# *Experience with and learnings from regulatory interactions around innovative trial designs based on the NEOS study*

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# Simulation studies for complex innovative study designs

1. Example of NEOS: Bayesian non-inferiority trial in pediatric MS
2. Summary of regulatory interactions
3. Innovative trial designs & regulatory interactions – learnings from NEOS

# Background

- **Pediatric MS is rare:** Only ~3-5% of MS cases start in childhood or adolescence[1,2]
- **Disease similarity:** Disease biology of is fundamentally similar (but not identical) across the age span[3,4]
- **Vulnerable population:** Children with MS show higher disease activity (2-3 time higher relapse frequency compared to adults)[5], lose brain volume from the onset (i.e. no true remission)[6], and have worse long-term prognosis, i.e. disabled at younger age[7]
- **High unmet need, competitive trial environment:**[8,9] ~20 approved therapies in adults, pediatric patients only 1 approved based on a successful randomized controlled trial (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] Waubant et al., (2019) Clinical trials of disease-modifying agents in pediatric MS: Opportunities, challenges, and recommendations from the IPMSSG. Neurology.
[4] Dahlke et al., (2021) .Characterisation of MS phenotypes across the age span using a novel data set integrating 34 clinical trials (NO. MS cohort): Age is a key contributor to presentation.
[5] Gorman et al., 2009 Increased relapse rate in pediatric-onset compared with adultonset multiple sclerosis. Arch Neurol 2009; 66: 54-9.
[6] 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 356: 2603-13.
[8] Rose et al., (2016) Children with multiple sclerosis should not become therapeutic hostages. Therapeutic advances in Neurology.
[9] Sormani & Waubant (2021) Paediatric multiple sclerosis: a lesson from TERIKIDS. Lancet Neurology.

# 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)
- **Interim analysis for efficacy stopping** when last patient completed 1 year

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

# Innovative design features – why?

| Key clinical challenges | Innovative design feature / efforts made | Impact |
|---|---|---|
| **Vulnerable population**<br>(Risk of irreversible disability) | **Non-inferiority design vs active control**<br>(de-facto standard of care, fingolimod) | • Avoids low efficacy controls |
| **Rare population**<br>(Highly competitive environment with several trials in pediatric MS patients ongoing) | **Choice of NI margin:** Narrow enough to ensure efficacy of new test treatments, but wide enough to make it feasible. Informed by:<br>• Systematic literature review<br>• Meta-analysis to inform NI margin | • Scientifc rigor<br>• Feasibility |
| **Integration of prior knowledge**<br>(completed phase 3 programs in adults; available knowledge from pediatric patients – how to integrate this knowledge?) | **Bayesian design**<br>• Model-based extrapolation from adults to pediatrics after studying 'disease similarity'<br>• Robust MAP priors | • Leverages existing knowledge about the disease and drugs<br>• Reduces sample size<br>• MAP priors mimimize risk of prior data conflict |
| **Few tested theurapeutic options for pediatric MS patients** | **Adaptive design**<br>• Efficacy stopping to make new tested drugs available as soon | • Brings new tested medication to patients ASAP<br>• Interim analysis ensures adaptation of study duration |

# Summary of regulatory interactions

# 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»<br>• Exploration and discussion of (all) other possible prognostic or effect modifying factors required<br>• Finally accepted after providing requested information | • No specific concerns based on submitted information |
| **NI-margin** (prior to start of study) | • Sponsor proposed margin of 3[1] deemed too large (some discounting is required)<br>• Lack of pediatric data to assess between-trial variability<br>• Systematic literature review and meta-analysis requested to have a comprehensive understanding all potentially relevant prior knowledge<br>• Finally, margin of 2 implemented based on FDA's advise | • Initially proposed NI-margin of 3 was initially discussed as large but deemed acceptable for OMB PIP by PDCO based on scientific and feasibility considerations<br>• However, NEOS trial initiated with NI-margin 2.0 based on FDA feedback |
| **NI-margin** (after start of study) | • Margin 3 would now be deemed acceptable by FDA (FDA unsolicited letter)<br>• Adjustment of sample size to margin 3 requires discussion | • Margin 3 deemed acceptable and adjustment of sample size to the primary NI-criterion deemed adequate |
| **Bayesian design** | • «Bayesian framework may be useful»<br>• Concerns about double-use of historical information in Bayesian non-inferiority design<br>• Extensive simulations requested to understand operating characteristics under all conditions; finally deemed adequate | • Bayesian design not accepted for initial OMB PIP<br>• SAWP primarily concerned with lack of type I error control and subjectivity of weight given to historical information<br>• Accepted as feature of the final design |
| **Interim analysis** | • An interim analysis for efficacy stopping is endorsed | • Interim analyis not accepted for initial PIP<br>• Concerns related to inadequate assessment of long-term safety<br>• Interim analysis not endorsed by SAWP due to adding another level of complexity to already complex design<br>• Interm analysis finally endorsed after clarifying its impact |

[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. It would ensure superiority over historical data with Interferon beta-1a.

