Long-term Efficacy and Safety of Fingolimod in Paediatric Multiple Sclerosis Patients: Analysis of the PARADIG*MS* Study up to 6 Years of Treatment

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Disclosures

Kumaran Deiva received personal compensation for speaker activities from Novartis, Servier, Biogen and Sanofi.

Brenda Banwell served as a consultant for Biogen Idec, Novartis, Teva Neuroscience, Merck Serono, Canadian MS Society Scientific Research Foundation, National Multiple Sclerosis Society and Canadian Institutes of Health Research. She served as a remunerated central MRI reviewer for the present study.

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Gregory Lewis Pearce, **Mia Debarros**, **Imran Ali Khan**, **Ajay Kilaru** and **Jun Li** are employees of Novartis.

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Background

- The Phase 3 PARADIG*MS* trial (NCT01892722) of fingolimod was the first randomised, controlled study of an MS disease modifying therapy conducted in paediatric MS (PedMS) patients aged 10−17 years.
- **In the PARADIG*MS* study[1,2]**
  - Fingolimod demonstrated superior efficacy over IFN β-1a
  - Fingolimod reduced the ARR by 82% and the annualised rate of new/newly enlarging T2 lesions by 53% versus IFN β-1a
  - The safety profile of fingolimod in the PedMS population was consistent with that observed in Phase 3 fingolimod trials in adults
- Fingolimod is approved for MS in children aged 10 and above[3,4]
- The PARADIG*MS* study includes ongoing long-term extension phase in which patients are being treated with open-label fingolimod for up to an additional 5 years

ARR, annualised relapse rate; IFN β, interferon beta; n/ne, new/newly enlarged; MS, multiple sclerosis; PedMS, paediatric multiple sclerosis

1.Chitnis T, *et al. NEJM*. 2018.379;11:1017-1027. 2. Arnold DL, et al. *J Neurol Neurosurg Psychiatry*. 2020;91(5):483-492. 3. Gilenya SMPC available at Gilenya, INN-fingolimod (europa.eu) Accessed on September 30 2022. 4. GILENYA (fingolimod) capsules prescribing information available at label (fda.gov). Accessed on September 30 2022

Objective and endpoints

Objective

- To assess the long-term efficacy and safety of fingolimod in PedMS patients treated for up to 6 years in the core and/or extension phases of the PARADIG*MS* study[a]

Endpoints

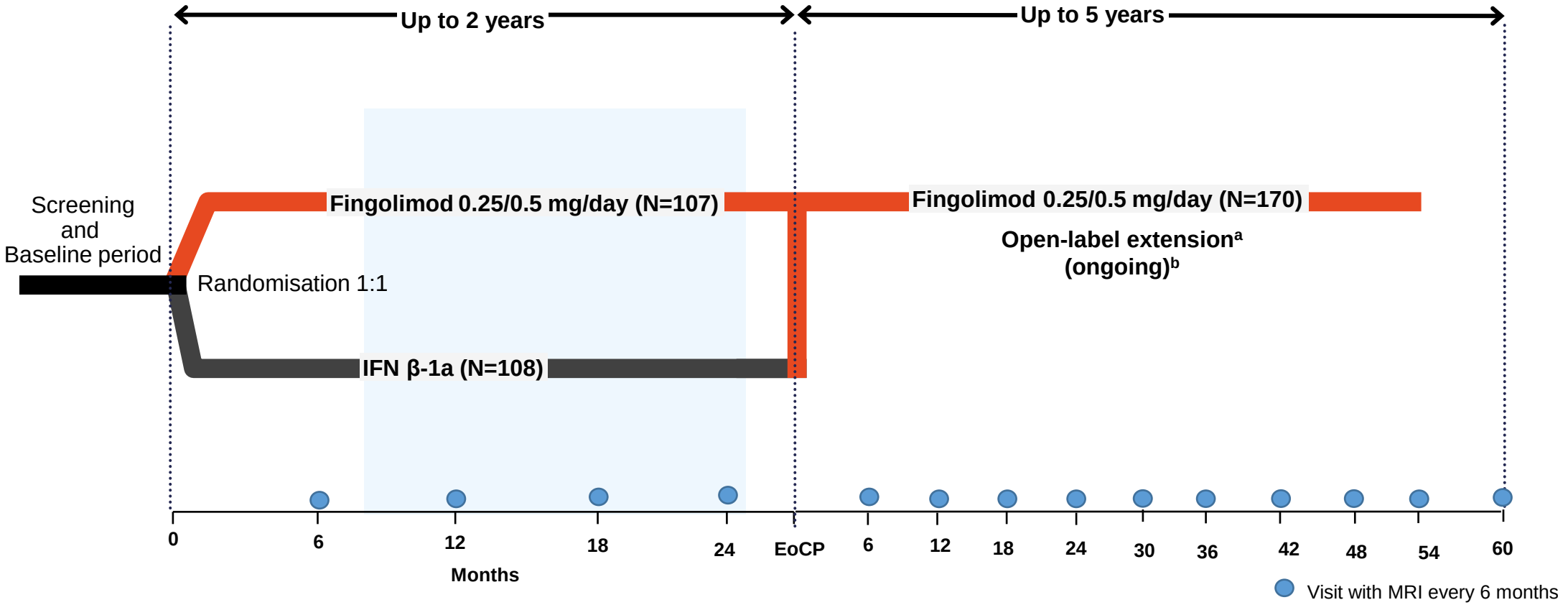
- ARR[b]
- Annualised rate of new or newly enlarged T2 lesions[b] on T2-weighted MRI scans
- Safety (AEs, SAEs and AESIs)

