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Title:

Rituximab vs Ocrelizumab in Relapsing-Remitting Multiple Sclerosis

Date:

2023-08-14

Citation:

Roos, I., Hughes, S., McDonnell, G., Malpas, C. B., Sharmin, S., Boz, C., Alroughani, R., Ozakbas, S., Buzzard, K., Skibina, O., Van Der Walt, A., Butzkueven, H., Lechner-Scott, J., Kuhle, J., Terzi, M., Laureys, G., Van Hijfte, L., John, N., Grammond, P., ... Kalincik, T. (2023). Rituximab vs Ocrelizumab in Relapsing-Remitting Multiple Sclerosis. *JAMA Neurology*, 80 (8), pp.789-797. <https://doi.org/10.1001/jamaneurol.2023.1625>.

Persistent Link:

<https://hdl.handle.net/11343/337535>

1 **Rituximab versus ocrelizumab in relapsing-remitting multiple sclerosis**

2 **Subtitle: A non-inferiority observational study**

3

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71 Word count: 3138

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73 Date of revision: 13 February 2023

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75 **KEY POINTS**

76

77 **Question:** Is treatment with rituximab non-inferior to ocrelizumab in preventing relapses and  
78 disability in patients with relapsing-remitting multiple sclerosis?

79 **Findings:** In this multicentre cohort study of 710 ocrelizumab and 186 rituximab-treated  
80 patients with multiple sclerosis, rituximab was not non-inferior to ocrelizumab, and rituximab  
81 treatment was associated with a higher rate and risk of relapse. There was no evidence for a  
82 difference in disability outcomes.

83 **Meaning:** Lack of a clinically relevant difference in the effectiveness between ocrelizumab  
84 and rituximab should not be assumed and is being further evaluated in clinical trials.

85

86 **ABSTRACT**

87 **Importance:** Ocrelizumab, a humanised monoclonal antibody targeted against CD20+ B  
88 cells, reduces the frequency of relapses by 46% and disability worsening by 40% compared  
89 to interferon- $\beta$  1a in relapsing-remitting multiple sclerosis (MS). Rituximab, a chimeric  
90 monoclonal anti-CD20 agent, is often prescribed as an off-label alternative to ocrelizumab.

91 **Objective:** To evaluate whether the effectiveness of rituximab is non-inferior to ocrelizumab  
92 in relapsing-remitting MS

93 **Design:** Observational cohort study conducted between 2015-2021. Patients were included in  
94 the treatment group for the duration of study therapy.

95 **Setting:** MSBase and Danish MS registry [DMSR]

96 **Participants:** Of 6027 patients with MS treated with ocrelizumab or rituximab, 1613 were  
97 included. Included patients had relapsing-remitting MS, minimum six-month follow-up, and  
98 sufficient data to calculate the propensity score. Patients with comparable baseline  
99 characteristics were 1-to-6 matched with propensity score on age, sex, MS duration, disability

100 (EDSS), prior relapse rate, prior therapy, disease activity (relapses, disability accumulation,  
101 or both), MRI lesion burden (missing values imputed), and country.

102 **Exposure:** Treatment with ocrelizumab or rituximab after 2015.

103 **Main outcomes and Measures:** Non-inferiority comparison of annualised rate of relapses  
104 (ARR), with a pre-specified non-inferiority margin of 1.63 rate ratio. Secondary endpoints  
105 were relapse and 6-month confirmed disability accumulation in pairwise-censored groups.

106 **Results:** 710 ocrelizumab-treated patients (414 MSBase, 296 DMSR) were matched with 186  
107 rituximab-treated patients (110 MSBase, 76 DMSR). The mean age was 41 years, and 68%  
108 were female. Over a pairwise censored mean follow-up of 1.4 years, the ARR ratio was  
109 higher in rituximab-treated than OCR-treated patients (rate ratio 1.8 [95%CI 1.4-2.4]; ARR  
110 0.20 vs 0.09,  $p < 0.001$ ). The cumulative hazard of relapses was higher among patients treated  
111 with rituximab than ocrelizumab (HR 2.1 [1.5-3.0]). No difference in the risk of disability  
112 accumulation was observed between groups. Results were confirmed in sensitivity analyses.

113 **Conclusion:** In this non-inferiority comparative effectiveness observational study, we did not  
114 show non-inferiority of treatment with rituximab compared to ocrelizumab. As administered  
115 in everyday practice, rituximab was associated with a higher risk of relapses than  
116 ocrelizumab. The efficacy of rituximab and ocrelizumab administered at uniform doses and  
117 intervals is being further evaluated in randomised non-inferiority clinical trials.

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122

## 123 INTRODUCTION

124 Ocrelizumab (OCR), rituximab (RTX), ofatumumab, and ublituximab are monoclonal  
125 antibodies targeting CD20 cell surface proteins. B-cell depletion therapies are highly  
126 effective therapies for multiple sclerosis (MS) and have become an important part of the  
127 treatment armamentarium.

128

129 RTX is widely used in the treatment of haematological malignancies and rheumatological  
130 conditions and is listed in the WHO list of essential medicines for those indications.<sup>1</sup> Despite  
131 the successful phase II randomised controlled trial of RTX vs placebo in patients with  
132 relapsing-remitting MS (RRMS),<sup>2</sup> further clinical development of RTX was deferred in  
133 favour of OCR. In the pivotal phase III RRMS trial, OCR reduced the frequency of relapses  
134 by 46% and disability progression by 40% compared to interferon-beta, and subsequently  
135 became the first licensed B cell therapy for treatment of RRMS.<sup>3</sup> RTX is however frequently  
136 used as an off-label alternative to OCR. In June 2017, 53% of Swedish patients who started a  
137 DMT were prescribed RTX.<sup>4</sup> Accumulating evidence from observational studies, and a recent  
138 randomised controlled trial of RTX vs dimethyl fumarate, support the use of RTX as an  
139 effective and well tolerated treatment in patients with RRMS.<sup>5-8</sup> Ofatumumab and  
140 ublituximab are newer therapies with comparatively less real-world clinical experience.

141

142 Whereas RTX is a chimeric monoclonal antibody, OCR is humanised, with the proposed  
143 advantage of less immunogenicity and fewer indirect complement mediated effects.<sup>2,3</sup>

144 Whether RTX is unacceptably less clinically effective compared to OCR however remains  
145 unexplored. Data from large observational registries can be used to guide clinical decision-  
146 making by emulating a clinical trial.<sup>9-11</sup> In this study we used data from two MS registries to

147 evaluate the clinical non-inferiority of RTX compared to OCR in the treatment of patients  
148 with relapsing-remitting MS.<sup>12, 13</sup>

149

## 150 **METHODS**

151

### 152 **Setting**

153 The MSBase registry (ID ACTRN12605000455662) was approved by the Melbourne Health  
154 Human Research Ethics Committee and local ethics committees in all centers. The study was  
155 approved by the Danish Data Protection Agency through the joint notification of the Capital  
156 Region of Denmark. In keeping with Danish law, studies consisting solely of registry data do  
157 not require approval from The National Committee on Health Research Ethics. Written  
158 informed consent was obtained from all included patients. STROBE reporting guidelines  
159 were followed.

