IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports - Commission No. A11-23

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: 11.01.2012). 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

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Fingolimod – Benefit assessment according to § 35a Social Code Book V

Contracting agency:
Federal Joint Committee

Commission awarded on:
14.10.2011

Internal Commission No.:
A11-23

Address of publisher:
Institute for Quality and Efficiency in Health Care
Dillenburger Str. 27
51105 Cologne
Germany

Tel: +49-(0)221/35685-0
Fax: +49-(0)221/35685-1
E-mail: berichte@iqwig.de
www.iqwig.de

Medical and scientific advice:

- Bernd Kieseier, Department of Neurology, Düsseldorf University Hospital

IQWiG thanks the external expert for his contribution to the dossier assessment. However, he was not involved in the actual preparation of the dossier assessment. Individual sections and conclusions in the dossier assessment therefore do not necessarily reflect his opinion.

IQWiG employees involved in the dossier assessment:[2]

- Volker Vervölgyi
- Lars Beckmann
- Andreas Gerber
- Elke Hausner
- Thomas Kaiser
- Michaela Florina Kerekes
- Christoph Schürmann
- Min Zhou

Keywords: fingolimod; multiple sclerosis, relapsing-remitting; benefit assessment

[2] Due to legal data protection regulations, employees have the right not to be named.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
EDSS	Extended Disability Status Scale
EQ-5D	EuroQoL Questionnaire-5 Dimension
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IFN	interferon
IFN-β	beta-interferon
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
MRI	magnetic resonance imaging
MSFC	Multiple Sclerosis Functional Composite
PRIMUS	Patient Reported Indices for Multiple Sclerosis
QoL	quality of life
RCT	randomized controlled trial
RRMS	relapsing-remitting multiple sclerosis
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
U-FIS	Unidimensional Fatigue Impact Scale

2. Benefit assessment

2.1 Executive summary of the benefit assessment

Background

On 14.10.2011, in accordance with § 35a SGB (Social Code Book) V, the Federal Joint Committee (G-BA) wrote to IQWiG to commission the benefit assessment of the drug fingolimod. The assessment was based on a dossier compiled by the pharmaceutical company.

Research question

In the benefit assessment fingolimod was compared with

- glatiramer acetate in patients with highly active relapsing-remitting multiple sclerosis (RRMS), who have failed to respond to a full and adequate course (normally at least one year) of beta-interferon (IFN-β) (subsequently referred to as patients with highly active RRMS, full previous treatment with IFN-β),
- IFN-β 1a in patients with highly active RRMS, who have not yet received adequate treatment with IFN-β (subsequently referred to as patients with highly active RRMS, incomplete previous treatment with IFN-β) and
- IFN-β 1a in patients with rapidly evolving severe RRMS.

Results

A total of one relevant study (TRANSFORMS) was available. TRANSFORMS was a pivotal study for the approval of fingolimod. This trial was randomized, controlled, double-blind and compared fingolimod with IFN-β 1a in patients with RRMS. Based on an analysis of a subpopulation of this trial, data were available for 1 of the 3 above-named subindications (rapidly evolving severe RRMS). No evaluable data for the benefit assessment were submitted for the populations of patients with highly active RRMS who had received full previous treatment with IFN-β, or for those patients with highly active RRMS who had not received full treatment with IFN-β.

The results obtained for the 3 above-named subindications were as follows:

Patients with highly active RRMS, full previous treatment with IFN-β

The pharmaceutical company submitted no evaluable data for the population of patients with highly active RRMS who had received full treatment with IFN-β. An added benefit of fingolimod over glatiramer acetate is not proven.

Patients with highly active RRMS, incomplete previous treatment with IFN-β

The pharmaceutical company submitted no evaluable data for the population of patients with highly active RRMS who had not received full treatment with IFN-β. An added benefit of fingolimod over IFN-β is not proven.

Patients with rapidly evolving severe RRMS

For patients with rapidly evolving severe RRMS, the pharmaceutical company submitted data on a subpopulation of the TRANSFORMS study. Since, on the basis of the information available for the TRANSFORMS study, this patient group could not be classified fully in accordance with the approved subindication, the company chose a classification that it considered approximated the criteria named in the approval most closely. Thus the company used previously untreated (therapy-naïve) patients who had had at least 2 relapses in the previous year and at least 1 Gadolinium-enhancing lesion. The results on this population can be used for the benefit assessment for patients with rapidly evolving severe RRMS, but are subject to a high degree of uncertainty.

There was no statistically significant difference between the treatment groups for any of the outcomes of "relapses", "disability progression" and "health-related quality of life". No data regarding the outcomes "fatigue" and "activities of daily living" were available for the relevant population. In terms of the "overall rate of adverse events", "overall rate of serious adverse events" and "discontinuations due to adverse events", there was also no statistically significant difference between the treatment groups. In terms of specific adverse events, there was a statistically significant difference in favour of fingolimod only for the frequency of flu-like symptoms. There was an indication of lesser harm for this outcome, with the extent "minor".

Overall, from the available results on patients with rapidly evolving RRMS, there was a "hint" of a minor added benefit of fingolimod in comparison with IFN-β. This hint arises from the indication of lesser harm in respect of the outcome "flu-like symptoms" (non-serious adverse event). It takes account of the uncertain data for other outcomes (in particular "relapses" and "serious adverse events"), because the small patient population makes the estimations imprecise. In addition, also because of the problem mentioned above of the classification of the patient group according to the approval status, there is a higher degree of uncertainty. This lack of certainty regarding the data leads to an overall downgrading of the probability of the conclusion on added benefit from an "indication" to a "hint".

Probability and extent of the added benefit, patient groups with therapeutically important added benefits

Based on the results presented, the extent and probability of an added benefit of the drug fingolimod is assessed as follows:

For 2 of the 3 subindications (patients with highly active RRMS, full previous treatment with IFN-β; patients with highly active RRMS, incomplete previous treatment with IFN-β) the added benefit of fingolimod over the respective appropriate comparator therapy (ACT) is not proven.

For the population of patients with rapidly evolving severe RRMS, there is a "hint" of a minor added benefit of fingolimod in comparison with IFN-β.

The decision regarding added benefit is made by the G-BA.

2.2 Research question

In specifying the ACT, the G-BA divided the approved therapeutic indication of fingolimod into 3 populations. According to the Summary of Product Characteristics (SPC) [1] fingolimod is approved for the following groups of patients:

- "Patients with high disease activity despite treatment with a beta-interferon. 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 beta-interferon. Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial MRI [magnetic resonance imaging] or at least 1 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 relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI."

The G-BA divided the patients with high disease activity despite treatment with IFN-β (first bulletpoint above) into the following 2 populations for specifying the ACT [2]:

1) Patients, who have not responded to a full and adequate course, normally lasting at least 1 year, of beta-interferon therapy.
2) Patients, who have not yet received adequate treatment with a beta-interferon.

The G-BA derived a third population from the patients with rapidly evolving severe RRMS (second bulletpoint above).

In agreement with the specification of the G-BA, the pharmaceutical company designated the following as ACTs:

- glatiramer acetate as ACT for patients with highly active RRMS, who have not responded to a full and adequate course, normally lasting 1 year, of IFN-β
- IFN-β 1a by intramuscular injection (i.m.) for the population of patients with highly active RRMS, who have not yet received adequate treatment with IFN, as well as for the patients with rapidly evolving RRMS

The above-named ACTs were used for the benefit assessment of fingolimod. The individual subindications and the respective ACTs are listed in Table 1.

Table 1: Subindication, appropriate comparator therapy

	Subindication	Appropriate comparator therapy
1	Patients with highly active RRMS, full previous treatment with IFN-β	Glatiramer acetate
2	Patients with highly active RRMS, incomplete previous treatment with IFN-β	IFN-β 1a i.m.
3	Patients with rapidly evolving severe RRMS	IFN-β 1a i.m.
IFN-β: beta-interferon; i.m.: intramuscular; RRMS: relapsing-remitting multiple sclerosis		

In the research question, the pharmaceutical company defines the completeness of previous treatment via the compliance of patients to the treatment. Patients, who have already been treated with a complete course of IFN-β are considered by the company to be adherent patients. Those who have not yet received full previous treatment with IFN-β are defined as non-adherent patients. The Institute does not concur with this evaluation, because completeness should be recorded via the actual duration of previous treatment and the dose during the treatment. Regardless of this, the definition of previous treatment by the company has no consequence for the assessment. Since, according to the company, there is no adequate information for the studies included in the assessment on the compliance of patients to treatment prior to the study, the company does not divide patients according to the completeness of the previous treatment. On the other hand, had the company defined completeness via the duration of treatment, such a division would probably have been possible using the data from the relevant pivotal study TRANSFORMS. Relevant data would then have been available - at least for the population of patients with highly active RRMS who have not received full previous treatment with IFN-β. An explanation about this can be found in Section 2.7.2.2 of the full dossier assessment.

The assessment was carried out in relation to patient-relevant outcomes.

Further information about the research question can be found in Module 3, Section 3.2 and Module 4, Section 4.2.1 of the dossier and in Sections 2.7.1 and 2.7.2.1 and 2.7.2.4.2 of the full dossier assessment.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled from the following data:

- Studies completed by the pharmaceutical company up to 26.07.2011 on fingolimod in relapsing-remitting multiple sclerosis
- Results of a bibliographical literature search and a search in trial registries for studies on fingolimod, glatiramer acetate and IFN-β (last search for fingolimod on 25.07.2011, for glatiramer acetate on 21.07.2011, for IFN-β on 13.09.2011 in bibliographical databases

and for fingolimod and glatiramer acetate on 26.07.2011 and IFN-β on 29.07.2011 in trial registries; searches by the company)

- Independent searches by the Institute for studies on fingolimod in trial registries on 31.10.2011 to check the company's search results. The check produced no deviations from the study pool presented in the company's dossier (studies with fingolimod).

The resulting study pool for the direct comparison fingolimod vs. IFN-β 1a i.m. corresponded to that of the company. However the only identified study was not used for both relevant populations, which is explained in more detail in Section 2.3.1 below.

No study was submitted for the direct comparison fingolimod vs. glatiramer acetate. The studies submitted by the company on the indirect comparison of fingolimod and glatiramer acetate were not used, because they did not contain any evaluable data for the benefit assessment. This represents a substantial deviation from the company's procedure, which is also explained in more detail in Section 2.3.1 below.

Further information about the inclusion criteria for studies in the present benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier and in Sections 2.7.2.1 and 2.7.2.3.1 and 2.7.2.4.1 of the full dossier assessment.

2.3.1 Studies included in the assessment

Table 2 shows the study pool for the comparison of fingolimod with the respective ACT.

