IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Fingolimod (new therapeutic indication) – Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Fingolimod (neues Anwendungsgebiet – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 26 September 2014). 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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List of abbreviations

Abbreviation	Meaning
9-HPT	9-Hole Peg Test
ACT	appropriate comparator therapy
EDSS	Expanded Disability Status Scale
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IFN-β	interferon beta
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MFIS	Modified Fatigue Impact Scale
MRI	magnetic resonance imaging
MSFC	Multiple Sclerosis Functional Composite
PASAT	Paced Auditory Serial Addition Test-3
PRIMUS	Patient-Reported Indices for Multiple Sclerosis
QoL	quality of life
RCT	randomized controlled trial
RRMS	relapsing remitting multiple sclerosis
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
T25-FW	Timed 25-Foot Walk
TI	therapeutic indication
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug fingolimod (new therapeutic indication). The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 19 June 2014.

Research question

The aim of this report was to assess the added benefit of fingolimod in comparison with the appropriate comparator therapy (ACT) for the expansion of the therapeutic indication of fingolimod approved in May 2014. This expansion includes adult patients with highly active relapsing remitting multiple sclerosis (RRMS) who have received pretreatment with a disease-modifying therapy other than interferon beta (IFN-β).

2 research questions result from this, for which the G-BA specified the ACT presented in Table 2.

Table 2: Subindications and ACT for fingolimod

Research question	Subindication	ACT specified by the G-BA
1	Patients with highly active RRMS, full previous treatment with disease-modifying therapy (other than IFN-β)	GA or IFN-β1a or 1b. Switching depended on prior therapy.
2	Patients with highly active RRMS, incomplete treatment with disease-modifying therapy (other than IFN-β)	Continuation of the disease-modifying therapy started with GA[a], with an optimized dosage according to the approval up to an adequate course (normally lasting at least one year). If the disease-modifying therapy was started with other drugs, switching to GA or IFN-β with an optimized dosage according to the approval up to an adequate course is to be conducted.
a: In the specification of the ACT for the total patient population, the G-BA also named IFN-β as possible treatment to be continued. However, this is not relevant for the assessment of the expansion of the therapeutic indication. ACT: appropriate comparator therapy; GA: glatiramer acetate; G-BA: Federal Joint Committee; IFN-β: interferon beta; RRMS: relapsing remitting multiple sclerosis		

The assessment was conducted based on patient-relevant outcomes and on randomized controlled trials (RCTs).

Results for research question 1: patients with highly active RRMS, full previous treatment with disease-modifying therapy (other than IFN-β)

The TRANSFORMS study, a multicentre three-arm RCT with a treatment duration of 12 months was included in the assessment. Fingolimod was compared with IFN-β1a. A total of 866 patients were included in the study arms relevant for the assessment, of which only 402 patients (46.4%) had high disease activity. Of the 402 patients with high disease activity, 263 patients (30.4% of the total study population) had received full previous treatment with a disease-modifying therapy. Only 42 of the 263 patients (just under 5% of the total study population) had been pretreated with a disease-modifying therapy other than IFN-β and therefore corresponded to the subpopulation relevant for the present benefit assessment (17 patients in the fingolimod arm and 25 patients in the IFN-β1a arm). This considerably reduces the informative value of the study for the present research question.

The risk of bias of the study was rated as low. The risk of bias at outcome level was rated as high for some outcomes.

Mortality

Deaths

No deaths occurred. An added benefit of fingolimod compared with IFN-β1a for deaths is therefore not proven.

Morbidity

Relapses

There was no statistically significant difference between the treatment groups for any of the analyses on relapses. An added benefit of fingolimod compared with IFN-β1a for relapses is therefore not proven.

Disability progression

There was no statistically significant difference between the treatment groups for any of the analyses on disability progression. An added benefit of fingolimod compared with IFN-β1a for disability progression is therefore not proven.

Disability severity

The company's dossier contained no evaluable data on disability severity for the relevant subpopulation. An added benefit of fingolimod compared with IFN-β1a for disability severity is therefore not proven.

Fatigue

Fatigue was recorded with the Modified Fatigue Impact Scale (MFIS). The company's dossier contained no evaluable data on fatigue for the relevant subpopulation. An added benefit of fingolimod compared with IFN-β1a for fatigue is therefore not proven.

Activities of daily living

Activities of daily living were recorded with the Patient-Reported Indices for Multiple Sclerosis (PRIMUS) activities. The company's dossier contained no evaluable data on activities of daily living for the relevant subpopulation. An added benefit of fingolimod compared with IFN-β1a for activities of daily living is therefore not proven.

Health status

Health status was recorded with the European Quality of Life-5 Dimensions visual analogue scale (EQ-5D VAS). The company's dossier contained no evaluable data on this outcome for the relevant subpopulation. An added benefit of fingolimod compared with IFN-β1a for the EQ-5D VAS is therefore not proven.

Health-related quality of life

Health-related quality of life was recorded with the PRIMUS quality of life (QoL). The company's dossier contained no evaluable data on health-related quality of life for the relevant subpopulation. An added benefit of fingolimod compared with IFN-β1a for health-related quality of life is therefore not proven.

Adverse events

There was no statistically significant difference with regard to serious adverse events or discontinuation due to adverse events. Greater or lesser harm from fingolimod compared with IFN-β1a for adverse events is therefore not proven.

Results for research question 2: patients with highly active RRMS, incomplete treatment with disease-modifying therapy (other than IFN-β)

No data were available for a comparison of fingolimod versus the ACT for patients with highly active RRMS who received incomplete treatment with a disease-modifying therapy other than IFN-β. An added benefit of fingolimod is therefore not proven for this population.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

Research question 1: patients with highly active RRMS, full previous treatment with disease-modifying therapy (other than IFN-β)

In summary, there is no proof of added benefit of fingolimod versus the ACT IFN-β1a for patients with highly active RRMS who received full previous treatment with a disease-modifying therapy other than IFN-β.

