Leveraging external data for efficient pediatric study design in multiple sclerosis

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Adept 7 workshop

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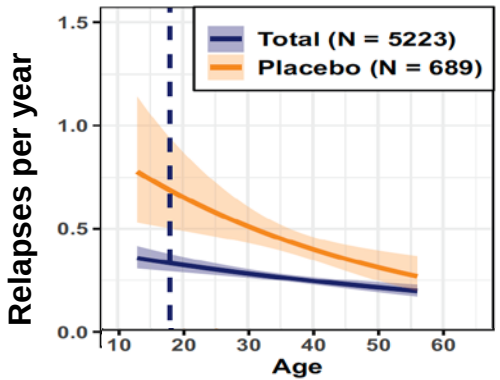
Background

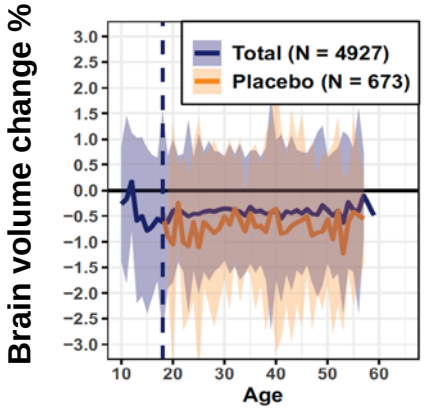
- **Pediatric MS is rare:** Only ~3-5% of MS cases start in childhood or adolescence[1,2]
- **Vulnerable population:** Children with MS show higher disease activity (2-3 time higher relapse frequency compared to adults)[3], lose brain volume from the onset (i.e. no true remission)[4], and have worse 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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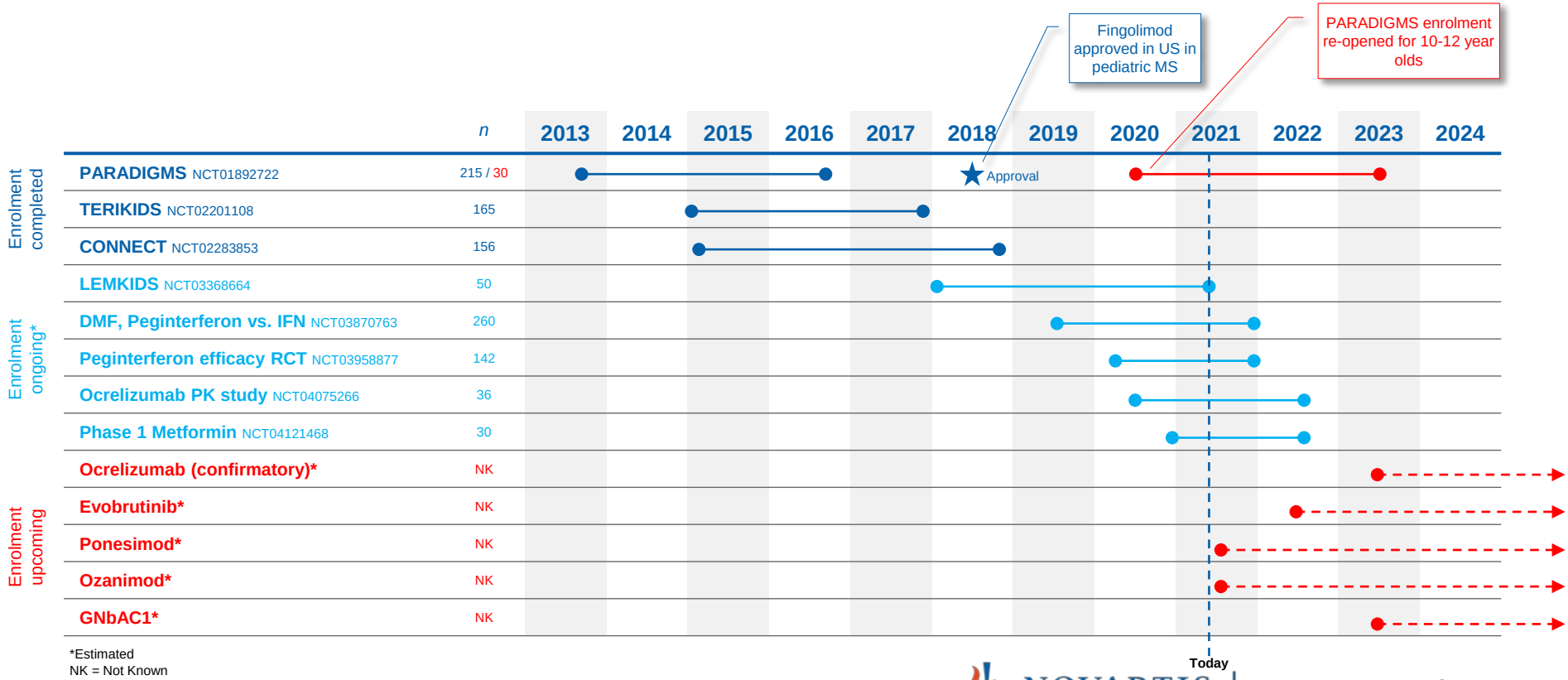
Challenging recruitment with competitive trial landscape and rarity of pediatric MS population makes feasibility a key concern



