P097

Using Historical Relapse Rates for the Design of an Innovative Phase 3 Study with Ofatumumab and Siponimod in Paediatric Multiple Sclerosis

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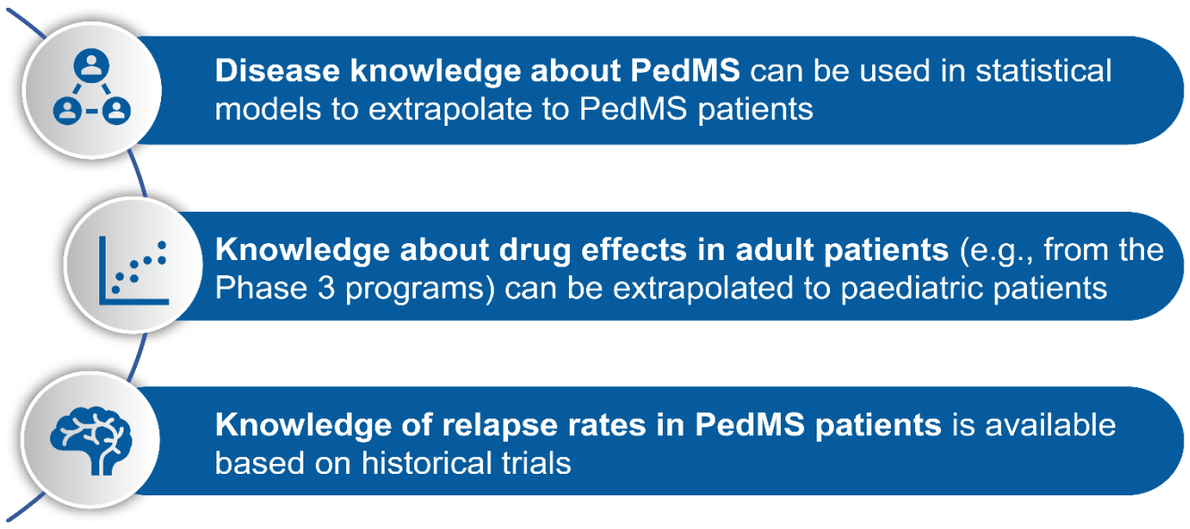
Introduction

- Approximately 20 treatment options are approved for use in adult patients with multiple sclerosis (MS), while in patients with paediatric MS (PedMS), fingolimod is the only successfully tested and world-wide approved therapy, and so a high unmet need continues to exist[1,2]
- The pathophysiology of PedMS and adult-onset MS patients is fundamentally similar; however, young patients, and particularly PedMS patients experience more frequent relapses and associated neurological symptoms compared to adult MS patients[3]
- PedMS patients are a vulnerable population, they lose brain volume from disease onset and accumulate disability at a younger age vs patients with adult-onset MS[2,4-5]
- Conducting studies in PedMS is challenging due to the rarity of the disease, competing recruitment trials and ethical concerns on testing new drugs versus placebo or low-efficacy controls because of the risk of relapses and irreversible residual deficits[6,7]
- Innovative study designs that leverage prior disease- and drug-related knowledge can help to make new trials in PedMS more feasible and efficient, and minimize the risk of relapses and residual deficits for participants (**Figure 1**)



Objective

- To systematically review and summarize the current knowledge on relapse rates in PedMS based on existing literature and patient-level data, and to leverage this information in the newly planned NEOS Phase 3 trial of ofatumumab and siponimod in PedMS patients using a Bayesian framework

