Leveraging external data for efficient pediatric study design in multiple sclerosis

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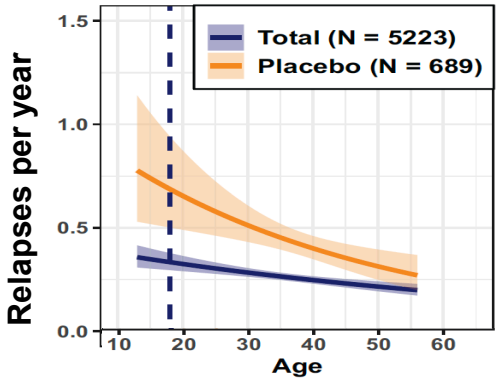
Background

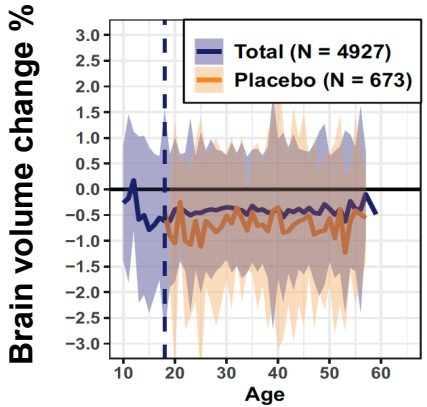
- **Pediatric MS is rare:** Only ~3-5% of MS cases start in childhood or adolescence[1,2]
- **Vulnerable population:** Children with MS show higher disease activity (2-3 time higher relapse frequency compared to adults)[3], lose brain volume from the onset (i.e. no true remission)[4], and have worse 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 EU + US (Gilenya, based on PARADIGMS study)

[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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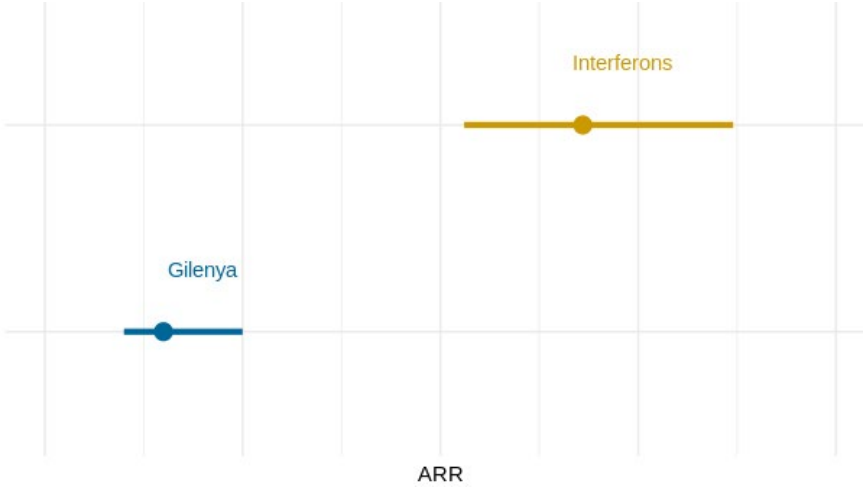
NEOS trial summary

- **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
- **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
- **Primary endpoint:** Annualized relapse rate (ARR), analyzed via negative binomial model (standard phase 3 endpoint in MS)

[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



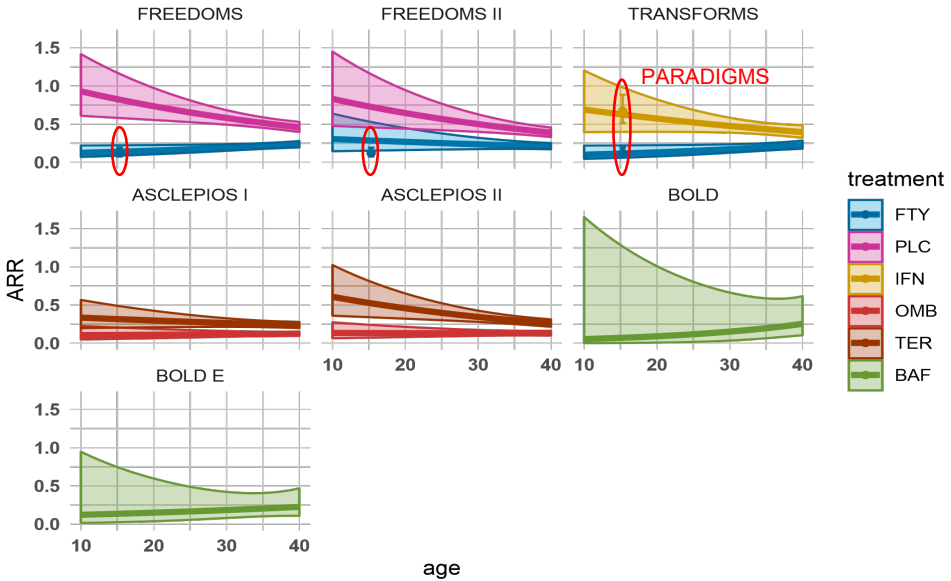
Patients on interferons (or untreated patients) have much higher relapse rates than with more modern DMTs such as Gilenya.

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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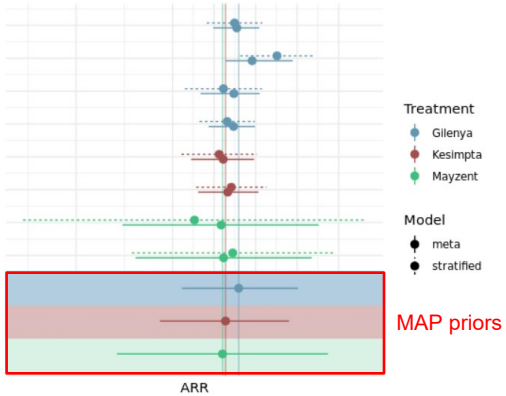
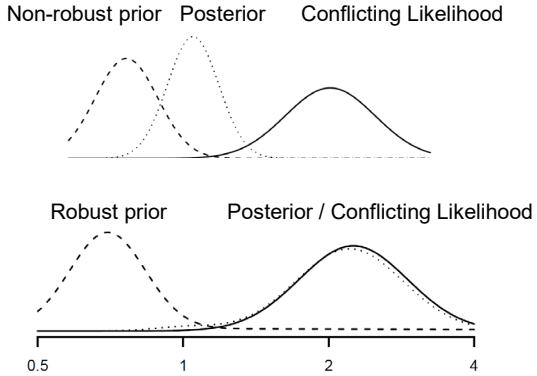
Leveraging historical data through robust Bayesian design

Meta-analytic predictive approach[1,2]



- Combine historical information through meta analytic approach
- Takes into account variability between between trials

Robustification for prior-data conflicts[3]



- Robustify by adding weakly informative prior component
- Improves operating characteristics and reduces type I error rates

NEOS hybrid trial design

- **Efficiently uses existing knowledge**
- Sample size **180 instead of 270** with standard design
- **Reduces patient burden and timelines** until availability of new treatments
- **Acceptable type I error** control for relevant scenarios

[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.
[3] 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.

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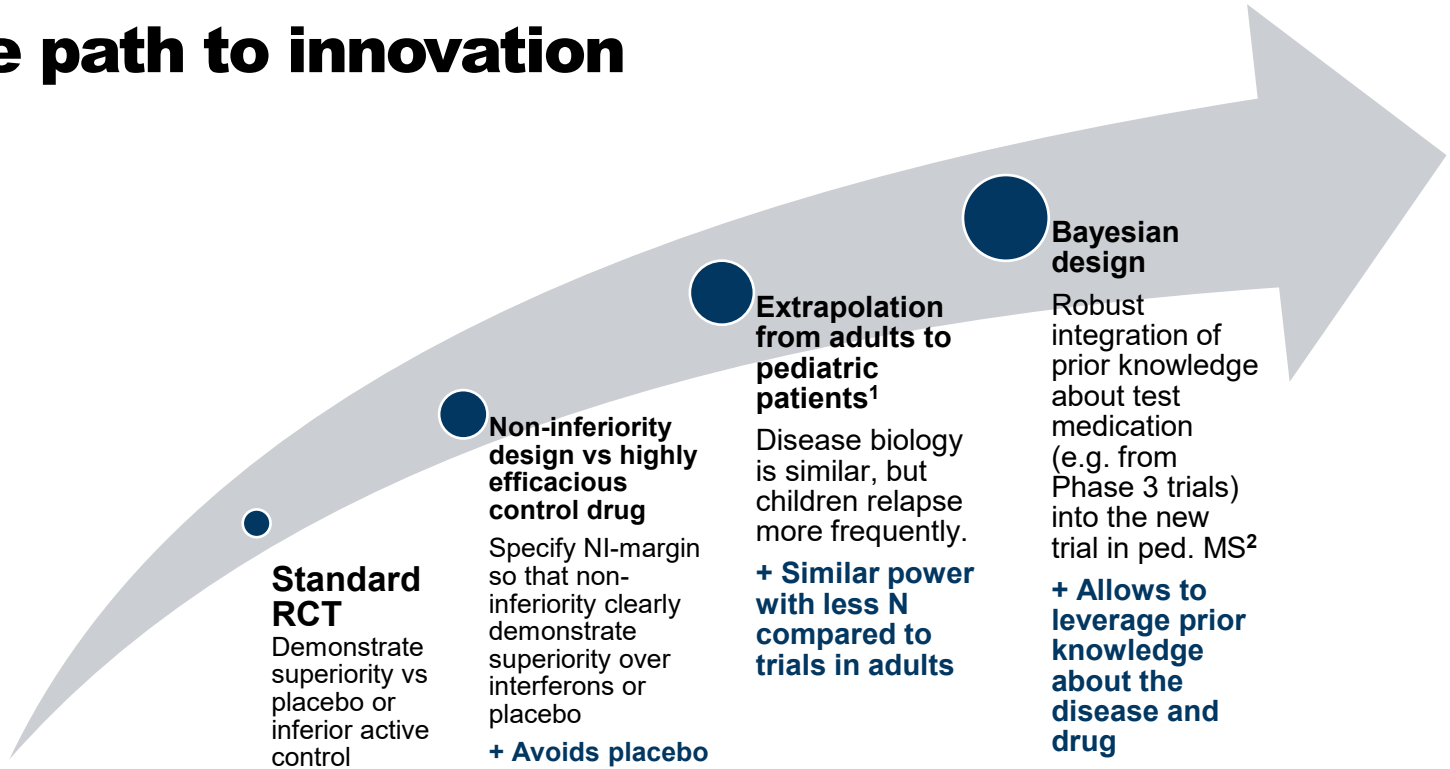
The path to innovation



