Amsterdam, 11 November 2021
EMA/CHMP/716292/2021
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Gilenya

fingolimod

Procedure no: EMEA/H/C/002202/P46/039

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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1. Introduction

On 5th of August 2021, the MAH submitted a final report of Gilenya study CFTY720D1401 for the 14 pediatric patients that completed this study in Japan, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that CFTY720D1401 is part of a clinical development program.

2.2. Information on the pharmaceutical formulation used in the study

Gilenya is already indicated in Europe as single disease modifying therapy in highly active relapsing remitting Multiple Sclerosis for the following groups of adult patients (since 2011) and paediatric patients aged 10 years and older (since 2018) :

-Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy or

-Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

Gilenya is available as capsules of 0.5 mg and 0.25 mg (for pediatric patients ≤40 kg) which are taken orally once-daily. Same formulation was used in the present study.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for the 14 pediatric MS patients that were included in CFTY720D1401 (hereafter referred to as D1401). Data in adult were not assessed since only pediatric data are concerned in this Preliminary assessment report for paediatric studies submitted in accordance with article 46 of regulation.

2.3.2. Clinical study

Study D1401: a drug use investigation (all-case surveillance) study conducted in Japan

Description

Study D1401 was conducted jointly by Novartis and Mitsubishi Tanabe Pharma Corporation, based on the conditions for approval of fingolimod in Japan. Study D1401 was a drug use-results survey in Japanese MS patients (all-case surveillance) that started in November 2011 when the drug was launched in Japan.

In study D1401, a total 6,765 patients were enrolled. After removing the number of patients with multiple registration before and after hospital transfer, 6,642 patients as the actual number of patients enrolled. It was agreed with Pharmaceuticals and Medical Devices Agency (PMDA) that CRFs would be

collected from 1,792 patients who started treatment with fingolimod by May 31, 2013. Data from these 1,792 patients were analyzed and reported in the CSR. Of these, there were 14 pediatric MS patients (defined as below 18 years of age at the study participation).

Methods

Objective(s)

The primary purpose of the study was to collect and evaluate information on the safety and efficacy of fingolimod in patients with multiple sclerosis under long-term clinical use in Japan

Study population /Sample size

The overall population was defined as one consisting of patients whose CRFs were collected. This population consisted of patients who received Gilenya/Imusera for the first time and patients who had a history of use of an investigational drug/post-marketing clinical study drug containing the same active ingredient as Gilenya/Imusera.

Treatments

Outcomes/endpoints

Efficacy analysis set:

The efficacy analysis set is defined as a population consisting of patients for efficacy analysis in the overall population. No summary/analysis was performed for this population.

Statistical Methods

N/A

Results

Recruitment/ Number analysed

A total 6,765 patients were enrolled. Of these, there were 14 pediatric MS patients (defined as below 18 years of age at the study participation).

Baseline data

Patients enrolled in the study D1401 included 14 pediatric patients (3 males and 11 females) with RRMS. At treatment initiation, these patients were 12-17 years of age with mean and median age of 15.6 and 16, respectively and a mean/median body weight of 53.3/50.4 kg (no patient had a bodyweight $\leq$40 kg).

Seven patients completed the study duration of 2 years. The remaining 7 patients discontinued the study due to reasons as reported in the case report form (CRF): Adverse event(s) (2 patients), this includes lymphocyte count decrease (non-serious) and optic neuritis (serious), Lack of efficacy (1 patient), Transferred to another hospital (2 patients) or other (2 patients).

Table 6-1 Demographic summary (Pediatric Safety set)

		FTY720 N=14
Age at first study treatment (years)		
	N	14
	Mean	15.6
	SD	1.74
	Minimum	12
	Median	16.0
	Maximum	17
Age group (years), n (%)		
	<10	0
	>=10 to 12	1 (7.1)
	>12 to <=14	2 (14.3)
	>14 to <=16	5 (35.7)
	>16 to <18	6 (42.9)
Sex, n (%)		
	Male	3 (21.4)
	Female	11 (78.6)
Weight (kg)		
	n	13
	Mean	53.3
	SD	9.79
	Minimum	42
	Median	50.4
	Maximum	78
Weight group (kg), n (%)		
	<=40	0
	>40	13 (92.9)
	Missing/Unknown	1 (7.1)
Height (cm)		
	n	13
	Mean	160.0
	SD	5.42
	Minimum	151
	Median	157.9
	Maximum	169
BMI (kg/m^2)		
	n	13
	Mean	20.8

Efficacy results

Summary of efficacy results

The following sections present the descriptive data of the key efficacy measures of the survey (Clinical relapse, Physician's assessment of efficacy and Expanded Disability Status Scale (EDSS)) in the 14 pediatric patients.

Annualized relapse rate

Study D1401 was an observational study, hence no confirmation of relapse was conducted and ARR were calculated based on ALL relapses as reported by the investigators. In the 14 pediatric patients, before the start of treatment with fingolimod, the annualized relapse rate (ARR) was 1.93 (95% Confidence interval (CI) 1.33 - 2.81). The ARRs at 12 months and 24 months after treatment with fingolimod were 0.52 (95% CI 0.24 - 1.13) and 0.35 (95% CI 0.17 - 0.71) respectively (Table 6-5).

