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The proposed ‘two-step approach’ for MS treatments with a significant effect on immunity

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Agenda

- MS background
  - MS disease progression
  - Importance of early intervention
- Current EMA draft guideline: two step approach
  - May deny beneficial medicines to patients
  - May delay access to medicines for patients
  - Makes assumptions about immune compounds
- EFPIA recommendations: parallel approach
  - Parallel approach enables earlier access to medicines and better outcome for patients
  - MS population targeted should be defined by benefit-risk and stage of disease
- Conclusion
- Acknowledgments

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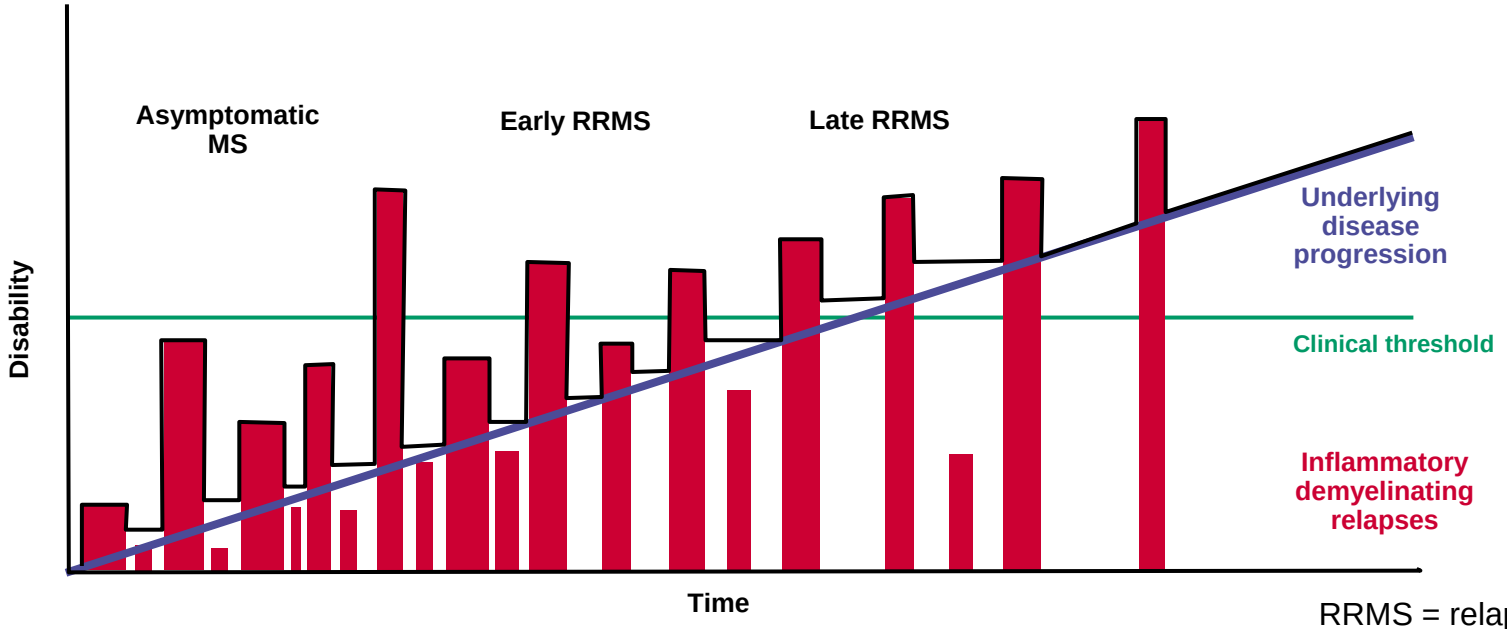
MS is a serious disease progressively evolving into severe disability

- The pathology of MS starts with inflammation caused by an autoimmune reaction, followed by demyelination of axons, and eventual neurodegeneration.
- The brain's ability to compensate for neuronal loss allows for a great deal of disease progression in MS to be clinically silent[1].
- As the level of CNS damage progresses, the compensatory ability of the CNS is gradually lost and allows for the appearance of more and more symptomatic relapses.



RRMS = relapsing-remitting MS

1. Barkoff F, *et al. AJR Am J Roentgeno.* 1992;159(5):1041-7

Importance of early intervention

Early intervention in MS slows disease progression and improves long-term outcomes by:

- Minimizing nerve damage and inflammation that occur in the early stages of MS.
- Preventing new lesions and clinical deficits, which is easier than trying to repair old ones.

In summary, high efficacy disease-modifying therapy given at the earliest stages of disease has the greatest potential to reduce the risk of disease progression and of permanent disability for patients.

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EMA Draft Guideline: two-step approach

Current EMA draft guideline

The two-step approach as currently stated in draft EMA guideline

Insufficient response/ (anticipated) rapid progression

Broader MS population

Draft guideline states:

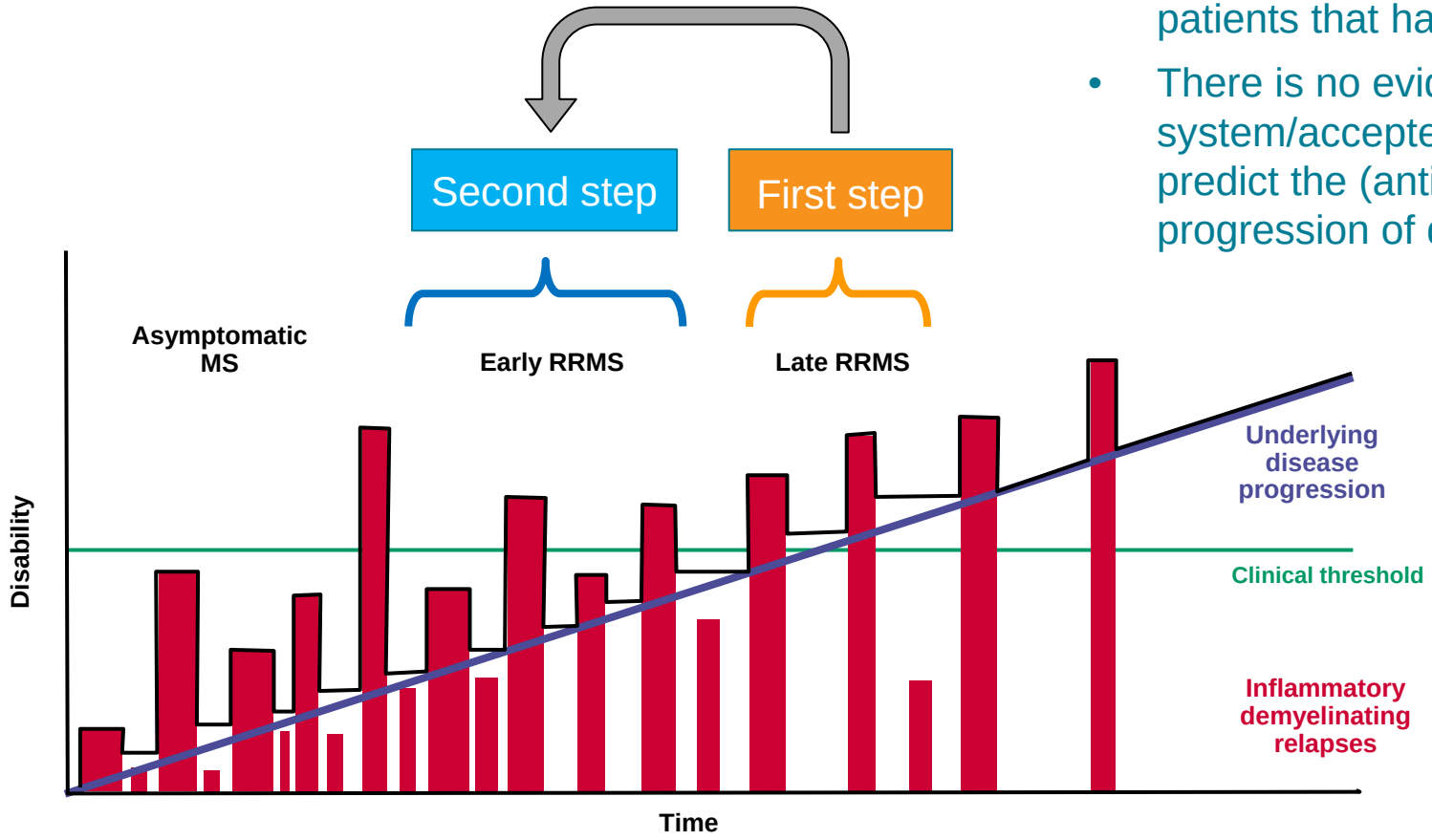
"For compounds with an anticipated profound effect on the immune system and thus potential serious safety concerns these risks may be outweighed by a larger effect. Usually these products are restricted to patients partly responsive to first line treatment and/or an (anticipated) rapid progression of their disease. Therefore a two step approach is recommended. As a first step, the product should be evaluated in a comparative superiority study in patients insufficient responsive [sic] to first line treatment and/or an (anticipated) rapid progression of their disease. (….) As a second step, if the safety has raised no major concern, superiority studies versus first line treatment /placebo may be considered to evaluate efficacy in a broader multiple sclerosis population[2]."