Research question 2: patients with highly active RRMS, incomplete treatment with disease-modifying therapy (other than IFN-β)

Since the company submitted no data for patients with highly active RRMS who received incomplete treatment with a disease-modifying therapy other than IFN-β, an added benefit of fingolimod versus the ACT is not proven for this subpopulation.

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

[4] 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), see [1]. 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, no added benefit, or less benefit), see [2].

Table 3: Fingolimod – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Patients with highly active RRMS, full previous treatment with disease-modifying therapy (other than IFN-β)	GA or **IFN-β1a** or 1b. Switching depended on prior therapy.	Added benefit not proven
Patients with highly active RRMS, incomplete treatment with disease-modifying therapy (other than IFN-β)	Continuation of the disease-modifying therapy started with GA[b], with an optimized dosage according to the approval up to an adequate course. If the disease-modifying therapy was started with other drugs, switching to GA or IFN-β with an optimized dosage according to the approval up to an adequate course is to be conducted.	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: In the specification of the ACT for the total patient population, the G-BA also named IFN-β as possible treatment to be continued. However, this is not relevant for the assessment of the expansion of the therapeutic indication.
ACT: appropriate comparator therapy; GA: glatiramer acetate; G-BA: Federal Joint Committee; IFN-β: interferon beta; RRMS: relapsing remitting multiple sclerosis

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

2.2 Research question

The aim of this report was to assess the added benefit of fingolimod in comparison with the ACT for the expansion of the therapeutic indication of fingolimod approved in May 2014.

The assessment refers to adult patients with highly active RRMS who have high disease activity despite treatment with at least one disease-modifying therapy (other than IFN-β). These patients may be defined as those who have failed to respond to a full and adequate course (normally at least one year of treatment) of at least one disease-modifying therapy. Patients should have had at least one relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial magnetic resonance imaging (MRI) or at least one Gadolinium-enhancing lesion. A "non-responder" could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.

The assessment of fingolimod in patients with highly active RRMS despite IFN-β pretreatment was already the subject of the benefit assessment A11-23 after the first approval of fingolimod [3] and is not the subject of the present assessment. Fingolimod is also approved for patients with rapidly evolving severe RRMS (according to the definition provided in the Summary of Product Characteristics [SPC] [4]). This patient population is not affected by the expansion of approval. The benefit assessment for this population was also conducted in A11-23 [3] and is not subject of the present assessment.

2 research questions result from the benefit assessment on the expansion of the therapeutic indication, for which the G-BA specified the ACT presented in Table 4.

Table 4: Subindications and ACT for fingolimod

Research question	Subindication	ACT specified by the G-BA
1	Patients with highly active RRMS, full previous treatment with disease-modifying therapy (other than IFN-β)	GA or IFN-β1a or 1b. Switching depended on prior therapy.
2	Patients with highly active RRMS, incomplete treatment with disease-modifying therapy (other than IFN-β)	Continuation of the disease-modifying therapy started with GA[a], with an optimized dosage according to the approval up to an adequate course (normally lasting at least one year). If the disease-modifying therapy was started with other drugs, switching to GA or IFN-β with an optimized dosage according to the approval up to an adequate course is to be conducted.
a: In the specification of the ACT for the total patient population, the G-BA also named IFN-β as possible treatment to be continued. However, this is not relevant for the assessment of the expansion of the therapeutic indication. ACT: appropriate comparator therapy; GA: glatiramer acetate; G-BA: Federal Joint Committee; IFN-β: interferon beta; RRMS: relapsing remitting multiple sclerosis		

The research question of the present benefit assessment deviates from the company's approach in various aspects.

Patient population

The company included the total population of patients with highly active RRMS, also the ones with IFN-β pretreatment, in its assessment. This deviates from the research question that was required and considered in the present dossier assessment, and which exclusively considers the patients affected by the expansion of approval (highly active RRMS despite pretreatment with disease-modifying therapy [other than IFN-β]).

Appropriate comparator therapy

The company chose IFN-β1a as ACT for both research questions (full previous treatment and incomplete pretreatment).

This choice was adequate for subpopulation 1 (full previous treatment with a disease-modifying therapy other than IFN-β) because switching treatment is appropriate in this subpopulation.

For subpopulation 2 (incomplete pretreatment with a disease-modifying therapy [other than IFN-β]), this choice was only adequate for part of the patients affected by the expansion of approval, namely those patients who had not been pretreated with IFN-β or with glatiramer acetate. For patients pretreated with glatiramer acetate, continued glatiramer acetate treatment is appropriate. For patients whose treatment was started with disease-modifying drugs other than IFN-β or glatiramer acetate, glatiramer acetate or IFN-β are appropriate.

The assessment was conducted based on patient-relevant outcomes and on RCTs.

Further information about the research question can be found in Module 3, Section 3.1, and Module 4, Section 4.2.1 of the dossier, and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

2.3 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 fingolimod (studies completed up to 28 April 2014)
- bibliographical literature search on fingolimod (last search on 28 April 2014)
- search in trial registries for studies on fingolimod (last search on 28 April 2014)

To check the completeness of the study pool:

- search in trial registries for studies on fingolimod (last search on 3 July 2014)

No additional relevant study was identified from the check.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.3.1 Research question 1: patients with highly active RRMS, full previous treatment with disease-modifying therapy (other than IFN-β)

2.3.1.1 Studies included

The TRANSFORMS study listed in the following table was included in the benefit assessment of fingolimod for patients with highly active RRMS despite full previous treatment with disease-modifying therapy other than IFN-β. This concurs with the company's approach.

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

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
TRANSFORMS	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. IFN-β: interferon beta; RCT: randomized controlled trial; vs.: versus			

Only a subpopulation of this study was relevant for the present benefit assessment. This is explained in Section 2.3.1.2.

Section 2.6 contains a reference list for the study included.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier, and in Sections 2.7.2.3.1 and 2.7.2.3.2 of the full dossier assessment.

