IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Fingolimod (Addendum to Commission A15-48)[1]

Addendum

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

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List of abbreviations

Abbreviation	Meaning
CI	confidence interval
EQ-5D VAS	European Quality of Life-5 Dimensions visual analogue scale
IFN-β	interferon beta
IM	intramuscular
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
SC	subcutaneous
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 12 April 2016, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A15-48 (Fingolimod [new therapeutic indication] – Benefit assessment according to §35a Social Code Book (SGB) V [1]).

The dossier assessment A15-48 was conducted due to a change in the therapeutic indication of fingolimod [1]. This change referred to patients with relapsing remitting multiple sclerosis. This change particularly clarified that fingolimod in this patient group is only approved in patients with highly active disease despite a full and adequate course of treatment with at least one disease-modifying therapy [2]. Consistently with its approach in several previous benefit assessments, the pharmaceutical company (hereinafter referred to as "the company") had defined a full and adequate course based on the treatment duration (at least 1 year) [3] and submitted corresponding data on the TRANSFORMS study. These analyses corresponded to the ones from a previous assessment and resulted in no added benefit of fingolimod [1,4].

With its written comments [5,6] and subsequent to the oral hearing [7], the company submitted further analyses on the TRANSFORMS study. To be able to make a decision on the added benefit of fingolimod, the G-BA commissioned IQWiG to assess the data subsequently submitted, particularly regarding the question whether the analyses submitted by the company could be used for answering the research question.

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

2 Assessment

2.1 Analyses subsequently submitted

With its written comments, the company subsequently submitted new analyses on the known TRANSFORMS study on the comparison of fingolimod with interferon beta 1a (IFN-β1a) intramuscular (IM) [6]. All patients with highly active disease who were pretreated with disease-modifying therapy were included in these analyses. These data differed from the data presented in the dossier in 2 aspects:

1) Whereas in the dossier the company only included patients with a pretreatment duration of at least 1 year (operationalization of a full and adequate course by the company), patients with any pretreatment duration (from 1 day) were included in the data subsequently submitted.
2) The analyses in the dossier only referred to patients with glatiramer acetate pretreatment. In the company's view, the treatment in the comparator group (IFN-β1a IM) used in the TRANSFORMS study concurred with the appropriate comparator therapy only for these patients. With the comments, however, the company submitted analyses for patients with any kind of pretreatment, on the one hand a joint analysis, and on the other 4 separate analyses according to pretreatment (IFN-β1a IM, IFN-β1a SC, IFN-β1b SC, glatiramer acetate).

After the oral hearing, the company subsequently submitted further analyses on the TRANSFORMS study [7]. These differed from the data subsequently submitted with the written comments as follows:

1) Patients with a pretreatment duration of less than 3 months were excluded.
2) Only a joint analysis including any kind of pretreatment was presented. There were no separate analyses according to pretreatment (IFN-β1a SC, IFN-β IM, IFN-β1b SC, glatiramer acetate).

2.2 Relevance of the data subsequently submitted

Neither the data subsequently submitted by the company with the written comments nor the data subsequently submitted after the oral hearing were relevant for the benefit assessment of fingolimod.

- In the **data subsequently submitted with the written comments**, the criterion "full and adequate" was not considered at all, because all pretreated patients were generally included. Treatment-naive and pretreated patients with any pretreatment duration were included in the TRANSFORMS study. A complete course of pretreatment was not a prerequisite for the latter group. Correspondingly, patients with any pretreatment duration, i.e. also patients who had received disease-modifying treatment only for 1 day, were included in the TRANSFORMS study. It could be assumed from the company's analyses

subsequently submitted that the pretreatment duration was less than 1 year in about 50% of the patients with glatiramer acetate pretreatment: Whereas in the dossier 42 patients were included in the analysis (pretreatment duration at least 1 year), 85 patients were included in the analyses subsequently submitted (any pretreatment duration). Hence the data presented by the company with the written comments were potentially dominated by patients with incomplete pretreatment.