Table 6-5 **Annual relapse rates at respective assessment time points (Pediatric Efficacy analysis set)**

	Number of patients#	Total observation duration (day)	Relapse frequency	Annual relapse rate	95%CI (lower limit - upper limit)
Before start of treatment with Gilenya/Imusera	14	5113.5	27	1.93	1.33 - 2.81
From start of treatment with Gilenya/Imusera - Month 12	14	4231	6	0.52	0.24 - 1.13
From start of treatment with Gilenya/Imusera - Month 24	14	7405	7	0.35	0.17 - 0.71
From start of treatment with Gilenya/Imusera - last assessment*	14	7405	7	0.35	0.17 - 0.71

Population: patients with relapse assessments before and after treatment with Gilenya/Imusera (incl. relapse-free patients)
* Including data with unknown relapse dates

The Applicant concluded that due to the very limited number of patients, the observed ARR has a high variation, however the reduction of relapse activity after treatment was overall consistent to what has been observed in the pediatric Phase 3 trial D2311.

Physician's efficacy evaluations

The study included an efficacy measure of physician's evaluation, which is a comprehensive evaluation of multiple sclerosis symptoms/findings (considering recurrence rate/severity of recurrence, EDSS, neurological findings, MRI findings, etc.) by the physician to categorize the patient as a "responder" or "non-responder" to fingolimod treatment. The assessment was performed at the time points of 6 months, 12 months, 24 months and last observation after treatment with fingolimod.

Of the 14 pediatric patients, 10, 9 and 8 patients at Months 6, 12 and 24 respectively, were assessed as "responders". At Months 6, four patients were categorized as "not assessable". No non-responders were identified at any time point (please refer to Table 6-6).

Table 6-6 **Physician's assessments of efficacy (Pediatric Efficacy analysis set)**

Time of assessments	Physician's assessments of efficacy						Physician's assessments of efficacy (other than "not assessable")					
	Population	Responders		Non-responders		Not assessable	Population	Responders		Non-responders		
	Number of patients	Number of patients (%)		Number of patients (%)		Number of patients (%)	Number of patients	Number of patients (%)		Number of patients (%)		
Month 6	14	10	(71.4)	0	(0.0)	4 (28.6)	10	10	(100.0)	0	(0.0)	
Month 12	9	9	(100.0)	0	(0.0)	0 (0.0)	9	9	(100.0)	0	(0.0)	
Month 24	8	8	(100.0)	0	(0.0)	0 (0.0)	8	8	(100.0)	0	(0.0)	
Last observation	14	11	(78.6)	0	(0.0)	3 (21.4)	11	11	(100.0)	0	(0.0)	

The physician subjectively determines responders/non-responders based on the evaluation of multiple sclerosis symptoms/finding. In addition, "not assessable" was provided as an option in the Case Report Form (CRF).

The evaluation information at Month 24 describes information from Month12 to 24 months

EDSS

The Expanded Disability Status Scale (EDSS) evaluations were performed at the start of treatment with Gilenya/Imusera, every 3 months after the start of treatment with Gilenya/Imusera and treatment discontinuation based on expanded disability statuses of MS observed within routine care.

Of the 8 pediatric patients for whom this assessment is available at the start of treatment, the mean EDSS score was 2.06 (median 1.75, minimum 0 and maximum 5.5), the average EDSS score throughout the survey remained in the range of 0.92 – 1.44 with fingolimod treatment. Of note, the number of patients with available data is very low; however, there is no trend of worsening in EDSS over time (Table 6-7).

Overall, data collected from these limited number of pediatric patients, in an observational setting, showed results consistent with the known benefits of fingolimod in this population according to the applicant.

Table 6-7 **EDSS at the start and during Gilenya/Imusera administration period (Pediatric Efficacy analysis set)**

	Observed values							
	Number of patients#	Mean EDSS	SD	Min	Q1	Median	Q3	Max
At start	8	2.06	1.917	0.0	0.50	1.75	3.25	5.5
Month 3	8	1.44	2.195	0.0	0.00	0.00	3.00	5.5
Month 6	8	1.19	2.235	0.0	0.00	0.00	2.00	5.5
Month 9	6	1.33	2.066	0.0	0.00	0.00	4.00	4.0
Month 12	4	1.00	2.000	0.0	0.00	0.00	2.00	4.0
Month 15	6	0.92	1.625	0.0	0.00	0.00	1.50	4.0
Month 18	6	0.92	1.625	0.0	0.00	0.00	1.50	4.0
Month 21	5	1.10	1.746	0.0	0.00	0.00	1.50	4.0
Month 24	3	1.33	2.309	0.0	0.00	0.00	4.00	4.0
Last observation	8	1.19	1.811	0.0	0.00	0.00	2.75	4.0

Population: patients with data at the start and at least one data after the start of treatment with Gilenya/I musera

CHMP comments:

This drug used study (CFTY720D1401 or D1401) was conducted only in Japan. This study is submitted in accordance with Article 46 of Regulation (EC) No1901/2006 and therefore only paediatric patients are considered. 14 paediatric patients were included (3 males and 11 females) with RRMS. All these patients were between 12 and 17 year old at initiation. They were all with a body weight > 50 kg and were treated at the dose of 0,5 mg/day.

