IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Fingolimod (multiple sclerosis in children and adolescents) –

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

Extract

[1] Translation of Sections 2.1 to 2.7 of the dossier assessment *Fingolimod (multiple Sklerose bei Kindern und Jugendlichen) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 27 March 2019). 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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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CI	confidence interval
EDSS	Expanded Disability Status Scale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
Gd-T1 lesion	gadolinium-enhancing T1-lesion
IFN	Interferon
IM	intramuscular
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MRI	magnetic resonance imaging
PedsQL	Pediatric Quality of Life Inventory
RCT	Randomized controlled Trial
RR	relative risk
RRMS	relapsing remitting multiple sclerosis
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summaries of Product Characteristics
TPC	treatment in accordance with physician’s choice

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 19 December 2018.

Research question

The aim of this report was to assess the added benefit of fingolimod in comparison with the appropriate comparator therapy (ACT) in children and adolescents with highly active or rapidly evolving relapsing remitting multiple sclerosis (RRMS).

The research questions presented in Table 2 resulted from the ACTs specified by the G-BA for the present benefit assessment of fingolimod.

Table 2: Research questions of the benefit assessment of fingolimod

Research question	**Subindication**	**ACT[a]**
Children and adolescents (≥ 10 and < 18 years) with highly active RRMS despite a full and adequate course of treatment with at least one disease-modifying therapy,		
A1	for whom treatment escalation is indicated	Treatment of Physician's Choice[b] (TPC)
A2	for whom change within the basic therapeutic agents is indicated	**Interferon beta** (**IFNβ)1a** or 1b or glatiramer acetate under consideration of the approval
Children and adolescents (≥ 10 and < 18 years) with rapidly evolving severe RRMS[c]		
B1	who have not yet received disease-modifying therapy	**IFNβ1a** or 1b or glatiramer acetate under consideration of the approval
B2	Despite disease-modifying therapy	TPC[b]

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Suitable comparator is natalizumab. The drug natalizumab is not approved for the present therapeutic indication (children and adolescents ≥ 10 and < 18 years). There is a discrepancy between the drugs approved for the therapeutic indication and those used in health care or recommended in the guidelines.
c: 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 recently conducted MRI.
G-BA: Federal Joint Committee; IFNβ: interferon beta; MRI: magnetic resonance imaging; RRMS: relapsing remitting multiple sclerosis

The assessment was conducted in comparison with the ACTs specified by the G-BA. The company requested no consultation on the ACT by the G-BA before the dossier was compiled

and based the present assessment on data pertaining to the ACT in adults from 2016. In doing so, it partly deviated from the G-BA's specification for children and adolescents.

Assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results on research question A1: pretreated children and adolescents with highly active RRMS for whom escalation treatment is indicated

No relevant study was identified for the assessment of the added benefit of fingolimod in comparison with treatment in accordance with physician's choice (TPC) for the treatment of pretreated children and adolescents with highly active RRMS for whom escalation treatment is indicated.

Results on research question A2: pretreated children and adolescents with highly active RRMS for whom change within the basic therapy is indicated

The PARADIGMS study was included in the benefit assessment of fingolimod in comparison with interferon beta (IFNβ)1a in pretreated children and adolescents with highly active RRMS for whom change within the basic therapy is indicated.

Study design

The PARADIGMS study is a randomized, double-blind, actively controlled parallel-group study on the comparison of fingolimod with IFNβ1a in paediatric and adolescent patients with RRMS.

Children and adolescents (≥ 10 to < 18 years) with ≥ 1 relapse in the past year or ≥ 2 relapses during the past 2 years or ≥ 1 gadolinium-enhancing T1-lesion (Gd-T1 lesion) within the last six months before study inclusion and a maximum Expanded Disability Status Scale (EDSS) score of 5.5 were included in the study.

A total of 215 children and adolescents were randomly assigned to treatment with fingolimod (N = 107) or IFNβ1a (N = 108). The children and adolescents were treated in compliance with the recommendations of the respective Summaries of Product Characteristics (SPC).

The duration of the blinded phase of the study was changed from a fixed duration of 24 months to a flexible duration of at most 24 months by a change in the study protocol. After termination of the blinded phase of the study, the children and adolescents could switch to treatment with fingolimod or continue this treatment within an open-label extension phase (up to 5 years). The extension phase of the study is still ongoing. The present assessment is exclusively based on data from the blinded phase of the study at database closure on 11 August 2017.

Subpopulation relevant for research question A2

The subpopulation relevant for research question A2 comprises children and adolescents (≥ 10 and < 18 years) with highly active RRMS despite a full and adequate course of treatment with at least one disease-modifying therapy for whom a change within the basic therapy is indicated.

This relevant population constitutes a subpopulation of the PARADIGMS study. In its dossier, the company presented analyses of a subpopulation in which it included all patients with highly active RRMS who had been pretreated with a basic therapy. Operationalization of the criteria "highly active RRMS" and "full and adequate course" was also adequate here. However, the subpopulation presented by the company was not usable, because the company had not considered the criterion "change of the basic therapy" when choosing the subpopulation. Consequently, the verifiably inadequate basic therapy with IFNβ1a was continued in about 70% of the patients of the subpopulation chosen by the company.

However, the company also presented subgroup analyses on subpopulation D presented by it, subdivided by the type of prior therapy (IFNβ1a vs. IFNβ1b vs. glatiramer acetate). For the present research question, the subgroup data of the patients pretreated with IFNβ1b and glatiramer acetate can therefore be used for the assessment, because a change within the basic therapy had taken place for this population.

The results of this subpopulation are very imprecise, because the resulting relevant sub-population has only very low numbers of patients and events. Therefore, the results were primarily considered in qualitative terms in the present benefit assessment, and the overall extent of the added benefit was derived on this basis.

Risk of bias

The risk of bias across outcomes was rated as low for the PARADIGMS study. Except for the results on the outcome "all-cause mortality", the respective outcome-specific risk of bias of the results on all other outcomes is assessed as potentially having a high risk of bias.

Mortality

All-cause mortality

No deaths occurred until the end of the blinded phase of the PARADIGMS study. This resulted neither in an advantage nor in a disadvantage of fingolimod in comparison with IFNβ1a. This resulted in no hint of an added benefit of fingolimod in comparison with IFNβ1a for this outcome; an added benefit is therefore not proven.

Morbidity

Confirmed relapses (EDSS-based)

Two operationalizations were used for the assessment of the confirmed relapses (annualized rate of confirmed relapses and time to first confirmed relapse), which were jointly interpreted. In both operationalizations, there was an effect estimate in favour of fingolimod in a comparable

magnitude versus IFNβ1a. Thereby, a statistically significant result was only shown for the operationalization "time to first confirmed relapse". Overall, this resulted in a hint of an added benefit of fingolimod in comparison with IFNβ1a for the outcome complex "confirmed relapses".

Confirmed change of the disability (EDSS-based)

The operationalizations "confirmed disability progression" and "confirmed improvement of the disability", which were jointly interpreted, were used for the assessment of "confirmed change of the disability".

