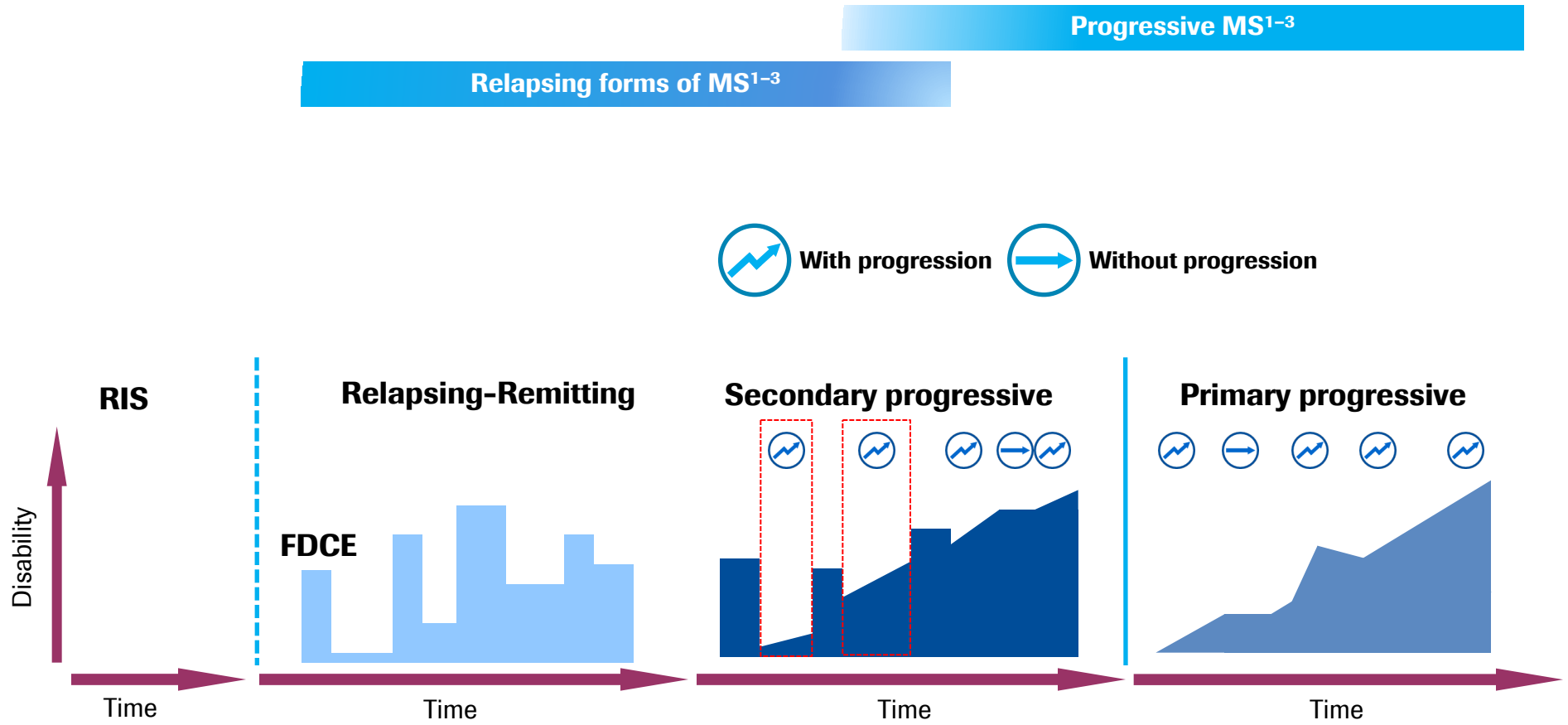
Efficacy independent of relapse
HA interactions before ICH E9 R1

Fabian Model

MS disease course – 2013 consensus

An evolving picture and understanding



FDCE, First Demyelinating Clinical Episode; RIS, radiologically isolated syndrome; RRMS, relapsing-remitting multiple sclerosis

1. Lublin FD, Reingold SC. Neurology 1996;46:907–11; 2. Adapted from Lublin FD, et al. Neurology 2014;83:278–86; 3. Antel J, et al. Acta Neuropathol 2012:123:627–38.