[a]As of data cut-off of 4th August 2021. [b]ARR and n/ne T2 lesions analyses were performed using negative binomial regression adjusted for region, pubertal status and number of relapses within 2 years before randomization

AEs, adverse event; AESIs, adverse event of special interest; ARR, annualised relapse rate; MRI, magnetic resonance imaging; PedMS, paediatric multiple sclerosis; SAEs, serious adverse event

Study design: PARADIG*MS* core+extension

PARADIG*MS* is a double-blind, active-controlled, randomised trial in PedMS patients with a core phase of up to 2 years (completed) followed by an open-label extension phase (ongoing; duration up to 5 years)



[a]Open-label treatment starts when a patient completes the core phase. Fingolimod was dosed at 0.5 mg/day, or 0.25 mg/day based on body weight (patients weighing >40kg received the 0.5 mg/d dose) and exposure is up to the cut-off date.
[b]The long term data presented are from patients originally enrolled in the PARADIG*MS* study (core and extension phase). Fingolimod was dosed at 0.5 mg/day or 0.25 mg/day based on body weight (patients weighing >40kg received the 0.5mg/d dose) and exposure is up to the cut-off date.

EoCP, end of core part; IFN, interferon; MRI, magnetic resonance imaging; PedMS, paediatric multiple sclerosis; PYs, patient year

