**Supplemental material 2**

**Changes to methods and outcome measures after trial commencement**

All authorities initially approved version 2 of the protocol on September 12, 2016, and all authorities approved version 5 on February 21, 2020. Due to recruitment issues, the age criterion was increased from 60 to 65 years of age (version 3), were approved by all authorities on May 3, 2017. Extension of the expected duration of the study and changes to secondary endpoints (removal of MMP9, sCD163, and CXCL13; and addition of sCD27, sCD14, and BCMA due to new findings on these subjects) and clinical outcomes (removal of Low Contrast Visual Acuity Test due to technical issues) were approved by all authorities (version 4) on October 31, 2018. Additionally, changes to the statistical analysis plan and one secondary endpoint (removal of cell count due to technical issues) were added for the latest version of the protocol (version 5), which was approved on February 21, 2020. The primary endpoint remained unchanged throughout the study period.

**Recruitment**

Patients were enlisted from our own site, referred from other MS clinics in Denmark or recruited via the MS patient society.

**Authorisation and oversight**

Ethical approval was granted by the local ethics committee (H-16032162), and the study was approved by the Danish Medicines Agency (EudraCT no.: 2016-000283-41). The participants signed a written, informed consent form. Independent monitoring was provided by the Good Clinical Practice Unit at Copenhagen University Hospital Bispebjerg, Copenhagen. The trial was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki.