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Changes in Patient Population

Insufficient Treatment Response

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MS Population & Insufficient Rx Response

Topic

- **The changing multiple sclerosis population and the definition of an ‘insufficient treatment response’, as well as their impact on the benefit-risk assessment of new medicines**

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Changing MS Population

Baseline Characteristics

	Betaseron ~1990	Rebif ~1995	Tysabri ~2000	Gilenya ~2005	Aubagio ~2010	Tecfidera ~2010	
Age	35	35	36	37	38	38	37
% Female	70	69	70	69	72	73	69
Disease Duration	-	5	5	8	9	6	5
% Prior Rx	**0**	**0**	**6**	**41**	**27**	**41**	**30**
EDSS	2.9	2.5	2.3	2.4	2.7	2.4	2.6
Relapse in 2 yr pre-study	**3.4**	**3.0**	1.5¶	**2.1**	**2.2** 1.4¶	1.3¶	1.4¶

¶ relapses in year prior to study

Changing MS Population

Relapse Outcomes On Study

		Betaseron ~1990	Rebif ~1995	Tysabri ~2000	Gilenya ~2005	Aubagio ~2010	Tecfidera ~2010	
Relapse Rate	Active	0.90	0.86	0.23	0.18	0.37	0.17	0.22
	Control	**1.31**	**1.28**	**0.73**	**0.40**	**0.54**	**0.36**	**0.40**
Relapse Free	Active	25%	27%	72%	70%	59%	73%	71%
	Control	**16%**	**16%**	**46%**	**47%**	**46%**	**54%**	**59%**

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Changing MS Population

Factor	Change	Potential Impact
Age	Slight increase	Potentially less responsive to Rx, but difference minimal
Gender	No substantive change	None
Level of Pre-study Relapse Activity	Lower by ~ 1/3rd	Lower on-study activity and less precision in estimate of effect size
Level of Disability	Varies, but trend is to lower EDSS	Greater challenge to interpret clinical meaning of change at low end of EDSS
Disease Duration	Variable	Potentially milder disease course to entry for longer duration
Proportion Previously Treated with DMT	Higher	Generally less responsive to Rx
Revised Diagnostic Criteria	Earlier diagnosis of Definite MS	CIS disappears; earlier stage of disease at enrolment; more responsive to Rx
Reduced Relapse Activity on-study	Several-fold change in ARR (or increase in % relapse-free)	Floor effect; interpretability of Rx effect size

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Patient Population: Additional Specific Issues

"New compounds with an anticipated modest efficacy and mild safety profile will be used in patients with early MS and/or a benign course of their disease"

- Early disease does not equate to benign
- Early disease may be most responsive to alteration in natural history (CIS experience)
- Such patients should not, *a priori*, be relegated to potentially less effective therapies

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Patient Population: Additional Specific Issues

"this indication [CIS] is covered by an approval for the treatment of relapsing RMS. The inclusion of these patients in the development of a product for an indication for MS is welcomed"

- Non-contentious
- Issue of radiologically isolated syndrome (RIS) not addressed but is currently premature to include in Guidance
- If RIS development considered, recommend prior discussion with agency

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Patient Population: Additional Specific Issues

"to evaluate the efficacy of a product against disability progression in SPMS, it is recommended to target only SPMS patients without relapses in order to exclude possible effects on disability related to effects on relapse activity"

- Relapsing SPMS forms part of the spectrum of SPMS
- A portion of the disability progression in SPMS relates to relapses
- Precise definition of nrSPMS not available
- nrSPMS patients enrolled in studies have subsequently developed relapses in substantial proportion
- Stratification and sensitivity analyses can help dissect independent effects of relapse-related vs. non-relapse-related progression

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Patient Population: Additional Specific Issues

"*Clinical trials in children /adolescents with RRMS are difficult to conduct because of the low number of paediatric MS patients. Nevertheless, the generation of specific data is expected. This might be done by performing clinical trials tailored to children, by incorporating adolescent MS patients into the adult trials and/or by extrapolating efficacy observed in adult MS patients to children provided the dose and short term safety is established and the long term safety is evaluated*."

