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Innovative Phase 3 NEOS Study Design Evaluating Efficacy and Safety of Ofatumumab and Siponimod Versus Fingolimod in Paediatric Multiple Sclerosis

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Introduction

- Despite numerous treatment options available for adult patients with multiple sclerosis (MS), a high unmet need remains in children and adolescents with MS[1]
  - Fingolimod is the only therapy approved worldwide for use in the paediatric MS (pedMS) population based on the results of the successful PARADIG*M*S phase 3 trial[2,3]
- 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[1,4,5]
- There are substantial challenges in conducting randomised clinical trials (RCTs) for pedMS including[5]
  - 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 extension part (up to 5 years)**

Study objectives and endpoints

Table 1. Study Objectives and Endpoints

Primary Endpoint: Demonstrate the **non-inferiority** of ofatumumab and/or 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: Demonstrate the **superiority** of ofatumumab and/or siponimod compared to historical interferon (IFN) β-1a data assessed by ARR

(See ECTRIMS 2021 ePoster P097 for more details)

Other Secondary Endpoints: Annualised T2 lesion rate; serum NfL concentrations; PK properties of ofatumumab and siponimod (and its metabolite M17); proportion of participants with anti-ofatumumab antibodies; safety and tolerability of ofatumumab and siponimod (AEs, C-SSRS, ECG, laboratory and ophthalmological data, PFTs and vital signs)

AE, adverse event; ARR, annualised relapse rate; C-SSRS, Columbia Suicide Severity Rating Scale; ECG, electrocardiogram; MS, multiple sclerosis; NfL, neurofilament light chain; PFT, pulmonary function test; PK, pharmacokinetic.

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

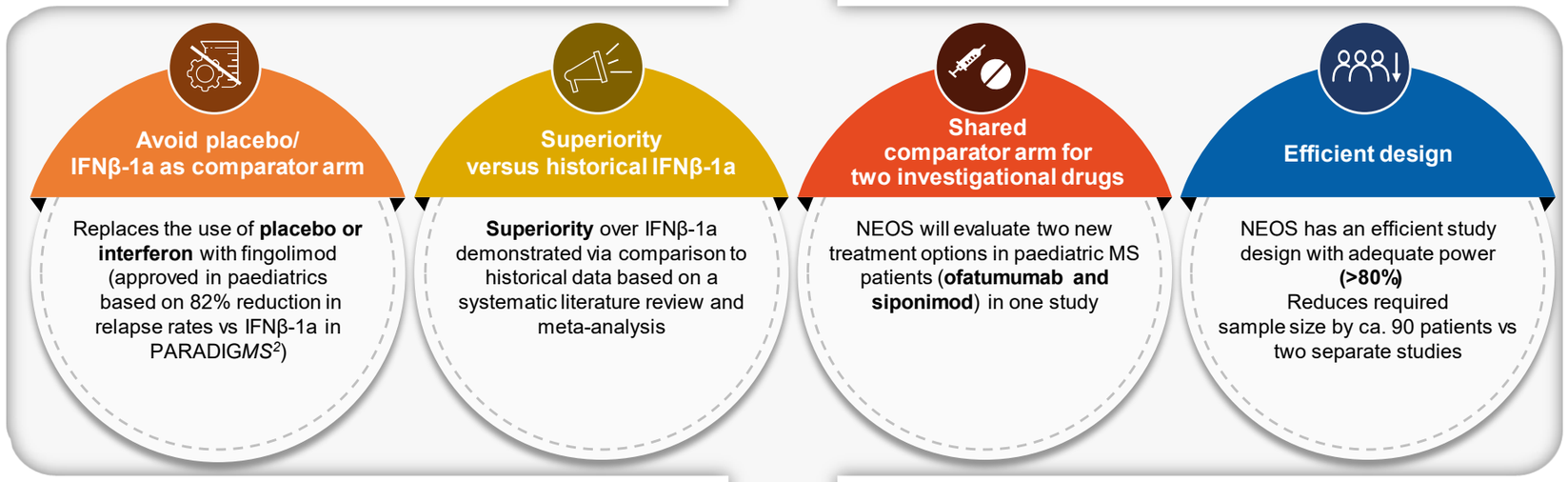
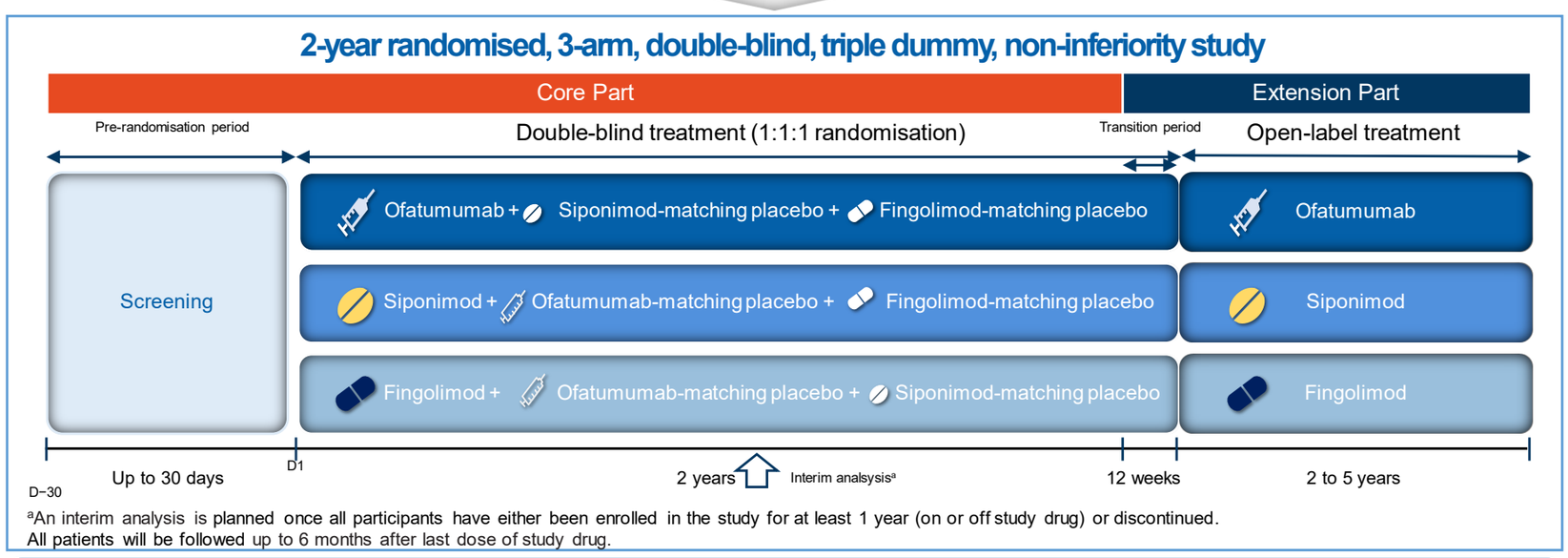


