IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Fingolimod – 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 – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 June 2015). 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.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
EDSS	Expanded Disability Status Scale
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IFN-β	interferon beta
IM	intramuscular
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
PT	Preferred Term
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)
SOC	System Organ Class
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. 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 25 March 2015.

The pharmaceutical company (hereinafter abbreviated to "the company") submitted a first dossier of the drug to be evaluated on 14 October 2011 for the early benefit assessment. In this procedure, by decision of 29 March 2012, the G-BA limited its decision until 29 March 2015.

Research question

The aim of this report is to assess the added benefit of fingolimod in comparison with the appropriate comparator therapy (ACT) in adult patients with highly active relapsing remitting multiple sclerosis (RRMS).

The present dossier assessment only refers to the therapeutic indication of the first approval of fingolimod from the year 2011 and hence to the following patient groups:

- Patients with high disease activity despite treatment with a beta-interferon (interferon beta [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.
- Patients with rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with one or more Gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

The present benefit assessment was conducted separately for the 3 research questions presented in Table 2 versus the ACTs specified by the G-BA.

Table 2: Subindications and ACTs for fingolimod

Research question	Subindication	ACT specified by the G-BA
A	Patients with highly active RRMS, full previous treatment with IFN-β	Glatiramer acetate or IFN-β1a or 1b, switching depended on prior therapy
B	Patients with highly active RRMS, no full previous treatment with IFN-β	Continuation of disease-modifying therapy with IFN-β, with an optimized dosage according to the approval up to an adequate course (normally lasting at least one year)
C	Patients with rapidly evolving severe RRMS	Glatiramer acetate or IFN-β (1a or 1b)
ACT: appropriate comparator therapy; 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 the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 12 months were included.

Results for research question A: patients with highly active RRMS, full previous treatment with IFN-β

An adjusted indirect comparison of fingolimod versus the ACT glatiramer acetate with the common comparator placebo was available for patients with highly active RRMS who have received full previous treatment with IFN-β (≥ one year).

Only analyses on the respective total populations of the studies FREEDOMS, FREEDOMS II and CONFIRM were available for the present benefit assessment. However, treatment-naive patients and patients who had not been pretreated with IFN-β for at least one year, i.e. patients who do not concur with the present research question, were included to a large proportion in these studies. The proportion of the relevant subpopulations was far below 80% of the total populations in all 3 studies.

The adjusted indirect comparison presented by the company is therefore unsuitable to derive conclusions on the added benefit of fingolimod in comparison with the ACT specified by the G-BA for the relevant patient population in research question A. An added benefit of fingolimod is not proven for this population.

Results for research question B: patients with highly active RRMS, no full previous treatment with IFN-β

The TRANSFORMS study was included in the assessment. This study was already presented in the dossier from 21 September 2011 for the first benefit assessment of fingolimod (Commission A11-23). For the present benefit assessment, the company presented new analyses of the data already presented in the dossier from 21 September 2011 in its dossier

from 19 March 2015. The data underlying the analyses of the TRANSFORMS study are therefore unchanged.

The TRANSFORMS study was a multicentre, double-blind RCT. Adult patients with RRMS were enrolled. 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). According to the company, 110 of these patients (12.7% of the study population) corresponded to the relevant subpopulation of patients with highly active RRMS who have not received full previous treatment with IFN-β (fingolimod: n = 54 patients, IFN-β: n = 56 patients).

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 events occurred in both treatment groups for the outcome "deaths". Hence there was no hint of an added benefit of fingolimod in comparison with IFN-β1a. An added benefit for this outcome is therefore not proven.

Morbidity

Relapses

For the annualized relapse rate, which was considered to be the decisive operationalization of the outcome, there was a statistically significant difference in favour of fingolimod in comparison with IFN-β1a. There was no statistically significant difference between the treatment groups for the time to first confirmed relapse. However, the effect pointed in the same direction as the effect in the annualized relapse rate and therefore did not raise doubts about it. Overall, there is thus an indication of an added benefit of fingolimod in comparison with IFN-β1a for the outcome "relapses".

Disability progression

There was no statistically significant difference between the treatment groups for the time to first confirmed disability progression. Hence there was no hint of an added benefit of fingolimod in comparison with IFN-β1a. An added benefit for this outcome is therefore not proven.

Disability severity

There was no statistically significant difference between the treatment groups for the outcome "disability severity" for the Multiple Sclerosis Functional Composite standard score (MSFC-z score, total score). Hence there was no hint of an added benefit of fingolimod in comparison with IFN-β1a. An added benefit for this outcome is therefore not proven.

Fatigue

There were no evaluable data for the outcome "fatigue (Modified Fatigue Impact Scale [mFIS])". Hence there was no hint of an added benefit of fingolimod in comparison with IFN-β1a. An added benefit for this outcome is therefore not proven.

Activities of daily living

There were no evaluable data for the outcome "activities of daily living (Patient-Reported Indices for Multiple Sclerosis [PRIMUS] activities)". Hence there was no hint of an added benefit of fingolimod in comparison with IFN-β1a. An added benefit for this outcome is therefore not proven.

Health status

There was no statistically significant difference between the treatment groups for the outcome "health status (European Quality of Life-5 Dimensions visual analogue scale [EQ-5D VAS])". Hence there was no hint of an added benefit of fingolimod in comparison with IFN-β1a. An added benefit for this outcome is therefore not proven.

Health-related quality of life

PRIMUS QoL

No evaluable data were available for health-related quality of life (Patient-Reported Indices for Multiple Sclerosis quality of life [PRIMUS QoL]). Hence there was no hint of an added benefit of fingolimod in comparison with IFN-β1a. An added benefit for this outcome is therefore not proven.

Adverse events

Serious adverse events and discontinuation due to adverse events

There was no statistically significant difference between the treatment groups for the outcomes "serious adverse events (SAEs)" and "discontinuation due to adverse events (AEs)". Hence there was no hint of greater or lesser harm from fingolimod in comparison with IFN-β1a; greater or lesser harm for these outcomes is therefore not proven.

Infections

There was no statistically significant difference between the treatment groups for the outcome "infections". Hence there was no hint of greater or lesser harm from fingolimod in comparison with IFN-β1a; greater or lesser harm for this outcome is therefore not proven.

Influenza like illness

There was a statistically significant difference in favour of fingolimod in comparison with IFN-β1a for the outcome "influenza like illness". This results in an indication of lesser harm from fingolimod in comparison with IFN-β1a.

Constipation

There was a statistically significant difference to the disadvantage of fingolimod in comparison with IFN-β1a for the outcome "constipation". An only marginal effect cannot be excluded, however. Hence there was no hint of greater harm from fingolimod in comparison with IFN-β1a; greater or lesser harm for this outcome is therefore not proven.

Results for research question C: patients with rapidly evolving severe RRMS

The TRANSFORMS study was also included in the assessment. Also for research question C, this study was already presented in the dossier from 21 September 2011 for the first benefit assessment of fingolimod (Commission A11-23). For the present benefit assessment, the company presented new analyses of the data already presented in the dossier from 21 September 2011 in its dossier from 19 March 2015. The data underlying the analyses of the TRANSFORMS study are therefore unchanged.

Of the total of 866 patients included in the relevant treatment arms of the TRANSFORMS study, according to the company, 121 patients (14% of the study population) concurred with the relevant subpopulation of patients with rapidly evolving severe RRMS (fingolimod: n = 56 patients, IFN-β: n = 65 patients). These included both treatment-naive and pretreated patients.

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 events occurred in both treatment groups for the outcome "deaths". Hence there was no hint of an added benefit of fingolimod in comparison with IFN-β1a. An added benefit for this outcome is therefore not proven.

Morbidity

Relapses

For the annualized relapse rate, which was considered to be the decisive operationalization of the outcome, there was a statistically significant difference in favour of fingolimod in comparison with IFN-β1a. There was no statistically significant difference between the treatment groups for the time to first confirmed relapse. However, the effect pointed in the same direction as the effect in the annualized relapse rate and therefore did not raise doubts about it.

Additionally, there was an indication (annualized relapse rate) and proof (time to first confirmed relapse) of an effect modification by the characteristic "sex" for these outcomes. This resulted in a statistically significantly lower annualized relapse rate and a statistically significantly longer time to first confirmed relapse under treatment with fingolimod in

comparison with IFN-β1a for women. For the subgroup of women, there was thus an indication of an added benefit in comparison with IFN-β1a for the outcome "relapses". For men, treatment with fingolimod produced no statistically significant difference in comparison with IFN-β1a in annualized relapse rate or in the time to first confirmed relapse. For the subgroup of men, there was thus no hint of an added benefit of fingolimod in comparison with IFN-β1a for the outcome "relapses". An added benefit is therefore not proven.

Disability progression

There was no statistically significant difference between the treatment groups for the time to first confirmed disability progression. Hence there was no hint of an added benefit of fingolimod in comparison with IFN-β1a. An added benefit for this outcome is therefore not proven.

Disability severity

There was no statistically significant difference between the treatment groups for the outcome "disability severity" for the MSFC-z score. Hence there was no hint of an added benefit of fingolimod in comparison with IFN-β1a. An added benefit for this outcome is therefore not proven.

Fatigue

There were no evaluable data for the outcome "fatigue (mFIS)". Hence there was no hint of an added benefit of fingolimod in comparison with IFN-β1a. An added benefit for this outcome is therefore not proven.

Activities of daily living

There were no evaluable data for the outcome "activities of daily living (PRIMUS activities)". Hence there was no hint of an added benefit of fingolimod in comparison with IFN-β1a. An added benefit for this outcome is therefore not proven.

Health status

There was no statistically significant difference between the treatment groups for the outcome "health status (EQ-5D VAS)". Hence there was no hint of an added benefit of fingolimod in comparison with IFN-β1a. An added benefit for this outcome is therefore not proven.

Health-related quality of life

PRIMUS QoL

There were no evaluable data for health-related quality of life (PRIMUS QoL). Hence there was no hint of an added benefit of fingolimod in comparison with IFN-β1a. An added benefit for this outcome is therefore not proven.

Adverse events

Serious adverse events

There was a statistically significant difference to the disadvantage of fingolimod in comparison with IFN-β1a for the outcome "SAEs". There was an indication of greater harm from fingolimod in comparison with IFN-β1a for this outcome.

Discontinuation due to adverse events

There was no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". Hence there was no hint of greater or lesser harm from fingolimod in comparison with IFN-β1a; greater or lesser harm for this outcome is therefore not proven.

Infections

There was no statistically significant difference between the treatment groups for the outcome "infections". Hence there was no hint of greater or lesser harm from fingolimod in comparison with IFN-β1a; greater or lesser harm for this outcome is therefore not proven.

Influenza like illness

There was a statistically significant difference in favour of fingolimod in comparison with IFN-β1a for the outcome "influenza like illness". This results in an indication of lesser harm from fingolimod in comparison with IFN-β1a for this outcome.

Gastrointestinal disorders

There was a statistically significant difference to the disadvantage of fingolimod in comparison with IFN-β1a for the outcome "gastrointestinal disorders". This was of only marginal effect size, however. Hence there was no hint of greater or lesser harm from fingolimod in comparison with IFN-β1a; greater or lesser harm for this outcome is therefore not proven.

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

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

[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). 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). For further details see [1,2].

Research question A: patients with highly active RRMS, full previous treatment with IFN-β

The available data do not provide proof of an added benefit of fingolimod in comparison with the ACT specified by the G-BA for patients with highly active RRMS who have received full previous treatment with IFN-β. Hence there are also no patient groups for whom a therapeutically important added benefit can be derived.

Research question B: patients with highly active RRMS, no full previous treatment with IFN-β

Overall, there are 2 positive effects with the same probability, but with different extent.

There was an indication of minor added benefit in the category "non-serious/non-severe symptoms/late complications" for the outcome "relapses" regarding the annualized relapse rate. Additionally, there was lesser harm with considerable extent in the category "non-serious/non-severe AEs" regarding influenza like illness.

In summary, there is an indication of considerable added benefit of fingolimod in comparison with the ACT IFN-β1a for patients with highly active RRMS who have not received full previous treatment with IFN-β.

Research question C: patients with rapidly evolving severe RRMS

Overall, 2 positive effects with the same probability and extent, and one negative effect with non-quantifiable extent remain for female patients. For male patients, one positive and one negative effect with the same probability, but with different extent, remain.

For female patients, there is an indication of considerable added benefit of fingolimod in the category "non-serious/non-severe symptoms/late complications" (relapses). There is an indication of lesser harm from fingolimod with the extent "considerable" in the category "non-serious/non-severe AEs" (influenza like illness). In contrast, there is an indication of non-quantifiable greater harm from fingolimod in the category "serious/severe AEs" (SAEs).

In summary, there is an indication of considerable added benefit of fingolimod in comparison with the ACT IFN-β1a for female patients with rapidly evolving severe RRMS.

For male patients, there is an indication of lesser harm from fingolimod with the extent "considerable" in the category "non-serious/non-severe AEs" (influenza like illness). In contrast, there is an indication of non-quantifiable greater harm from fingolimod in the category "serious/severe AEs" (SAEs). The total number of SAEs was very low so that the negative effect in this outcome did not completely outweigh the positive effect regarding the outcome "influenza like illness".

In summary, there is therefore an indication of minor added benefit of fingolimod in comparison with the ACT IFN-β1a for male patients with rapidly evolving severe RRMS.