160

### 161 **Participants**

162 Patient data were obtained from two MS registries: MSBase, the largest international MS  
163 registry,<sup>14</sup> and the nationwide population-based Danish Multiple Sclerosis Registry  
164 (DMSR)<sup>15</sup>. Patients with relapsing-remitting MS (RRMS) who were treated with either OCR  
165 or RTX for  $\geq 6$  months after 2015 were included in the study. Included patients required 6-  
166 month pre-treatment follow up, a baseline visit 6 months before to 1 month after treatment  
167 start, and two follow up visits at least 6 months apart. The baseline visit could not occur  
168 within 30 days of the last relapse. Patients previously included in a randomised controlled  
169 trial, previously treated with stem cell therapy or alemtuzumab, or treated with mitoxantrone  
170 in the preceding 3 years, were excluded from the analysis.

171

## 172 **Procedures**

173 Baseline was defined as the first date of OCR or RTX treatment after 2015. OCR was  
174 intravenously administered as two doses of 300mg 14 days apart, followed by 600mg  
175 6monthly, as per previously reported trial protocols.<sup>3</sup> In most patients, RTX was  
176 intravenously administered as two doses of 1000mg 14 days apart, followed by 500-1000mg  
177 6 monthly. Treatment protocols were at the discretion of each treating centre. RTX originator  
178 and biosimilar products were merged into one RTX group. Patients treated with the  
179 comparator therapy before 2015 were excluded (i.e., patients in the OCR treatment group  
180 who previously received RTX). Patients treated with a single course of OCR or RTX were  
181 presumed to be treated for 6 months. Consecutive OCR and RTX treatment entries were  
182 merged into a continuous entry, given there was no intervening therapy, and the gap between  
183 entries did not exceed 1 year. Patients were included in the treatment group for the duration  
184 of study therapy or until the last visit (whichever occurred first).

185

186 Data were recorded as part of routine clinical practice, mostly in large tertiary MS centres.  
187 Data were entered into the MSBase data entry system or into COMPOS® (DMSR). All  
188 participating centres required Neurostatus certification. MRI information was included as  
189 reported by local radiologists based on local MRI protocols and reporting standards. A brain  
190 MRI performed within 12 months prior, and 1 month after, treatment initiation was  
191 considered the baseline MRI. Missing MRI data were handled through multiple imputation.  
192 Rigorous data quality assurance procedures were applied (eTable 1).<sup>16</sup>

193

## 194 **Study Outcomes**

195 The primary study endpoint was a non-inferiority comparison of annualised relapse rate  
196 (ARR). Secondary endpoints were cumulative hazards of relapse and 6-month confirmed

197 disability accumulation and improvement outcomes in pairwise-censored groups, and  
198 cumulative hazard of treatment discontinuation. Secondary endpoints were assessed for  
199 superiority.

200

201 Relapses were defined as new symptoms, or exacerbation of existing symptoms, for at least  
202 24 hours in the absence of a concurrent illness or fever, and occurring  $\geq 30$  days after the  
203 previous relapse.<sup>17</sup> Relapses were analysed as recorded by the treating physician, and did not  
204 require confirmation with a change in disability score. Disability accumulation was defined  
205 as an increase in Expanded Disability Status Scale (EDSS) by  $\geq 1$  step (1.5 step if EDSS 0, or  
206 0.5 step if EDSS  $> 5.5$ ), confirmed over at least 6 months (in the absence of a relapse in the  
207 preceding 30 days), and sustained until the end of follow up. Disability improvement was  
208 defined as a decrease in EDSS by  $\geq 1$  step (1.5 steps if EDSS 1.5, or 0.5 step if EDSS  $> 6$ )  
209 confirmed over at least 6 months.<sup>18</sup> Treatment discontinuation, and the reasons for treatment  
210 discontinuation (where available), were described as recorded by the treating clinician.

211

## 212 **Statistical analysis**

213 Propensity scores were calculated for each individual patient using a logistic regression  
214 model based on the following baseline variables: age, sex, MS duration (from MS onset),  
215 EDSS score, number of relapses in the previous 12 months, number of previous therapies,  
216 disease activity in the prior 12 months (relapse, disability accumulation, both or neither),  
217 MRI lesion burden (categorised as 1-2, 3-8 or  $\geq 9$  lesions), presence/absence of contrast  
218 enhancing lesions on cerebral MRI at baseline, and country.<sup>19</sup>

219

220 If baseline MRI data were not available, multiple imputation with an expectation  
221 maximisation with bootstrapping algorithm was used to impute missing values.<sup>20, 21</sup> Multiple

222 imputation was based on patient ID, treatment group, age, MS duration, baseline EDSS,  
223 prebaseline disease activity, prebaseline therapy, and time since prebaseline therapy.

224

225 Patients were matched, without replacement, in a 6:1 variable ratio using nearest neighbour  
226 matching and a calliper of 0.1 standard deviations of the propensity score.<sup>22</sup> Covariate  
227 balance was assessed using standardised mean differences. Subsequent analyses were  
228 performed in paired models, weighted for matching ratio. Attrition bias was controlled by  
229 pairwise censoring in all analyses (i.e., on-treatment follow up was the shorter follow up  
230 within each patient pair), except for analysis of treatment persistence.

231 ARR<sub>s</sub> were calculated using a marginal weighted negative binomial model with cluster term  
232 per patient pair. Cumulative hazard of relapses and disability outcomes were analysed with  
233 weighted conditional proportional hazards models for recurrent events. Disability models  
234 were adjusted for visit density. The cumulative hazard of discontinuing therapy was assessed  
235 using weighted conditional proportional hazards models without pairwise censoring. The  
236 proportionality assumption was evaluated using Schoenfeld's global test. Time to event data  
237 were visualised using Kaplan-Meier plots. The minimum magnitude of unmeasured  
238 confounders required to change the conclusion of the analysis was calculated using  
239 Rosenbaum sensitivity test for Hodges-Lehmann  $\Gamma$ .<sup>23</sup>

240

241 The non-inferiority margin was identified based on the known efficacy of OCR, and as the  
242 smallest difference in effectiveness between OCR and RTX which was felt to be clinically  
243 relevant: 1 relapse every 10 patient-years.<sup>24</sup> This is in keeping with two presently ongoing  
244 trials of OCR vs RTX, which set their non-inferiority margins at 1 new/enlarging/enhancing  
245 cerebral lesion every 10 patient-years.<sup>25,26</sup> The ARR of the OCR group in the Phase III  
246 pivotal trial of OCR vs interferon-beta was 0.16.<sup>3</sup> If the ARR in the trial comparator group

247 exceeded the OCR group by 1 relapse every 10 patient-years, this would equate to an  
248 absolute ARR of 0.16 vs 0.26. Therefore, the non-inferiority margin for the relative ARR  
249 ratio of OCR vs RTX was set as 1.63. Non-inferiority would be established if the upper  
250 bounds of the two-sided 95% confidence interval (95%CI) of ARR ratio did not exceed this  
251 pre-defined non-inferiority margin. A two-sided alpha of 0.05 was used for superiority testing  
252 of all secondary endpoints.