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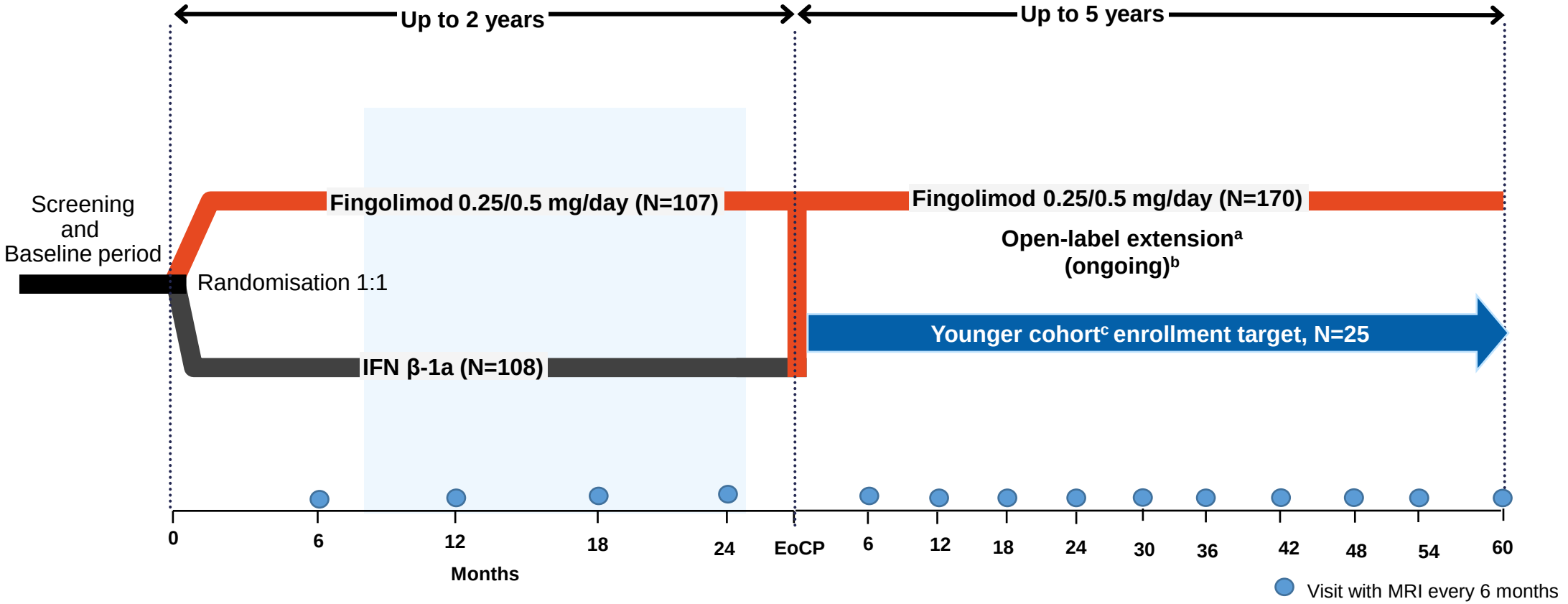
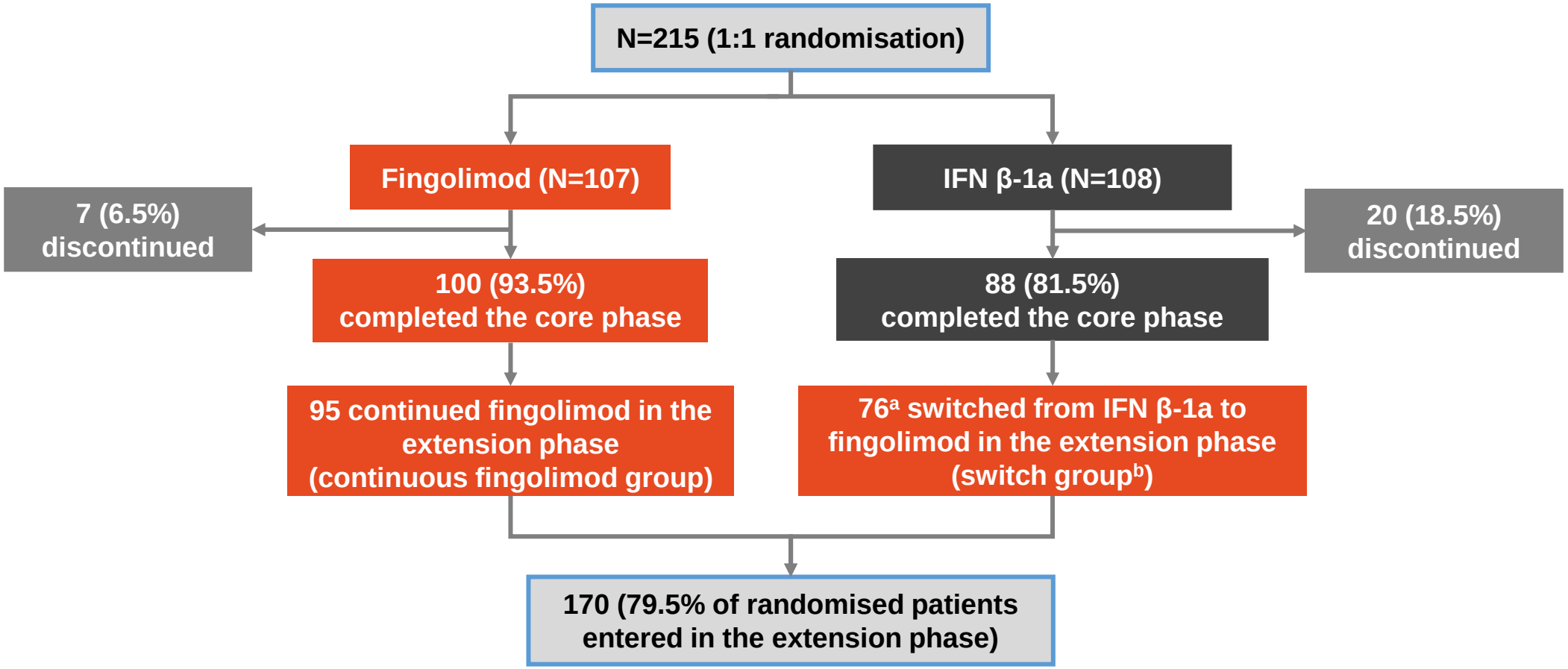


. [a]Open-label treatment starts when a patient completes the core phase. Fingolimod was dosed at 0.5 mg/day, or 0.25 mg/day based on body weight (patients weighing >40kg received the 0.5 mg/d dose) and exposure is up to the cut-off date. [b]The long term data presented are from patients originally enrolled in the PARADIG*MS* study (core and extension phase). [c]Younger cohort up to the data cut off (4th August 2021) (N=8), who were ≤ 12 years of age, or weighing ≤ 40 kg, or pre-pubertal (pubertal status of Tanner stage < 2) were recruited directly in extension phase, enrollment is ongoing