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

Table 3: Fingolimod – extent and probability of added benefit

Research question	Subindication	ACT[a]	Extent and probability of added benefit
A	Patients with highly active RRMS, full previous treatment with IFN-β	**Glatiramer acetate**[b] or IFN-β1a or 1b, switching depended on prior therapy	Added benefit not proven
B	Patients with highly active RRMS, no full previous treatment with IFN-β	Continuation of disease-modifying therapy with IFN-β, with an optimized dosage according to the approval up to an adequate course (normally lasting at least one year)[c]	Indication of considerable added benefit
C	Patients with rapidly evolving severe RRMS	Glatiramer acetate or **IFN-β** (**1a** or 1b)	Sex: female indication of considerable added benefit
			Sex: male indication of minor added benefit

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. In the present case, the company limited the ACT to intramuscular administration of IFN-β1a. This limitation was not followed.
b: The company cited glatiramer acetate as comparator therapy because of the patients' pretreatment.
c: The company cited IFN-β1a as comparator therapy.
ACT: appropriate comparator therapy; 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 questions of the dossier assessment

The aim of this report is to assess the added benefit of fingolimod in comparison with the ACT in adult patients with highly active RRMS.

The G-BA had limited its decision on fingolimod from 29 March 2012 to 3 years. At the expiry of that period, the company submitted a new dossier. The present dossier assessment only refers to the therapeutic indication of the first approval of fingolimod from the year 2011 (see Section 5.1 of dossier assessment A11-23 [3]) and hence to the following patient groups:

- Patients with high disease activity despite treatment with a beta-interferon (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 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.

- Patients with rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with one or more Gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

The assessment of fingolimod in patients with highly active RRMS despite treatment with disease-modifying therapy other than IFN-β was the subject of the benefit assessment A14-21 after expansion of the therapeutic indication of fingolimod in May 2014 [4] and is not the subject of the present assessment.

The present benefit assessment was conducted separately for the 3 research questions presented in Table 4 versus the ACTs specified by the G-BA.

Table 4: Subindications and ACTs for fingolimod

Research question	Subindication	ACT specified by the G-BA
A	Patients with highly active RRMS, full previous treatment with IFN-β	Glatiramer acetate or IFN-β1a or 1b, switching depended on prior therapy
B	Patients with highly active RRMS, no full previous treatment with IFN-β	Continuation of disease-modifying therapy with IFN-β, with an optimized dosage according to the approval up to an adequate course (normally lasting at least one year)
C	Patients with rapidly evolving severe RRMS	Glatiramer acetate or IFN-β (1a or 1b)
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IFN-β: interferon beta; RRMS: relapsing remitting multiple sclerosis		

For research question A, the company followed the G-BA with regard to the ACT. Due to the prior therapy according to the research question (IFN-β), the company chose glatiramer acetate as ACT from the options specified by the G-BA. For research questions B and C, the company chose IFN-β1a from the options specified by the G-BA, but limited its choice to the intramuscular (IM) administration of IFN-β1a. According to the G-BA's specification at drug level however, all IFN-β1a preparations have to be considered irrespective of the manner of administration. Since the check of the company's study pool did not produce any additionally relevant study with IFN-β1a (without limitation regarding the manner of administration), the company's approach for the derivation of the added benefit had no consequences for the present benefit assessment.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. RCTs with a minimum duration of 12 months were included.

2.3 Research question A: patients with highly active RRMS, full previous treatment with IFN-β

2.3.1 Information retrieval and study pool (research question A)

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

Sources of the company in the dossier:

- study lists on fingolimod (studies completed up to 30 January 2015)
- bibliographical literature search on fingolimod (last search on 16 January 2015)
- search in trial registries for studies on fingolimod (last search on 14 January 2015)
- bibliographical literature search on the ACT (last search on 5 January 2015)
- search in trial registries for studies on the ACT (last search on 8 January 2015)

To check the completeness of the study pool:

- search in trial registries for studies on fingolimod (last search on 13 April 2015)
- search in trial registries for studies on the ACT (last search on 13 April 2015)
- bibliographical literature search on the ACT (last search on 13 April 2015)

No additional relevant study was identified from the check.

Direct comparison

There were no direct comparative studies of fingolimod in comparison with the ACT glatiramer acetate for patients with highly active RRMS who have received full previous treatment with IFN-β. This concurs with the company's assessment.

Indirect comparison

From the steps of information retrieval mentioned, the company identified the following fingolimod studies: CFTY720D2301 (hereinafter referred to as "FREEDOMS") [5] and CFTY720D2309 (hereinafter referred to as "FREEDOMS II") [6] and the CONFIRM study with glatiramer acetate [7]. Placebo served as common comparator.

The adjusted indirect comparison presented by the company is unsuitable to derive conclusions on the added benefit of fingolimod in comparison with the ACT specified by the G-BA for the relevant patient population in research question A. This is justified below. For this purpose, at first the studies used by the company are presented.

The study pool of the company is shown in Table 5.

Table 5: Study pool of the company – RCT, indirect comparison: fingolimod + placebo vs. glatiramer acetate + placebo (research question A)

Study	**Study category**		
	Study for approval of the drug to be assessed (yes/no)	**Sponsored study[a] (yes/no)**	**Third-party study (yes/no)**
Studies with fingolimod			
CFTY720D2301 (FREEDOMS)[b]	Yes	Yes	No
CFTY720D2309 (FREEDOMS II)[b]	Yes	Yes	No
Study with glatiramer acetate			
CONFIRM	No	No	Yes
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. b: Hereinafter referred to as “FREEDOMS” and “FREEDOMS II”. RCT: randomized controlled trial; vs.: versus			

The studies included by the company in its indirect comparison are described in Table 6.

Table 6: Characteristics of the studies included by the company – RCT, indirect comparison: fingolimod vs. glatiramer acetate (research question A)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
FREEDOMS	RCT, double-blind, parallel, multicentre, placebo-controlled	Adults with RRMS at least 1 relapse in the past year, or at least 2 relapses in the past 2 years EDSS 0–5.5	Fingolimod 1.25 mg (N = 429)[b] fingolimod 0.5 mg (N = 425) placebo (N = 418) Relevant subpopulation A[c] thereof: fingolimod 0.5 mg (n = 1) placebo (n = 1)	Screening: 45 days Treatment phase: 24 months Follow up for 3 months or participation in the extension phase at the patient's request	138 centres in 22 countries worldwide: Australia, Canada, Europe (including Israel), South Africa 1/2006–7/2009	Primary: annualized relapse rate Secondary: further relapse-related outcomes, disability progression, disability severity, health-related quality of life, AEs
FREEDOMS II	RCT, double-blind, parallel, multicentre, placebo-controlled	Adults with RRMS at least 1 relapse in the past year, or at least 2 relapses in the past 2 years EDSS 0–5.5	Fingolimod 1.25 mg (N = 370)[b] fingolimod 0.5 mg (N = 358) placebo (N = 355) Relevant subpopulation A[c] thereof: fingolimod 0.5 mg (n = 2) placebo (n = 2)	Screening: 45 days Treatment phase: 24 months Follow up for 3 months or participation in the extension phase at the patient's request	117 centres in 8 countries worldwide: Australia, Canada, Europe, United States 6/2006–6/2011	Primary: annualized relapse rate Secondary: further relapse-related outcomes, disability progression, disability severity, activities of daily living, fatigue, health-related quality of life, AEs
Study with glatiramer acetate						
CONFIRM	RCT, double-blind[d], multicentre, placebo- and active-controlled	Adults with RRMS at least 1 relapse in the past year, or at least 1 Gadolinium-enhancing lesion in the past 6 weeks EDSS 0–5	Dimethyl fumarate 2x daily (N = 362)[b] dimethyl fumarate 3x daily (N = 345)[b] glatiramer acetate (N = 360) placebo (N = 363) Relevant subpopulation A[c] thereof: glatiramer acetate (n = ND) placebo (n = ND)	Screening: 6 weeks Treatment phase: 24 months Follow up for 4 weeks or participation in the extension phase at the patient's request	200 centres in 28 countries worldwide 6/2007–8/2011	Primary: annualized relapse rate Secondary: further relapse-related outcomes, disability progression, disability severity, health-related quality of life, AEs

(continued)

Table 6: Characteristics of the studies included by the company – RCT, indirect comparison: fingolimod vs. glatiramer acetate (research question A) (continued)

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: The arm is not relevant for the assessment and is not shown in the next tables.
c: Relevant subpopulation A: adult patients with highly active RRMS who have received full previous treatment (≥ 1 year) with IFN-β.
d: In the CONFIRM study, the placebo arm and the dimethyl fumarate arm were blinded. The glatiramer acetate arm was not blinded.
AE: adverse event; EDSS: Expanded Disability Status Scale; IFN-β: interferon beta; ND: no data; N: number of randomized patients; n: relevant subpopulation; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; vs.: versus

Study FREEDOMS

The FREEDOMS study was a multicentre, randomized, double-blind, placebo-controlled study of the company. Adult patients with RRMS were enrolled. The diagnosis of multiple sclerosis had to be made using the revised McDonald criteria [8]. The patients should have had at least one documented relapse in the previous year or 2 documented relapses in the 2 previous year. The baseline value on the Expanded Disability Status Scale (EDSS) had to be between 0 and 5.5. Pretreatment remained open in the study. Regarding pretreatment with IFN-β, the only limitation was that patients were excluded who had received IFN-β treatment within the last 3 months before randomization.

The study had a 3-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 placebo once daily. Only the dosage of 0.5 mg daily is approved for fingolimod; therefore the treatment arm with 1.25 mg fingolimod daily will not be considered further. The treatment duration was 24 months in total.

A total of 843 patients were randomly assigned in a ratio of 1:1 to the 2 study arms considered in the assessment (fingolimod 0.5 mg, placebo).

The primary outcome of the study was the annualized relapse rate; secondary outcomes were other relapse-related outcomes, disability progression, disability severity, health-related quality of life, and AEs.

Study FREEDOMS II

The FREEDOMS II study largely concurs with the FREEDOMS study regarding study design and inclusion and exclusion criteria.

The study had a 3-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 placebo once daily. The treatment arm with 1.25 mg fingolimod daily will not be considered further because this dosage is not approved. The treatment duration was 24 months in total.

A total of 713 patients were randomly assigned in a ratio of 1:1 to the 2 study arms relevant for the assessment (fingolimod 0.5 mg, placebo).

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

Study CONFIRM

The CONFIRM study was a study not sponsored by the company. The data provided by the company were based on information from a publication on this study [7] and the corresponding trial registry entries [9,10].

The CONFIRM study was a multicentre, randomized, placebo- and active-controlled double-blind study. Adult patients with RRMS according to the revised McDonald criteria [8] were included in the study. The patients should have had at least one relapse in the previous 12 months before randomization, documented with an MRI scan demonstrating brain lesions consistent with the disease multiple sclerosis. Alternatively, the patients should have had at least one Gadolinium-enhancing lesion in an MRI scan within the last 6 weeks before randomization. The baseline value on the EDSS had to be between 0 and 5.0. Pretreatment was partly limited. Patients who had received treatment with IFN-β or glatiramer acetate within the last 3 months before randomization were excluded.

The study had a 4-arm design. In 2 treatment arms, the patients received 240 mg dimethyl fumarate (BG-12) (oral administration) twice or 3 times daily. In the third treatment arm, the patients received oral placebo 3 times daily. In the fourth treatment arm, the patients received 20 mg glatiramer acetate as subcutaneous injection once daily.

A total of 423 patients were randomly assigned in a ratio of 1:1 to the 2 study arms considered in the assessment (glatiramer acetate, placebo).

The primary outcome of the study was the annualized relapse rate; secondary outcomes were other relapse-related outcomes, disability progression, disability severity, health-related quality of life, and AEs.

Relevant subpopulations of the studies

Table 7 shows the characteristics of the patients (total study populations and relevant subpopulations) in the studies included by the company.

Table 7: Characteristics of the study populations and relevant subpopulations – RCT, indirect comparison: fingolimod + placebo vs. glatiramer acetate + placebo (research question A)

Study Group	N	Age [years] mean (SD)	Sex [F/M] %	Duration of disease[a] [years] mean (SD)	Baseline EDSS mean (SD)	Number of relapses in the last year mean (SD)	Number of relapses in the last 2 years mean (SD)	Patients without Gd-enhancing T1 lesions n (%)	Patients without pre-treatment[b] n (%)	Treatment discontin-uations n (%)
FREEDOMS										
Study population										
Fingolimod	425	37 (9)	70/30	4.8 (5.1)	2.3 (1.3)	1.5 (0.8)	2.1 (1.1)	263 (62)[c]	244 (57)	80 (19)
Placebo	418	37 (9)	71/29	5.2 (5.2)	2.5 (1.3)	1.4 (0.7)	2.2 (1.2)	262 (63)[c]	249 (60)	115 (28)
Relevant subpopulation										
Fingolimod	1	26 (NA)	100/0	8.4 (NA)	3.5 (NA)	1 (NA)	1 (NA)	0 (0)	0 (0)	ND
Placebo	1	46 (NA)	100/0	4.9 (NA)	4.0 (NA)	3 (NA)	5 (NA)	1 (100)	0 (0)	ND
FREEDOMS II										
Study population										
Fingolimod	358	41 (8)	77/23	6.0 (5.7)	2.4 (1.3)	1.4 (0.9)	2.2 (1.4)	218 (61)[d]	94 (26)	116 (32)
Placebo	355	40 (8)	81/19	6.2 (5.8)	2.4 (1.3)	1.5 (0.9)	2.2 (1.5)	225 (64)[d]	96 (27)	123 (35)
Relevant subpopulation										
Fingolimod	2	42 (8)	100/0	7.3 (4.3)	2.3 (1.1)	1.0 (0.0)	1.5 (0.7)	2 (100)	0 (0)	ND
Placebo	2	30 (4)	100/0	6.0 (2.9)	2.0 (0.7)	1.5 (0.7)	2.5 (0.7)	1 (50)	0 (0)	ND
CONFIRM										
Study population										
Glatiramer acetate	350	37 (9)	71/29[e]	4.4 (4.7)	2.6 (1.2)	1.4 (0.6)	ND	ND	247 (71)[e]	86 (25)
Placebo	363	37 (9)	69/31[e]	4.8 (5.0)	2.6 (1.2)	1.4 (0.8)	ND	ND	252 (69)[e]	129 (36)

(continued)

Table 7: Characteristics of the study populations and relevant subpopulations – RCT, indirect comparison: fingolimod + placebo vs. glatiramer acetate + placebo (research question A) (continued)

a: Time since diagnosis.
b: Patients who have received no disease-modifying therapy.
c: According to the company's calculation, the percentages only refer to 424 patients in the fingolimod arm and 416 patients in the placebo arm; the company did not provide further information.
d: According to the company's calculation, the percentages only refer to 357 patients in the fingolimod arm and 354 patients in the placebo arm; the company did not provide further information.
e: Institute's calculation.
F: female; Gd: Gadolinium; M: male; N: number of randomized (or included) patients; n: number of patients with event; NA: not applicable because there was only one patient in the subpopulation; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The subpopulation relevant for research question A consists of patients with high disease activity who have been pretreated with IFN-β for at least one year. Patients with high disease activity, according to the definition of the Summary of Product Characteristics (SPC) [11], are those patients with at least one relapse in the previous year and either at least one Gadolinium-enhancing lesion or at least 9 T2 lesions at enrolment or the same number or more relapses in comparison with the previous year (non-responders).