[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.

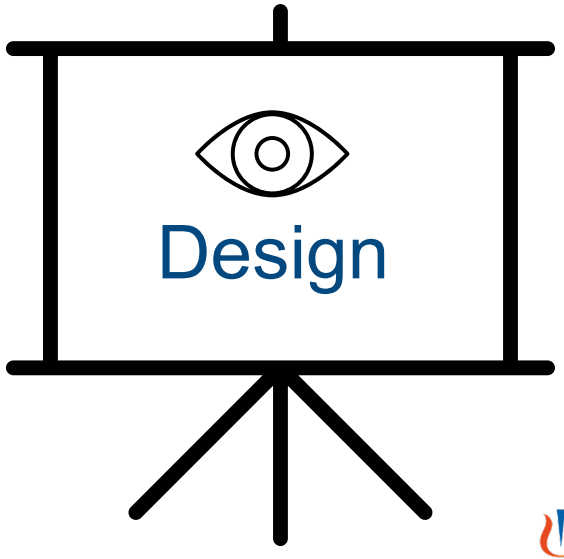
Stakeholder views on innovative study design – alignment needed to reach agreement

Patient

- **Minimize risk** (adverse events, low efficacy drugs)
- **Provide access to tested drugs** (highly efficacious, safe, easy to use)

Sponsor

- Bring efficacious and safe medications to patients as **efficiently** as possible (faster, lower sample size)



Regulator

- **Minimize erroneous decisions** (type I & II errors)
- **Caution: «no shortcuts»**
- Fairness between competing sponsors
- Alignment between global regulatory agencies

Disease similarity (adults vs pediatric) opens doors to many innovative approaches

Dissimilar
Prior information from adults is irrelevant for the drug development in pediatric patients.

Similar
Adult and pediatric disease is similar but not identical; opens options for many innovative options

Identical
Adult and pediatric disease is identical (same biology and effect size expected in peds and adults).

It's a gradient

- No borrowing of information from adults is possible due to the dissimilar nature of the disease.
- **Note: Assuming dissimilarity and accepting irrelevance of historic information from adults is a strong assumption!**
- Efficacy and safety have to be demonstrated in a new phase 3 program in RCTs in pediatric patients

Innovative features may be feasible if they have objective advantages over a default design:

- Borrowing information from adults (e.g. Bayesian)
- Integrating knowledge from historical trials
- Extrapolation from adults
- Biomarker bridging strategy
- Modeling
- If diseases are similar enough, showing consistency of effect size in pediatic patients to the effect size in adults may be sufficient (e.g. «no full powering»)

Our common goal:
To bring tested medications to pediatric MS patients

- Pediatric MS is rare and of high burden to patients; ethical and feasibility constrainst should be taken into account – placebo and low efficacy controls should be avoided.
- When initiating pediatric studies, prior knowledge is typically available from phase 3 programs in adults and based on historical trials. This prior knowledge may be used for extrapolation to pediatric patients, to inform non-inferiority margins for comparison vs highly efficacious medications, and/or as priors in a Bayesian framework.
- We designed a Bayesian NI trial (NEOS) that integrates our prior knowledge about pediatric MS and offers efficacious treatment to all participants in alignment with the regulators in the US and EU

Thank you

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