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Fingolimod (multiple sclerosis in children and adolescents) –

Addendum to Commission A18-87[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
D-KEFS	Delis-Kaplan Executive Function System
EDSS	Expanded Disability Status Scale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
Gd lesion	Gadolinium-enhancing lesion
IFN	interferon
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
MS	multiple sclerosis
PedsQL	Pediatric Quality of Life Inventory
RRMS	relapsing remitting multiple sclerosis
SDMT	Symbol Digit Modality Test
SOC	System Organ Class
SRT	Selective Reminding Test
TMT	Trail Making Test
VMI	Beery Developmental Test of Visual-Motor Integration

1 Background

On 6 May 2019 and on 13 May 2019, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A18-87 (Fingolimod – Benefit assessment according to §35a Social Code Book V) [1].

In its written comments from 19 April 2019 and after the oral hearing, the pharmaceutical company (hereinafter referred to as "the company") presented further analyses on the PARADIGMS study, which went beyond the information provided in the dossier [2,3].

The G-BA's commission comprised the following aspects:

- on research question A2 (highly active relapsing remitting multiple sclerosis [RRMS], change within the basic therapy): assessment of the data subsequently submitted on patient characteristics, risk of bias and adverse events (AEs) under psychiatric disorders and cardiac disorders and information on the handling of missing values on the Pediatric Quality of Life Inventory (PedsQL)
- on research question B1 (rapidly evolving severe RRMS, treatment-naive): assessment of the data subsequently submitted and of the company's operationalization of disability progression
- assessment of the data submitted after the oral hearing on cognitive function on research questions A1 and B1

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

The aspects commissioned by the G-BA are assessed in the following sections. The assessment is divided as follows:

- Section 2.1: assessment of the data subsequently submitted on research question A2 (highly active RRMS, change within the basic therapy)
- Section 2.2: assessment of the data subsequently submitted on research question B1 (rapidly evolving severe RRMS, treatment-naive)
- Section 2.3: data submitted after the oral hearing on cognitive function
- Section 2.4: Summarizing conclusion on the added benefit under consideration of the assessments in the previous sections

2.1 Analysis of the data subsequently submitted on research question A2 – highly active RRMS, change within the basic therapy

2.1.1 Patient characteristics – highly active RRMS, change within the basic therapy

In the dossier, the company presented no information on the patient characteristics of the relevant subpopulation (children and adolescents with highly active RRMS for whom change within the basic therapy is indicated). The company subsequently submitted this information in its comments. The patient characteristics of the subpopulation relevant for research question A2 are shown in Table 1.

Table 1: Characteristics of the subpopulation of children and adolescents with highly active RRMS with treatment switch within the basic therapy (research question A2) – RCT, direct comparison: fingolimod vs. IFN-β1a

Study Characteristics Category	**Fingolimod**	**IFN-β1a**
PARADIGMS	**N[a] = 9**	**N[a] = 11**
Age [years], mean (SD)	16 (2)	15 (2)
Age groups, n (%)		
≥ 10 to ≤ 12 years	1 (11)	1 (9)
> 12 to < 18 years	8 (89)	9 (82)
≥ 18 years	0 (0)	1 (9)
Sex [F/M], %	100/0	36/64
Ethnicity, n (%)		
White	8 (88.9)	10 (90.9)
Other[b]	1 (11.1)	1 (9.1)
Body weight [kg], n (%)		
≤ 40	1 (11.1)	0 (0)
> 40	8 (88.9)	11 (100.0)
Puberty status (Tanner stage), n (%)		
Prepubertal < 2	1 (11.1)	0 (0)
Pubertal (≥ 2)	8 (88.9)	11 (100.0)
EDSS at the start of the study		
Mean (SD)	1.78 (1.18)	1.86 (0.98)
Median [min; max]	2.00 [0.0; 3.5]	1.50 [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)	1.80 (1.18)	2.64 (1.68)
Time since occurrence of MS symptoms [years], mean (SD)	2.72 (2.06)	3.67 (2.40)
Number of relapses in the year before the start of the study, mean (SD)	1.7 (0.50)	1.5 (0.69)
Number of relapses in the last 2 years before the start of the study, mean (SD)	3.2 (1.39)	2.9 (1.04)

(continued)