- In contrast to the data presented in the dossier and the ones subsequently submitted with the written comments, the **data subsequently submitted after the oral hearing** contained no analysis of the results depending on the type of pretreatment (further details on this can be found below under "No implementation of the appropriate comparator therapy"). Furthermore, the company addressed the criterion "full and adequate", but did so only in an inadequate way because of the general use of the criterion "pretreatment duration > 3 months". In its dossier, the company had only considered those patients to have received adequate pretreatment whose pretreatment duration had been at least 1 year. According to the company, this operationalization was "meaningful and, as shown, scientifically and clinically justified" [3]. This approach was principally followed in dossier assessment A15-48. It was additionally pointed out that, in individual cases, a treatment duration of less than 1 year can be considered to be full and adequate, but that the non-consideration by the company did not compromise the result of the assessment due to the exceptional character [1]. The company described in its dossier and in its comments that the completeness of the pretreatment has to be assessed on an individual basis in these cases [3,5], but with the general use of the criterion of 3 months did not consider this in its analyses. It could be derived from the company's analyses that the approval criterion "highly active disease" was mostly determined on the basis of clinical criteria (relapses) of up to one year before, and only in very few cases on the basis of imaging techniques. It could therefore be assumed that the diagnosis "highly active" in the patients with less than 1 year of pretreatment mostly referred to a time point *before the start of the prior therapy*, thus having been the reason for the prior therapy, but not its result. As a result, it was not regularly ensured that the patients in the TRANSFORMS study with less than 1 year of pretreatment concurred with the research question (and the approval) of fingolimod; and the shorter the treatment duration was, the more this was the case. Hence at least additional sensitivity analyses for a pretreatment duration of 6 and 9 months would have been required, and (also for the criterion of 3 months), in particular, not as a joint analysis across all types of prior therapy, but separately for any kind of prior therapy.

No implementation of the appropriate comparator therapy

In its original dossier, the company had only considered patients with glatiramer acetate pretreatment in its analysis on patients with full and adequate pretreatment. The company had assumed that the drug IFN-β1a used in the TRANSFORMS study constituted an appropriate comparator therapy only for those patients.

In its analyses subsequently submitted, in contrast, the company considered any type of pretreatment. In its written comments, it combined this with arguments proposing the change of the appropriate comparator therapy. Specifically, the company described that any disease-modifying treatment (treatment escalation, change within the basic therapy, change within the interferon beta class, continuation of ongoing treatment) constitutes a relevant treatment option, which should be decided on an individual basis. The company's reasoning is contradictory in itself, however. Particularly, if the company argues in favour of individually optimized treatment under consideration of prior therapies, side effects, etc., then the "forced" specification of treatment with IFN-ß1a IM without consideration of individual criteria (as in the TRANSFORMS study) is not adequate. Following the company's arguments, the TRANSFORMS study would be principally irrelevant for the benefit assessment.

There might be an exception for patients with glatiramer acetate pretreatment because for these patients, in the case of highly active disease despite full and adequate pretreatment with glatiramer acetate, the switch to interferon treatment would be a meaningful and commonly used treatment option. Analyses on these patients were available in the documents subsequently submitted with the written comments, but were missing in the documents subsequently submitted by the company after the oral hearing. The company did not justify this.

This was inadequate not only with regard to content, but also methodologically because it was shown in the documents subsequently submitted with the written comments that the type of pretreatment is a strong effect modifier [6]. Appendix A contains Kaplan-Meier curves for the multiple sclerosis-related outcome "relapses" for illustration. A statistically significant result in favour of fingolimod was only shown for patients with IFN-β1a pretreatment (who continued this treatment in the TRANSFORMS study) (Figure 1 and Figure 2). These patients constituted 64% of the total population. Hence the result of the joint analysis across all types of pretreatment was dominated exactly by the patients who were certainly irrelevant both for the appropriate comparator therapy specified by the G-BA and by the comparator therapy proposed by the company. No noticeable difference between the treatment groups was shown for patients who switched treatment within the same substance class (i.e. from IFN-β1b to IFN-β1a, Figure 3); the result was not statistically significant.