2.3.1.2 Study characteristics

Characteristics of the study and of the intervention

Table 6 and Table 7 describe the TRANSFORMS study included in the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: fingolimod vs. IFN-β1a

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
TRANSFORMS	RCT, double-blind, parallel, multicentre, active-controlled, double-dummy	Adults with RRMS 1 relapse in the past year or 2 relapses in the past 2 years EDSS 0 – 5.5	Fingolimod 1.25 mg (N = 426)[b] fingolimod 0.5 mg (N = 431) IFN-β1a 30 µg IM (N = 435) relevant subpopulation thereof[c]: Fingolimod 0.5 mg (n = 17.4%)[d] IFN-β1a 30 µg IM (n = 25.7%)[d]	Screening: 45 days baseline phase: 7 days treatment duration: 12 months	Worldwide in 18 countries: Argentina (7 centres), Australia (7), Austria (6), Belgium (4), Brazil (6), Canada (9), Switzerland (2), Egypt (5), France (6), Germany (28), Greece (6), Hungary (6), Italy (22), Korea (4), Spain (8), Portugal (5), Great Britain (4), United States (37) 5/2006 – 11/2008	Primary: annualized relapse rate secondary: further relapse-related outcomes, disability progression, disability severity, fatigue, activities of daily living, health-related quality of life, adverse events

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes exclusively contain information on the relevant available outcomes for this benefit assessment.

b: The study arm is not relevant for the assessment because the dosage used does not conform to the approval and is no longer shown in the following tables.

c: Relevant subpopulation: adult patients with highly active RRMS who have high disease activity despite treatment with at least one disease-modifying therapy (other than IFN-β).

d: Percentages relative to the total population of the respective study arm; Institute's calculation.

EDSS: Expanded Disability Status Scale; IFN-β: interferon beta; IM: intramuscular; N: number of randomized patients; n: relevant subpopulation; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: fingolimod vs. IFN β1a

Study	Intervention	Comparison	Concomitant medication
TRANSFORMS	Fingolimod 0.5 mg oral administration once daily + placebo IM once weekly	IFN-β1a 30 µg IM once weekly + placebo oral administration once daily	Corticosteroids for treatment of relapse not allowed: immunosuppressants, immunoglobulins, monoclonal antibodies, IFN-β (except IFN-β1a), glatiramer acetate, ACTH
ACTH: adrenocorticotropic hormone; IFN-β: interferon beta; IM: intramuscular; RCT: randomized controlled trial; vs.: versus			

The TRANSFORMS study was a multicentre, double-blind RCT in which adult patients with RRMS were enrolled. The diagnosis of multiple sclerosis was made using the revised McDonald criteria [5]. Patients were enrolled who had experienced at least 1 relapse in the previous year or 2 relapses in the previous 2 years, and who had a baseline Expanded Disability Status Scale (EDSS) between 0 and 5.5. There were no limitations with regard to pretreatment.

The subpopulation relevant for the benefit assessment comprised the patients with high disease activity who had been pretreated with disease-modifying therapy other than IFN-β. With regard to the criterion of high disease activity, according to the definition of the SPC [4], these were those patients with at least 1 relapse in the previous year (and either at least 1 Gadolinium-enhancing lesion or at least 9 T2 lesions at enrolment) or the same number or more relapses in comparison with the previous year.

The study had a three-arm design. In 2 treatment arms, the patients received 0.5 mg or 1.25 mg fingolimod (oral administration) once daily. In the third treatment arm, the patients received IFN-β1a (30 µg) once weekly as intramuscular injection. All treatment groups also received a placebo of the respective other intervention (double-dummy design). Only the dosage of 0.5 mg daily is approved for fingolimod; therefore the treatment arm with 1.25 mg fingolimod daily is not relevant for the benefit assessment and will not be considered further.

A total of 866 patients were randomly assigned in a ratio of 1:1 to the 2 study arms relevant for the assessment (fingolimod 0.5 mg; IFN-β1a). However, only 402 patients (46.4%) of these had high disease activity [6]. Of the 402 patients with high disease activity, 263 patients (30.4% of the total study population) had received full previous treatment with a disease-modifying therapy. Only 42 of the 263 patients (just under 5% of the total study population) had been pretreated with a disease-modifying therapy other than IFN-β and therefore corresponded to the subpopulation relevant for the present benefit assessment (17 patients in the fingolimod arm and 25 patients in the IFN-β1a arm).

The primary outcome of the study was the annualized relapse rate; secondary outcomes were other relapse-related outcomes, disability progression, disability severity, fatigue, activities of daily living, health-related quality of life, and adverse events.

Characteristics of the study population

Table 8 shows the characteristics of the patients in the study included, referring to the subpopulation relevant for the assessment.

Table 8: Characteristics of the relevant subpopulation, highly active RRMS – RCT, direct comparison: fingolimod vs. IFN-β1a

Study characteristics category	**Fingolimod N = 17**	**IFN-β1a N = 25**
TRANSFORMS		
Age [years]: mean (SD)	38 (8)	36 (10)
Sex [F/M], %	59/41	64/36
Duration of disease [years]: mean (SD)	7.2 (4.2)	8.5 (8.0)
Baseline EDSS: mean (SD)	2.9 (1.4)	2.3 (2.5)
Number of relapses in last year: mean (SD)	1.7 (0.8)	1.8 (1.2)
Number of relapses in the last 2 years: mean (SD)	2.6 (1.4)	2.8 (2.5)
Patients without Gd-enhancing T1 lesions: n/N (%)	12 (70.6)	15 (62.5)[a]
Patients without pretreatment: n (%)	0 (0.0)	0 (0.0)
Treatment discontinuations: n (%)	ND[b]	ND[b]

a: According to the company's calculations, the percentages only refer to 24 patients; the company did not provide further information.

b: No information is available for the relevant patient population (research question 1).