Table 1: Characteristics of the subpopulation of children and adolescents with highly active RRMS with treatment switch within the basic therapy (research question A2) – RCT, direct comparison: fingolimod vs. IFN-β1a (continued)

Study Characteristics Category	Fingolimod	IFN-β1a
PARADIGMS	**N[a] = 9**	**N[a] = 11**
Pretreatment with MS therapy, n (%)		
Treatment-naive	0 (0)	0 (0)
Pretreated	9 (100.0)	11 (100.0)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)	0 (0)	1 (9.1)

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 Asian and other ethnicities.
EDSS: Expanded Disability Status Scale; F: female; Gd: Gadolinium; IFN-β: interferon beta; M: male; max: maximum; min: minimum; MD: mean difference; MS: multiple sclerosis; 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

Overall, the patient characteristics between the treatment groups were sufficiently balanced against the background of the small sample sizes. The only noteworthy difference was in the sex ratio: All children and adolescents in the fingolimod arm were female, whereas in the IFN-β1a arm of the study only 1 third of the children and adolescents were female.

2.1.2 Risk of bias and results on health-related quality of life and on side effects – highly active RRMS, change within the basic therapy

Risk of bias

The company presented no complete information on potentially biasing aspects for the relevant subpopulation A2 of the PARADIGMS study. Hence, the risk of bias of the results of all outcomes, except for the results on the outcome "overall survival", were rated as high in the dossier assessment.

In its comments, the company provided information on study discontinuations, observation periods and the handling of missing values on the outcome "PedsQL" for the relevant sub-population A2. Based on the information subsequently submitted, the risk of bias for the results of all relevant outcomes was rated as low for the present addendum.

This change in the assessment of the risk of bias had no consequence for the conclusion on the added benefit drawn in the dossier assessment for the following reasons: On the one hand, regardless of the risk of bias, a statistically significant result was observed only for one of 2 operationalizations of the outcome on which the hint of the added benefit was based (relapses). On the other, effects of different magnitudes, depending on the pretreatment

(glatiramer acetate or IFN-β1b), were shown in this operationalization. Overall, the certainty of conclusions was therefore still restricted on the basis of the available data, so that there is only a hint of an added benefit.

Health-related quality of life (PedsQL)

Regarding the outcome "health-related quality of life" (recorded with the PedsQL), the company's dossier contained no information on the extent to which missing values were imputed in the analysis. In its comments, the company subsequently submitted information on the handling of missing values of the PedsQL. According to the information provided in the comments, no values were imputed regarding the analyses on the data cut-off relevant here (end of study) [2]. Correspondingly, there was no potential bias of the results of the PedsQL caused by the imputation of missing values.

In addition, baseline values, changes, and variances in the individual study arms regarding the outcome "PedsQL" were missing in Module 4 of the company's dossier. These were subsequently submitted with the comments.

Table 2 shows the results on the PedsQL including the baseline values, changes and variances in the individual study arms subsequently submitted.

Table 2: Results (health-related quality of life) – RCT, direct comparison: fingolimod vs. IFN-β1a (research question A2 – highly active RRMS, change within the basic therapy)

Outcome category Outcome	Fingolimod			IFN-β1a			Fingolimod vs. IFN-β1a
Pretreatment	N[a]	Values at start of study mean (SD)	Change at end of study mean (SE)[b]	N[a]	Values at start of study mean (SD)	Change at end of study mean (SE)[b]	MD [95% CI]; p-value[b]
Health-related quality of life							
PedsQL, total score[c] (patient-reported)							
Glatiramer acetate	5	77.61 (19.30)	10.75 (6.31)	6	77.72 (14.19)	−6.63 (6.58)	17.38 [1.34 33.42]; 0.034
IFN-β1b	4	67.66 (7.18)	9.70 (7.67)	4	80.71 (10.52)	−1.24 (7.57)	10.94 [−7.56 29.43]; 0.241
Total	9			10			14.62 [2.50; 26.73]; 0.018[d]

a: Number of patients considered in the analysis for the calculation of the effect estimation; the values at the start of the study (possibly at other time points) may be based on other patient numbers.
b: Results of subgroup analysis regarding prior therapy (glatiramer acetate, IFN-β1a, IFN-β1b) in the subpopulation for research question A2; ANCOVA, adjusted for baseline value and with treatment, prior therapy, treatment x prior therapy, region, puberty status (Tanner stage) and number of relapses in the last 2 years before randomization.
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: analysis of covariance; CI: confidence interval; IFN-β: interferon beta; MD: mean difference; N: number of analysed patients; PedsQL: Pediatric Quality of Life Inventory; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; SD: standard deviation; SE: standard error; vs.: versus

