Amsterdam, 13 November 2025
EMADOC-1700519818-2443340
Human Medicines Division

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

Gilenya

Fingolimod

Procedure no: EMA/PAM/0000295236

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
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Status of this report and steps taken for the assessment			
Current step[1]	**Description**	**Planned date**	**Actual Date**
☐	Start date	15 September 2025	15 September 2025
☐	CHMP Rapporteur AR	20 October 2025	20 October 2025
☐	CHMP comments	3 November 2025	23 October 2025
☐	Updated CHMP Rapporteur AR	6 November 2025	n/a
☒	CHMP outcome	13 November 2025	13 November 2025

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

Administrative information

Procedure resources	
Rapporteur	**Alexandre Moreau**

Table of contents

1. Introduction

On 2 September 2025, the MAH submitted a completed paediatric study for Gilenya (CFTY720D2419), 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

In the EU/EEA, Gilenya (fingolimod) was granted marketing authorization on 17- Mar-2011 as single disease modifying therapy in highly active relapsing remitting multiple sclerosis in adult patients. On 22-Nov-2018, the indication was extended to include pediatric patients aged 10 years and older. In China, Gilenya was granted marketing authorization on 12- Jul-2019 for both adult patients and pediatric patients aged 10 years and older.

The approval of fingolimod in pediatric MS patients aged 10 years and older was based on the Phase III study CFTY720D2311 (PARADIGMS) in 215 patients, which provided evidence of favourable benefit-risk profile of fingolimod in pediatric MS patients in a randomized, controlled trial.

The MAH stated that study CFTY720D2419 (hereafter called D2419) is a standalone study. This 24-month, open-label, prospective, multicenter, interventional, single-arm study assesses the efficacy and safety of fingolimod (Gilenya) 0.5 mg in relapsing multiple sclerosis (RMS) adult and pediatric patients in China.

Study D2419 is part of a post-approval commitment to China's health authorities. Indeed, NMPA in China was requested to collect the efficacy and safety data of fingolimod 0.5 mg/day in Chinese patients, including pediatric patients which were recruited based on natural occurrence.

2.2. Information on the pharmaceutical formulation used in the study

The formulation used in China and in EU/EEA for adult and pediatric patients (>10 years; ≤ 40 kg) is capsule of 0.5 mg taken orally once daily.

Of note, in the EU/EEA, 0.25 mg capsules are used for pediatric patients under 40 kg.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for Study D2419 entitled 'A 24-month, open-label, prospective, multicenter, interventional, single-arm study assessing the efficacy and safety of fingolimod (Gilenya) 0.5 mg in relapsing multiple sclerosis (RMS) patients in China'.

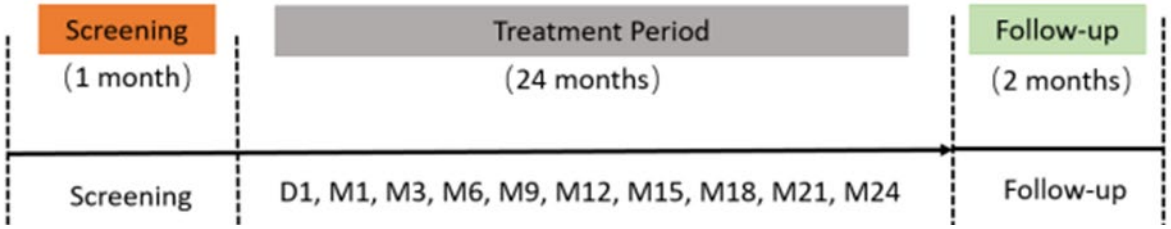
2.3.2. Clinical study

Study D2419: A 24-month, open-label, prospective, multicenter, interventional, single-arm study assessing the efficacy and safety of fingolimod (Gilenya) 0.5 mg in relapsing multiple sclerosis (RMS) patients in China

Description

Approximately 100 Chinese participants with relapsing multiple sclerosis were planned to be enrolled, including both adult participants aged 18 - 65 years (inclusive) and pediatric participants aged 10 - 17 years (inclusive) with weight more than 40 kg.

Figure 1: Study design



Source: [Study D2419 final analysis-Section 9.1]

The study will consist of three Phases (Figure 1):

- Screening (up to 1 month): After signing informed consent, participants will enter a Screening Phase to determine eligibility according to inclusion and exclusion criteria. The investigator must ensure that all patients meet the inclusion and exclusion criteria to be eligible to enter the study.

- Treatment Period (24 months): On visit Day 1, all eligibility criteria will be confirmed, including a pre-dose ECG and vital signs. The first dose of study drug will be taken in the clinic on Day 1 and the participant will be monitored for at least 6 hours after the first dose of administration before discharge. Then the participant should come to the site and be evaluated for the first month and then every three months till the end of treatment up to 24 months.

- Follow Up (2 months): Participants who completed Treatment Period will return for the Follow-up visit 2 months after the last dose of study drug.

No randomization was performed in this study. There was only one treatment arm in this study, which was fingolimod 0.5 mg, orally, once daily.

The study treatment could be permanently discontinued for any reason at any time, and study treatment could be initiated by the investigator or the participant. When discontinuation from study treatment occurred, the Investigator made a reasonable effort to understand the primary reason and recorded the information. Participants who discontinued study treatment were not considered withdrawn from the study and were asked to return for the EOT and follow-up visits.

Participants could voluntarily withdraw consent to participate in the study for any reason at any time. Discontinuation from study occurred when the participant permanently stopped receiving the study treatment and had no further protocol-required assessments or follow-up, for any reason.

Study completion was defined as when the last participant finished his 2-month follow-up visit and any repeat assessments associated with this visit had been documented and followed up appropriately by the Investigator (e.g. Each participant was required to complete the study in its entirety and thereafter no further study treatment was made available to them in the scope of the trial).

Methods

Study participants

The study population consisted of adult relapsing multiple sclerosis subjects aged 18-65 (inclusive) and in pediatric relapsing multiple sclerosis subjects of 10 years of age and older weighing more than 40kg. Approximately 100 patients were planned to be enrolled from around 10 to 15 centers in China.

Treatments

Study drug

The study drug fingolimod was administered as continuous oral daily dose of 0.5 mg capsule.

Dose modification of the study treatment were not permitted. Dose interruptions of the study treatment were permitted during the study.

Concomitant medication

All drugs used in previous MS disease modifying treatment were captured on the "Previous MS Disease Modifying Treatment" eCRF. All other concomitant medications taken within 30 days prior to Screening and during the study were captured in the concomitant medication eCRF. The participants were instructed to notify the study site about any new medications taken after the start of the study drug.

Unauthorized medication

The following treatments were not allowed during the whole course of the study (use was considered if the study drug had been permanently discontinued):

- anti-neoplastic;
- immunomodulatory or immunosuppressive therapies was prohibited due to the risk of additive immune system effects (e.g. cyclosporine, azathioprine, methotrexate, cyclophosphamide);
- other concomitant treatments: immunoglobulins, monoclonal antibodies (including rituximab), other MS DMTs (including but not limited to IFN- ß, teriflunomide), ACTH;
- during and for up to two months after treatment with fingolimod, vaccination may be less effective. The use of live attenuated vaccines may carry a risk of infections and was therefore avoided.

Objectives and Endpoints

Table 1: Objectives and endpoints

Objectives	**Endpoints**
Primary objective	**Primary endpoint**
• To evaluate the efficacy of fingolimod 0.5 mg on annualized relapse rate (ARR) in participants with RMS treated for up to 24 months.	• Annualized relapse rate (ARR)
Secondary objectives	**Secondary Endpoints**
• To evaluate the safety and tolerability of fingolimod 0.5 mg in participants with RMS treated for up to 24 months.	• Adverse events (AE) and serious adverse events (SAE) • Laboratory tests (hematology, biochemistry) • Vital signs • Electrocardiogram (ECG) • Ophthalmology
• To evaluate the efficacy of fingolimod 0.5 mg on MRI lesions.	• T1 hypo-intense lesion number and volume; T2 lesion volume, T2 lesion- new/newly enlarged T2 lesion number; Gd-enhancing T1 lesion number and volume.