Only analyses on the basis of the respective total populations of the studies FREEDOMS, FREEDOMS II and CONFIRM were available for the indirect comparison presented for this benefit assessment. However, treatment-naive patients and patients who had not been pretreated with IFN-β for at least one year, i.e. patients who do not concur with the present research question, were included to a large proportion in these studies.

In the studies FREEDOMS and FREEDOMS II, the proportion of patients who correspond to the relevant subpopulation was far below 80% (0.2% and 0.6% in the studies FREEDOMS and FREEDOMS II). Considering the total population is inadequate solely with regard to the patients' pretreatment. In the FREEDOMS study, approximately 60% of the patients were treatment-naive in both relevant treatment arms (fingolimod 0.5 mg: 57%; placebo: 60%), in the FREEDOMS II study, these were approximately 27% of the patients (fingolimod 0.5 mg: 26%; placebo: 27%) (see Table 7).

Regarding the CONFIRM study, it was not clear from the publication on the study [7] how many patients concurred with the criteria of the relevant patient population for research question A. However, it can be assumed on the basis of the information on the patients' pretreatment alone that the relevant subpopulation was smaller than 80% of the total population of the study also in this case. Only about 30% of the patients had been pretreated with disease-modifying therapy in both relevant treatment arms of the CONFIRM study (29% in the glatiramer acetate arm; 31% in the placebo arm). A total of 21% and 11% of the patients from the total population had received pretreatment with IFN-β1a and IFN-β1b. The patients were allowed to have received several treatments so that double counting cannot be excluded.

From the company's point of view, the patient numbers of the relevant subpopulations of the studies FREEDOMS and FREEDOMS II (2 and 4 patients) allowed no valid comparison of the treatment arms. On the other hand, the company considered the characteristics of the relevant subpopulations to be comparable with the ones of the total populations, and concludes that the results of the total populations are transferable to the research question despite the low patient numbers. The company did not consider differences between the total populations and the relevant subpopulations, particularly regarding pretreatment. Regarding the CONFIRM study, the company had made an enquiry to the sponsor of the study to transfer the data sets that, from the company's point of view, would have allowed an analysis for the relevant subpopulation. This request was declined.

For the reasons stated above, the company used the results of the total populations of the studies FREEDOMS, FREEDOMS II and CONFIRM for the assessment of the added benefit of fingolimod in comparison with glatiramer acetate.

This approach was not accepted because the total populations are not comparable with the relevant subpopulations because of the pretreatment alone. The results for the total population were not used for the present benefit assessment.

Hence overall, no evaluable data were available for the derivation of the added benefit of fingolimod in comparison with the ACT glatiramer acetate.

2.3.2 Results on added benefit (research question A)

There were no evaluable data for the assessment of the added benefit of fingolimod for patients with highly active RRMS who have received full previous treatment with IFN-β. The added benefit of fingolimod versus the ACT glatiramer acetate is therefore not proven for these patients.

2.3.3 Extent and probability of added benefit (research question A)

The available data do not provide proof of an added benefit of fingolimod in comparison with the ACT specified by the G-BA for patients with highly active RRMS who have received full previous treatment with IFN-β. Hence there are also no patient groups for whom a therapeutically important added benefit can be derived.

In contrast, the company derived a hint of a minor added benefit for patients with highly active RRMS who have received full previous treatment with IFN-β.

2.3.4 List of included studies (research question A)

Not applicable as the company in its assessment did not present any relevant studies on the comparison of fingolimod with the ACT glatiramer acetate for research question A.

2.4 Research question B: patients with highly active RRMS, no full previous treatment with IFN-β

2.4.1 Information retrieval and study pool (research question B)

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 30 January 2015)
- bibliographical literature search on fingolimod (last search on 16 January 2015)
- search in trial registries for studies on fingolimod (last search on 14 January 2015)

To check the completeness of the study pool:

- search in trial registries for studies on fingolimod (last search on 13 April 2015)

No additional relevant study was identified from the check.

2.4.1.1 Studies included

The CFTY720D2302 (TRANSFORMS) study listed in the following table was included in the benefit assessment.

Table 8: 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)
CFTY720D2302 (TRANSFORMS)[b]	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. b: Hereinafter referred to as "TRANSFORMS". IFN-β: interferon beta; RCT: randomized controlled trial; vs.: versus			

The TRANSFORMS study was identified. This study was already presented in the dossier from 21 September 2011 for the first benefit assessment of fingolimod (Commission A11-23 [3]). For the present benefit assessment, the company presented new analyses of the data already presented in the dossier from 21 September 2011 in its dossier from 19 March 2015. The data underlying the analyses of the TRANSFORMS study are therefore unchanged.

Only the subpopulation of patients with high disease activity who have not received full pretreatment with IFN-β (< one year) is relevant for research question B. Patients with high disease activity, according to the definition of the SPC [11], were those patients with at least one relapse in the previous year and either at least one Gadolinium-enhancing lesion or at least 9 T2 lesions at enrolment or the same number or more relapses in comparison with the previous year. Section 2.4.4 contains a reference list for the study included.

2.4.1.2 Study characteristics

Characteristics of the study and of the interventions

Table 9 and Table 10 describe the TRANSFORMS study used for the benefit assessment.

Table 9: 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	Adults with RRMS at least 1 relapse in the past year, or at least 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) Of which: Relevant subpopulation for research question B[c]: fingolimod 0.5 mg (n = 54) IFN-β1a 30 µg IM (n = 56) Relevant subpopulation for research question C[d]: fingolimod 0.5 mg (n = 56) IFN-β1a 30 µg IM (n = 65)	Screening: 45 days Baseline phase: 7 days Treatment phase: 12 months Follow up for 3 months or participation in the extension phase at the patient's request	172 centres in 18 countries worldwide: Argentina (7), Australia (7), Austria (7), Belgium (4), Brazil (6), Canada (9), Egypt (5 centres), France (6), Germany (28), Greece (6), Hungary (6), Italy (22), Korea (4), Portugal (5), Spain (8), Switzerland (2), United Kingdom (4), USA (37) 5/2006 – 11/2008	Primary: annualized relapse rate Secondary: further relapse-related outcomes, disability progression, disability severity, activities of daily living, health-related quality of life, AEs

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively 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 for research question B: adult patients with highly active RRMS who have not received full previous treatment (< 1 year) with IFN-β.
d: Relevant subpopulation for research question C: adult patients with rapidly evolving severe RRMS.

AE: adverse event; 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 10: Characteristics of the interventions – RCT, direct comparison: fingolimod vs. IFN-β1a

Study	Intervention	Comparison	Concomitant medication
TRANSFORMS	Fingolimod 0.5 mg, once daily, oral administration + placebo, once daily, IM	IFN-β1a 30 µg, once weekly, IM + placebo, once daily, oral administration	Concomitant medication allowed: ▪ corticosteroids for treatment of relapse Non-permitted concomitant medication: ▪ immunosuppressants ▪ immunoglobulins, monoclonal antibodies, IFN-β (except IFN-β1a), glatiramer acetate, ACTH
ACTH: adrenocorticotrophic hormone; IFN-β: interferon beta; IM: intramuscular; RCT: randomized controlled trial; vs.: versus			

The TRANSFORMS study was a multicentre, double-blind RCT. Adult patients with RRMS were enrolled. The diagnosis of multiple sclerosis was made using the revised McDonald criteria [8]. Patients should have experienced at least one relapse in the past year or 2 relapses in the past 2 years; baseline EDSS had to be between 0 and 5.5. There were no limitations with regard to pretreatment.

Only a subpopulation of the study was relevant for the benefit assessment. This subpopulation included patients with high disease activity who have not received full pretreatment with IFN-β (< one year). Patients with high disease activity, according to the definition of the SPC [11], were those patients with at least one relapse in the previous year and either at least one Gadolinium-enhancing lesion or at least 9 T2 lesions at enrolment or the same number or more relapses in comparison with the previous year (non-responders).

The study had a 3-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 IM 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). According to the company, 110 of these patients (12.7% of the study population) corresponded to the relevant subpopulation of patients with highly active RRMS who have not received full previous treatment with IFN-β (fingolimod: n = 54 patients, IFN-β: n = 56 patients) (see Section 2.7.3.4.1 of the full dossier assessment).

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 AEs.

Characteristics of the relevant subpopulation

Table 11 shows the characteristics of the patients in the study included, referring to the subpopulation relevant for the assessment of research question B.

Table 11: Characteristics of the relevant subpopulation – RCT, direct comparison: fingolimod vs. IFN-β1a (research question B)

Study Characteristics Category	Fingolimod N = 54	IFN-β1a N = 56
TRANSFORMS		
Age [years], mean (SD)	37 (10)	37 (9)
Sex [F/M], %	72/28	70/30
Duration of disease[a] [years], mean (SD)	5.2 (5.3)	5.0 (5.8)
Baseline EDSS, mean (SD)	2.5 (1.4)	2.4 (1.2)
Number of relapses in the last year, mean (SD)	1.5 (0.7)	1.5 (0.7)
Number of relapses in the last 2 years, mean (SD)	2.1 (1.3)	2.2 (0.9)
Patients without Gd-enhancing T1 lesions, n (%)	34 (63)	30 (54)[b]
Patients without pretreatment[c], n (%)	0 (0)	0 (0)
Treatment discontinuations, n (%)	ND[d]	ND[d]

a: According to the company, the duration of disease is the time since the first symptom. However, the data for the total study population, which were also cited in Module 4 B, do not concur with the data of the time since diagnosis of the disease in the CSR. It therefore remains unclear what the duration of disease refers to.
b: According to the company's calculation, the percentages only refer to 55 patients; the company did not provide further information.
c: Patients who have not received previous treatment with IFN-β1a (IM or SC), IFN-β1b (SC), glatiramer acetate or natalizumab.
d: No information is available for the relevant patient population (research question B).
EDSS: Expanded Disability Status Scale; F: female; Gd: Gadolinium; IFN-β: interferon beta; IM: intramuscular; M: male; N: number of randomized (or included) patients; n: number of patients in the category; ND: no data; RCT: randomized controlled trial; SC: subcutaneous; 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 70%). Disease duration was about 5 years (5.2 years in the fingolimod arm, and 5.0 years in the IFN-β arm). The mean number of relapses was 1.5 in the past year (both treatment arms), and slightly more than 2 relapses in the past 2 years (2.1 relapses in the fingolimod arm, and 2.2 relapses in the IFN-β arm). At least one third of the patients had at least one Gadolinium-enhancing lesion. There was no information on the number of treatment discontinuations for the relevant subpopulation.

Risk of bias

Table 12 shows the risk of bias at study level.

Table 12: 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.

2.4.2 Results on added benefit (research question B)

2.4.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.3.4.3 of the full dossier assessment):

- Mortality
  - all-cause mortality (deaths)
- Morbidity
  - relapses (based on EDSS)
    - annualized relapse rate
    - time to first confirmed relapse
  - disability progression (based on EDSS)
    - time to first confirmed disability progression
  - disability severity
    - mean change in MSFC-z
  - fatigue (mFIS)
  - activities of daily living (PRIMUS activities)
  - health status (EQ-5D VAS)
- Health-related quality of life
  - recorded with PRIMUS QoL
- Adverse events

- SAEs
- discontinuation due to AEs
- infections (System Organ Class [SOC])
- influenza like illness (Preferred Term [PT])
- constipation (PT)

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 B) (for further reasons, see Section 2.7.3.4.3 of the full dossier assessment).

Table 13 shows for which outcomes data were available in the study included.