Table 2: Study pool – RCTs with the drug to be assessed

Sub-indication Study	Study category		
	Pivotal study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Patients with highly active RRMS, full previous treatment with IFN-β			
	No relevant study available		
Patients with highly active RRMS, incomplete previous treatment with IFN-β			
	No relevant study available		
Patients with rapidly evolving severe RRMS			
CFTY720D2302 (TRANSFORMS)	yes	yes	no
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. IFN: interferon.; RCT: randomized controlled trial; RRMS: relapsing-remitting multiple sclerosis			

The results of the pivotal study TRANSFORMS (even for subpopulations) could not be used for the assessment of patients with highly active RRMS with or without full previous treatment with IFN-β for the following crucial reasons: prior treatment with IFN-β is a prerequisite for the approval-conforming use of fingolimod. However in the TRANSFORMS

study, only 57% of patients had been previously treated, 49 % with an IFN-β (IFN-β 1a or IFN-β 1b). In addition, according to the approval of fingolimod, a high or very high disease activity is required. Not all patients in the TRANSFORMS study met this criterion because patients with lower disease activity were also included. It is not clear from the data submitted by the company how many patients had a lower disease activity. Furthermore, according to the company, the criteria named in the marketing authorization for a high disease activity cannot always be shown by information in the study (e.g. the criteria "ongoing severe relapses" or "≥ 2 relapses/year with disability progression"). The formation of subpopulations that meet exactly the approval criteria is accordingly impossible. This might be because the approved therapeutic indication for fingolimod is not based solely on data from the TRANSFORMS study. The text on the approved therapeutic indication from the SPC for fingolimod is almost identical to that for natalizumab, another drug for the treatment of RRMS [3]. However it should also be noted that the company chose very wide inclusion criteria for the study, which meant that a heterogeneous population was investigated, e.g. both treatment-naïve as well as patients already treated (for several years) with IFN-β. Treatment experience is known to be a potential effect modifier. However, the study was not designed to identify such effect modifiers, since such subgroup analyses were not predefined in the study. Such subgroup analyses would, however, have been necessary for the benefit assessment.

Although the company did submit data of subpopulations of the TRANSFORMS study for the population of patients with highly active RRMS, who had not received full previous treatment with IFN-β, these subpopulations do not cover the relevant population adequately. An incomplete previous treatment with IFN-β is required for this population. Since the company did not, however, have the necessary information, it included all patients with previous treatment with IFN-β in this subpopulation and thus contradicted its own definition of an incomplete previous treatment with IFN-β. However, it is assumed that most of these patients had already received adequate previous treatment with IFN-β, because 70% of the patients previously treated with IFN-β had been treated in the study for more than 1 year [4]. In addition, the company carried out an unsuitable division of the patients with previous IFN-β treatment from the study according to the nature of the disease activity into two populations, which cannot be combined because of overlaps. For these reasons, the data presented by the company cannot be used for the benefit assessment (see also Section 2.7.2.2 of the full dossier assessment).

Furthermore, for the population of patients with highly active RRMS who had received a full previous treatment with IFN-β, the comparator therapy of IFN-β 1a i.m. investigated in the TRANSFORMS study is not the ACT specified by the G-BA, but glatiramer acetate, which was also accepted by the company. There is no direct comparative study for this research question. For this reason, the company submitted an indirect comparison of fingolimod and glatiramer acetate. According to the available information, probably a subpopulation of the TRANSFORMS study would have been relevant for the indirect comparison. This would have been the population of patients who had already been previously treated with IFN-β for

more than 1 year (as definition for a complete previous treatment) and had a high disease activity according to the conditions of the approved therapeutic indication. However, the company uses the total population of the study for the indirect comparison which – as described above – is far broader than the relevant population. The same applies to the placebo-controlled FREEDOMS study carried out by the company, which is likewise included as a whole in the indirect comparison. The indirect comparison itself is also not relevant for the benefit assessment, because the company extended the research question to all patients with RRMS. This meant that patients with a lower-than-required disease activity as well as almost exclusively those without IFN-β previous treatment were included (see Section 2.7.2.4.2 of the full dossier assessment).

The company has presented a subpopulation of the TRANSFORMS study solely for the population of patients with rapidly evolving severe RRMS. However the approval criteria were not fully considered by the company when classifying the patient population, also due to the fact that the information required for this was not systematically recorded in the TRANSFORMS study (see Section 2.7.2.2 of the full dossier assessment). In the Institute's view, the classification by the company is plausible but leads to a greater uncertainty of the conclusions.

Taken as a whole, only the subpopulation of patients with rapidly evolving severe RRMS from the TRANSFORMS study is relevant for the present benefit assessment. Therefore only results for this population will be shown below. So far as was necessary for the benefit assessment, data for this population from Module 5 of the dossier were added. To obtain an impression of the overall results of the TRANSFORMS study, the results for the total population of the study – if they were available in Module 4 of the dossier – are nonetheless also shown in Appendix A of the present benefit assessment.

Section 2.6 contains a list of data sources named by the company for the study included.

Further information about the results of information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier and in Sections 2.7.2.3.1 and 2.7.2.4.1 of the full dossier assessment.

2.3.2 Study characteristics

Table 3 and Table 4 describe the TRANSFORMS study included for the benefit assessment. This trial is a pivotal study for the approval of fingolimod. However, only a subpopulation of the study is relevant for the Institute's benefit assessment, namely that of those patients with rapidly evolving severe RRMS according to the approved therapeutic indication. The information about the relevant subpopulation, and as additional information, that on the total population is shown below.