Exploratory objectives	Exploratory Endpoints
• To evaluate the efficacy of 0.5 mg fingolimod on disability progression as measured by Expanded Disability Status Scale (EDSS) in participants treated for up to 24 months.	• 6-month confirmed disability progression (6m-CDP)
• To evaluate the efficacy of fingolimod 0.5 mg on clinical and MRI disease activity.	• No evidence of disease activity (NEDA-3)
• To evaluate the efficacy of fingolimod 0.5 mg on the patient reported outcome of Health Related Quality of Life (EQ-5D) in participants treated for up to 24 months.	• Patient reported outcome: Health Related Quality of Life (EQ-5D)

Sample size

The assumption of true Annualized Relapse Rate (ARR) was based on previous studies of fingolimod and literature review. Assuming ARR at 0.38 and considering a 20% drop-out rate, a sample size of approximately 100 participants was expected to show a lower ARR than placebo, with 95% probability within [0.22, 0.54].

Statistical Methods

Analysis sets

Full Analysis Set (FAS): The FAS comprises all subjects who have signed the Informed Consent and who have received at least one dose of study treatment. The FAS will be used for the summary of demography and baseline characteristics as well as for all efficacy analyses.

Safety Set (SAF): The SAF includes all subjects who have signed the Informed Consent and who have received at least one dose of study treatment. The Safety Set is identical to FAS in this study and will be used for all safety analyses in the final analysis.

All screened subjects (SCR): The SCR set comprises all subjects who have signed the Informed Consent and were screened.

Subgroups for efficacy safety analyses:

Age at baseline:

- Adult group is defined as subjects who have baseline age ≥18
- Child group is defined as subjects who have baseline age < 18.

This subgroup is defined to assess the efficacy and safety of fingolimod on adult and pediatric subjects separately.

Primary endpoint

The primary endpoint was the ARR, defined as the number of confirmed MS relapses in a year. ARR was estimated by a negative binomial regression model with log-link function, the cumulative number of confirmed MS relapses per participant as the response variable, number of relapses in the previous two years before enrollment and baseline EDSS as continuous covariates. Natural log of time on study in years was used as the offset variable to account for the varying lengths of participants' time in the study.

The adjusted ARR (i.e., model-based estimate adjusted for covariates) and the corresponding 95% confidence interval were obtained. In case of non-convergence, continuous covariates were removed from the regression model in the order of: baseline EDSS, number of relapses in the previous two years.

Primary endpoint supportive analyses

The primary analysis was only performed for the adult group. The primary analysis was repeated to analyze all reported MS relapses (confirmed and unconfirmed) for adult group. ARR time-based and ARR participant-based by age group were provided for confirmed relapses and then for all relapses (confirmed and unconfirmed). ARRs using a "time-based approach" were calculated by taking the total number of relapses observed for all participants within an age group divided by the total number of days in study of all participants within the group and multiplied by 365.25 days. The "Participant-based approach" was calculated in the way where individual ARRs were computed and summarized over participants within an age group.

Secondary efficacy endpoints

Secondary efficacy endpoints included:

- Number and volume of T1 hypo-intense lesions
- Number of new or newly enlarged T2 lesions and volume of T2 lesions
- Number and volume of Gd-enhancing T1 lesions.

The annualized rate of new or newly enlarged T2 lesions for adult group was estimated by a negative binomial regression model with log-link function, the total number of new or newly enlarged T2 lesions within 30 days from the last dose date (per participant) as the response variable. Natural log of time from screening scan in years was used as the offset.

The model included baseline age and baseline volume of T2 lesions as continuous covariates. The estimated number of new or newly enlarged T2 lesions was obtained together with the corresponding 95% confidence interval. The number of Gd-enhancing T1 lesions per scan for adult group was estimated using the same methods as the annualized rate of new or newly enlarged T2 lesions for adult group except that the number of scans was used as the offset.

Secondary endpoint supportive analyses

Descriptive summary statistics (mean, median, standard deviation, min, max) were provided by age group and by visit for the following: number of new or enlarged T2 lesions, number of Gd-enhancing T1 lesions, volume of T2 lesions, volume of Gd-enhancing T1 lesions, number of T1 hypo-intense lesions, volume of T1 hypo-intense lesions, change and % change in volume of T2 lesions, Gd-enhancing T1 lesions and T1 hypo-intense lesions from baseline. The number and percentage of participants free of new or newly enlarged T2 lesions or free of Gd-enhancing T1 lesions were also provided by age group.

Safety analysis

The number and percentage of participants were summarized for TEAEs. Serious AEs, treatment-related AEs (suspected to be related to the study treatment), AEs leading to premature discontinuation, and AEs leading to interruption of study drug were presented in a similar format as that of TEAEs. Additionally, the incidence of any TEAEs were summarized by age group, primary SOC, PT and maximum severity (Mild, Moderate and Severe). The severity grade was evaluated by investigators. An eCRS was used to map reported AEs to the AESI groupings. AESIs included bradyarrhythmia, liver transaminase elevation, macular edema, opportunistic infections, lymphoma, skin cancer, and other malignant neoplasms. Leukopenia and lymphopenia were incorrectly listed as important risks in the safety system of MedDRA v27.1 and were manually removed from the CSR body.

Interim analysis

An interim analysis was performed when 68 participants (including early withdrawn) had completed one year of treatment to meet the requirement of license renewal in 2023. All data collected up to the interim cut-off of 19-Jan-2023 was analyzed and reported in an earlier report of this study dated 29-Mar-2023 (referred to as Study D2419 interim CSR).

CHMP comment:

Study D2419 aimed to evaluate the efficacy and safety data of fingolimod 0.5 mg in Chinese patients with RMS treated for up to 24 months.

Primary efficacy objective was to evaluate the efficacy of fingolimod 0.5 mg on annualized relapse rate (ARR) in adult participants with RMS treated for up to 24 months. Supportive analysis for primary endpoint was provided for the pediatric group.

Secondary objectives were to evaluate the safety and tolerability of fingolimod 0.5 mg in both groups with RMS treated for up to 24 months and to evaluate the efficacy of fingolimod 0.5mg on MRI lesions.

Only descriptive results were provided for pediatric patients and will be analysed further below.

Proposed objectives, endpoints and the corresponding statistical methods were considered acceptable when data from the end of the interim analysis (data cut-off:19-Jan-2023) were analysed as part of the assessment of Gilenya procedure No. EMA/PAM/0000295236.

Assessment of the current P46 procedure will mainly focus on the full analysis set (i.e. all subjects who received at least 1 oral dose of fingolimod 0.5 mg capsule) demonstrating a sustained benefit with treatment.

Results

Participant flow

A total of 125 participants were screened, of which 98 participants (78.4%) were enrolled into the study and treated.

Of the 98 participants, 11 participants were in the <18 years group (10 to 17 years at the time of consent, herein referred to as pediatric group) and 87 participants, were in the ≥18 years group (herein referred to as adult group).

In the pediatric group, a total of 8 participants (72.7%) completed the study treatment and 3 participants (27.3%) discontinued the treatment, which were equally due to adverse event, physician decision and participant decision (9.1%). (Table 2)

Table 2: Participant disposition by age group and overall (FAS)

Disposition Reason	< 18 years N=11 n (%)	≥ 18 years N=87 n (%)	Overall N=98 n (%)
Participants completed the treatment	8 (72.7)	73 (83.9)	81 (82.7)
Participants discontinued the treatment	3 (27.3)	14 (16.1)	17 (17.3)
Primary reason for discontinuing			
Adverse event	1 (9.1)	5 (5.7)	6 (6.1)
Death	0	0	0
Lost to follow-up	0	1 (1.1)	1 (1.0)
Physician decision	1 (9.1)	1 (1.1)	2 (2.0)
Pregnancy	0	1 (1.1)	1 (1.0)
Protocol deviation	0	0	0
Study terminated by sponsor	0	0	0
Technical problems	0	0	0
Participant decision	1 (9.1)	6 (6.9)	7 (7.1)
Guardian decision	0	0	0
New therapy for study indication	0	0	0
Participants completed the study	10 (90.9)	75 (86.2)	85 (86.7)

Disposition Reason	< 18 years N=11 n (%)	≥ 18 years N=87 n (%)	Overall N=98 n (%)
Participants discontinued the study	1 (9.1)	12 (13.8)	13 (13.3)
Primary reason for discontinuing			
Adverse event	0	2 (2.3)	2 (2.0)
Death	0	0	0
Lost to follow-up	0	1 (1.1)	1 (1.0)
Physician decision	0	2 (2.3)	2 (2.0)
Pregnancy	0	0	0
Protocol deviation	0	0	0
Study terminated by sponsor	0	0	0
Technical problems	0	0	0
Participant decision	1 (9.1)	7 (8.0)	8 (8.2)
Guardian decision	0	0	0
New therapy for study indication	0	0	0

All percentages were calculated based on N.

Recruitment

Table 3: Inclusion and exclusion criteria

Key inclusion criteria	1. Clinical definite diagnosis of Multiple Sclerosis according to the 2010 Revised McDonald criteria. 2. Patients with a diagnosis of relapsing multiple sclerosis prior to their enrollment to the study (signing the study consent form): • At least two documented relapses during the past 2 years, or • At least one documented relapse during the last year. 3. With RMS that never used fingolimod before enrollment (including naïve patients and patients who switched from previous DMTs). 4. Patients with EDSS score of 0 - 6.0 (inclusive) at Screening.
Key exclusion criteria	1. Conditions included in the contraindication section and special warning section as latest approval label in China. 2. Patients treated with any other investigational drug for MS during the period. 3. Pregnant or nursing woman or woman of child-bearing potential not using effective contraception. 4. Patients intolerant to undergo MRI or presented contraindications to MRI (e.g., metallic implants, metallic foreign bodies, pacemaker, defibrillator) and the use of gadolinium-based agents (e.g. patients with severe kidney failure, patients with previous severe allergic/anaphylactoid reaction to a gadolinium-based contrast agent; patients with severe renal disease (Estimated Glomerular Filtration Rate (eGFR) <30 mL/min/1.73 m^2), or acutely deteriorating renal function, who would be at risk of nephrogenic systemic fibrosis). 5. Pediatric patient without confirmed history of chickenpox or confirmed documentation of a full vaccination course against varicella zoster virus (VZV). 6. Any disability that may prevent the patients from completing all study requirements, as assessed by the treating physician (e.g., mental disorder, blindness or deafness that was not appropriate for age, severe language difficulty). 7. Current medical or neurological condition that might impact efficacy assessments e.g. dementia, schizophrenia, bipolar disorder, major depression, history of multiple traumatic brain injuries, alcohol/drug abuse or dependence currently, or dependence within the last two years.

Protocol amendments

The study protocol was amended 3 times. Previous sections of this report describe the study conduct as amended. The key features of each amendment are given in the table below. (Table 4) The first participant was included on the 20-Feb-2021.

Table 4: Protocol amendments

Version and date	Summary of key changes
01 (28-Aug-2020)	• Added detailed pulmonary function monitoring guidance. • Updated the description of severe uncontrolled respiratory disease in pulmonary function test. • Revised the Liver Safety Monitoring Guidance according to the China fingolimod label. • Clarified the ECG requirement for baseline and first dose monitoring. • Clearly defined the 6m-CDP as measured by EDSS. • Updated protocol to adapt to the ongoing COVID-19 pandemic.
02 (11-Oct-2021)	• Introduced the measures in response to public health emergencies (e.g. COVID-19 pandemic). • Updated the ophthalmic guidance on diagnosis of macular edema.
03 (13-Jun-2023)	• Removed the maximum 5 days requirement for the use of corticosteroids. • Removed proton density in the efficacy assessment. • Changed the language regarding new findings in MRI images. • Clarified the detailed definition of highly effective contraception. • Clarified and detailed the identification and situation when EOS visit was required in the study. • Described more clearly about the analysis of T2 lesion-related MRI parameters that were analyzed as secondary endpoints. • Updated language to align with the Novartis protocol template Version 5.0.

Protocol deviations

A total of 6/11 participants (54.5%) in the pediatric had at least one protocol deviation. The most common categories of protocol deviations were "Other", which were mostly COVID-19 related, and "Prohibited concomitant medication" (Table 5).

Table 5: Protocol deviations by age group and overall (FAS)

Category Protocol deviation	< 18 years N=11 n (%)	≥ 18 years N=87 n (%)	Overall N=98 n (%)
Any protocol deviation	6 (54.5)	49 (56.3)	55 (56.1)
Other	6 (54.5)	49 (56.3)	55 (56.1)
Visit done outside study site due to covid-19	2 (18.2)	28 (32.2)	30 (30.6)
Assessment done by virtual due to covid-19	2 (18.2)	17 (19.5)	19 (19.4)
pre-dose ECG / 6h post-dose ECG/ extended ECG missing during FDO	1 (9.1)	8 (9.2)	9 (9.2)
Scheduled EDSS assessments/data missing	0	9 (10.3)	9 (9.2)
Relapses were not confirmed within 7 days or were not confirmed by investigator	1 (9.1)	6 (6.9)	7 (7.1)
Visit extended due to COVID-19	1 (9.1)	5 (5.7)	6 (6.1)
Participants who need to re-initiate first dose monitoring after interrupting the study drug but did not re-initiate first dose	1 (9.1)	3 (3.4)	4 (4.1)
Scheduled (M12/M24) MRI assessments not done or done out of the permitted time window (6 months delay of the scheduled date) or mandatory MRI data missing.	1 (9.1)	3 (3.4)	4 (4.1)
Prohibited concomitant medication	0	6 (6.9)	6 (6.1)
Immunomodulatory/immunosuppressive therapies prohibited as per protocol	0	6 (6.9)	6 (6.1)

Numbers (n) represent counts of participants. A participant with multiple occurrences of a protocol deviation was counted only once for that specific protocol deviation criterion. A participant might have had multiple protocol deviations.

CHMP comment:

Eligibility criteria are consistent with the study objectives and endpoints.

The first participant was included on the 20-Feb-2021 under the first version of the protocol.

Concerning protocol amendments, main changes include improved patient safety, updated pulmonary function monitoring guidance and ophthalmic guidance, revised liver safety monitoring guidance, clarified ECG requirements and first dose monitoring. None of those changes are considered to have had an impact on study conduct.

Concerning protocol deviations, the rate is considered acceptable since all deviations were related to the COVID-19 pandemic.

Baseline data

Demographics and baseline disease characteristics

Of the 11 pediatric participants in the FAS, the median (range) age was 13.0 (10-16) years. A total of 3 participants (27.3%) in the pediatric group were female. (Table 6).

Table 6: Demographics and baseline characteristics by age group (FAS)

Characteristic Categories/Statistics	< 18 years N=11	≥ 18 years N=87
Age (years) at screening		
n	11	87
Mean (SD)	12.8 (1.60)	32.3 (9.11)
Median	13.0	31.0
Min-Max	10-16	18-61
Sex –n (%)		
Male	8 (72.7)	36 (41.4)
Female	3 (27.3)	51 (58.6)
Race –n (%)		
Asian (Chinese)	11 (100.0)	87 (100.0)
Height (cm) at baseline		
n	11	87
Mean (SD)	158.24 (10.894)	164.85 (8.455)
Median	159.10	163.00
Min-Max	136.0-174.0	145.0-186.0
Weight (kg) at baseline		
n	11	87
Mean (SD)	56.46 (15.624)	60.14 (12.402)
Median	52.50	59.00
Min-Max	40.3-80.6	38.0-115.0
BMI (kg/m^2) at baseline		
n	11	87
Mean (SD)	22.238 (4.3350)	22.045 (3.6306)
Median	21.788	21.576
Min-Max	17.30-31.84	14.66-35.06

BMI (kg/m^2): body mass index, computed as weight[kg] /(height[m]**2)
n: Number of participants meeting the criterion (for categorical variables); number of participants with non-missing assessment (for continuous variables).

Baseline MS disease history by age group for FAS is presented in Table 7. The median duration of MS since diagnosis was 0.76 years (range: 0.1-6.3 years) in the pediatric group. The median duration of MS since first symptom was 1.14 years (range: 0.3-7.1 years) in the pediatric.

Table 7: MS disease history by age and overall (FAS)

	< 18 years N=11	≥ 18 years N=87	Overall N=98
Duration of MS since diagnosis (years)			
n	11	87	98
Mean (SD)	1.79 (1.993)	3.46 (3.938)	3.27 (3.799)
Median	0.76	1.90	1.86
Min-Max	0.1-6.3	0.1-16.8	0.1-16.8
Duration of MS since first symptom (years)			
n	11	87	98
Mean (SD)	2.46 (2.497)	5.26 (4.699)	4.95 (4.584)
Median	1.14	3.63	3.37
Min-Max	0.3-7.1	0.2-22.9	0.2-22.9
Number of relapses in the last 12 months prior to screening			
n	11	87	98
Mean (SD)	1.7 (1.27)	1.2 (0.47)	1.3 (0.62)
Median	1.0	1.0	1.0
Min-Max	0-4	1-3	0-4
Number of relapses in 12 to 24 months prior to screening			
n	11	87	98
Mean (SD)	0.8 (1.25)	0.7 (0.84)	0.7 (0.89)
Median	0.0	0.0	0.0
Min-Max	0-4	0-3	0-4
Time since the onset of the most recent relapse prior to screening (months)			
n	11	87	98
Mean (SD)	5.46 (5.062)	5.24 (3.419)	5.27 (3.607)
Median	2.86	3.94	3.93
Min-Max	1.1-16.8	0.9-15.0	0.9-16.8

n: The number of participants with non-missing values.
Duration of MS since diagnosis was derived as [(first dose date - MS diagnosis start date + 1)/365.25].
Duration of MS since first symptom was derived as [(first dose date - first MS symptom date + 1)/365.25].
Time since onset of most recent relapse was derived as [(first dose date - most recent relapse onset date + 1)/ 30.4375].

Table 8: MS baseline characteristics by age group and overall (FAS)

Baseline characteristics	< 18 years N=11	≥ 18 years N=87	Overall N=98
EDSS			
n	11	87	98
Mean (SD)	0.8 (1.01)	1.9 (1.58)	1.8 (1.56)
Median	0.0	1.5	1.5
Min-Max	0-3	0-6	0-6
Number of T1 hypo-intense lesions			
n	11	87	98
Mean (SD)	13.6 (12.73)	17.0 (15.36)	16.6 (15.07)
Median	11.0	14.0	14.0
Min-Max	0-36	0-88	0-88
Volume of T1 hypo-intense lesions (µL)			
n	11	87	98
Mean (SD)	3237.5 (3621.97)	4078.7 (4608.06)	3984.2 (4499.99)
Median	3083.0	2740.0	2815.5
Min-Max	0-12677	0-23663	0-23663
Number of Gd-enhancing T1 lesions			
n	11	87	98
Mean (SD)	1.6 (2.11)	2.3 (5.71)	2.2 (5.42)
Median	1.0	1.0	1.0
Min-Max	0-6	0-49	0-49
Volume of Gd-enhancing T1 lesions (µL)			
n	11	87	98
Mean (SD)	284.6 (444.23)	334.5 (754.57)	328.9 (724.84)
Median	39.0	46.0	42.5
Min-Max	0-1393	0-5046	0-5046
Number of T2 lesions			
n	11	87	98
Mean (SD)	28.5 (16.52)	25.9 (18.74)	26.2 (18.45)
Median	25.0	23.0	23.0
Min-Max	10-65	1-133	1-133
Volume of T2 lesions (mL)			
n	11	87	98
Mean (SD)	11.9 (8.69)	10.5 (11.32)	10.6 (11.03)
Median	9.7	7.9	8.1
Min-Max	2-33	0-62	0-62
Total intracranial volume (mL)			
n	11	87	98
Mean (SD)	1160.2 (155.97)	1036.9 (102.04)	1050.7 (115.20)
Median	1148.7	1046.2	1049.6
Min-Max	932-1431	800-1412	800-1431

Baseline was defined as the last non-missing assessment obtained prior to the first administration of study drug.
Source: Table 14.1-6.1

The most commonly reported medical history at baseline (incidence ≥ 20%) by SOC were:

- In the pediatric group:

- nervous system disorders (100.0%), infections and infestations (36.4%), eye disorders (27.3%), respiratory, thoracic and mediastinal disorders (27.3%).

- In the nervous system disorders SOC, the most common conditions (occurring in ≥ 2 participants) were epilepsy (2 participants, 18.2%) in addition to multiple sclerosis (100%).

- In the infections and infestations SOC, the conditions were sinusitis, bronchitis, encephalitis, helicobacter infection and upper respiratory tract infection (1 (9.1%) participant each).

- In the eye disorders SOC, the most common condition (occurring in ≥ 2 participants) was refraction disorder (2 participants, 18.2%).

- In the respiratory, thoracic and mediastinal disorders SOC, the conditions were pulmonary mass, paranasal cyst, adenoidal hypertrophy, asthma and rhinitis allergic (1 (9.1%) participant each).

CHMP comment:

Only results from the pediatric group will be discussed below.

Regarding baseline demographics, in total, 98 participants (11 in the pediatric group and 87 in the adult group) were included in the FAS. Of the 98 participants, the median (range) age was 13.0 (10-16) years in the pediatric group. In the pediatric group 3 participants were female.

The median duration of MS since diagnosis was 0.76 years (range: 0.1-6.3 years) in the pediatric group

The median duration of MS since first symptom was 1.14 years (range: 0.3-7.1 years) in the pediatric group.

The median number of relapses in the last 12 months prior to screening was 1.0 (range: 0-4) in the pediatric group.

The median number of relapses in 12 to 24 months prior to screening was 0 (range: 0-4) in the pediatric group.

The median baseline EDSS score was low in both pediatric group (0.0) indicating no disability. The median number of Gd-enhancing T1 lesions was 1.0.

The data for most commonly reported medical history at baseline (incidence ≥ 20%) by SOC indicates that nervous system disorders were the dominant baseline condition in the pediatric groups, reported in 100% of participants.

In the pediatric group, comorbid conditions were relatively diverse but occurred at lower frequencies. The presence of epilepsy (18.2%) in addition to MS points to possible neurological complexity in younger patients. Other conditions such as infections, eye disorders, and respiratory issues were present in over a quarter of the group, but each individual condition within these SOCs was rare (≤ 9.1%), reflecting a low but broad spectrum of comorbidities.

Previous disease-modifying therapy

The most commonly (incidence ≥ 10%) used disease-modifying drugs prior to the start of the study was mycophenolate mofetil (27.3%) in the pediatric group (Table 9).

Table 9: Number of treatment naive participant and MS medication history of previous disease modifying drugs by preferred drug name, age group and overall (FAS)

Preferred drug name	< 18 years N=11 n (%)	≥ 18 years N=87 n (%)	Overall N=98 n (%)
Number of treatment-naive participants	8 (72.7)	54 (62.1)	62 (63.3)
Number of participants with at least one previous disease-modifying drugs	3 (27.3)	33 (37.9)	36 (36.7)
Approved disease-modifying drugs of MS			
teriflunomide	0	23 (26.4)	23 (23.5)
interferon α-1β	0	2 (2.3)	2 (2.0)
dimethyl fumarate	0	1 (1.1)	1 (1.0)
Off-label immunosuppressants			
azathioprine	1 (9.1)	10 (11.5)	11 (11.2)
mycophenolate mofetil	3 (27.3)	2 (2.3)	5 (5.1)
rituximab	1 (9.1)	1 (1.1)	2 (2.0)
methotrexate	0	1 (1.1)	1 (1.0)
tacrolimus	0	1 (1.1)	1 (1.0)

Preferred drug names were sorted by descending frequency in overall column.
Treatment-naive participants were those participants who had not been treated with any disease-modifying drug before study enrollment.
WHODD version: WhoDrugGlobalB3 24.9
Source: Table 14.1-6.3

Prior and concomitant therapies

Prior

Medications prior to the start of study drug were taken by 5 participants (45.5%) in the pediatric group. Each prior medication was taken by 1 participant, except for calcium carbonate/colecalciferol, which was taken by 2 participants. Non-drug therapies or procedures prior to the start of study drug were not conducted in the pediatric group.