Study D1401 was an observational study. Some efficacy parameters were collected at 6 months, 1 year, 2 years from the start of treatment with fingolimod: relapse rate, EDSS, MRI findings.

7/14 patients completed the study duration of 2 years. Reasons of discontinuation for the 7 other patients were: Adverse event(s) (2 patients: this includes lymphocyte count decrease (non-serious) and optic neuritis (serious), Lack of efficacy (1 patient), Transferred to another hospital (2 patients) or other (2 patients). Of note, 9 patients were treated during one year.

These data are informative only, it is difficult to conclude anything regarding efficacy considering the very limited number of Japanese patients and the design of the study e.g. open with no comparative arm.

Overall these very limited data are consistent with efficacy results of the pivotal study in paediatric patients more than 12 year-old and with a body weight > 50 kg (PARADIGMS D2311) on MS relapse.

Safety results

The median exposure for these 14 patients was 626.5 days, the mean (min, max) exposure was 482.6 (21, 720) days, 9 and 6 patients have exposure for at least 1 and 2 years, respectively.

Adverse events

8/14 pediatric patients reported at least one adverse event. The most frequently affected System organ class (SOCs) were Investigations (4 (28.6%) patients) and Nervous system disorders (4 (28.6%) patients) followed by respiratory, thoracic and mediastinal disorders (3 (21.4%) patients).

Serious adverse events

Three of the 14 patients experienced SAEs. Two patients reported SAEs under the SOC of nervous system disorders (preferred Term (PT) of Multiple sclerosis and Optic neuritis, respectively), 1 patient reported SAEs under the SOC of Investigations (PT Lymphocytes count decreased) (Table 6-10).

Table 6-10 Serious adverse events, regardless of study treatment relationship, by primary system organ class, preferred term (Pediatric Safety set)

Primary system organ class Preferred term	FTY720 N=14 n (%)
-Any primary system organ class	
-Total	3 (21.4)
Investigations	
-Total	1 (7.1)
Lymphocyte count decreased	1 (7.1)
Nervous system disorders	
-Total	2 (14.3)
Multiple sclerosis relapse	1 (7.1)
Optic neuritis	1 (7.1)

There were no deaths reported in this group of 14 pediatric patients.

CHMP comments:

Analysis of PTs by SOC of adverse effects reported in the 14 pediatric patients retrieves mainly central nervous system adverse effects, non-serious investigations AE, mainly decreased lymphocytes, respiratory, thoracic and mediastinal disorders.

The reported adverse events are consistent with the EU SmPC and the RMP of fingolimod.

2.3.3. Discussion on clinical aspects

This drug used study (CFTY720D1401 or D1401) was conducted only in Japan. This study is submitted in accordance with Article 46 of Regulation (EC) No1901/2006 and therefore only paediatric patients are considered. 14 paediatric patients were included (3 males and 11 females) with RRMS. All these patients were between 12 and 17 year old at initiation. They were all with a body weight > 50 kg and were treated at the dose of 0,5 mg/day.

Study D1401 was an observational study. Some efficacy parameters were collected at 6 months, 1 year, 2 years from the start of treatment with fingolimod: relapse rate, EDSS, MRI findings.

7/14 patients completed the study duration of 2 years. 9 patients were treated during one year.

Considering the very limited number of Japanese patients and the design of the study e.g. open study with no comparative arm, it is difficult to conclude anything regarding efficacy considering.

Overall these very limited data are consistent with efficacy and safety results of the pivotal study in paediatric patients (PARADIGMS) on MS relapse.

To remember, D2311 study enrolled patients from 10 to 18 years old. The number of patients aged 10-12 years, with a weight <40 kg and / or pre-pubertal (<2 Tanner stage scoring) enrolled in this study was underrepresented. Further long term safety data was requested especially in this specific population. No new information was reported in this D1401 study since the 14 patients were more than 12-year-old and > 40 kg.

3. Rapporteur's overall conclusion and recommendation

This Japanese open drug use study is submitted in accordance with Article 46 of Regulation (EC) No1901/2006 and therefore only paediatric patients are considered. 14 MS paediatric patients were included: these patients were between 12 and 17 year old at initiation with a body weight > 50 kg and were treated at the dose of 0,5 mg/day. 7/14 patients completed the study duration of 2 years. 9 patients were treated during one year. Data are therefore limited. No new information was reported regarding the 14 patients observation in this drug use study.

The benefit/risk balance of Gilenya remains positive in the approved indications.

☒ **Fulfilled:**

No regulatory action required.