EDSS: Expanded Disability Status Scale; F: female; Gd: Gadolinium; IFN-β: interferon beta; M: male; N: number of randomized (or included) patients; n: number of patients with event; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

There were no important differences between the treatment groups. The mean age of the patients was 37 years and the majority were women (approximately 60%). The disease duration in patients in the fingolimod arm was somewhat below the disease duration in the IFN-β1a patients (7.2 versus 8.5 years). The patients had approximately 1.8 relapses in the last year and approximately 2.7 relapses in the last 2 years. Approximately 65% of the patients had Gadolinium-enhancing T1 lesions. All patients had received pretreatment. There was no information on the number of treatment discontinuations for the relevant patient population.

Table 9 shows the risk of bias at study level.

Table 9: Risk of bias at study level – RCT, direct comparison: fingolimod 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
			Patient	Treating staff			
TRANSFORMS	Yes	Yes	Yes	Yes	Yes	Yes	Low
IFN-β: interferon beta; RCT: randomized controlled trial; vs.: versus							

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

Further information on study design, study populations and the risk of bias at study level can be found in Module 4, Sections 4.3.1.2.1, 4.3.1.2.2 and 4.3.2.1.2, and in Appendix 4-F of the dossier, and in Sections 2.7.2.4.1, 2.7.2.4.2 and 2.7.2.5 of the full dossier assessment.

2.3.2 Research question 2: patients with highly active RRMS, incomplete treatment with disease-modifying therapy (other than IFN-β)

The company presented no relevant study for the assessment of the added benefit of fingolimod versus the ACT in patients with highly active RRMS who received incomplete treatment with a disease-modifying therapy other than IFN-β.

2.4 Results on added benefit

2.4.1 Research question 1: patients with highly active RRMS, full previous treatment with disease-modifying therapy (other than IFN-β)

2.4.1.1 Outcomes included

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

- Mortality
  - all-cause mortality (deaths)
- Morbidity
  - relapse-related outcomes
    - time to first confirmed relapse
    - proportion of patients with confirmed relapse
    - annualized relapse rate
  - disability progression
    - time to first confirmed disability progression at month 12
    - proportion of patients with confirmed disability progression
  - disability severity
    - mean change in Multiple Sclerosis Functional Composite (MSFC-z) score
    - mean change in Timed 25-Foot Walk (T25-FW)
    - mean change in 9-Hole Peg Test (9-HPT)
    - mean change in Paced Auditory Serial Addition Test-3 (PASAT-3)
  - fatigue (MFIS)
  - activities of daily living (PRIMUS activities)
  - health status (EQ-5D VAS)
- Health-related quality of life
  - PRIMUS-QoL
- Adverse events
  - overall rate of serious adverse events
  - treatment discontinuation due to adverse events

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

Further information on the choice of outcomes can be found in Module 4, Sections 4.3.1.3 and 4.3.2.1.3 of the dossier, and in Sections 2.7.2.4.3 and 2.7.2.5 of the full dossier assessment.

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

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

Study	Outcomes									
	All-cause mortality	Relapse-related outcomes	Disability progression	Disability severity (MSFC-z)	Fatigue (MFIS)	Activities of daily living (PRIMUS activities)	Health status (EQ-5D VAS)	Health-related quality of life (PRIMUS QoL)	SAEs	Discontinuation due to AEs
TRANSFORMS	Yes	Yes	Yes	No[a]	No[a]	No[a]	No[a]	No[a]	Yes	Yes

a: No evaluable data available (for reasons, see Section 2.7.2.4.3 of the full dossier assessment).
AE: adverse event; EQ-5D: European Quality of Life-5 Dimensions; IFN-β: interferon beta; MFIS: Modified Fatigue Impact Scale; MSFC-z: Multiple Sclerosis Functional Composite; PRIMUS: Patient-Reported Indices for Multiple Sclerosis; QoL: quality of life; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

The available documents contained data for all relevant outcomes. For some outcomes however, the available data were not evaluable. This referred to the outcomes "disability severity", "activities of daily living (PRIMUS activities)" and "health status (EQ-5D VAS)" (here the differences in the proportions of patients who were not considered was above 15 percentage points), as well as the outcomes "fatigue (MFIS)" and "health-related quality of life (PRIMUS QoL)" (here it could not be excluded with certainty that the differences in the proportions of patients who were not considered was above 15%). According to the Institute's calculations, these differences could be between 8 and 21 percentage points. There was no statistically significant or clinically relevant difference with regard to these outcomes; hence the exclusion of these outcomes also had no influence on the overall result of the benefit assessment. Further information can be found in Section 2.7.2.4.3 or the full dossier assessment.

2.4.1.2 Risk of bias

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

Table 11: Risk of bias at study and outcome level – RCT, direct comparison: fingolimod vs. IFN-β1a

Study	Study level	Outcomes									
		All-cause mortality	Relapse-related outcomes	Disability progression	Disability severity (MSFC-z)[b]	Fatigue (MFIS)	Activities of daily living (PRIMUS activities)	Health status (EQ-5D VAS)	Health-related quality of life (PRIMUS QoL)	SAEs	Discontinuation due to AEs
TRANSFORMS	L	L	L	L	–[a]	–[c]	–[a]	–[a]	–[c]	L	L

a: No evaluable data available. The proportion of patients who were not considered in the analysis differed by > 15 percentage points between the arms.
b: The risk of bias was not determined for the subscales because no evaluable data were available for the total scale due to the high proportion of patients who were not considered in the analysis.
c: No evaluable data available. The difference of the proportions of patients who were not considered in the analysis between the arms remains unclear (for reasons, see Section 2.7.2.4.3 of the full dossier assessment).

AE: adverse event; EQ-5D: European Quality of Life-5 Dimensions; IFN-β: interferon beta; L: low; MFIS: Modified Fatigue Impact Scale; PRIMUS: Patient-Reported Indices for Multiple Sclerosis; QoL: quality of life; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

There was a low risk of bias for the following outcomes: all-cause mortality, time to first relapse, patients with confirmed relapse, annualized relapse rate, time to first confirmed disability progression, patients with confirmed disability progression, serious adverse events, and discontinuation due to adverse events. This concurs with the company's assessment.

There were no evaluable data for the remaining outcomes. Therefore no outcome-specific assessment of the risk of bias was conducted for these outcomes.

