**Introduction**

- Despite numerous treatment options available for adult patients with multiple sclerosis (MS), a high unmet need remains in children and adolescents with MS.
  - Fingolimod is the only therapy approved worldwide for use in the paediatric MS (pEDMS) population based on the results of the successful PARADIGM phase 3 trials.
- Although the pathophysiology driving the MS disease course is similar between pEDMS and adult onset MS, young, and particularly pEDMS patients, experience higher levels of inflammation (MRI lesions, clinical relapses and associated neurological symptoms); pEDMS patients also experience brain volume loss from disease onset and accumulate disability at a younger age versus patients with adult-onset MS.
- There are substantial challenges in conducting randomised clinical trials (RCTs) for pEDMS including:
  - Limited number of patients (rare disease; incidence of 0.13 to 0.66/100 000 children/year).
  - Competition for recruiting patients across different trials.
  - Ethical concerns regarding the use of placebo or low-efficacy therapies as a control arm.

**Objective**

- To present the innovative Bayesian non-inferiority design of the phase 3 NEOS study, which aims to assess the efficacy and safety of ofatumumab and siponimod versus fingolimod in patients with pEDMS aged 10 to <18 years.

**Methods**

**NEOS Study Design**

- NEOS is composed of a 2-year double-blind core part and an open-label extension part (Figure 1).
- A total of 180 eligible patients will be randomised 1:1:1 to subcutaneous ofatumumab, oral siponimod or oral fingolimod on day 1.
- The double-blind part of the study may be stopped early for futility or for evidence of compelling efficacy at the pre-planned interim analysis.
- Participants completing the double-blind part will be eligible to enter the open extension part (up to 5 years).

**Study objectives and endpoints**

**Table 1. Study Objectives and Endpoints**

<table>
<thead>
<tr>
<th>Objective</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td><strong>Study population</strong></td>
<td>Patients from 31 countries (approximately 92 centres worldwide) will participate in this study.</td>
</tr>
<tr>
<td><strong>Key eligibility criteria</strong></td>
<td>Presented in Table 2.</td>
</tr>
</tbody>
</table>

**Study objectives**

- Diagnosis of pEDMS 10 to <18 years of age at randomization
- EDSS > 0.5 at screening
- MS relapse/attack 21 days during the previous year or 2 in the previous 2 years prior to screening, or evidence of ≥1 new T2 lesions or Gd-enhancing T1 lesions compared to prior MRI conducted within 12 months prior to randomisation

**Endpoints**

- **Primary Endpoint**
  - Demonstrate the non-inferiority of ofatumumab and siponimod compared to fingolimod as assessed by ARR in pEDMS participants treated for up to 2 years using a Bayesian negative binomial regression model.
- **Key Secondary Endpoint**
  - Assess the superiority of ofatumumab and siponimod compared to fingolimod as assessed by ARR in pEDMS participants treated for up to 2 years using a Bayesian negative binomial regression model and an open-label extension part (up to 5 years) (See ECTRIMS 2021 Poster P097 for more details).

**Other Secondary Endpoints**

- Annualised T2 lesion volume
- Serum NfL concentrations
- PK properties of ofatumumab and siponimod (and its metabolite M11)
- Description of OFA and SPO including anti-AQP4 antibodies; safety and tolerability of ofatumumab and siponimod (A/S, C/S/SRS, ECG, laboratory and ophthalmological data; PFTs and vital signs).

**Disclosures**

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**Advantages of the novel NEOS study design**

Integration of knowledge from historical paediatric and adult MS clinical trials

Further details are being presented at this congress: ECTRIMS 2021 ePoster P097

**Figure 1. NEOS Study Design**

- 2-year randomised, 3-arm, double-blind, triple dummy, non-inferiority study.

**Study population**

- Patients from 31 countries (approximately 92 centres worldwide) will participate in this study.

**Key eligibility criteria**

- Presented in Table 2.

**Table 2. Key Inclusion and Exclusion Criteria**

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
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<tbody>
<tr>
<td>- Diagnosis of pEDMS 10 to &lt;18 years of age at randomization</td>
<td></td>
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<tr>
<td>- EDSS &gt; 0.5 (inclusive) at screening</td>
<td></td>
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<tr>
<td>- MS relapse/attack 21 days during the previous year or 2 in the previous 2 years prior to screening, or evidence of ≥1 new T2 lesions or Gd-enhancing T1 lesions compared to prior MRI conducted within 12 months prior to randomisation (including screening MRI)</td>
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**Conclusions**

- With the use of scientifically validated methodology based on ‘Bayesian priors’ **(ECTRIMS 2021 #P097)**, the NEOS study aims to:
  - Reduce the required sample size
  - Avoid the use of placebo or IFN-β 1a and offers study participants treatment with one of three active drugs (ofatumumab, siponimod or fingolimod), with demonstrated high efficacy in adults and of which the comparator (fingolimod) is approved in pEDMS
  - Reduce the risk of relapses and disease worsening compared to a conventional superiority design vs placebo or an interferon
  - If positive, will demonstrate that the tested treatments are similarly or more efficacious than fingolimod and more efficacious than historical interferons
  - An interim analysis ensures that the double-blind phase does not last longer than needed to detect the benefit-risk ratio of the new treatment options
  - The efficiency of the trial can bring two new therapies available to pEDMS patients.

**References**


**Acknowledgements**

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