Concomitant

All participants (100%) in the pediatric group had taken concomitant medications.

- In the pediatric group, the most frequently (incidence ≥ 20%) used concomitant medications were calcium sulfate dihydrate/dryopteris crassirhizoma rhizome/ephedra spp. herb/forsythia suspense fruit/glycyrrhiza spp. root with rhizome/houttuynia cordata herb/isatis tinctoria subsp. tinctoria root/lonicera japonica flower/menthol/pogostemon cablin herb/prunus spp. seed/rheum spp. root with rhizome/rhodiola crenulate root with rhizome (36.4%), sanguisorba officinalis root (36.4%), unspecified herbal and traditional medicine (27.3%), calcium carbonate/colecalciferol (27.3%), bupleurum spp. root/codonopsis spp. root/glycyrrhiza spp. root with rhizome/pinelli ternate tuber/scutellarin baicalensis root/zingiber officinale rhizome/ziziphus jujuba fruit (27.3%), pyridoxine hydrochloride (27.3%), ibuprofen (27.3%) and paracetamol (27.3%).

- In the pediatric group, the surgical and medical procedures used were acupuncture, acupoint application therapy, eye irrigation, nail operation and therapeutic procedure (1 (9.1%) participant each).

***CHMP comment*:**

In the pediatric group, 11 were treatment-naïve participant and 3 were participants with at least one previous disease modifying drug. The most commonly (incidence ≥ 10%) approved disease-modifying drugs prior to the start of the study was mycophenolate mofetil in the pediatric group.

The concomitant medications taken during this study were those expected with the population in the study and for the treatment of AEs. A total of 2 participants in the pediatric group used corticosteroid for MS relapse during the study (as allowed by the protocol and after the start of the study drug). Concomitant non-drug therapies or procedures were taken by 3 participants (27.3%) in the pediatric group.

Number analysed

Analysis set

The number of participants analyzed for each analysis set is summarized by age group. In total, 98 participants (11 in the pediatric group and 87 in the adult group) were included in the FAS and Safety set.

Table 10: Analysis sets by age group and overall (all screened participants)

	All participants		
	<18 years N=11	≥ 18 years N=114	Overall N=125
Analysis set	**n (%)**	**n (%)**	**n (%)**
All screened participants	11 (100.0)	114 (100.0)	125 (100.0)
Full analysis set	11 (100.0)	87 (76.3)	98 (78.4)
Safety analysis set	11 (100.0)	87 (76.3)	98 (78.4)

Efficacy results

Exposure and compliance with study treatment:

Table 11: Study treatment exposure and compliance by age group and overall (SAF)

	< 18 years N=11	≥ 18 years N=87	Overall N=98
Duration of exposure (Days)			
n	11	87	98
Mean (SD)	610.4 (187.28)	632.2 (195.30)	629.8 (193.60)
Median	710.0	715.0	714.5
Min-Max	210-726	2-732	2-732
Duration of exposure categories -n (%)			
≥ 30 days (1 month)	11 (100.0)	86 (98.9)	97 (99.0)
≥ 60 days (2 months)	11 (100.0)	84 (96.6)	95 (96.9)
≥ 90 days (3 months)	11 (100.0)	84 (96.6)	95 (96.9)
≥ 180 days (6 months)	11 (100.0)	79 (90.8)	90 (91.8)
≥ 270 days (9 months)	10 (90.9)	78 (89.7)	88 (89.8)
≥ 360 days (12 months)	10 (90.9)	76 (87.4)	86 (87.8)
≥ 450 days (15 months)	8 (72.7)	75 (86.2)	83 (84.7)
≥ 540 days (18 months)	8 (72.7)	74 (85.1)	82 (83.7)
≥ 630 days (21 months)	8 (72.7)	73 (83.9)	81 (82.7)
Participant years of exposure	18.4	150.6	169.0

	< 18 years N=11	≥ 18 years N=87	Overall N=98
Treatment Compliance (%)			
n	11	87	98
Mean (SD)	98.22 (2.512)	96.97 (8.726)	97.11 (8.265)
Median	99.72	99.72	99.72
Min-Max	93.5-100.0	45.5-100.0	45.5-100.0
Treatment compliance categories -n (%)			
≥90%	11 (100.0)	80 (92.0)	91 (92.9)
≥95%	9 (81.8)	77 (88.5)	86 (87.8)
≥98%	8 (72.7)	72 (82.8)	80 (81.6)
=100%	4 (36.4)	35 (40.2)	39 (39.8)

Duration of exposure (in days) was calculated as (last dose date − first dose date + 1 − sum of [days with temporary study treatment interruption]), where any day with no drug taken was considered a study treatment interruption. Treatment compliance was calculated as duration of exposure to study treatment in (days) / duration of on treatment period (in days) × 100.
Duration of on treatment: On-treatment period included days from the first dose date until the last dose date. Participant years were calculated as the sum of the duration of exposure for all participants in the group divided by 365.25.
Source: Table 14.3-1.1

The overall median duration of exposure to fingolimod was 714.5 days. Of the 11 participants in the pediatric group, 8 participants were exposed to ≥ 630 days (21 months) of study treatment. The overall cumulative participant years of exposure was 18.4. The mean (SD) treatment compliance was 98.22% (Table 11).

***CHMP comment*:**

100% of the participants in the pediatric group were compliant ≥ 90% with the treatment.

Supportive analysis of primary endpoint:

Table 12: Annualized relapse rate (ARR) time and participant-based for confirmed and all relapses by age group (FAS)

Relapse type	Time point	Endpoint	Statistics	< 18 years N=11	≥ 18 years N=87
Confirmed relapses	First treatment up to EOT	ARR (participant-based)	n	11	87
			Mean (SD)	0.0460 (0.15253)	0.0372 (0.24424)
			Median	0.0000	0.0000
			Min-Max	0.000-0.506	0.000-2.161
		Number of relapses	Sum	1	3
		Time in study (days)	Sum	6806	56234
		ARR (time-based)		0.054	0.019
All relapses (confirmed and unconfirmed)	First treatment up to EOT	ARR (participant-based)	n	11	87
			Mean (SD)	0.1952 (0.50314)	0.0969 (0.50002)
			Median	0.0000	0.0000
			Min-Max	0.000-1.642	0.000-4.322
		Number of relapses	Sum	3	10
		Time in study (days)	Sum	6806	56234
		ARR (time-based)		0.161	0.065

n: Total number of participants included in the analysis.
Time in study for ARR was calculated as (end of treatment period date – first dose date+1)/365.25
ARR (time-based) was calculated by taking the total number of relapses observed for all participants within the age group, divided by the total number of days in study of all participants within the age group and multiplied by 365.25 days.
ARR (participant-based) was the individual participant ARR which was calculated by taking the total number of relapses observed for a participant divided by the total number of days in study of that participant and multiplied by 365.25.
EOT: End of treatment.

For confirmed relapses, the mean (SD) patient-based ARR was 0.046 (0.153) and the estimated time-based ARR was 0.054 for the pediatric group. For all relapses (confirmed and unconfirmed), the mean (SD) patient-based ARR was 0.195 (0.503) and the estimated time-based ARR was 0.161 for the pediatric group. (Table 12)

Secondary efficacy endpoints:

- The mean number of Gd-enhancing T1 and T1 hypo-intense lesions were 0.0 and 13.4, in the pediatric group at Month 24.

- Compared to baseline:
  - The mean number of new or newly enlarged T2 was 2.1 in the pediatric group
  - The median volume of T2 lesions at Month 24 was -1.674 mL in the pediatric group
  - The median volume of Gd-enhancing T1 lesions at Month 24 decreased in the pediatric group (-56.000 µL).

- 87.5% of the participants (7/8) in the pediatric group were free of new or newly enlarged T2 lesions at Month 24. All participants (8/8) in the pediatric group were free of Gd-enhancing T1 lesions at Month 24.

Exploratory efficacy results:

- A total of 3 participants and 11 participants had 6m-CDP at Month 24 (Month 0-24) in the pediatric group and adult group, respectively.

- A total of 3 participants and 39 participants achieved NEDA-3 in 2 years (Month 0-24) in the pediatric group and adult group, respectively.