2. EMA/CHMP/771815/2011, Rev2 Ref: Line 201-209

[underlines added for emphasis]

Two-step approach: challenges in determining MS course/response to treatment

- There are no uniform criteria to define insufficient response, therefore it is challenging to prospectively define patients that have insufficient response.
- There is no evidence based system/accepted criterion available to predict the (anticipated) rapid progression of disease.



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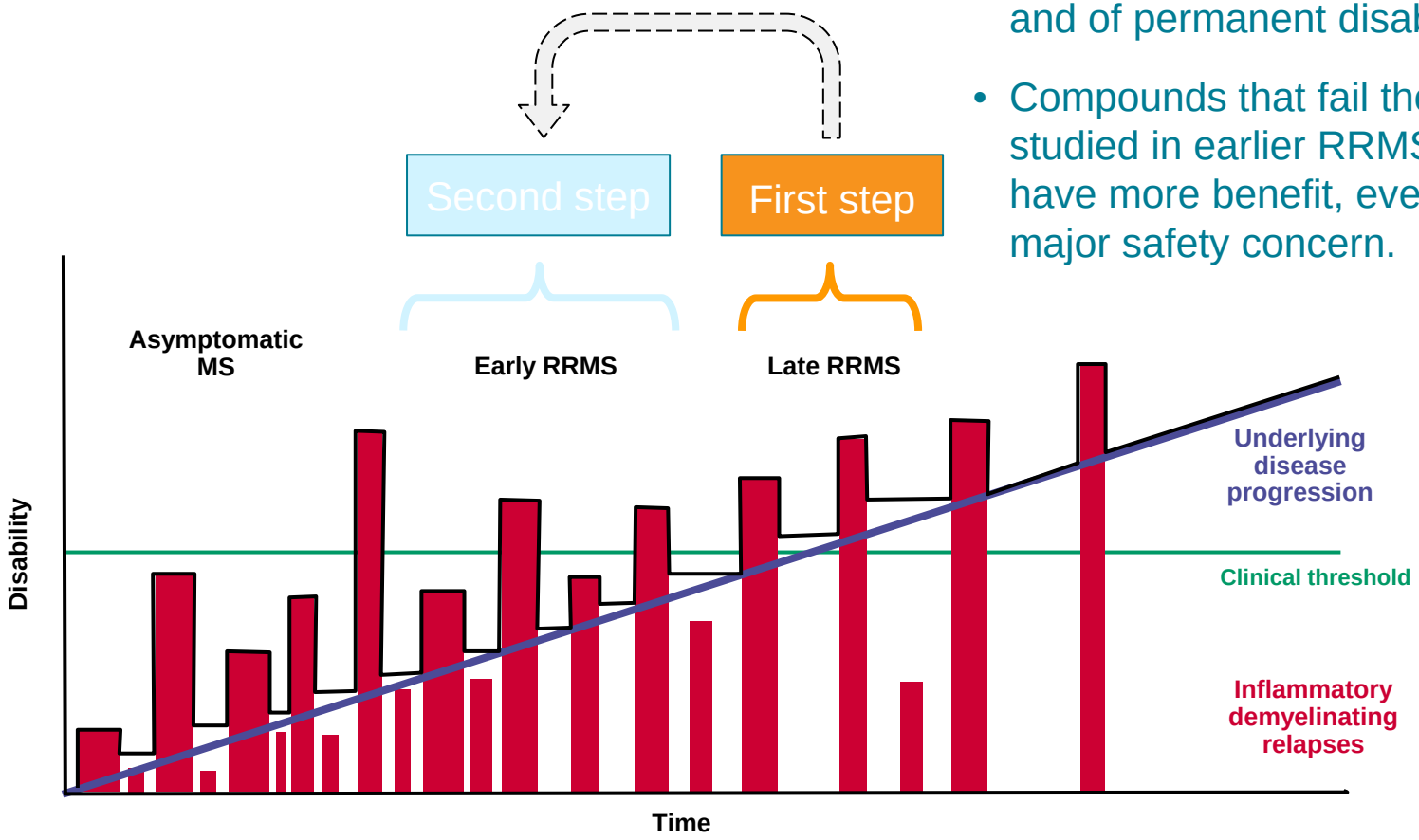
The two-step approach: may deny beneficial medicines to patients

- Lost opportunity for early intervention with high efficacy disease-modifying therapy, that may slow or reduce the risk of disease progression and of permanent disability for patients.
- Compounds that fail the first step may never be studied in earlier RRMS patients where it may have more benefit, even if there has not been a major safety concern.



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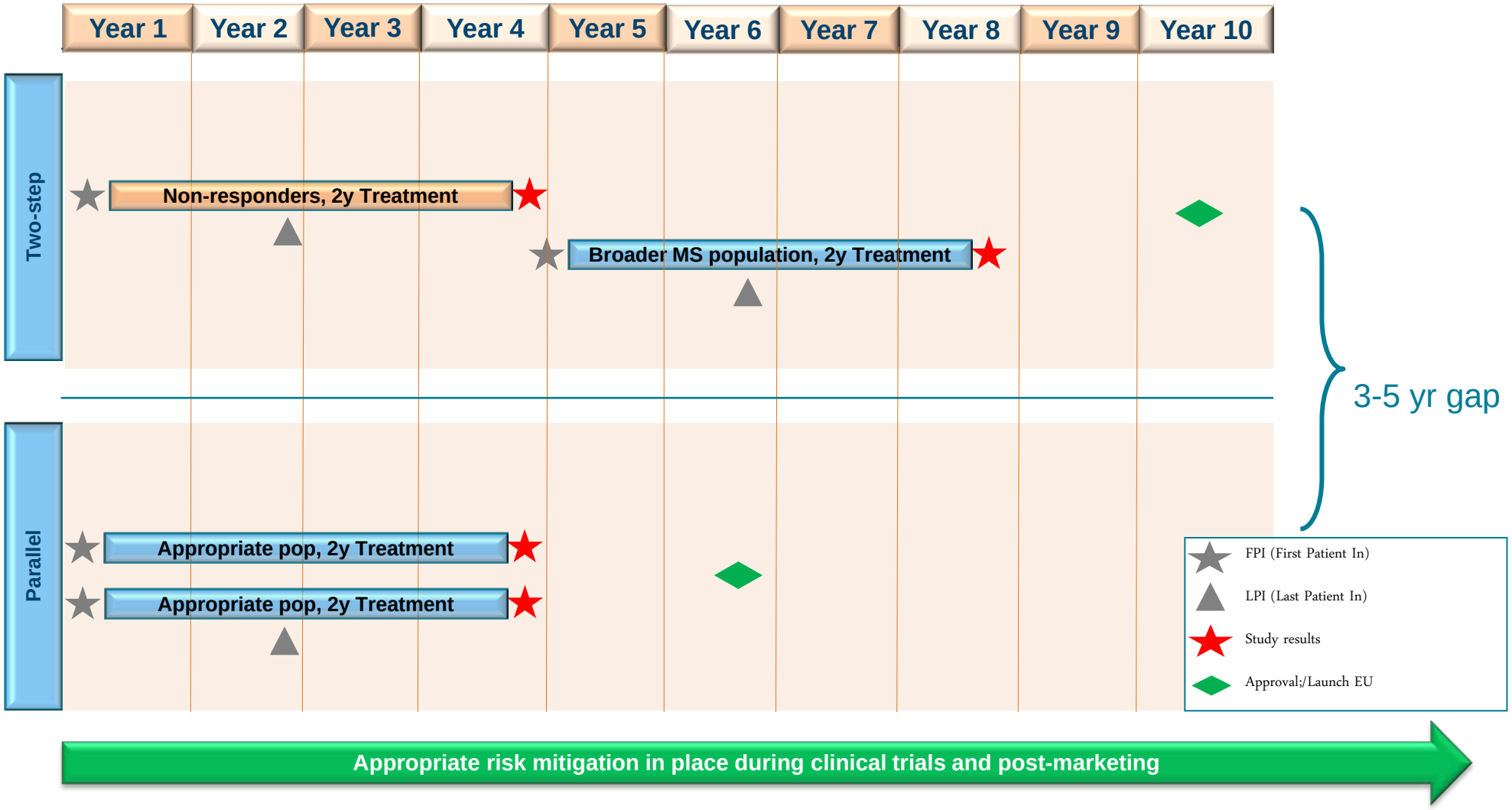
The two-step approach: may delay access to medicines for patients