Table 13: Matrix of outcomes – RCT, direct comparison: fingolimod vs. IFN-β1a (research question B)

Study	Outcomes												
	All-cause mortality	Relapses	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	Infections	Influenza like illness	Constipation
TRANSFORMS	Y	Y	Y	Y	No[a]	No[a]	Y	No[a]	Y	Y	Y	Y	Y

a: No evaluable data available. See Section 2.7.3.4.3 of the full dossier assessment for reasons.
AE: adverse event; EQ-5D: European Quality of Life-5 Dimensions; IFN-β: interferon beta; 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; Y: yes

The available documents contained data for all relevant outcomes. For some outcomes however, the available data were not evaluable. This applied to the outcomes “activities of daily living (PRIMUS activities)”, “fatigue (mFIS)”, and “health-related quality of life (PRIMUS QoL)”. It could not be excluded for these outcomes that the respective proportion of the patients not considered in the analysis was above 30%. However, there was no statistically significant difference between the treatment groups for these outcomes; hence the exclusion of these outcomes had no influence on the overall result of the benefit assessment. Further information can be found in Section 2.7.3.4.3 of the full dossier assessment.

2.4.2.2 Risk of bias

Table 14 shows the risk of bias for the relevant outcomes.

Table 14: Risk of bias at study and outcome level – RCT, direct comparison: fingolimod vs. IFN-β1a (research question B)

Study		Outcomes												
	Study level	All-cause mortality	Relapses	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	Infections	Flu-like illness	Constipation
TRANSFORMS	L	L	L	L	H[a]	–[b]	–[b]	H[c]	–[b]	L	L	L	L	L

a: Data from 96 patients (87.3% of the 110 patients in the relevant subpopulation) were considered in the analysis. It is unclear whether the remaining 14 patients (12.7%) received the questionnaire and hence would have had to be considered in the analysis.
b: No evaluable data available. It remains unclear in how many patients the questionnaire was recorded. It cannot be excluded that more than 30% of the patients were not considered in the analysis.
c: Data from 94 patients (85.5% of the 110 patients in the relevant subpopulation) were considered in the analysis. It is unclear whether the remaining 16 patients (14.5%) received the questionnaire and hence would have had to be considered in the analysis.
AE: adverse event; EQ-5D: European Quality of Life-5 Dimensions; H: high; IFN-β: interferon beta; 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, relapses (annualized relapse rate, time to first relapse), disability progression (time to first confirmed disability progression), SAEs, discontinuation due to AEs, infections, influenza like illness, and constipation. This concurs with the company's assessment.

For the outcomes "disability severity" and "health status", the risk of bias was high. There were no data for 12.7% and 14.5% of the patients, but it was unclear whether these patients had received the respective questionnaire and would have had to be considered in the analysis. In contrast, the company rated the risk of bias as low.

There were no evaluable data for the remaining outcomes (fatigue, activities of daily living, health-related quality of life). It could not be excluded that more than 30% of the patients were not considered in the analysis. Therefore no outcome-specific assessment of the risk of bias was conducted for these outcomes. Further information can be found in Section 2.7.3.4.2 of the full dossier assessment.

2.4.2.3 Results

Table 15, Table 16 and Table 17 summarize the results on the comparison of fingolimod and IFN-β1a in patients with highly active RRMS who have not received full previous treatment

with IFN-β. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations. Supplementary information on the most common AEs can be found in Table 35 in Appendix A of the full dossier assessment.

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.

Table 15: Results on mortality and morbidity – RCT, direct comparison: fingolimod vs. IFN β1a (research question B)

Study **Outcome category** **Outcome**	**Fingolimod**		**IFN-β1a**		**Fingolimod vs. IFN-ß1a**
	N	**Patients with events n (%)**	**N**	**Patients with events n (%)**	**RR [95% CI]; p-value**
TRANSFORMS					
Mortality					
Deaths	54	0 (0)	56	0 (0)	no data[a]
Morbidity					
Relapses (based on EDSS)					
	N	**Annualized relapse rate [95% CI]**	**N**	**Annualized relapse rate [95% CI]**	**Rate ratio [95% CI]; p-value**
Annualized relapse rate[b]	54	0.24 [0.13; 0.45]	56	0.60 [0.39; 0.93]	0.40 [0.19; 0.85]; 0.017
	N	**Median time [95% CI]/ Patients with events n (%)**	**N**	**Median time [95% CI]/ Patients with events n (%)**	**HR [95% CI]; p-value**
Time to first confirmed relapse	54	NA/ 11 (20.4)[c]	56	NA/ 19 (33.9)[c]	0.53 [0.25; 1.11]; 0.093
	N	**Number of relapses (%)**	**N**	**Number of relapses (%)**	**RR [95% CI]; p-value**
Number of relapses according to severity		Mild: 5 (38.5) moderate: 4 (30.8) severe: 4 (30.8)		Mild: 4 (12.5) moderate: 18 (56.3) severe: 10 (31.3)	
Disability progression (based on EDSS)					
	N	**Median time [95% CI]/ Patients with events n (%)**	**N**	**Median time [95% CI]/ Patients with events n (%)**	**HR [95% CI]; p-value**
Time to first confirmed disability progression	54	NA/ 3 (5.6)[c]	56	NA/ 4 (7.1)[c]	0.75 [0.17; 3.35]; 0.707

a: No effect estimation possible because no deaths occurred.
b: Probably results of a generalized linear model with outcome variable with negative binomial distribution (see Section 2.7.3.4.3 of the full dossier assessment).
c: Kaplan-Meier estimator at month 12 taken from the Kaplan-Meier curve.

CI: confidence interval; 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; vs.: versus

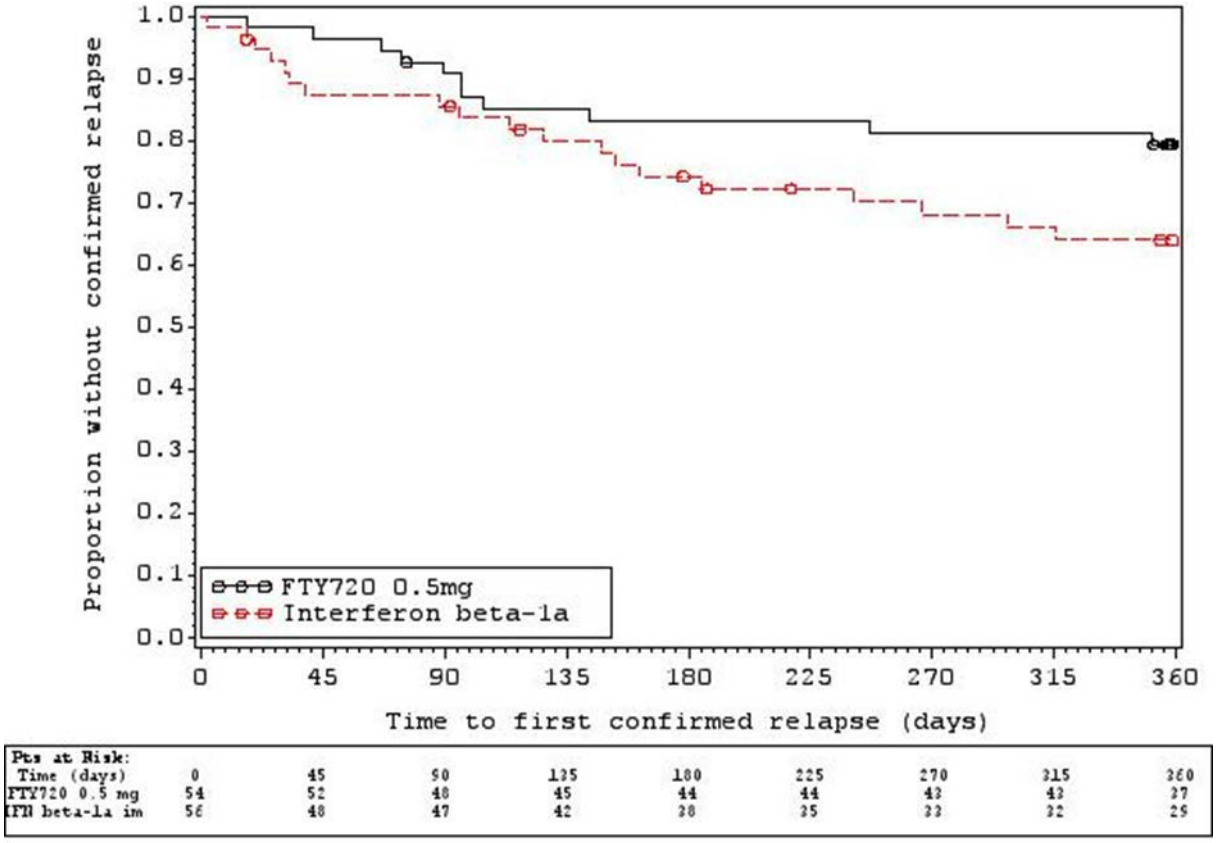

Figure 1: Kaplan-Meier curves of the time to first confirmed relapse (research question B)

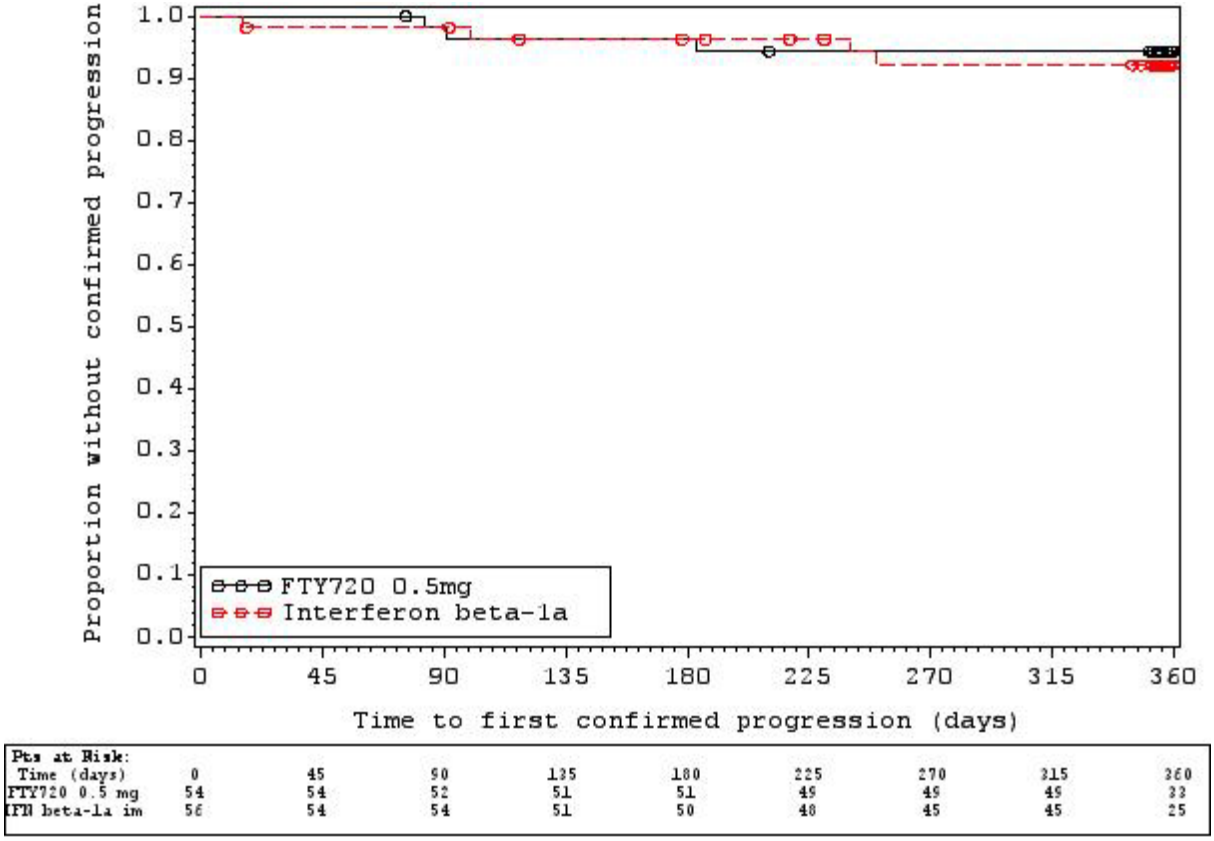

Figure 2: Kaplan-Meier curves of the time to first confirmed disability progression (research question B)

Table 16: Results on morbidity and health-related quality of life (continuous outcomes) – RCT, direct comparison: fingolimod vs. IFN-β1a (research question B)

Study Outcome category Outcome	Fingolimod			IFN-β1a			Fingolimod vs. IFN-ß1a
	N[a]	Baseline values mean (SE)	Change at end of study mean (SE)	N[a]	Baseline values mean (SE)	Change at end of study mean (SE)	Mean difference [95% CI]; p-value
TRANSFORMS							
Morbidity							
Disability severity							
MSFC-z[b]	50	−0.05 (0.08)	0.03 (0.04)	46	−0.00 (0.07)	−0.09 (0.05)	0.11 [−0.01; 0.24]; 0.080
subscale T25-FW[c]	50	6.20 (0.40)	0.50 (0.60)	46	6.20 (0.43)	0.10 (0.62)	0.40 [−1.32; 2.11]; 0.648
subscale 9-HPT[c]	50	22.43 (0.78)	−0.07 (0.39)	46	22.23 (0.80)	0.75 (0.41)	−0.82 [−1.94; 0.30]; 0.151
subscale PASAT-3[b]	50	47.50 (1.51)	1.84 (0.76)	46	49.52 (1.41)	−0.65 (0.79)	2.49 [0.30; 4.68]; 0.026 Hedges' g 0.45 [0.05; 0.86][d]
Fatigue							
mFIS[e]			No evaluable data[f]				
Activities of daily living							
PRIMUS activities[e]			No evaluable data[f]				
Health status							
EQ-5D VAS[c]	50	77.44 (2.29)	0.92 (1.93)	44	79.27 (1.85)	−0.39 (2.06)	1.31 [−4.29; 6.92]; 0.642
Health-related quality of life							
PRIMUS QoL[e]			No evaluable data[f]				

a: Number of patients considered in the analysis for the calculation of the effect estimate. The values at the start of the study may be based on other patient numbers.
b: Positive values/changes indicate improvement.
c: Negative values/changes indicate improvement.
d: Institute's calculation.
e: The questionnaire was recorded in selected countries (Australia [according to the CSR; according to the company in Module 4: Austria], Canada, France, Germany, Italy, Spain, Great Britain and United States).
f: It is unclear in how many patients the questionnaire was recorded. Possibly more than 30% of the patients were not considered in the analysis.