The company classified the instruments for recording fatigue (MFIS) and activities of daily living (PRIMUS activities) as health-related quality of life, and determined – together with the recordings using the EQ-5D and the PRIMUS QoL – a joint risk of bias for these outcomes. For this, the company assessed the risk of bias as low.

Further information on the risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3, and in Appendix 4-F of the dossier, and in Sections 2.7.2.4.2 and 2.7.2.5 of the full dossier assessment.

2.4.1.3 Results

Table 12 to Table 14 summarize the results on the comparison of fingolimod and IFN-β1a in patients with highly active RRMS despite full previous treatment with disease-modifying therapy other than IFN-β. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations.

Table 12: Results (mortality, morbidity) – RCT, direct comparison: fingolimod vs. IFN-β1a

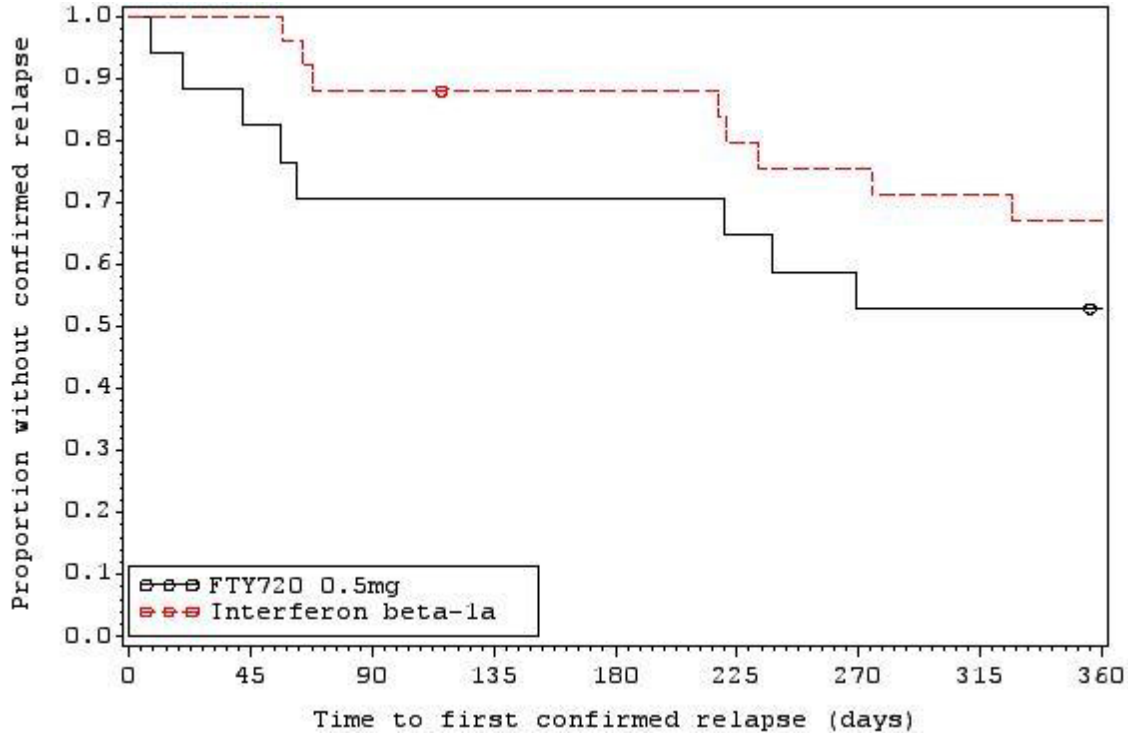
Study outcome category outcome	Fingolimod		IFN-β1a		Fingolimod vs. IFN-β1a
	N	**Patients with events n (%)**	**N**	**Patients with events n (%)**	**RR [95% CI]; p-value**
TRANSFORMS					
Mortality					
Deaths	17	0[a]	25	0[a]	ND[a]
Morbidity					
Relapses (based on EDSS)					
	N	**Median time [95% CI]**	**N**	**Median time [95% CI]**	**HR [95% CI]; p-value**
Time to first confirmed relapse	17	NA	25	NA	1.82 [0.67; 4.92] 0.237
	N	**Patients with events n (%)**	**N**	**Patients with events n (%)**	**RR [95% CI]; p-value**
Patients with confirmed relapse	17	8 (47.1)[b]	25	8 (32.0)[b]	1.47 [0.69; 3.15] 0.359[c]
	N	**Annualized relapse rate [95% CI]**	**N**	**Annualized relapse rate [95% CI]**	**Rate ratio [95% CI]; p-value**
Annualized relapse rate	17	0.67 [0.36; 1.25]	25	0.51 [0.28; 0.91]	1.32 [0.56; 3.10] 0.530
		Number of relapses (%)		**Number of relapses (%)**	
Number of relapses according to severity		mild: 6 (54.5) moderate: 4 (36.4) severe: 1 (9.1)		mild: 6 (46.2) moderate: 6 (46.2) severe: 1 (7.7)	
Disability progression					
	N	**Median time [95% CI]**	**N**	**Median time [95% CI]**	**HR [95% CI]; p-value**
Time to first confirmed disability progression at month 12	17	NA	25	NA	ND[d] > 0.999
	N	**Patients with events n (%)**	**N**	**Patients with events n (%)**	**RR [95% CI]; p-value**
Proportion of patients with confirmed disability progression at month 12	17	1 (5.9)[b]	25	1 (4.0)[b]	1.47 [0.10; 21.94] 0.807[c]

(continued)

Table 12: Results (mortality, morbidity) – RCT, direct comparison: fingolimod vs. IFN-β1a (continued)