There were different results depending on the operationalization. Whereas a numerical difference to the disadvantage of fingolimod was shown for "confirmed disability progression", a numerical difference in favour of fingolimod resulted for "confirmed improvement of the disability". However, none of the effects reached statistical significance. Overall, this resulted in no hint of an added benefit of fingolimod in comparison with IFNβ1a for the outcome complex "confirmed change of the disability"; an added benefit is therefore not proven.

Health-related quality of life

Pediatric Quality of Life Inventory (PedsQL)

Health-related quality of life was recorded using the PedsQL A statistically significant difference was shown in favour of fingolimod in comparison with IFNβ1a. The relevance of the difference is unclear. On the one hand, information on the handling of missing values is missing. On the other hand, there are no data on the baselines, on the changes and on the variance in the individual study arms.

Side effects

Serious adverse events (SAEs) and discontinuation due to adverse events (AEs) hardly occurred in both treatment arms. Noticeable differences suitable for a derivation of an advantage or disadvantage of fingolimod were not found for non-severe specific AEs.

Relevant data on specific AEs from the fields "psychiatric disorders" or "cardiac disorders" are missing.

Overall, this resulted in no hint of greater or lesser harm from fingolimod in comparison with IFNβ1a for the outcome complex "side effects"; greater or lesser harm is therefore not proven.

Results on research question B1: treatment-naive children and adolescents with rapidly evolving severe RRMS

Relevant data for the assessment of the added benefit of fingolimod in comparison with an ACT in the treatment of children and adolescents with rapidly evolving severe RRMS who have received no disease-modifying therapy to date are missing due to inadequate operationalization of the subpopulation presented by the company.

Research question B2: treatment-naive children and adolescents with rapidly evolving severe RRMS

Relevant data for the assessment of the added benefit of fingolimod in comparison with TCP for the treatment of children and adolescents with rapidly evolving severe RRMS despite treatment with disease-modifying therapy are missing due to inadequate operationalization of the subpopulation presented by the company and an inadequate comparator therapy.

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

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

Research question A1: pretreated children and adolescents with highly active RRMS for whom escalation treatment is indicated

No relevant study was identified for research question A1. An added benefit of fingolimod is therefore not proven for this research question.

Research question A2: pretreated children and adolescents with highly active RRMS for whom change within the basic therapy is indicated

For research question A2, a hint of an added benefit of fingolimod versus the ACT IFNβ1a was found for pretreated children and adolescents with highly active RRMS for whom a change in the basic therapy is indicated. This hint is based on the advantage of fingolimod observed for the outcome "confirmed relapses". The extent of added benefit is non-quantifiable in the present data situation.

Research question B1: treatment-naive children and adolescents with rapidly evolving severe RRMS

Due to inadequate operationalization of the subpopulation presented by the company, relevant data are not available for research question B1. An added benefit of fingolimod is therefore not proven for this research question.

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

Research question B2:

Due to inadequate operationalization of the subpopulation and an inadequate comparator therapy, relevant data are not available for research question B2. An added benefit of fingolimod is therefore not proven for this research question.

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

Table 3: Fingolimod – probability and extent of added benefit

Research question	**Subindication**	**ACT**[a]	**Probability and extent of added benefit**
Children and adolescents (≥ 10 and < 18 years) with highly active RRMS despite a full and adequate course of treatment with at least one disease-modifying therapy,			
A1	for whom treatment escalation is indicated	TPC	Added benefit not proven
A2	for whom change within the basic therapeutic agents is indicated	**IFNβ1a** or 1b or glatiramer acetate under consideration of the approval[c]	Hint of non-quantifiable added benefit
Children and adolescents (≥ 10 and < 18 years) with rapidly evolving severe RRMS[c]			
B1	who have not yet received disease-modifying therapy	**IFNβ1a** or 1b or glatiramer acetate under consideration of the approval	Added benefit not proven
B2	Despite disease-modifying therapy	TPC	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Suitable comparator is natalizumab. The drug natalizumab is not approved for the present therapeutic indication (children and adolescents ≥ 10 and < 18 years). There is a discrepancy between the drugs approved for the therapeutic indication and those used in health care or recommended in the guidelines.
c: 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 recently conducted MRI.
G-BA: Federal Joint Committee; IFNβ: interferon beta; MRI: magnetic resonance imaging; RRMS; relapsing remitting multiple sclerosis; TPC: treatment of physician's choice

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

2.2 Research question

The aim of this report is to assess the added benefit of fingolimod in comparison with the ACT in children and adolescents with highly active or rapidly evolving RRMS.

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

Table 4: Research questions of the benefit assessment of fingolimod

Research question	**Subindication**	**ACT**[a]
Children and adolescents (≥ 10 and < 18 years) with highly active RRMS despite a full and adequate course of treatment with at least one disease-modifying therapy,		
A1	for whom treatment escalation is indicated	TPC[b]
A2	for whom change within the basic therapeutic agents is indicated	**IFNβ1a** or 1b or glatiramer acetate under consideration of the approval
Children and adolescents (≥ 10 and < 18 years) with rapidly evolving severe RRMS[c]		
B1	who have not yet received disease-modifying therapy	**IFNβ1a** or 1b or glatiramer acetate under consideration of the approval
B2	Despite disease-modifying therapy	TPC

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Suitable comparator is natalizumab. The drug natalizumab is not approved for the present therapeutic indication (children and adolescents ≥ 10 and < 18 years). There is a discrepancy between the drugs approved for the therapeutic indication and those used in health care or recommended in the guidelines.
c: 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 recently conducted MRI.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IFNβ: interferon beta; MRI: magnetic resonance imaging; RRMS: relapsing remitting multiple sclerosis; TPC: treatment of physician's choice

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

- Research question A1: pretreated children and adolescents with highly active RRMS for whom escalation treatment is indicated (in short: highly active RRMS, escalation treatment)
- Research question A2: pretreated children and adolescents with highly active RRMS for whom change within the basic therapy is indicated (in short: highly active RRMS, change within the basic therapy)
- Research question B1: treatment-naive children and adolescents with rapidly evolving severe RRMS (in short: rapidly evolving severe RRMS, treatment-naive)
- Research question B2: pretreated children and adolescents with rapidly evolving severe RRMS (in short: rapidly evolving severe RRMS, pretreated)

The company requested no consultation on the ACT by the G-BA before the dossier was compiled and based the present assessment on data pertaining to the ACT in adults from 2016. In doing so, it partly deviated from the G-BA's specification for children and adolescents (see Section 2.8.1 of the full dossier assessment).

The assessment was conducted in comparison with the ACT specified by the G-BA and by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

2.3 Research question A1: highly active RRMS, escalation treatment

2.3.1 Information retrieval and study pool (research question A1 – highly active RRMS, escalation treatment)

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 (status: 1 October 2018)
- bibliographical literature search on fingolimod (last search on 24 September 2018)
- search in trial registries for studies on fingolimod (last search on 25 September 2018)

To check the completeness of the study pool:

- search in trial registries for studies on fingolimod (last search on 16 January 2019)

No relevant study was identified from the check.

This concurs with the result of the company's information retrieval, which also identified no relevant study on this research question.

2.3.2 Results on added benefit (research question A1 – highly active RRMS, escalation treatment)

No data were available for the assessment of the added benefit of fingolimod in comparison with TPC for the treatment of pretreated children and adolescents with highly active RRMS for whom escalation treatment is indicated. Hence, there was no hint of an added benefit of fingolimod in comparison with the ACT; an added benefit is therefore not proven.

2.3.3 Overall conclusion on added benefit (research question A1 – highly active RRMS, escalation treatment)

In its dossier, the company presented no data for the assessment of the added benefit of fingolimod in comparison with TPC for the treatment of pretreated children and adolescents with highly active RRMS for whom escalation treatment is indicated. An added benefit of fingolimod is therefore not proven for these patients.

2.3.4 List of included studies (research question A1 – highly active RRMS, escalation treatment)

Not applicable as the company presented no relevant data for the benefit assessment.

2.4 Research question A2: highly active RRMS, change within the basic therapy

2.4.1 Information retrieval and study pool (research question A2 – highly active RRMS, change within the basic therapy)

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 (status: 1 October 2018)
- bibliographical literature search on fingolimod (last search on 24 September 2018)
- search in trial registries for studies on fingolimod (last search on 25 September 2018)

To check the completeness of the study pool:

- search in trial registries for studies on fingolimod (last search on 16 January 2019)

The check identified no additional relevant study.

2.4.1.1 Studies included

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

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

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Study NCT01892722 (PARADIGMS[b])	Yes	Yes	No

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

Section 2.4.4 contains a reference list for the studies included.

2.4.1.2 Study characteristics and study design

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

Table 6: Characteristics of the study included – RCT, direct comparison: fingolimod vs. IFNβ1a

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
PARADIGMS	RCT, double-blind, parallel	Paediatric (≥ 10 to < 18 Jahre)[b] patients with RRMS; ≥ 1 relapse in the past year or ≥ 2 relapses in the past 2 years or ≥ 1 Gd-positive lesion within the last 6 months before study inclusion, EDSS 0–5.5	Fingolimod (N = 107) IFNβ1a (N = 108) Relevant subpopulation thereof: ▪ Research question A1[c, d] ▪ Research question A2[e]: ▫ Fingolimod (n = 9[f]) ▫ IFNβ1a (n = 11[f]) ▪ Research question B1[g]: ▫ Fingolimod (n = 22) ▫ IFNβ1a (n = 13) ▪ Research question B2[c, h]	**Screening**: 45 days **Treatment:** ▪ Blinded phase: up to 24 months[i] ▪ Optional extension phase: unblinded, only fingolimod, at most 60 months **Follow-up:** ▪ at least 3 months to at most until end of study	87 centres in 26 countries: Australia, Austria, Belarus, Canada, Croatia, Brazil, Bulgaria, Estonia, France, Germany, Italy, Latvia, Lithuania, Mexico, Netherlands, Poland, Romania, Russia, Sweden, Serbia, Slovakia, Spain, Turkey, Ukraine, United Kingdom, USA ▪ Blinded phase: 07/2013–07/2017[j] ▫ Database closure of the final analysis: 11 August 2017 ▪ Extension phase: ongoing	Primary: confirmed annualized relapse rate Secondary: symptoms, health-related quality of life, AEs

(continued)

Table 6: Characteristics of the study included – RCT, direct comparison: fingolimod vs. IFNβ1a (continued)

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes contain exclusively information on relevant available outcomes for this benefit assessment/from the information provided by the company in Module 4 of the dossier.
b: If a certain age limit presented a contraindication in the national approval of IFNβ 1a (AVONEX), children and adolescents below this age limit were not included in the respective country.
c: No data or no relevant data. This subpopulation is no longer shown in the following tables.
d: Patients with highly active RRMS despite adequate and full treatment with at least one disease-modifying therapy for whom treatment escalation was indicated.
e: Patients with highly active RRMS despite adequate and full treatment with at least one disease-modifying therapy (which was not IFNβ1a) for whom change within the basic therapy was indicated.
f: Institute's calculation.
g: Patients with rapidly evolving severe RRMS who have not yet received disease-modifying therapy.
h: Patients with rapidly evolving severe RRMS despite disease-modifying therapy.
i: The study design was changed from a fixed duration of 24 months to a flexible, information-based design with a maximum study duration of 24 months by a change in the study protocol (16 November 2016). Accordingly, the blinded part of the study was to be terminated upon achievement of a power of 80% for the detection of a relative treatment effect of 50% of the annualized relapse rate (2-sided 5% alpha level).
j: Based on blinded assessment of the required patient numbers, the blinded phase of the study was terminated on 14 July 2017.

AE: adverse event; EDSS: Expanded Disability Status Scale; Gd: Gadolinium; IFNβ: interferon beta; n: relevant subpopulation; N: number of randomized (included) patients; RRMS: relapsing remitting multiple sclerosis; RCT: randomized controlled trial; vs.: versus

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

Study	Intervention	Comparison
PARADIGMS	Fingolimod, orally, once daily, ▪ Body weight ≤ 40 kg 0.25 mg[a] ▪ Body weight > 40 kg 0.5 mg ▪ Initial dose or first dose after restart following discontinuation must be administered under particular observation.	IFNβ1a, 30 µg/0.5 ml solution IM, once weekly ▪ Within the first 3 injections, up-titration to the full dose can be performed by injection of ¼ or ½ increments of the final volume (0.5 ml).
	no further dose adjustment planned	no further dose adjustment planned
	+	+
	Placebo injection IM once weekly for IFNβ1a	placebo once daily, orally for fingolimod
	Premedication: ▪ Antipyretic analgesic for the prevention of flu-like symptoms	
	Prohibited prior and concomitant treatment ▪ Immunosuppressants ▪ Immunoglobulins, monoclonal antibodies ▪ Live vaccines up to 2 months after the last dose ▪ Other MS drugs ▪ Antiarrhythmics, heart-rate reducing drugs	
	Permitted concomitant treatment ▪ Therapies for symptom control ▪ Antipyretic analgesic for the treatment of flu-like symptoms	

a: Patients receive a higher dose as soon as the body weight remains stable (for 3 months) above 40 kg
IFNβ: interferon beta; IM: intramuscular; RCT: randomized controlled trial; vs.: versus

Description of the study design

The PARADIGMS study is a randomized, double-blind, actively controlled parallel-group study on the comparison of fingolimod with IFNβ1a – administered intramuscularly (IM) – in paediatric and adolescent patients with RRMS.

Children and adolescents (≥ 10 to < 18 years) with ≥ 1 relapse in the past year or ≥ 2 relapses during the past 2 years or ≥ 1 Gd-T1 lesion within the last six months before study inclusion and a maximum EDSS score of 5.5 were included in the studies. Diagnosis and classification of the MS were based on the revised consensus criteria for paediatric MS of 2007 and the revised McDonald criteria of 2010 [3,4].

A total of 215 children and adolescents were randomly assigned to treatment with fingolimod (N = 107) or IFNβ1a (N = 108). Randomization was stratified by the factors “region” (Eastern

Europe, Western Europe, Central and South America, North America, Australia) and puberty status (pre-adolescent, adolescent). Blinding was ensured using a double-dummy design.

The children and adolescents were treated in accordance with the regimen described in Table 7, which was in compliance with the respective SPC [5,6].