Table 3: Characteristics of the study included in the assessment

Study	Study design	Population	Interventions (number of randomized patients)	Duration of study	Location and period of study	Primary outcome; secondary outcomes[a]
TRANSFORMS	RCT, double-blind, parallel, active-controlled	Adults with RRMS 1 relapse in the past year or 2 relapses in the past 2 years EDSS 0–5.5	Fingolimod 1.25 mg (N = 426)[b] Fingolimod 0.5 mg (N = 431); of whom relevant patients[c]: n = 27 (6.3%)[d] IFN-β 1a i.m. (N = 435); of whom relevant patients[c]: n = 30 (6.9%)[d]	Treatment: 12 months	Worldwide in 18 countries 5/2006–11/2008	Primary: annualized relapse rate Secondary: further relapse-related outcomes, disability progression, fatigue, activities of daily living, health-related quality of life, adverse events

a: Extracted primary outcome criteria contain information without consideration of relevance for this benefit assessment. Extracted secondary outcome criteria contain exclusively information on the relevant available outcomes for this benefit assessment.
b: The arm is not relevant for the assessment because the dose does not conform to the approval status and is no longer shown in the subsequent tables
c: Approval population: patients with rapidly evolving RRMS (IFN-naïve, ≥ 2 relapses in previous year and ≥ 1 gadolinium-enhancing T1-lesions at baseline).
d: Percentages relative to the total population of the respective study arm; Institute's calculation

EDSS: Expanded Disability Status Scale; IFN: interferon; i.m.: intramuscular; N, n = number of patients; RCT: randomized controlled trial: RRMS: relapsing-remitting multiple sclerosis

Table 4: Characteristics of the interventions

Study	Fingolimod	IFN-β 1a
TRANSFORMS	Fingolimod 0.5 mg 1x daily+ placebo i.m. 1x/week	IFN-β-1a i.m. 30 µg 1x/week + placebo 1x daily
IFN: interferon; i.m.: intramuscular		

The TRANSFORMS study was a multicentre, randomized, controlled, double-blind trial in which adult patients with RRMS were enrolled. The diagnosis of multiple sclerosis was made using the revised McDonald criteria [5]. Patients were to have experienced at least 2 relapses in the previous 2 years or at least 1 relapse in the previous year, EDSS at baseline was to be between 0 and 5.5. No restriction was placed on the previous treatment. The subpopulation relevant for the benefit assessment comprised those patients who had suffered at least 2 relapses in the previous year and had at least 1 Gadolinium-enhancing lesion in MRI. In addition, these patients were treatment-naïve. Thus, this population deviated from the approved therapeutic indication, which leads to a greater uncertainty of the conclusions (see Section 2.7.2.2 of the full dossier assessment). The treatment period was 12 months and was thus shorter than that recommended by the regulatory authorities [6]. The study consisted of 3 treatment arms. In 2 of them, the patients received one capsule of fingolimod, each 1.25 mg or 0.5 mg, daily and in the third arm, patients were given a once-weekly intramuscular injection of 30 µg IFN-β 1a. All treatment groups also received a placebo of the respective other drug.

Since only the 0.5 mg dose of fingolimod is approved, the treatment arm with 1.25 mg is not relevant for the benefit assessment and will not be mentioned further. Therefore the term “total population” and “relevant subpopulation” will subsequently always mean only the two relevant treatment arms, in which a total of approx. 860 patients were randomized in a 1:1 ratio. The relevant subpopulation of patients with rapidly evolving severe RRMS represents merely 7% of the total population, so that in this population 27 patients received fingolimod and 30 patients IFN-β 1a. The primary outcome of the study was the annualized relapse rate, secondary outcomes were other relapse-related outcomes, disability progression, fatigue, activities of daily living, health-related quality of life, and adverse events.

The evaluation of the relevant outcomes deviates markedly from that of the company, which did not include fatigue and activities of daily living in its assessment. In the manufacturer’s dossier, data on these outcomes were only present for the total population of the TRANSFORMS study, but not for the population of patients with rapidly evolving severe RRMS.

Table 5 shows the characteristics of the patients in the study included in the assessment.

Table 5: Characteristics of the study population

Study Group	N[a]	Age (years) mean (SD)	Sex f / m [%]	Disease duration[b] [years] mean (SD)	Baseline EDSS mean (SD)	Number of relapses in last year mean (SD)	Number of relapses in the last 2 years mean (SD)
Patients with rapidly evolving severe RRMS							
TRANSFORMS							
Fingolimod	27	31.4 (8.52)	74 / 26	3.7 (3.31)	1.80 (0.96)	2.3 (0.47)	2.6 (0.69)
IFN-β 1a	30	34.8 (7.15)	77 / 23	4.0 (5.16)	1.95 (1.46)	2.2 (0.46)	2.6 (0.76)
Total population (additional information)							
TRANSFORMS							
Fingolimod	431	36.7 (8.81)	65 / 35	7.5 (6.20)	2.24 (1.33)	n.k.	2.3 (2.20)
IFN-β 1a	435	36.0 (8.29)	68 / 32	7.4 (6.33)	2.19 (1.26)		2.3 (1.22)

a: Number of randomized patients.
b: From the first symptoms.

EDSS: Expanded Disability Status Scale; f: female; IFN: interferon; m: male; N: number of patients; n.k.: not known; RRMS: relapsing-remitting multiple sclerosis; SD: standard deviation

There were no substantial differences between the treatment groups in respect of sex, duration of disease or severity as measured by baseline EDSS or number of relapses in the previous years, neither for the total population nor for the relevant subpopulation of patients with rapidly evolving severe RRMS. In the relevant subpopulation, the patients who received IFN-β 1a were on average 3 years older than the patients in the fingolimod group. Patients with rapidly evolving severe RRMS were somewhat younger in comparison with the total population and the proportion of women (approx. 75%) was about 10 percentage points higher. Whereas the total population included both treatment-naïve as well as treatment-experienced patients (49% of patients were previously treated with IFN-β), because of the selection undertaken by the company, all patients with rapidly evolving severe RRMS were IFN-naïve.