Methods

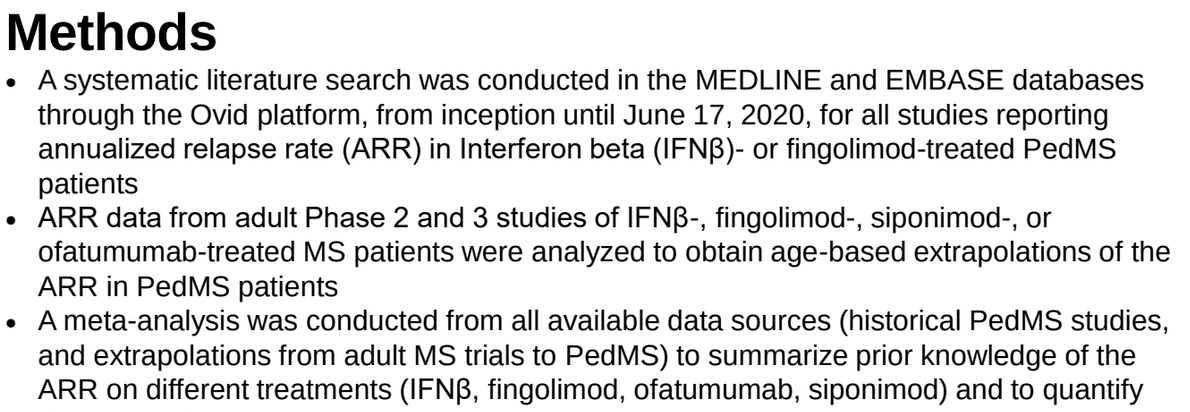
- A systematic literature search was conducted in the MEDLINE and EMBASE databases through the Ovid platform, from inception until June 17, 2020, for all studies reporting annualized relapse rate (ARR) in Interferon beta (IFNβ)- or fingolimod-treated PedMS patients
- ARR data from adult Phase 2 and 3 studies of IFNβ-, fingolimod-, siponimod-, or ofatumumab-treated MS patients were analyzed to obtain age-based extrapolations of the ARR in PedMS patients
- A meta-analysis was conducted from all available data sources (historical PedMS studies, and extrapolations from adult MS trials to PedMS) to summarize prior knowledge of the ARR on different treatments (IFNβ, fingolimod, ofatumumab, siponimod) and to quantify the uncertainty
- Robust Bayesian meta-analytic predictive priors[8,9] were used to incorporate the historical information in the Bayesian design of the new study
- The amount of information in priors was quantified using the effective sample size[10]

Results

Age-based extrapolation from adults to PedMS

- Age-based extrapolation from the adult Phase 3 TRANSFORMS trial (fingolimod vs IFNβ) conducted in year 2010 was highly accurate in predicting the outcome of the PARADIG*MS* trial (fingolimod vs IFNβ in PedMS patients) in year 2017. Similar results were obtained for other Phase 3 fingolimod studies (**Figure 2**)
- Extrapolation of ARR from adults to PedMS patients can be done but needs to consider that relapse rates in paediatric patients may be higher than in adults

Figure 2 Extrapolation of ARR from Phase 3 adult studies to PedMS patients, and superimposed ARR of pediatric PedMS patients



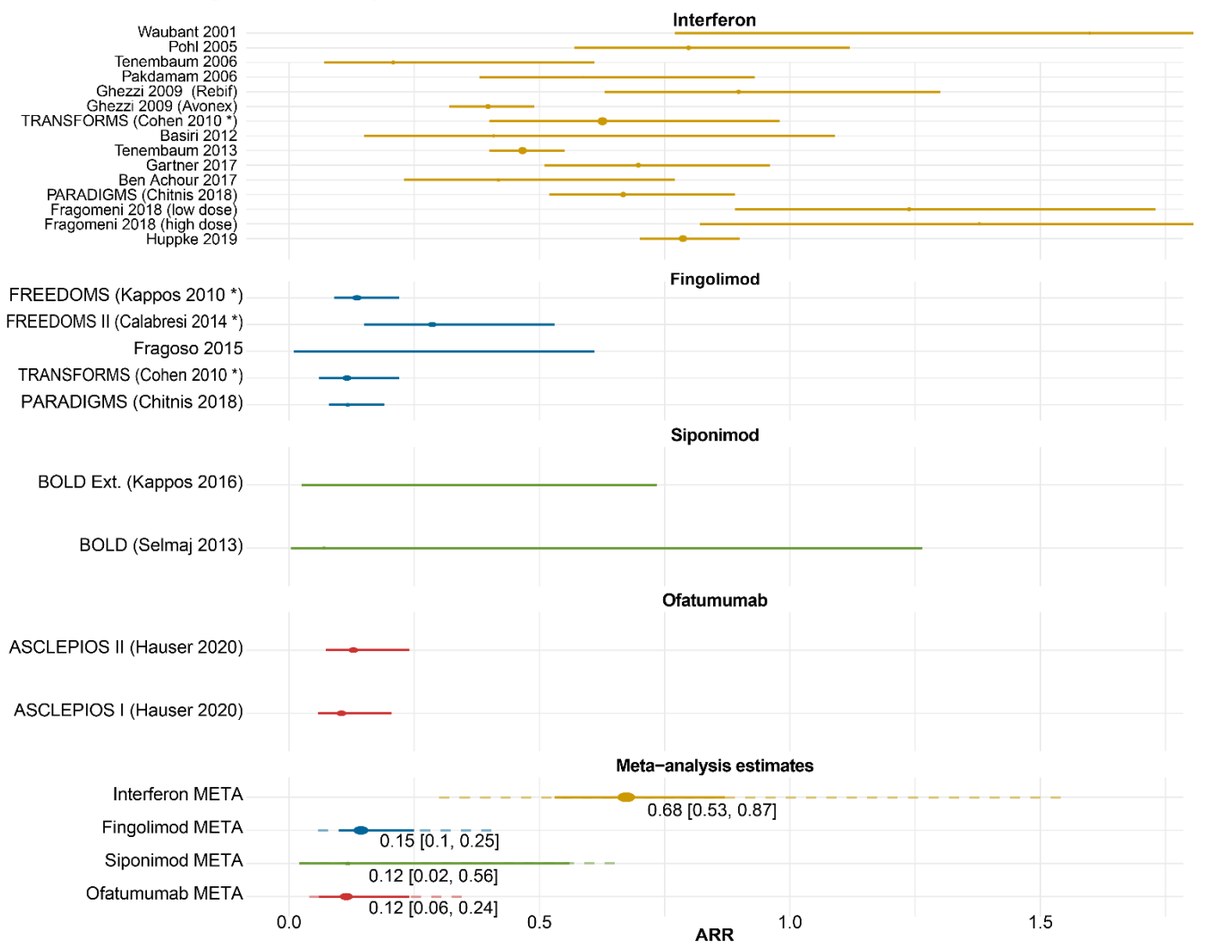
Lines and confidence boundaries are based on negative binomial models of relapse rates, extrapolated from adult studies to paediatric patients. The point estimates and confidence intervals represent the observed ARRs in children in PARADIG*MS*

