later. According to the company, data on the prevalence of paediatric MS in Germany also show a sex ratio that corresponds to that of the relevant subpopulation.

The company did not provide any further information on the transferability of the study results to the German health care context.

I 4 Results on added benefit

I 4.1 Outcomes included

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

- Mortality
  - all-cause mortality
- Morbidity
  - confirmed relapses (operationalized through the annualized relapse rate)
  - confirmed disability progression (EDSS-based, confirmed over a 24-month period)
  - cognitive functioning measured using the BVMT-R and the SDMT
  - fatigue measured using the PedsQL Multidimensional Fatigue Scale
- Health-related quality of life
  - measured using the PedsQL Quality of Life Scale
- Side effects
  - SAEs
  - discontinuation due to AEs
  - vascular disorders (AE, System Organ Class [SOC])
  - flu-like illness (AE, Preferred Term [PT])
  - gastrointestinal disorders (AE, SOC)
  - infections and infestations (SAE, SOC)
  - further specific AEs, if any

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

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

Table 10: Matrix of outcomes – RCT, direct comparison: dimethyl fumarate vs. IFN-β1a

Study	Outcomes													
	All-cause mortality[a]	Confirmed relapses[b]	Confirmed disability progression (based on EDSS)[c]	Cognitive functioning (BVMT-R, SDMT)	Fatigue (PedsQL Multidimensional Fatigue Scale)	Health-related quality of life (PedsQL)	SAEs	Discontinuation due to AEs	Vascular disorders (AE, SOC)	Flu-like illness (AE, PT)	Gastrointestinal disorders (AE, SOC)	Infections and infestations (SAE, SOC)	Skin and subcutaneous tissue disorders (AE, SOC)	Injury, poisoning and procedural complications (AE, SOC)
CONNECT	Yes	Yes	Yes	No[d]	No[d]	No[d]	No[d]	No[d]	Yes	Yes	Yes	Yes	Yes	Yes

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Defined as new or recurrent neurological symptoms not associated with fever or infection, lasting at least 24 hours and confirmed by new objective neurological findings after assessment by the treating neurologist; according to the company's information in Module 4 B of the dossier, confirmation was provided by an examining neurologist who was blinded to the treatment; operationalized via the annualized relapse rate.
c. Defined as an increase in the EDSS score of at least 1.5 points on the EDSS in patients with a baseline EDSS score of 0.0; or an increase of at least 1.0 point in patients with a baseline EDSS score of ≥ 1.0; according to the information provided by the company in Module 4 B of the dossier, the EDSS was recorded by an examining neurologist or a certified EDSS assessor who was blinded to the treatment; confirmed over a period of 24 weeks.
d. No suitable data available; see text below for explanation.

AE: adverse event; BVMT-R: Brief Visuospatial Memory Test Revised; EDSS: Expanded Disability Status Scale; IFN: interferon; PedsQL: Pediatric Quality of Life Inventory; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SDMT: Symbol Digit Modalities Test; SOC: System Organ Class

Confirmed relapses

In its benefit assessment, the company used results on multiple operationalizations for the outcome of confirmed relapses, including the annualized relapse rate and time to first relapse. The present assessment operationalizes the outcome using annualized relapse rate. Time to first relapse does not allow drawing conclusions regarding the total number of relapses and additionally depends on the annualized relapse rate. In the present benefit assessment, this operationalization is therefore presented only as supplementary information.

Confirmed disability progression (EDSS-based)

For its benefit assessment, the company used results on several operationalizations for the outcome "confirmed disability progression", including time-to-event analyses on the time to confirmed disability progression, each with confirmation after 12 or 24 weeks. For the outcome of confirmed disability progression, the time-to-event analyses are operationalized as time to disability progression with confirmation after 24 weeks.

In addition to analyses on confirmed disability progression, the company also used analyses on confirmed improvement in disability (also EDSS-based) for its assessment, which were not planned according to the study design and were prepared by the company post hoc for the dossier. These analyses were not used for the present benefit assessment. In Module 4 B of the dossier, the company itself describes that disability rarely occurs in paediatric patients with MS in the first 10 years of the disease. In the CONNECT study, three quarters of the children and adolescents in the relevant subpopulation had an EDSS of ≤ 1.5 at baseline, which corresponds to no disability. Only 6 children and adolescents had baseline EDSS scores of ≥ 3.0, which exceeded the presence of minimal disability. The mean time since the onset of the first MS symptoms was 1.2 to 1.6 years for the relevant subpopulation. Therefore, analyses on the confirmed improvement in disability were not relevant for the present benefit assessment.

Cognitive functioning (recorded using BVMT-R or SDMT)

The BVMT-R and the SDMT are both test methods used to assess cognitive functioning in patients with MS. In BVMT-R, patients are presented with a template containing 6 geometric shapes for 10 seconds, which they are asked to trace from memory as accurately as possible. There are a total of 3 rounds (learning trials 1 to 3), during which the same shapes are shown and traced. Based on the correct tracing and the correct indication of the shapes' position, 0 to 12 points can be achieved for each learning trial, with higher values indicating better cognitive functioning. The SDMT measures the attention and cognitive processing speed in patients with MS by assigning numerical values to symbols. The number of numerical values correctly assigned to the corresponding symbols corresponds to the total score. As with the BVMT-R, higher values indicate better cognitive functioning.

