**Supplementary tables**

**Suppl**. **Table 1**  **Rituximab** phase 2 and 3 trials for the treatment of multiple sclerosis

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| --- | --- | --- |
| **Trial** | **Primary endpoint**  ***Result*** | **Secondary endpoint**  ***Result*** |
| Phase 2 RRMS  Hauser et al. 2008  NEJM  (HERMES)  n=104 patients | * Total number of gadolinium-positive T1 lesions in serial brain MRIs at weeks 12, 16, 20, 24: * *Rituximab is more effective than placebo* | * Proportion of relapsing patients; * Annualised relapse rate; * Absolute number of new gadolinium-positive T1 lesions in serial brain MRIs at weeks 12, 16, 20, 24; and * changes in T2 lesion volume compared to baseline: * *Rituximab is more effective than placebo* |
| Phase 2/3 PPMS  Hawker et al. 2009  Ann. Neurol .  (OLYMPUS)  n=439 patients | * Time until onset of CDP, * Percentage of patients with CDP: * *No evidence of any significant difference* | * Change in absolute T2 lesion volume at week 96 compared to baseline, * Change in brain volume at week 96 compared to baseline: * *Patients who received rituximab had a significantly lower increase in T2 lesion volume* |

MRI = Magnetic Resonance Imaging, CDP = Confirmed Disability Progression, CDI = Confirmed Disability Improvement.

**Suppl. Table 2:** Indications for the use of **ocrelizumab / ofatumumab**

**As defined by EMA** https://www.ema.europa.eu/en/medicines

Ocrelizumab is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease as defined by clinical findings or by imaging.

Ocrelizumab is indicated for the treatment of adult patients with early primary progressive multiple sclerosis (PPMS), as characterised by disease duration and degree of disability, as well as by imaging features indicative of inflammatory activity.

Ofatumumab is not yet approved

**As defined by the FDA** [www.accessdata.fda.gov/drugsatfda\_docs](http://www.accessdata.fda.gov/drugsatfda_docs)

Ocrelizumab is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (and primary progressive multiple sclerosis (PPMS).

Ofatumumab is indicated for the treatment of adult patients with relapsing forms of MS (CIS, RRMS, active secondary progressive MS).

**As defined by Health Canada** [www.canada.ca/en/services/health/drug-health-products](http://www.canada.ca/en/services/health/drug-health-products)

Ocrelizumab is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical and imaging features.

Ocrelizumab is indicated for the treatment of adult patients with early primary progressive multiple sclerosis (PPMS), as defined by disease duration and level of disability, in conjunction with imaging features characteristic of inflammatory activity.

Ofatumumab is not yet approved.

**As defined by Australian Therapeutic Goods Administration (TGA)** www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/PICMI?OpenForm&t=&q=ocrelizumab

Ocrelizumab is indicated for the treatment of patients with relapsing forms of multiple sclerosis (RMS) to delay the progression of physical disability and to reduce the frequency of relapse.

Ocrelizumab is indicated for the treatment of patients with primary progressive multiple sclerosis (PPMS) to delay the progression of physical disability.

Ofatumumab is not yet approved.

**Suppl. Table 3** Overview of oral Bruton`s tyrosine kinase inhibitors trials in multiple sclerosis (MS).

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| --- | --- | --- | --- | --- | --- |
| Trial | **Evobrutinib (M2951)** | | | **SAR442168** | |
| Relapsing MS | Progressive MS | Relapsing MS | | Progressive MS |
| Phase 2 | Evobrutinib *versus* placebo and dimethyl fumarate  (NCT02975349) 42  Placebo, Evobrutinib 25 mg qd, 75 mg qd, 75 mg BID, or dimethylfumarate 240 mg BID  n=267 participants | ./. | SAR442168  *versus* placebo (NCT03889639)  n=129 participants  (NCT03996291)  long-term extension  n=126 planned participants | | ./. |
| Phase 3 | Evobrutinib BID *versus* teriflunomide 14 mg qd  (NCT04338022 and NCT04338061)  Primary outcome: Annualized Relapse Rate  930 planned participants each | ./. | GEMINI I and GEMINI II  (NCT4410978 and NCT04410991)  SAR442168 *versus* teriflunomide 14 mg once daily  Primary outcome: Annualized Relapse Rate  900 planned participants each | | HERCULES (nrSPMS)  (NCT04411641)  SAR442168 *versus* placebo once daily  Primary outcome:  6 month confirmed disability progression  1290 planned participants |

PPMS = primary progressive MS, nrSPMS = non-relapsing secondary progressive MS.

Roche has initiated a clinical development program of the oral Bruton’s Tyrosine kinase inhibitor fenobrutinib (GDC-0853) in both relapsing and progressive MS with several phase 3 trials about to get started.