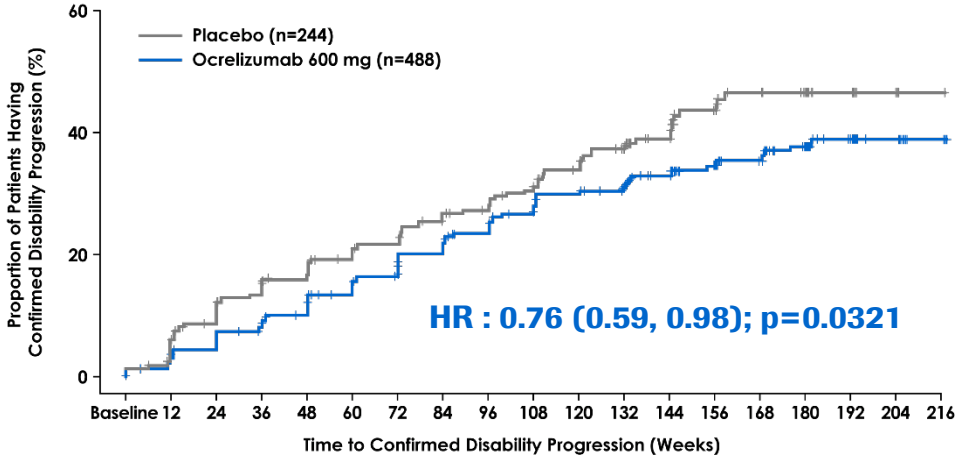
Ocrelizumab experience

Ocrelizumab – Pivotal Studies in RMS and PPMS

Treatment effect on 12-week Confirmed Disability Progression

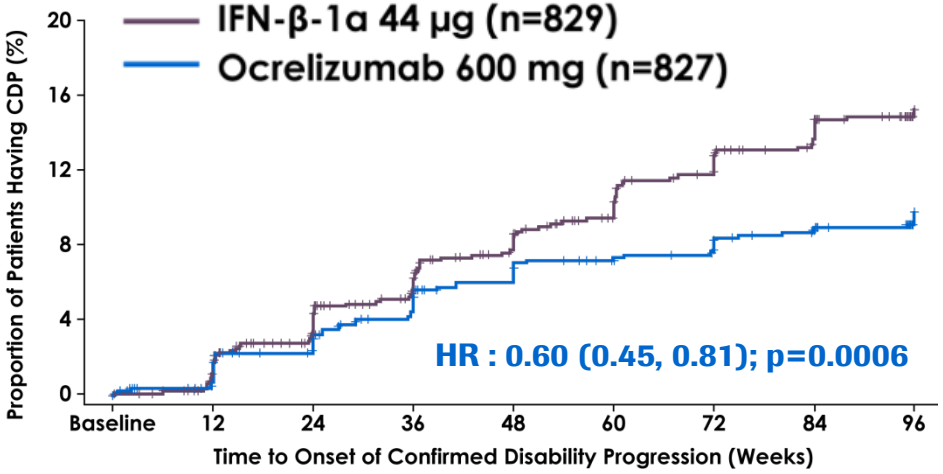
Primary Progressive MS (PPMS)

- Single study (ORATORIO)
- Primary endpoint: 12-week CDP
- Secondary endpoint: T25FW
- Exploratory endpoint: 9HPT



Relapsing MS (RMS)

