Longitudinal T-Cell Responses After a Third SARS-CoV-2 Vaccination in Patients With Multiple Sclerosis on Ocrelizumab or Fingolimod

Virginia Palomares Cabeza, MSc,* Laura Y.L. Kummer, MD,* Luuk Wieske, PhD, Ruth R. Hagen, BSc, Mariel Duurland, BSc, Veronique A.L. Konijn, MSc, Koos P.J. van Dam, MD, Eileen W. Stalman, MD, Carolien E. van de Sandt, PhD, Laura Boekel, BSc, Niels J.M. Verstegen, MSc, Maurice Steenhuis, PhD, Theo Rispens, PhD, Sander W. Tas, PhD, Gertjan Wolbink, PhD, Joep Killestein, PhD, Taco W. Kuipers, PhD, S. Marieke van Ham, PhD, Filip Eftimov, PhD, Anja ten Brinke, PhD,† and Zoë L.E. van Kempen, PhD,‡ on behalf of the Target-to-B! (T2B!) SARS-CoV-2 study group

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Abstract

Objectives
To evaluate whether a third vaccination shows an added effect on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) T-cell responses in patients with multiple sclerosis treated with ocrelizumab or fingolimod.

Methods
This is a substudy of a prospective multicenter study on SARS-CoV-2 vaccination in patients with immune-mediated diseases. Patients with MS treated with ocrelizumab, fingolimod, and no disease-modifying therapies and healthy controls were included. The number of interferon (IFN)-γ secreting SARS-CoV-2–specific T cells at multiple time points before and after 3 SARS-CoV-2 vaccinations were evaluated.

Results
In ocrelizumab-treated patients (N = 24), IFN-γ–producing SARS-CoV-2–specific T-cell responses were induced after 2 vaccinations with median levels comparable to healthy controls (N = 12) and patients with MS without disease-modifying therapies (N = 10). A third vaccination in ocrelizumab-treated patients (N = 8) boosted T-cell responses that had declined after the second vaccination, but did not lead to higher overall T-cell responses as compared to immediately after a second vaccination. In fingolimod-treated patients, no SARS-CoV-2–specific T cells were detected after second (N = 12) and third (N = 9) vaccinations.

Discussion
In ocrelizumab-treated patients with MS, a third SARS-CoV-2 vaccination had no additive effect on the maximal T-cell response but did induce a boost response. In fingolimod-treated patients, no T-cell responses could be detected following both a second and third SARS-CoV-2 vaccination.

*These authors contributed equally to the manuscript as first authors.
†These authors contributed equally as last authors.

From the Department of Immunopathology (V.P.C., L.Y.L.K., M.D., V.A.L.K., N.J.M.V., M.S., T.R., G.W., S.M.v.H., A.t.B.), Sanquin Research and Landsteiner Laboratory, Amsterdam UMC; Department of Neurology and Neurophysiology (L.K., L.W., K.P.J.v.D., E.W.S., F.E.), Amsterdam Neuroscience, Amsterdam UMC, location AMC, University of Amsterdam; Department of HematoPoiesis (R.R.H., C.E.v.d.S.), Sanquin Research and Landsteiner Laboratory, Amsterdam UMC; Department of Experimental Immunohematology (R.R.H.), Sanquin Research and Landsteiner Laboratory, Amsterdam, the Netherlands; Department of Microbiology and Immunology (C.E.v.d.S.), University of Melbourne, Peter Doherty Institute for Infection and Immunity, Victoria, Australia; Amsterdam Rheumatology and Immunology Center (L.B., G.W.), Deventer, Department of Rheumatology; Amsterdam Rheumatology and Clinical Immunology, University of Amsterdam; Department of Neurology (J.K., 2.L.E.v.K.), Amsterdam UMC, Vrije Universiteit; Department 32 of Pediatric Immunology (T.W.K.K.), Rheumatology and Infectious Diseases, Amsterdam UMC, location AMC, University of Amsterdam; and Swammerdam Institute for Life Sciences (S.M.v.H.), University of Amsterdam, the Netherlands.

Go to Neurology.org/NF for full disclosures. Funding information is provided at the end of the article.

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Target-to-B! (T2B!) SARS-CoV-2 study group coinvestigators are listed in appendix 2 at the end of the article.

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In patients with multiple sclerosis (MS), both ocrelizumab (OCR) and fingolimod (FTY) are associated with decreased humoral responses following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination. Based on the decreased humoral response, patients with MS treated with OCR or FTY are offered a third SARS-CoV-2 vaccination in many countries. Given the poor humoral response, antiviral defense may be more reliant on T cells. The objective of this study was to evaluate longitudinal T-cell responses after second and third SARS-CoV-2 vaccinations in OCR- and FTY-treated patients with MS.

### Methods

This is a substudy of a prospective multicenter multiarm cohort study on SARS-CoV-2 vaccination in patients with various immune-mediated inflammatory diseases (Target-to-B!). Participants were recruited from February 16, 2021 to August 20, 2021. Participants diagnosed with MS using OCR, FTY, and no disease-modifying therapy (DMT) and healthy controls (HCs) were included. Cryopreserved peripheral blood mononuclear samples, collected before the first vaccination (OCR), after the second vaccination (OCR + FTY), and prior and 1 week after the third vaccination, were analyzed for longitudinal T-cell responses.

### Table: Characteristics of Included Study Subjects

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<tr>
<th></th>
<th>DMT</th>
<th>No DMT</th>
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<tr>
<td></td>
<td>MS</td>
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<tr>
<td></td>
<td>OCR (n = 24)</td>
<td>FTY (n = 12)</td>
</tr>
<tr>
<td><strong>Age, y, mean (SD)</strong></td>
<td>44 (10.1)</td>
<td>45 (7.8)</td>
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<tr>
<td><strong>Female sex, n (%)</strong></td>
<td>17 (70)</td>
<td>8 (67)</td>
</tr>
<tr>
<td><strong>First and second vaccinations</strong></td>
<td>24 (100)</td>
<td>8 (67)</td>
</tr>
<tr>
<td>Vaccine type</td>
<td>CX-024414 (Moderna), n (%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>BNT162b2 (Pfizer/BioNtech), n (%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Seroconversion after the second vaccination, n (%)^a</td>
<td>3 (13)</td>
<td>3 (25)</td>
</tr>
<tr>
<td>Anti-RBD IgG titer, median (IQR)</td>
<td>0.5 (0.1–1.3)</td>
<td>0.1 (0.1–2.1)</td>
</tr>
<tr>
<td><strong>Third vaccination</strong></td>
<td>OCR (n = 8)</td>
<td>FTY (n = 9)</td>
</tr>
<tr>
<td>Vaccine type</td>
<td>CX-024414 (Moderna), n (%)</td>
<td>8 (100)</td>
</tr>
<tr>
<td></td>
<td>Interval between second and third vaccinations in days, median (IQR)</td>
<td>119 (117–119)</td>
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<td></td>
<td>Interval between the last OCR infusion and the third vaccination in days, median (IQR)</td>
<td>122 (98–144)</td>
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<td>Peripheral B- and T-cell counts before the third vaccination</td>
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<td>CD19^+ B cells, number/μL, median (IQR)</td>
<td>0.5 (0–3)</td>
<td>15 (13–26)</td>
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<td>CD4^+ T cells, number/μL, median (IQR)</td>
<td>986 (751–1,100)</td>
<td>24 (24–41)</td>
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<td>CD8^+ T cells, number/μL, median (IQR)</td>
<td>341 (247–480)</td>
<td>71 (66–85)</td>
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<td>Seroconversion after the third vaccination, n (%)^b</td>
<td>3 (38)</td>
<td>5 (56)</td>
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<tr>
<td>Newly seroconverted, n (%)^c</td>
<td>1 (17)</td>
<td>2 (33)</td>
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<tr>
<td>Anti-RBD IgG titer, median (IQR)</td>
<td>0.1 (0.1–6.0)</td>
<td>5.5 (1.5–7.6)</td>
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</table>

**Abbreviations:** DMT = disease-modifying therapy; FTY = fingolimod; HC = healthy control; Ig = immunoglobulin; IQR = interquartile range; MS = multiple sclerosis; NA = not available; OCR = ocrelizumab; RBD = receptor-binding domain.

Participants received 2 or 3 vaccinations with CX-024414 (Moderna) or BNT162b2 (Pfizer/BioNtech) following the Dutch national vaccination campaign guidelines. Patients previously infected with SARS-CoV-2 (as evidenced by self-reported positive PCR and/or anti-spike or anti-nucleocapsid protein antibodies at baseline and follow-up) were excluded. SARS-CoV-2 antibodies were measured using an in-house developed anti-RBD IgG ELISA. Anti-RBD IgG titers were expressed as arbitrary units (AU) per milliliter. Seroconversion after vaccination was defined as antibodies >4 AU/mL. Eighteen OCR-treated patients were diagnosed with relapsing-remitting MS and 6 with primary progressive MS.