In Module 4 B of the dossier, the company presented both responder analyses on the proportion of children and adolescents with improvement or worsening by 15% of the scale range and continuous analyses on the change from baseline at weeks 48 and 96 for cognitive functioning, which was recorded using BVMT-R and SDMT. Due to uncertainties regarding the percentage of missing values, the analyses are not suitable for the benefit assessment. This is explained below.

The assessment of cognitive functioning using BVMT-R or SDMT was only introduced in the CONNECT study with protocol version 4 of 8 February 2016, whereby - according to information of the company in Module 4 B of the dossier - the approval of the amendment took until 2017 in some cases, depending on the study centre. At the start of the study, surveys were available for both tests for 58% of the children and adolescents in the relevant subpopulation, while no survey was available for 42% (for an overview of the missing and imputed values for both tests, see Table 19 in I Appendix D). However, the company provided no information on how many of the children and adolescents in total should have been surveyed at the start of the study, i.e. how many children and adolescents of the relevant subpopulation were included in the study from protocol version 4, or for what proportion there was no survey, as the approval of the amendment was delayed. It therefore remains unclear what proportion of the missing values at baseline is due to administrative reasons, i.e. due to the late or delayed introduction of the tests, and what proportion is due to other, potentially informative reasons. The assessment report of the European regulatory authority shows that 68 children and adolescents were randomized after protocol version 5 was finalised on 25 July 2017 [11]. However, the dossier provided no information on how many children and adolescents were randomized from protocol version 4. In addition, as described in Section I 3.2, there are potentially up to 6 additional children and adolescents with missing values (5 in the control arm and 1 in the intervention arm) due to the uncertainty regarding the adequate implementation of the ITT principle. Based on the available information , it is therefore not possible to assess whether the results can still be interpreted despite the high percentage of missing values of missing values.

In the responder analyses on the proportion of children and adolescents with an improvement or worsening by 15% of the scale range, children and adolescents for whom a baseline value was available but no survey was available at week 48 or 96 were replaced by means of non-responder imputation (NRI). The proportion of NRI-imputed values for the two tests was up to 3% at week 48 and up to 16% at week 96. The approximately 42% of children and adolescents in the relevant subpopulation without baseline value were not imputed in these analyses (see Table 19 of the full dossier assessment). As described above, it remains unclear for how many of the children and adolescents a baseline survey should be available, so that the percentage of missing values for administrative or other reasons cannot be assessed. In addition, the NRI imputation strategy used for the responder analyses is not adequate in the present therapeutic indication. For children and adolescents in the present therapeutic indication, both worsening and improvement in cognitive functioning is possible, which may also be due to developmental processes. The responder analyses presented by the company are therefore unsuitable for the benefit assessment.

Missing values were not imputed for the analyses on the change since the start of the study. In these analyses, the percentage of missing values at week 48 was up to 45% and at week 96

up to 59% of the relevant subpopulation (see Table 19 of the full dossier assessment). As already described above, it remains also unclear for the continuous analyses for how many of the children and adolescents a baseline survey should be available, so that the percentage of missing values for administrative or other reasons cannot be assessed. Due to the high percentage of missing values, the continuous analyses are thus also not suitable for the benefit assessment.

Irrespective of the uncertainties described above, it also remains unclear whether the analyses on the BVMT-R presented by the company correspond to the analyses intended for this test. For the BVMT-R, the company only presented analyses on the 3 individual learning trials. However, the sources on the BVMT-R presented by the company also describe analyses on all 3 learning trials [12,13]. Since the company did not present a source in which the planned analyses of the BVMT-R are described (such as the manual), it remains unclear whether a joint analysis on all 3 learning trials might be preferable.

Fatigue and health-related quality of life (measured using the PedsQL Multidimensional Fatigue Scale and PedsQL Quality of Life Scale)

In Module 4 B of the dossier, the company presented both responder analyses on the proportion of children and adolescents with improvement or worsening by 15% of the scale range and continuous analyses on the change from baseline at weeks 24, 48, 72 and 96 for the outcomes of fatigue (PedsQL Multidimensional Fatigue Scale) and health-related quality of life (PedsQL Multidimensional Fatigue Scale). Due to the high percentage of missing values, the analyses are not suitable for the assessment. This is explained below.

In the responder analyses on the proportion of children and adolescents with an improvement or worsening by 15% of the scale range, children and adolescents for whom a baseline value was available but no survey at week 48, 72 or 96 was available were imputed by means of NRI (for an overview of the missing and imputed values, see Table 19 of the full dossier assessment). The proportion of NRI-imputed values for the PedsQL Multidimensional Fatigue Scale was 13% at week 48, 20% at week 72 and 25% at week 96; for the PedsQL Quality of Life Scale it was approx. 23% at week 48, approx. 34% at week 72 and approx. 49% at week 96. For around 17 to 19% (depending on the scale) of the children and adolescents without a baseline value, no imputation was carried out in these analyses either. However, as described above for the analyses on cognitive functioning, the NRI imputation strategy used for the responder analyses is also not adequate for fatigue and health-related quality of life in the present therapeutic indication, as both an improvement and a worsening of fatigue and health-related quality of life are possible for children and adolescents in the present therapeutic indication. The responder analyses presented by the company are therefore unsuitable for the benefit assessment.

