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# Employing Novel Indirect Treatment Comparison Methodologies to Differentiate the Efficacy of Ofatumumab and Other High Efficacy Therapies versus Orally Administered Disease Modifying Therapies for Relapsing Multiple Sclerosis

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## SUMMARY

1 A multi-faceted, indirect treatment comparison approach was undertaken to clarify the relative efficacy of high efficacy therapies (HETs) and oral therapies, with a specific focus on the HET ofatumumab
- The various analyses leveraged both individual patient data (where available) and summary level data from randomised clinical trials

2 Propensity score and simulated treatment comparison demonstrated overall superiority of ofatumumab over oral therapies on key efficacy outcomes, including relapse rate and disability progression

## INTRODUCTION

- Emerging evidence challenges whether oral disease modifying therapies (DMTs) achieve similar efficacy to high efficacy therapies (HETs) in the treatment of relapsing multiple sclerosis (RMS)[1].
- In the absence of head-to-head randomised controlled trials (RCT), indirect treatment comparisons (ITCs) can be used to estimate the relative efficacy between HETs and oral therapies.

## OBJECTIVE

- To differentiate HETs from oral therapies based on efficacy measures (annualised relapse rate (ARR), 3 and 6 month confirmed disease progression (3mCDP and 6mCDP)) using different ITC approaches.

## METHODS

- Propensity score (PS) analyses were conducted to compare ofatumumab (OMB) to fingolimod (FIN) using inverse probability of treatment weighting (IPTW). PS analyses used pooled individual patient data (IPD) from ASCLEPIOS I/II for OFA and from FREEDOMS, FREEDOMS II and TRANSFORMS for FIN.
- Unanchored simulated treatment comparisons (STCs) were conducted to compare OMB to each of three oral treatments, FIN, ozanimod (OZA) and cladribine (CLA), by fitting a regression model for outcomes of interest. STCs leveraged pooled ASCLEPIOS I/II IPD (OMB) and summary-level data (SLD) (orals) from phase 3 RCTs.
- Results of PS and STC analyses were compared to a previously published network meta-analysis (NMA)[1] which compared the efficacy of DMTs for RMS, including HETs and oral therapies, using SLD from relevant RCTs.