CI: confidence interval; CSR: clinical study report; EQ-5D: European Quality of Life-5 Dimensions; 9-HPT: 9-Hole Peg Test; IFN-β: interferon beta; mFIS: Modified Fatigue Impact Scale; MSFC: Multiple Sclerosis Functional Composite; N: number of analysed patients; 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 17: Results on AEs – RCT, direct comparison: fingolimod vs. IFN-β1a (research question B)

Study Outcome category Outcome	Fingolimod N	Fingolimod Patients with events n (%)	IFN-β1a N	IFN-β1a Patients with events n (%)	Fingolimod vs. IFN-ß1a RR [95% CI]; p-value[a]
TRANSFORMS					
Adverse events					
AEs	54	50 (92.6)	56	49 (87.5)	
SAEs	54	6 (11.1)	56	2 (3.6)	3.11 [0.66; 14.75]; 0.144
Discontinuation due to AEs	54	2 (3.7)	56	3 (5.4)	0.69 [0.12; 3.98]; 0.767
Infections	54	30 (55.6)	56	32 (57.1)	0.97 [0.70; 1.35]; 0.905
Influenza like illness	54	0 (0)	56	16 (28.6)	0.03 [0.00; 0.51]; < 0.001
Constipation	54	4 (7.4)	56	0 (0.0)	9.33 [0.51; 169.2]; 0.045[b]

a: Institute's calculation, unconditional exact test (CSZ method according to [12]).
b: Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.
AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; 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

The company did not draw conclusions on the added benefit at outcome level in Module 4 B. Hence it is not commented on in how far the assessment of the outcomes in the present benefit assessment deviates from that of the company.

Mortality

Deaths

No events occurred in both treatment groups for the outcome "deaths". Hence there was no hint of an added benefit of fingolimod in comparison with IFN-β1a. An added benefit for this outcome is therefore not proven.

Morbidity

Relapses

There were several operationalizations for the outcome "relapses". The results of these operationalizations were assessed for the outcome "relapses" in their totality.

For the annualized relapse rate, which was considered to be the decisive operationalization, there was a statistically significant difference in favour of fingolimod in comparison with IFN-β1a. There was no statistically significant difference between the treatment groups for the time to first confirmed relapse. However, the effect pointed in the same direction as the

effect in the annualized relapse rate and therefore did not raise doubts about it. In addition, the occurred relapses were milder under treatment with fingolimod than under IFN-β1a (38.5% mild relapses versus 12.5%).

Overall, there is thus an indication of an added benefit of fingolimod in comparison with IFN-β1a for the outcome "relapses".

Disability progression

There was no statistically significant difference between the treatment groups for the time to first confirmed disability progression. Hence there was no hint of an added benefit of fingolimod in comparison with IFN-β1a. An added benefit for this outcome is therefore not proven.

Disability severity

There was no statistically significant difference between the treatment groups for the outcome "disability severity" for the MSFC-z score (total score). Hence there was no hint of an added benefit of fingolimod in comparison with IFN-β1a. An added benefit for this outcome is therefore not proven.

Fatigue

There were no evaluable data for the outcome "fatigue (mFIS)". Hence there was no hint of an added benefit of fingolimod in comparison with IFN-β1a. An added benefit for this outcome is therefore not proven.

Activities of daily living

There were no evaluable data for the outcome "activities of daily living (PRIMUS activities)". Hence there was no hint of an added benefit of fingolimod in comparison with IFN-β1a. An added benefit for this outcome is therefore not proven.

Health status

There was no statistically significant difference between the treatment groups for the outcome "health status (EQ-5D VAS)". Hence there was no hint of an added benefit of fingolimod in comparison with IFN-β1a. An added benefit for this outcome is therefore not proven.

Health-related quality of life

PRIMUS QoL

There were no evaluable data for health-related quality of life (PRIMUS QoL). Hence there was no hint of an added benefit of fingolimod in comparison with IFN-β1a. An added benefit for this outcome is therefore not proven.

Adverse events

Serious adverse events and discontinuation due to adverse events

There was no statistically significant difference between the treatment groups for the outcomes "SAEs" and "discontinuation due to AEs". Hence there was no hint of greater or lesser harm from fingolimod in comparison with IFN-β1a; greater or lesser harm for these outcomes is therefore not proven.

Infections

There was no statistically significant difference between the treatment groups for the outcome "infections". Hence there was no hint of greater or lesser harm from fingolimod in comparison with IFN-β1a; greater or lesser harm for this outcome is therefore not proven.

Influenza like illness

There was a statistically significant difference in favour of fingolimod in comparison with IFN-β1a for the outcome "influenza like illness". This results in an indication of lesser harm from fingolimod in comparison with IFN-β1a.

Constipation

There was a statistically significant difference to the disadvantage of fingolimod in comparison with IFN-β1a for the outcome "constipation". A valid determination of the confidence interval was not possible because of the low number of events. An only marginal effect can therefore not be excluded. Hence there was no hint of greater harm from fingolimod in comparison with IFN-β1a; greater or lesser harm for this outcome is therefore not proven.

2.4.2.4 Subgroups and other effect modifiers

The following potential effect modifier was investigated (for reasons, see Section 2.7.3.4.3 of the full dossier assessment):

- sex (male/female)

The prerequisite for proof of different effects is a statistically significant interaction test ($p < 0.05$). A p-value between 0.05 and 0.2 provides an indication of different effects. There was no proof or indication of effect modification by sex for the outcomes considered in the present benefit assessment.

2.4.3 Extent and probability of added benefit (research question B)

The derivation of extent and probability of added benefit is presented below at outcome level, taking into account the different 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.

2.4.3.1 Assessment of added benefit at outcome level

The data presented in Section 2.4.2 of this benefit assessment resulted in an indication of an added benefit of fingolimod in comparison with the ACT IFN-β1a for the outcome "relapses (annualized relapse rate)" for patients with highly active RRMS who have not received full previous treatment with IFN-β. For the outcome "influenza like illness", there was an indication of lesser harm from fingolimod in comparison with the ACT IFN-β1a. The extent of the respective added benefit at outcome level was estimated from these results (see Table 18).

Determination of the outcome category for the outcome "relapses"

The assessment of the outcome category for the outcome "relapses" on the one hand depended on the severity of the relapses occurred in the TRANSFORMS study. In the TRANSFORMS study, relapses were recorded with the EDSS or with the corresponding functional systems, with a relapse being defined as a (temporary) increase in the EDSS score by ≥ 0.5 points or an increase in the score of 1 to 3 functional systems by ≥ 1 point. The severity of a relapse therefore also depended on the initial situation of the patients in the study.

In the study, relapses were also classified by severity into mild, moderate and severe. As shown in Table 15 and Table 23, the vast majority of the relapses that occurred in the TRANSFORMS study in research questions B and C were mild or moderate. In the subpopulation relevant for research question B, 4 severe relapses (30.8% in relation to the number of all relapses in the respective treatment arm) occurred in the fingolimod arm, and 10 severe relapses (31.3%) in the IFN-β arm in the course of the study. In the subpopulation relevant for research question C, however only one severe relapse (6.7%) occurred in the fingolimod arm and 7 severe relapses (19.7%) in the IFN-β arm. Hospitalization was only necessary in few relapses (in a total of 6 relapses in research question B, and in 3 relapses in research question C). Overall, the number of severe relapses was too low to categorize the outcome "relapses" as "serious/severe symptoms/late complications". There was no further information that would allow an assessment of the severity of relapses in multiple sclerosis, such as the proportion of relapses leading to disability progression, for example.

Hence the results on relapses were allocated to the outcome category "non-serious/non-severe symptoms/late complications". This allocation had no influence on the overall conclusion on added benefit.

Table 18: Extent of added benefit at outcome level: fingolimod vs. IFN-β1a (research question B)

Outcome category **Outcome**	**Fingolimod vs. IFN-ß1a** **Median time to event/ proportion of events/ mean change** **effect estimate [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
Deaths	0% vs. 0%	Lesser benefit/added benefit not proven
Morbidity		
Relapses (based on EDSS)		
Annualized relapse rate	0.24 vs. 0.60 rate ratio 0.40 [0.19; 0.85] p = 0.017 probability: “indication”	Outcome category: non-serious/non-severe symptoms/late complications $0.80 < CI_u < 0.90$ added benefit, extent: “minor”
Time to first confirmed relapse	NA vs. NA HR 0.53 [0.25; 1.11] p = 0.093	Lesser benefit/added benefit not proven
Disability progression (based on EDSS)		
Time to first confirmed disability progression	NA vs. NA HR 0.75 [0.17; 3.35] p = 0.707	Lesser benefit/added benefit not proven
Disability severity		
MSFC-z	0.03 vs. −0.09 MD 0.11 [−0.01; 0.24] p = 0.080	Lesser benefit/added benefit not proven
Fatigue		
mFIS	No evaluable data	
Activities of daily living		
PRIMUS activities	No evaluable data	
Health status		
EQ-5D VAS	0.92 vs. −0.39 MD 1.31 [−4.29; 6.92] p = 0.642	Lesser benefit/added benefit not proven
Health-related quality of life		
PRIMUS QoL	No evaluable data	

(continued)

Table 18: Extent of added benefit at outcome level: fingolimod vs. IFN-β1a (research question B) (continued)

Outcome category **Outcome**	**Fingolimod vs. IFN-ß1a** **Median time to event/ proportion of events/ mean change** **effect estimate [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Adverse events		
SAEs	11.1% vs. 3.6% RR 3.11 [0.66; 14.75] p = 0.144	Lesser/greater harm not proven
Discontinuation due to AEs	3.7% vs. 5.4% RR 0.69 [0.12; 3.98] p = 0.767	Lesser/greater harm not proven
Infections	55.6% vs. 57.1% RR 0.97 [0.70; 1.35] p = 0.905	Lesser/greater harm not proven
Influenza like illness	0% vs. 28.6% RR 0.03 [0.00; 0.51] p < 0.001 probability: "indication"	Outcome category: non-serious/non-severe AEs CI_u < 0.80 lesser harm, extent: "considerable"
Constipation	7.4% vs. 0% RR 9.33 [0.51; 169.2] RR[c] 0.11 [0.01; 1.95] p = 0.045[d] probability: "indication"	Outcome category: non-serious/non-severe AEs Lesser/greater harm not proven[e]

a: Probability provided if statistically significant differences were present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Proportion of events IFN-β1a vs. fingolimod (reversed direction of effect to allow direct use of limits to derive the extent of added benefit).
d: Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.
e: No valid determination of CI possible because of the low number of events. An only marginal effect cannot be excluded.

AE: adverse event; CI: confidence interval; CI_u: upper limit of CI; EDSS: Expanded Disability Status Scale; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; IFN-β: interferon beta; MD: mean difference; mFIS: Modified Fatigue Impact Scale; MSFC-z: Multiple Sclerosis Functional Composite standard score; PRIMUS: Patient-Reported Indices for Multiple Sclerosis; QoL: quality of life; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.4.3.2 Overall conclusion on added benefit

Table 19 summarizes the results that were included in the overall conclusion on the extent of added benefit for patients with highly active RRMS who have not received full previous treatment with IFN-β.

Table 19: Positive and negative effects from the assessment of fingolimod compared with IFN-β1a (research question B)

Positive effects	Negative effects
Indication of added benefit – extent "minor" (non-serious /non-severe symptoms/late complications: relapses)	-
Indication of lesser harm – extent: "considerable" (non-serious/non-severe adverse events: influenza like illness)	
IFN-β: interferon beta	

Overall, there are 2 positive effects with the same probability, but with different extent.

There was an indication of minor added benefit in the category "non-serious/non-severe symptoms/late complications" for the outcome "relapses" regarding the annualized relapse rate. Additionally, there was lesser harm with considerable extent in the category "non-serious/non-severe AEs" regarding influenza like illness.

In summary, there is an indication of considerable added benefit of fingolimod in comparison with the ACT IFN-β1a for patients with highly active RRMS who have not received full previous treatment with IFN-β.

This only partly concurs with the company's assessment, which also derived an indication of considerable added benefit of fingolimod, but limited it to the IM administration of IFN-β1a.

2.4.4 List of included studies (research question B)

TRANSFORMS

Agius M, Meng X, Chin P, Grinspan A, Hashmonay R. Fingolimod therapy in early multiple sclerosis: an efficacy analysis of the TRANSFORMS and FREEDOMS studies by time since first symptom. CNS Neurosci Ther 2014; 20(5): 446-451.

Chinea Martinez AR, Correale J, Coyle PK, Meng X, Tenenbaum N. Efficacy and safety of fingolimod in Hispanic patients with multiple sclerosis: pooled clinical trial analyses. Adv Ther 2014; 31(10): 1072-1081.

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.

Cohen JA, Barkhof F, Comi G, Izquierdo G, Khatri B, Montalban X et al. Fingolimod versus intramuscular interferon in patient subgroups from TRANSFORMS. J Neurol 2013; 260(8): 2023-2032.