Missing values were not imputed for the analyses on the change since the start of the study. In these analyses, the percentage of missing values for the PedsQL Multidimensional Fatigue Scale was 32% at week 48, 39% at week 72 and 44% at week 96; for the PedsQL Quality of Life Scale it was approx. 40% at week 48, approx. 51% at week 72 and approx. 66% at week 96 (see Table 19 of the full dossier assessment). In addition, as described in Section I 3.2, there are potentially 6 additional children and adolescents with missing values (5 in the control arm and 1 in the intervention arm) due to the uncertainty regarding the adequate implementation of the ITT principle. Due to the high percentage of missing values, these analyses are thus also not suitable for the benefit assessment.

Side effects

Analyses on the basis of the relative risk

In Module 4 B of the dossier, the company presented analyses based on the RR for the outcomes of the side effects category for the relevant subpopulation. As described in Section I 3.2, the difference in the proportion of children and adolescents who discontinued treatment led to a difference of 14.3% between the study arms in the mean duration of exposure to the study medication for the total population of the study. Since the observation of the outcomes in the side effects category was linked to the duration of treatment, it is assumed that similar differences between the study arms also result for the duration of observation for these outcomes. For the relevant subpopulation, the company presented neither data on study and treatment discontinuations nor on the treatment durations or the outcome-specific observation durations of the study arms, which are necessary for the benefit assessment. The relevant subpopulation accounts for 90% of the total study population that received at least 1 dose of the study medication. Based on the available data for the total population, it is therefore assumed for this population that - as in the total population - treatment durations or observation durations are sufficiently comparable. This means that the analyses presented by the company can be interpreted on the basis of RRs. However, the extent of the observed effects for outcomes of the side effects category cannot be quantified due to the remaining uncertainty regarding the outcome-specific observation durations for the relevant subpopulation (missing data). Due to the different proportions of treatment discontinuations and the resulting different observation durations, there are also incomplete observations for potentially informative reasons. This is taken into account when assessing the risk of bias (see Section I 4.2).

SAEs and discontinuation due to AEs

In the analyses on the outcomes of SAEs and discontinuation due to AEs presented by the company in Module 4 B of the dossier, events attributable to the progression of the underlying disease (MS relapse, PT, see Table 21 and Table 22 in I Appendix E to the full dossier assessment) were apparently also recorded in addition to treatment-related AEs. The overall rates of SAEs and discontinuations due to AEs without disease-related events had to be

analysed for an adequate assessment of the side effects. The overall rates of SAEs and discontinuations due to AEs are therefore not suitable for the present benefit assessment.

Infections and infestations (SAE)

For infections and infestations, the company only presents analyses for the total population of the study and no analyses for the relevant subpopulation in Module 4 B of the dossier. Since the relevant subpopulation accounts for 90% of the total study population who received at least 1 dose of the study medication, the results of the total population are used as an approximation for the present benefit assessment.

I 4.2 Risk of bias

Table 11 describes the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: dimethyl fumarate vs. IFNβ1a

Study	Study level	Outcomes													
		All-cause mortality[a]	Confirmed relapses[b]	Confirmed disability progression (based on EDSS)[c]	Cognitive functioning (BVMT-R, SDMT)	Fatigue (PedsQL Multidimensional Fatigue Scale)	Health-related quality of life (PedsQL)	SAEs	Discontinuation due to AEs	Vascular disorders (AE, SOC)	Flu-like illness (AE, PT)	Gastrointestinal disorders (AE, SOC)	Infections and infestations (SAE, SOC)	Skin and subcutaneous tissue disorders (AE, SOC)	Injury, poisoning and procedural complications (AE, SOC)
CONNECT	H	H[d, e]	H[d, e]	H[d, e]	–[f]	–[f]	–[f]	–[f]	–[f]	H[d, e, g]	H[d, e, g]	H[d, e, g]	H[d, e]	H[d, e, g]	H[d, e, g]

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Defined as new or recurrent neurological symptoms not associated with fever or infection, lasting at least 24 hours and confirmed by new objective neurological findings after assessment by the treating neurologist; according to the company's information in Module 4 B of the dossier, confirmation was provided by an examining neurologist who was blinded to the treatment; operationalized via the annualized relapse rate.
c. Defined as an increase in the EDSS score of at least 1.5 points on the EDSS in patients with a baseline EDSS score of 0.0; or an increase of at least 1.0 point in patients with a baseline EDSS score of ≥ 1.0; according to the information provided by the company in Module 4 B of the dossier, the EDSS was recorded by an examining neurologist or a certified EDSS assessor who was blinded to the treatment; confirmed over a period of 24 weeks.
d. High risk of bias across outcomes.
e. Incomplete observations for potentially informative reasons.
f. No suitable data available; for the reasoning, see Section I 4.1 of the present dossier assessment.
g. Lack of blinding in subjective recording of outcomes or subjective outcome.