- Pediatric MS studies are exceedingly difficult to design and conduct for a number of reasons, including very limited population, lack of precedent, resistance to placebo-control, lag time to diagnosis from onset, lag time for use of other therapies before investigational therapy, ethical considerations of vulnerable population etc.
- MS in pre-pubertal patients is rare and likely beyond the ability to conduct a clinical efficacy study
- Recommend that extrapolating results from adults be the generally accepted norm for adolescents (post-pubertal) with requirement for safety assessment

Changing Outcome Definitions & Analysis Methods

- Baseline EDSS variation (Olympus, CombiRx)
- Degree of EDSS change needed to “progress”
- Confirmation of relapses
- MRI definitions
- Brain volume measurement methods

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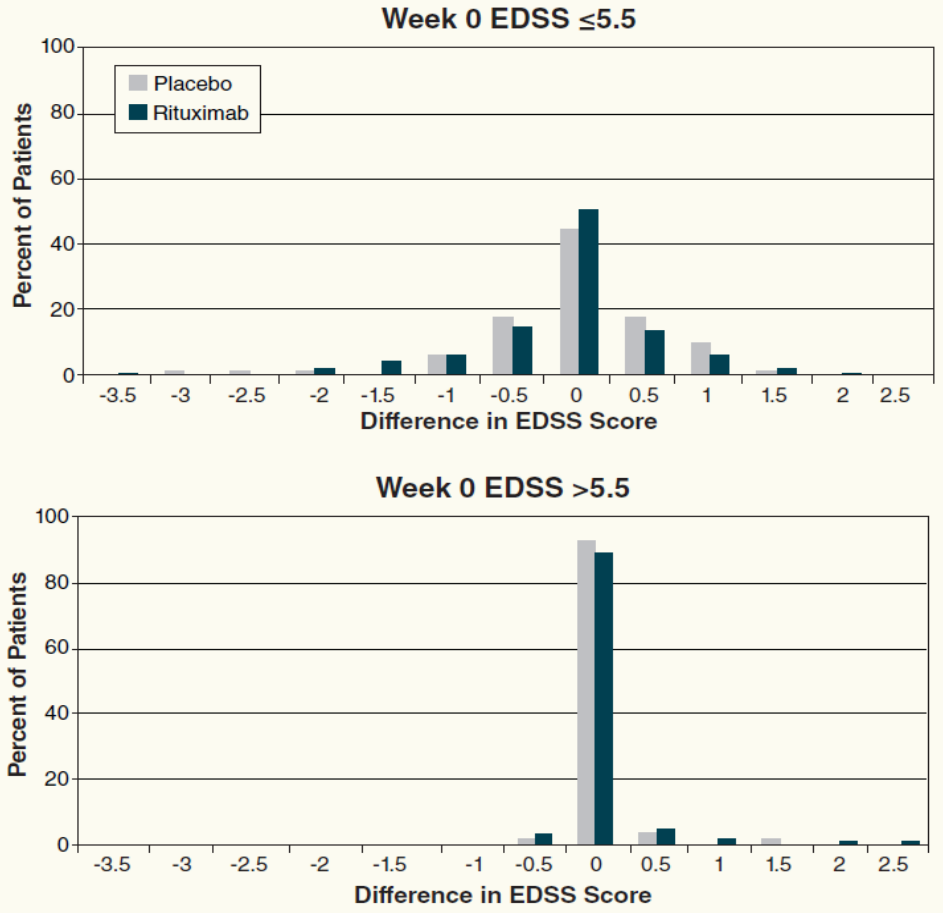
EDSS variability at baseline OLYMPUS Study

Figure 2. Distribution of EDSS Change from Screening to Week 0, by Treatment Arm and Week 0 EDSS (≤5.5 or >5.5)