EoCP, end of core part; IFN, interferon; MRI, magnetic resonance imaging; PedMS, paediatric multiple sclerosis; PYs, patient year

Patient disposition: Core+extension

Data cut-off of 4th August 2021



[a]One patient treated with IFN β-1a in the core phase entered the extension phase but did not receive fingolimod due to local regulations. [b]Switch group consisted of patients who switched from IFNβ-1a in the core phase to fingolimod in the extension phase

IFN, interferon, N, number of patients

Baseline demographics

For extension trial

Characteristic	Continuous fingolimod group (N=95)	Switch group[a] (IFN β-1a/fingolimod) (N=75)
Age at first dose (years), Mean (SD)	15.1 (2.02)	15.4 (1.65)
Sex		
Male, n (%)	33 (34.7)	33 (44.0)
Female, n (%)	62 (65.3)	42 (56.0)
Weight		
Group A (≤40 kg)	7 (7.4)	1 (1.3)
Group B (>40 kg)	88 (92.6)	74 (98.7)
Height (cm), mean (SD)	165.5 (11.1)	167.9 (8.1)
BMI (kg/m^2), mean (SD)	22.6 (4.8)	22.5 (3.8)
Number of relapses in the last 2 year, mean (SD)	2.4 (1.49)	2.3 (0.98)
EDSS score, mean (SD)	1.45 (1.08)[b]	1.53 (0.95)
Number of Gd+ T1 lesions	2.7 (6.3)[c]	2.4 (4.78)[d]
Pubertal status by tanner staging score		
Pre-pubertal [<2])	6 (6.3)[e]	1 (1.3)
Pubertal [≥2])	87 (91.6)[e]	74 (98.7)

The above values presented as n (%), [a]Switch group consisted of patients who switched from IFNβ-1a in the core phase to fingolimod in the extension phase [b]refers to mean and SD values for n=93, [c]refers to mean and SD values for n=94 [d]refers to mean and SD values for n=74. [e]In the continuous fingolimod group, pubertal status data presented for n=93 patients. Parameters having subcategories are presented in bold.

BMI, body mass index; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; IFN, interferon; SD, standard deviation

Duration of exposure to study drug

Cut-off: 4th August 2021

Duration of exposure to study drug	Continuous fingolimod group N=95; n (%)	Switch group[a] (IFN β-1a/fingolimod) N=75; n (%)
≥1 day	95 (100)	75 (100)
≥6 months	95 (100)	75 (100)
≥12 months	95 (100)	75 (100)
≥24 months	93 (97.9)	74 (98.7)
≥3 years	89 (93.7)	71 (94.7)
≥4 years	85 (89.5)	66 (88.0)
≥5 years	79 (83.2)	61 (81.3)
≥6 years	35 (36.8)	24 (32.0)
≤7 years	3 (3.2)	0 (0.0)
Study drug exposure in months, mean (SD)	66.6 (14.0)	66.1 (13.2)
Patient-time (PYs)	520.0[b]	407.3[c]

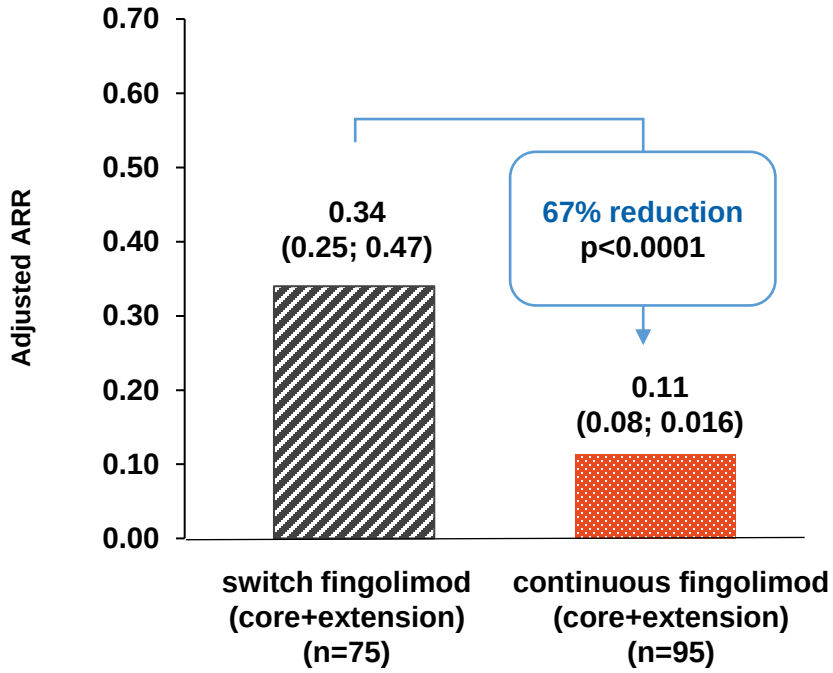
[a]Switch group consisted of patients who switched from IFNβ-1a in the core phase to fingolimod in the extension phase.
[b]PY 520.0 from continuous fingolimod patients + 285.0 from switched fingolimod patients equals a total exposure value of 805.0.
[c]Out of 407.3 PYs (value is relevant for efficacy parameters like ARR and n/ne T2 lesions) study drug exposure 285.0 PYs (value relevant for safety parameters like AEs) were on fingolimod