DiMarco JP, O'Connor P, Cohen JA, Reder AT, Zhang-Auberson L, Tang D et al. First-dose effects of fingolimod: pooled safety data from three phase 3 studies. Mult Scler Relat Disord 2014; 3(5): 629-638.

Kappos L, Cohen J, Collins W, De Vera A, Zhang-Auberson L, Ritter S et al. Fingolimod in relapsing multiple sclerosis: an integrated analysis of safety findings. Mult Scler Relat Disord 2014; 3(4): 494-504.

Khatri B, Barkhof F, Comi G, Hartung HP, Kappos L, Montalban X et al. Comparison of fingolimod with interferon beta-1a in relapsing-remitting multiple sclerosis: a randomised extension of the TRANSFORMS study. Lancet Neurol 2011; 10(6): 520-529.

Khatri BO, Pelletier J, Kappos L, Hartung HP, Comi G, Barkhof F et al. Effect of prior treatment status and reasons for discontinuation on the efficacy and safety of fingolimod vs. interferon beta-1a intramuscular: subgroup analyses of the trial assessing injectable interferon vs. Fingolimod oral in relapsing-remitting multiple sclerosis (TRANSFORMS). Mult Scler Relat Disord 2014; 3(3): 355-363.

Meng X, Chin PS, Hashmonay R, Zahur Islam M, Cutter G. Effect of switching from intramuscular interferon beta-1a to oral fingolimod on time to relapse in patients with relapsing-remitting multiple sclerosis enrolled in a 1-year extension of TRANSFORMS. Contemp Clin Trials 2015; 41: 69-74.

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. 14 January 2014 [accessed: 1 June 2015]. URL: https://clinicaltrials.gov/show/NCT00340834.

Novartis. Efficacy and safety of fingolimod in patients with relapsing-remitting multiple sclerosis with optional extension phase (TRANSFORMS): study results [online]. In: ClinicalTrials.gov. 14 January 2014 [accessed: 3 June 2015]. URL: https://clinicaltrials.gov/ct2/show/results/NCT00340834.

Novartis. A 12-month double-blind, randomized, multicenter, active-controlled, 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 no CFTY720D2302; full clinical study report [unpublished]. 2008.

Novartis Pharma. A 12-month double-blind, randomized, multicenter, active controlled, parallel-group study comparing the efficacy and safety of 0.5 mg and 1.25 mg fingolimod (FTY720) administered orally once daily versus interferon β-1a (Avonex) administered i.m. once weekly in patients with relapsing-remitting multiple sclerosis with optional extension phase [online]. In: EU Clinical Trials Register. [Accessed: 1 June 2015]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2006-000704-17/DE.

2.5 Research question C: patients with rapidly evolving severe RRMS

2.5.1 Information retrieval and study pool (research question C)

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 30 January 2015)
- bibliographical literature search on fingolimod (last search on 16 January 2015)
- search in trial registries for studies on fingolimod (last search on 14 January 2015)

To check the completeness of the study pool:

- search in trial registries for studies on fingolimod (last search on 13 April 2015)

No additional relevant study was identified from the check.

2.5.1.1 Studies included

The TRANSFORMS study listed in Table 8 (Section 2.4.1.1, research question B) was included in the benefit assessment. This study was already presented in the dossier from 21 September 2011 for the first benefit assessment of fingolimod (Commission A11-23 [3]). For the present benefit assessment, the company presented new analyses of the data already presented in the dossier from 21 September 2011 in its dossier from 19 March 2015. The data underlying the analyses of the TRANSFORMS study are therefore unchanged.

Only the subpopulation of patients with rapidly evolving severe RRMS is relevant for research question C. According to the definition in the SPC [11], these are patients with 2 or more relapses in one year and at least one Gadolinium-enhancing lesion at enrolment. Section 2.5.4 contains a reference list for the studies included.

2.5.1.2 Study characteristics

Characteristics of the study and of the interventions

The characteristics of the TRANSFORMS study are presented in Section 2.4.1.2 on research question B (Table 9 and Table 10).

Of the total of 866 patients included in the relevant treatment arms of the TRANSFORMS study, according to the company, 121 patients (14% of the study population) concurred with the relevant subpopulation of patients with rapidly evolving severe RRMS (fingolimod: n = 56 patients, IFN-β: n = 65 patients). In contrast to the dossier from 21 September 2011 for the first benefit assessment of fingolimod (Commission A11-23 [3]), the company, concurring with the SPC [11], included both treatment-naive and pretreated patients in Module 4 C. The patient numbers therefore differed from the ones in Assessment A11-23.

Characteristics of the relevant subpopulation

Table 20 shows the characteristics of the patients in the study included, referring to the subpopulation relevant for the assessment of research question C.

Table 20: Characteristics of the relevant subpopulation – RCT, direct comparison: fingolimod vs. IFN-β1a (research question C)

Study Characteristics Category	Fingolimod N = 56	IFN-β1a N = 65
TRANSFORMS		
Age [years], mean (SD)	32 (8)	35 (7)
Sex [F/M], %	70/30	72/28
Duration of disease[a] [years], mean (SD)	3.0 (3.2)	4.5 (5.3)
Baseline EDSS, mean (SD)	2.0 (1.3)	2.4 (1.4)
Number of relapses in the last year, mean (SD)	2.3 (0.5)	2.4 (0.7)
Number of relapses in the last 2 years, mean (SD)	2.9 (1.0)	3.2 (1.5)
Patients without Gd-enhancing T1 lesions, n (%)	0 (0)	0 (0)
Patients without pretreatment[b], n (%)	28 (50)	30 (46)
Treatment discontinuations, n (%)	ND[c]	ND[c]

a: According to the company, the duration of disease is the time since the first symptom. However, the data for the total study population, which were also cited in Module 4 C, do not concur with the data of the time since diagnosis of the disease in the CSR. It therefore remains unclear what the duration of disease refers to.
b: Patients who have not received previous treatment with IFN-β1a (IM or SC), IFN-β1b (SC), glatiramer acetate or natalizumab.
c: No information is available for the relevant patient population (research question C).
EDSS: Expanded Disability Status Scale; F: female; Gd: Gadolinium; IFN-β: interferon beta; IM: intramuscular; M: male; N: number of randomized (or included) patients; n: number of patients in the category; ND: no data; RCT: randomized controlled trial; SC: subcutaneous; SD: standard deviation; vs.: versus

There were no important differences between the treatment groups. The average age of the patients in the fingolimod was somewhat lower than the one of the patients in the IFN-β arm (32 versus 35 years). Most patients were female (approximately 70%). Disease duration was longer in the IFN-β arm (4.5 years) than in the fingolimod arm (3.0 years). The number of relapses was 2.0 and 2.4 in the past year (fingolimod versus IFN-β1a), and about 3 relapses in the past 2 years (2.9 relapses in the fingolimod arm, and 3.2 relapses in the IFN-β arm). All patients had at least one Gadolinium-enhancing lesion. About half the patients were treatment-naive (50% in the fingolimod arm and 46% in the IFN-β arm). There was no information on the number of treatment discontinuations for the relevant subpopulation.

Risk of bias

The risk of bias at study level is shown in Section 2.4.1.2 on research question B (Table 12). It was rated as low for the TRANSFORMS study included. This concurs with the company's assessment.

2.5.2 Results on added benefit (research question C)

2.5.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.3.4.3 of the full dossier assessment):

- Mortality
  - all-cause mortality (deaths)
- Morbidity
  - relapses (based on EDSS)
    - annualized relapse rate
    - time to first confirmed relapse
  - disability progression (based on EDSS)
    - time to first confirmed disability progression
  - disability severity
    - mean change in MSFC-z
  - fatigue (mFIS)
  - activities of daily living (PRIMUS activities)
  - health status (EQ-5D VAS)
- Health-related quality of life
  - recorded with PRIMUS QoL
- Adverse events
  - SAEs
  - discontinuation due to AEs
  - infections (SOC)
  - influenza like illness (PT)
  - gastrointestinal disorders (SOC)

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 B) (for further reasons, see Section 2.7.3.4.3 of the full dossier assessment).

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

Table 21: Matrix of outcomes – RCT, direct comparison: fingolimod vs. IFN-β1a (research question C)

Study	Outcomes												
	All-cause mortality	**Relapses**	**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)**	**Serious adverse events**	**Discontinuation due to adverse events**	**Infections**	**Influenza like illness**	**Gastrointestinal disorders**
TRANSFORMS	Y	Y	Y	Y	No[a]	No[a]	Y	No[a]	Y	Y	Y	Y	Y

a: No evaluable data available. See Section 2.7.3.4.3 of the full dossier assessment for reasons.
EQ-5D: European Quality of Life-5 Dimensions; IFN-β: interferon beta; mFIS: Modified Fatigue Impact Scale; MSFC-z: Multiple Sclerosis Functional Composite standard score; PRIMUS: Patient-Reported Indices for Multiple Sclerosis; QoL: quality of life; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus; Y: yes

The available documents contained data for all relevant outcomes. For some outcomes however, the available data were not evaluable. This applied to the outcomes “activities of daily living (PRIMUS activities)”, “fatigue (mFIS)”, and “health-related quality of life (PRIMUS QoL)”. It could not be excluded for these outcomes that the respective proportion of the patients not considered in the analysis was above 30%. There was no statistically significant 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 2.7.3.4.3 of the full dossier assessment.

2.5.2.2 Risk of bias

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

Table 22: Risk of bias at study and outcome level – RCT, direct comparison: fingolimod vs. IFN-β1a (research question C)

Study		Outcomes												
	Study level	All-cause mortality	Relapses	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)	Serious adverse events	Discontinuation due to adverse events	Infections	Influenza like illness	Gastrointestinal disorders
TRANSFORMS	L	L	L	L	H[a]	–[b]	–[b]	H[c]	–[b]	L	L	L	L	L

a: Data from 103 to 105 patients (85.1% to 86.8% of the 121 patients in the relevant subpopulation) were considered in the analysis. It is unclear whether the remaining 16 to 18 patients (13.2 to 14.9%) received the questionnaire and hence would have had to be considered in the analysis.
b: No evaluable data available. It is unclear in how many patients the questionnaire was recorded. It cannot be excluded that more than 30% of the patients were not considered in the analysis.
c: Data from 100 patients (82.6% of the 121 patients in the relevant subpopulation) were considered in the analysis. It is unclear whether the remaining 21 patients (17.4%) received the questionnaire and hence would have had to be considered in the analysis.
EQ-5D: European Quality of Life-5 Dimensions; H: high; IFN-β: interferon beta; L: low; mFIS: Modified Fatigue Impact Scale; MSFC-z: Multiple Sclerosis Functional Composite standard score; PRIMUS: Patient-Reported Indices for Multiple Sclerosis; QoL: quality of life; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

There was a low risk of bias for the following outcomes: all-cause mortality, relapses (annualized relapse rate, time to first relapse), disability progression (time to first confirmed disability progression), SAEs, discontinuation due to AEs, infections, influenza like illness, and gastrointestinal disorders. This concurs with the company's assessment.

For the outcomes "disability severity" and "health status", the risk of bias was high. There were no data for 13.2% to 14.9% of the patients for the outcome "disability severity", and for 17.4% of the patients for the outcome "health status", but it was unclear whether these patients had received the respective questionnaire and would have had to be considered in the analysis. In contrast, the company rated the risk of bias as low.

There were no evaluable data for the remaining outcomes (fatigue, activities of daily living, health-related quality of life). It could not be excluded that more than 30% of the patients were not considered in the analysis. Therefore no outcome-specific assessment of the risk of

bias was conducted for these outcomes. Further information can be found in Section 2.7.3.4.2 of the full dossier assessment.

2.5.2.3 Results

Table 23, Table 24 and Table 25 summarize the results on the comparison of fingolimod and IFN-β1a in patients with rapidly evolving severe RRMS. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations. Supplementary information on the most common AEs can be found in Table 36 in Appendix A of the full dossier assessment.

Figure 3 and Figure 4 show the Kaplan-Meier curves of the time to first confirmed relapse and of the time to first confirmed disability progression.

Table 23: Results on mortality and morbidity – RCT, direct comparison: fingolimod vs. IFN-β1a (research question C)

Study **Outcome category** **Outcome**	**Fingolimod**		**IFN-β1a**		**Fingolimod vs. IFN-ß1a**
	N	**Patients with events n (%)**	**N**	**Patients with events n (%)**	**RR [95% CI]; p-value**
TRANSFORMS					
Mortality					
Deaths	56	0 (0)	65	0 (0)	no data[a]
Morbidity					
Relapses (based on EDSS)					
	N	**Annualized relapse rate [95% CI]**	**N**	**Annualized relapse rate [95% CI]**	**Rate ratio [95% CI]; p-value**
Annualized relapse rate[b]	56	0.27 [0.15; 0.47]	65	0.56 [0.38; 0.83]	0.48 [0.24; 0.94]; 0.031
	N	**Median time [95% CI]/ Patients with events n (%)**	**N**	**Median time [95% CI]/ Patients with events n (%)**	**HR [95% CI]; p-value**
Time to first confirmed relapse	56	NA/ 11 (19.6)[c]	65	NA/ 23 (35.4)[c]	0.54 [0.27; 1.09]; 0.087
	N	**Number of relapses (%)**	**N**	**Number of relapses (%)**	**RR [95% CI]; p-value**
Number of relapses according to severity		Mild: 4 (26.7) moderate: 10 (66.7) severe: 1 (6.7)		Mild: 10 (27.8) moderate: 19 (52.8) severe: 7 (19.4)	
Disability progression (based on EDSS)					
	N	**Median time [95% CI]/ Patients with events n (%)**	**N**	**Median time [95% CI]/ Patients with events n (%)**	**HR [95% CI]; p-value**
Time to first confirmed disability progression	56	NA/ 4 (7.1)[c]	65	NA/ 5 (7.7)[c]	0.95 [0.25; 3.53]; 0.935

a: No effect estimation possible because no deaths occurred.
b: Probably results of a generalized linear model with outcome variable with negative binomial distribution (see Section 2.7.3.4.3 of the full dossier assessment).
c: Kaplan-Meier estimator at month 12 taken from the Kaplan-Meier curve.