The risk of bias at study level is shown in Table 6. The outcome-overlapping aspects apply to the total population as well as the subpopulation of patients with rapidly evolving RRMS.

Table 6: Risk of bias at study level

Study	Adequate randomization sequence generation	Group allocation concealment	Blinding		Indications of selective outcome reporting	Other points affecting the risk of bias	Risk of bias at study level
			Patient	Treating persons			
TRANSFORMS	yes	yes	yes	yes	yes[a]	no	low
a: Unclear whether and which subgroup analyses were planned at the start of the study							

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

Further information about the study design, study populations and risk of bias at study level can be found in Module 4 Sections 4.3.1.2.1, and 4.3.1.2.2 of the dossier and in Sections 2.7.2.3.2, 2.7.2.3.3 and 2.7.2.4.2 of the full dossier assessment.

2.4 Results concerning added benefit

This assessment covers the following patient-relevant outcomes (for more detailed reasoning, see Section 2.7.2.3.4 of the full dossier assessment):

- Mortality
  - deaths during the study
- Morbidity
  - relapses
    - annualized relapse rate
    - proportion of patients without relapse
    - number of relapses according to severity
  - disability progression
    - proportion of patients without disability progression
    - mean change in Multiple Sclerosis Functional Composite (MSFC-z) Score
  - fatigue
  - activities of daily living
  - health-related quality of life
- Adverse events

- overall rate of adverse events (AEs)
- overall rate of serious adverse events (SAEs)
- overall rate of adverse events that led to withdrawal from the study (discontinuations due to AEs)
- flu-like symptoms
- macular oedema
- bradyarrhythmia / AV conduction disorders
- infections
- reactions at the injection site

The outcomes “health-related quality of life”, “AEs”, “SAEs”, “discontinuations due to AEs”, “relevant AEs”, “relapses”, “disability progression” and “health-related quality of life” were included in the assessment in the company’s dossier. The Institute also included the outcomes “deaths”, “fatigue”, “activities of daily living” and “reactions at the injection site”, to enable a comprehensive assessment of the added benefit. For reasons of overlap, other outcomes were not taken into account in the benefit assessment (see also Section 2.7.2.3.4 of the full dossier assessment). Table 7 shows the data available for the particular outcomes in the study included in the assessment. Table 8 and Table 9 provide the risk of bias for these outcomes.

Table 7: Matrix of outcomes of the included RCT

Outcome / Study population	Mortality	Relapses	Disability progression	Activities of daily living	Fatigue	Quality of life	Adverse drug reactions: Adverse events	Serious adverse events	Discontinuation due to adverse events	Flu-like symptoms	Bradycardia	Macular oedema	Infections	Reactions at the injection site
TRANSFORMS														
Patients with rapidly evolving severe RRMS	yes	yes	yes	no	no	yes[a]	yes	yes	yes	yes	yes	yes	yes	yes

a: Only results for EQ-5D are available for this population
IFN: interferon; RRMS: relapsing-remitting multiple sclerosis

Table 8: Risk of bias at study and outcome levels – morbidity and quality of life

Outcome / Study population	Study level	Annualized relapse rate	Number of relapses according to relapse severity	Proportion of relapse-free patients	Patients without disability progression	MSFC-z Score change	Fatigue	Activities of daily living	Quality of life (using PRIMUS QoL)	Quality of life (using EQ-5D)
TRANSFORMS										
Patients with rapidly evolving severe RRMS	low	low	low	low	low	high[a]	-[b]	-[b]	-[b]	high[a]

a: High proportion of patients not taken into account in the analysis (non-considered proportion > 10%.)

b: No analyses available for the relevant subpopulation.

IFN: interferon; EQ-5D: EuroQol Questionnaire-5 Dimension; MSFC: Multiple Sclerosis Functional Composite; PRIMUS: Patient Reported Indices for Multiple Sclerosis; RRMS: relapsing-remitting multiple sclerosis

Table 9: Risk of bias at study and outcome levels – adverse events and mortality

Outcome / Study population	Study level	Adverse events	Serious adverse events	Discontinuation due to adverse events	Deaths	Flu-like symptoms	Bradycardia	Macular oedema	Infections	Reactions at the injection site
TRANSFORMS										
Patients with rapidly evolving severe RRMS	low	low	low	low	low	low	low	low	low	–[a]
a: No usable analyses available for these outcomes. For reasoning, see Section 2.7.2.3.4 of the full dossier assessment.										
IFN: interferon; RRMS: relapsing-remitting multiple sclerosis										

There was a low risk of bias for most of the outcomes included by the company. Only for the outcomes "health-related quality of life", measured with the EQ-5D, and "mean change in MSFC score" was the risk of bias high, because a high proportion of patients were not considered in the analysis (> 10%), which is regarded as a violation of the ITT (intention to treat) principle. This deviates from the company's evaluation, which had assumed a low risk of bias for these outcomes.

For the outcomes additionally included in this assessment "fatigue", "activities of daily living" and "health-related quality of life" measured with the PRIMUS (Patient Reported Indices of Multiple Sclerosis) QoL, the company's dossier contained no data for the relevant subpopulation. An assessment of the risk of bias was accordingly, not possible.

Further information about the choice of outcome and risk of bias at the outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier and in Sections 2.7.2.3.3., 2.7.2.3.4 and 2.7.2.4.2 of the full dossier assessment.

2.4.1 Results for patients with highly active RRMS, full previous treatment with IFN-β

No evaluable data are available for the comparison of fingolimod and glatiramer acetate in the population of patients with highly active RRMS who had received full previous treatment with IFN-β. The data presented by the company from an indirect comparison do not show the relevant population, since almost exclusively patients not previously treated with IFN-β and sometimes patients with a lower disease activity than that required were included (see Section 2.7.2.4.2 of the full dossier assessment).

Hence an added benefit of fingolimod in relation to this population is not proven. This evaluation deviates substantially from that of the company, which, on the basis of an indirect comparison, derived a major added benefit for this population.

Further information about the outcome results of the indirect comparison for the population of patients with highly active RRMS, who had received full and complete treatment with IFN-β can be found in Module 4 Sections 4.3.2.1.3.1.1 to 4.3.2.1.3.1.4 and 4.4 of the dossier and in Sections 2.7.2.4.2 and 2.7.2.7 of the full dossier assessment.

2.4.2 Results for patients with highly active RRMS, incomplete previous treatment with IFN-β

No evaluable data are available for the comparison of fingolimod and IFN-β 1a for the population of patients with highly active RRMS who had not received full previous treatment with IFN-β. The data submitted by the company on subpopulations from the TRANSFORMS study represent the relevant population only inadequately, because it must be assumed that for the most part, patients with full previous treatment were included (see Section 2.7.2.2 of the full dossier assessment).

Hence an added benefit of fingolimod in relation to this population is not proven. This evaluation deviates substantially from that of the company, which derived a major added benefit for this population.

Further information about the outcome results of the comparison for the population of patients with highly active RRMS, who had not yet received adequate treatment with IFN-β can be found in Module 4 Sections 4.3.1.3.1.1 to 4.3.1.3.3 and 4.4 of the dossier and in Sections 2.7.2.3.2 and 2.7.2.7 of the full dossier assessment.

2.4.3 Results for patients with rapidly evolving severe RRMS

The company uses a subpopulation from the TRANSFORMS study for this comparison. Further details can be found in sections 2.3.1 and 2.3.2.

Table 10 summarizes the results on the comparison of fingolimod vs. IFN-β 1a in patients with rapidly evolving severe RRMS.

Table 10. Results on the comparison fingolimod vs. IFN-β 1a, subpopulation of patients with rapidly evolving severe RRMS from the TRANSFORMS study

Outcome	**Fingolimod**		**IFN-ß 1a**		**Fingolimod vs. IFN-ß 1a**	
	N	**Patients with events (%)**	**N**	**Patients with events (%)**	**Relative risk [95% CI]**	**p-value**
Mortality						
Deaths	27	0 (0)	30	0 (0)	n.r.	n.r.
Morbidity						
	N	**Annualized relapse rate [95 % CI]**	**N**	**Annualized relapse rate [95 % CI]**	**Rate Ratio [95 % CI]**	**p-value**
Annualized relapse rate[a]	27	0.226 [0.094; 0.542]	30	0.303 [0.146; 0.631]	0.746 [0.238; 2.333]	0.614
	N	**KM estimator[b] [95% CI]**	**N**	**KM estimator[b] [95% KI]**	**Hazard ratio [95% CI]**	**p-value**
Proportion of relapse-free patients (%)	27	80.1 [58.54; 91.25]	30	76.3 [56.54; 87.92]	0.76 [0.24; 2.39]	0.637
	N	**Number of relapses**	**N**	**Number of relapses**	**Effect estimator [95 % CI]**	**p-value**
Number of relapses according to severity	27	Mild: 2 Moderate: 4 Severe 0	30	Mild: 3 Moderate: 5 Severe: 1	n.k.	1.000[c]

(continued on next page)

Table 10: Results on the comparison fingolimod vs. IFN-β 1a, subpopulation of patients with rapidly evolving severe RRMS from the TRANSFORMS study (continuation)

Outcome	Fingolimod		IFN-ß 1a		Fingolimod vs. IFN-ß 1a	
	N	KM estimator[b] [95% CI]	N	KM estimator[b] [95% CI]	Hazard ratio [95% CI]	p-value
Proportion of patients without disability progression (%)	27	100 n.r.	30	86.5 [67.99; 94.73]	n.r.	0.054[d]
	N	Mean change (SD)	N	Mean change (SD)	Effect estimator [95 % CI]	p-value
MSFC-z score change[e]	21	0.02 (0.033) [f]	26	0.03 (0.061) [f]	n.k.	0.856
MSFC-subscale: 25-foot timed walking test (seconds)	23	-0.38 (1.438)	26	-0.17 (1.360)	n.k.	0.351
MSFC-subscale: 9-hole peg test (seconds)	22	0.55 (5.927)	26	-0.16 (2.675)	n.k.	0.910
MSFC-subscale: PASAT-3 (number of correct responses)	21	-0.14 (2.988)	26	1.15 (7.460)	n.k.	0.475
Fatigue (using U-FIS)	No data on relevant population available.					
Activities of daily living (using PRIMUS activities)	No data on relevant population available.					
Health-related quality of life						
EQ-5D (Index)	23	0.04 (0.023) [f]	23	-0.02 (0.029) [f]	n.k.	0.101
EQ-5D (VAS)	23	2.78 (4.770) [f]	22	0.00 (3.006) [f]	n.k.	0.699
PRIMUS-QoL	No data on relevant population available.					
	N	Patients with events (%)	N	Patients with events (%)	Relative risk [95 % CI]	p-value
Adverse events						
AE	27	23 (85.2)	30	25 (83.3)	1.02 [0.82; 1.28]	0.882[d]
SAE	27	1 (3.7)	30	0 (0)	n.r.	0.315[d]
Discontinuation due to AE	27	1 (3.7)	30	0 (0)	n.r.	0.315[d]
Flu-like symptoms	27	1 (3.7)	30	9 (30.0)	0.12 [0.02; 0.91]	0.010[d]
Bradycardia/AV-conduction disorders[g]	27	0 (0)	30	1 (3.3)	n.r.	0.361[d]