*Estimated
NK = Not Known

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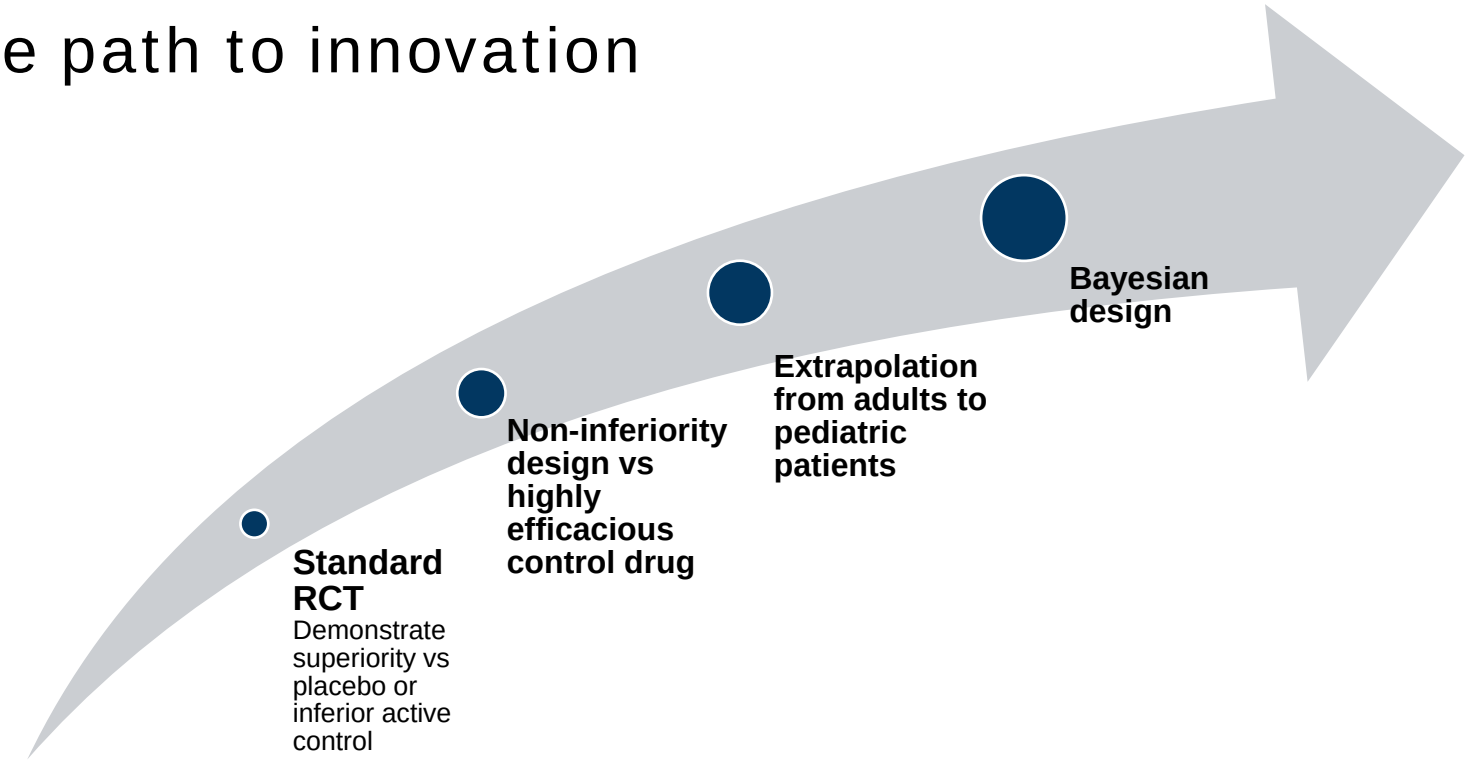
The path to innovation



