NEOS: An innovative Bayesian non-inferiority trial design in pediatric multiple sclerosis

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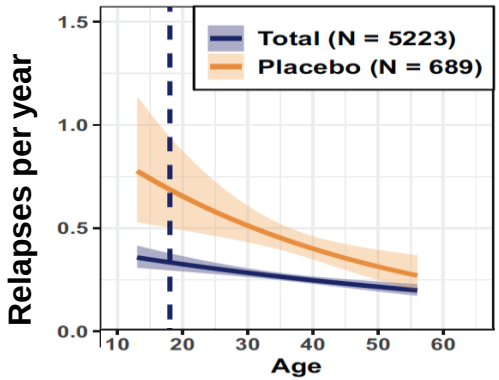
Background

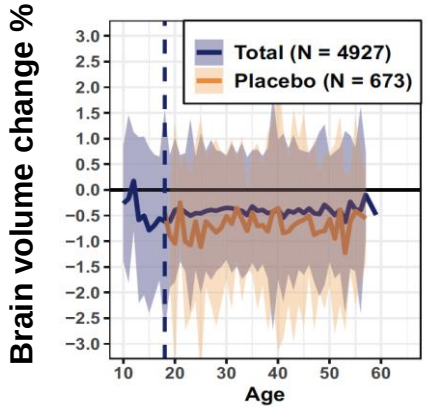
- **Pediatric MS is rare:** Only ~3-5% of MS cases start in childhood or adolescence[1,2]
- **Vulnerable population:** Children with MS show higher disease activity (2-3 time higher relapse frequency compared to adults)[3], lose brain volume from the onset (i.e. no true remission)[4], and have worse long-term prognosis, i.e. disabled at younger age[5]
- **High unmet need:** ~20 approved therapies in adults, pediatric patients only 1 approved based on randomized controlled trials in the US (Gilenya, based on only successful trial so far, PARADIGMS)

[1] Ghezzi et al. (1997) Multiple sclerosis in childhood: clinical features of 149 cases. Multiple Sclerosis Journal
[2] Chitnis T et al. (2009) Demographics of pediatric-onset multiple sclerosis in an MS center population from the Northeastern United States. Multiple Sclerosis Journal
[3] Gorman et al., 2009 Increased relapse rate in pediatric-onset compared with adultonset multiple sclerosis. Arch Neurol 2009; 66: 54-9.
[4] Arnold et al., 2019 Effect of fingolimod on MRI outcomes in patients with paediatric-onset multiple sclerosis: results from the phase 3 PARADIGMS study. Neurology, Neurosurgery & Psychiatry
[5] Renoux et al. (2007) Natural history of multiple sclerosis with childhood onset. N Engl J Med 2007; 356: 2603-13.

Pediatric MS
Key facts

- **Biological processes involved in MS are largely shared across age span**[1]
- **Higher relapse rates** than adults but also stronger relative effect size
- Irreversible **brain volume** and **loss of neurons** from the start (=**no true remission**)





[1] Waubant et al. Neurology 2019.
Figures from Dahlke et al. (2021) Characterization of MS phenotypes across the age span. Multiple Sclerosis Journal. Total refers to active and placebo treated patients.

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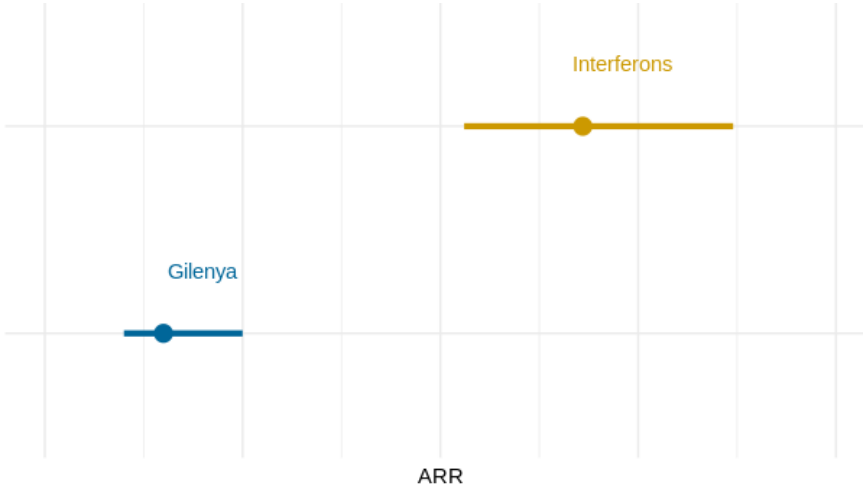
NEOS trial summary

- **2-year double-blind, triple-dummy Phase 3 study in pediatric MS** to establish the efficacy and safety 2 novel MS treatments :
  - **New test drug 1: Kesimpta (ofatumumab):** first fully human anti-CD20 monoclonal antibody treatment, approved worldwide in adults
  - **New test drug 2: Mayzent (siponimod):** S1P modulator, approved worldwide in adults
- **Primary endpoint:** Annualized relapse rate (ARR), analyzed via negative binomial model (standard phase 3 endpoint in MS)
- **Non-inferiority design vs active control Gilenya (fingolimod):**
  - **Active control: Gilenya (fingolimod):** Approved treatment for pediatric MS; reduced relapse rates vs interferon beta-1a by 82% in a randomized double-blind clinical trial (PARADIGMS[1])
  - Active control avoids placebo or low efficacy comparator, minimizing the risk of MS relapses, which can be associated with irreversible disability
- **Interim analysis when all patients have reached one year of follow-up:**
  - Potential to reduce double-blind part of the study by one year if both test drugs are non-inferior to fingolimod

[1]PARADIGMS is so far the only successfully completed RCT to confirm the efficacy of a DMT in pediatric MS.

Motivation for non-inferiority design

Estimated ARR based on meta-analysis of historical studies



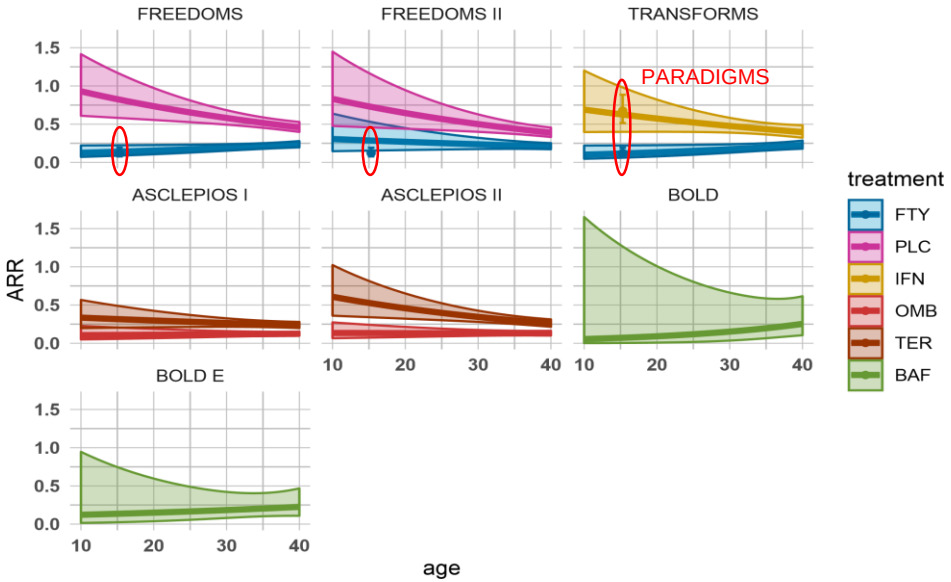
Patients on interferons (or untreated patients) have much higher relapse rates than with more modern DMTs such as Gilenya.

Showing **non-inferiority (NI-margin of 2.0[1]) against a tested highly efficacious treatment** and superiority over historical IFN in an indirect comparison **avoids the use of placebo or low efficacy comparators**

[1] If non-inferiority of a new test drug can be demonstrated vs Gilenya, the probability that the new drug is more efficacious than IFN beta-1a is >99% (based on the historical data).

Phase 3 data in adults with MS is typically available at the start of a new pediatric study and can be leveraged

Extrapolation from adult phase 3 data to pediatric patients for placebo and different DMTs



Relapse frequency is strongly age dependent in untreated patients or under low efficacy treatment.

Age-dependent extrapolation from adults to pediatric MS patients should be considered to inform new trial design options

Lines and confidence boundaries are based on negative binomial models of relapse rates, extrapolated from trials in adults to pediatric patients. N refers to the sample size of the trials in adults. The point estimates and confidence intervals represent the observed ARR in children in PARADIGMS.

