

Use of RWD to contextualize post-hoc analysis in regulatory submission: an example from the ORATORIO Trial and the Long-Term MSBase Registry

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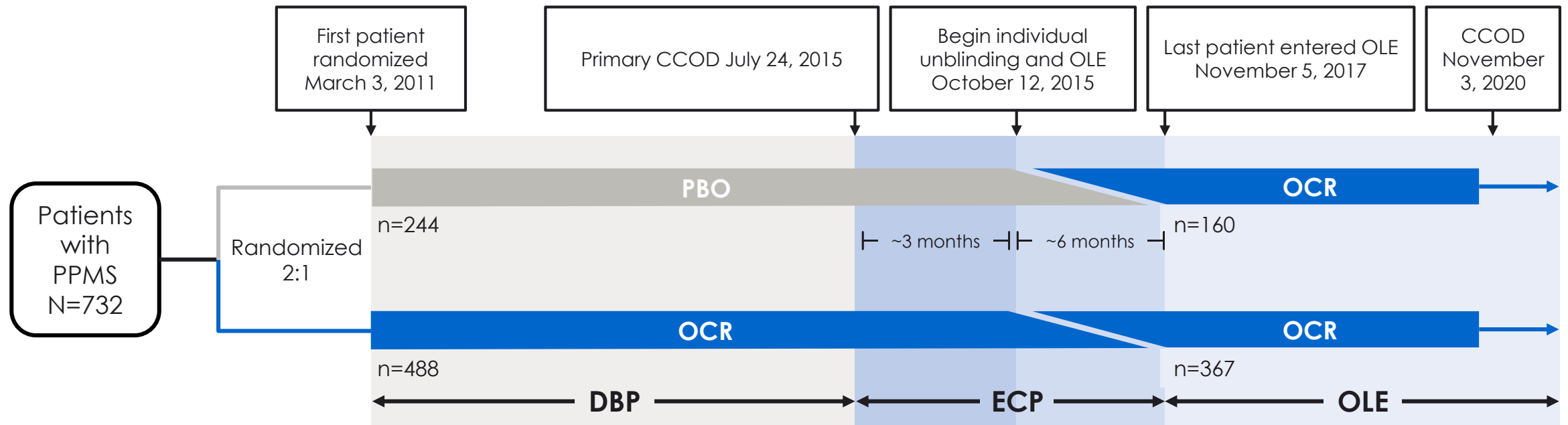
EFSPi regulatory statistics workshop, 15 September 2021

Background

- Ocrelizumab (OCR) is approved for treatment of adult patients with relapsing forms of multiple sclerosis (RMS) and primary progressive multiple sclerosis (PPMS)
- Post-hoc analysis was performed to assess the effect of OCR vs placebo on time to wheelchair on clinical study ORATORIO in the PPMS population
- In natural history cohorts of PPMS patients, the median time to wheelchair varies but is often between 12 and 17 years; evaluation of such long-term endpoints is not feasible in controlled clinical trials alone, which are primarily restricted to 3 years
- Data from the controlled and the open-label parts of ORATORIO was used to inform on time to wheelchair in patients treated with OCR
- Real world data from a PPMS natural history cohort within the MSBase registry was used to contextualize the results in patients treated with placebo

ORATORIO study design

- Double blind period (DBP): Patients received OCR 600 mg IV infusions or placebo every 24 weeks for ≥ 120 weeks until a prespecified number of confirmed disability progression events occurred
- Extended controlled period (ECP): Upon completion of the DBP, patients remained on blinded treatment as randomized until the outcome of the trial was evaluated
- Open label extension (OLE): When the study was determined to be positive, sites were unblinded, and patients could enter the OLE phase