- **As of 04th August 2021, the mean exposure to fingolimod in the core and/or extension phase was 5.4 years with a total exposure of 805.0[b] PY**

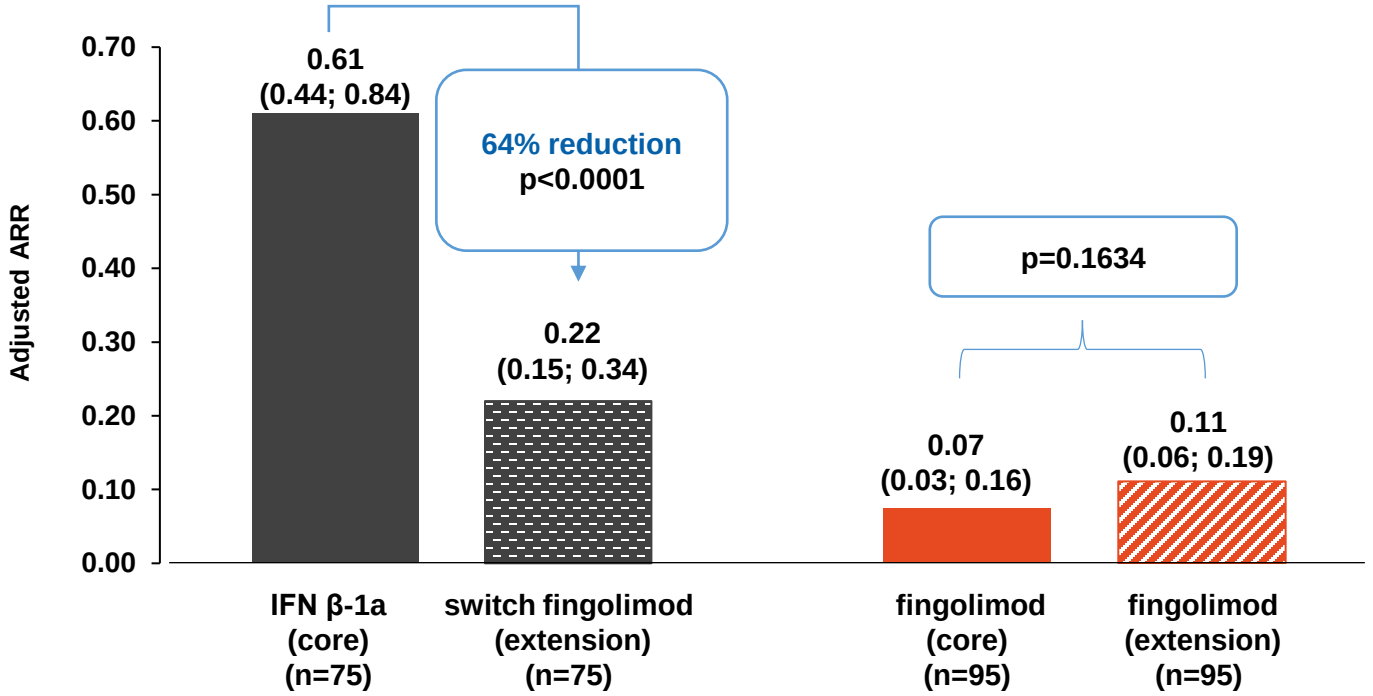
IFN, interferon; PYs, patient year; n/ne, new/newly enlarging; SD, standard deviation

Results: Persistent reduction in ARR with fingolimod

Between group comparison (switch fingolimod vs continuous fingolimod)



Within-group comparison (Within the IFN β-1a and fingolimod groups)