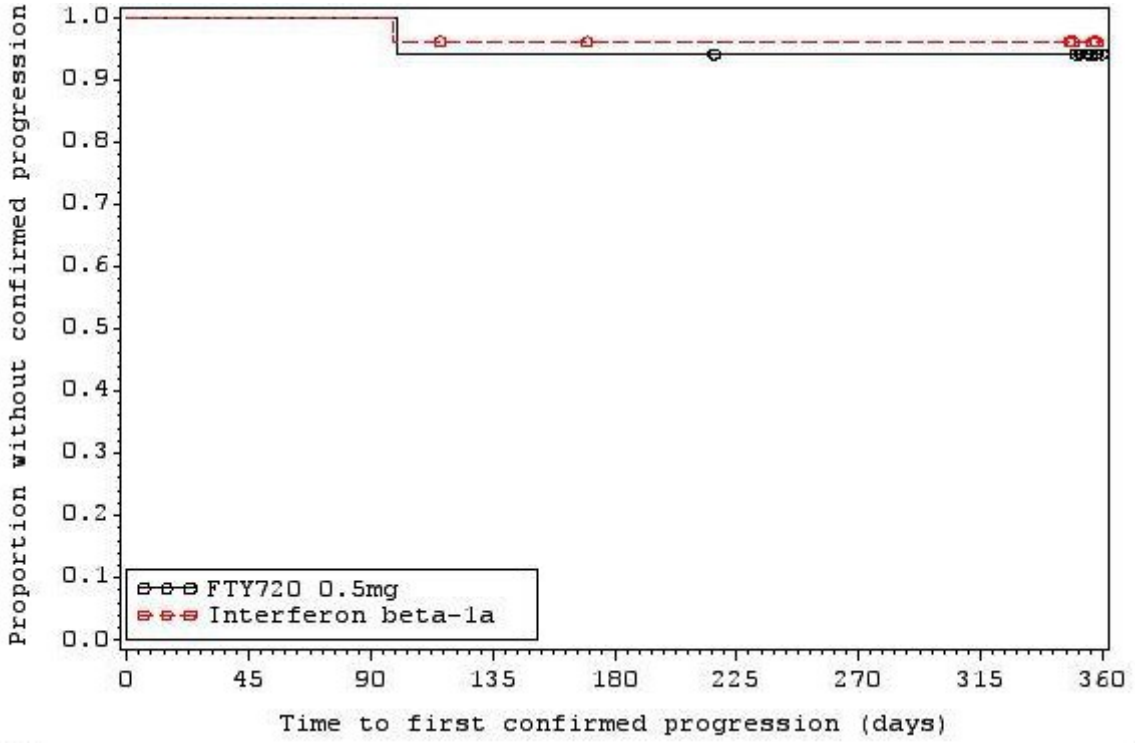
a: No effect estimation possible because no deaths occurred.
b: The values for the relevant patient population were taken from the Kaplan-Meier curves.
d: Institute's calculation, unconditional exact test (CSZ method according to [7]).
d: According to the information provided by the company, this value cannot be estimated because "no adjustment of the model is possible".
CI: confidence interval; CSZ: convexity, symmetry, z score; EDSS: Expanded Disability Status Scale; HR: hazard ratio; IFN-β: interferon beta; N: number of analysed patients; n: number of patients with event; NA: not achieved; RCT: randomized controlled trial; RR: relative risk; SE: standard error; vs.: versus

Figure 1 and Figure 2 show the Kaplan-Meier curves of the time to first confirmed relapse and of the time to first confirmed disability progression.



Patients at risk									
Time (days)	0	45	90	135	180	225	270	315	360
Fingolimod 0.5 mg	17	14	12	12	12	11	9	9	8
IFN-β1a	25	25	22	21	21	19	18	17	16

Figure 1: Kaplan-Meier curves of the time to first confirmed relapse



Patients at risk									
Time (days)	0	45	90	135	180	225	270	315	360
Fingolimod 0.5 mg	17	17	17	16	16	15	15	15	8
IFN-β1a	25	25	25	23	22	22	22	22	16

Figure 2: Kaplan-Meier curves of the time to first confirmed disability progression

Table 13: Results (continuous outcomes, morbidity and health-related quality of life) – RCT, direct comparison: fingolimod vs. IFN-β1a

Study outcome category outcome	Fingolimod			IFN-β1a			Fingolimod vs. IFN-β1a
	N[a]	Values at start of study mean (SE)	Change at end of study mean (SE)	N[a]	Values at start of study mean (SE)	Change at end of study mean (SE)	MD [95% CI]; p-value
TRANFORMS							
Morbidity							
Disability severity MSFC							
MSFC-z score	No evaluable data available[b]						
MSFC subscale: T25-FW	No evaluable data available[c]						
MSFC subscale: 9-HPT	No evaluable data available[c]						
MSFC subscale: PASAT	No evaluable data available[c]						
Fatigue							
MFIS[d]	No evaluable data available[e]						
Activities of daily living							
PRIMUS[d] activities	No evaluable data available[b]						
Health status							
EQ-5D VAS	No evaluable data available[b]						
Health-related quality of life							
PRIMUS-QoL[d]	No evaluable data available[e]						

a: Number of patients in the analysis at the end of the study, the values at the start of the study (or at other points in time) may be based on other patient numbers.
b: As the difference of the proportions of patients who were not considered between the groups was larger than 15 percentage points, the data were not considered for the assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment).
c: Due to the difference of the proportions of patients who were not considered between the groups in the total MSFC scale, the data of the subscales were not considered for the assessment.
d: The questionnaire was recorded in selected countries (Australia, Canada, France, Germany, Italy, Spain, Great Britain and United States).
e: As the difference of the proportions of patients who were not considered between the groups was unclear, the data were not considered (for reasons, see Section 2.7.2.4.3 of the full dossier assessment).

CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; 9-HPT: 9-Hole Peg Test; IFN-β: interferon beta; ITT: intention to treat; MFIS: Modified Fatigue Impact Scale; MSFC: Multiple Sclerosis Functional Composite; N: number of valid observations;; PASAT: Paced Auditory Serial Addition Test; PRIMUS: Patient-Reported Indices for Multiple Sclerosis; QoL: quality of life; RCT: randomized controlled trial; SE: standard error; T25-FW: Timed 25-Foot Walk; VAS: visual analogue scale; vs.: versus

Table 14: Results (adverse events) – RCT, direct comparison: fingolimod vs. IFN-β1a

Study outcome category outcome	Fingolimod		IFN-β1a		Fingolimod vs. IFN-β1a
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]; p-value
TRANSFORMS					
Adverse events					
AEs	17	15 (88.2)	25	23 (92.0)	
SAEs	17	1 (5.9)	25	1 (4.0)	1.47 [0.10; 21.94] 0.780
Discontinuation due to AEs	17	2 (11.8)	25	0 (0.0)	7.22 [0.37; 141.67] 0.193

AE: adverse event; CI: confidence interval; IFN-β: interferon beta; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

In general it is to be pointed out that the company conducted the assessment of the added benefit for the total population of patients with highly active RRMS despite pretreatment with at least one disease-modifying therapy (including IFN-β). For the patients who were exclusively affected by the expansion of approval (highly active RRMS despite pretreatment with disease-modifying therapy other than IFN-β), the company presented the results on the outcomes considered by the company. But it presented them as sensitivity analysis without deriving conclusions on the added benefit of fingolimod for this patient group.

Mortality

Deaths

In both groups, there were no events for the outcome “deaths”. An added benefit of fingolimod compared with IFN-β1a for this outcome is not proven.

Morbidity

Relapses

There was no statistically significant difference between the groups for the time to first confirmed relapse, the proportion of patients with confirmed relapse or the annualized relapse rate. An added benefit of fingolimod compared with IFN-β1a for the outcome “relapses” is not proven.

Disability progression

There was no statistically significant difference between the groups for the time to first confirmed disability progression at month 12 or for the proportion of patients with confirmed disability progression at month 12. An added benefit of fingolimod compared with IFN-β1a for the outcome “disability progression” is not proven.

Disability severity

Due to the large difference in missing values between the arms (> 15%), the results could not be meaningfully interpreted for the outcome "disability severity (MSFC-z score)". An added benefit of fingolimod versus IFN-β1a for this outcome is therefore not proven.

Fatigue

No assessment was conducted for the outcome "fatigue (MFIS)" because the size of the proportions of patients who were not considered between the groups was not sufficiently clear and the data could therefore not be interpreted with certainty. There were therefore no evaluable data for the MFIS. An added benefit of fingolimod versus IFN-β for this outcome is therefore not proven.

Activities of daily living

Due to the large difference in missing values between the arms (> 15%), the results cannot be meaningfully interpreted for the outcome "activities of daily living (PRIMUS activities)". An added benefit of fingolimod versus IFN-β for this outcome is therefore not proven.

Health status (EQ-5D VAS)

Due to the large difference in missing values between the arms (> 15%), the results could not be meaningfully interpreted for the outcome "EQ-5D VAS". An added benefit of fingolimod versus IFN-β for this outcome is therefore not proven.

Health-related quality of life

PRIMUS QoL

No assessment was conducted for the outcome "PRIMUS QoL" because the size of the proportions of patients who were not considered between the groups was not sufficiently clear and the data could therefore not be interpreted with certainty. There were therefore no evaluable data for the PRIMUS QoL. An added benefit of fingolimod versus IFN-β for this outcome is therefore not proven.

Adverse events

Overall rate of serious adverse events and discontinuation due to adverse events

There was no statistically significant difference between the treatment groups for the outcome "serious adverse events" or for the outcome "discontinuation due to adverse events". Greater or lesser harm from fingolimod than from IFN-β is not proven with regard to these outcomes.

Further information on the outcome results can be found in Module 4, Sections 4.3.1.3 and 4.3.2.1.3 of the dossier, and in Sections 2.7.2.4.3 and 2.7.2.5 of the full dossier assessment.

2.4.1.4 Subgroups and other effect modifiers

The available data on subgroups and other effect modifiers could not be meaningfully interpreted (for reasons, see Section 2.7.2.4.3 of the full dossier assessment).

Further information on the subgroup results can be found in Module 4, Sections 4.3.1.3.2 and 4.3.2.1.3.2 of the dossier, and in Sections 2.7.2.4.3 and 2.7.2.5 of the full dossier assessment.

2.4.2 Research question 2: patients with highly active RRMS, incomplete treatment with disease-modifying therapy (other than IFN-β)

No relevant data were available for the assessment of fingolimod in patients with highly active RRMS who received incomplete treatment with a disease-modifying therapy other than IFN-β. Hence an added benefit of fingolimod versus the ACT is not proven.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit for both patient populations at outcome level is shown below, taking into account the various outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on 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.

2.5.1 Research question 1: patients with highly active RRMS, full previous treatment with disease-modifying therapy (other than IFN-β)

2.5.1.1 Assessment of added benefit at outcome level

No added benefit of fingolimod in patients with highly active RRMS despite full previous treatment with a disease-modifying therapy other than IFN-β can be derived from the data presented in Section 2.4.1 for any of the outcomes investigated (see Table 15).

Table 15: Extent of added benefit at outcome level: fingolimod vs. IFN-β1a

Outcome category **outcome**	**Fingolimod vs. IFN-β1a** **median of time to event or proportion of events** **effect estimate [95% CI]** **p-value** **probability**[a]	**Derivation of extent**
Mortality		
Deaths	0% vs. 0%	Lesser benefit/added benefit not proven
Morbidity		
Relapse-related outcomes (based on EDSS)		
Time to first confirmed relapse	NA vs. NA HR 1.82 [0.67; 4.92] 0.237	Added benefit not proven
Proportion of patients with confirmed relapse	47.1% vs. 32.0% RR 1.47 [0.69; 3.15] 0.359[b]	Added benefit not proven
Annualized relapse rate	0.67 vs. 0.51 rate ratio 1.32 [0.56; 3.10] 0.530	Added benefit not proven
Disability progression (based on EDSS)		
Time to first confirmed disability progression at month 12	NA vs. NA ND[c] > 0.999	Added benefit not proven
Proportion of patients with confirmed disability progression at month 12	5.9% vs. 4.0% RR 1.47 [0.10; 21.94] 0.807[b]	Added benefit not proven
Disability severity (MSFC)	No evaluable data available	Added benefit not proven
Fatigue (using MFIS)	No evaluable data available	Added benefit not proven
Activities of daily living (using PRIMUS activities)	No evaluable data available	Added benefit not proven
Health status (EQ-5D VAS)	No evaluable data available	Added benefit not proven
Health-related quality of life		
PRIMUS-QoL	No evaluable data available	Added benefit not proven
Adverse events		
SAEs	5.9% vs. 4.0% RR 1.47 [0.10; 21.94] 0.780	Lesser/greater harm not proven
Discontinuation due to AEs	11.8% vs. 0.0% RR 7.22 [0.37; 141.67] 0.193	Lesser/greater harm not proven