NEOS (NCT04926818): An innovative, efficient trial design in pediatric MS

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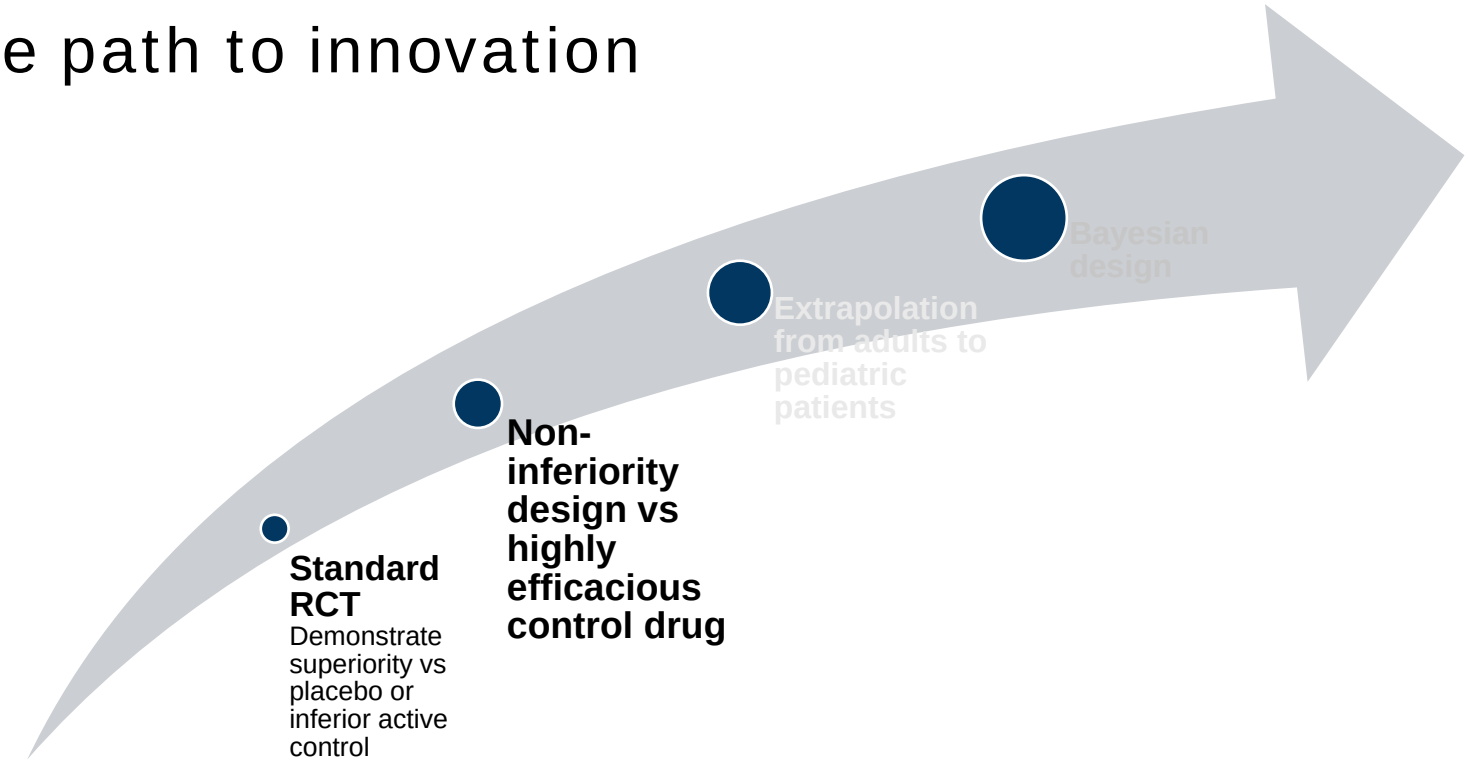
NEOS trial summary

- **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)

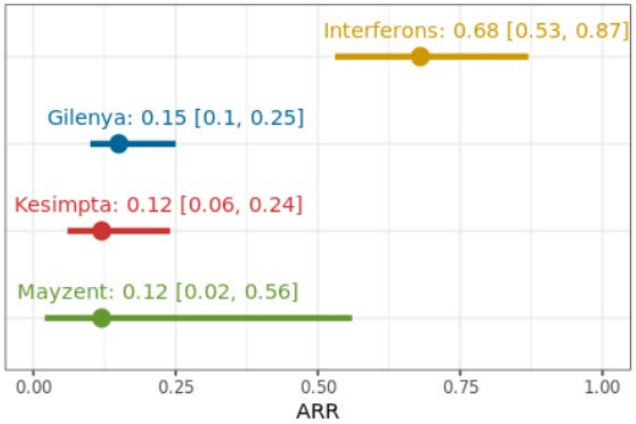
[1]PARADIGMS is so far the only successfully completed RCT to confirm the efficacy of a DMT in pediatric MS.

The path to innovation



Summary of historical information from adults and children

Estimated ARR based on meta-analysis of historical studies

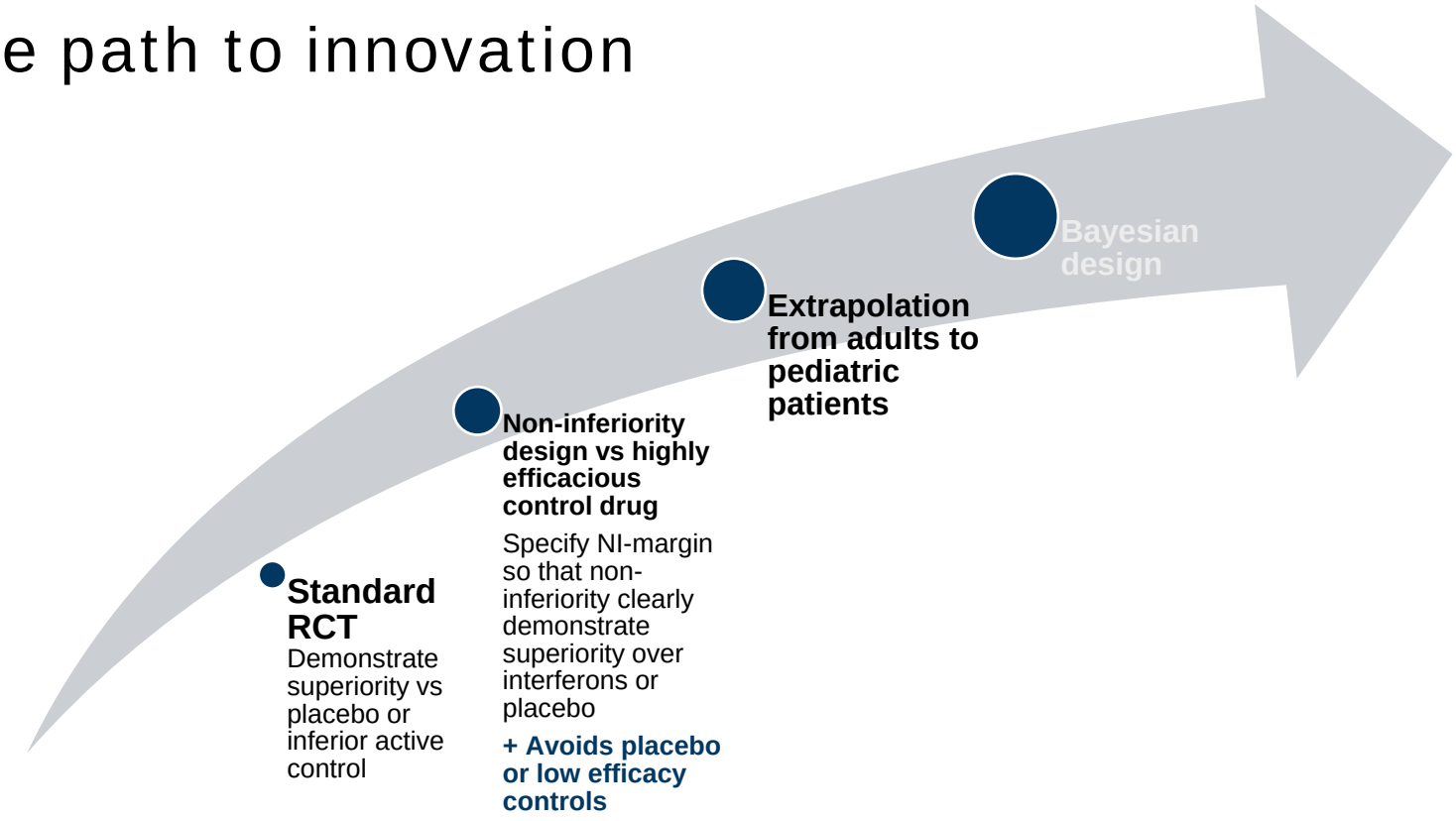


Patients on interferons (or untreated patients) have much higher relapse rates than with more modern DMTs.

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).