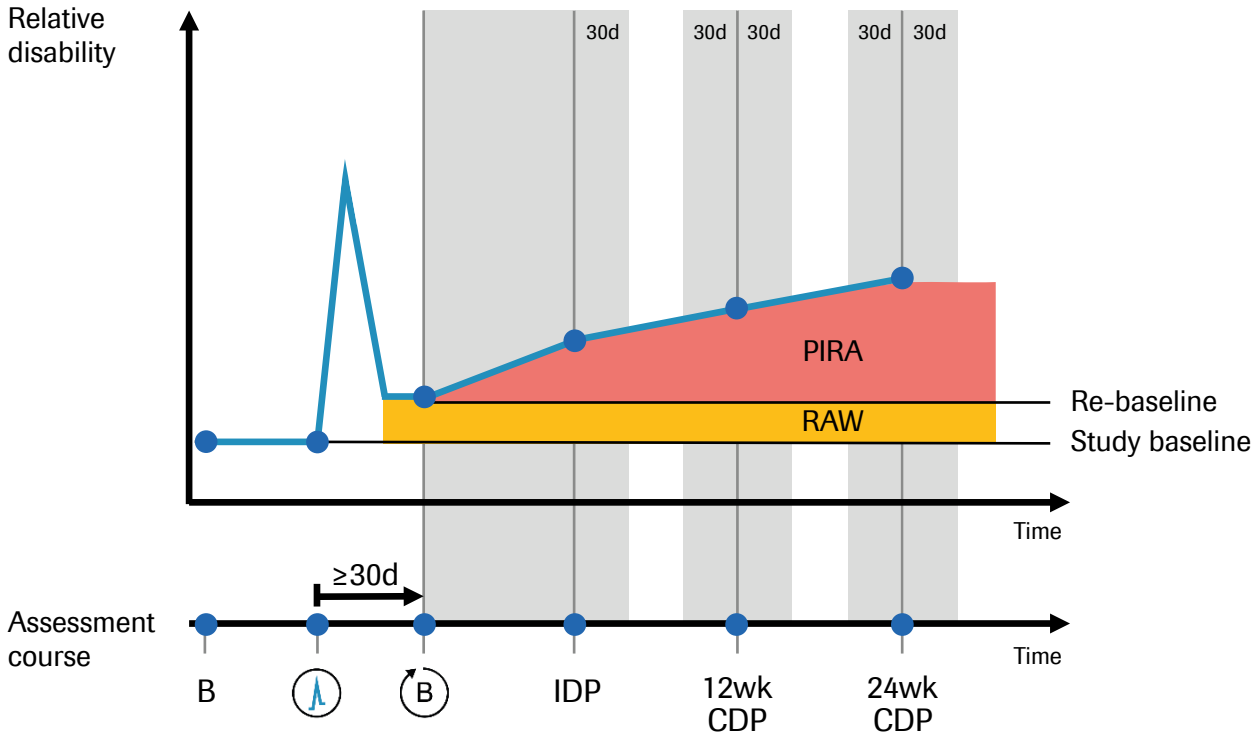
- Two identically designed studies (OPERA1 + OPERA2)
- Primary endpoint: Relapse Rate (46% and 47% reduction)
- Key Secondary: 12-week CDP (Pooled OPERA1+OPERA2)
- Exploratory endpoint: T25FW, 9HPT



HA interactions with regard to PIRA

Indication	HA Discussions	Analysis	Outcome
PPMS	**FDA:** Potential impact of few observed relapses during study on 12-week CDP treatment effect	**Pre-specified analysis:** Subgroup of patients without on-study relapse **Pre-BLA meeting:** Suggestion to perform analysis where outcome is re-baselined after each relapse	No formal question received

Methods for assessing Progression Independent of Relapse (PIRA)



B	Study baseline	IDP	Initial Disability Progression
	Onset of relapse	12wk CDP	12-week Confirmed Disability Progression
≥30d	30 days	24wk CDP	24-week Confirmed Disability Progression
B	Re-baseline	RAW	Relapse Associated Worsening
	Relapse-free phase	PIRA	Progression Independent of Relapse Activity