A reverse effect to the disadvantage of fingolimod was shown in patients with glatiramer acetate pretreatment, however; the result was not statistically significant (Figure 4). Moreover, results to the disadvantage of fingolimod were found for other relevant outcomes in this group. There was a statistically significant disadvantage in the outcome "health status"

(European Quality of Life-5 Dimensions visual analogue scale [EQ-5D VAS], difference of the change in comparison with baseline: −10.5 with 95% confidence interval [CI] [−16.4; −4.50]). This difference was also relevant (Institute's calculation of Hedges' g: −0.75 with 95% CI [−1.20; −0.31]). Furthermore, the recording of adverse events in the organ class "neurologic disorders" showed a statistically significant result to the disadvantage of fingolimod (patients with event: 19 [52.8%] versus 14 [28.6%]; p = 0.026). Overall it can therefore not be excluded that lesser benefit of fingolimod versus IFN β1a IM would result for patients with glatiramer acetate pretreatment from the results of the TRANSFORMS study if the criterion "highly active disease despite full and adequate pretreatment" was considered adequately.

2.3 Summary

The data presented by the company were unsuitable for the benefit assessment of fingolimod versus the appropriate comparator therapy. This applies both to the data subsequently submitted with the written comments and after the oral hearing, and both to the appropriate comparator therapy specified by the G-BA and to the new comparator therapy proposed by the company in the comments.

In summary, the data subsequently submitted by the company did not change the assessment of dossier assessment A15-48: The added benefit of fingolimod for patients with relapsing remitting multiple sclerosis is not proven.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Fingolimod (neues Anwendungsgebiet): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A15-48 [online]. 26.02.2016 [Accessed: 01.03.2016]. (IQWiG-Berichte; Volume 368). URL: https://www.iqwig.de/download/A15-48_Fingolimod-neues-Anwendungsgebiet_Nutzenbewertung-35a-SGB-V.pdf.

2. Novartis Pharma. Gilenya: Fachinformation [online]. 1.2016 [accessed: 26.04.2016]. URL: http://www.fachinfo.de.

3. Novartis Pharma GmbH. Fingolimod (Gilenya): Dossier zur Nutzenbewertung gemäß § 35a SGB V; Modul 4 A; Patienten mit schubförmig-remittierender Multipler Sklerose mit hochaktiver Erkrankung, die nicht auf einen vollständigen und angemessenen Zyklus mit mindestens einer krankheitsmodifizierenden Therapie angesprochen haben [online]. 20.11.2015 [accessed: 26.04.2016]. URL: https://www.g-ba.de/downloads/92-975-1234/2015-11-20_Modul4A_Fingolimod.pdf.