Figure 1. NEOS Study Design



[a]An interim analysis is planned once all participants have either been enrolled in the study for at least 1 year (on or off study drug) or discontinued. All patients will be followed up to 6 months after last dose of study drug.

The study will start enrolling patients soon
Refer to clinical trials.gov | NCT04926818 for updates

Study population

- Patients from 31 countries (approximately 92 centres worldwide) will participate in this study
- Key eligibility criteria are presented in **Table 2**

Table 2. Key Inclusion and Exclusion Criteria

Inclusion

- Diagnosis of pedMS **10 to <18 years** of age at randomization
- **EDSS 0 to 5.5** (inclusive) at screening
- **MS relapse/attack: ≥1** 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)

Exclusion

- **Progressive MS**
- Participants with **ADEM** or **neuromyelitis optica** or (at screening) **aquaporin 4+** or **anti-MOG+** or **other demyelinating disorder** suggested by screening MRI
- Homozygous for CYP2C9 *3/*3
- An active, chronic immune system-related disease other than MS
- Significant ECG findings
- Other criteria as described in protocol

ADEM, acute disseminated encephalomyelitis; CYP2C9, cytochrome P450 2C9; ECG, electrocardiogram; EDSS, Expanded Disability Status Scale; GFR, glomerular filtration rate; MOG, Myelin Oligodendrocyte Glycoprotein; MRI, magnetic resonance imaging; MS, multiple sclerosis.

Conclusions

- **With the use of scientifically validated methodology based on 'Bayesian priors' (ECTRIMS 2021 #P097), the NEOS study aims to:**
  - Reduces the required sample size
  - Avoids the use of placebo or IFNβ-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
  - Reduces 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 assess the benefit–risk ratio of the new treatment options
  - The efficiency of the trial can bring two new therapies available to pedMS patients

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