253

254 Five sensitivity analyses were performed: Using data from (i) DMSR only, (ii) MSBase  
255 only, (iii) applying an 'intention to treat' approach, where all subsequent events were  
256 analysed irrespective of changes in treatment status (to eliminate the potential effect of  
257 informative censoring), (iv) excluding the MRI variables from the estimation of the  
258 propensity score (to eliminate the effects of multiple imputation); (v) only including patients  
259 who started a study therapy after 2016, when both therapies were more widely available than  
260 in 2015 (to explore potential contribution of the positivity assumption); (vi) only including  
261 patients where the dose and frequency of study therapy was recorded, and patients received at  
262 least OCR 600mg 6-monthly or RTX 1g 6-monthly (to minimise the contribution of variable  
263 dosing practices).

264

## 265 **RESULTS**

266 Of 6027 patients (4128 MSBase, 1899 DMSR) with MS treated with either RTX or OCR,  
267 1613 patients (898 MSBase, 715 DMSR) fulfilled the inclusion criteria and were included in  
268 the analysis (Fig 1). Patient disposition per contributing centre, and demographic features of  
269 patients treated with a study therapy who were excluded from the analysis are shown in  
270 eTables 2 and 3. The positivity assumption was not violated (eTable 4).

271

272 The probability of being treated with RTX vs OCR was calculated using a logistic regression  
273 model (eTable 5). RTX treated patients tended to have higher disability scores, more relapses  
274 and MRI activity in the prior 12 months, and received more prior MS therapies than patients  
275 treated with OCR. Table 1 shows patient characteristics before and after propensity score  
276 matching. 710 OCR-treated patients (414 MSBase, 296 DMSR) were matched with 186  
277 RTX-treated patients (110 MSBase, 76 DMSR). Propensity score matching resulted in a 71%  
278 improvement in balance between the matched groups (eTable 6), with a standardised mean  
279 difference of 0.10 or less achieved for all variables. Clinocodemographic details of patients  
280 who were not propensity score matched resemble the included cohort before matching  
281 (eTable 7).

282

### 283 **Effectiveness**

284 The mean ARR was higher in patients treated with RTX than OCR (ARR 0.20 vs 0.09,  
285  $p < 0.001$ , Figure 2A). Similarly, the ARR ratio was higher in RTX- than OCR-treated patients  
286 (ARR ratio 1.8, 95%CI 1.4-2.4, Figure 2B). Both the estimate of the effect size, and the upper  
287 bounds of the 95%CI were higher than the pre-determined non-inferiority margin of 1.63.  
288 The difference was resistant to unmeasured confounders to a magnitude of 40% of the  
289 reported treatment effect. The cumulative hazard of relapses was higher in RTX-treated  
290 patients (HR 2.1, 95%CI 1.5-3.0, Figure 2C). No evidence of difference in disability  
291 accumulation (HR 1.51, 95%CI 0.86-2.64) or disability improvement (HR 0.80, 95%CI 0.49-  
292 1.31) was observed between study therapies over a mean 1.4 year pairwise-censored follow  
293 up (Figure 3).

294

### 295 **Persistence**

296 Patients were more likely to discontinue RTX than OCR (HR 3.11, 95%CI 2.36-4.11, Figure  
297 4). While recording the reason for treatment discontinuation does not form part of the  
298 minimum dataset, data were available in 66% of OCR and 49% of RTX discontinuations  
299 (eTable 8). The most common reasons for RTX discontinuation were patient/clinician  
300 decision (33%) and other/unknown reasons (48%). 69% of patients who discontinued RTX  
301 were subsequently treated with OCR. It is therefore likely that many of these switches were  
302 prompted by the availability and regulatory approval of OCR. Very few patients discontinued  
303 OCR or RTX due to lack of tolerance (16 and 9 patients respectively). The available adverse  
304 event data were insufficient to allow comparison between therapies.

305

### 306 **Sensitivity analyses**

307 Further sensitivity analysis using (1) an 'intention to treat' approach, (2) excluding MRI  
308 variables from the estimation of the propensity score, (3) only including patients who  
309 commenced study therapy after 2016, (4) using data from MSBase only, and (5) only  
310 including patients who received at least OCR 600mg 6-monthly or RTX 1g 6-monthly  
311 (eTable 9), showed results consistent with the primary analysis. A sensitivity analysis using  
312 data from the DMSR only was inconclusive (ARR ratio 1.41, 95%CI 0.99-2.01), likely due to  
313 insufficient power.

314

### 315 **DISCUSSION**

316

317 Whether RTX is non-inferior to OCR is a clinically relevant question. While both therapies  
318 have similar mechanisms of action, the significantly lower cost of RTX may motivate its  
319 preferential use despite 'off-label' status. Whether these two therapies are interchangeable  
320 however remains an ongoing topic of debate.<sup>27, 28</sup> In this comparative effectiveness study

321 from the international MSBase and nationwide population-based Danish MS registries, we  
322 evaluated the noninferiority of treatment with RTX compared to OCR in patients with  
323 RRMS.

324 The effect of RTX on relapses was inferior to OCR with an ARR of 0.20 vs 0.09, translating  
325 into a difference of 1 relapse every 9 patient-years. The study did not find evidence for a  
326 difference in the probability of disability accumulation or improvement. Treatment  
327 discontinuation was more common in RTX-treated patients, for which OCR was the most  
328 frequent subsequent therapy.

329

330 Although the study was designed to assess non-inferiority of RTX compared to OCR, our  
331 findings demonstrated that patients treated with RTX experienced more relapses. To meet the  
332 pre-defined definition of non-inferiority, the upper bound of the 95%CI of the ARR must not  
333 exceed 1.63. The ARR ratio was calculated as 1.8, with a two-sided 95% CI of 1.4-2.4.  
334 Therefore, based on recommendations on the interpretation of non-inferiority studies<sup>29,30</sup>,  
335 our results suggest the inferiority of RTX over OCR on relapses. While it is still plausible  
336 that the true relative difference in ARR is less than the non-inferiority margin, relapse  
337 frequency was significantly higher when treated with RTX than with OCR. The magnitude of  
338 this difference exceeded the predefined clinically meaningful difference between the  
339 compared therapies. The probability that the frequency of relapses in RTX-treated patients  
340 exceeded that of OCR by more than 1 relapse every 10 patient-years was 80%.