ARR, annualized relapse rate; DMT, disease-modifying therapy; MS, multiple sclerosis; PedMS, paediatric MS

Systematic literature review and meta-analysis

- A total of 24 adult and PedMS studies (IFNβ, 15; fingolimod, 5; siponimod, 2; ofatumumab, 2) were included in the analysis
- The estimated ARRs after extrapolating from the adult MS studies were as follows: IFNβ, 0.68 (0.53, 0.87); fingolimod, 0.15 (0.1, 0.25); siponimod, 0.12 (0.02, 0.56); ofatumumab, 0.12 (0.06, 0.24) (**Figure 3**)

Figure 3 Meta-analysis of ARRs (95% CI) reported in PedMS patients with interferon, fingolimod, siponimod, ofatumumab



Point sizes of individual studies are proportional to the sample size. Dashed line for meta estimates show the predictive 95% interval for a new trial. Meta is obtained using Bayesian random-effects model for the log-ARRs, assuming the same between−trial variability for all treatments. *Study in adult patients. ARR in children extrapolated using negative binomial models adjusting for age and baseline number of relapses on individual patient data.

ARR, annualized relapse rate; CI, confidence interval; Meta, meta-analysis; MS, multiple sclerosis; PedMS, paediatric MS

- A non-inferiority margin of 2.0 against a tested highly efficacious disease modifying therapy (fingolimod) would conclusively suggest superiority of the new drugs (siponimod and ofatumumab) over IFNβ
- In a Bayesian framework, the meta-analytic priors obtained from the historical information have an effective sample sizes of 48, 7, and 30 for fingolimod, siponimod, and ofatumumab, respectively

Conclusions

- Extrapolation of the ARR from adult data to PedMS patients can be done and needs to account for differences in inflammatory disease activity in PedMS patients compared to that of adult MS patients
- The systematic literature review and meta-analysis confirm the consistently high relapse rates in PedMS patients treated with IFNβ compared to those treated with fingolimod
- Meta-analytic priors can be used in a Bayesian framework to design more efficient new studies in PedMS and to reduce burden and risk to patients
- A 2-year, double-blind, triple-dummy, Phase 3 trial in PedMS patients (NEOS [NCT04926818]) has been designed to incorporate historical information in a Bayesian non-inferiority innovative study design, thereby avoiding the use of placebo or IFNβ controls, and optimizing the sample size
- The NEOS study evaluates the efficacy and safety of ofatumumab and siponimod versus fingolimod in PedMS patients. The detailed NEOS study design is being presented at this congress (ECTRIMS 2021 ePoster #P102)

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Disclosures

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