AE: adverse event; BVMT-R: Brief Visuospatial Memory Test Revised; EDSS: Expanded Disability Status Scale; H: high; IFN: interferon; L: low; PedsQL: Pediatric Quality of Life Inventory; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SDMT: Symbol Digit Modalities Test; SOC: System Organ Class

The risk of bias across outcomes for the CONNECT study is high due to the great number of protocol violations in the study, for which it remains unclear to what extent the study design was deviated from and how the deviations affected the data integrity or the safety of the

children and adolescents (see Section I 3.2 for a detailed explanation). This also leads to a high risk of bias for the results of all individual outcomes surveyed in the study.

As described in Section I 3.2, there are differences in the duration of treatment and observation between the study arms. This results in uncertainty due to incomplete observations for potentially informative reasons, which also contribute to the high risk of bias of the results for the outcomes in the side effects category and the outcomes of all-cause mortality, confirmed relapses and confirmed disability progression. Results on non-serious specific AEs have an additional high risk of bias due to the lack of blinding.

No suitable data are available for further outcomes in the categories “morbidity” and “health-related quality of life”, as there are uncertainties in the proportions of missing values or the proportions of missing values are too high (see Section I 4.1 for details). Hence, the risk of bias of the results is not assessed for these outcomes.

Summary assessment of the certainty of conclusions

For the subpopulation of the CONNECT study presented by the company, it remains unclear whether it also includes children and adolescents with highly active disease despite appropriate pretreatment with a disease-modifying therapy in addition to children and adolescents in the present research question. Even if the proportion of this patient group in the subpopulation presented by the company is low at up to 14%, it remains unclear whether the results of this population can be transferred without restriction to the target population of treatment-naive and of pretreated children and adolescents without highly active disease (see Section I 3.2 for a detailed explanation). In addition, the risk of bias across outcomes for the CONNECT study is deemed high due to a large number of protocol deviations because it remains unclear whether the deviations affect the results of the study (for a detailed discussion, see Section I 3.2). Overall, this reduces the certainty of conclusions of the study results for the present research question. Based on the CONNECT study, at most hints, e.g. of an added benefit, can be derived for all presented outcomes.

I 4.3 Results

Table 12, Table 13 and Table 14 summarize the results of the comparison of dimethyl fumarate with IFN-β1a in children and adolescents (≥ 13 to < 18 years) with RRMS who had not yet received disease-modifying therapy or children and adolescents with disease-modifying pretreatment whose disease is not highly active. Where necessary, calculations conducted by the Institute are provided to supplement the data from the company’s dossier.

Table 12: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: dimethyl fumarate versus IFN-β1a (multipage table)

Study outcome category outcome	Dimethyl fumarate		IFN-β1a		Dimethyl fumarate vs. IFN-β 1a
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
CONNECT					
Mortality					
All-cause mortality[b]	71	0 (0)	64	0 (0)	-
Morbidity					
Cognitive functioning					
BVMT-R			No suitable data available[c]		
SDMT			No suitable data available[c]		
Fatigue (PedsQL Multidimensional Fatigue Scale)			No suitable data available[c]		
Health-related quality of life					
PedsQL Quality of Life Scale			No suitable data available[c]		
Side effects					
AEs (supplementary information)	71	68 (96)	64	61 (95)	-
SAEs			No suitable data available[c]		
Discontinuation due to AEs			No suitable data available[c]		
Vascular disorders (AE, SOC)[d]	71	34 (48)	64	6 (9)	5.11 [2.30; 11.36]; < 0.001
Flu-like illness (AE, PT)	71	2 (3)	64	33 (52)	0.05 [0.01; 0.22]; <0.001
Gastrointestinal disorders (AE, SOC)[e]	71	53 (75)	64	20 (31)	2.39 [1.62; 3.52]; <0.001
Infections and infestations (SAE, SOC)[f]	78	2 (3)	72	0 (0)	4.62 [0.23; 94.64] 0.223[g]
Side effects					
Skin and subcutaneous tissue disorders (AE, SOC)[h]	71	22 (31)	64	3 (5)	6.61 [2.08; 21.04]; 0.001
Injury, poisoning and procedural complications (AE, SOC)	71	16 (23)	64	4 (6)	3.61 [1.27; 10.22]; 0.016

Table 12: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: dimethyl fumarate versus IFN-β1a (multipage table)

Study outcome category outcome	Dimethyl fumarate		IFN-β1a		Dimethyl fumarate vs. IFN-β 1a
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]

a. CI and p-value according to Wald's method.
b. The results on all-cause mortality are based on the data on fatal AEs.
c. See Section I 4.1 of the present dossier assessment for the reasoning.
d. Mainly includes the following events (MedDRA coding): flush (PT) and hot flush (PT).
e. Chiefly comprises the following events (MedDRA coding): abdominal pain (PT), vomiting (PT), diarrhoea (PT), abdominal pain upper (PT) and nausea (PT).
f. No data on the relevant subpopulation available; data refer to patients aged ≥ 10 to < 18 years who received at least 1 dose of the study medication.
g. Institute's calculation of effect (due to 0 events in one study arm with correction factor 0.5 in both study arms); CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [14]).
h. Mainly includes the following events (MedDRA coding): rash (PT) and erythema (PT).