In health-related quality of life, a statistically significant advantage of fingolimod was shown for the outcome "PedsQL total score" (patient-reported) for the mean difference pooled across the subpopulations by pretreatment (see Table 2). Hedges' g was estimated on the basis of the effect estimations to assess clinical relevance. The calculation showed an effect in the order of 1 standard deviation for the effect estimator (Hedges' g: 0.97 [−0.02; 1.96]). However, due to the small sample size, the estimations for the 95% confidence interval are uncertain and, regarding statistical significance, inconsistent with the result for the mean difference. The confidence interval was therefore not usable for assessing the relevance of the effect. Due to the described effect size (about 1 standard deviation), a hint of an added benefit was nonetheless derived for the outcome "PedsQL" in the present special data situation.

Side effects psychiatric disorders and cardiac disorders

In its dossier, the company presented no results on the specific AEs "psychiatric disorders" and "cardiac disorders" (both operationalized as System Organ Class [SOC] of the standardized Medical Dictionary for Regulatory Activities [MedDRA]). The company subsequently submitted these results in its comments. These are shown in Table 3.

Table 3: Results (mortality, morbidity, side effects; dichotomous) – RCT, direct comparison: fingolimod vs. IFN-β1a (research question A2 - highly active RRMS, change within the basic therapy)

Outcome category Outcome	Fingolimod		IFN-β1a		Fingolimod vs. IFN-β1a
	N	Patients with event n (%[a])	N	Patients with event n (%[a])	RR [95% CI]; p-value[a]
Psychiatric disorders (AEs, SOC)	9	1 (11.11)	11	1 (9.09)	1.22 [0.09 16.93]; 0.967
Cardiac disorders (AEs, SOC)	9	1 (11.11)	11	0 (0)	3.60 [0.16 79.01]; 0.340
a: Institute's calculation, unconditional exact test (CSZ method according to [4]). AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; IFN-β: interferon beta; N: number of analysed patients; n: number of patients with (at least one) event; RCT: randomized controlled trial; RR: relative risk; RRMS: relapsing remitting multiple sclerosis; SAE: serious adverse event; SOC: System Organ Class; vs.: versus					

No statistically significant difference was shown for either of the 2 outcomes "psychiatric disorders" and "cardiac disorders". This resulted in no hint of greater or lesser harm from fingolimod in comparison with IFN-β1a for either of these outcomes; an added benefit is therefore not proven.

2.1.3 Overall conclusion on the added benefit – highly active RRMS, change within the basic therapy

Table 4 summarizes the results that were considered in the overall conclusion on the added benefit on the subpopulation A2.

Table 4: Positive and negative effects from the assessment of fingolimod in comparison with IFN-β1a (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: hint of an added benefit	–
IFN-β: interferon beta, PedsQL: Pediatric Quality of Life Inventory; RRMS: relapsing remitting multiple sclerosis	

As in dossier assessment A18-87 [1], the assessment of the data subsequently submitted resulted in a hint of an added benefit for the outcome "relapses". In the category of health-related quality of life, the assessment of the data subsequently submitted on the PedsQL also resulted in a hint of an added benefit.

In the overall consideration, the data subsequently submitted did not change the result of the overall conclusion on the added benefit on the subpopulation A2 from dossier assessment

A18-87 [1]. As a result, there is a hint of an added benefit of fingolimod versus the appropriate comparator therapy IFN-β1a for pretreated children and adolescents with highly active RRMS for whom a change in the basic therapy is indicated. This hint was based on the observed advantages of fingolimod for the outcomes "confirmed relapses" and "health-related quality of life" (recorded with the PedsQL).

In the present data situation, the extent of the added benefit is non-quantifiable (see also dossier assessment A18-87 [1]).

2.2 Analysis of the data subsequently submitted on research question B1 – rapidly evolving severe RRMS, treatment-naive

The population relevant for research question B1 comprises treatment-naive children and adolescents with rapidly evolving severe RRMS.