CI: confidence interval; 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; vs.: versus

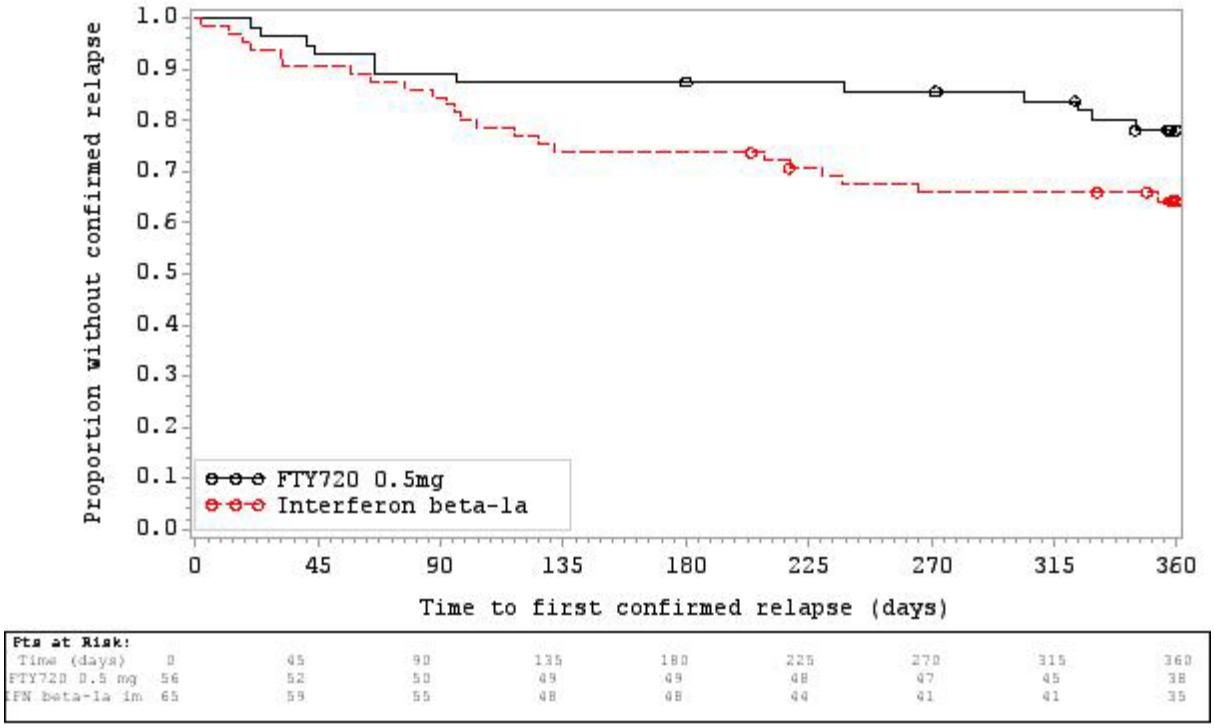

Figure 3: Kaplan-Meier curves of the time to first confirmed relapse (research question C)

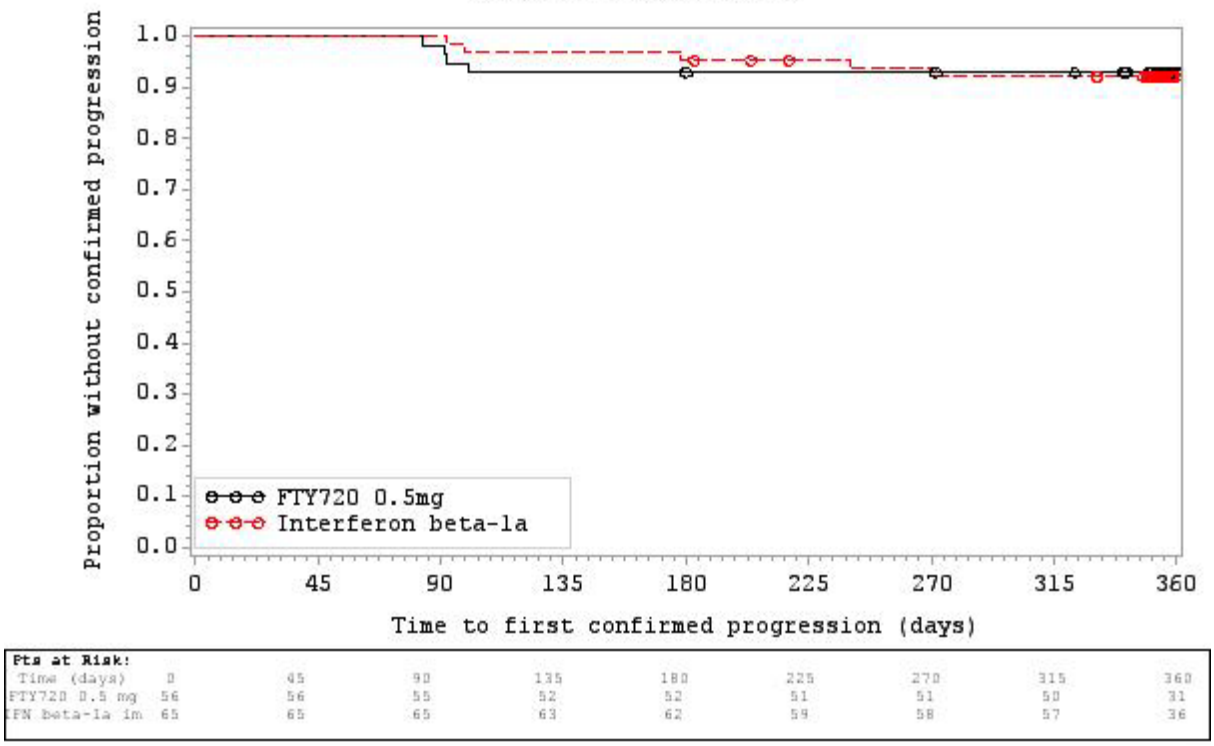

Figure 4: Kaplan-Meier curves of the time to first confirmed disability progression (research question C)

Table 24: Results on morbidity and health-related quality of life (continuous outcomes) – RCT, direct comparison: fingolimod vs. IFN-β1a (research question C)

Study Outcome category Outcome	Fingolimod			IFN-β1a			Fingolimod vs. IFN-ß1a
	N[a]	Baseline values mean (SE)	Change at end of study mean (SE)	N[a]	Baseline values mean (SE)	Change at end of study mean (SE)	Mean difference [95% CI]; p-value
TRANSFORMS							
Morbidity							
Disability severity							
MSFC-z[b]	47	0.07 (0.07)	0.04 (0.04)	56	0.01 (0.07)	−0.00 (0.04)	0.04 [−0.06; 0.14]; 0.454
subscale: T25-FW[c]	49	6.20 (0.41)	−0.27 (0.26)	56	5.61 (0.28)	0.23 (0.25)	−0.50 [−1.22; 0.21]; 0.165
subscale: 9-HPT[c]	48	21.50 (0.82)	0.05 (0.51)	56	21.44 (0.61)	−0.02 (0.47)	0.07 [−1.31; 1.45]; 0.919
subscale: PASAT-3[b]	47	49.28 (1.67)	1.15 (0.84)	56	47.48 (1.46)	0.74 (0.77)	0.41 [−1.86; 2.68]; 0.720
Fatigue							
mFIS[d]			No evaluable data[e]				
Activities of daily living							
PRIMUS activities[d]			No evaluable data[e]				
Health status							
EQ-5D VAS[c]	48	79.38 (2.36)	2.21 (2.14)	52	77.67 (2.06)	−0.74 (2.05)	2.95 [−2.94; 8.84]; 0.323
Health-related quality of life							
PRIMUS QoL[d]			No evaluable data[e]				

a: Number of patients considered in the analysis for the calculation of the effect estimate. The values at the start of the study may be based on other patient numbers.
b: Positive values/changes indicate improvement.
c: Negative values/changes indicate improvement.
d: The questionnaire was recorded in selected countries (Australia [according to the CSR; according to the company in Module 4: Austria], Canada, France, Germany, Italy, Spain, Great Britain and United States).
e: It is unclear in how many patients the questionnaire was recorded. Possibly more than 30% of the patients were not considered in the analysis.

CI: confidence interval; CSR: clinical study report; EQ-5D: European Quality of Life-5 Dimensions; 9-HPT: 9-Hole Peg Test; IFN-β: interferon beta; mFIS: Modified Fatigue Impact Scale; MSFC: Multiple Sclerosis Functional Composite; N: number of analysed patients; 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 25: Results on AEs – RCT, direct comparison: fingolimod vs. IFN-β1a (research question C)

Study Outcome category Outcome	Fingolimod N	Fingolimod Patients with events n (%)	IFN-β1a N	IFN-β1a Patients with events n (%)	Fingolimod vs. IFN-ß1a RR [95% CI]; p-value[a]
TRANSFORMS					
Adverse events					
AEs	56	50 (89.3)	65	58 (89.2)	
SAEs	56	4 (7.1)	65	0 (0.0)	10.42 [0.57; 189.44]; 0.029[b]
Discontinuation due to AEs	56	3 (5.4)	65	2 (3.1)	1.74 [0.30; 10.05]; 0.596
Infections	56	33 (58.9)	65	35 (53.8)	1.09 [0.80; 1.50]; 0.636
Influenza like illness	56	1 (1.8)	65	24 (36.9)	0.05 [0.01; 0.35]; < 0.001
Gastrointestinal disorders	56	22 (39.3)	65	14 (21.5)	1.82 [1.03; 3.22]; 0.037

a: Institute's calculation, unconditional exact test (CSZ method according to [12]).
b: Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.
AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; 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

The company did not draw conclusions on the added benefit at outcome level in Module 4 C. Hence it is not commented on in how far the assessment of the outcomes in the present benefit assessment deviates from that of the company.

Mortality

Deaths

No events occurred in both treatment groups for the outcome "deaths". Hence there was no hint of an added benefit of fingolimod in comparison with IFN-β1a. An added benefit for this outcome is therefore not proven.

Morbidity

Relapses

There were several operationalizations for the outcome "relapses". The results of these operationalizations were assessed for the outcome "relapses" in their totality.

For the annualized relapse rate, which was considered to be the decisive operationalization, there was a statistically significant difference in favour of fingolimod in comparison with IFN-β1a. There was no statistically significant difference between the treatment groups for the time to first confirmed relapse. However, the effect pointed in the same direction as the

effect in the annualized relapse rate and therefore did not raise doubts about it. Moreover, the number of severe relapses under treatment with IFN-β1a was greater than under treatment with fingolimod (19.7% severe relapses versus 6.7%).

Additionally, there was an indication (annualized relapse rate) and proof (time to first confirmed relapse) of an effect modification by the characteristic "sex" for these outcomes. This resulted in a statistically significantly lower annualized relapse rate and a statistically significantly longer time to first confirmed relapse under treatment with fingolimod in comparison with IFN-β1a for women. For the subgroup of women, there was thus an indication of an added benefit in comparison with IFN-β1a for the outcome "relapses".

For men, treatment with fingolimod produced no statistically significant difference in comparison with IFN-β1a in annualized relapse rate or in the time to first confirmed relapse. For the subgroup of men, there was thus no hint of an added benefit of fingolimod in comparison with IFN-β1a for the outcome "relapses". An added benefit is therefore not proven.

Disability progression

There was no statistically significant difference between the treatment groups for the time to first confirmed disability progression. Hence there was no hint of an added benefit of fingolimod in comparison with IFN-β1a. An added benefit for this outcome is therefore not proven.

Disability severity

There was no statistically significant difference between the treatment groups for the outcome "disability severity" for the MSFC-z score. Hence there was no hint of an added benefit of fingolimod in comparison with IFN-β1a. An added benefit for this outcome is therefore not proven.

Fatigue

There were no evaluable data for the outcome "fatigue (mFIS)". Hence there was no hint of an added benefit of fingolimod in comparison with IFN-β1a. An added benefit for this outcome is therefore not proven.

Activities of daily living

There were no evaluable data for the outcome "activities of daily living (PRIMUS activities)". Hence there was no hint of an added benefit of fingolimod in comparison with IFN-β1a. An added benefit for this outcome is therefore not proven.

Health status

There was no statistically significant difference between the treatment groups for the outcome "health status (EQ-5D VAS)". Hence there was no hint of an added benefit of fingolimod in comparison with IFN-β1a. An added benefit for this outcome is therefore not proven.

Health-related quality of life

PRIMUS QoL

There were no evaluable data for health-related quality of life (PRIMUS QoL). Hence there was no hint of an added benefit of fingolimod in comparison with IFN-β1a. An added benefit for this outcome is therefore not proven.

Adverse events

Serious adverse events

There was a statistically significant difference to the disadvantage of fingolimod in comparison with IFN-β1a for the outcome "SAEs". There was an indication of greater harm from fingolimod in comparison with IFN-β1a for this outcome.

Discontinuation due to adverse events

There was no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". Hence there was no hint of greater or lesser harm from fingolimod in comparison with IFN-β1a; greater or lesser harm for this outcome is therefore not proven.