Results: Progression Independent of Relapse

Clinical measures of disability: EDSS, 25 Foot Timed Walk, 9 Hole Peg Test

Analysis	Endpoint	KM estimates at Week 96 (%)		HR (95% CI)	p-value
		IFN β-1a (N=829)	OCR (N=827)		
Overall Progression (pre-specified)	**Composite CDP**	**29.7**	**21.0**	**0.66 (0.54–0.81)**	**<0.001**
	EDSS	15.2	9.8	0.60 (0.45–0.81)	<0.001
	T25FW	18.6	14.1	0.72 (0.55–0.93)	0.013
	9HPT	4.6	3.6	0.80 (0.47–1.34)	0.39
Re-baselined PIRA	**Composite PIRA**	**23.3**	**18.5**	**0.78 (0.63–0.98)**	**0.029**
	EDSS–PIRA	9.5	7.0	0.75 (0.53–1.07)	0.11
	T25FW–PIRA	15.5	12.6	0.77 (0.58–1.03)	0.075
	9HPT–PIRA	4.0	3.1	0.78 (0.44–1.37)	0.38
Sensitivity Analyses	**Composite CDP** Relapse Free Subgroup	**24.8**	**19.2**	**0.75 (0.59 – 0.96)**	**0.024**
	Composite PIRA Censoring at Relapse	**25.1**	**20.1**	**0.77 (0.61 – 0.96)**	**0.023**

HA interactions with regard to PIRA

Indication	HA Discussions	Analysis	Outcome
PPMS	**FDA:** Potential impact of few observed relapses during study on 12-week CDP treatment effect	**Pre-specified analysis:** Subgroup of patients without on-study relapse **Pre-BLA meeting:** Suggestion to perform analysis where outcome is re-baselined after each relapse	No formal question received
RMS	**EMA:** • Is Ocrelizumab effective in SPMS patients? Should the label be Relapsing Remitting MS (RRMS) or Relapsing MS (RMS)? • Supportive evidence from RMS studies that ocrelizumab is effective on progressive component of disease to support single study PPMS filing	**Main analysis:** Estimation of PIRA treatment effect based on re-baselining after each relapse **Sensitivity Analyses:** • Subgroup of patients without on-study relapse • Censoring at first relapse	• RMS data not considered as conclusive support for PPMS efficacy • Data was considered supportive for RMS indication

Challenge: Communication of statistical methods and implications for validity of causal inference to clinicians and regulators!

Pre-Estimand Experience

- Progression independent of relapse was an unexpected and difficult challenge
  - No formal clinical definition of SPMS or progression independent of relapse exist
  - Clinical concept based on presence/absence of causal relationship between relapses and progression
  - Limitations of interpreting on-study events that are modified by treatment and linked to outcome poorly understood and difficult to explain
- In a pre-Estimand world
  - Discussions with clinicians and regulators tended to focused on algorithm description rather than clinical concepts
  - Language to describe intercurrent events and target of estimation was imprecise, resulting in frequent misunderstandings and frustration