In its dossier, the company presented a subpopulation of the PARADIGMS study, which it formed based on the criteria of presence of at least 2 relapses in the previous 12 months and at least 1 Gadolinium-enhancing lesion (Gd lesion). The company had not considered the necessary criterion "disability progression" (as a consequence of relapses). However, it is precisely this criterion that clinically defines rapidly evolving severe RRMS, thus distinguishing population B from population A (highly active RRMS). Based on the patient characteristics on the Expanded Disability Status Scale (EDSS), it was additionally shown that the EDSS total score was overall low on study inclusion with the range of the median including the value 0. The subpopulation presented by the company in the dossier included children and adolescents with no (EDSS = 0) or only minor impairment by disability on study entry. Overall, the subpopulation presented by the company in the dossier therefore did not address the population of interest of children and adolescents with rapidly evolving severe RRMS.

In its comments, the company presented a new operationalization of the subpopulation [2]. The only change compared with the subpopulation presented in the dossier was the exclusion of children and adolescents with an EDSS value of 0. Thus, the company again did not consider the necessary criterion of relapse-related disability progression. The company confirmed the non-consideration of this criterion in the oral hearing [5]. Hence, the necessary clinical differentiation from the group of children and adolescents with highly active but not rapidly evolving RRMS is also missing for the newly formed subpopulation. The results on the outcome "confirmed disability progression" in this subpopulation newly formed by the company support this assessment: This outcome occurred in only 1 patient during the observation period of about 2 years (in the fingolimod group, see Figure 2 in Appendix A.3).

In summary, the analyses subsequently submitted by the company were unsuitable for the assessment of subpopulation B1 (rapidly evolving severe RRMS). Hence, the assessment of the dossier assessment (added benefit not proven) has not changed. Regardless of this, the patient characteristics and results of the subpopulation presented by the company with the comments are presented in Appendix A.

2.3 Data on cognitive function submitted after the hearing

The PARADIGMS study examined cognitive function with a test battery of 5 tests. However, the company did not present any detailed results on this in its dossier or in the comments. These were subsequently submitted by the company after the oral hearing [3].

The test battery on cognition used in the PARADIGMS study comprised 5 tests: the Symbol Digit Modality Test (SDMT), the Beery Developmental Test of Visual-Motor Integration (VMI), the Trail Making Test (TMT), the Selective Reminding Test (SRT) and the Delis-Kaplan Executive Function System (D-KEFS) Category Fluency Test. According to the international paediatric multiple sclerosis (MS) study group, these tests reflect the core domains for the assessment of cognitive function in children [6].

The PARADIGMS study only required the tests SDMT and VMI to be conducted in all study centres, however. The other tests were only conducted in those study centres that agreed to do so. This is reflected in the different response rates of the tests. With the exception of the SDMT and the VMI tests, only a very small number and/or proportions of children and adolescents with large differences between the treatment groups were included in the analyses of the respective subpopulations. The results of the optional tests TMT, SRT and D-KEFS were therefore not informative. Although the response rates of the remaining 2 tests (SDMT, VMI) were sufficiently high, these tests do not cover all core domains for the assessment of cognitive function and therefore cannot provide an adequate representation of this outcome. Overall, the data subsequently submitted on cognitive function were therefore not informative.

Regardless of this, the results presented by the company showed no relevant difference between the treatment groups.

2.4 Summary

For research question A2, the assessment of the data subsequently submitted yielded, in addition to a hint of an added benefit in the outcome “relapses”, also a hint of an added benefit in the category “health-related quality of life” (PedsQL).

In the overall consideration, the data subsequently submitted by the company in the commenting procedure did not change the conclusion on the added benefit of fingolimod from dossier assessment A18-87.

The following Table 5 shows the result of the benefit assessment of fingolimod under consideration of dossier assessment A18-87 and the present addendum.

Table 5: Fingolimod – probability and extent of added benefit

Research question	**Therapeutic indication**	**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	Treatment of physician's choice[b]	Added benefit not proven
A2	for whom change within the basic therapeutic agents is indicated	**IFN-β1a** or IFN-β1b 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	**IFN-β1a** or IFN-β1b or glatiramer acetate under consideration of the approval	Added benefit not proven
B2	Despite disease-modifying therapy	Treatment of physician's choice[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; IFN-β: interferon beta; MRI: magnetic resonance imaging; RRMS: relapsing remitting multiple sclerosis

The G-BA decides on the added benefit.