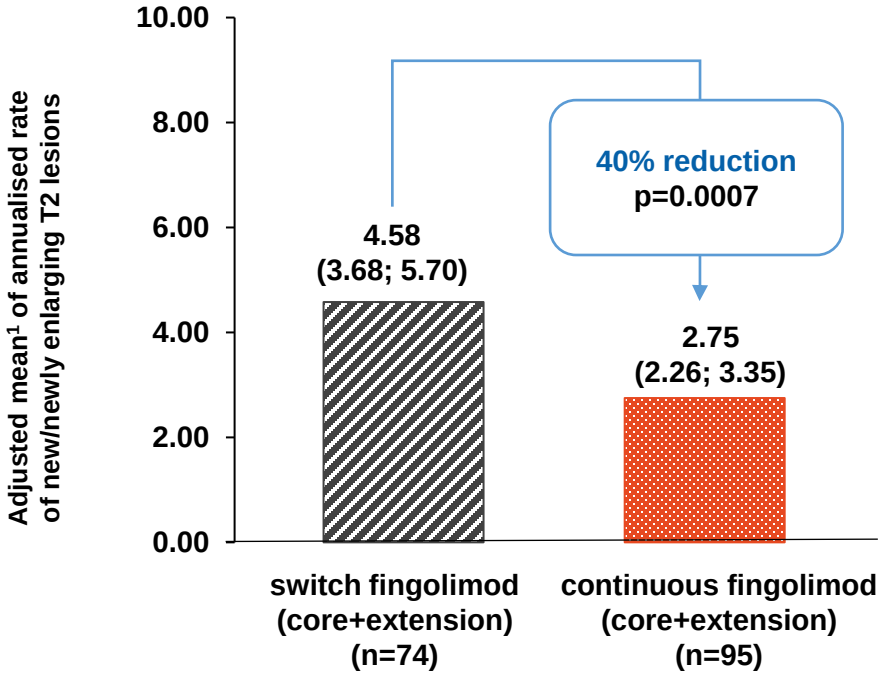
- Patients receiving IFN in core part benefited from significant reduction of ARR after switching to fingolimod in the extension phase
- ARR remained low and comparable to core part throughout extension for patients who were continuously on fingolimod

n: Total number of subjects included in the analysis. Adjusted ARR is obtained from fitting a negative binomial regression model adjusted for region, pubertal status (the stratification factor in IVRS), and the number of relapses in the previous two years before randomisation/enrollment (offset: time in study).

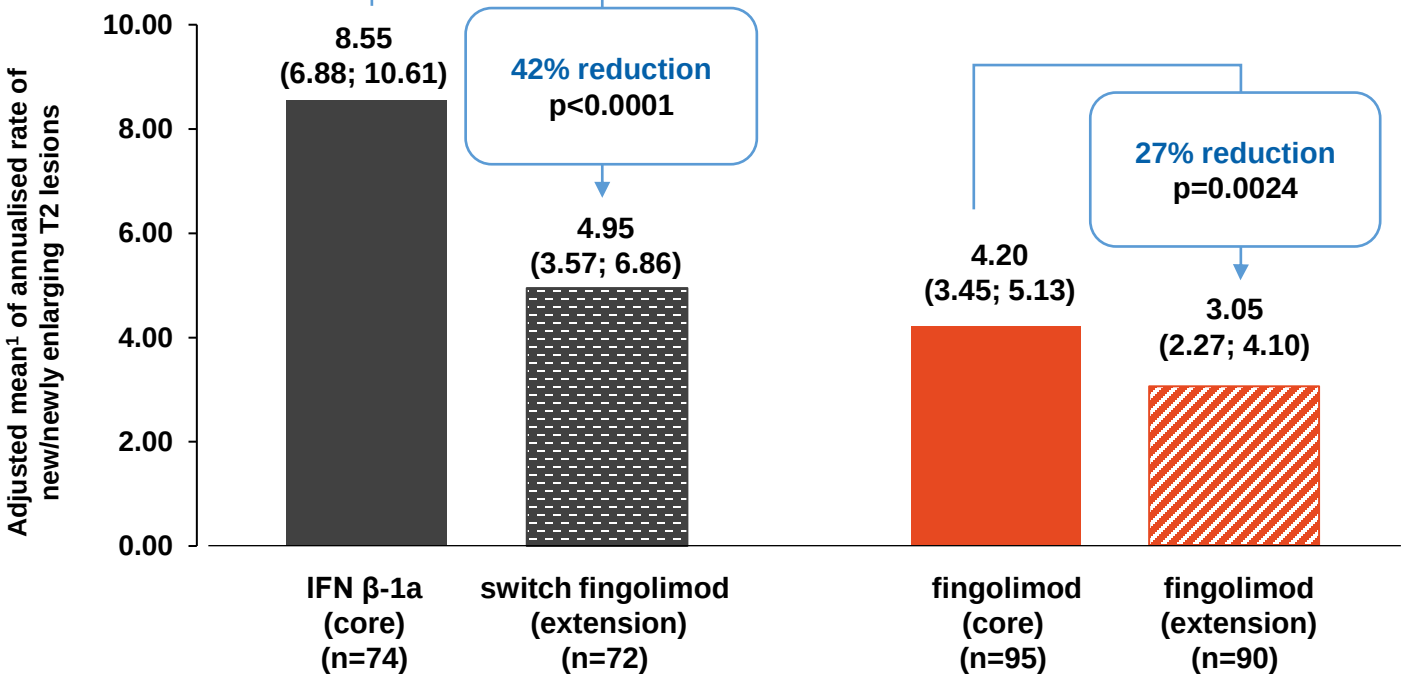
ARR, annualised relapse rate; CI, confidence interval; IFN, interferon