The path to innovation



Should we be more confident in extrapolating from adults to children in MS?

<u>Extrapolation</u> from adult patients from the TRANSFORMS study in <u>year 2010</u>. Predictions of relapse rates at age 15.3 (the mean age of the PARADIGMS study) from a negative binomial model with age x treatment interaction (the model was built in year 2010).

Projections		Between-treatment comparison		
Treatment	Adjusted ARR (95% CI)	% rate reduction	ARR ratio (95% CI)	P-value
IFNß-1a N=431	**0.667**	**81.7%**	0.183	<.001
FTY720 N=429	**0.122**			

K=0.824

Model contained all FAS patients from TRANSFORMS, including 420 on FTY 1.25 mg. Shown here are only FTY 0.5mg and IFN beta-1a

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Observed primary results from PARADIGMS (FTYD2311) in year 2017

- Gilenya: **25 relapses** in 180 patient-years: ARR=0.14
- IFN: **120 relapses** in 163 patient-years: ARR=0.73

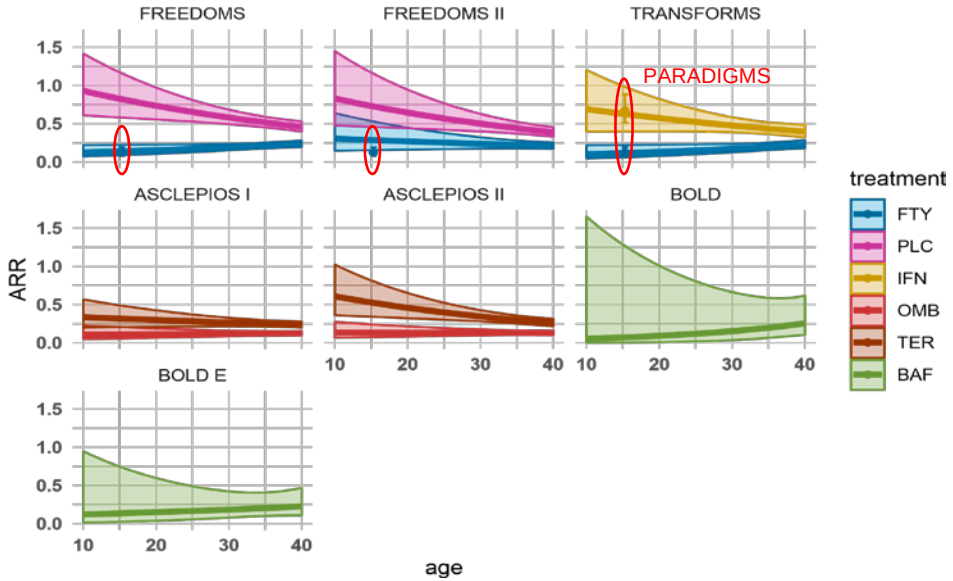
Treatment	Adjusted ARR (95% CI)	% rate reduction	ARR ratio (95% CI)	P-value
IFNß-1a N=107	**0.675** (0.515,0.885)	**81.9%**	0.181 (0.108,0.303)	<.001
FTY720 N=107	**0.122** (0.078,0.192)			

K=0.835

Model contained all FAS patients from PARADIGMS which included an FTY and an IFN beta-1a arm