The duration of the blinded phase of the study was changed from a fixed duration of 24 months to a flexible duration of at most 24 months by a change in the study protocol. In accordance with the criteria of the protocol change, the blinded phase of the study was terminated in July 2017, after a power of 80% for the detection of a relative treatment effects of 50% had been achieved for the primary outcome. After termination of the blinded phase of the study, the children and adolescents could switch to treatment with fingolimod or continue this treatment within an open-label extension phase (up to 5 years). The extension phase of the study is still ongoing. The present assessment is exclusively based on data from the blinded phase of the study at database closure on 11 August 2017.

Subpopulation relevant for research question A2

The population relevant for research question A2 comprises children and adolescents (≥ 10 and < 18 years) with highly active RRMS despite a full and adequate course of treatment with at least one disease-modifying therapy for whom a change within the basic therapy is indicated.

This relevant population constitutes a subpopulation of the PARADIGMS study. In its dossier, the company presented analyses of a subpopulation (referred to as subpopulation D in the company's dossier) in which it included all patients with highly active RRMS who had been pretreated with a basic therapy. Operationalization of the criteria "highly active RRMS" and "full and adequate course" was also adequate here. However, the subpopulation presented by the company was not usable, because the company had not considered the criterion "change of the basic therapy" when choosing the subpopulation. Consequently, the verifiably inadequate basic therapy with IFNβ1a was continued in about 70% of the patients of the subpopulation chosen by the company (see Section 2.8.4.1 of the full dossier assessment).

However, the company also provided subgroup analyses subdivided according to the type of the prior therapy (IFNβ 1a vs. IFNβ 1b vs. glatiramer acetate) on the subpopulation presented by it. For the present research question, the subgroup data of the patients pretreated with IFNβ1b and glatiramer acetate can therefore be used for the assessment, because a change within the basic therapy had taken place for this population.

Patient characteristics on this relevant subpopulation are not available. Therefore, patient characteristics of the total population and of subpopulation D used by the company for the assessment (also comprises patients pretreated with IFNβ1a) are presented hereinafter.

Table 8 shows the characteristics of the patients included in the study.

Table 8: Characteristics of the total study population and subpopulation of the children and adolescents with highly active RRMS pretreated with the basic therapy – RCT, direct comparison: fingolimod vs. IFN1β1a

Study	**PARADIGMS**			
Characteristics	**Total population**		**Subpopulation pretreated with the basic therapy**	
Category	**Fingolimod**	**IFNβ1a**	**Fingolimod**	**IFNβ1a**
	N[a] = 107	**N[a] = 107**	**N[a] = 32**	**N[a] = 39**
Age [years], mean (SD)	15.2 (2.0)	15.4 (1.6)	15.6 (1.9)	15.7 (1.4)
Age groups, n (%)				
< 10 years	0 (0)	0 (0)	0 (0)	0 (0)
≥ 10 to ≤ 12 years	13 (12)	9 (8)	3 (6)	1 (3)
> 12 to < 18 years	94 (88)	95 (89)	30 (94)	37 (95)
> 18 years	0 (0)	3 (3)	0 (0)	1 (3)
Sex [F/M], %	65/35	60/40	69/31	62/38
Ethnicity, n (%)				
White	100 (93)	97 (91)	28 (88)	35 (90)
Other[b]	7 (7)[c]	10 (9)[c]	4 (13)[c]	4 (10)[c]
Body weight [kg], n (%)				
≤ 40	9 (8)	1 (1)	3 (9)	0 (0)
> 40	98 (92)	109 (99)	29 (91)	39 (100)
Puberty status (Tanner's stages), n (%)				
Pre-adolescent < 2	7 (7)	3 (3)	3 (9)	0 (0)
Adolescent (≥ 2)	98 (92)	104 (97)	28 (88)	39 (100)
No data	2 (2)[c]	0 (0)[c]	1 (3)[c]	0 (0)[c]
EDSS at the start of the study				
Mean (SD)	1.5 (1.2)	1.6 (0.90)	1.8 (1.2)	1.7 (0.8)
Median [min; max]	1.5 [0; 6]	1.5 [0; 4]	1.5 [0; 6]	1.5 [0; 4]
Gd-enhancing T1-lesions,				
Proportion without lesions, n (%)	47 (44)	59 (55)	ND	ND
Number, mean (SD)	2.6 (6.0)	3.1 (6.5)	ND	ND
Number, median [min; max]	1.0 [0; 52]	0 [0; 37]	ND	ND
T2 lesions				
Proportion without lesions, n (%)	0 (0)	0 (0)	ND	ND
Number, mean (SD)	41.9 (30.3)	45.6 (33.9)	ND	ND
Number, median [min; max]	31.0 [2; 126]	32.0 [1; 145]	ND	ND
Time since RRMS diagnosis [years], mean (SD)	1.1 (1.25)	1.3 (1.4)	1.7 (1.4)	2.0 (1.4)
Time since occurrence of MS symptoms [years], mean (SD)	1.9 (1.7)	2.4 (2.1)	2.4 (1.8)	3.3 (2.6)

(continued)

Table 8: Characteristics of the total study population and subpopulation of the children and adolescents with highly active RRMS pretreated with the basic therapy – RCT, direct comparison: fingolimod vs. IFN1β1a (continued)

Study	PARADIGMS			
Characteristics Category	Total population		Subpopulation pretreated with the basic therapy	
	Fingolimod	IFNβ1a	Fingolimod	IFNβ1a
	Na = 107	Na = 107	Na = 32	Na = 39
Number of relapses in the year before the start of the study, mean (SD)	1.5 (1.0)	1.5 (0.9)	1.6 (0.9)	1.5 (1.1)
Number of relapses in the last 2 years before the start of the study, mean (SD)	2.4 (1.4)	2.5 (1.3)	2.7 (1.7)	2.8 (1.7)
Pretreatment with MS therapy, n (%)				
Treatment-naive	69 (64)	67 (63)	0 (0)	0 (0)
Pretreated	38 (36)	40 (37)	32 (100)	39 (100)
Treatment discontinuation, n (%)	8 (7)	26 (24)	ND	ND
Study discontinuation, n (%)	7 (7)	19 (18)	2 (6)	10 (26)

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Composed of the ethnicities native American, Asian, black/African American and other ethnicities.
c: Institute's calculation.
EDSS: Expanded Disability Status Scale; F: female; Gd: Gadolinium; IFNβ: interferon beta; max: maximum; min: minimum; MS: multiple sclerosis; MD: mean difference; M: male; n: number of patients in the category; N: number of randomized (or included) patients; ND: no data; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; SD: standard deviation; vs.: versus

Based on the available data, there were no important differences between treatment groups for both the total population and the subpopulation.

The average age of the children and adolescents was 15 to 16 years. About 2 thirds were female and about 90% were white. At the start of the study, the median EDSS score was 1.5 and the children and adolescents had on average 1.5 relapses in the year before the start of the study.

Slightly more than one third of the children and adolescents of the total population had been pretreated. The majority of them had already received interferon treatment (IFNβ1a or 1b).

In the total population, almost three times more children and adolescents discontinued the study or the treatment in the IFNβ1a arm than in the fingolimod arm. In the IFNβ1a arm of the study, the main reason for treatment discontinuation was the lacking therapeutic effect, the main reasons in the fingolimod arm were side effects.