AE: adverse event; BVMT-R: Brief Visuospatial Memory Test-Revised; CI: confidence interval; IFN: interferon; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of patients aged ≥ 13 to < 18 years who received at least 1 dose of the study medication; PT: preferred term; RCT: randomized controlled trial; RR: relative risk; SDMT: Symbol Digit Modalities Test; AE: serious adverse event; SOC: System Organ Class

Table 13: Results (morbidity, confirmed relapses) – RCT, direct comparison: dimethyl fumarate vs. IFN-β1a

Study outcome category outcome	Dimethyl fumarate			IFN-β1a			Dimethyl fumarate vs. IFN-β 1a
	N	n_E	annualized relapse rate [95% CI]	N	n_E	annualized relapse rate [95% CI]	rate ratio [95 % CI]; p-value
CONNECT							
Morbidity							
Confirmed relapses[a, b]							
Annualized relapse rate	70	32	0.22 [0.13; 0.37][c]	64	52	0.60 [0.39; 0.92][c]	0.37 [0.20; 0.68]; 0.002[c]

a. Defined as new or recurrent neurological symptoms not associated with fever or infection, lasting at least 24 hours and confirmed by new objective neurological findings as assessed by the treating neurologist.
b. One patient from the intervention arm was excluded from the analyses due to missing information on relapses prior to the study.
c. Estimated using a negative binomial regression model, adjusted for relapse rate at baseline (the number of relapses in the 3 years prior to the study divided by 3), age group and EDSS at baseline.

IFN: interferon; CI: confidence interval; N number of patients aged ≥ 13 to < 18 years who received at least 1 dose of the study medication; n_E: number of events; RCT: randomized controlled trial

Table 14: Results (morbidity, time to event) – RCT, direct comparison: dimethyl fumarate vs. IFN-β1a

Study outcome category outcome	Dimethyl fumarate N	Dimethyl fumarate median time to event in weeks [95% CI] patients with event n (%)	IFN-β1a N	IFN-β1a median time to event in weeks [95% CI] patients with event n (%)	Dimethyl fumarate vs. IFN-β 1a HR [95% CI]; p-value
CONNECT					
Morbidity					
Confirmed relapses[a, b]					
Time to first confirmed relapse (supplementary information)	*70*	*NA* *20 (28)*	*64*	*94.4 [61.0; NC]* *29 (45)*	*0.42 [0.23; 0.77]; 0.005*[c]
Confirmed disability progression (EDSS-based)[d]	71	NA 3 (4)	64	NA 4 (6)	0.58 [0.13; 2.65]; 0.485[c]

a. Defined as new or recurrent neurological symptoms not associated with fever or infection, lasting at least 24 hours and confirmed by new objective neurological findings as assessed by the treating neurologist.
b. One patient from the intervention arm was excluded from the analyses due to missing information on relapses prior to the study.
c. Hazard ratio calculated using a Cox proportional hazards model, adjusted for relapse rate at baseline (the number of relapses in the 3 years before the study, divided by 3), age group and EDSS at baseline.
d. Time to first confirmed 24-week disability progression; defined as an increase in EDSS score of at least 1.5 points on the EDSS in patients with an EDSS score of 0.0 at baseline; or an increase of at least 1.0 point in patients with an EDSS score of ≥ 1.0 at baseline; confirmed over a 24-week period.

CI: confidence interval; HR: hazard ratio; IFN: interferon; n: number of patients with (at least 1) event; N: number of patients aged ≥ 13 to < 18 years who received at least 1 dose of the study medication; NA: not achieved; NC: not calculable; RCT: randomized controlled trial

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (see Section I 4.2).

Mortality

All-cause mortality

The results on all-cause mortality are based on data on fatal AEs. No deaths occurred within the framework of the study. There is no hint of an added benefit of dimethyl fumarate in comparison with IFN-β1a; an added benefit is therefore not proven.

Morbidity

Confirmed relapses

A statistically significant difference between treatment groups in favour of dimethyl fumarate was shown for the outcome of confirmed relapses. There is a hint of added benefit of dimethyl fumarate in comparison with IFN-β 1a.

Confirmed disability progression (EDSS-based)

No statistically significant difference between treatment groups was found for the outcome of confirmed disability progression (EDSS-based). There is no hint of an added benefit of dimethyl fumarate in comparison with IFN-β1a; an added benefit is therefore not proven.

Cognitive functioning (recorded using BVMT-R or SDMT)

No suitable data are available for the outcome of cognitive functioning (recorded with BVMT-R or SDMT) (for reasons, see Section I 4.1). There is no hint of an added benefit of dimethyl fumarate in comparison with IFN-β1a; an added benefit is therefore not proven.