MSBase registry

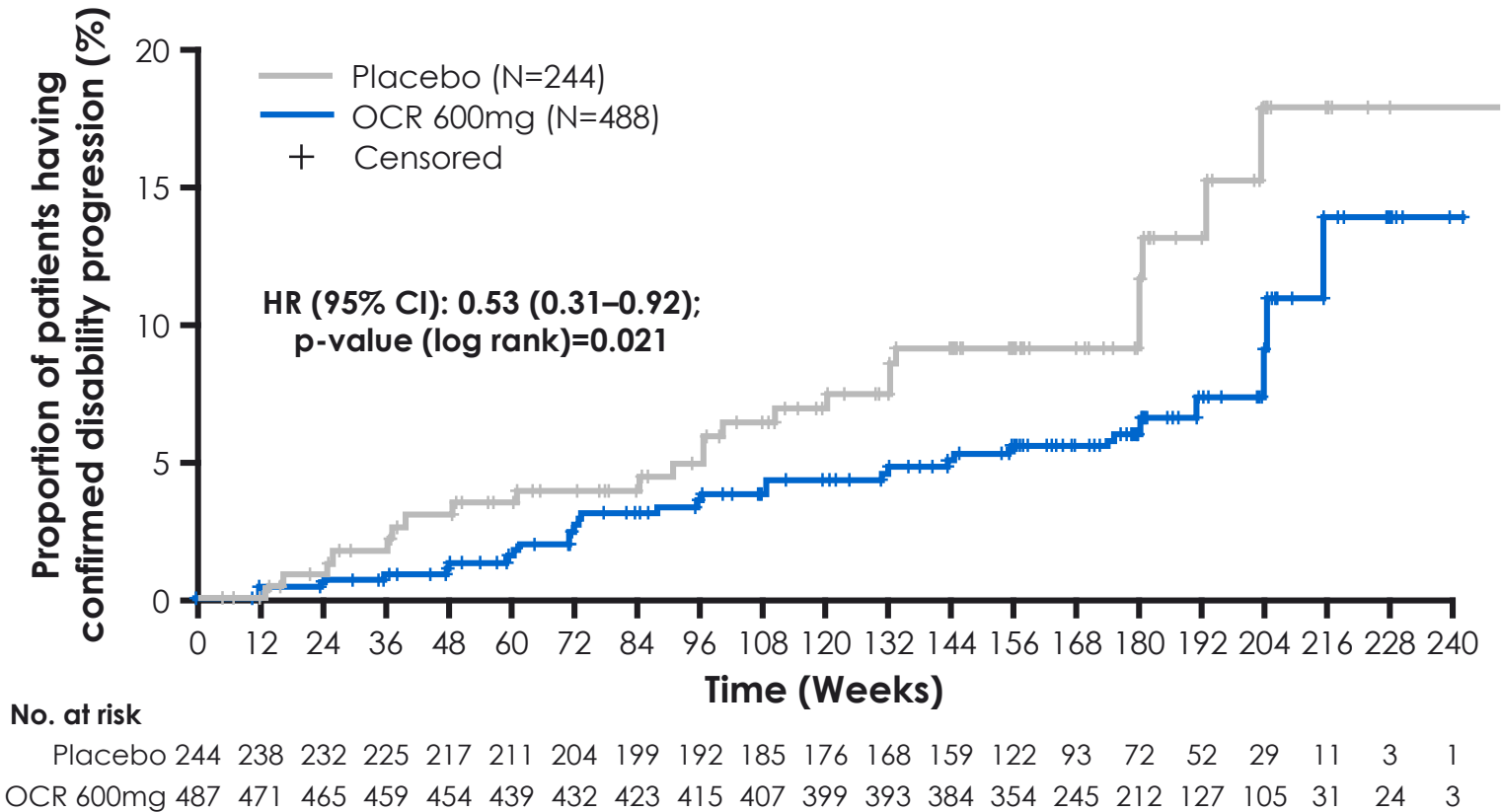
- MSBase is a prospective, international, registry collecting standardized clinical outcomes in patients with MS
- Using MSBase, a real-world cohort of patients with PPMS was created applying main eligibility criteria from the ORATORIO trial

Baseline characteristics were consistent between the ORATORIO placebo group and an MSBase PPMS natural history cohort

Parameter	ORATORIO ITT		MSBase PPMS natural history cohort (N=775) ^a
	OCR 600 mg (N=488)	Placebo (N=244)	
Age, mean (SD), years	44.7 (7.9)	44.4 (8.3)	43.4 (10.1)
Female, n (%)	237 (48.6)	124 (50.8)	437 (56.4)
Time since MS symptom onset, median (IQR), years	6.0 (3.8–8.7)	5.5 (3.3–8.3)	5.8 (3.0–10.8)
Time since MS diagnosis, median (IQR), years	1.6 (0.5–4.1)	1.3 (0.5–3.9)	0.4 (0–3.9)
Score on first eligible EDSS, median (IQR) ^b	4.5 (3.5–6.0) ^c	4.5 (3.5–6.0) ^c	4.5 (3.5–6.0)
DMT exposure, n (%)			
Ever exposed in 2 years pre-baseline	55 (11.3)	30 (12.3)	0 (0)
Never exposed in 2 years pre-baseline	433 (88.7)	214 (87.7)	775 (100)
Time between consecutive EDSS visits, months			
Mean (SD)	3.0 (NA)	3.0 (NA)	11.0 (23.9)
Median (IQR)	NA	NA	6.8 (3.9–12.2)

^aBased on the MSBase registry definition of PPMS. ^bDate of first progressive MS diagnosis; ^cThe baseline EDSS value is the average score of the EDSS assessment at screening and Day 1 visit up to and including the date of randomisation. If one of the values is missing, the non-missing values will be used as baseline. DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale; IQR, interquartile range; ITT, intent-to-treat; MS, multiple sclerosis; PPMS, primary progressive multiple sclerosis; NA, not applicable; OCR, ocrelizumab.