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Appropriate risk mitigation ensures safety of patients

Examples of risk mitigation procedures in clinical trials/post-marketing

- Data Monitoring Committee
- Pre-specified lab alerts tailored to the MoA of the compound
- Pre-specified stopping rules
- Pre-planning and applying statistical procedures for safety signal detection
- Safety interim analysis
- Careful identification of safety risks and implementation of safety measures in clinical trials
- Post-marketing Risk Management Plan (RMP)

Procedures listed are potentially more effective at managing risk without unduly delaying or restricting access to novel treatments.

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Benefit-risk for Ph 3 should be derived from clinical data & MoA

Benefit-risk conclusion should be based on clinical data, rather than on assumptions about immune effect

- The guideline implies compounds with immune MoA are more likely to have serious safety risks, but this may not necessarily be the case
- Non-immune MoA compounds may have serious safety risks and they are seemingly excluded from this two-step approach
  - e.g. risks associated with fingolimod are not all driven by the drug's effect on the immune system (Macular edema, respiratory symptoms, CV)

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EFPIA Recommendation: A parallel approach

EFPIA recommend a parallel approach

1) **A parallel approach:** a parallel approach with appropriate risk mitigation procedures in the clinical trial setting, rather than a sequential two step approach for all compounds regardless of anticipated immune effect, and;
2) **An appropriate MS population defined by data:** the patient population to be studied in Phase 3 trials should be defined on a case-by-case basis according to a benefit-risk assessment from all available clinical data.

Appropriate MS population

Appropriate MS population

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Parallel approach enables earlier access to drugs and better outcome for patients

- Benefit-risk conclusion should be based on clinical data
- High efficacy drugs given at an early stage of MS are more likely to reduce the risk of disease progression and permanent disability for patients
- A parallel approach potentially allows getting a drug with a positive benefit-risk profile to the MS population 3-5 years faster
- Appropriate risk mitigation procedures in the clinical trial setting allows effective drugs to reach patients faster, while ensuring the safety of patients in the study.

Conclusion

We recommend:

"The parallel approach for all compounds regardless of anticipated immune effect, in MS patients defined by the stage of disease being targeted and available efficacy and safety data“

- Prevents delay in patient access to promising MS medicines
- Allows investigation of the appropriate MS population
- Ultimately supports development of medicines to prevent accumulation of severe disability

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