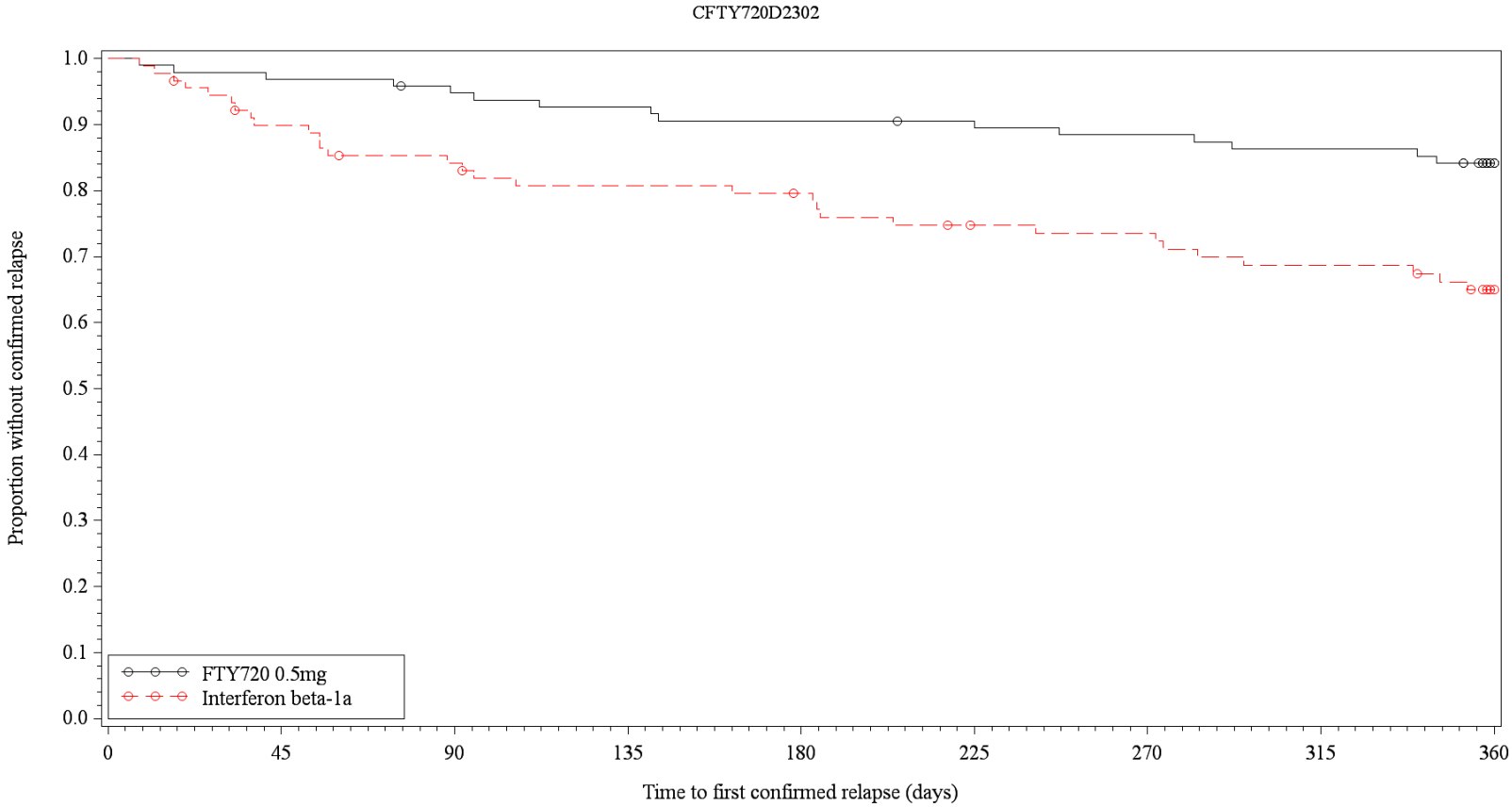
4. Gemeinsamer Bundesausschuss. Fingolimod (neues Anwendungsgebiet) - Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII [online]. 18.12.2014 [accessed: 26.04.2016]. URL: https://www.g-ba.de/downloads/39-261-2129/2014-12-18_AM-RL-XII_Fingolimod_nAWG_2014-07-01-D-116_BAnz.pdf.

5. Novartis Pharma GmbH. Stellungnahme zum IQWiG-Bericht Nr. 368: fingolimod (neues Anwendungsgebiet); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A15-48. 2016: [Soon available under: https://www.g-ba.de/informationen/nutzenbewertung/202/#tab/beschluesse in the document "Zusammenfassende Dokumentation"].

6. Novartis Pharma GmbH. Fingolimod (Gilenya): Ergänzende Daten zur TRANSFORMS-Studie; Auswertungen zu vorbehandelten Patienten mit jeglicher Vorbehandlungsdauer [unpublished]. 2016.