Time to wheelchair in ORATORIO ECP



- OCR significantly reduced the risk of wheelchair vs placebo by 47% during the ECP of ORATORIO

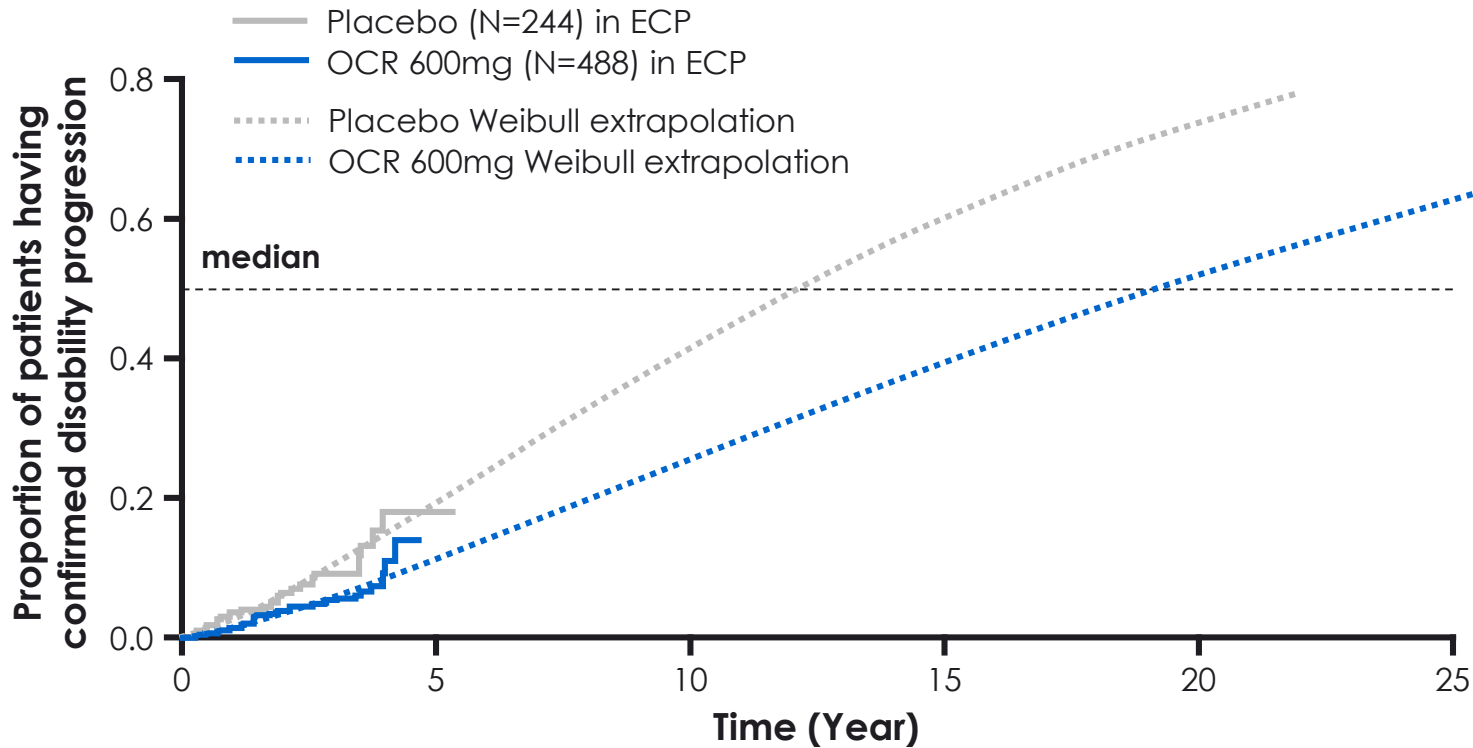
Hazard ratios were estimated using Cox regression stratified by geographical region (US vs ROW) and age (≤ 45 vs >45 years).

Patients with a post-baseline EDSS ≥ 7.0 which are sustained for at least 24 weeks are considered as having an event.

Data cut-off for ECP in ORATORIO: January 2020.

ECP, extended controlled period; EDSS, Expanded Disability Status Scale; HR, hazard ratio; OCR, ocrelizumab; ROW, rest of world.