Follow-up observation and treatment duration

Due to a change of the study design, the fixed study duration of the PARADIGMS study was changed from 24 months to a flexible information-based study duration. Consequently, not all children and adolescents included were observed over the originally planned 2 years. Moreover, different observation periods resulted between the treatment arms, which is possibly due to the different discontinuation rates. Table 9 shows the mean and median treatment duration of the children and adolescents as well as the mean and median observation period in the total population and subpopulation D. Data on the observation periods of the individual outcomes are not available.

Table 9: Data on the course of the study of the total study population and the subpopulation of the children and adolescents with highly active RRMS pretreated with the basic therapy – RCT, direct comparison: fingolimod vs. IFN1β1a

Study	**PARADIGMS**			
Characteristics	**Total population**		**Subpopulation pretreated with the basic therapy**	
Category	**Fingolimod**	**IFNβ1a**	**Fingolimod**	**IFNβ1a**
	N = 107	**N = 107**	**N = 32**	**N = 39**
Follow-up observation period [years], mean (SD)				
Median [min; max]	1.8 [0.0; 2.1][a]	1.5 [0.1; 2.1][a]	1.8 [1.1; 2.1][a]	1.5 [0.3; 2.1][a]
Mean (SD)	1.7 (0.4)[a]	1.5 (0.5)[a]	1.7 (0.3)[a]	1.4 (0.6)[a]
Proportion < 1 year in study, n (%)	5 (5)	19 (18)	0 (0)	8 (21)
Proportion ≥ 1 and < 2 years in study, n (%)	88 (82)[a]	81 (76)[a]	27 (84)[a]	29 (74)[a]
Proportion < 2 years in study, n (%)	14 (13)	7 (7)	5 (16)	2 (5)
Treatment duration [years]				
Median [min; max]	1.7 [0.0; 2.1][a]	1.5 [0.1; 2.1][a]	ND	ND
Mean (SD)	1.7 (0.4)[a]	1.4 (0.5)[a]	ND	ND

a: Institute's calculation.

IFNβ: interferon beta; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized (or included) patients; ND: no data; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; SD: standard deviation; vs.: versus

Follow-up observation was at least 3 months or at most until the end of the study. The median observation period in the total population was about 17% longer in the fingolimod arm than in the IFNβ1a arm. Only about 13% of the children and adolescents in the fingolimod arm of the total population and 7% in the IFNβ1a arm of the study were observed for periods longer than 2 years. There were thus no long-term data available for the present benefit assessment.

Information on the observation and treatment times is not available for the relevant sub-population.

Risk of bias across outcomes (study level)

Table 10 shows the risk of bias across outcomes (risk of bias at study level).

Table 10: Risk of bias across outcomes (study level) – RCT, direct comparison: fingolimod vs. IFNβ1a

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

The risk of bias across outcomes was rated as low for the PARADIGMS study. This concurs with the company's assessment

2.4.2 Results on the added benefit (research question A2 – highly active RRMS, change within the basic therapy)

2.4.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.8.4.3.2 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - Confirmed relapses (EDSS-based)
  - Confirmed change of the disability (EDSS-based)
- health-related quality of life
  - Measured using the Pediatric Quality of Life Inventory (PedsQL)
- Side effects
  - Serious AEs (SAEs)
  - discontinuation due to AEs

- Infections and infestations
- Flu-like illness
- Psychiatric disorders
- Cardiac disorders
- If applicable, further specific adverse events

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4) (see Section 2.8.4.3 of the full dossier assessment).

Table 11 shows for which outcomes data were available in the study included.

Table 11: Matrix of outcomes – RCT, direct comparison: fingolimod vs. IFNβ1a

Study	Outcomes									
	All-cause mortality	Confirmed relapses[a]	Confirmed change of the disability (EDSS)[b]	Health-related quality of life (PedsQL)	Serious adverse events	Discontinuation due to AEs	Infections and infestations (AE, SOC)	Flu-like illness (AE, PT)	Psychiatric disorders	Heart disease
PARADIGMS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[c]	No[c]

a: The annualized rate of confirmed relapses as well as the time to first confirmed relapse were considered.
b: Confirmed progression as well as confirmed improvement of the disability were considered.
c: No data for the relevant subpopulation.
AE: adverse event; EDSS: Expanded Disability Status Scale; IFNβ: interferon beta; PedsQL: Pediatric Quality of Life Inventory; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

2.4.2.2 Risk of bias

Table 12 describes the risk of bias for the results of the relevant outcomes.

Table 12: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: fingolimod vs. IFNβ1a

Study	Study level	Outcomes									
		All-cause mortality	Confirmed relapses[a]	Confirmed change of the disability (EDSS)[b]	Health-related quality of life (PedsQL)	Serious adverse events	Discontinuation due to AEs	Infections and infestations (AE, SOC)	Flu-like illness (AE, PT)	Psychiatric disorders	Heart disease
PARADIGMS	L	L	H[c]	H[c]	H[c, d]	H[c]	H[c]	H[c]	H[c]	–[e]	–[e]

a: The annualized rate of confirmed relapses as well as the time to first confirmed relapse were considered.
b: Confirmed progression as well as confirmed improvement of the disability were considered.
c: Possibly high and differential proportions of incompletely observed patients; no data for the relevant subpopulation.
d: No data on the proportion of patients in the relevant subpopulation who were imputed using LOCF.
e: No data for the relevant subpopulation.
AE: adverse event; EDSS: Expanded Disability Status Scale; H: high; IFNβ: interferon beta; L: low; LOCF: last observation carried forward; PedsQL: Pediatric Quality of Life Inventory; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Expect for the results on the outcome "all-cause mortality", the results on all other outcomes are rated as potentially having a high risk of bias (see also Section 2.8.4.2 of the full dossier assessment). This was caused by the possible high number of incompletely observed patients, which also differed between the treatment groups. This potential bias cannot be exactly assessed due to missing information on the relevant subpopulation, which results in a high risk of bias. Moreover, data providing information on how large the proportion of missing values imputed using the last observation carried forward (LOCF) method was for the outcome "health-related quality of life" (recorded using the PedsQL) are also missing. No relevant data are available on the outcomes "psychiatric disorders" and "cardiac disorders" (see Section 2.8.4.3.2 of the full dossier assessment).

This assessment deviates from that of the company, which, except for the outcome "all-cause mortality", derived a low risk of bias for the results of all outcomes.

2.4.2.3 Results

Table 13, Table 14 and Table 15 summarize the results on the comparison of fingolimod with IFNβ1a in pretreated children and adolescents with highly active RRMS for whom a change within the basic therapy was indicated (research question A2).

Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. Some event time analyses could not be calculated due to a lack of events. For reasons of better readability, relative risk (RR) is used as an effect measure for all outcomes except for the outcomes "relapses" and "health-related quality of life" despite the different observation periods (22 vs. 18 months median observation periods in subpopulation D).

The results of the patients who had been pretreated with glatiramer acetate and those who had been pretreated with IFNβ1b were summarized in a meta-analysis. Models with a fixed effect were calculated. The Mantel-Haenszel method was used for binary outcomes and the inverse variance method was used for continuous outcomes.