Chin et al. 2009
ECTRIMS

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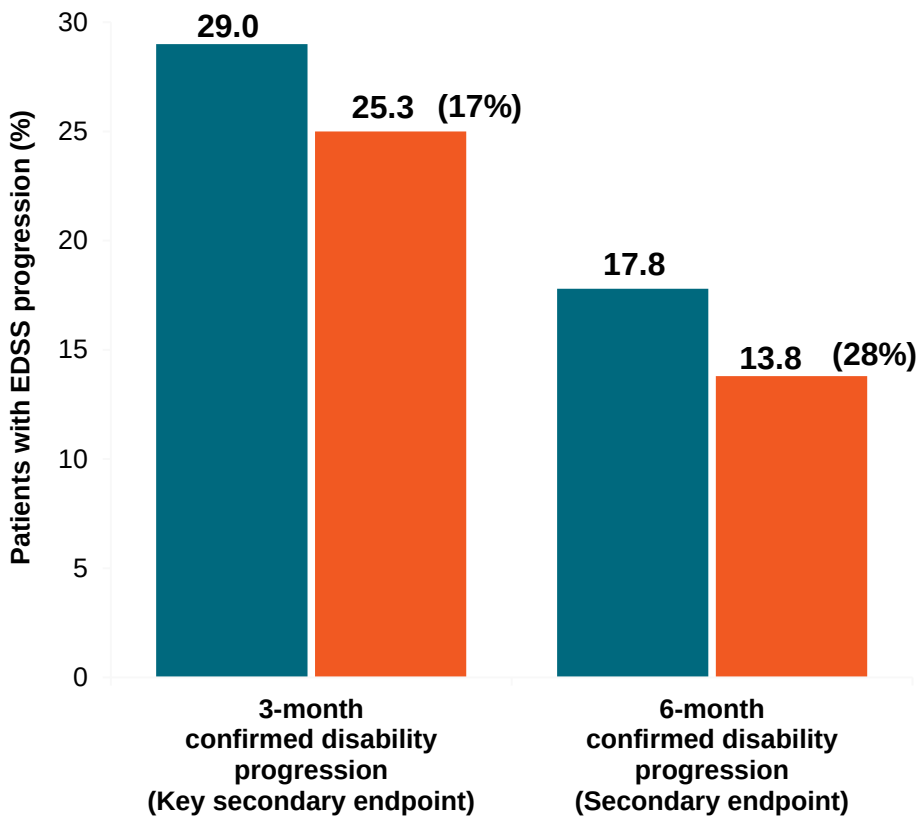
Impact of low EDSS on disability progression – FREEDOMS II

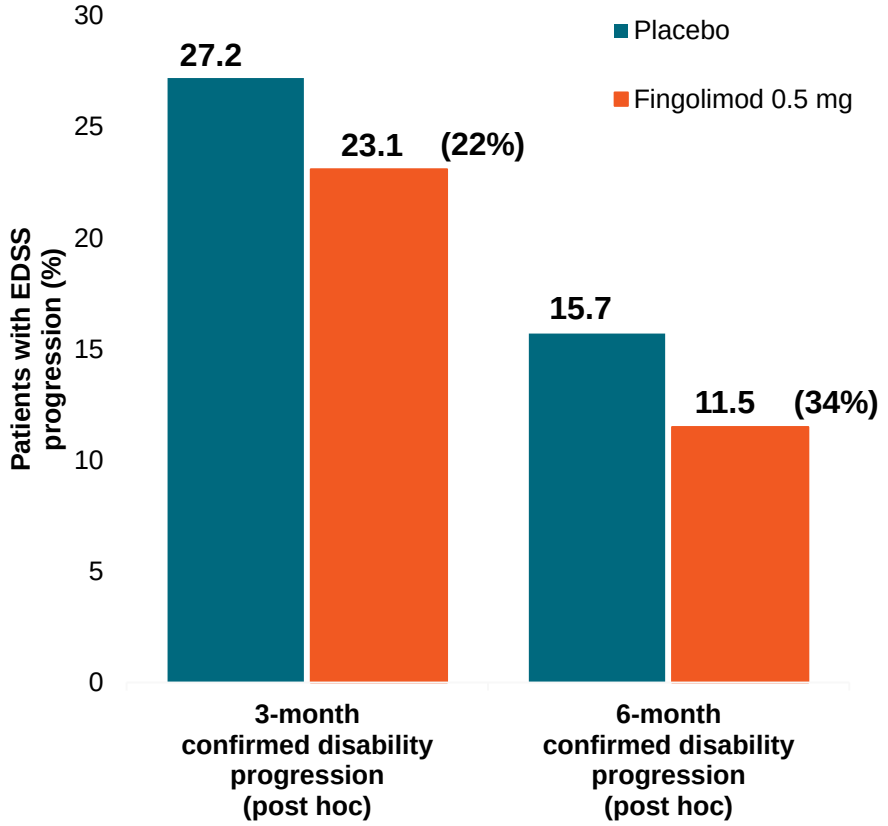
Protocol-defined progression

EDSS score increase 1 point
(0.5 points if baseline EDSS score > 5)