## RESULTS

### OMB demonstrated superior efficacy over FIN in PS analyses

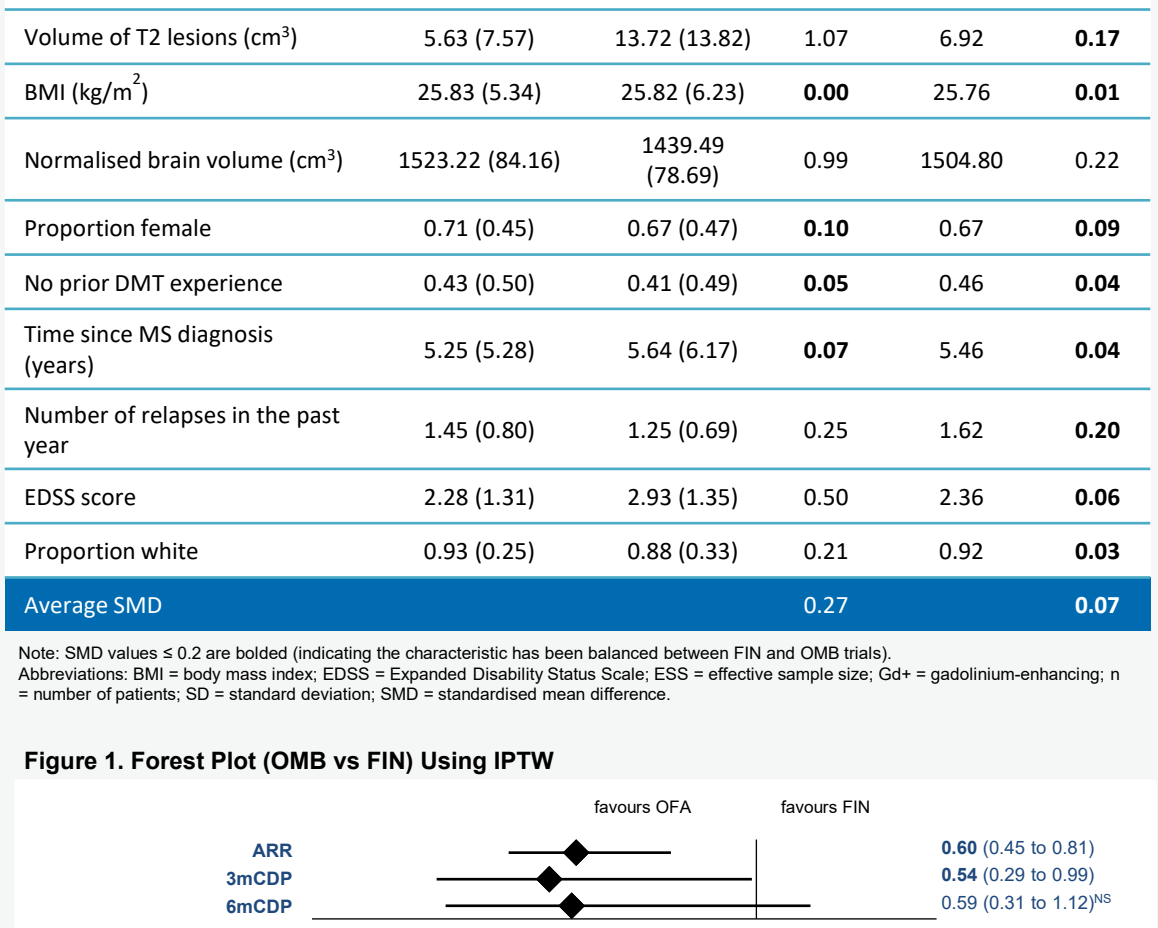
- Covariate balancing for ARR resulted in similar patient characteristics for OMB and FIN (Table 1); patient characteristics were also similar between OMB and FIN with covariate balancing for 3mCDP and 6mCDP (data not shown).
- OMB reduced ARR by 40% and delayed time to 3mCDP by 46% compared to FIN (Fig. 1).
- No significant difference was observed in time to 6mCDP between OMB and FIN (Fig. 1).

**Table 1. Balance of Covariates for PS Analysis Using IPTW for Outcome of ARR**

| Patient Characteristic | Pooled FREEDOMS, FREEDOMS II, TRANSFORMS (FIN) | ASCLEPIOS I/II (OMB) | | | |
|---|---|---|---|---|---|
| | | Unadjusted | | Adjusted | |
| | Mean (SD) | Mean (SD) | SMD | Mean | SMD |
| n or ESS | n=1031 | n=945 | | ESS=283 | |
| Age group (16-30) | 0.23 (0.42) | 0.24 (0.43) | **0.01** | 0.23 | **0.01** |
| Age group (31-45) | 0.53 (0.50) | 0.50 (0.50) | **0.06** | 0.54 | **0.02** |
| Age group (46-60) | 0.23 (0.42) | 0.26 (0.44) | **0.06** | 0.23 | **0.01** |
| Number of Gd+ T1 lesions | 1.39 (4.40) | 1.68 (4.53) | **0.07** | 1.65 | **0.06** |
| Volume of T2 lesions ($cm^3$) | 5.63 (7.57) | 13.72 (13.82) | 1.07 | 6.92 | **0.17** |
| BMI ($kg/m^2$) | 25.83 (5.34) | 25.82 (6.23) | **0.00** | 25.76 | **0.01** |
| Normalised brain volume ($cm^3$) | 1523.22 (84.16) | 1439.49 (78.69) | 0.99 | 1504.80 | 0.22 |
| Proportion female | 0.71 (0.45) | 0.67 (0.47) | **0.10** | 0.67 | **0.09** |
| No prior DMT experience | 0.43 (0.50) | 0.41 (0.49) | **0.05** | 0.46 | **0.04** |
| Time since MS diagnosis (years) | 5.25 (5.28) | 5.64 (6.17) | **0.07** | 5.46 | **0.04** |
| Number of relapses in the past year | 1.45 (0.80) | 1.25 (0.69) | 0.25 | 1.62 | **0.20** |
| EDSS score | 2.28 (1.31) | 2.93 (1.35) | 0.50 | 2.36 | **0.06** |
| Proportion white | 0.93 (0.25) | 0.88 (0.33) | 0.21 | 0.92 | **0.03** |
| Average SMD | | | 0.27 | | **0.07** |