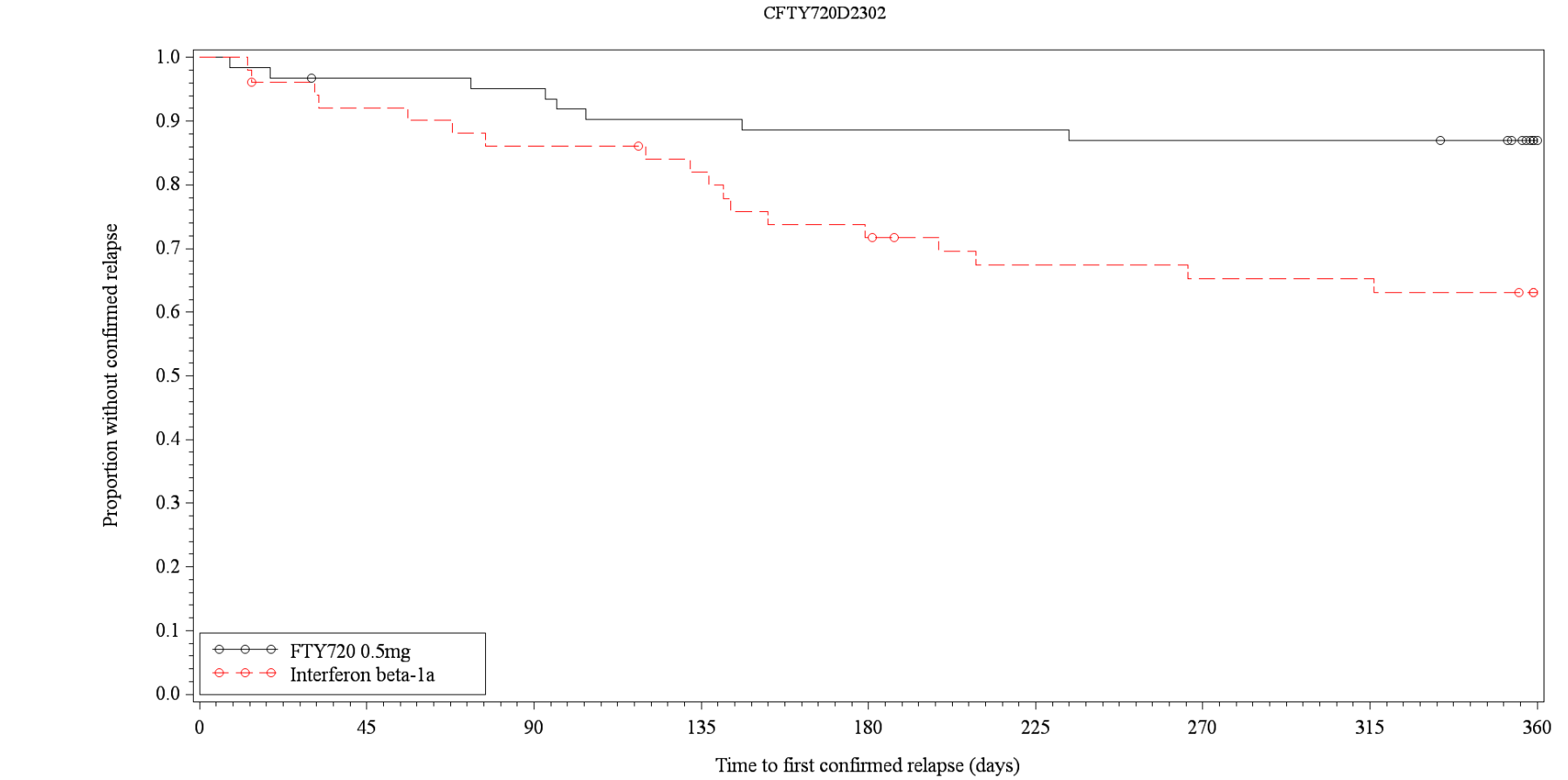
7. Novartis Pharma GmbH. Fingolimod (Gilenya): Ergänzende Daten zur TRANSFORMS-Studie; Auswertungen zu vorbehandelten Patienten mit Vorbehandlungsdauer 3 Monate oder länger [unpublished]. 2016.

Appendix – Kaplan-Meier curves on the outcome "relapses"