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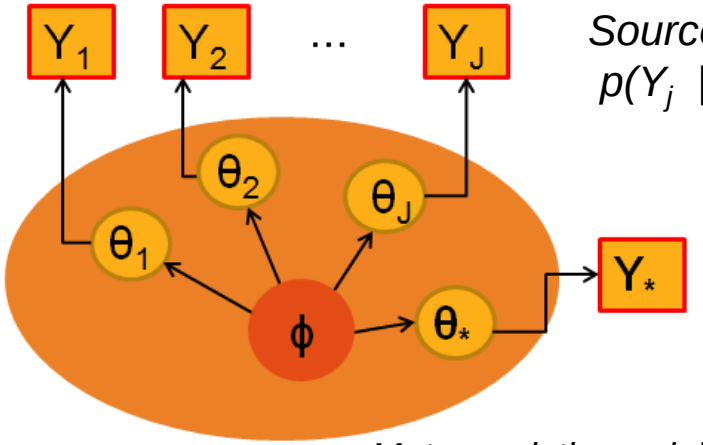
Incorporating historical data via meta-analytic predictive approach [1, 2]



Source data models
$p(Y_j \mid \theta_j)$ $j=1,\ldots,J$

Target data model for planned trial
$p(Y_* \mid \theta_*)$

Meta-analytic model to link parameters (hyper-parameter ϕ): $p(\theta_*, \theta_1, \ldots, \theta_J \mid \phi)$

MAP-prior for new study: $p_{MAP}(\theta_*) = p(\theta_* \mid Y_1, \ldots, Y_J)$

- Parameters from different studies are linked through hierarchical model
- Takes between-trial heterogeneity into account

[1] Spiegelhalter, D. J., Abrams, K. R., & Myles, J. P. (2004). *Bayesian approaches to clinical trials and health-care evaluation* (Vol. 13). John Wiley & Sons.
[2] Neuenschwander B, Capkun-Niggli G, Roychoudhury S, et al (2010). Summarizing historical information on controls in clinical trials. Clin Trials; 7(1): 5-18.

Protecting against prior-data conflicts

- Extrapolation from adults accurate and consistent, however **limited data from pediatric trials available** (in particular none for test drugs)

- Exchangeability assumption can be relaxed **by adding vague, weakly-informative components to the MAP mixture**[1] :

$$p_{Robust}(\theta_*) = (1-\varepsilon)\, p_{MAP}(\theta_*) + \varepsilon\, p_{Vague}(\theta_*)$$

  - Mixture weight ε chosen to reflect skepticism on relevance of source data
  - Robust priors are heavy-tailed, and hence **informative part is discarded in case of prior-data conflicts**

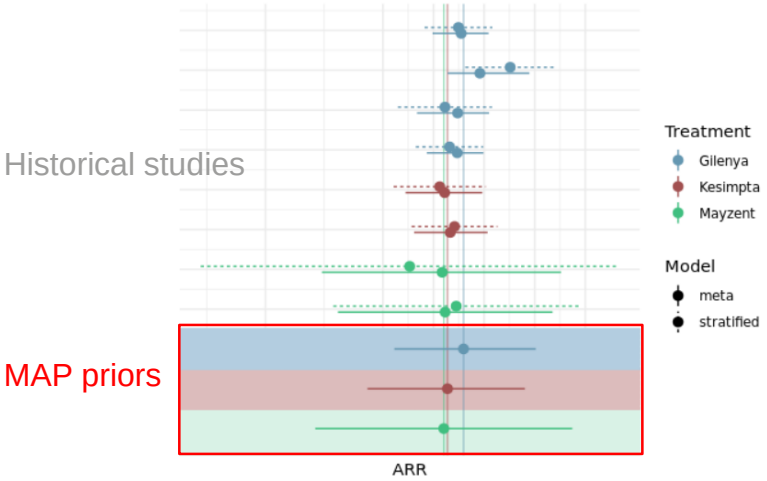
- Use ε = 0.2 for fingolimod and ε = 0.5 for ofatumumab and siponimod to reflect lack of pediatric data for the investigational drugs

[1] Schmidli H, Gsteiger S, Roychoudhury S, et al (2014). Robust meta-analytic-predictive priors in clinical trials with historical control information. Biometrics; 70(4): 1023-1032.