341

342 The respective effects of OCR and RTX in RRMS have previously been studied in two  
343 randomised trials. In the HERMES phase II RTX trial, patients were treated with two doses  
344 of RTX 1g on days 1 and 14.<sup>2</sup> At week 24, the ARR in RTX-treated patients was 0.4 (95% CI  
345 0.23-0.60). In the phase II OCR trial, patients were treated with OCR on days 1 and 15

346 (300mg per day), and at week 24 (600mg).<sup>31</sup> At week 24, the ARR in patients treated with  
347 600mg OCR was 0.13 (95% CI 0.03-0.29). Although direct comparison of outcomes between  
348 these two studies should be avoided due to differences between the cohorts and the definition  
349 of relapse (objective worsening of neurological disability was required in the OCR trial),  
350 these findings suggest that the rate of relapse is higher in patients treated with RTX compared  
351 to OCR. Similarly, in our study using patients with comparable baseline characteristics and  
352 uniform definitions, we report higher rates of relapse in patients treated with RTX than OCR.  
353

354 A head-to-head comparison of RTX vs OCR has not previously been performed, apart from  
355 an analysis in primary progressive MS, which did not account for baseline group  
356 differences.<sup>32</sup> Observational data have, however, been used to explore the effectiveness of  
357 both RTX and OCR in comparison with other disease modifying therapies. In two analyses  
358 from Sweden, patients treated with injectable therapies (interferon-beta and glatiramer  
359 acetate) had significantly higher risk of relapse than RTX-treated patients.<sup>6,7</sup> After propensity  
360 score adjustment, there was no evidence of a difference in ARR between RTX-treated  
361 patients and patients receiving dimethyl fumarate, fingolimod, or natalizumab.<sup>7</sup> A study from  
362 the MSBase registry reported superior control of relapses under OCR compared to interferon-  
363 beta and fingolimod, but no evidence of a difference compared to natalizumab.<sup>33</sup> These  
364 findings may indirectly indicate a potential difference in effectiveness between OCR and  
365 RTX. Potential biological differences between OCR- and RTX-treated patients have been  
366 described, with more pronounced T-cell reduction in patients treated with OCR.<sup>34</sup> The  
367 clinical relevance of these findings remain uncertain. The present study is the first non-  
368 inferiority direct comparison of OCR and RTX, using rigorous methodology to mitigate  
369 group differences that allows direct comparison between therapies. Two randomised  
370 controlled trials exploring the non-inferiority of RTX vs OCR are presently under recruitment

371 in Norway and Denmark, with expected completion of recruitment in late 2022 and May  
372 2023 respectively.<sup>25,26</sup> Both trials are designed to primarily assess radiological outcomes,  
373 with a pre-specified non-inferiority margin of 1 new/enlarging/enhancing cerebral lesion  
374 every 10 patient-years.

375

376 While our large cohort from two non-overlapping MS registries provides this study with  
377 power, the observational nature of the data is the main limitation. Observational data are  
378 vulnerable to multiple forms of bias.<sup>35</sup> Rigorous attention has been paid to data quality, using  
379 an operationalised data quality process.<sup>16</sup> Propensity score matching was performed to  
380 control indication bias, with pairwise censoring to mitigate attrition bias. Additionally, our  
381 findings were confirmed in sensitivity analyses that address potential informative censoring,  
382 and the effects of the positivity assumption. Whereas OCR is a single commercial product,  
383 the RTX group contains both the originator and biosimilar products. Differential treatment  
384 effects can therefore not be excluded. As RTX is used off label, there is also potential  
385 variability in dosing and administration schedules. While it is possible that our findings may  
386 not be generalisable to all treatment schedules, the findings remained consistent in a  
387 sensitivity analysis only including patients who received RTX at a dose of at least 1g 6-  
388 monthly or OCR at 600mg 6-monthly. Our results should however be interpreted as the  
389 effectiveness of OCR and RTX as prescribed in routine practice, and not as the efficacy of  
390 these therapies under strictly controlled trial conditions. Our analyses were performed in  
391 propensity score-matched groups with a moderate degree of disability, mean MS duration of  
392 11 years and previous treatment with 2-3 MS therapies. These findings may therefore not be  
393 generalisable to newly diagnosed patients, or patients who are commencing OCR or RTX as  
394 their first MS therapy. Our conclusions are based on a mean on-treatment follow up of 1.4  
395 years, which is insufficient for the assessment of long-term outcomes such as disability.

396 Partial availability of MRI data, lack of biological data (such as CD19+ B cell counts) and  
397 adverse effects preclude the evaluation of these outcomes.<sup>25, 26</sup>

398

399 In this non-inferiority study, we did not show non-inferiority of treatment with RTX  
400 compared to OCR in routine clinical practice. In fact, relapse rate in patients treated with  
401 RTX was higher than in OCR. Treatment selection for the individual patient, however,  
402 remains a complex and highly personalised decision, which considers additional factors such  
403 as availability and affordability of therapy, and adverse effects. Nevertheless, lack of a  
404 clinically relevant difference in the effectiveness between these two therapies should not be  
405 assumed. The efficacy of RTX compared to OCR is being further explored in two  
406 randomised non-inferiority clinical trials.<sup>25, 26</sup>

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517

## 518 **FIGURE LEGENDS**

519

### 520 **Figure 1:**

521 Patients previously treated with the comparator therapy were treated with OCR or RTX after  
522 2015, but had previously received the comparator therapy. Patients excluded due to  
523 insufficient on-treatment follow up did not have a baseline visit (with EDSS recorded) within  
524 a calliper of 180 days before or 30 days after commencement of therapy or had fewer than 2  
525 post-baseline visits more than 6 months apart. Of patients with progressive MS, 393 had  
526 secondary progressive MS and 225 had primary progressive MS.

527 RTX – rituximab; OCR – ocrelizumab

528

### 529 **Figure 2:**

530 Comparison of relapse outcomes for rituximab vs ocrelizumab. (A) Annualised relapse rate  
531 (mean plus 95% confidence interval), (B) Annualised relapse rate ratio (mean plus 95%  
532 confidence interval) with non-inferiority margin indicated by the dashed line, (C) Cumulative  
533 hazard of relapses

534

535 **Figure 3:**

536 Comparison of disability outcomes for rituximab vs ocrelizumab. (A) Cumulative hazard of  
 537 disability accumulation, (B) Cumulative hazard of disability improvement

538

539 **Figure 4:**

540 Persistence on study therapy

541

542 **TABLES**543 **Table 1:** Clinicodemographic characteristics before and after propensity score matching

	Before Matching			After Matching		
	OCR	RTX	d	OCR	RTX	d
Patients, n (% female)	1354 (67)	259 (69)	0.03	710 (68)	186 (68)	0.002
Registry, n (%)						
<i>M</i> SB <i>a</i> se	716 (53)	182 (70)		414 (58)	110 (59)	
<i>D</i> M <i>S</i> R	638 (47)	77 (30)		296 (42)	76 (41)	
Age, y, mean (SD)	42.2 (10.9)	40.8 (10.7)	0.14	41.3 (10.5)	41.8 (10.7)	0.05
Disease duration, y, mean (SD)	11.3 (8.0)	11.5 (8.0)	0.03	11.3 (7.9)	11.7 (8.3)	0.06
Disability, EDSS step, mean (SD)	3.0 (1.8)	3.5 (1.9)	0.25	3.4 (1.8)	3.5 (1.8)	0.02
No of relapses in 12 mo before baseline, mean (SD)	0.5 (0.7)	0.7 (1.0)	0.18	0.7 (0.9)	0.7 (0.9)	0.01
Recent disease activity, n (%)						
<i>n</i> one	625 (46)	99 (38)		265 (37)	71 (38)	
<i>p</i> rogression	171 (12)	43 (16)		125 (18)	31 (17)	
<i>r</i> elapse	350 (25)	75 (29)		201 (28)	53 (29)	
<i>r</i> elapse and progression	208 (15)	42 (16)		119 (17)	31 (17)	
MRI Brain: T2 lesion, n (%)						
Imaging available at baseline	562 (42)	99 (38)		276 (38)	83 (44)	
1-2	18 (3) <sup>a</sup>	12 (12) <sup>a</sup>		22 (8) <sup>a</sup>	5 (6) <sup>a</sup>	
3-8	39 (7) <sup>a</sup>	8 (8) <sup>a</sup>		16 (6) <sup>a</sup>	8 (10) <sup>a</sup>	
9+	505 (89) <sup>a</sup>	79 (80) <sup>a</sup>		238 (86) <sup>a</sup>	70 (84) <sup>a</sup>	
MRI Brain: new or contrast enhancing lesions, n (%)						
Imaging available at baseline	950 (70)	173 (67)		473 (67)	124 (67)	
Absent	565 (59) <sup>a</sup>	117 (68) <sup>a</sup>		309 (65) <sup>a</sup>	82 (66) <sup>a</sup>	
Present	385 (41) <sup>a</sup>	56 (32) <sup>a</sup>		154 (35) <sup>a</sup>	42 (34) <sup>a</sup>	
Number of previous DMTs, median [quartiles]	2.0 [1.0, 3.0]	2.0 [2.0, 3.0]	0.20	2.0 [1.0, 4.0]	3.0 [2.0, 4.0]	0.001
Pre-baseline follow up, years, median [quartiles]	6.9 [1.2, 11.1]	6.0 [2.3, 10.5]	0.18	5.9 [2.6, 10.3]	5.0 [2.7, 9.7]	0.14
Pre-baseline proportion of time on treatment, years, median [quartiles]	0.6 [0.3, 0.8]	0.6 [0.4, 0.8]	0.10	0.6 [0.4, 0.8]	0.6 [0.3, 0.8]	0.08
Post-baseline follow-up, y, mean (SD)	2.0 (0.8)	2.2 (1.3)	0.18	1.4 (0.7) <sup>b</sup>	1.4 (0.7) <sup>b</sup>	0.00
Visit interval, months, mean (SD)	5.2 (2.3)	3.6 (2.5)	0.45	6.1 (2.6)	5.7 (3.7)	0.10

544

545 <sup>a</sup> Proportion of patients with available MRI

546 <sup>b</sup> Follow-up and persistence after pairwise censoring, as per the primary analysis

547

## 548 **ACKNOWLEDGEMENTS**

549 We thank the patients who have agreed to participate in the global MSBase cohort study and

550 Danish MS Registry. The list of MSBase Study Group coinvestigators and contributors is

551 given in the online supplement.

552

## 553 **CONFLICTS OF INTEREST**

554 Izanne Roos served on scientific advisory boards, received conference travel support and/or

555 speaker honoraria from Roche, Novartis, Merck and Biogen. Izanne Roos is supported by MS

556 Australia and the Trish Multiple Sclerosis Research Foundation.

557 Stella Hughes has received unrestricted educational grants or speaking honoraria from

558 Biogen, Merck Serono, Novartis, Roche and Sanofi Genzyme.

559 Gavin McDonnell did not declare any competing interests.

560 Charles Malpas has received conference travel support from Merck, Novartis, and Biogen.

561 He has received research support from the National Health and Medical Research Council,

562 Multiple Sclerosis Research Australia, The University of Melbourne, The Royal Melbourne

563 Hospital Neuroscience Foundation, and Dementia Australia.

564 Sifat Sharmin did not declare any competing interests.

565 Cavit Boz received conference travel support from Biogen, Novartis, Bayer-Schering, Merck

566 and Teva; has participated in clinical trials by Sanofi Aventis, Roche and Novartis.

567 Raed Alroughani received honoraria as a speaker and for serving on scientific advisory

568 boards from Bayer, Biogen, GSK, Merck, Novartis, Roche and Sanofi-Genzyme.

569 Serkan Ozakbas did not declare any competing interests.

570 Katherine Buzzard received honoraria and consulting fees from Biogen, Teva, Novartis,  
571 Genzyme-Sanofi, Roche, Merck, CSL and Grifols.

572 Olga Skibina has received honoraria and consulting fees from Bayer Schering , Novartis,  
573 Merck, Biogen and Genzyme companies.

574 Anneke van der Walt served on advisory boards and receives unrestricted research grants  
575 from Novartis, Biogen, Merck and Roche She has received speaker's honoraria and travel  
576 support from Novartis, Roche, and Merck. She receives grant support from the National  
577 Health and Medical Research Council of Australia and MS Research Australia.

578 Helmut Butzkueven received institutional (Monash University) funding from Biogen, F.  
579 Hoffmann-La Roche Ltd, Merck, Alexion, CSL, and Novartis; has carried out contracted  
580 research for Novartis, Merck, F. Hoffmann-La Roche Ltd and Biogen; has taken part in  
581 speakers' bureaus for Biogen, Genzyme, UCB, Novartis, F. Hoffmann-La Roche Ltd and  
582 Merck; has received personal compensation from Oxford Health Policy Forum for the Brain  
583 Health Steering Committee.