(continued on next page)

Table 10: Results on the comparison fingolimod vs. IFN-β 1a, subpopulation of patients with rapidly evolving severe RRMS from the TRANSFORMS study (continuation)

Outcome	Fingolimod		IFN-ß 1a		Fingolimod vs. IFN-ß 1a	
	N	Patients with events (%)	N	Patients with events (%)	Relative risk [95 % CI]	p-value
Macular oedema	27	0 (0)	30	0 (0)	n.r.	1.000[d]
Reactions at the injection site	No evaluable data available.					
Infections	27	14 (51,9)	30	16 (53.3)	0.97 [0.59; 1.59]	0.971[d]

a: Annualized relapse rate: number of confirmed relapses divided by the number of patients in the treatment group multiplied by 365.25.
b: At the time 12 months.
c: Overall p-value (Fisher's exact test).
d: p-value from Institute's calculation; unconditional exact test (CSZ method according to [7]).
e: Positive change denotes improvement.
f: Standard error.
g: Construct from various Preferred Terms associated with bradycardia and the SMQ "Bradyarrhythmias (incl. conduction defects and disorders of sinus node function)"

AE: adverse event; AV: atrioventricular; CI: confidence interval; CSZ: convexity, symmetry, z score; IFN: interferon; KM: Kaplan Meier; MSFC: Multiple Sclerosis Functional Composite; N: number of evaluated patients; n.k.: not known; n.r.: not reported; PRIMUS: Patient Reported Indices for Multiple Sclerosis; RRMS: relapsing-remitting multiple sclerosis; SAE: serious adverse event; SD: standard deviation; VAS: visual analogue scale.

Because of the low number of patients of the population with rapidly evolving severe RRMS, the TRANSFORMS study did not meet the requirements to be met for the derivation of an added benefit from a single study.

Mortality

No patients died in the two relevant arms of the TRANSFORMS study. But because of its size and also its duration, the study was not designed to uncover differences in relation to mortality. An added benefit of fingolimod is therefore not proven for this outcome.

Morbidity

No statistically significant difference between the treatment groups was found, neither for the relapse-related outcomes nor the outcome "disability progression". An added benefit of fingolimod is not proven in relation to these outcomes.

The outcomes "fatigue" and "activities of daily living" were recorded in the TRANSFORMS study using the instruments Unidimensional Fatigue Impact Scale (U-FIS) and Patient Reported Indices for Multiple Sclerosis (PRIMUS) activities, which the Institute regards as valid measuring instruments for these outcomes (see also Section 2.7.2.2 of the full dossier assessment). This deviates from the company's evaluation, which did not include these

instruments in its benefit assessment. Accordingly, the company's dossier does not contain results for the subpopulation of patients with rapidly evolving RRMS. There are data only on the total population. An added benefit of fingolimod in respect of these outcomes is not proven.

Health-related quality of life

Health-related quality of life was recorded in the TRANSFORMS study using the instruments EQ-5D and PRIMUS QoL. In the Institute's view, both instruments are suitable for the benefit assessment, because they represent at least partial areas of health-related quality of life. This deviates from the company's evaluation, which did not take account of the PRIMUS QoL in its benefit assessment. Therefore the company's dossier does not contain any relevant data for the PRIMUS QoL.

In terms of EQ-5D, there was no statistically significant difference between the treatment groups, neither for the index nor for the visual analogue scale of the EQ-5D. Possible advantages that might arise through the manner of administration (oral versus intramuscular) are not represented in the results. It is, however, also questionable whether this is possible at all with the double-dummy technique used in the TRANSFORMS study.

In summary, an added benefit of fingolimod in relation to health-related quality of life is not proven.

Adverse events

The proportion of patients with adverse events in the relevant subpopulation did not differ substantially between fingolimod and IFN-β 1a. With regard to discontinuations due to adverse events and serious adverse events together, in each category only 1 patient suffered an event under fingolimod. In each case, the result was not statistically significant.

There are likewise almost no events recorded for the adverse events of macular oedema, bradycardia and/or AV conduction disorders. In respect of infections, the treatment groups did not differ substantially. Once again, the respective results were in each case not statistically significant.

No evaluable data were available on reactions at the injection site. The study report of the TRANSFORMS study contains several Preferred Terms of the MedDRA system that could be classified as reactions at the injection site. However, as in each case, the proportion of patients with such an event is analysed, it is not possible to add together the data from the individual categories because multiple counting of patients could occur.

The adverse event "flu-like symptoms" based on a single Preferred Term is the only one for which a statistically significant difference between the treatment groups in favour of fingolimod was found in the relevant subpopulation. Due to the small number of patients and the associated wide confidence interval, the upper limit of the confidence interval (0.91) is

close to the null effect. These events are practically all non-serious, which is also clear from the low number of serious adverse events in the population of patients with rapidly evolving RRMS. The overwhelming proportion of the events concerning flu-like symptoms occurred in the study initially in the first month after the study started and were only occasional in the months thereafter. Since treatment of RRMS generally lasts years, the relevance of this event is questionable. Overall there is an indication of lesser harm from fingolimod for this outcome.