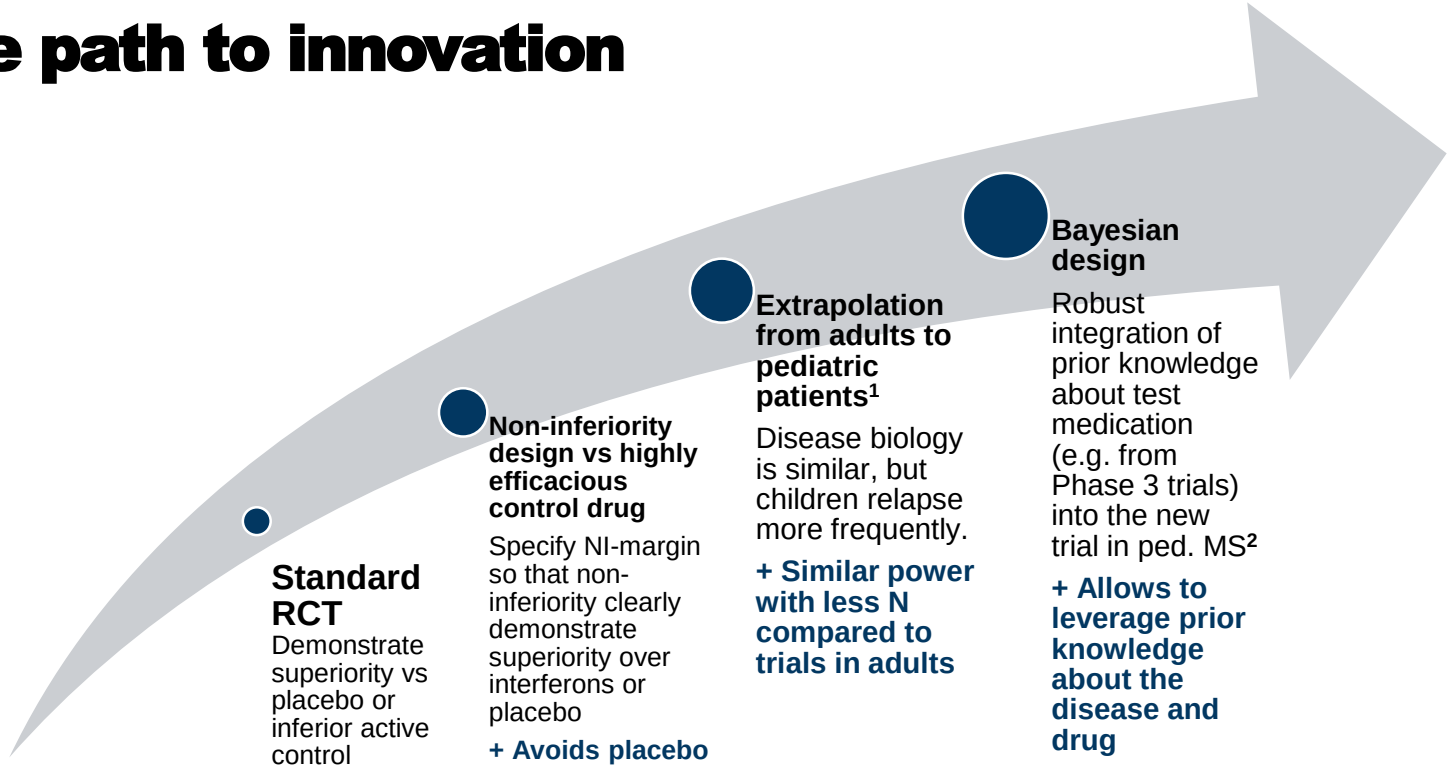
Bayesian study design is efficient and robust

- Meta-analytic predictive approach allows **robust incorporation of historical data from adults**
- **Reduction in required sample size:** prior information is worth approx. 90 patients, reduces sample size by > 30%
- **Allows for an efficient study design with adequate power** that is also scientifically robust (i.e. type I error rates are controlled for relevant scenarios)

Extrapolated ARR estimates from individual studies and derived MAP-priors



The path to innovation



Standard RCT

Demonstrate superiority vs placebo or inferior active control

Non-inferiority design vs highly efficacious control drug

Specify NI-margin so that non-inferiority clearly demonstrate superiority over interferons or placebo

+ Avoids placebo or low efficacy controls

Extrapolation from adults to pediatric patients[1]

Disease biology is similar, but children relapse more frequently.