# Innovative trial designs & regulatory interactions – learnings from NEOS

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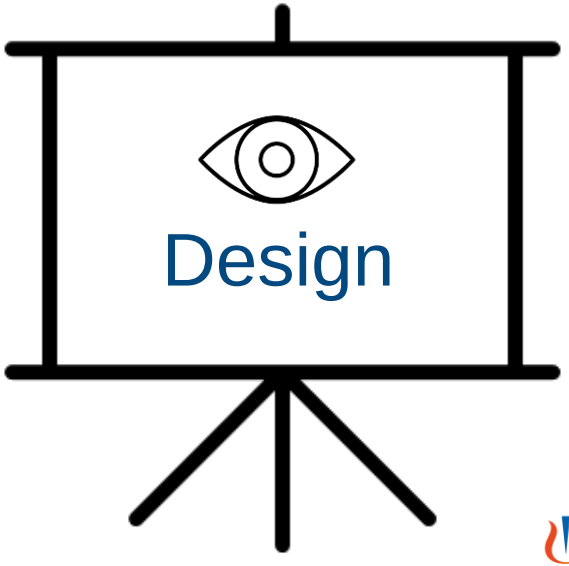
# Stakeholder views on innovative study design – alignment needed to reach agreement

## 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, but with scientific rigor)




## Regulator

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

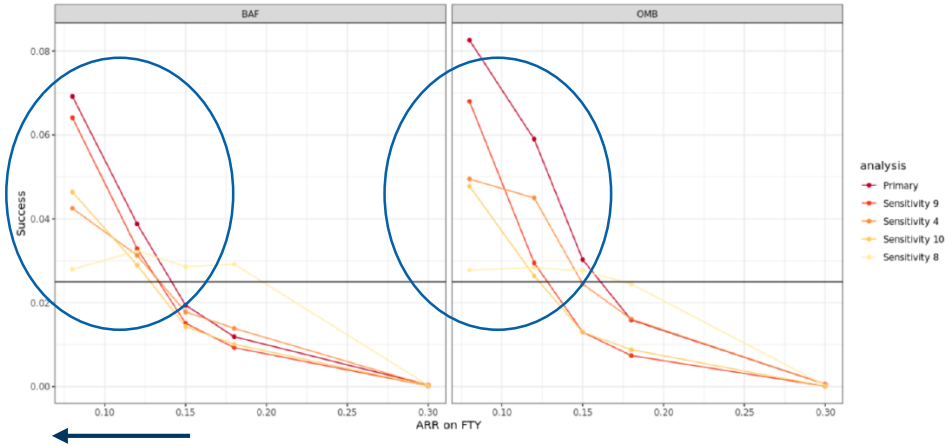
# Innovation breaks with established tradition

- **Innovation deviates from «gold standard» in at least one dimension: «Why?»**
- **Simulations help in discussions of subjective components of innovation**
  - **Advantages of the novel design** vs. a standard RCT? (e.g. patient burden vs sample size)
  - **Weight given to historical data**, e.g. Bayesian priors? (e.g. disease similarity)
  - When is **type-I error inflation** acceptable, if ever?
- **Simulations («What if?») can help in aligning different stakeholders on best design options**

- **Acceptability of innovation influenced by the clinical context, «no one size fits all»**
  - **Collaboration between statisticians and clinicians is essential** (sponsor, regulator)

# Example: Type I error rates

**Figure 3-2** **Type I error rate for the primary analysis and selected sensitivity analyses**




ARR<0.15:
1 relapse in > 6 years

## Statistical finding

- ***Type I error rate is inflated*** **when relapse rates on trial are very low**.
- Interpretation of type I error: If relapses are rare, one may incorrectly conclude that the test treatment is non-inferior to the active control treatment.

## Clinical context

- However, historically, ***pediatric MS patients always relapsed at high (ARR>0.5) frequency*** (systematic literature review and meta-analysis).

## Type I error rate inflation is deemed acceptable in the specific clinical context:

- ***If patients relapse infrequently in the new RCT*** *(on test and control drug)* ***efficacy is very strongly implied*** *(vs historical control).*

# Understanding operating characteristics under clinically plausible settings of parameters **Before** and **After** the study

- **Prior to study (simulations):**
  - Understand operating characteristics through simulations
  - **No cherry picking:** Not only the «per-protocol scenario» but all *other* plausible scenarios should be covered.
  - Need to take plausibility of scenarios into account when assessing results

- **After the study (sensitivity analyses):**
  - Sensitivity analyses
  - Tipping point analyses (across clinically plausible parameters)

# Proposed guiding principles for complex innovative designs

**Common objective** (Patients, Sponsors, Regulators): Test the efficacy and safety of a new drug efficiently and with low burden to patients, without loss of scientific rigor to make new therapeutic options available to patients.

1. **Understand and articulate advantage of innovative trial features over default solution**
   - Innovative design features should be preferred over standard trial options (only) if they have objective advantages.
   - Simulations prior to the trial conduct help to understand and clearly articulate these advantages.

2. **Understand operating characteristics and limit risk of erroneous decisions at the design stage**
   - **Simulations *prior*** to the trial provide understanding of operating characteristics under *other* plausible settings than the per-protocol assumptions, i.e. «no cherry picking», and help in aligning different stakeholders
   - **Power** considerations: type II errors are particularly severe in pediatric & rare indications, «typically one shot on target»
   - **Type-I error:** comprehensive understanding (not necessarily control) of type I error required based on simulations; provide clinical context
   - **Bias:** Assess possible sources and quantitatify impact of bias under clinically plausible scenarios
   - **Extrapolation**: Extrapolation approaches are useful when the relationship between the source and target population is well understood

3. **Results and regulatory decisions should be explainable and supportable by all stakeholders**
   - **Clinical & statistical sucess criterion** should be predefined in confirmatory trials (per-protocol scenario)
   - **Tipping point analyses *after*** the trial (across clinically plausible scenarios) help understanding the robustness of results; e.g. less weight given to historical data

# Thank you

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