- The mean changes from baseline in EQ-5D (utility and Visual Analog Scale scores) at Month 24 was -0.050 and 2.9, respectively, in the pediatric group and -0.005 and 1.3, respectively, in the adult group.

CHMP comment:

Primary analysis was focused on adult patients and will not be discussed in this AR. Assessment will focus on the supportive analysis of primary endpoint for pediatric group and pediatric secondary analyses.

Concerning supportive analysis of primary endpoint, the mean (SD) patient-based ARR was 0.046 (0.153) and the estimated time-based ARR was 0.054 for the pediatric group for confirmed relapses. For all relapses (confirmed and unconfirmed), the mean (SD) patient-based ARR was 0.195 (0.503) and the estimated time-based ARR was 0.161 for the pediatric group.

These data demonstrated that fingolimod was effective in reducing both clinical relapses and MRI lesion activity over 24 months which was consistent with the PARADIGMS study where fingolimod was associated with a lower rate of relapse and less accumulation of lesions on MRI over a 2-year period than interferon beta-1a. The mean annualized relapse rate (ARR) for confirmed relapses was low at 0.046, and 0.195 when including unconfirmed relapses. MRI findings further supported efficacy: the mean number of new or newly enlarged T2 lesions was 2.1, but 87.5% of patients were free of such lesions at Month 24. Additionally, there were no new gd-enhancing T1 lesions observed, with 100% of patients remaining lesion-free in this category and a median reduction in lesion volume of 56.0 µL. T1 hypo-intense lesions were present, with a mean of 13.4, but their volume also decreased by a median of 641.415 µL. Overall, the clinical data suggest that fingolimod provided acceptable disease control in pediatric patients with multiple sclerosis.

Overall, data collected from these 11 pediatric patients showed results consistent with the known benefits of fingolimod in this population.

Safety results

Exposure

The median (min-max) duration of exposure to fingolimod for these 11 pediatric patients was 710.0 days (210-726). In the pediatric group, 8 patients (72.7%) were exposed to ≥ 630 days (21 months) of study treatment. The overall cumulative exposure was 18.4 patient years and the mean treatment compliance was 98.22%. Pediatric patients had a median (range) age of 13.0 (10-16) years and a mean body weight of 56.46 kg.

Overview of adverse events (AEs)

All participants in the pediatric group and experienced at least 1 TEAE. Treatment-emergent SAEs occurred in 3 participants (27.3%) in the pediatric group.

In the pediatric group, the most common TEAEs (incidence ≥ 30%) by PT were lymphopenia (63.6%), leukopenia (45.5%), weight decreased (45.5%), pyrexia (36.4%), nasopharyngitis (36.4%), pharyngitis (36.4%), white blood cell count decreased (36.4%) and weight increased (36.4%).

Table 13: Treatment-emergent adverse events by primary SOC, PT and age group (SAF)

Primary system organ class Preferred term	< 18 years N=11 n (%)	≥ 18 years N=87 n (%)
Number of participants with at least one event	11 (100.0)	86 (98.9)
Blood and lymphatic system disorders	8 (72.7)	38 (43.7)
Lymphopenia	7 (63.6)	24 (27.6)
Leukopenia	5 (45.5)	22 (25.3)
Neutropenia	3 (27.3)	2 (2.3)
Cardiac disorders	1 (9.1)	20 (23.0)
Sinus bradycardia	0	13 (14.9)
Eye disorders	2 (18.2)	5 (5.7)
Gastrointestinal disorders	4 (36.4)	11 (12.6)
Diarrhoea	3 (27.3)	5 (5.7)
Nausea	2 (18.2)	1 (1.1)
Vomiting	2 (18.2)	1 (1.1)
General disorders and administration site conditions	6 (54.5)	21 (24.1)
Pyrexia	4 (36.4)	12 (13.8)
Hepatobiliary disorders	0	13 (14.9)
Hepatic function abnormal	0	9 (10.3)
Infections and infestations	7 (63.6)	57 (65.5)
COVID-19	2 (18.2)	36 (41.4)
Upper respiratory tract infection	3 (27.3)	21 (24.1)
Urinary tract infection	0	16 (18.4)
Nasopharyngitis	4 (36.4)	8 (9.2)

Primary system organ class Preferred term	< 18 years N=11 n (%)	≥ 18 years N=87 n (%)
Pharyngitis	4 (36.4)	0
Investigations	11 (100.0)	71 (81.6)
Lymphocyte count decreased	2 (18.2)	53 (60.9)
Alanine aminotransferase increased	2 (18.2)	33 (37.9)
White blood cell count decreased	4 (36.4)	22 (25.3)
Aspartate aminotransferase increased	1 (9.1)	19 (21.8)
Gamma-glutamyltransferase increased	0	10 (11.5)
Weight decreased	5 (45.5)	8 (9.2)
Weight increased	4 (36.4)	8 (9.2)
White blood cells urine positive	2 (18.2)	8 (9.2)
Neutrophil count decreased	2 (18.2)	4 (4.6)
Protein urine present	2 (18.2)	1 (1.1)
Liver function test abnormal	2 (18.2)	0
Metabolism and nutrition disorders	0	17 (19.5)
Hyperlipidaemia	0	9 (10.3)
Musculoskeletal and connective tissue disorders	1 (9.1)	12 (13.8)
Nervous system disorders	5 (45.5)	21 (24.1)
Headache	2 (18.2)	10 (11.5)
Seizure	2 (18.2)	0
Renal and urinary disorders	2 (18.2)	3 (3.4)
Respiratory, thoracic and mediastinal disorders	2 (18.2)	14 (16.1)
Cough	2 (18.2)	10 (11.5)
Skin and subcutaneous tissue disorders	2 (18.2)	12 (13.8)

Primary system organ classes were presented alphabetically; preferred terms were presented within primary system organ class by descending frequency of ≥18 years column.
A participant with multiple occurrences of an AE for a preferred term or primary system organ class was counted only once in each specific category.
Data up to safety cutoff i.e. 45 days after the last dose administration of study drug and all SAEs / deaths (irrespective of time after last dose of study drug) were included.
MedDRA Version 27.1
Source: Table 14.3.1-2

Adverse Reactions and Adverse Events

The majority of TEAEs were mild or moderate in severity in the pediatric group and no participants in experienced severe TEAEs.

The incidence of TEAEs assessed by the investigators as having a reasonable possibility of being related to treatment was 90.9% in the pediatric group. The most common TEAEs (incidence ≥ 30%) considered related to study treatment by PT were lymphopenia (63.6%), leukopenia (45.5%), and white blood cell count decreased (36.4%). (Table 14).

Table 14: Treatment-emergent adverse events related to study treatment by primary SOC, PT and age group (SAF)

Primary system organ class Preferred term	< 18 years N=11 n (%)	≥ 18 years N=87 n (%)
Number of participants with at least one event	10 (90.9)	81 (93.1)
Blood and lymphatic system disorders	7 (63.6)	36 (41.4)
Lymphopenia	7 (63.6)	24 (27.6)
Leukopenia	5 (45.5)	22 (25.3)
Cardiac disorders	1 (9.1)	19 (21.8)
Sinus bradycardia	0	11 (12.6)
Gastrointestinal disorders	2 (18.2)	1 (1.1)
General disorders and administration site conditions	4 (36.4)	2 (2.3)
Pyrexia	3 (27.3)	2 (2.3)
Hepatobiliary disorders	0	13 (14.9)
Hepatic function abnormal	0	9 (10.3)
Infections and infestations	4 (36.4)	15 (17.2)
Upper respiratory tract infection	3 (27.3)	8 (9.2)
Pharyngitis	2 (18.2)	0
Investigations	9 (81.8)	66 (75.9)
Lymphocyte count decreased	2 (18.2)	53 (60.9)
Alanine aminotransferase increased	2 (18.2)	33 (37.9)
White blood cell count decreased	4 (36.4)	22 (25.3)
Aspartate aminotransferase increased	1 (9.1)	19 (21.8)
Neutrophil count decreased	2 (18.2)	3 (3.4)
Liver function test abnormal	2 (18.2)	0
Nervous system disorders	3 (27.3)	4 (4.6)
Seizure	2 (18.2)	0

Primary system organ classes were presented alphabetically; preferred terms were presented within primary system organ class by descending frequency of ≥ 18 years column.
A participant with multiple occurrences of an AE for a preferred term or primary system organ class was counted only once in each specific category.
Data up to safety cutoff i.e. 45 days after the last dose administration of study drug and all SAEs / deaths (irrespective of time after last dose of study drug) were included.
MedDRA Version 27.1
Source: Table 14.3.1-4

***CHMP comment*:**

All pediatric patients reported at least one adverse event. The most common TEAEs (incidence ≥ 30%) by PT were lymphopenia (63.6%), leukopenia (45.5%), weight decreased (45.5%), pyrexia (36.4%), nasopharyngitis (36.4%), pharyngitis (36.4%), white blood cell count decreased (36.4%) and weight increased (36.4%), which was consistent with that observed in the interim analysis. Most AEs were mild or moderate in severity. No TEAE of macular edema was reported.