584 Jeannette Lechner-Scott travel compensation from Novartis, Biogen, Roche and Merck. Her  
585 institution receives the honoraria for talks and advisory board commitment as well as  
586 research grants from Biogen, Merck, Roche, TEVA and Novartis.

587 Jens Kuhle did not declare any competing interests.

588 Murat Terzi received travel grants from Novartis, Bayer-Schering, Merck and Teva; has  
589 participated in clinical trials by Sanofi Aventis, Roche and Novartis.

590 Guy Laureys received travel and/or consultancy compensation and/or research grants from  
591 Sanofi-Genzyme, Roche, Teva, Merck, Novartis, Celgene, Biogen, Bristol Myers Squibb.

592 Liesbeth Van Hijfte did not declare any competing interests.

593 Nevin Johnis a local principal investigator on commercial studies funded by Novartis,  
594 Biogen, Amicus and Sanofi.

595 Pierre Grammond has served in advisory boards for Novartis, EMD Serono, Roche, Biogen  
596 idec, Sanofi Genzyme, Pendopharm and has received grant support from Genzyme and  
597 Roche, has received research grants for his institution from Biogen idec, Sanofi Genzyme,  
598 EMD Serono.

599 Francois Grand'Maison received honoraria or research funding from Biogen, Genzyme,  
600 Novartis, Teva Neurosciences, and ATARA Pharmaceuticals.

601 Aysun Soysal did not declare any competing interests.

602 Ana Isabel Figueira Jensen,

603 Peter Vestergaard Rasmussen has served on scientific advisory boards for, served as  
604 consultant for, received support for congress participation or received speaker honoraria from  
605 Alexion, Biogen, Bristol Myers Squibb, Merck, Novartis, Roche and Sanofi Genzyme.

606 Kristina Bacher Svendsen did not declare any competing interests.

607 Ismael Barzinji did not declare any competing interests.

608 Helle Hvilsted Nielsen did not declare any competing interests.

609 Tobias Sejbæk did not declare any competing interests.

610 Sivagini Prakash did not declare any competing interests.

611 Morten Leif Munding Stilund has served on scientific advisory boards for Sanofi, received  
612 support for congress participation or received speaker honoraria from Biogen, Teva, Merck,  
613 Roche and Sanofi. M. Stilund has received grants for his research from Novartis, and is  
614 currently engaged in sponsor-initiated research projects by Bayer, Jansen, Shionogi and  
615 Sanofi.

616 Arkadiusz Weglewski served on scientific advisory boards for Merck and Roche, received  
617 conference travel support from Biogen, Merck, Roche and Sanofi and speaker honoraria from  
618 Roche, Merck and Sanofi.

619 Nadia Mubder Issa did not declare any competing interests.

620 Matthias Kant did not declare any competing interests.

621 Finn Sellebjerg has served on scientific advisory boards, been on the steering committees of  
622 clinical trials, served as a consultant, received support for congress participation, received  
623 speaker honoraria, or received research support for his laboratory from Biogen, Merck,  
624 Novartis, Roche, Sanofi Genzyme and Teva.

625 Orla Gray received honoraria as consultant on scientific advisory boards for Genzyme,  
626 Biogen, Merck, Roche and Novartis; has received travel grants from Biogen, Merck, Roche  
627 and Novartis; has participated in clinical trials by Biogen and Merck; has received research  
628 grant support from Biogen.

629 Melinda Magyari has served on scientific advisory boards for Abbvie, Biogen, Merck,  
630 Novartis, Roche, Sanofi and Teva, has received honoraria for lecturing from Biogen,  
631 Genzyme, Merck, Novartis and Sanofi, support for congress participation from Biogen,  
632 Genzyme, Roche and Teva, and research grants from Merck, Novartis and Sanofi.

633 Tomas Kalincik served on scientific advisory boards for MS International Federation and  
634 World Health Organisation, BMS, Roche, Sanofi Genzyme, Novartis, Merck and Biogen,  
635 steering committee for Brain Atrophy Initiative by Sanofi Genzyme, received conference  
636 travel support and/or speaker honoraria from WebMD Global, Novartis, Biogen, Sanofi-  
637 Genzyme, Teva, BioCSL and Merck and received research or educational event support from  
638 Biogen, Novartis, Genzyme, Roche, Celgene and Merck.

639

#### 640 **FUNDING**

641

642 This study was supported by the NHMRC [1140766, 1129189, 1157717]. IR is supported by  
643 a MS Australia postdoctoral fellowship grant. The MSBase Foundation is a not-for-profit  
644 organization that receives support from Biogen, Novartis, Merck, Roche, Teva and

645 Sanofi Genzyme. Design and conduct of the study; collection, management, analysis, and  
646 interpretation of the data; preparation, review, or approval of the manuscript; and decision to  
647 submit the manuscript for publication were conducted separately and apart from the guidance  
648 of the sponsors.

649

#### 650 **DATA ACCESS, RESPONSIBILITY AND ANALYSIS**

651

652 IR and TK had full access to all the data in the study and takes responsibility for the integrity  
653 of the data and the accuracy of the data analysis