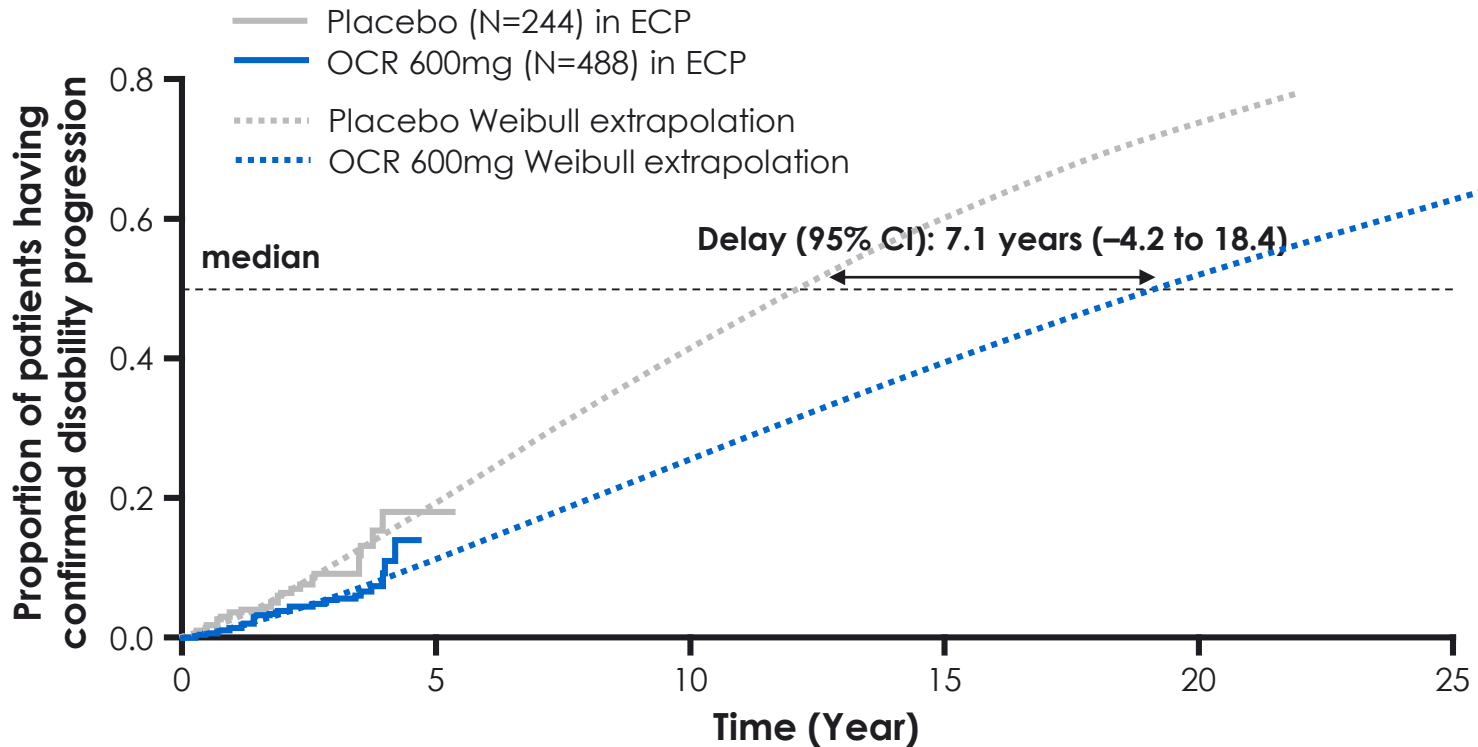
Weibull extrapolation of time to wheelchair in ORATORIO ECP



- The extrapolated median time to wheelchair was 12.0 years for placebo and 19.1 years for OCR

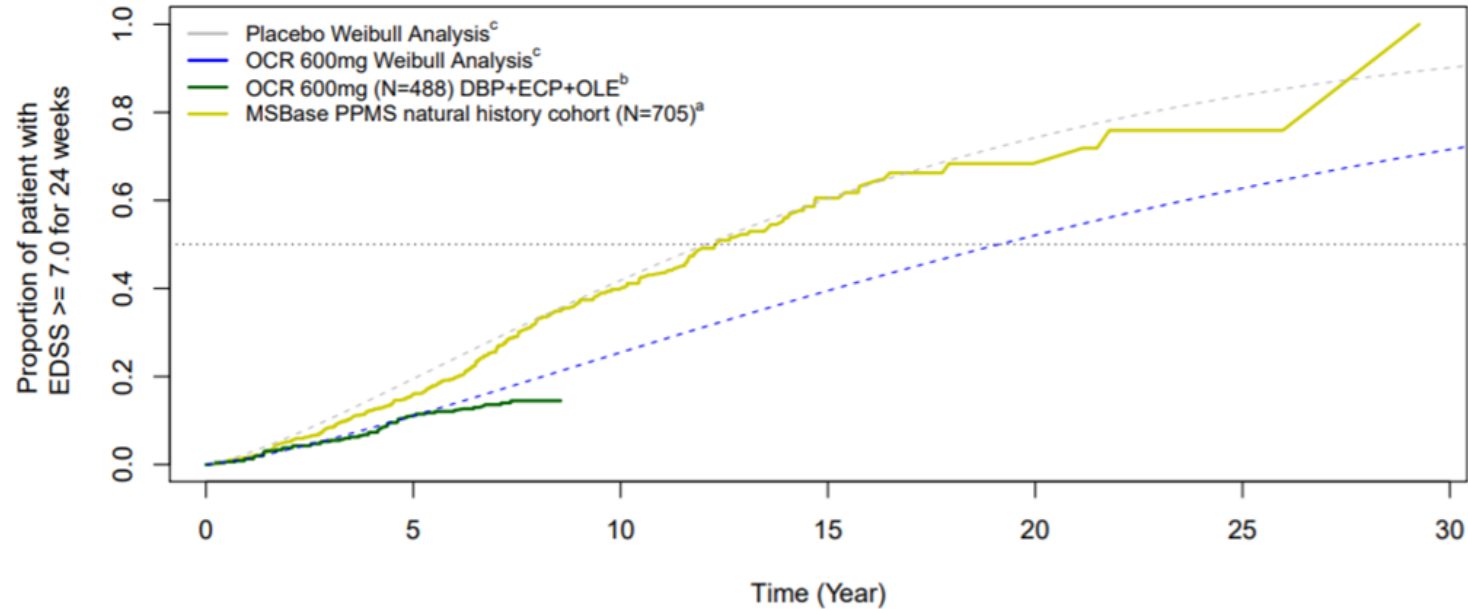
Patients with a post-baseline EDSS ≥ 7.0 which are sustained for at least 24 weeks are considered as having an event.
Data cut-off for ECP in ORATORIO: January 2020.
ECP, extended controlled period; OCR, ocrelizumab.

Weibull extrapolation of time to wheelchair in ORATORIO ECP



- The extrapolated median time to wheelchair was 12.0 years for placebo and 19.1 years for OCR (expected 7.1 years delay)

Contextualization of extrapolation using external registry - Time to Wheelchair in MSBase PPMS natural history cohort and ORATORIO-ECP+OLE



No. of patients at Risk		0	5	10	15	20	25	30
OCR		487	314	NA	NA	NA	NA	NA
PLACEBO		244	137	NA	NA	NA	NA	NA
MSBASE		705	413	128	37	9	3	NA

- The observed median time to wheelchair in MSBase PPMS natural history cohort was 12.4 years, which supports the extrapolated time of 12.0 years for PPMS patients on placebo in ORATORIO ECP

Patients with a post-baseline EDSS ≥ 7.0 which are sustained for at least 24 weeks are considered as having an event.

^aTime to EDSS ≥ 7.0 for MSBase PPMS natural history cohort. ^bExtended controlled period and open label extension of ORATORIO data cut-off from January 2020.

^cWeibull extrapolation from extended controlled period of ORATORIO data cut-off from January 2020.

ECP, extended controlled period; EDSS, Expanded Disability Status Scale; OCR, ocrelizumab; OLE, open label extension; PPMS: primary progressive multiple sclerosis.

Conclusions

- OCR significantly reduced the risk of becoming wheelchair confined vs placebo by 46% in patients with PPMS in the ORATORIO ECP
- Extrapolation from the ORATORIO ECP suggest OCR may delay the median time to becoming wheelchair confined vs placebo by 7.1 years
- The plausibility of the extrapolated median time to reach this milestone on placebo was supported by observed real-world data from the MSBase registry
- Strength: Time to wheelchair is a well-defined outcome that allows comparisons to be made across studies and cohorts
- Limitation: Extrapolations are based on relatively short observed periods, limiting the precision of the long-term extrapolation

Health Authority Feedback

- EMA acknowledges the difficulties to demonstrate efficacy for long-term disability and agrees that time to wheelchair be included in the label as an exceptional case, if presented in a balanced manner reflecting the limited robustness of exploratory observations.
- The extrapolation results supported by RWD were assessed as compelling, but not considered as appropriate for inclusion in the label as they are still extrapolations and as such are limited by the assumptions introduced.