Fatigue (recorded using the PedsQL Multidimensional Fatigue Scale)

No suitable data were available for the outcome "fatigue" (recorded using the PedsQL Multidimensional Fatigue Scale) (for reasons, see Sections I 4.1). There is no hint of an added benefit of dimethyl fumarate in comparison with IFN-β1a; an added benefit is therefore not proven.

Health-related quality of life (recorded using the PedsQL Quality of Life Scale)

No suitable data were available for health-related quality of life (recorded using the PedsQL Quality of Life Scale) (for reasons, see Sections I 4.1). There is no hint of an added benefit of dimethyl fumarate in comparison with IFN-β1a; an added benefit is therefore not proven.

Side effects

SAEs, discontinuation due to AEs

The analyses on the outcomes "SAEs" and "discontinuations due to AEs" presented by the company consider disease-related events. As a result, the overall rates on "SAEs" and "discontinuations due to AEs" are not suitable for the assessment of the side effects of dimethyl fumarate. However, based on the results on frequent SAEs and discontinuations due to AEs (see I Appendix E), in view of the low proportion of children and adolescents with events for the outcomes of SAEs and discontinuation due to AEs, no negative effects are expected to an extent that could call into question the added benefit of dimethyl fumarate. For the outcomes, there is no hint of greater or lesser harm from dimethyl fumarate in comparison with IFN-β1a; greater or lesser harm is therefore not proven.

Vascular disorders (AE), gastrointestinal disorders (AE), skin and subcutaneous tissue disorders (AE) and injury, poisoning and procedural complications (AE)

For the outcomes of vascular disorders (AE), gastrointestinal disorders (AE), skin and subcutaneous tissue disorders (AE) and injury, poisoning and procedural complications (AE), there is a statistically significant difference between the treatment groups to the disadvantage of dimethyl fumarate. There is a hint of greater harm from dimethyl fumarate in comparison with IFN-β 1a.

Flu-like illness (AE)

A statistically significant difference between treatment groups in favour of dimethyl fumarate was shown for the outcome of flu-like illness (AE). There is a hint of lesser harm from dimethyl fumarate in comparison with IFN-β 1a.

Infections and infestations (SAEs)

No statistically significant difference between the treatment groups was shown for the outcome "infections and infestations" (SAEs). There is no hint of greater or lesser harm from dimethyl fumarate in comparison with IFN-β1a; greater or lesser harm is therefore not proven.

I 4.4 Subgroups and other effect modifiers

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

- Age (13 to 14 years vs. 15 to 17 years)
- sex (female versus male)

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least 1 subgroup.

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

In accordance with the methods described, no relevant effect modification by the characteristics “age” or “sex” was identified for the outcomes for which suitable data were available.

I 5 Probability and extent of added benefit

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

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

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Chapter I 4 (see Table 15).

Determination of the outcome category for symptom outcomes

It cannot be inferred from the dossier whether the following symptoms outcome is serious/severe or non-serious/non-severe. The classification of this outcome is explained below.

Confirmed relapses

For the outcome of confirmed relapses, data available to categorize the severity category as serious/severe are insufficient.

A total of 84 events occurred in 49 children and adolescents for the outcome of confirmed disease relapses. As part of the analyses on AEs, the company presented data on the PT “MS relapse”, whereby it also made a classification according to severity (mild, moderate, severe). However, this classification is not relevant for the present benefit assessment, as the delineation of the individual categories is not considered suitable. This is particularly due to the fact that impacts on the daily lives of the children and adolescents were categorized as both moderate and severe. According to the company's information in Module 4 B of the dossier, moderate was defined as effects on performance and activities of daily living, while severe was defined as considerable effects on daily living. However, the extent to which this was differentiated remains unclear on the basis of the information available. In addition, this categorization results in a contradiction to the available data on SAEs that occurred for the PT. This is explained below.

In the relevant subpopulation, a total of 54 children and adolescents had at least one AE for the PT “MS relapse”. Of these, 18 children and adolescents had at least one mild AE, 32 had at least one moderate AE and 4 had at least one severe AE according to the categorization carried out by the company. However, the information on common SAEs shows that at least one SAE for this PT occurred in 27 of the 54 children and adolescents. It remains unclear what

proportion of these SAEs represent confirmed disease relapses and what proportion of these SAEs occurred within the observation period for the outcome of confirmed disease relapses (i.e. under treatment excluding the up to 4-week follow-up period). Information on the proportion of children and adolescents with at least one SAE of the PT that occurred during treatment is required to assess the severity of the outcome “confirmed relapses”. In view of the discrepancies with the classification by severity presented by the company and the insufficient information on SAEs for the PT “MS relapse”, the outcome “confirmed relapses” was assigned to the outcome category “not serious/not severe”.