(continued)

Table 15: Extent of added benefit at outcome level: fingolimod vs. IFN-β1a (continued)

a: Probability provided if statistically significant differences were present.
b: Institute's calculation, unconditional exact test (CSZ method according to [7]).
c: According to the information provided by the company, this value cannot be estimated because "no adjustment of the model is possible".

AE: adverse event; CI: confidence interval; EDSS: Expanded Disability Status Scale; EQ-5D: European Quality of Life-5 Dimensions; 9-HPT: 9-Hole Peg Test; HR: hazard ratio; IFN-β: interferon beta; MFIS: Modified Fatigue Impact Scale; MSFC: Multiple Sclerosis Functional Composite; NA: not achieved; ND: no data; PASAT: Paced Auditory Serial Addition Test, PRIMUS: Patient-Reported Indices for Multiple Sclerosis, QoL: quality of life; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SE: standard error; T25-FW: Timed 25-Foot Walk; VAS: visual analogue scale; vs.: versus

2.5.1.2 Overall conclusion on added benefit

In summary, the added benefit of fingolimod versus the ACT for patients with highly active RRMS despite full previous treatment with a disease-modifying therapy other than IFN-β is not proven.

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

2.5.2 Research question 2: patients with highly active RRMS, incomplete treatment with disease-modifying therapy (other than IFN-β)

Since the company submitted no data for patients with highly active RRMS who received incomplete treatment with a disease-modifying therapy other than IFN-β, an added benefit of fingolimod versus the ACT is not proven for this patient population.

2.5.3 Extent and probability of added benefit – summary

The extent of the added benefit in comparison with the respective ACT is given in Table 16 for the 2 populations within the newly approved therapeutic indication of fingolimod:

Table 16: Fingolimod – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Patients with highly active RRMS, full previous treatment with disease-modifying therapy (other than IFN-β)	GA or **IFN-β1a** or 1b. Switching depended on prior therapy.	Added benefit not proven
Patients with highly active RRMS, incomplete treatment with disease-modifying therapy (other than IFN-β)	Continuation of the disease-modifying therapy started with GA[b], with an optimized dosage according to the approval up to an adequate course. If the disease-modifying therapy was started with other drugs, switching to GA or IFN-β with an optimized dosage according to the approval up to an adequate course is to be conducted.	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.

b: In the specification of the ACT for the total patient population, the G-BA also named IFN-β as possible treatment to be continued. However, this is not relevant for the assessment of the expansion of the therapeutic indication.

ACT: appropriate comparator therapy; GA: glatiramer acetate; G-BA: Federal Joint Committee; IFN-β: interferon beta; RRMS: relapsing remitting multiple sclerosis

The company conducted no assessment of the added benefit of fingolimod versus the ACT for the 2 populations relevant for the assessment.

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier, and in Section 2.7.2.8 of the full dossier assessment.

2.6 List of included studies

Cohen JA, Barkhof F, Comi G, Hartung HP, Khatri BO, Montalban X et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med 2010; 362(5): 402-415.

McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol 2001; 50(1): 121-127.

Novartis. A 12-month double-blind, randomized, multicenter, activecontrolled, parallel-group study comparing the efficacy and safety of 0.5 mg and 1.25 mg fingolimod (FTY720) administered orally once daily versus interferon ß-1a (Avonex) administered i.m. once weekly in patients with relapsing-remitting multiple sclerosis with optional extension phase: study CFTY720D2302; full clinical study report [unpublished]. 2008.

Novartis. Efficacy and safety of fingolimod in patients with relapsing-remitting multiple sclerosis with optional extension phase (TRANSFORMS): full text view [online]. In: ClinicalTrials.gov. 16 July 2012 [accessed: 23 September 2013]. URL: http://www.clinicaltrials.gov/ct2/show/study/NCT00340834.

Novartis. Efficacy and safety of fingolimod in patients with relapsing-remitting multiple sclerosis with optional extension phase: TRANSFORMS [online]. In: International Clinical Trials Registry Platform. 17 October 2012 [accessed: 25 August 2014]. URL: http://apps.who.int/trialsearch/Trial.aspx?TrialID=NCT00340834.

Novartis. Study FTY720D2302 (Transforms); additional analysis: patient numbers per new-defined subpopulation [unpublished]. 2014.

Novartis. Zusätzliche Analysen zur TRANSFORMS-Studie [unpublished]. 2014.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General Methods: version 4.1 [online]. 28 November 2013 [accessed: 7 August 2014]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-1.pdf.

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3. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Fingolimod: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A11-23 [online]. 11 January 2012 [accessed: 11 March 2013]. (IQWiG-Berichte; Volume 113). URL: https://www.iqwig.de/download/A11-23_Fingolimod_Nutzenbewertung_35a_SGB_V.pdf.

4. Novartis Pharma. Gilenya: Fachinformation [online]. May 2014. URL: http://www.fachinfo.de.

5. Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol 2005; 58(6): 840-846.

6. Novartis. Study FTY720D2302 (Transforms); additional analysis: patient numbers per new-defined subpopulation [unpublished]. 2014.

7. 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.

The full report (German version) is published under https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a14-21-fingolimod-neues-anwendungsgebiet-nutzenbewertung-gemaess-35a-sgb-v-dossierbewertung.6273.html.