Sensitivity analysis progression

EDSS score increase 1.5 if baseline score = 0
(0.5 points if baseline EDSS score > 5)



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Patient Population: Recommendations

- Studies in RRMS must be adequately sized, with replication, to have confidence in the effect size shown on relapses given low level of activity in present-day studies
- Direct comparative studies are needed if information on relative effectiveness is required as populations and analysis methods differ
  - Modeling of patient level data, with adjustments for population differences, may provide additional insights for e.g. benefit-risk assessment or development of virtual placebo groups
- Early MS patients should not be relegated to potentially less effective therapies *a priori*
- Agree with Guidance regarding disappearance of CIS as a distinct entity; consider inclusion of language on RIS
- Disagree with Guidance language regarding inclusion of only non-relapsing SPMS patients in SPMS studies of disability progression
- Studies in pediatric MS requires further consideration on requirements for clinical trials

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"Insufficient Rx Response" Draft Guidance

"For compounds with an anticipated profound effect on immune surveillance patients ***unresponsive to first-line treatment*** and/or an (***anticipated***) rapid progression of their disease are the appropriate patient population"

"…compounds with an anticipated profound effect on the immune system … should be evaluated in a comparative superiority study in patients ***insufficiently responsive*** to first-line treatment…"

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"Insufficient Response" or "Unresponsive" - Definitions

- What duration of Rx before deemed "unresponsive"
  - 6, 12 months or more? Does it vary by product?
- Clinical criteria
  - Relapses: Number (1, 2, more; "same or more than before"), Severity, Residua
  - Disability progression
- MRI criteria
  - 9 MRI lesions, new Gd+, active T2, how many?
- How to address issues of safety, tolerability and patient preference (oral vs. injectable)
- Arbitrary *post-facto* definitions used in some SmPC indications despite fact that population(s) not tested

"Insufficient Rx Response" Recommendations

Given that:

- There is no consensus on the ***minimum*** clinical or MRI activity that would be agreed as demonstrating insufficient treatment response
- EFPIA does not agree to a staggered approach to development of drugs deemed to be potent immune modulators

- Recommend to remove language from MS Guidance on "insufficient response" or "apparently unresponsive"
  - May likewise avoid issues around *post-hoc* SmPC definitions

- Sponsors may themselves target sub-groups due to safety concerns and Guidance should be open to this

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Benefit-Risk Considerations

- “In the development of new compounds intended to modify the natural course of MS, the anticipated benefit-risk profile needs to be taken into consideration. ...the more effective agents also have an increased risk of opportunistic infections and malignancies...the anticipated benefit-risk profile should be weighed against the benign/malignant course of MS... could be based on ...studies in animals, pharmacodynamic studies, use of the product in other indications or known mechanism of action”

Benefit-Risk Considerations

- Animal data may be misleading (e.g. S1P3 cardiac effect in rodents vs. S1P1 in man)
- PD data may not predict risk (e.g. lymphopenia with S1P modulators)
- Many MS compounds are first-in-class without other indications (e.g. S1P, laquinimod, glatiramer acetate, natalizumab)
- Modification of a parent compound may mitigate issues of concern with parent (e.g. DMF, laquinimod, S1P next generation)

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Benefit-Risk Considerations

- Animal & PD data, & class of compound useful but alone should not necessarily define, *a priori*, sub-population to be studied
- Benefit-risk profile evolves during development and needs to incorporate new data, clinical or other
- Benefit-risk needs to carefully evaluate safety risk but must adequately take into consideration consequences (relapses / disability progression) to the patient of under-treating disease
- Risks are often associated with early phase of treatment while benefits may continue while remaining on therapy

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Comparing Benefits vs. Risks Fingolimod Phase 3 Data

For Every 1000 MS Patients Treated with 0.5mg Fingolimod Compared to Placebo Over Two Years

	Type of Event	Number
Benefit	Relapses Avoided	440
	Increase in Patients free of Relapse	248
	Increase in Patients without Disability Progression	64
Risk	Confirmed Macular Edema	4
	Transient High-Grade AV Block	1
	5-fold Elevation of Hepatic Transaminases	9
	Elevated Blood Pressure	23
	Pneumonia	3

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Benefit-Risk Recommendations

- Include language in Guidance to highlight impact of reduced efficacy in consideration of benefit-risk

- Consider including language regarding exploration of structured benefit-risk evaluations