Note: SMD values ≤ 0.2 are bolded (indicating the characteristic has been balanced between FIN and OMB trials).
Abbreviations: BMI = body mass index; EDSS = Expanded Disability Status Scale; ESS = effective sample size; Gd+ = gadolinium-enhancing; n = number of patients; SD = standard deviation; SMD = standardised mean difference.

**Figure 1. Forest Plot (OMB vs FIN) Using IPTW**

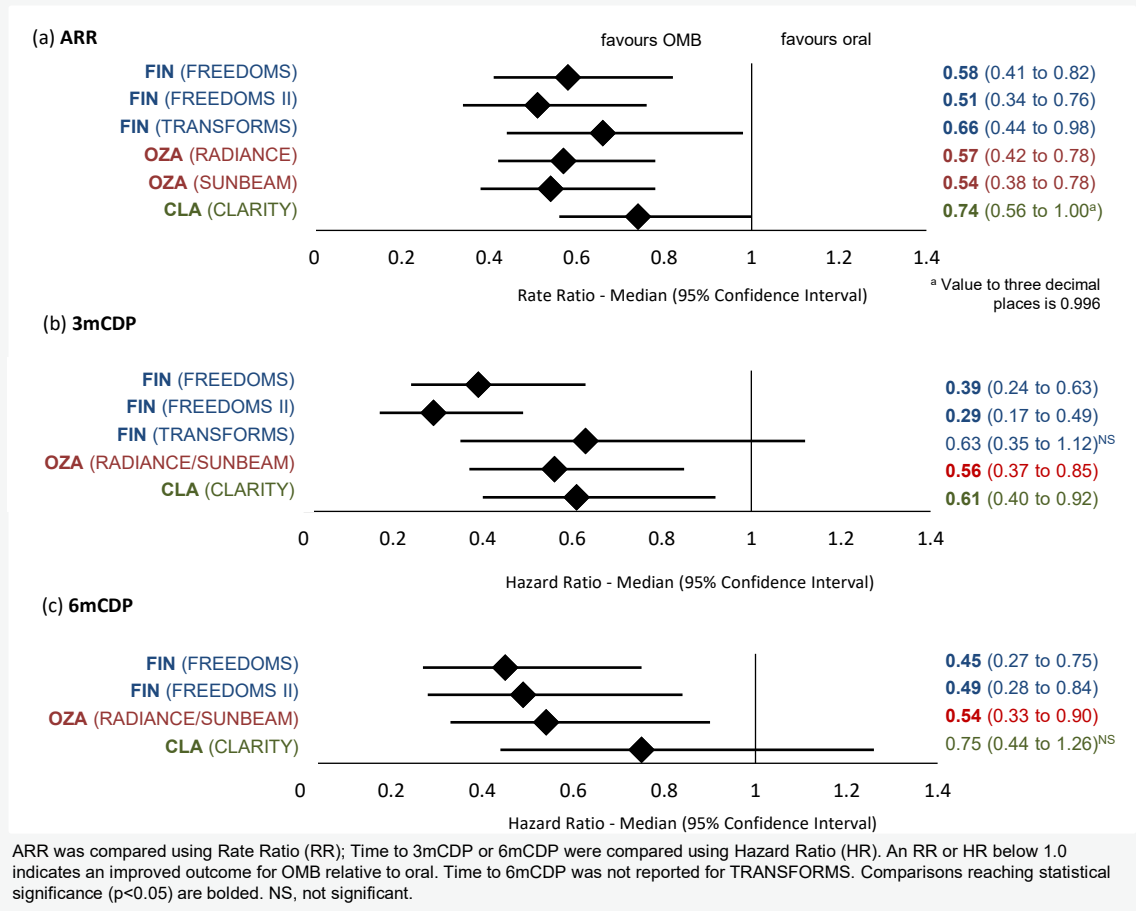



ARR was compared using Rate Ratio (RR); Time to 3mCDP or 6mCDP were compared using Hazard Ratio (HR). An RR or HR below 1.0 indicates an improved outcome for OMB relative to FIN. Comparisons reaching statistical significance (p<0.05) are bolded. NS, not significant.