NOVARTIS

Efficacy independent of relapse
HA interactions after ICH E9 R1

Nicolas Rouyrre and Nikolaos Sfikas

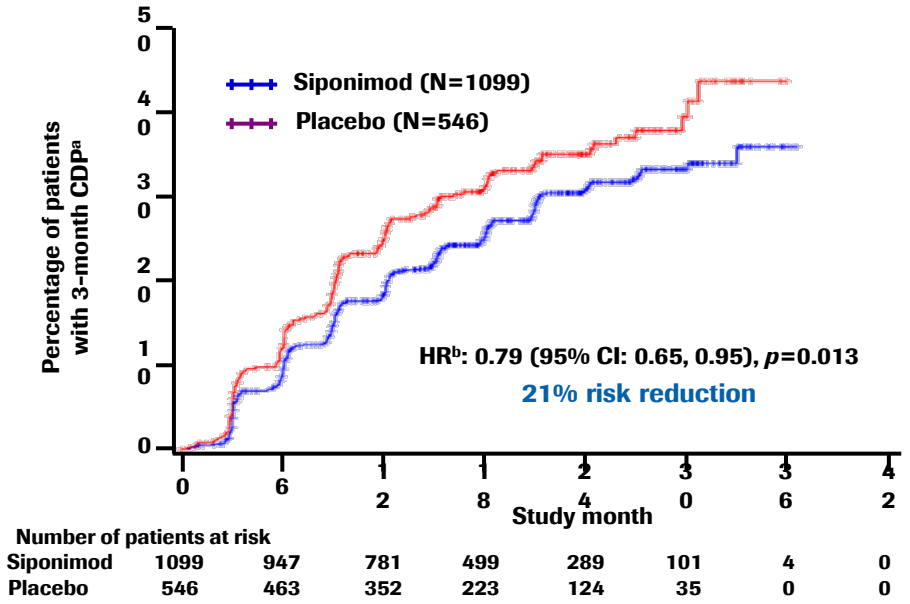
Siponimod experience

Siponimod – Pivotal Study in SPMS

Treatment effect on 3month Confirmed Disability Progression

Secondary Progressive MS (SPMS)

- Single study (EXPAND)
- Primary endpoint: 3-month CDP
- Key Secondary endpoints:
  - T25FW
  - T2 lesion volume
- Secondary endpoint: ARR



First HA interactions with regard to Efficacy independent of treatment effect on relapse

Indication	HA Discussions	Analysis
SPMS	**FDA:** Potential impact of few observed relapses during study on 3month confirmed CDP treatment effect	**Pre-specified analysis:** - Subgroup of patients without on-study relapse - Subgroup of patients without relapses within 2 years prior to screening - Analysis where outcome is re-baselined after each relapse

Outcome
Agency would need to see additional suportive results to be convinced

Using the estimand framework to reformulate the question(S) of interest

How patients could benefit from the treatment apart from its direct effect on relapses?

2 different but related questions of medical importance:

- Efficacy of siponimod in non-relapsing patients ~ Efficacy in the more advanced/less inflammatory subgroup of patients?
  => **Subgroup type** of analysis

- Efficacy of siponimod, in the overall population, on disability progression not due to relapses ?
  => **Overall population** but without confounding from intercurrent relapses

Question 1:
Efficacy of siponimod in non-relapsing patients
Preplanned Subgroup analyses

- 2 pre-planned subgroup analyses

Estimator	Drawback/assumptions	Hazard Ratio 3mCDP	Hazard Ratio 6mCDP
Subgroup of patients without relapse in the 2 years prior to inclusion	Unbiased Not efficient: absence of relapse prior to study does not preclude on-study relapse activity	**0.87** (0.68;1.11)	**0.82** (0.62; 1.08)
Subgroup of patients without on-study relapse	Subgroup defined by post-randomization outcome that is impacted by treatment (likely biased) and by follow-up duration.	0.85 (0.69;1.06)	0.76 (0.60; 0.97)

Although providing valuable information these 2 analyses fail to evaluate treatment effect in **true non-relapsing patients**

Question 1:
Efficacy of siponimod in non-relapsing patients
Principal stratum analysis

- One particular estimand of interest suggested in ICH E9 R1:

  principal stratum analysis

  - Focus on the subgroup “Non-relapsers”, i.e. patients who would not relapse over the specified period of time regardless of treatment assignment (siponimod or placebo).

  - Patients are classified based on potential intercurrent events on both treatments