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

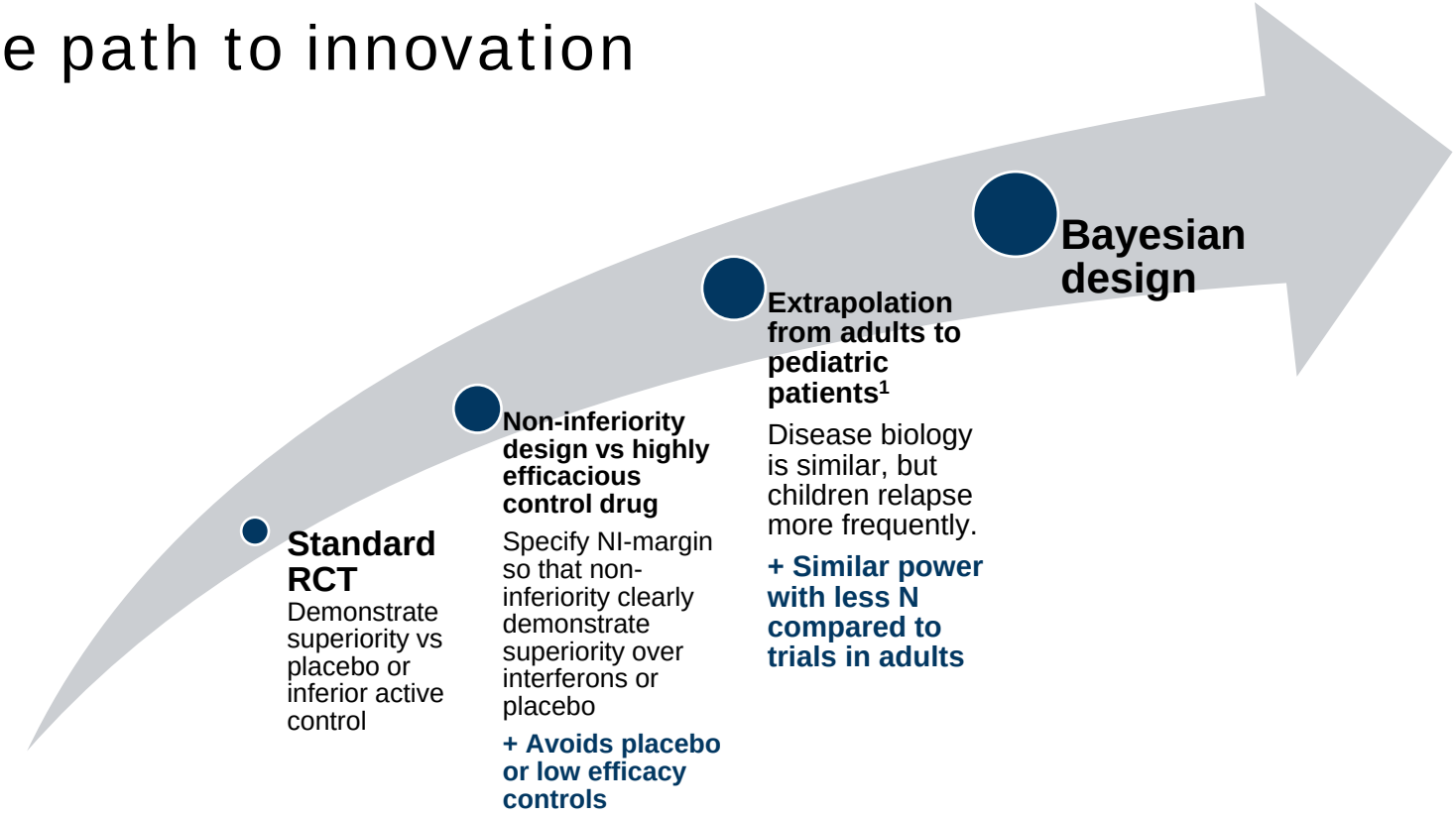


Relapse frequency is strongly age dependent in untreated patients or under low efficacy treatment.

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

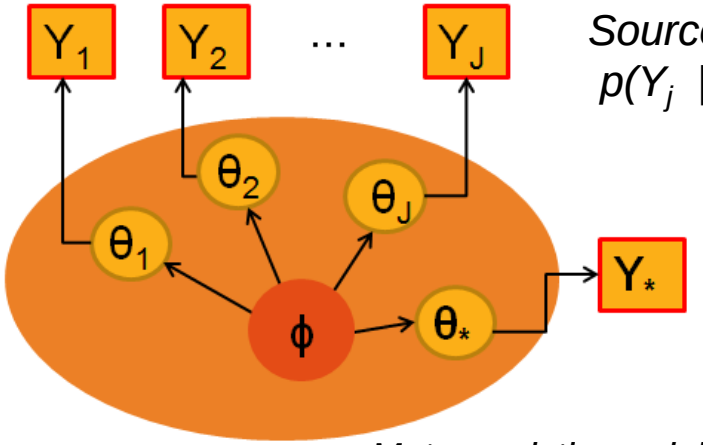
Lines and confidence boundaries are based on negative binomial models of relapse rates, extrapolated from trials in adults to pediatric patients. N refers to the sample size of the trials in adults. The point estimates and confidence intervals represent the observed ARR in children in PARADIGMS.

The path to innovation



[1]Schmidli et al., (2020) Beyond Randomized Clinical Trials: Use of External Controls. Clinical pharmacology & Therapeutics.