Further information about the outcome results of the direct comparison on patients with rapidly evolving severe RRMS can be found in Module 4, Sections 4.3.1.3.1 and 4.3.1.3.2 of the dossier and in Section 2.7.2.3.4 of the full dossier assessment.

2.5 Extent and probability of the added benefit

Derivation of the extent and probability of added benefit is discussed below for each subindication at the outcome level, taking into account outcome categories and effect sizes.

The procedure for formulating an overall conclusion regarding added benefit based on the aggregation of the conclusions derived at the outcome level is a proposal from IQWiG. The decision regarding added benefit is made by the G-BA.

2.5.1 Patients with highly active RRMS, full treatment with IFN-β

As described in Section 2.4.1, there were no evaluable data on this research question.

The added benefit of fingolimod over the ACT glatiramer acetate is not proven for the population of patients with highly active RRMS, who have not responded to a full course of treatment with IFN.

2.5.2 Patients with highly active RRMS, incomplete treatment with IFN-β

As described in Section 2.4.2, there were no evaluable data on this research question.

The added benefit of fingolimod over the ACT glatiramer acetate is not proven for the population of patients with highly active RRMS, who have not yet received a full course of IFN-β treatment.

2.5.3 Patients with rapidly evolving severe RRMS

The data presented in Section 2.4.3 showed that in terms of the outcomes “relapses”. “disability progression” and “health-related quality of life”, there is no statistically significant effect. Because of the very small (total 57) subpopulation of patients with rapidly evolving severe RRMS in the TRANSFORMS study, effects could only be estimated in a very imprecise manner. This produced very wide confidence intervals, particularly for the outcome “relapses”, so that here, conclusions in favour and to the detriment of fingolimod are possible. An added benefit could not be derived for any of the outcomes used in the benefit assessment.

In terms of the outcomes “deaths”, “overall rates of adverse events”, “overall rates of serious adverse events” and “discontinuations due to adverse events”, and most of the specific adverse events considered, either no or hardly any events occurred in the study, or the proportion in the groups were of a similar order of magnitude. With regard to serious adverse events in particular, the data is unclear because of the very low event rate. Only for flu-like symptoms was there a greater difference between the treatment groups, which was also statistically significant in favour of fingolimod. For this outcome, there is an indication of lesser harm from fingolimod for the population of patients with rapidly evolving severe RRMS.

In addition, the company submitted no results for the relevant subpopulation for the outcomes “fatigue” and “activities of daily living” recorded in the TRANSFORMS study.

Taken as a whole, the available results on patients with rapidly evolving RRMS give a “hint” of a minor added benefit of fingolimod in comparison with IFN-β. This hint arises from the indication of lesser harm in respect of the outcome “flu-like symptoms” (non-serious adverse event). It takes account of the uncertain data for other outcomes (in particular “relapses” and “serious adverse events”), because the small patient population makes the estimations imprecise. In addition, also because of the problem mentioned above of the classification of the patient group according to the approval status, there is a high degree of uncertainty. This lack of certainty regarding the data leads to an overall downgrading of the probability of the conclusion on added benefit from an “indication” to a “hint”.

2.5.4 Extent and probability of the added benefit - summary

The following summary of the extent and probability of the added benefit in comparison with the respective ACT is given for the various populations within the approved therapeutic indication of fingolimod:

Table 11: Fingolimod: extent and probability of the added benefit

	Population	**Appropriate comparator therapy**	**Extent and probability of the added benefit**
1	Patients with highly active RRMS, full previous treatment with IFN-β	Glatiramer acetate	Added benefit not proven.
2	Patients with highly active RRMS, incomplete previous treatment with IFN-β	IFN-β 1a i.m.	Added benefit not proven.
3	Patients with rapidly evolving severe RRMS	IFN-β 1a i.m.	Hint of a minor added benefit of fingolimod
IFN: interferon; i.m.: intramuscular; RRMS: relapsing-remitting multiple sclerosis.			

This overall assessment deviates substantially from that of the pharmaceutical company, which claimed a major added benefit of fingolimod in comparison with the respective ACT for all 3 subpopulations.

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier and in Section 2.7.2.7 of the full dossier assessment

2.6 List of included studies

TRANSFORMS

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.

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; clinical study report [unpublished]. 2009.

Novartis. Additional analyses TRANSFORMS und FREEDOMS [unpublished]. 2011.

References for English extract (please see full dossier assessment for full reference list)

1) Product information. 03/02/2012. Gilenya -EMEA/H/C/002202 -N/007. Annex 1 Summary of Product Characteristics. [Accessed on 25.04.2012]. URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002202/WC500104528.pdf

2) Gemeinsamer Bundesausschuss. Verfahrensordnung des Gemeinsamen Bundesausschusses [Federal Joint Committee - Code of Procedure]. [online]. 20.01.2011 [Accessed on: 25.04.2012]. URL: http://www.g-ba.de/downloads/62-492-548/VerfO_2011-08-04.pdf

3) Product information. 14/11/2011. Tysabri -EMEA/H/C/000603 -N/0042. Annex 1 Summary of Product Characteristics. [Accessed on 25.04.2012]. URl: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000603/WC500044686.pdf

4) European Medicines Agency. Gilenya: assessment report [online]. 17.11.2006 [Accessed on: 25.04.2012]. URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002202/WC500104529.pdf.

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

6) European Medicines Agency. Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis [online]. 16.11.2006 [Accessed on: 25.04.2012]. URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003485.pdf.

The full report (German version) is published under www.iqwig.de