654

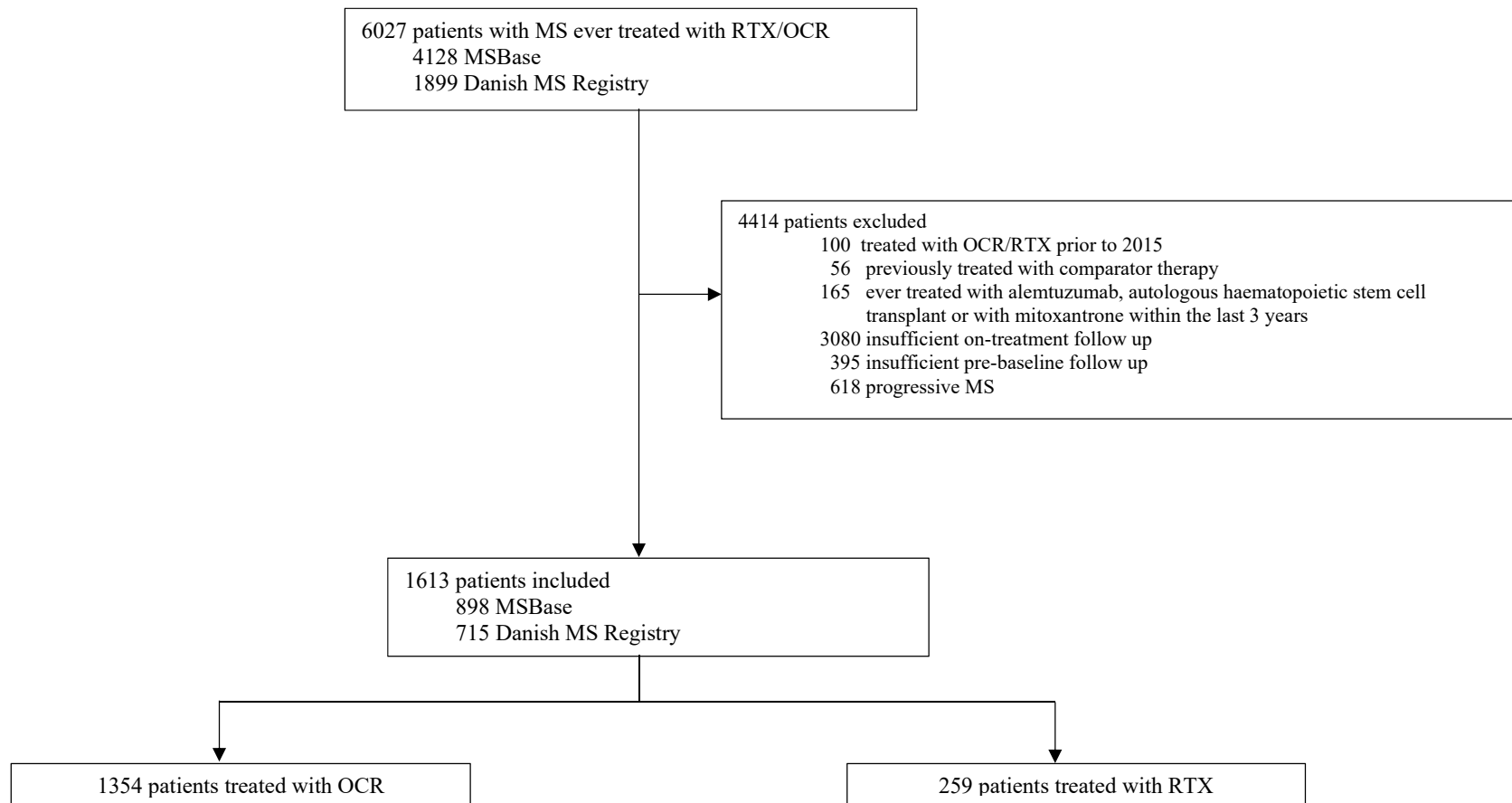
#### 655 **DATA SHARING STATEMENT**

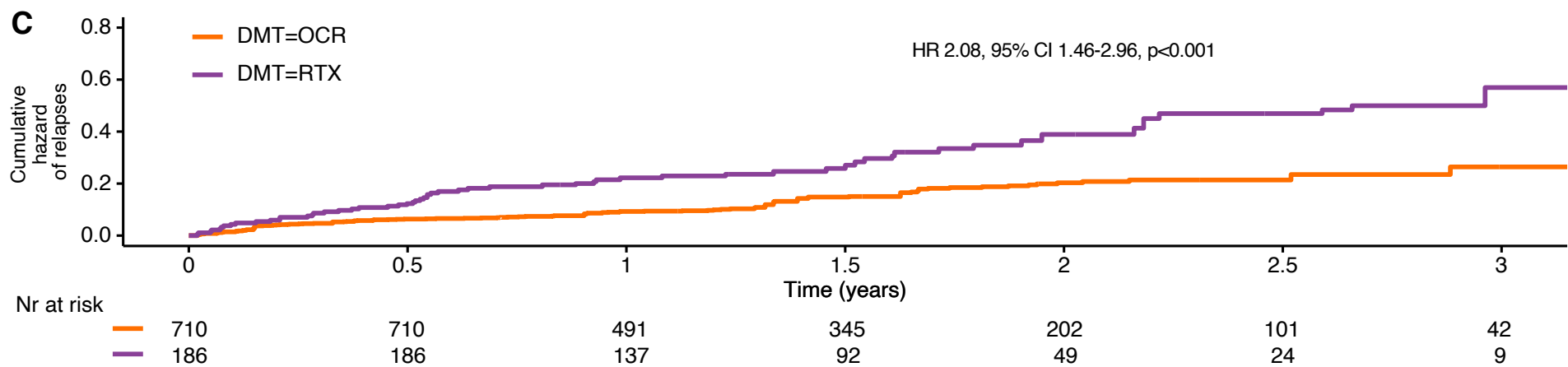
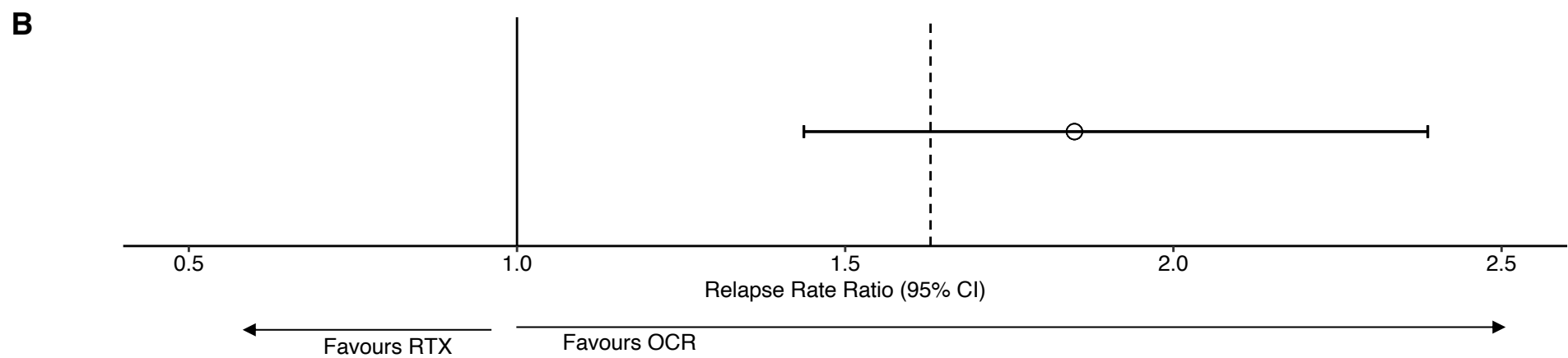
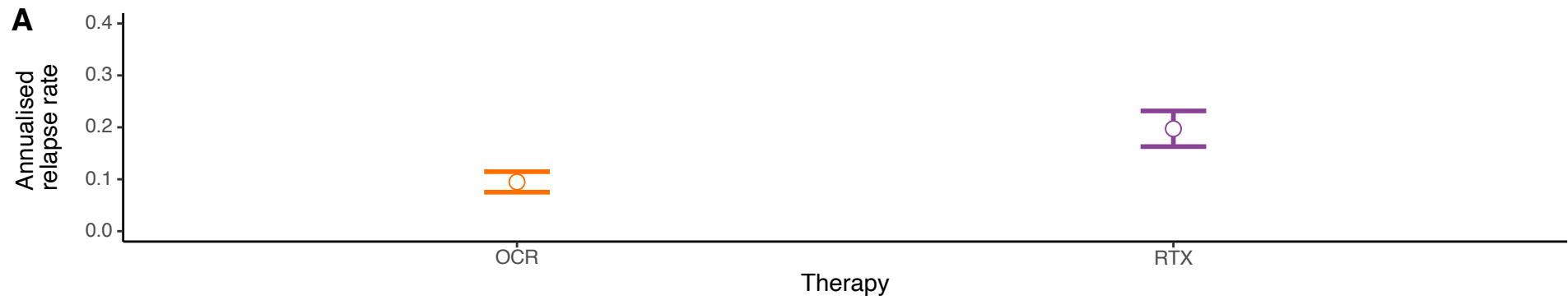
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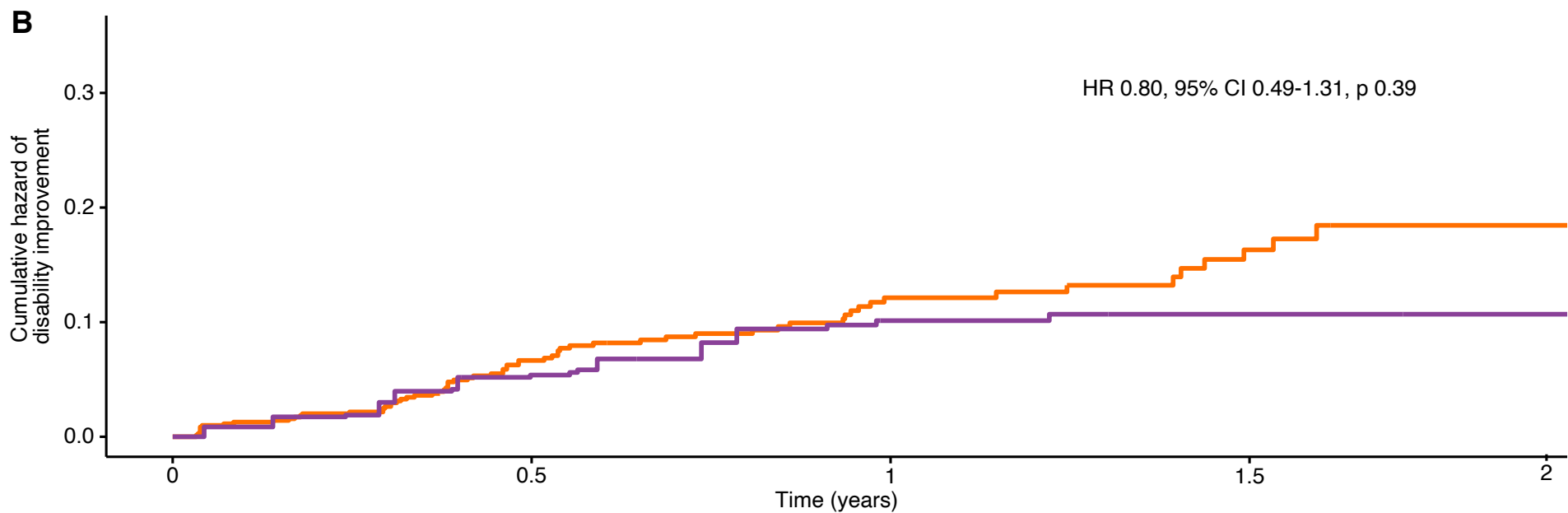
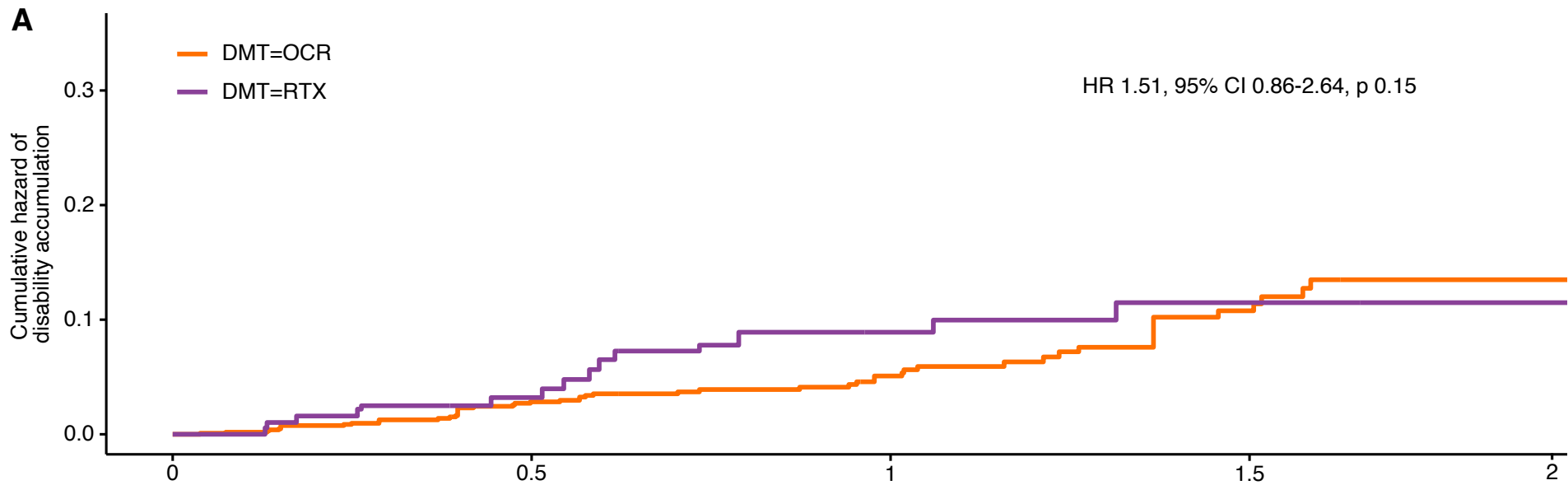
657 The MSBase registry is a data processor and warehouses data from individual principal  
658 investigators who agree to share their datasets on a project-by-project basis. Data  
659 access to external parties can be granted on reasonable request at the sole discretion of the  
660 principal investigators, who will need to be approached individually for permission. Data  
661 from the Danish MS Registry is accessible to authorised researchers after application to the  
662 Danish Health Data Authority and the board of the Danish Multiple Sclerosis Registry.

663

664







Nr at risk

	0	0.5	1	1.5	2
710	710	528	292	139	43
186	186	139	75	36	10