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



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

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

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

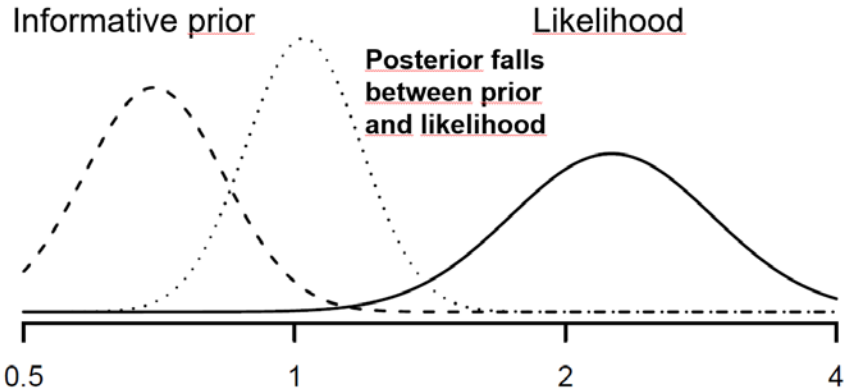
MAP-prior for new study: $p_{MAP}(\theta_*) = p(\theta_* \mid Y_1, ..., Y_J)$

- 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.

Prior-data conflict potential issue with Bayesian design

- Extrapolation from adults accurate and consistent, however **limited data from pediatric trials available** (in particular none for ofatumumab and siponimod)
- Possibility that exchangeability assumptions does not hold and as a result a **prior-data conflict** occurs, has to be considered:



Protecting against prior-data conflicts

- 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

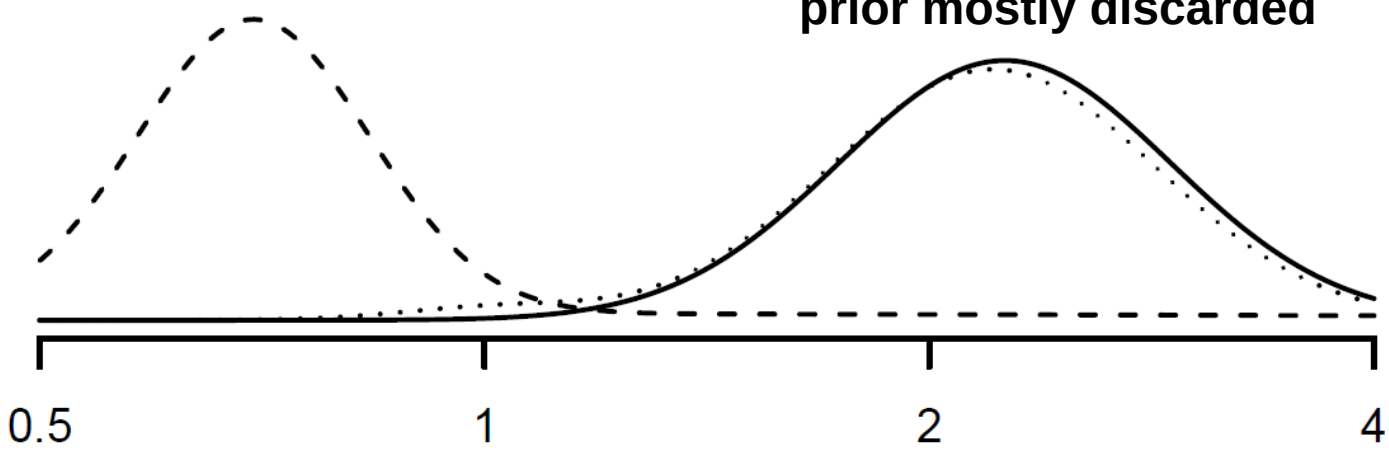
[1] Schmidli H, Gsteiger S, Roychoudhury S, et al (2014). Robust meta-analytic-predictive priors in clinical trials with historical control information. Biometrics; 70(4): 1023-1032.

Prior-data conflict with robust prior

Robust heavy-tailed prior

Likelihood

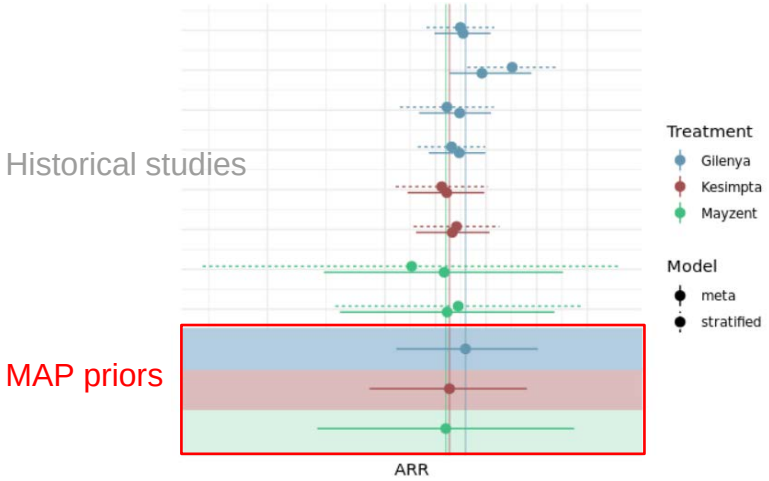
Posterior close to likelihood, prior mostly discarded