### OMB demonstrated superior efficacy over orals in STC analyses

- ARR was significantly lower for OMB compared with CLA, FIN and OZA (Fig. 2a).
- 3mCDP was significantly lower for OMB compared with CLA, OZA and with FIN in FREEDOMS and FREEDOMS II; no significant difference was observed between OMB and FIN in TRANSFORMS (Fig. 2b).
- 6mCDP was significantly lower for OMB compared with OZA and FIN; no significant difference was observed between OMB and CLA (Fig. 2c).

**Figure 2. Forest Plot (OMB vs Orals) Using Unanchored STC Analysis**

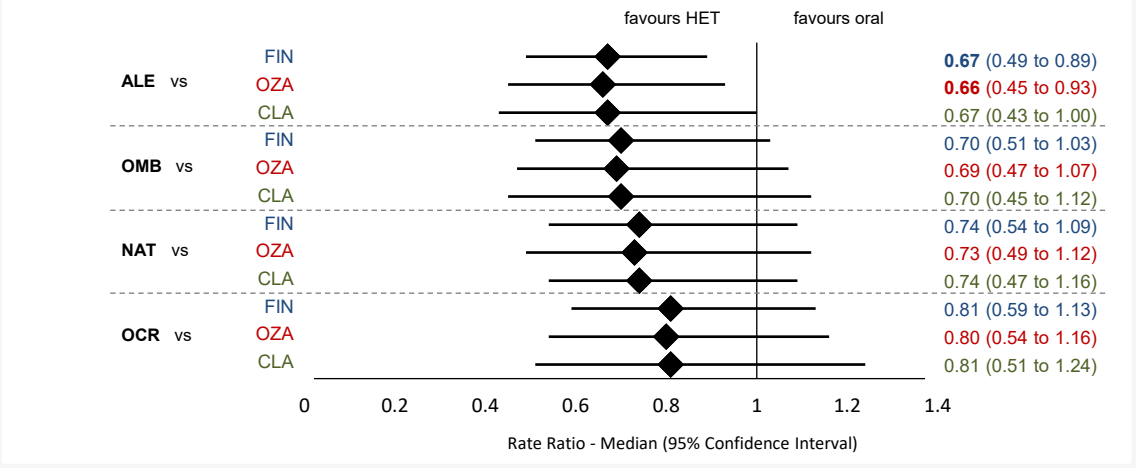



ARR was compared using Rate Ratio (RR); Time to 3mCDP or 6mCDP were compared using Hazard Ratio (HR). An RR or HR below 1.0 indicates an improved outcome for OMB relative to oral. Time to 6mCDP was not reported for TRANSFORMS. Comparisons reaching statistical significance (p<0.05) are bolded. NS, not significant.

### Comparison of efficacy with other HETs and orals using NMA

- Alemtuzumab (ALE), OFA, natalizumab (NAT) and ocrelizumab (OCR) demonstrated a similar trend for lower ARR than orals (Fig. 3); results for 3mCDP and 6mCDP available via publication[1].

**Figure 3. Forest Plot of ARR (HET vs Orals) Using NMA**




ARR was compared using Rate Ratio (RR). An RR below 1.0 indicates an improved outcome for HET relative to oral. Comparisons reaching statistical significance (p<0.05) are bolded.

## CONCLUSION

- PS and STC analyses support the therapeutic superiority of OMB over oral therapies with respect to reducing relapses and delaying disease progression.
- By leveraging IPD, PS and STC analyses offer more robust and complementary approaches to NMA for indirectly comparing HETs and oral DMTs.

**REFERENCES:** 1.Samjoo, I.A., et al. *J. Comp. Eff. Res.*. 2023; 12(7)

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