Table 15: Extent of added benefit at outcome level: dimethyl fumarate vs. IFN-β1a (multipage table)

Outcome category **outcome**	**Dimethyl fumarate vs. IFN-β 1a** **median time to event (weeks) or proportion of events (%) or annualized rate** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0% RR: -	Lesser/added benefit not proven
Morbidity		
Confirmed relapses	Annualized rate: 0.22 vs. 0.60 Rate ratio: 0.37 [0.20; 0.68] p = 0.002 probability: hint	Outcome category: non-serious/non-severe symptoms/late complications $CI_U < 0.80$ added benefit; extent: “considerable”
Confirmed disability progression (EDSS-based)	Median: NA vs. NA HR: 0.58 [0.13; 2.65] p = 0.485	Lesser/added benefit not proven
cognitive functioning		
BVMT-R	No suitable data	Lesser benefit/added benefit not proven
SDMT	No suitable data	Lesser/added benefit not proven
Fatigue (PedsQL Multidimensional Fatigue Scale)	No suitable data	Lesser/added benefit not proven
Health-related quality of life		
PedsQL Quality of Life Scale	No suitable data	Lesser/added benefit not proven
Side effects		
SAEs	No suitable data	Greater/lesser harm not proven
Discontinuation due to AEs	No suitable data	Greater harm/lesser harm not proven
Vascular disorders (AE)	48% vs. 9% RR: 5.11 [2.30; 11.36] RR: 0.20 [0.09; 0.43][c] p < 0.001 probability: hint	Outcome category: non-serious/non-severe side effects greater harm, extent: "non-quantifiable”[d]
Flu-like illness (AE)	3% vs. 52% RR: 0.06 [0.01; 0.22] p < 0.001 probability: hint	Outcome category: non-serious/non-severe side effects lesser harm, extent: "non-quantifiable"[d]

Table 15: Extent of added benefit at outcome level: dimethyl fumarate vs. IFN-β1a (multipage table)

Outcome category **outcome**	**Dimethyl fumarate vs. IFN-β 1a** **median time to event (weeks) or proportion of events (%) or annualized rate** **effect estimation [95% CI];** **p-value** **probability[a]**	**Derivation of extent[b]**
Gastrointestinal disorders (UE)	75% vs. 31% RR: 2.39 [1.62; 3.52] RR: 0.42 [0.28; 0.62][c] p < 0.001 probability: hint	Outcome category: non-serious/non-severe side effects greater harm, extent: "non-quantifiable"[d]
Infections and infestations (SAEs)[e]	3% vs. 0% RR: 4.62 [0.23; 94.64] p = 0.223	Greater/lesser harm not proven
Skin and subcutaneous tissue disorders (AEs)	31% vs. 5% RR: 6.61 [2.08; 21.04] RR: 0.15 [0.05; 0.48][c] p = 0.001 probability: hint	Outcome category: non-serious/non-severe side effects greater harm, extent: "non-quantifiable"[d]
Injury, poisoning and procedural complications (AE)	23% vs. 6% RR: 3.61 [1.27; 10.22] RR: 0.28 [0.10; 0.79][c] p = 0.016 probability: hint	Outcome category: non-serious/non-severe side effects greater harm, extent: "non-quantifiable"[d]

a. Probability provided there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
d. The extent of the observed effects for the outcomes of the side effects category cannot be quantified due to uncertainties regarding the outcome-specific observation periods for the relevant subpopulation (for explanation see Section I 4.1).
e. No data on the relevant subpopulation available; data refer to patients aged ≥ 10 to < 18 years who received at least 1 dose of the study medication.

AE: adverse event; BVMT-R: Brief Visuospatial Memory Test-Revised; CI: confidence interval; CI_o: upper limit of the confidence interval; IFN: interferon; NA: not achieved; PedsQL: Pediatric Quality of Life Inventory; SAE: serious adverse event; SDMT: Symbol Digit Modalities Test

I 5.2 Overall conclusion on added benefit

Table 16 summarizes the results included in the overall conclusion on the extent of added benefit.

Table 16: Positive and negative effects from the assessment of dimethyl fumarate in comparison with the ACT

Positive effects	**Negative effects**
Morbidity ▪ confirmed relapses: hint of added benefit – extent: “considerable”	–
Non-serious/non-severe side effects ▪ flu-like illness (AE): hint of lesser harm; extent: “non-quantifiable”	Non-serious/non-severe side effects ▪ vascular disorders (AE): hint of greater harm – extent: “non-quantifiable” ▪ gastrointestinal disorders (AE): hint of greater harm – extent: "non-quantifiable" ▪ skin and subcutaneous tissue disorders (AE): hint of greater harm – extent: "non-quantifiable" ▪ injury, poisoning, and procedural complications (AE): hint of greater harm – extent: “non-quantifiable”
No suitable data are available for the outcomes of cognitive functioning, fatigue, health-related quality of life, SAEs and discontinuation due to AEs.	
AE: adverse event; SAE: serious adverse event	

Overall, there were positive effects of dimethyl fumarate compared to IFN-β 1a with the extent “considerable” or “non-quantifiable” for the outcomes of confirmed relapses and flu-like illness (AE) . This was accompanied by several negative effects for the outcomes of side effects. However, the extent of the observed negative effects for these outcomes cannot be quantified due to uncertainties regarding the outcome-specific observation periods for the relevant subpopulation (for explanation see Section I 4.1). For the present benefit assessment, it is therefore not possible to estimate whether or to what extent the negative effects raise doubts about the positive effects. However, in the present data situation it is assumed that the positive effects are not completely questioned.