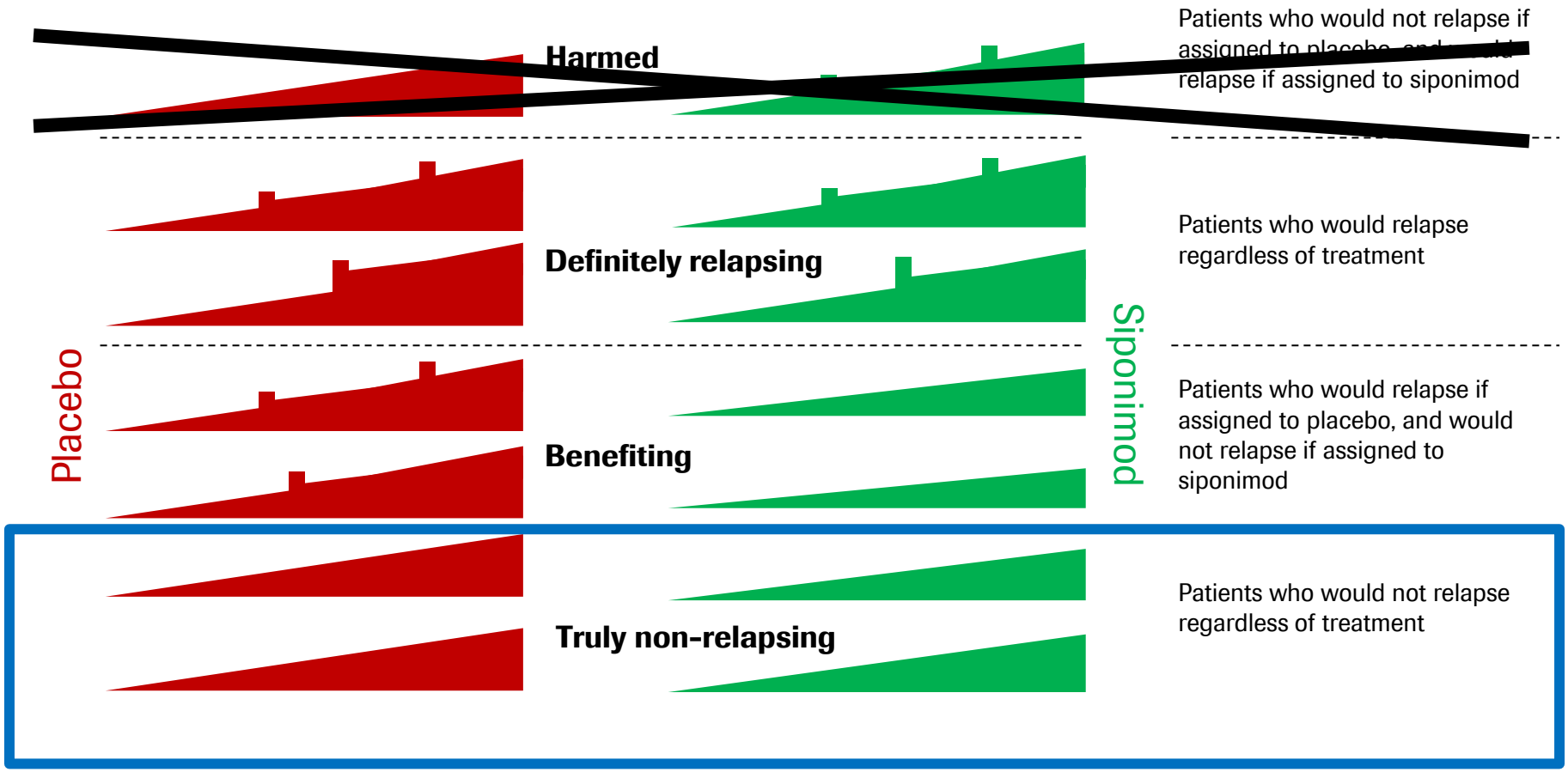
Question 1:
Efficacy of siponimod in non-relapsing patients
Principal stratum analysis

Population	Non-relapsers, i.e. patients who would not relapse over the specified period of time regardless of treatment assignment (siponimod or placebo), within the targeted SPMS population
Variable	Occurrence of 3 month confirmed disability progression over the specified period of time
Intercurrent event	On-study relapse. The intercurrent event of is captured through the population definition
Population-level summary	Risk Ratio

Question 1:
Principal Strata analysis
Comparing Apples with Apples

Monotonicity assumption

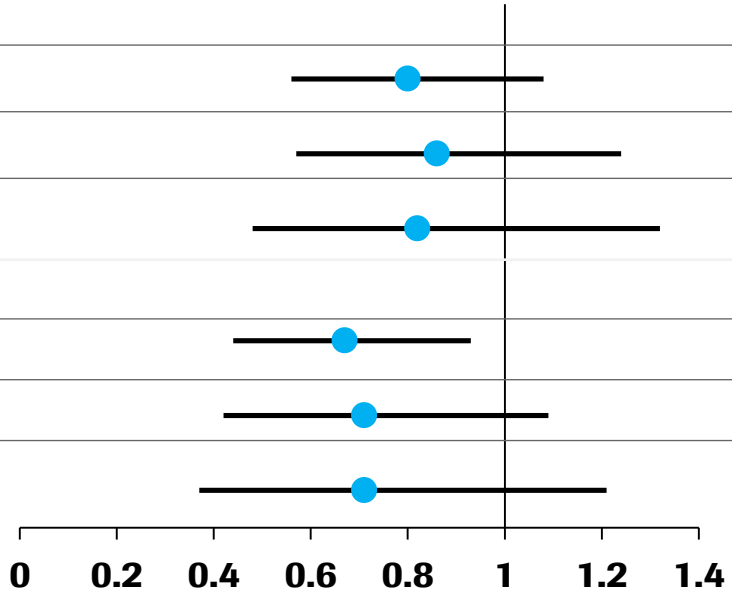
No patient was “harmed”: siponimod did not provoke relapses in patients who would not have relapsed under placebo



Results – Principal stratum strategy

Efficacy in non-relapsing patients

Principal stratum: non-relapsing pts*	ß Favors siponimod / Favors placebo à	Risk ratio (95% CrI)
3m-CDP		
12 months		0.80 (0.56, 1.08)
18 months		0.86 (0.56, 1.24)
24 months		0.82 (0.48, 1.32)
6m-CDP		
12 months		0.67 (0.44, 0.93)
18 months		0.71 (0.42, 1.09)
24 months		0.71 (0.37, 1.21)



The principal stratum analysis gives the best possible unbiased estimate of treatment effect in non-relapsing patients

CDP, 3-month confirmed disability progression; CrI, credibility interval. *Patients who would not relapse over the specified period of time on-study regardless of treatment assignment.

Question 2:
Efficacy of siponimod, in the overall population, on disability progression not due to efficacy on relapses

Hypothetical strategy

Population	SPMS population
Variable	Occurrence of 3 month confirmed disability progression over the specified period of time
Intercurrent event	On-study relapse. The intercurrent event be handled using two hypothetical strategies: - Assuming no patients would experience intercurrent relapses (**hypothetical prescriptive**) - Assuming patients in both treatment arms would have the same risk of experiencing intercurrent relapses (**hypothetical natural**)
Population-level summary	Hazard Ratio