Results: Reduction in annualised rate of new/newly enlarging T2 lesions

Between group comparison (switch fingolimod vs continuous fingolimod)



Within-group comparison (Within the IFN β-1a and fingolimod groups)



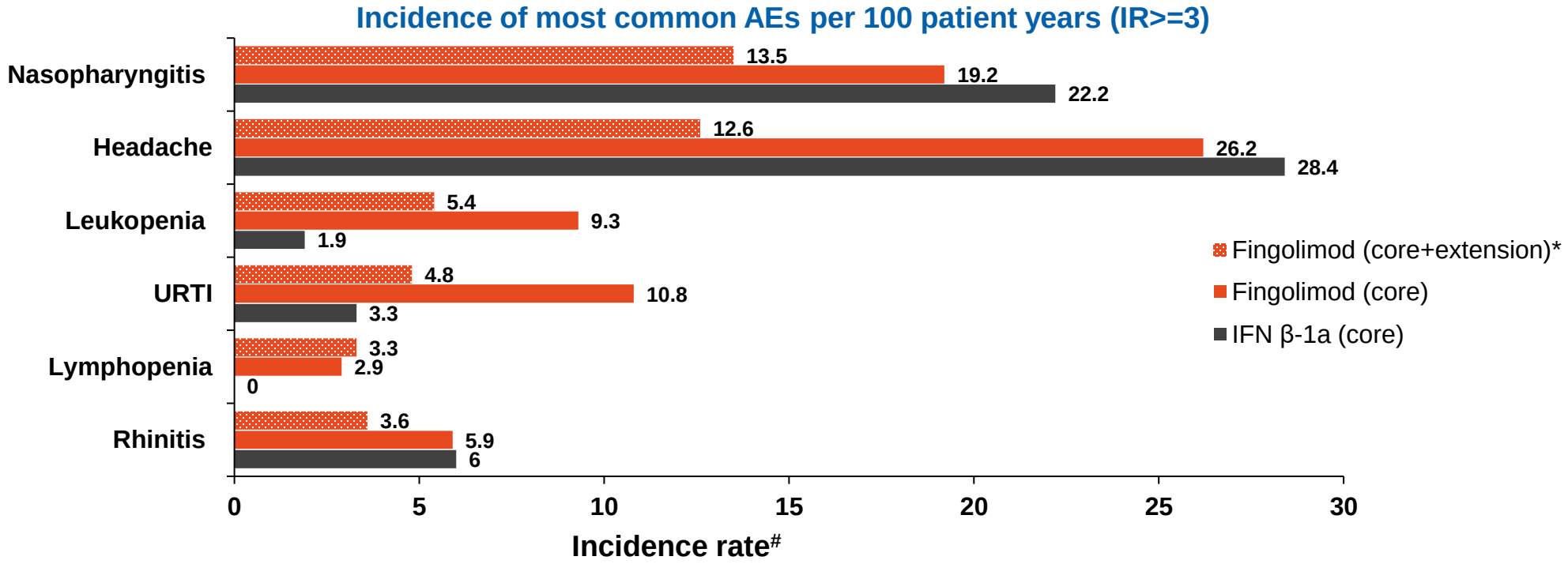
- **Patients receiving IFN in core part benefited from significant reduction of annualised rate of new/newly enlarging T2 lesions after switching to fingolimod in the extension phase**
- **Annualised rate of new/newly enlarging T2 lesions remained low and comparable to core part throughout extension for patients who were continuously on fingolimod**