Kaplan-Meier curves on the event time analyses can be found in Appendix A.1. The forest plots of the meta-analyses calculated by the Institute can be found in Appendix A.2 of the full dossier assessment. The dossier contained no lists of the AEs for the relevant subpopulation. The AEs of subpopulation D of the company (all patients with highly active RRMS pretreated with basic therapy) are presented for the present research question (see Appendix A.3). Recordings of SAEs and discontinuation-causing AEs are also missing for this population created by the company.

Table 13: Results (morbidity, annualized relapse rate, time to event) – RCT, direct comparison: fingolimod vs. IFNβ1a (research question A2 - highly active RRMS, change within the basic therapy)

Outcome category **Outcome**	**Fingolimod**			**IFNβ1a**			**Fingolimod vs. IFNβ1a**
	N	**n/patient years**	**Annualized relapse rate [95% CI]**	**N**	**n/patient years**	**Annualized relapse rate [95% CI]**	**Rate ratio [95% CI]; p-value[a]**
Morbidity							
Confirmed relapses (EDSS-based)							
Annualized rate of confirmed relapses	9	4/ND	ND	11	19/ND	ND	0.33 [0.08; 1.35]; 0.123[b]
		Median time to event in months [95% CI] **Patients with event n (%[c])**			**Median time to event in months [95% CI]** **Patients with event n (%[c])**		**MD [95% CI]; p-value[d]**
Time to first confirmed relapse	9	ND 2 (22)		11	ND 7 (64)		0.18 [0.03; 0.95]; 0.043[b]

a: Results of subgroup analyses regarding prior therapy (glatiramer acetate, IFNβ1a, IFNβ1b) in the subpopulation relevant for research question D; negative binomial model with treatment, prior therapy, treatment x prior therapy, region, puberty status (Tanner's stages) as well as the number or relapses in the past 2 years; duration of the observation in years as offset.
b: Institute's calculation; meta-analysis with fixed effect; inverse variance method.
c: Institute's calculation.
d: Results of subgroup analyses regarding prior therapy (glatiramer acetate, IFNβ1a, IFNβ1b) in the subpopulation relevant for research question D; Cox proportional hazards model with treatment, prior therapy and treatment x prior therapy.

CI: confidence interval; EDSS: Expanded Disability Status Scale; HR: Hazard Ratio; IFNβ: interferon beta; n: number of relapses; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; vs.: versus

Table 14: Results (mortality, morbidity, side effects; dichotomous) – RCT, direct comparison: fingolimod vs. IFNβ1a (research question A2 - highly active RRMS, change within the basic therapy)

Outcome category Outcome	Fingolimod		IFNβ1a		Fingolimod vs. IFNβ1a
	N	Patients with event n (%[a])	N	Patients with event n (%[a])	RR [95% CI]; p-value[b]
Mortality					
all-cause mortality	9	0 (0)	11	0 (0)	NC
Morbidity					
Confirmed change of the disability (EDSS-based)					
Confirmed progression	9	2 (22)	11	1 (9)	1.90 [0.32 11.41]; 0.483
Confirmed improvement	9	2 (22)	11	2 (18)	1.23 [0.24 6.22]; 0.802
Side effects					
AEs (additional information)	9	9 (100)	11	11 (100)	–
Serious adverse events	9	2 (22)	11	1 (9)	1.90 [0.32 11.41]; 0.483
Discontinuation due to AEs	9	0 (0)	11	1 (14)	0.44 [0.02; 9.11]; 0.557[c, d]
Infections and infestations (AE, SOC)	9	7 (78)	11	7 (64)	1.24 [0.70 2.21]; 0.459
Flu-like illness (AE, PT)	9	0 (0)	11	3 (43)	0.19 [0.01; 3.03]; 0.129[c, d]
Psychiatric disorders	No relevant data				
Cardiac disorders	No relevant data				

a: Institute's calculation.
b: Institute's calculation, meta-analysis with fixed effect, Mantel-Haenszel method.
c: Institute's calculation, unconditional exact test (CSZ method according to [7]).
d: Effect of the children and adolescents with highly active RRMS pretreated with glatiramer acetate. No events occurred for patients pretreated with IFNβ1b.

AE: adverse event; CI: confidence interval; EDSS: Expanded Disability Status Scale; IFNβ: interferon beta; N: number of analysed patients; n: number of patients with (at least 1) event; NC: not calculable; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; RRMS: relapsing remitting multiple sclerosis; SOC: System Organ Class; SAE: serious adverse event; vs.: versus

Table 15: Results (health-related quality of life) – RCT, direct comparison: fingolimod vs. IFNβ1a (research question A2 – highly active RRMS, change within the basic therapy)

Outcome category Outcome	Fingolimod			IFNβ1a			Fingolimod vs. IFNβ1a
	N[a]	Values at baseline mean (SD)	Change at end of study mean (SE)	N[a]	Values at baseline mean (SD)	Change at end of study mean (SE)	MD [95% CI]; p-value[b]
Health-related quality of life							
PedsQL, total score[c] (patient-reported)	9	ND	ND	11	ND	ND	14.62 [2.50; 26.73]; 0.018[d]

a: Number of patients considered in the analysis for the calculation of the effect estimate, the values at the start of the study (possibly at other time points) may be based on other patient numbers.
b: Results of subgroup analyses regarding the prior therapy (glatiramer acetate, IFNβ1a, IFNβ1b) in the subpopulation relevant for research question D; ANCOVA, adjusted for the baseline value and with treatment, prior therapy, treatment x prior therapy, region, puberty status (Tanner's stages) and number of relapses in the past 2 years before randomization; missing values at the end of the study were imputed with the LOCF.
c: A positive change from the start until the end of the study indicates improvement; a positive effect estimate indicates an advantage for fingolimod.
d: Institute's calculation, meta-analysis with fixed effect, inverse variance - method.
ANCOVA: covariance analysis; CI: confidence interval; IFN-β: interferon beta; LOCF: last observation carried forward; MD: mean difference; N: number of analysed patients; ND: no data; PedsQL: Pediatric Quality of Life Inventory; RRMS: relapsing remitting multiple sclerosis; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; vs.: versus

Based on the available data, at most an indication, e.g. of an added benefit, can be derived for the outcome "all-cause mortality", and at most hints for all other outcomes due to the high risk of bias.

The results of this subpopulation are very imprecise, because the relevant subpopulation has only very low numbers of patients and events. Therefore, the results are primarily considered in qualitative terms in the present benefit assessment, and the overall extent of added benefit is derived on this basis.

Mortality

All-cause mortality

No deaths occurred until the end of the blinded phase of the PARADIGMS study. This resulted neither in an advantage nor in a disadvantage of fingolimod in comparison with IFNβ1a. This resulted in no hint of an added benefit of fingolimod in comparison with IFNβ1a for this outcome; an added benefit is therefore not proven.

Morbidity

Confirmed relapses (EDSS-based)

Two operationalizations were used for the assessment of the confirmed relapses (annualized rate of confirmed relapses and time to first confirmed relapse), which were jointly interpreted.

In both operationalizations, there was an effect estimate in favour of fingolimod in a comparable magnitude versus IFNβ1a. Thereby, a statistically significant result was only shown for the operationalization "time to first confirmed relapse". Overall, this resulted in a hint of an added benefit of fingolimod in comparison with IFNβ1a for the outcome complex "confirmed relapses".