3 References

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Appendix A – Analyses subsequently submitted by the company on research question B1 (treatment-naive children and adolescents with rapidly evolving severe RRMS)

A.1 – Patient characteristics of the subpopulation subsequently submitted by the company on research question B1

Table 6: Characteristics of the subpopulation subsequently submitted by the company on research question B1 – RCT, direct comparison: fingolimod vs. IFN-β1a

Study **Characteristics** **Category**	**Fingolimod**	**IFN-β1a**
PARADIGMS	**N[a] = 17**	**N[a] = 12**
Age [years], mean (SD)	15 (2)	15 (2)
Age groups, n (%)		
≥ 10 to ≤ 12 years	1 (6)	2 (17)
> 12 to < 18 years	16 (94)	10 (83)
Sex [F/M], %	76/24	67/33
Ethnicity, n (%)		
White	17 (100)	12 (100)
Body weight [kg], n (%)		
≤ 40	1 (5.9)	0 (0)
> 40	16 (94.1)	12 (100)
Puberty status (Tanner stage), n (%)		
Pubertal (≥ 2)	17 (100)	12 (100)
EDSS at the start of the study		
Mean (SD)	1.93 (1.07)	1.83 (0.49)
Median [min; max]	2.00 [1.0; 4.0]	2.00 [1.0; 3.0]
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)	0.50 (0.41)	0.84 (1.28)
Time since occurrence of MS symptoms [years], mean (SD)	1.08 (0.69)	1.70 (1.59)
Number of relapses in the year before the start of the study, mean (SD)	2.5 (0.72)	2.2 (0.39)
Number of relapses in the last 2 years before the start of the study, mean (SD)	3.5 (1.59)	3.1 (0.79)

(continued)

Table 6: Characteristics of the subpopulation subsequently submitted by the company on research question B1 – RCT, direct comparison: fingolimod vs. IFN-β1a (continued)

Study Characteristics Category	Fingolimod	IFN-β1a
PARADIGMS	**N[a] = 17**	**N[a] = 12**
Pretreatment with MS therapy, n (%)		
Treatment-naive	ND	ND
Pretreated	ND	ND
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)	0 (0)	1 (8.3)

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; IFN-β: interferon beta; M: male; max: maximum; MD: mean difference; min: minimum; MS: multiple sclerosis; 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

A.2 – Results on the subpopulation subsequently submitted by the company on research question B1

Table 7: Results (morbidity, annualized relapse rate, time to event) – RCT, direct comparison: fingolimod vs. IFN-β1a (subpopulation subsequently submitted by the company on research question B1)

Outcome category Outcome	Fingolimod			IFN-β1a			Fingolimod vs. IFN-β1a
	N	n/patient years	Annualized relapse rate [95% CI]	N	n/patient years	Annualized relapse rate [95% CI]	Rate ratio [95% CI]; p-value
Morbidity							
Relapses (EDSS-based)							
Annualized relapse rate	17	6/ND	0.11 [0.03; 0.49]	12	14/ND	0.84 [0.28; 2.53]	0.13 [0.02 0.93]; 0.043
		Median time to event in weeks [95% CI] Patients with event n (%)			Median time to event in weeks [95% CI] Patients with event n (%)		HR [95% CI]; p-value
Time to first relapse	17	NA 3 (17.6[a])		12	NA 5 (41.7[a])		0.29 [0.06 1.46]; 0.132

a: Institute's calculation.