+ Similar power with less N compared to trials in adults

Bayesian design

Robust integration of prior knowledge about test medication (e.g. from Phase 3 trials) into the new trial in ped. MS[2]

+ Allows to leverage prior knowledge about the disease and drug

[1]Schmidli et al., (2020) Beyond Randomized Clinical Trials: Use of External Controls. Clinical pharmacology & Therapeutics.
[2]Schmidli et al., (2014) Robust meta-analytic-predictive priors in clinical trials with historical control information. Biometrics.

Health authority interactions and timelines

2017-2018

- **Initially two separate studies planned:**
  - Proposed **Kesimpta** Bayesian non-inferiority design accepted for FDA's Complex Innovative Designs (CID) Pilot program
  - Initial proposal for **Mayzent** is a open-label superiority study vs interferon

2019

- **Discussions with HAs on proposed studies:**
  - Two CID F2F meetings
  - Based on HA discussion similar Bayesian non-inferiority design as for Kesimpta is proposed for Mayzent

2020

- **FDA strongly encourages a combined trial, EMA concurs:**
  - Follow-up discussions with focus on Bayesian design elements with FDA
  - NEOS design (combined Kesimpta and Mayzent design) accepted by US FDA
  - Discussion on NEOS design with SAWP in EU: Design and PIP modification accepted by EMA/PDCO

2021-2026

- **NEOS study:**
  - Final protocol in Jan 2021
  - Study initiated in Oct 2021
  - LPLV planned for 2026

Summary of regulatory feedback: Reaching global alignment for non-standard design features can be a challenge

Topic	FDA CID discussions	EMA (PDCO and SAWP)
Extrapolation	• Concerns about extrapolation models relying on «unverifiable assumptions» • Exploration and discussion of (all) other possible prognostic or effect modifying factors required	• No specific concerns
NI-margin	• Proposed margin of 3[1] too large (some discounting is required) • Lack of pediatric data to assess between-trial variability • Systematic literature review and meta-analysis requested to have a comprehensive understanding all potentially relevant prior knowledge	• Initially proposed NI-margin of 3 was discussed as large but finally accepted for Kesimpta PIP by PDCO based on scientific and feasibility considerations
Bayesian design	• «Bayesian framework may be useful» • Concerns about double-use of historical information in Bayesian non-inferiority design • Extensive simulations requested to understand operating characteristics under all conditions	• Bayesian design not accepted for initial Kesimpta PIP • SAWP primarily concerned with lack of type I error control and subjectivity of weight given to historical information
Interim analysis	• An interim analysis for efficacy stopping is endorsed	• Interim analyis not accepted for initial PIP • Concerns related to inadequate assessment of long-term safety • Interim analysis not endorsed by SAWP due to adding another level of complexity to already complex design

[1] Initially sponsor proposed NI margin of 3.0 was derived based on the 95% confidence limit of the ARR-ratio between fingolimod and interferon beta-1a based in PARADIG*MS* a phase 3 trial in pediatric multiple sclerosis.

Key modifications on study design based on HA feedback

- Non-inferiority margin, after discounting, changed to 2.0 (instead of 3.0) with additional upper limit of the ARR (0.3) on test drugs to conclude non-inferiority vs Gilenya
- Key secondary analysis added to compare test treatments versus historical interferon data (based on a meta-analysis of historical studies)
- Kesimpta and Mayzent studies were combined into one design based on recommendation from FDA and EMA
- Tipping point sensitivity analysis prespecified to assess robustness of conclusions from Bayesian analysis under different weights to prior information; i.e. from pre-spedified weight to a «no borrowing» strategy (frequentist design)

Final study design was accepted by both FDA and EMA/PDCO

Conclusions

- The Bayesian non-inferiority design integrates our prior knowledge about MS and offers efficacious treatment to all participants
- Reduction in sample size through informative Bayesian priors critical to ensure feasibility in a rare disease
- F2F Discussions within FDA's Complex Innovative Designs (CID) pilot program helpful to align on innovative design features and improve the design
- First patient was recruited into the study in October 2021

Thank you

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