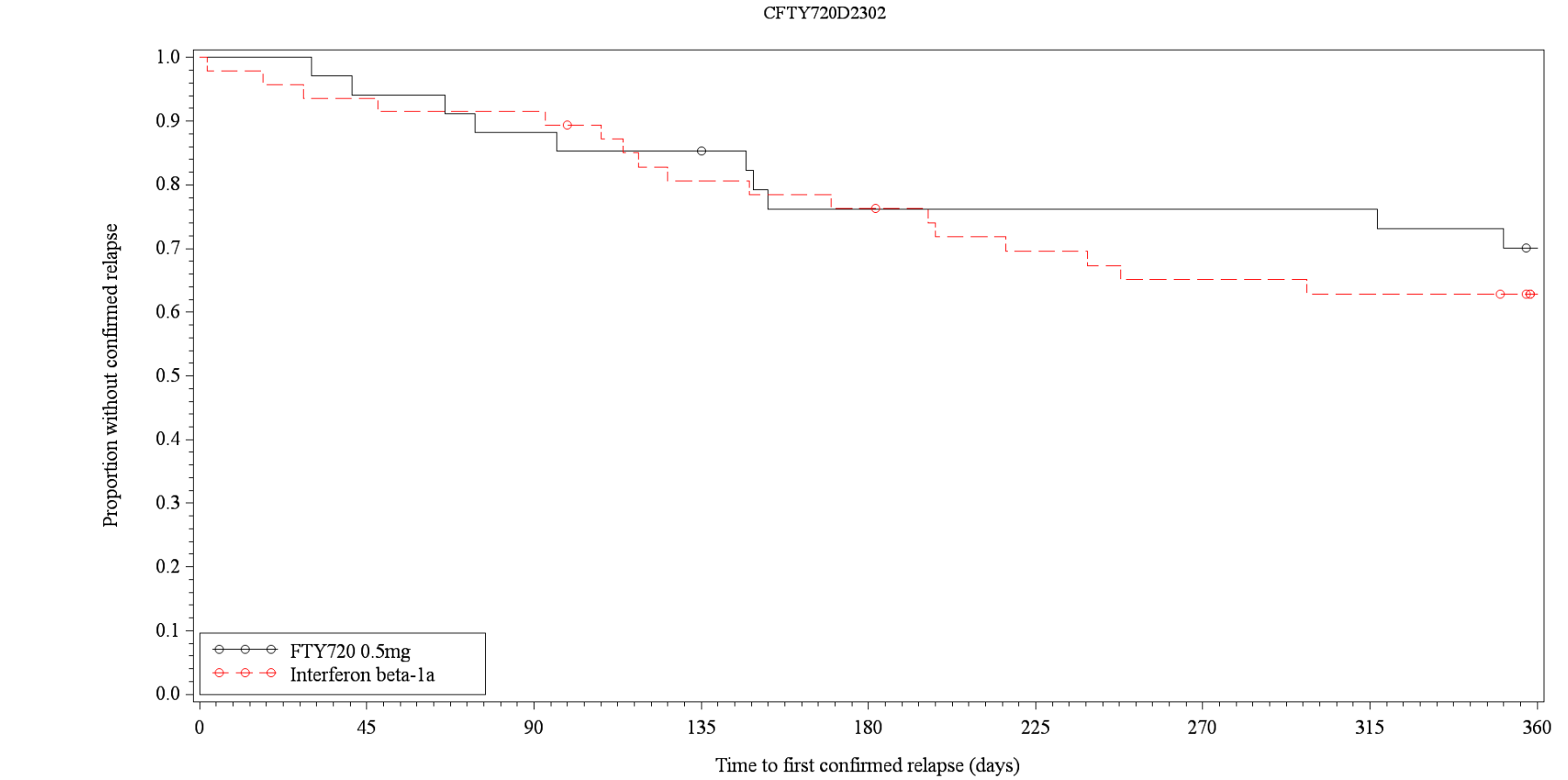
Pts at Risk:									
Time (days)	0	45	90	135	180	225	270	315	360
FTY720 0.5 mg	96	93	90	88	86	85	83	81	68
IFN beta-1a im	90	79	73	69	67	61	60	56	48

Figure 1: Kaplan-Meier curve of the time to first relapse (patients pretreated with IFN-β1a IM)