Confirmed change of the disability (EDSS-based)

The operationalizations "confirmed disability progression" and "confirmed improvement of the disability", which were jointly interpreted, were used for the assessment of "confirmed change of the disability".

There were different results depending on the operationalization. Whereas a numerical difference to the disadvantage of fingolimod was shown for "confirmed disability progression", a numerical difference in favour of fingolimod resulted for "confirmed improvement of the disability". However, none of the effects reached statistical significance. Overall, this resulted in no hint of an added benefit of fingolimod in comparison with IFNβ1a for the outcome complex "confirmed change of the disability"; an added benefit is therefore not proven.

Health-related quality of life

PedsQL

Health-related quality of life was recorded using the PedsQL. The continuous analyses of the patient-reported questionnaires of the PedsQL were considered (see Section 2.8.4.3.2 of the full dossier assessment). A statistically significant difference was shown in favour of fingolimod in comparison with IFNβ1a. The relevance of the difference is unclear. On the one hand, information on the handling of missing values is missing (see above and Section 2.8.4.2 of the full dossier assessment). On the other hand, there are no data on the baselines, on the changes and on the variance in the individual study arms.

Side effects

SAEs and discontinuations due to AEs hardly occurred in both treatment arms. Noticeable differences suitable for a derivation of an advantage or disadvantage of fingolimod were not found for non-severe specific AEs.

Relevant data on specific AEs from the fields "psychiatric disorders" or "cardiac disorders" are missing (see Section 2.8.4.3.2 of the full dossier assessment).

Overall, this resulted in no hint of greater or lesser harm from fingolimod in comparison with IFNβ1a for the outcome complex "side effects"; greater or lesser harm is therefore not proven.

2.4.2.4 Subgroups and other effect modifiers

There are no subgroup analyses for the relevant subpopulation. However, due to the low number of patients, subgroup analyses of the relevant subpopulation would not be meaningfully interpretable either.

2.4.3 Overall conclusion on the added benefit (research question A2 – highly active RRMS, change within the basic therapy)

Table 16 summarizes the results that were considered in the overall conclusion on added benefit.

Table 16: Positive and negative effects from the assessment of fingolimod in comparison with IFNβ1a (research question A2 - highly active RRMS, change within the basic therapy)

Advantage of the intervention	Disadvantage of the intervention
Morbidity: ▪ Confirmed relapses: hint of an added benefit	–
▪ Health-related quality of life (PedsQL): effect in favour of fingolimod, the relevance of the difference is unclear due to missing data. ▪ Relevant data on specific AEs from the fields “psychiatric disorders” or “cardiac disorders” are missing	
IFNβ: interferon beta, PedsQL: Pediatric Quality of Life Inventory; RRMS: relapsing remitting multiple sclerosis	

In summary, this resulted in a hint of an added benefit of fingolimod versus the ACT IFNβ1a for pretreated children and adolescents with highly active RRMS for whom a change in the basic therapy is indicated. This hint is based on the advantage of fingolimod observed for the outcome “confirmed relapses”. The extent of added benefit is non-quantifiable in the present data situation.

The company, in contrast, derived an indication of major added benefit from this. However, the advantage postulated by the company is largely based on the effects in those children and adolescents who have continued their demonstrably insufficient therapy with IFNβ 1a.

2.4.4 List of included studies (research question A2 – highly active RRMS, change within the basic therapy)

PARADIGMS study

Chitnis T, Arnold DL, Banwell B, Bruck W, Ghezzi A, Giovannoni G et al. Trial of fingolimod versus interferon beta-1a in pediatric multiple sclerosis. N Engl J Med 2018; 379(11): 1017-1027.

Novartis. A two-year, double-blind, randomized, multicenter, activecontrolled core phase study to evaluate the safety and efficacy of fingolimod administered orally once daily versus interferon β-1a im once weekly in pediatric patients with multiple sclerosis with five-year fingolimod extension phase; study CFTY720D2311; clinical study report [unpublished]. 2017.

Novartis. A two-year, double-blind, randomized, multicenter, activecontrolled core phase study to evaluate the safety and efficacy of fingolimod administered orally once daily versus interferon β-1a im once weekly in pediatric patients with multiple sclerosis with five-year fingolimod extension phase; study CFTY720D2311; Zusatzanalysen [unpublished]. 2018.

Novartis Pharma. A two-year, double-blind, randomized, multicenter, active controlled study to evaluate the safety and efficacy of fingolimod administered orally once daily versus interferon β-1a i.m. once weekly in pediatric patients with multiple sclerosis with five-year fingolimod extension phase [online]. In: EU Clinical Trials Register. [Accessed: 07.02.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2011-005677-23.

Novartis Pharmaceuticals. Safety and efficacy of fingolimod in pediatric patients with multiple sclerosis: study results [online]. In: ClinicalTrials.gov. 19.09.2018 [Accessed: 07.02.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01892722.

Novartis Pharmaceuticals. Safety and efficacy of fingolimod in pediatric patients with multiple sclerosis: study details [online]. In: ClinicalTrials.gov. 19.09.2018 [Accessed: 07.02.2019]. URL: https://ClinicalTrials.gov/show/NCT01892722.

2.5 Research question B1 – rapidly evolving severe RRMS, treatment-naive

2.5.1 Information retrieval and study pool (research question B1 – rapidly evolving severe RRMS, treatment-naive)

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 (status: 1 October 2018)
- bibliographical literature search on fingolimod (last search on 24 September 2018)
- search in trial registries for studies on fingolimod (last search on 25 September 2018)

To check the completeness of the study pool:

- search in trial registries for studies on fingolimod (last search on 16 January 2019)

The check identified no additional relevant study.

Contrary to the requirements specified by the G-BA, the company does not distinguish between the pretreatment status in children and adolescents with rapidly evolving severe RRMS. In its research question F, the company summarizes both treatment-naive (research question B1) and pretreated children and adolescents (research question B2) with rapidly evolving severe RRMS.

The company used the PARADIGMS study to answer its research question F. This same study was used for the assessment of research question A2. Table 6 and Table 7 show the study characteristics as well as interventions on the PARADIGMS study. The study design is described in Section 2.4.1 of research question A2.

The PARADIGMS study is potentially suitable to answer the present research question, however, the operationalization of the subpopulation for this research question chosen by the company is not adequate. This is explained below.

Subpopulation relevant for research question B1

The population relevant for the present research question comprises treatment-naive children and adolescents with rapidly evolving severe RRMS. This population is a potential subpopulation of the PARADIGMS study.

In Module 4 F, the company explained having created subpopulation F used by it based on the criteria "occurrence of at least 2 disabling relapses with disability progression" and "at least 1 Gd-T1 lesion". The criterion "significant increase of T2 lesions" used in addition by the G-BA could not be used due to missing reference magnetic resonance imaging (MRI) vs. baseline.

However, the patient characteristics of the subpopulation created by the company (see Table 17) did not show that the company had considered the criterion "with disability progression" when creating subpopulation F. In contrast, the available information implies that the criterion "disability progression" was not considered.

Table 17 presents the patient characteristics of subpopulation F used by the company.