[1] Obtained from fitting a negative binomial regression model adjusted for region, pubertal status (the stratification factor in IVRS), and core baseline number of T2 lesions (Offset: time in study).

n: Total number of subjects included in the analysis; n/ne, new/newly enlarging lesions; IFN , Interferon

Results: Incidence of AEs

SAEs



- **Overall, no qualitative and quantitative changes were observed in the reported AE profile with long-term exposure to fingolimod**
- **A similar observation was made for SAEs. Overall, low incidences of SAEs were reported with no observed increases in exposure-adjusted IRs with long-term treatment (IR/100 PYs: fingolimod [core], 11.8, IFN [core] 6.6, fingolimod [core+extension]* 5.5)**
- **The majority of the SAEs reported were single events**

#IR=the incidence rate expressed per 100 patient-years of the at-risk population. *The number of patients treated with fingolimod in the continuous and switch groups was 170 at the time of the analysis
AEs, adverse event; IR, incidence rate; IFN , Interferon; PY patient year; SAEs, serious adverse event; URTI, upper respiratory tract infection

Results: Incidence of AESIs per 100 PYs

Safety Supporting data _ AESI

AESIs	Core phase		Core+extension phase		
	Fingolimod (N=107a), n(IR)	IFN β-1a (N=107a), n(IR)	Continuous fingolimod (N=95), n(IR)	Switch-fingolimod (N=75), n(IR)	Total (N=170), n(IR)
Bradyarrhythmia and bradycardia	4 (2.3)	2 (1.3)	4 (0.8)	1 (0.2)	5 (0.5)
Macular oedema	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0)
Infections and infestations	64 (71.2)	60 (64.7)	80 (48.4)	68 (56.5)	148 (51.8)
Varicella zoster virus infections	1 (0.6)	1 (0.6)	3 (0.6)	5 (1.2)	8 (0.9)
Herpes simplex virus infections	2 (1.1)	2 (1.3)	5 (1.0)	4 (1.0)	9 (1.0)
Liver-related signs and symptoms	9 (5.3)	6 (3.9)	17 (3.7)	15 (4.0)	32 (3.8)
Convulsions	6 (3.4)	1 (0.6)	8 (1.6)	5 (1.2)	13 (1.4)
Epilepsy	3 (1.7)	0 (0.0)	3 (0.6)	1 (0.2)	4 (0.4)
Seizure	2 (1.1)	1 (0.6)	3 (0.6)	4 (1.0)	7 (0.7)
Generalised tonic-clonic seizure	1 (0.6)	0 (0.0)	1 (0.2)	1 (0.2)	2 (0.2)
Partial seizures	1 (0.6)	0 (0.0)	3 (0.6)	0 (0.0)	3 (0.3)
Partial seizures with secondary generalization	1 (0.6)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)

- **Overall, there were no unexpected increases from the core phase in the IRs of AESIs with long-term exposure to fingolimod**

MedDRA Version 24.0 was used for the reporting of adverse events. IR=the incidence rate expressed per 100 patient-years of the at-risk population. a, here n=107 instead of 108, one patient on IFN during the core phase entered the extension phase but never received a dose of fingolimod. Since incidence is based on exposure and there was no exposure, that patient is not included in the above table.

AESIs, adverse events of special interest; IR, incidence rate; MedDRA, Medical Dictionary for Regulatory Activities; N=Number of patients in the analysis set; n, number of patients with at least one AE in the corresponding category an adverse event; PYs, patient-year

Conclusions

- In PedMS patients aged 10–17 years treated with fingolimod for up to 6 years in PARADIGMS (core and/or extension phase), the ARR and the annualised rate of new/newly enlarging remained low with continuous fingolimod and were significantly reduced for patients who switched from IFNβ-1a to fingolimod, demonstrating persistent efficacy with fingolimod treatment
- The nature of AEs (including SAEs) and AESIs reported with long-term treatment were in line with the core phase and consistent with the known safety profile of S1P modulators in adult patients. No new safety signals were observed
- These results continue to support the positive benefit-risk profile of fingolimod in PedMS patients

AEs, adverse events; AESIs, adverse events of special interest; ARR, adjusted relapse rate; ; IFN β-1a , Interferon β-1a; PedMS, paediatric multiple sclerosis, SAEs, serious adverse events

Future directions

- **PARADIG*MS* study provides valuable information on future study design in paediatric MS**
  - A phase 3 NEOS study (NCT04926818) which aims to assess the efficacy and safety of ofatumumab and siponimod versus fingolimod in patients with PedMS (aged 10–17 years) is recruiting

PedMS, paediatric multiple sclerosis

Acknowledgements

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