Serious adverse events

No death occurred in this study. The incidence of treatment-emergent SAEs was 27.3% in pediatric participants and 13.8% (Table 15). Treatment-emergent SAEs reported by at least 2 participants were seizure (2 participants, 18.2%) in the pediatric group, both of whom had a history of epilepsy.

Table 15: Treatment-emergent serious adverse events by primary SOC, PT and age group (SAF)

Primary system organ class Preferred term	< 18 years N=11 n (%)	≥ 18 years N=87 n (%)
Number of participants with at least one event	**3 (27.3)**	**12 (13.8)**
Eye disorders	**0**	**1 (1.1)**
Iridocyclitis	0	1 (1.1)
Hepatobiliary disorders	0	5 (5.7)
Liver injury	0	3 (3.4)
Drug-induced liver injury	0	2 (2.3)
Infections and infestations	1 (9.1)	2 (2.3)
COVID-19	0	2 (2.3)
Febrile infection	1 (9.1)	0
Infection	1 (9.1)	0
Pneumonia	1 (9.1)	0
Tonsillitis	1 (9.1)	0
Injury, poisoning and procedural complications	0	2 (2.3)
Fractured sacrum	0	1 (1.1)
Limb injury	0	1 (1.1)
Musculoskeletal and connective tissue disorders	1 (9.1)	0
Muscle twitching	1 (9.1)	0
Nervous system disorders	3 (27.3)	1 (1.1)
Acute disseminated encephalomyelitis	0	1 (1.1)
Epilepsy	1 (9.1)	0
Seizure	2 (18.2)	0
Syncope	1 (9.1)	0
Pregnancy, puerperium and perinatal conditions	0	2 (2.3)
Abortion	0	1 (1.1)
Abortion complete	0	1 (1.1)

Primary system organ classes were presented alphabetically; preferred terms were presented within primary system organ class by descending frequency of ≥18 years column.
A participant with multiple occurrences of an AE for a preferred term or primary system organ class was counted only once in each specific category.
Data up to safety cutoff i.e. 45 days after the last dose administration of study drug and all SAEs / deaths (irrespective of time after last dose of study drug) were included.
MedDRA Version 27.1
Source: Table 14.3.1-3

CHMP comment:

3 of the 11 pediatric patients experienced SAEs. One patient experienced seizure, muscle twitching and epilepsy. Second patient experienced tonsillitis, infection, seizure, febrile infection and pneumonia. Third patient experienced syncope, which occurred after fingolimod treatment discontinuation. Both of the patients who experienced seizure had a history of epilepsy. All SAEs were moderate in severity and recovered thereafter. There were no deaths reported in the 11 pediatric patients.

AEs leading to discontinuation or interruption of the study treatment

One pediatric participant experienced AE (tonsillitis) which led to discontinuation of study treatment.

Three pediatric participants had AEs leading to interruption of study treatment:1 participant had AEs of infection, seizure and tonsillitis, 1 participant had white blood cell count decreased and 1 participant had liver function test abnormal.

Adverse events of special interest (AESIs)

Adverse events of special interest for fingolimod are based on the current search strategy and represent important identified or potential risks associated with fingolimod. AESIs included bradyarrhythmia, liver transaminase elevation and liver function test abnormal. Only liver transaminase elevation AESIs was reported with relevant events (Table 16).

Table 16: Treatment-emergent adverse events of special interest by risk name, PT and age group (SAF)

Risk name Preferred term	< 18 years N=11 n (%)	≥ 18 years N=87 n (%)
Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose	**2 (18.2)**	**23 (26.4)**
Sinus bradycardia	0	13 (14.9)
Bradycardia	0	3 (3.4)
Electrocardiogram PR shortened	1 (9.1)	3 (3.4)
Bundle branch block right	0	1 (1.1)
Electrocardiogram QT prolonged	0	1 (1.1)
Nodal rhythm	0	1 (1.1)
Syncope	1 (9.1)	1 (1.1)
Wolff-Parkinson-White syndrome	0	1 (1.1)
Liver transaminase elevation	**5 (45.5)**	**51 (58.6)**

Risk name Preferred term	< 18 years N=11 n (%)	≥ 18 years N=87 n (%)
Alanine aminotransferase increased	2 (18.2)	33 (37.9)
Aspartate aminotransferase increased	1 (9.1)	19 (21.8)
Gamma-glutamyltransferase increased	0	10 (11.5)
Hepatic function abnormal	0	9 (10.3)
Transaminases increased	0	4 (4.6)
Liver injury	0	3 (3.4)
Blood bilirubin increased	0	2 (2.3)
Drug-induced liver injury	0	2 (2.3)
Hepatic enzyme increased	0	2 (2.3)
Bile acids increased	0	1 (1.1)
Bilirubin conjugated increased	0	1 (1.1)
Blood bilirubin unconjugated increased	0	1 (1.1)
Hypertransaminasaemia	0	1 (1.1)
Liver function test abnormal	2 (18.2)	0

Risk names were presented alphabetically; preferred terms were presented within risk name by descending frequency in the ≥18 years column.
A participant with multiple occurrences of an AE for a preferred term or risk name was counted only once in each specific category.
Data up to safety cutoff i.e. 45 days after the last dose administration of study drug and all SAEs/deaths (irrespective of time after last dose of study drug) were included.
Adverse Events of Special Interest (AESIs) were defined based on the electronic case retrieval sheet (eCRS). MedDRA Version 27.1 and FTY720 RMS (CRS ID 210090) Compound Case Retrieval Strategy definition for indication RMS (Relapsing Multiple Sclerosis) active from 2025-03-13.
Source: Table 14.3.1-8

Liver transaminase elevation AESI was the most common AESIs in the pediatric group. Most events were reported in a small proportion of participants.

- In the pediatric group, the most common events (incidence ≥ 10%) were alanine aminotransferase increased and liver function test abnormal.
- The most common events (incidence ≥ 10%) were not considered as serious AEs by investigator. The ALT and AST were increased to less than 3×ULN in most participants.

Bradyarrhythmia AESI was reported in 18.2% of participants in the pediatric group. No events were reported in ≥ 2 participants. None of these events were considered as serious AEs, except for syncope (1 participant) in the pediatric group, which occurred after fingolimod treatment discontinuation and was not considered related to study treatment by investigator.

Clinical laboratory evaluation

The percentage of participants with clinically notable haematological parameters abnormalities was low in both groups.

The number of participants with clinically notable biochemistry abnormal are presented in Table 17.

The most common clinically notable abnormalities in biochemistry parameters were total cholesterol (18.2%) in the pediatric group. One participant (9.1%) in the pediatric group had ALT ≥3 ×ULN and resulted in drug interruption and returned to normal.