Table 17: Characteristics of the subpopulation of children and adolescents with rapidly evolving RRMS – RCT, direct comparison: fingolimod vs. IFN1β1a

Study	**PARADIGMS**	
Characteristics **Category**	**Fingolimod**	**IFNβ1a**
	N[a] = 32	**N[a] = 22**
Sex [F/M], %	78/22	64/36
EDSS at the start of the study		
Mean (SD)	1.7 (1.2)	2.0 (0.8)
Median [min; max]	1.3 [0.0; 4.0]	2.0 [0.0; 3.5]
Gd-enhancing T1-lesions		
Proportion without lesions, n (%)	ND	ND
Number, mean (SD)	ND	ND
Number, median [min; max]	ND	ND
T2 lesions		
Proportion without lesions, n (%)	ND	ND
Number, mean (SD)	ND	ND
Number, median [min; max]	ND	ND
Time since RRMS diagnosis [years], mean (SD)	0.7 (0.7)	1.3 (1.3)
Time since occurrence of MS symptoms [years], mean (SD)	1.4 (1.3)	2.5 (2.7)
Relapses in the year before the start of the study		
Number, mean (SD)	2.5 (0.7)	2.5 (1.1)
Number, median [min; max]	2.0 [2; 4]	2.0 [2; 7]
Relapses in the last 2 years before the start of the study		
Number, mean (SD)	3.2 (1.6)	3.5 (1.5)
Number, median [min; max]	3.0 [2; 8]	3.0 [2; 9]
Pretreatment with MS therapy, n (%)		
Treatment-naive	22 (69)	13 (59)
Pretreated	10 (31)	9 (41)

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.

EDSS: Expanded Disability Status Scale; F: female; Gd: gadolinium; IFNβ: interferon beta; max: maximum; min: minimum; M: male; n: number of patients in the category; MS: multiple sclerosis; N: number of randomized (or included) patients; ND: no data; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; SD: standard deviation; vs.: versus

According to general definition, persistent increase of the EDSS total score by 1 point (at EDSS values < 5.5) presents a disability progression [8]. This is also the criterion that the company itself used in its dossier to assess the disability progression.

The number of relapses show that the criterion "2 or more relapses" was met in subpopulation F. However, the EDSS total score at study inclusion is overall low and the range of the median comprises the value "zero". Subpopulation F thus comprised children and adolescents who had no (EDSS = 0) or only low impairment by disability and who did thus not correspond to the definition of a rapidly evolving severe RRMS with at least two disease progressions in the previous year (see Table 4).

In summary, the company presented no relevant data for the assessment of an added benefit of fingolimod in treatment-naive children and adolescents with rapidly evolving severe RRMS.

2.5.2 Results on the added benefit (research question B1 – rapidly evolving severe RRMS, treatment-naive)

Relevant data for the assessment of the added benefit of fingolimod in comparison with an ACT in the treatment of children and adolescents with rapidly evolving severe RRMS who have received no disease-modifying therapy to date are missing due to inadequate operationalization of the subpopulation presented by the company.

2.5.3 Overall conclusion on the added benefit (research question B1 – rapidly evolving severe RRMS, treatment-naive)

The company presented no relevant data for children and adolescents with rapidly evolving severe RRMS. An added benefit of fingolimod is therefore not proven for this research question.

2.5.4 List of included studies (research question B1 – rapidly evolving severe RRMS, treatment-naive)

Information on the PARADIGMS study can be found in Section 2.4.4.

2.6 Research question B2 – rapidly evolving severe RRMS, pretreated)

2.6.1 Information retrieval and study pool (research question B2 – rapidly evolving severe RRMS, pretreated)

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 (status: 1 October 2018)
- bibliographical literature search on fingolimod (last search on 24 September 2018)
- search in trial registries for studies on fingolimod (last search on 25 September 2018)

To check the completeness of the study pool:

- search in trial registries for studies on fingolimod (last search on 16 January 2019)

No relevant study was identified from the check.

2.6.1.1 Study used by the company

As described in Section 2.5 on research question B1, the company did not distinguish between pretreated and treatment-naive patients in the therapeutic indication of rapidly evolving severe RMS in children and adolescents in its dossier. Even if it had considered this, the ACT would not have been adequately implemented in the PARADIGMS study, since all children and adolescents in the comparator arm received IFNβ1a independent of the prior therapy. Hence, it was not guaranteed that this was TPC. The G-BA cited natalizumab as suitable comparator for TPC (see also Section 2.8.1 of the full dossier assessment).

Moreover, the operationalization of subpopulation F chosen by the company is inadequate for this research question (see Section 2.5.1).

Due to the composition of subpopulation F and the inadequate implementation of the ACT, relevant data for the assessment are therefore not available for this research question B2.

2.6.2 Results on the added benefit (research question B2 – rapidly evolving severe RRMS, pretreated)

Relevant data for the assessment of the added benefit of fingolimod in comparison with TPC for the treatment of children and adolescents with rapidly evolving RRMS despite treatment with a disease-modifying therapy are missing due to inadequate operationalization of the subpopulation presented by the company and an inadequate comparator therapy.

2.6.3 Overall conclusion on the added benefit (research question B2 – rapidly evolving severe RRMS, pretreated)

The company presented no relevant data for children and adolescents with rapidly evolving severe RRMS. An added benefit of fingolimod is therefore not proven for this research question.

2.6.4 List of included studies (research question B2 – rapidly evolving severe RRMS, pretreated)

Not applicable as the company presented no data for the present research question that are relevant for the benefit assessment.

2.7 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of fingolimod in comparison with the ACT is summarized in Table 18.

Table 18: Fingolimod – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
Children and adolescents (≥ 10 and < 18 years) with highly active RRMS despite a full and adequate course of treatment with at least one disease-modifying therapy,			
A1	for whom treatment escalation is indicated	TPC	Added benefit not proven
A2	for whom change within the asic therapeutic agents is indicated	**IFNβ1a** or 1b or glatiramer acetate under consideration of the approval[c]	Hint of non-quantifiable added benefit
Children and adolescents (≥ 10 and < 18 years) with rapidly evolving severe RRMS[c]			
B1	who have not yet received disease-modifying therapy	**IFNβ1a** or 1b or glatiramer acetate under consideration of the approval	Added benefit not proven
B2	Despite disease-modifying therapy	TPC[b]	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Suitable comparator is natalizumab. The drug natalizumab is not approved for the present therapeutic indication (children and adolescents ≥ 10 and < 18 years). There is a discrepancy between the drugs approved for the therapeutic indication and those used in health care or recommended in the guidelines.
c: 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 recently conducted MRI.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IFNβ: interferon beta; MRI: magnetic resonance imaging; RRMS; relapsing remitting multiple sclerosis; TPC: treatment of physician's choice

The assessment described above deviates from that of the company, which derived an indication of major added benefit of fingolimod for research question A2 (in the company's dossier referred to as research question D). The company summarized research questions B1 and B2 (referred to as research question F in the company's dossier) and overall derived an indication of a major added benefit.

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

References for English extract

Please see full dossier assessment for full reference list.

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

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The full report (German version) is published under
https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-87-fingolimod-multiple-sclerosis-benefit-assessment-according-to-35a-social-code-book-v.11273.html