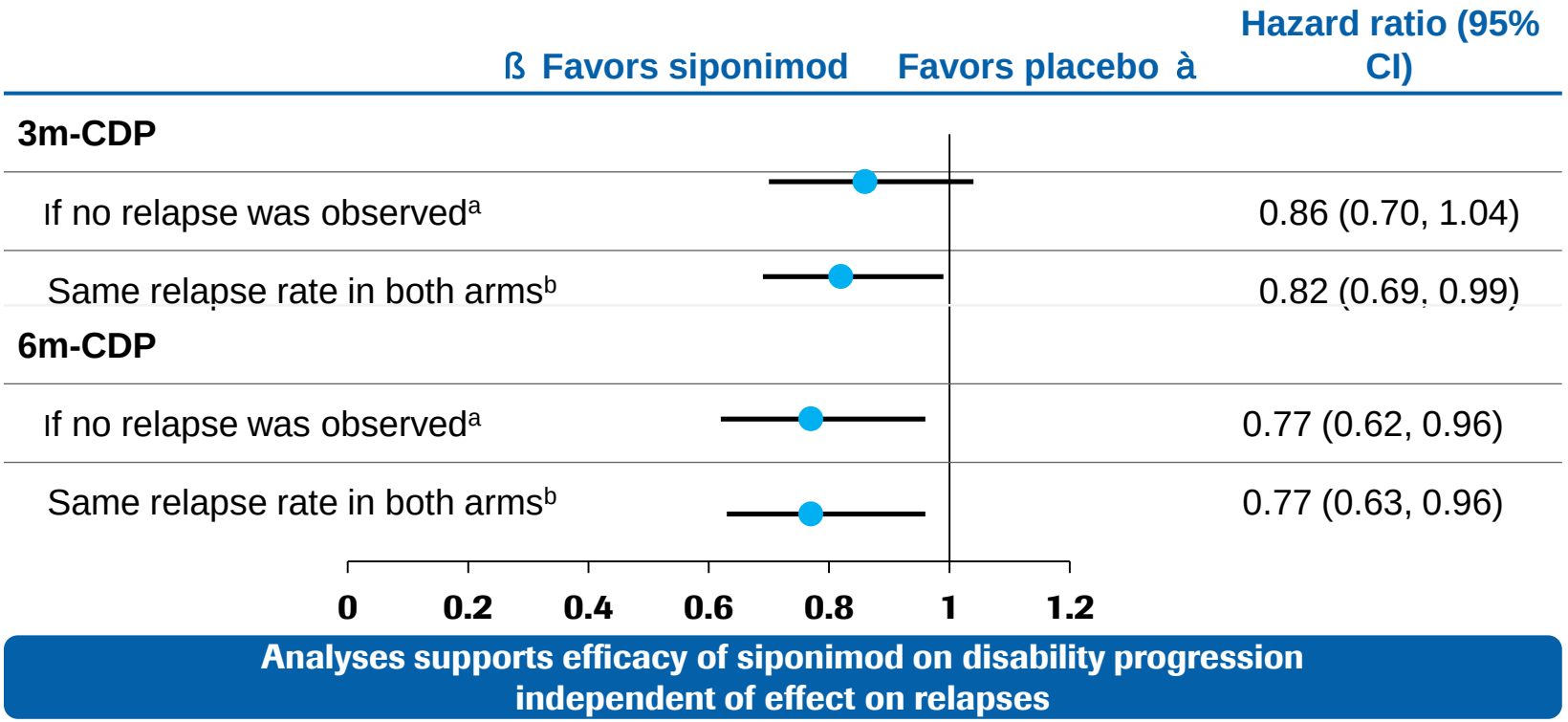
Question 2:
Efficacy of siponimod, in the overall population, on disability progression not due to efficacy on relapses

- Hypothetical prescriptive: Assuming that progression before the first relapse reflects the disability progression between relapsing episodes a Cox model censoring at first relapse would give valid answer

- Hypothetical natural: Bootstrap based method where we sample with reweighting of the patients to ensure balanced rate of relapses between the 2 treatment arms

Results – Hypothetical Strategies

Relapses would not interfere with the assessment of efficacy on CDP



Analyses supports efficacy of siponimod on disability progression independent of effect on relapses

CDP, confirmed disability progression; CI, confidence interval; IPCW, inverse probability of censoring weighted; m,month.

[a] Effect of siponimod if no relapse was observed: Cox model with censoring at the time of first confirmed relapse with IPCW correction for informative censoring.

[b] Effect of siponimod if the same relapse rate was observed in both arms: Cox model applied to samples simulated from empirical distribution.

Post-Estimand Experience

- Progression independent of relapse was still a difficult challenge but
  - Estimand framework provided the tools to provide formal definitions for questions of interest
  - Concept based on theoretical populations that should be evaluated after taking into account impact of intercurrent events
  - Limitations of interpreting results were easier to understand and explain
- In a post-Estimand world
  - Discussions with clinicians and regulators focus on target of estimation, intercurrent events and clinical concepts rather than algorithms to be applied
  - Language to describe intercurrent events and target of estimation is much clearer, resulting in less misunderstandings and more transparency in our interactions