Infections

There was no statistically significant difference between the treatment groups for the outcome "infections". Hence there was no hint of greater or lesser harm from fingolimod in comparison with IFN-β1a; greater or lesser harm for this outcome is therefore not proven.

Influenza like illness

There was a statistically significant difference in favour of fingolimod in comparison with IFN-β1a for the outcome "influenza like illness". This results in an indication of lesser harm from fingolimod in comparison with IFN-β1a for this outcome.

Gastrointestinal disorders

There was a statistically significant difference to the disadvantage of fingolimod in comparison with IFN-β1a for the outcome "gastrointestinal disorders". This was of only marginal effect size, however. Hence there was no hint of greater or lesser harm from fingolimod in comparison with IFN-β1a; greater or lesser harm for this outcome is therefore not proven.

2.5.2.4 Subgroups and other effect modifiers

The following potential effect modifiers were investigated (for reasons, see Section 2.7.3.4.3 of the full dossier assessment):

- sex (male/female)
- pretreatment (yes/no)

The prerequisite for proof of different effects is a statistically significant interaction test ($p < 0.05$). A p-value between 0.05 and 0.2 provides an indication of different effects.

Relapses

Annualized relapse rate and time to first confirmed relapse

Table 26 and Table 27 show the subgroups for the characteristic "sex" for the outcomes "annualized relapse rate" and "time to first confirmed relapse". There was at least an indication of effect modification for this characteristic. For the characteristic "pretreatment", there was no proof or indication of effect modification for the outcomes considered in the present benefit assessment.

Table 26: Subgroups: annualized relapse rate by the characteristic "sex", RCT, direct comparison: fingolimod vs. IFN-β1a (research question C)

Study Characteristic Subgroup	Fingolimod		IFN-β1a		Fingolimod vs. IFN-ß1a	
	N	Annualized relapse rate [95% CI]	N	Annualized relapse rate [95% CI]	Rate ratio [95% CI]	p-value
TRANSFORMS						
Sex						
Men	17	0.36 [0.15; 0.87]	18	0.33 [0.14; 0.80]	1.08 [0.31; 3.77]	0.898
Women	39	0.23 [0.11; 0.46]	47	0.65 [0.43; 0.99]	0.35 [0.16; 0.79]	0.012
					Interaction:	0.139

CI: confidence interval; IFN-β: interferon beta; N: number of analysed patients; RCT: randomized controlled trial; vs.: versus

Table 27: Subgroups: time to first confirmed relapse by the characteristic "sex", RCT, direct comparison: fingolimod vs. IFN-β1a (research question C)

Study Characteristic Subgroup	Fingolimod		IFN-β1a		Fingolimod vs. IFN-ß1a	
	N	Median time [95% CI]	N	Median time [95% CI]	HR [95% CI]	p-value
TRANSFORMS						
Sex						
Men	17	ND	18	ND	0.70 [0.28; 1.75]	0.449
Women	39	ND	47	ND	0.31 [0.12; 0.76]	0.011
					Interaction:	0.020

CI: confidence interval; HR: hazard ratio; IFN-β: interferon beta; N: number of analysed patients: ND: no data; RCT: randomized controlled trial; vs.: versus

For the outcome "relapses", there was an indication of an effect modification by the characteristic "sex" for the annualized relapse rate, and proof of an effect modification by the characteristic "sex" for the time to first confirmed relapse.

For women, treatment with fingolimod resulted in a statistically significantly lower annualized relapse rate and a statistically significantly longer time to first confirmed relapse under treatment with fingolimod in comparison with IFN-β1a. For this subgroup, there was thus an indication of an added benefit in comparison with IFN-β1a for the outcome "relapses".

For men, treatment with fingolimod produced no statistically significant difference in comparison with IFN-β1a regarding the annualized relapse rate or regarding the time to first confirmed relapse. In the annualized relapse rate, the effect estimate in the subgroup of men pointed in a different direction than in the total relevant subpopulation (see Table 23). Hence for the subgroup of men, there was no hint of an added benefit of fingolimod in comparison with IFN-β1a for the outcome "annualized relapse rate". An added benefit for this outcome is therefore not proven. Regarding the time to first confirmed relapse, in contrast, there was proof of an effect modification, and the subgroup was therefore considered separately from the total relevant subpopulation. There was no proof of an added benefit for the subgroup of men here either. Hence for the subgroup of men, there was no hint of an added benefit of fingolimod in comparison with IFN-β1a for the outcome "relapses". An added benefit for this outcome is therefore not proven.

2.5.3 Extent and probability of added benefit (research question C)

The derivation of extent and probability of added benefit is presented below at outcome level, taking into account the different 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.

2.5.3.1 Assessment of added benefit at outcome level

The data presented in Section 2.5.2 of this benefit assessment resulted in an indication of an added benefit of fingolimod in comparison with the ACT IFN-β1a for female patients with rapidly evolving severe RRMS for the outcome "relapses (annualized relapse rate, time to first confirmed relapse)". For the total relevant subpopulation, there was an indication of lesser harm from fingolimod in comparison with the ACT IFN-β1a for the outcome "influenza like illness". In contrast, there was an indication of greater harm from fingolimod in comparison with IFN-β1a in the total relevant subpopulation for the outcome "SAEs". The extent of the respective added benefit at outcome level was estimated from these results (see Table 28).

Determination of the outcome category for the outcome "relapses"

Reasons for the determination of the outcome category are presented in Section 2.4.3.1 of research question B.

Table 28: Extent of added benefit at outcome level: fingolimod vs. IFN-β1a (research question C)

Outcome category **Outcome**	**Fingolimod vs. IFN-ß1a** **Median time to event/ proportion of events/ mean change** **effect estimate [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
Deaths	0% vs. 0%	Lesser benefit/added benefit not proven
Morbidity		
Relapses (based on EDSS)		
Annualized relapse rate Sex male	0.36 vs. 0.33 rate ratio 1.08 [0.31; 3.77] p = 0.898	Lesser benefit/added benefit not proven
female	0.23 vs. 0.65 rate ratio 0.35 [0.16; 0.79] p = 0.012 probability: “indication”	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: “considerable”
Time to first confirmed relapse Sex male	ND vs. ND 0.70 [0.28; 1.75] p = 0.449	Lesser benefit/added benefit not proven
female	ND vs. ND 0.31 [0.12; 0.76] p = 0.011 probability: “indication”	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: “considerable”
Disability progression (based on EDSS)		
Time to first confirmed disability progression	NA vs. NA HR 0.95 [0.25; 3.53] p = 0.935	Lesser benefit/added benefit not proven
Disability severity		
MSFC-z score	0.04 vs. −0.00 MD 0.04 [−0.06; 0.14] p = 0.454	Lesser benefit/added benefit not proven
Fatigue		
mFIS	No evaluable data	

(continued)

Table 28: Extent of added benefit at outcome level: fingolimod vs. IFN-β1a (research question C) (continued)

Outcome category **Outcome**	**Fingolimod vs. IFN-ß1a** **Median time to event/ proportion of events/ mean change** **effect estimate [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Activities of daily living		
PRIMUS activities	No evaluable data	
Health status		
EQ-5D VAS	2.21 vs. −0.74 MD 2.95 [−2.94; 8.84] p = 0.323	Lesser benefit/added benefit not proven
Health-related quality of life		
PRIMUS QoL	No evaluable data	
Adverse events		
SAEs	7.1% vs. 0% RR 10.42 [0.57; 189.44] RR[c] 0.10 [0.01; 1.74] p = 0.029[d] probability: "indication"	Outcome category: serious/severe AEs greater harm, extent: "non-quantifiable"[e]
Discontinuation due to AEs	5.4% vs. 3.1% RR 1.74 [0.30; 10.05] p = 0.596	Lesser/greater harm not proven
Infections	58.9% vs. 53.8% RR 1.09 [0.80; 1.50] p = 0.636	Lesser/greater harm not proven
Influenza like illness	1.8% vs. 36.9% RR 0.05 [0.01; 0.35] p < 0.001 probability: "indication"	Outcome category: non-serious/non-severe AEs CI_u < 0.80 lesser harm, extent: "considerable"
Gastrointestinal disorders	39.3% vs. 21.5% RR 1.82 [1.03; 3.22] RR[c] 0.55 [0.31; 0.97] p = 0.037	Outcome category: non-serious/non-severe AEs CI_u > 0.90 Lesser/greater harm not proven[f]

(continued)

Table 28: Extent of added benefit at outcome level: fingolimod vs. IFN-β1a (research question C) (continued)

a: Probability provided if statistically significant differences were present. b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u. c: Proportion of events IFN-β1a vs. fingolimod (reversed direction of effect to allow direct use of limits to derive the extent of added benefit). d: Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods. e: Since in this case the CI is not regarded to be sufficiently reliable for the determination of the extent because of the asymptotic calculation, the extent of greater harm cannot be quantified. f: Lesser or greater harm is not proven because the effect size was only marginal. AE: adverse event; CI: confidence interval; CI_u: upper limit of CI; EDSS: Expanded Disability Status Scale; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; IFN-β: interferon beta; MD: mean difference; mFIS: Modified Fatigue Impact Scale; MSFC: Multiple Sclerosis Functional Composite; ND: no data; PRIMUS: Patient-Reported Indices for Multiple Sclerosis; QoL: quality of life; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.5.3.2 Overall conclusion on added benefit

Table 29 summarizes the results that were considered in the overall conclusion on the extent of added benefit for patients with rapidly evolving severe RRMS.

Table 29: Positive and negative effects from the assessment of fingolimod compared with IFN-β1a (research question C)

Positive effects	**Negative effects**
Sex: female indication of added benefit – extent "considerable" (non-serious /non-severe symptoms/late complications: relapses)	Indication of greater harm – extent: "non-quantifiable" (serious/severe adverse events: serious adverse events)
Indication of lesser harm – extent: "considerable" (non-serious/non-severe adverse events: influenza like illness)	
AE: adverse event; IFN-β: interferon beta; SAE: serious adverse event	

Overall, 2 positive effects with the same probability and extent, and one negative effect with non-quantifiable extent remain for female patients. For male patients, one positive and one negative effect with the same probability, but with different extent, remain.

For female patients, there is an indication of considerable added benefit of fingolimod in the category "non-serious/non-severe symptoms/late complications" (relapses). There is an indication of lesser harm from fingolimod with the extent "considerable" in the category "non-serious/non-severe AEs" (influenza like illness). In contrast, there is an indication of non-quantifiable greater harm from fingolimod in the category "serious/severe AEs" (SAEs).

In summary, there is an indication of considerable added benefit of fingolimod in comparison with the ACT IFN-β1a for female patients with rapidly evolving severe RRMS.

For male patients, there is an indication of lesser harm from fingolimod with the extent "considerable" in the category "non-serious/non-severe AEs" (influenza like illness). In contrast, there is an indication of non-quantifiable greater harm from fingolimod in the category "serious/severe AEs" (SAEs). The total number of SAEs was very low so that the negative effect in this outcome did not completely outweigh the positive effect regarding the outcome "influenza like illness".

In summary, there is therefore an indication of minor added benefit of fingolimod in comparison with the ACT IFN-β1a for male patients with rapidly evolving severe RRMS.

This deviates from the company's approach, which, for the total population of patients with rapidly evolving severe RRMS, derived an indication of considerable added benefit of fingolimod in comparison with the ACT IFN-β1a and also limited this to the IM administration of IFN-β1a.

2.5.4 List of included studies (research question C)

TRANSFORMS

Agius M, Meng X, Chin P, Grinspan A, Hashmonay R. Fingolimod therapy in early multiple sclerosis: an efficacy analysis of the TRANSFORMS and FREEDOMS studies by time since first symptom. CNS Neurosci Ther 2014; 20(5): 446-451.

Chinea Martinez AR, Correale J, Coyle PK, Meng X, Tenenbaum N. Efficacy and safety of fingolimod in Hispanic patients with multiple sclerosis: pooled clinical trial analyses. Adv Ther 2014; 31(10): 1072-1081.

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.

Cohen JA, Barkhof F, Comi G, Izquierdo G, Khatri B, Montalban X et al. Fingolimod versus intramuscular interferon in patient subgroups from TRANSFORMS. J Neurol 2013; 260(8): 2023-2032.

DiMarco JP, O'Connor P, Cohen JA, Reder AT, Zhang-Auberson L, Tang D et al. First-dose effects of fingolimod: pooled safety data from three phase 3 studies. Mult Scler Relat Disord 2014; 3(5): 629-638.

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2.6 Extent and probability of added benefit – summary

The result of the assessment of the added benefit of fingolimod in comparison with the ACT is summarized in Table 30.

Table 30: Fingolimod – extent and probability of added benefit

Research question	Subindication	ACT[a]	Extent and probability of added benefit
A	Patients with highly active RRMS, full previous treatment with IFN-β	**Glatiramer acetate**[b] or IFN-β1a or 1b, switching depended on prior therapy	Added benefit not proven
B	Patients with highly active RRMS, no full previous treatment with IFN-β	Continuation of disease-modifying therapy with IFN-β, with an optimized dosage according to the approval up to an adequate course (normally lasting at least one year)[c]	Indication of considerable added benefit
C	Patients with rapidly evolving severe RRMS	Glatiramer acetate or **IFN-β** (**1a** or 1b)	Sex: female indication of considerable added benefit
			Sex: male indication of minor added benefit

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. In the present case, the company limited the ACT to intramuscular administration of IFN-β1a. This limitation was not followed.
b: The company cited glatiramer acetate as comparator therapy because of the patients' pretreatment.
c: The company cited IFN-β1a as comparator therapy.
ACT: appropriate comparator therapy; 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.

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Please see full dossier assessment for full reference list.

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