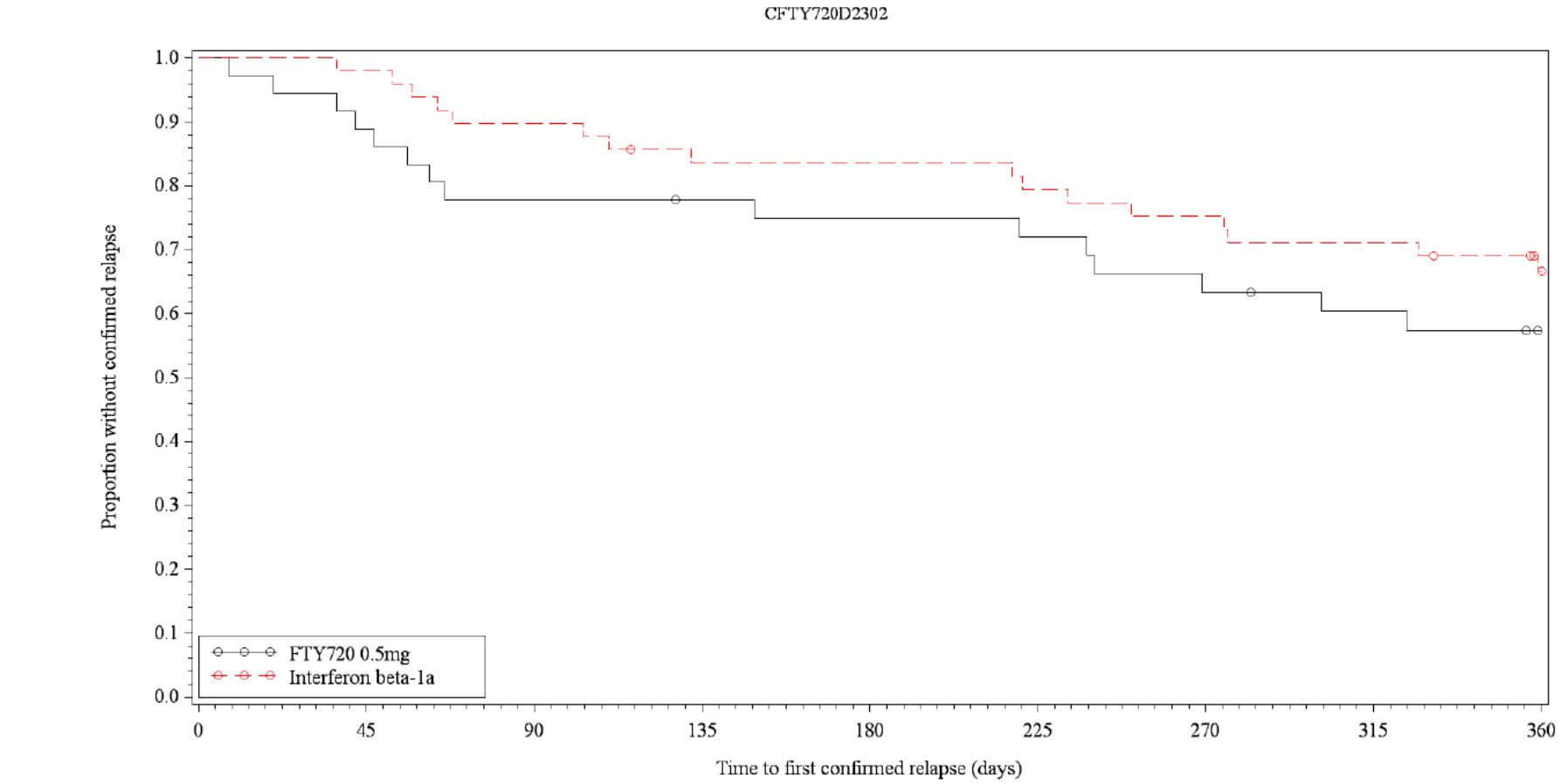
Pts at Risk:									
Time (days)	0	45	90	135	180	225	270	315	360
FTY720 0.5 mg	62	59	58	55	54	54	53	53	44
IFN beta-1a im	51	46	43	40	35	31	30	30	26

Figure 2: Kaplan-Meier curve of the time to first relapse (patients pretreated with IFN-β1a SC)



Pts at Risk:									
Time (days)	0	45	90	135	180	225	270	315	360
FTY720 0.5 mg	34	32	30	29	25	25	25	25	22
IFN beta-1a im	47	44	43	37	35	31	29	28	24

Figure 3: Kaplan-Meier curve of the time to first relapse (patients pretreated with IFN-β1b)



Pts at Risk:									
Time (days)	0	45	90	135	180	225	270	315	360
FTY720 0.5 mg	36	32	28	27	26	25	22	20	17
IFN beta-1a im	49	48	44	40	40	38	36	34	29

Figure 4: Kaplan-Meier curve of the time to first relapse (patients pretreated with glatiramer acetate)