Table 17: Summary of participants with clinically notable laboratory abnormalities by age group (SAF)

Parameter	Notable criterion	< 18 years N=11 n (%)	≥ 18 years N=87 n (%)
AST	>82 U/L	1 (9.1)	9 (10.3)
ALT	>90 U/L	1 (9.1)	29 (33.3)
Total bilirubin	≥34.2 µmol/L	0	1 (1.1)
Creatinine	≥176 µmol/L	0	0
Total cholesterol	≥6.21 mmol/L	2 (18.2)	20 (23.0)
Hemoglobin	≤100 g/L	0	3 (3.4)
Platelets	≤100 x 10^9/L	0	3 (3.4)
	≥600 x 10^9/L	0	0
Leukocytes (WBCs)	≤2.0 x 10^9/L	2 (18.2)	5 (5.7)
	≥15 x 10^9/L	0	0
Neutrophils (absolute)	≤1 x 10^9/L	2 (18.2)	3 (3.4)
	≥12 x 10^9/L	0	1 (1.1)
Lymphocytes (absolute)	<0.2 x 10^9/L	3 (27.3)	6 (6.9)
	≥8 x 10^9/L	0	0

Data up to safety cutoff i.e. 45 days after the last dose administration of study drug was included.
Source: Table 14.3-3.3

Vital signs, physical findings and other observations related to safety

Overall, no participant in the pediatric group had a sitting pulse below 50 beats/min. Clinically notable increase (≥ 20 mmHg increase from baseline) in sitting systolic BP and sitting diastolic BP (≥ 15 mmHg increase from baseline) was observed in 3 participants (27.3%) in the pediatric group.

Mean change in QTcF at Month 24 from baseline was -3.890 msec in the pediatric group. None of the participants had a QTcF prolongation of > 500 ms.

Other Safety Findings

All participants in this study were monitored in the clinic for a minimum of 6 hours after taking the first dose of fingolimod to monitor their hourly heart rate and BP. There was 1 pediatric participant with corrected QT interval prolonged 6 hours post dose (420.45 msec), with an increase of 30-60 msec from baseline (375.77 msec). This change was not considered clinically meaningful by investigators; no AEs related to this event were reported, and it did not lead to a prolongation of first dose monitoring. Of the 2 participants with symptomatic and / or treated bradycardia, AEs of atrial escape rhythm and sinus bradycardia were reported in 1 participant each; both events were recovered without dose adjustment or additional treatment.

Concerning ophthalmology assessment, no TEAEs of macular edema were reported.

Also, no reported AE related to respiratory disease during the treatment period. No additional pulmonary function test was conducted.

Summary of safety results:

- As of the LPLV, the overall median duration of exposure to fingolimod was 714.5 days and the cumulative exposure to fingolimod was 169.0 participant years.
- All participants in the pediatric group and 98.9% of participants in the adult group experienced at least 1 TEAE during the study and were predominantly mild or moderate in severity.
- The most common TEAEs (incidence ≥ 30%) by PT were lymphopenia, leukopenia, weight decreased, pyrexia, nasopharyngitis, pharyngitis, white blood cell count decreased, and weight increased in the pediatric group, and lymphocyte count decreased, COVID-19 and alanine aminotransferase increased in the adult group. No TEAE of macular edema was reported.
- Serious AEs were reported in 3 pediatric participants, relevant PT reported in at least 2 participants was seizure (2 participants, 18.2%) in the pediatric group.
- The incidence of AEs leading to permanent discontinuation of study treatment was 1 participant in the pediatric group.
- No deaths or life-threatening events were reported in this study.
- Bradyarrhythmia and liver transaminase elevation were AESIs with relevant events reported, the majority of these events were mild or moderate in severity. The clinical laboratory or vital signs findings did not reveal unexpected safety findings. One participant in the pediatric group had ALT ≥3 ×ULN. All these events were recovering/recovered. None of the participants met the Hy's law biochemistry criteria.
- Extended monitoring after 6 hours was required in 2 pediatric participants. One pediatric participant required a second dose monitoring in clinic after discharge

***CHMP comment*:**

The safety results of the study reported that 11 patients of the pediatric population reported at least one adverse event. The most common TEAEs (incidence ≥ 30%) by PT were lymphopenia (63.6%), leukopenia (45.5%), weight decreased (45.5%), pyrexia (36.4%), nasopharyngitis (36.4%),

pharyngitis (36.4%), white blood cell count decreased (36.4%) and weight increased (36.4%). Most AEs were mild or moderate in severity. No TEAE of macular edema was reported.

Three of the 11 pediatric patients experienced SAEs. One patient experienced seizure, muscle twitching and epilepsy. Second patient experienced tonsillitis, infection, seizure, febrile infection and pneumonia. Third patient experienced syncope, which occurred after fingolimod treatment discontinuation. Both of the patients who experienced seizure had a history of epilepsy. All SAEs were moderate in severity and recovered thereafter. There were no deaths reported in the 11 pediatric patients.

Three pediatric participants had AEs leading to interruption of study treatment:1 participant had AEs of infection, seizure and tonsillitis, 1 participant had white blood cell count decreased and 1 participant had liver function test abnormal.

Overall, the AEs reported were largely consistent with the known safety profile of the substance, and no new information was identified through the priority study items or the review focused on specific effects or populations.

2.3.3. Discussion on clinical aspects

This study was designed with the aim to obtain the efficacy, safety and health outcome data in Chinese RMS participants treated daily with one dose of 0.5mg fingolimod for up to 24 months.

MRI efficacy results continued to support the clinical outcomes of fingolimod in Chinese participants. A total of 7 participants (7/8, 87.5%) in the pediatric group were free of new or newly enlarged T2 lesions at Month 24. All participants (8/8, 100.0%) in the pediatric group were free of Gd-enhancing T1 lesions at Month 24. These results indicated a sustained anti-inflammatory effect of fingolimod, which was visible at Month 12 and maintained throughout the 2-year study.

In addition, the efficacy results of fingolimod were also confirmed by 6-month CDP, NEDA-3 and PRO results. A total of 3 participants had 6m-CDP at Month 24 (Month 0-24) in the pediatric group. A total of 3 participants achieved NEDA-3 in 2 years (Month 0-24) in the pediatric. The mean changes from baseline in EQ-5D (utility and Visual Analog Scale scores) at Month 24 was -0.050 and 2.9 in the pediatric group.

Fingolimod demonstrated efficacy in reducing clinical relapses and MRI lesion activity over 24 months, consistent with findings from the PARADIGMS study, in the pediatric population. MRI data showed a mean of 2.1 new or newly enlarged T2 lesions, with 87.5% of patients free from such lesions at Month 24. No new gadolinium-enhancing T1 lesions were detected, with all patients remaining lesion-free in this category and a median lesion volume reduction of 56.0 µL. T1 hypo-intense lesions were present (mean of 13.4), but their volume decreased by a median of 641.415 µL. Overall, findings from 11 pediatric patients were aligned with the known clinical benefits of fingolimod, indicating acceptable disease control in this population.

The overall median duration of exposure was 710 days in the pediatric group, which corresponds to the overall cumulative exposure of 18.4 participant years. In line with previously reported or the interim analysis report, treatment with fingolimod for 24 months was safe and well tolerated and no unexpected safety signals were observed.

The most common TEAEs were lymphopenia, leukopenia, weight decreased, pyrexia, nasopharyngitis, pharyngitis, white blood cell counts decreased, and weight increased in the pediatric group, which was consistent with that observed in the interim analysis. Most AEs were mild or moderate in severity. No TEAE of macular edema was reported.

No deaths or life-threatening events were reported. Overall, few participants experienced SAEs, and discontinued study treatment prematurely due to an adverse event. All SAEs were mild or moderate in severity. Most SAEs PTs were reported in 1 participant each, which was also consistent with that observed in the interim analysis. Most SAEs recovered.

Bradyarrhythmia and liver transaminase elevation AESIs were reported with relevant events as expected for an S1P modulator. The majority of AESI events were reported in a small proportion of participants. Most AESI events were mild or moderate in severity.

During the first dose monitoring, few participants were required to extend monitoring after 6 hours. No unexpected laboratory findings were observed. None of the participants met the Hy's law biochemistry criteria.

The safety profile of fingolimod observed in Chinese participants in Study D2419 was consistent with the known safety profile for fingolimod and no unexpected safety signals were identified.

The final analysis results of Study D2419 showed that fingolimod 0.5 mg administered orally every day for 24 months was safe and well-tolerated, which was consistent with that observed in the interim analysis report, dated 29-Mar-2023, and continued to reduce the MS relapse rate and MRI lesions in Chinese participants. There was no indication that changes to the previously established safety profile of fingolimod in China are warranted

3. Rapporteur's CHMP overall conclusion and recommendation

☒ **Fulfilled:**

No regulatory action required.