CI: confidence interval; EDSS: Expanded Disability Status Scale; HR: Hazard Ratio; IFN-β: interferon beta; n: number of relapses; N: number of analysed patients; NA: not achieved; ND: no data; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; vs.: versus

Table 8: Results (mortality, morbidity, side effects) – RCT, direct comparison: fingolimod vs. IFN-β1a (subpopulation subsequently submitted by the company on research question B1)

Outcome category Outcome	Fingolimod		IFN-β1a		Fingolimod vs. IFN-β1a
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
Mortality					
All-cause mortality	17	0 (0)	12	0 (0)	–
Morbidity					
Change of the disability (EDSS-based)					
Confirmed progression	17	1 (5.9[b])	12	0 (0)	2.17 [0.10 49.07]; 0.566
Confirmed improvement	17	9 (52.9[b])	12	1 (8.3[b])	6.35 [0.92 43.74]; 0.014
Side effects					
AEs (additional information)	17	14 (82.4)	12	12 (100)	–
SAEs	17	3 (17.7)	12	0 (0)	5.06 [0.28 89.71]; 0.141
Discontinuation due to AEs	17	0 (0)	12	0 (0)	–
Infections and infestations (AE, SOC)	17	7 (41.2)	12	5 (41.7)	0.99 [0.41; 2.38]; > 0.999
Influenza like illness (AE, PT)	17	1 (5.9)	12	4 (33.3)	0.18 [0.02 1.39]; 0.060
Psychiatric disorders (AEs, SOC)	17	2 (11.8)	12	1 (8.3)	1.41 [0.14 13.86]; 0.822
Cardiac disorders (AEs, SOC)	17	1 (5.9)	12	1 (8.3)	0.71 [0.05 10.21]; 0.913

a: Institute's calculation, p-value using unconditional exact test (CSZ method according to [4]); possible discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.
b: Institute's calculation.

AE: adverse event; CI: confidence interval; EDSS: Expanded Disability Status Scale; IFN-β: interferon beta; N: number of analysed patients; n: number of patients with (at least one) event; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; RRMS: relapsing remitting multiple sclerosis; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 9: Results (health-related quality of life) – RCT, direct comparison: fingolimod vs. IFN-β1a (subpopulation subsequently submitted by the company on research question B1)

Outcome category Outcome	Fingolimod			IFN-β1a			Fingolimod vs. IFN-β1a
	N[a]	Values at start of study mean (SD)	Change at end of study mean (SE)	N[a]	Values at start of study 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)	17	73.91 (17.05)	7.97 (2.56)	12	78.62 (12.31)	6.28 (3.07)	1.70 [–6.63; 10.02]; 0.679

a: Number of patients considered in the analysis for the calculation of the effect estimation; the values at the start of the study (possibly at other time points) may be based on other patient numbers.
b: ANCOVA, adjusted for baseline value and with treatment, prior therapy, treatment x prior therapy, region, puberty status (Tanner stage) and number of relapses in the last 2 years prior to randomization.
c: A positive change from the start until the end of the study indicates improvement; a positive effect estimate indicates an advantage for fingolimod.
ANCOVA: analysis of covariance; CI: confidence interval; IFN-β: interferon beta; MD: mean difference; N: number of analysed patients; PedsQL: Pediatric Quality of Life Inventory; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; SD: standard deviation; SE: standard error; vs.: versus

A.3 – Graphic display on event time analyses (Kaplan-Meier curves) of the subpopulation subsequently submitted by the company on research question B1

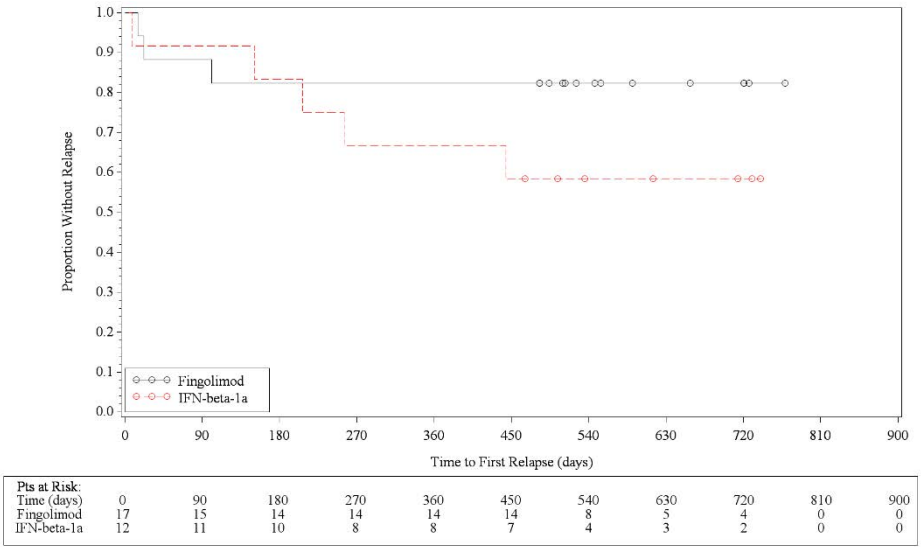

Figure 1: Kaplan-Meier curve on the outcome "time to first confirmed relapse" from the PARADIGMS study (subpopulation subsequently submitted by the company on research question B1) – database closure 14 July 2017