In summary, for children and adolescents aged ≥ 13 to < 18 years with RRMS who have not yet received disease-modifying therapy or children and adolescents who have received disease-modifying therapy and whose disease is not highly active, there is a hint of a non-quantifiable added benefit of dimethyl fumarate over IFN-β 1a.

The result of the assessment of the added benefit of dimethyl fumarate in comparison with the ACT is summarized in Table 17.

Table 17: Dimethyl fumarate – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Children and adolescents (≥ 13 to < 18 years) with RRMS who have not yet received disease-modifying therapy, or children and adolescents pretreated with disease-modifying therapy whose disease is not highly active[b]	**IFN-β1a** or IFN-β1b or glatiramer acetate under consideration of the approval status[c]	Hint of non-quantifiable added benefit

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. In analogy to the treatment algorithm recommended in the guidelines and the therapeutic indications approved to date for comparable treatment alternatives, a distinction is principally made between the patient populations with regard to previous therapy (treatment-naive or pretreated) and disease activity (not highly active, highly active). According to the G-BA, taking into account the drug properties of dimethyl fumarate, children and adolescents with highly active RRMS despite treatment with disease-modifying therapy are not considered to be the target population of dimethyl fumarate.
c. An unchanged continuation of the prior therapy is not considered an appropriate implementation of the ACT if there is a therapeutic indication to change the disease-modifying therapy.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IFN: interferon; RRMS: relapsing remitting multiple sclerosis

The assessment described above departs from that by the company, which, based on the results of the CONNECT study, derived an indication of a considerable added benefit for dimethyl fumarate compared with IFN-β 1a.

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

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 6.1 [online]. 2022 [Accessed: 27.01.2022]. URL: https://www.iqwig.de/methoden/allgemeine-methoden-v6-1.pdf.

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

3. Biogen. Open-Label, Randomized, Multicenter, Multiple-Dose, Active-Controlled, Parallel-Group, Efficacy and Safety Study of BG00012 in Children From 10 to Less Than 18 Years of Age With Relapsing-Remitting Multiple Sclerosis, With Optional Open-Label Extension; study 109MS306; Clinical Study Report [unpublished]. 2021.

4. Biogen. Phase 3 Efficacy and Safety Study of BG00012 in Pediatric Subjects With Relapsing-remitting Multiple Sclerosis (RRMS) (CONNECT) [online]. 2023 [Accessed: 02.08.2023]. URL: https://clinicaltrials.gov/ct2/show/NCT02283853.

5. Biogen Idec Research. Open-Label, Randomized, Multicenter, Multiple-Dose, Active Controlled, Parallel-Group, Efficacy and Safety Study of BG00012 in Children From 10 to Less Than 18 Years of Age With Relapsing-Remitting Multiple Sclerosis, With Optional Open-Label Extension [online]. [Accessed: 02.08.2023]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-002318-11/DE.

6. Vermersch P, Scaramozza M, Levin S et al. Effect of Dimethyl Fumarate vs Interferon beta-1a in Patients With Pediatric-Onset Multiple Sclerosis: The CONNECT Randomized Clinical Trial. JAMA Netw Open 2022; 5(9): e2230439. https://dx.doi.org/10.1001/jamanetworkopen.2022.30439.

7. Biogen Netherlands. Fachinformation TecfideraTM 120 mg/240 mg magensaftresistente Hartkapseln (Stand Mai 2022). 2022.

8. Biogen. AVONEX 30 Mikrogramm/0,5 ml Injektionslösung [online]. 2022 [Accessed: 15.09.2023]. URL: https://www.fachinfo.de/.

9. Blaschek DA, Müller-Felber PDW, Heinen UDF, Huppke PDP. S1-Leitlinie: Pädiatrische Multiple Sklerose. 2017.

10. Frahm N, Peters M, Bätzing J et al. Prevalence of pediatric multiple sclerosis in Germany: A nationwide population-based analysis. Eur J Neurol 2021; 28(9): 3173-3176. https://dx.doi.org/10.1111/ene.15015.

11. European Medicines Agency. TECFIDERA; Assessment report [online]. 2022 [Accessed: 10.07.2023]. URL: https://www.ema.europa.eu/documents/variation-report/tecfidera-h-c-2601-ii-0073-epar-assessment-report-variation_en.pdf.

12. Benedict RHB, Amato MP, Boringa J et al. Brief International Cognitive Assessment for MS (BICAMS): international standards for validation. BMC Neurol 2012; 12(1): 1-7.

13. Smerbeck AM, Parrish J, Yeh EA et al. Regression-Based Pediatric Norms for the Brief Visuospatial Memory Test – Revised and the Symbol Digit Modalities Test. Clin Neuropsychol 2011; 25(3): 402-412. https://dx.doi.org/10.1080/13854046.2011.554445.

14. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574. https://dx.doi.org/10.1016/0167-9473(94)90148-1.

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