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

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Scientific Session 6: Treating children with MS (‘Rogier Hintzen session’)
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The Phase 3 PARADIGMS 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 PARADIGMS 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 PARADIGMS 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

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 PARADIGMS study\textsuperscript{a}

Endpoints

• ARR\textsuperscript{b}
• Annualised rate of new or newly enlarged T2 lesions\textsuperscript{b} on T2-weighted MRI scans
• Safety (AEs, SAEs and AESIs)

\textsuperscript{a}As of data cut-off of 4\textsuperscript{th} August 2021. \textsuperscript{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
PARADIGMMS 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).

Study design: PARADIGMMS core+extension

*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.

The long term data presented are from patients originally enrolled in the PARADIGMMS 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
PARADIGMS 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)

Study design: PARADIGMS core+extension

- **Screening and Baseline period**
- **Randomisation 1:1**
- **Fingolimod 0.25/0.5 mg/day (N=107)**
- **IFN β-1a (N=108)**

**Fingolimod 0.25/0.5 mg/day (N=170)**

- **Open-label extension**
- **Younger cohort**

**Months**

- **0**  
- **6**  
- **12**  
- **18**  
- **24**  
- **EoCP**  
- **6**  
- **12**  
- **18**  
- **24**  
- **30**  
- **36**  
- **42**  
- **48**  
- **54**  
- **60**

- **Visit with MRI every 6 months**

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

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*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.

*The long term data presented are from patients originally enrolled in the PARADIGMS study (core and extension phase).

*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.
Patient disposition: Core+extension
Data cut-off of 4th August 2021

N=215 (1:1 randomisation)

Fingolimod (N=107)
- 7 (6.5%) discontinued
- 100 (93.5%) completed the core phase
- 95 continued fingolimod in the extension phase (continuous fingolimod group)

IFN β-1a (N=108)
- 20 (18.5%) discontinued
- 88 (81.5%) completed the core phase
- 76 switched from IFN β-1a to fingolimod in the extension phase (switch group)

170 (79.5% of randomised patients entered in the extension phase)

*One patient treated with IFN β-1a in the core phase entered the extension phase but did not receive fingolimod due to local regulations. *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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Continuous fingolimod group (N=95)</th>
<th>Switch groupa (IFN β-1a/fingolimod) (N=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first dose (years), Mean (SD)</td>
<td>15.1 (2.02)</td>
<td>15.4 (1.65)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>33 (34.7)</td>
<td>33 (44.0)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>62 (65.3)</td>
<td>42 (56.0)</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A (≤40 kg)</td>
<td>7 (7.4)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Group B (&gt;40 kg)</td>
<td>88 (92.6)</td>
<td>74 (98.7)</td>
</tr>
<tr>
<td>Height (cm), mean (SD)</td>
<td>165.5 (11.1)</td>
<td>167.9 (8.1)</td>
</tr>
<tr>
<td>BMI (kg/m²), mean (SD)</td>
<td>22.6 (4.8)</td>
<td>22.5 (3.8)</td>
</tr>
<tr>
<td>Number of relapses in the last 2 year, mean (SD)</td>
<td>2.4 (1.49)</td>
<td>2.3 (0.98)</td>
</tr>
<tr>
<td>EDSS score, mean (SD)</td>
<td>1.45 (1.08)b</td>
<td>1.53 (0.95)</td>
</tr>
<tr>
<td>Number of Gd+ T1 lesions</td>
<td>2.7 (6.3)c</td>
<td>2.4 (4.78)d</td>
</tr>
<tr>
<td><strong>Pubertal status by tanner staging score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-pubertal [&lt;2]</td>
<td>6 (6.3)e</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Pubertal [≥2]</td>
<td>87 (91.6)e</td>
<td>74 (98.7)</td>
</tr>
</tbody>
</table>

The above values presented as n (%). aSwitch group consisted of patients who switched from IFNβ-1a in the core phase to fingolimod in the extension phase brefers to mean and SD values for n=93. crefers to mean and SD values for n=74. dIn 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**

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

$^a$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

- 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/enrolment (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)

<table>
<thead>
<tr>
<th>Group</th>
<th>Adjusted mean of annualised rate of new/newly enlarging T2 lesions</th>
<th>40% reduction p=0.0007</th>
</tr>
</thead>
<tbody>
<tr>
<td>switch fingolimod (n=74)</td>
<td>4.58 (3.68; 5.70)</td>
<td></td>
</tr>
<tr>
<td>continuous fingolimod (n=95)</td>
<td>2.75 (2.26; 3.35)</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Group</th>
<th>Adjusted mean of annualised rate of new/newly enlarging T2 lesions</th>
<th>42% reduction p&lt;0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN β-1a (core) (n=74)</td>
<td>8.55 (6.88; 10.61)</td>
<td></td>
</tr>
<tr>
<td>IFN β-1a (extension) (n=72)</td>
<td>4.95 (3.57; 6.86)</td>
<td></td>
</tr>
<tr>
<td>fingolimod (core) (n=95)</td>
<td>4.20 (3.45; 5.13)</td>
<td>27% reduction p=0.0024</td>
</tr>
<tr>
<td>fingolimod (extension) (n=90)</td>
<td>3.05 (2.27; 4.10)</td>
<td></td>
</tr>
</tbody>
</table>

• 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**

Incidence of most common AEs per 100 patient years (IR≥3)

- **Nasopharyngitis**
  - Fingolimod (core+extension)*: 13.5
  - Fingolimod (core): 19.2
  - IFN β-1a (core): 22.2

- **Headache**
  - Fingolimod (core+extension)*: 12.6
  - Fingolimod (core): 26.2
  - IFN β-1a (core): 28.4

- **Leukopenia**
  - Fingolimod (core+extension)*: 9.3
  - Fingolimod (core): 3.3
  - IFN β-1a (core): 5.4

- **URTI**
  - Fingolimod (core+extension)*: 10.8
  - Fingolimod (core): 4.8
  - IFN β-1a (core): 3.3

- **Lymphopenia**
  - Fingolimod (core+extension)*: 2.9
  - Fingolimod (core): 3.3
  - IFN β-1a (core): 1.9

- **Rhinitis**
  - Fingolimod (core+extension)*: 5.9
  - Fingolimod (core): 6
  - IFN β-1a (core): 3.6

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- 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.

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*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.
Deiva K, et al. | Oral session: O069

Results: Incidence of AESIs per 100 PYs

<table>
<thead>
<tr>
<th>AESIs</th>
<th>Core phase</th>
<th>Core+extension phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fingolimod (N=107a), n(IR)</td>
<td>IFN β-1a (N=107a), n(IR)</td>
</tr>
<tr>
<td>Bradyarrhythmia and bradycardia</td>
<td>4 (2.3)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Macular oedema</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>64 (71.2)</td>
<td>60 (64.7)</td>
</tr>
<tr>
<td>Varicella zoster virus infections</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Herpes simplex virus infections</td>
<td>2 (1.1)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Liver-related signs and symptoms</td>
<td>9 (5.3)</td>
<td>6 (3.9)</td>
</tr>
<tr>
<td>Convulsions</td>
<td>6 (3.4)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>3 (1.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Seizure</td>
<td>2 (1.1)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Generalised tonic-clonic seizure</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Partial seizures</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Partial seizures with secondary generalization</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

• 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

• PARADIGM$MS$ study provides valuable information on future study design in paediatric MS
  
  o 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
We would like to express our gratitude to all the participating patients. In addition, we thank all participating study sites and investigators.