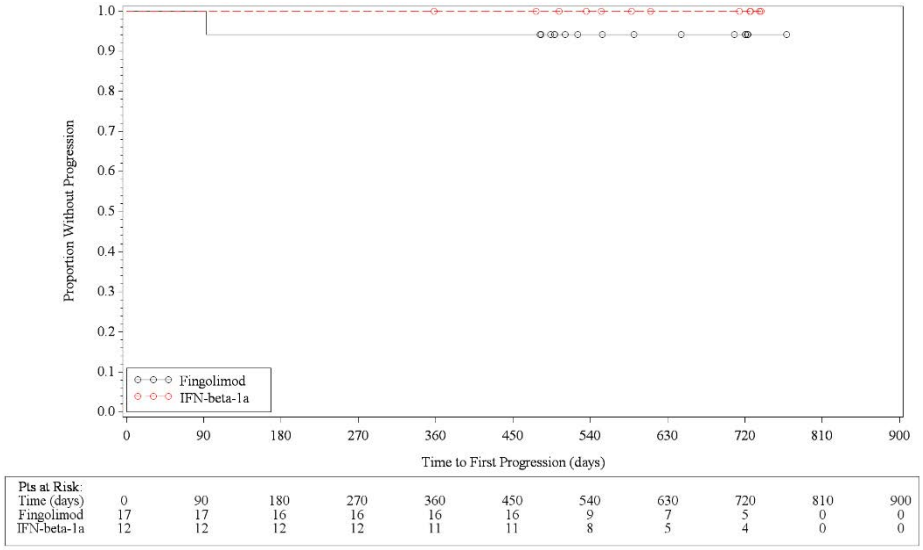

Figure 2: Kaplan-Meier curve on the outcome "time to first confirmed disability progression" from the PARADIGMS study (subpopulation subsequently submitted by the company on research question B1) – database closure 14 July 2017

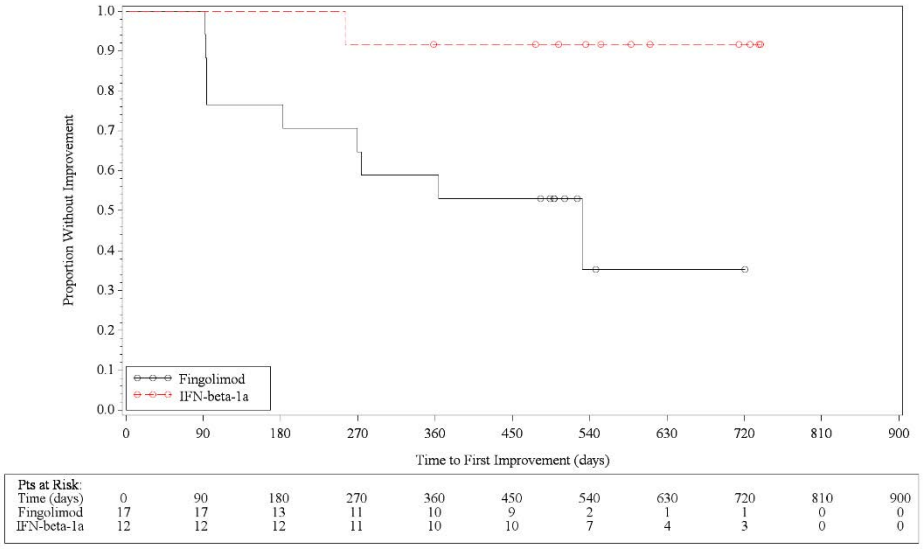

Figure 3: Kaplan-Meier curve on the outcome "time to first confirmed improvement of the disability" from the PARADIGMS study (subpopulation subsequently submitted by the company on research question B1) – database closure 14 July 2017