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
- **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



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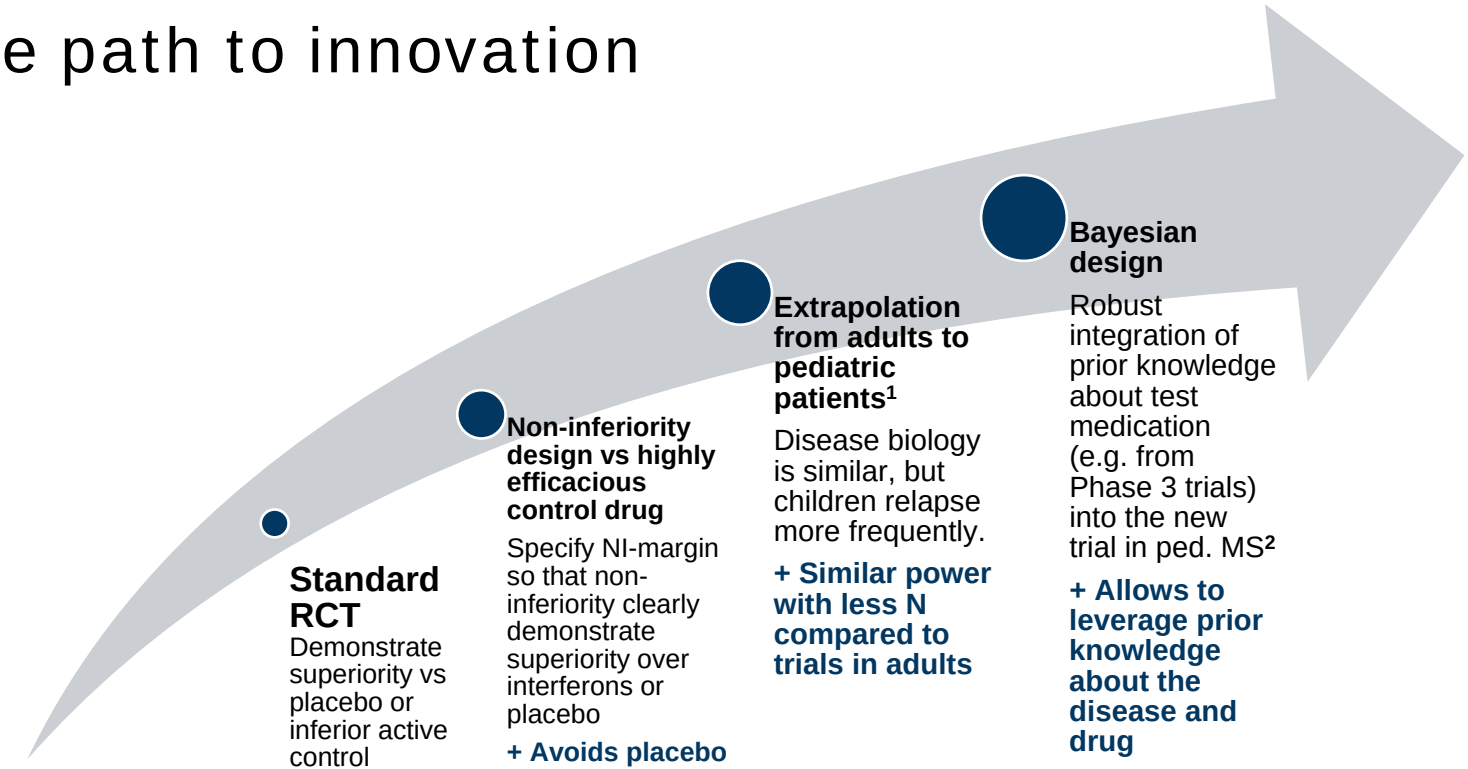

Standard RCT
Demonstrate superiority vs placebo or inferior active control

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.

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

- Pediatric MS is rare and of high burden to patients.
- Study designs need to be ethical, scientific and take feasibility issues into consideration.
- No true remission in MS – 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 – the NEOS trial is planned to start recruiting this year.

Thank you