^a Antibody levels were measured 7–10 days after the second vaccination in the HC, MS–No DMT, and MS-OCR groups vs 28 days after the second vaccination in the MS-FTY group.

^b Antibody levels were measured 7–10 days after the third vaccination.

^c Number of individuals with a negative SARS-CoV-2 IgG titer after 2 vaccinations and a positive antibody titer (>4 AU/mL) after the third vaccination.
vaccination (OCR + FTY), were evaluated in an ELISpot for spike-specific interferon (INF-γ) T-cell response. A total of 200,000 cells were stimulated for 16 hours with Spike-1 (S1) or Spike-2 (S2) (JPT-Innovative Peptide-Solutions) peptide pools (1 μg/mL per peptide) in triplicate.

**Standard Protocol Approvals, Registrations, and Patient Consents**

The ethics committee of the Amsterdam UMC, location AMC (2020.194), approved the study, and participants provided written informed consent. Dutch Trial register, ID: NL8900.

**Data Availability**

Data sets used during this study are available from the corresponding author on reasonable request.

**Results**

Baseline information of patients with MS treated with OCR (n = 24), FTY (n = 12), and no DMT (n = 10) and healthy controls (n = 12) is summarized in Table. T-cell responses against SARS-CoV-2 S-proteins were significantly induced in OCR-treated patients after 2 vaccinations and were comparable to those in HCs and patients with MS without DMT (Figure, A). In contrast, no T-cell responses were detectable in FTY-treated patients following 2 vaccinations.

T-cell responses in patients with MS treated with OCR (n = 8) or FTY (n = 9) were compared after the second vaccination with directly before the third vaccination and a week after the third vaccination (Figure, B). A third vaccination upregulated SARS-CoV-2–specific T cells in OCR-treated patients but not to a higher extent than directly after the second vaccination (in 6 of 8 patients T-cell response were slightly lower after the third vaccination). In contrast, the third vaccination did not yield significant SARS-CoV-2–specific T-cell responses in FTY-treated patients. Although a very limited significant increase in SFU after the third vaccination was observed, the SFU was still in range of the baseline response of HCs and MS without DMT (Figure, A vs Figure, B).

**Discussion**

In this study, SARS-CoV-2 T-cell responses following the second vaccination were found to be comparable in OCR-treated patients with MS, patients with MS without DMT, and HCs. We established that a third vaccination induces a recall of SARS-CoV-2 T cells in OCR-treated patients but does not further increase circulating SARS-CoV-2 T-cell numbers compared with after the second vaccination. This is in agreement with recent studies describing a T-cell recall against SARS-CoV-2 following 2 vaccinations.

In FTY-treated patients, we observed no detectable T-cell response against SARS-CoV-2 following 2 vaccinations. This is in line with previous findings that showed IFN-γ T-cell responses in only 14.3% of FTY-treated patients after 2 vaccinations. In our study, T-cell responses remained abrogated in FTY-treated patients. Although, recall responses to tetanus vaccination were normal in a placebo-controlled study involving FTY-treated healthy volunteers, although responses to a novel antigen were affected. Together, these data may indicate...
that FTY therapy affects vaccination responses to novel (neo)antigens, like SARS-CoV-2, but that recall responses to antigens exposed to before the start of FTY treatment are less affected. Despite the impaired humoral and cellular immune responses following SARS-CoV-2 vaccination in FTY-treated patients, the risk of severe COVID-19 in these patients seems similar to the general population,7 introducing a clinical/immunologic paradox. FTY is associated with only moderate increased risk of infectious diseases, despite the FTY-induced lymphopenia.8 A possible explanation could be that although circulatory T cells are severely reduced, the number and function of T cells in lymphoid tissue and mucosal tissues, like the lung, might not be affected.

In conclusion, in OCR-treated patients with MS, the third SARS-CoV-2 vaccination does not have an additive effect on the maximal T-cell response but does induce a booster response. In FTY-treated patients, both after a second and third SARS-CoV-2 vaccination, no SARS-CoV-2–specific T-cell responses are detected in the peripheral blood.

Acknowledgment
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Disclosure
J. Killestein reported speaking and consulting relationships with Biogen, Genzyme, Merck, Novartis, Roche, Sanofi, and TEVA. Amsterdam UMC, location VUmc, MS Center Amsterdam, has received financial support for research activities from Biogen, Celgene, Genzyme, Merck, Novartis, Roche, Sanofi, and TEVA. C.E. van de Sandt has received funding from the European Union’s Horizon 2020 research and innovation program under the Marie Sklodowska-Curie grant agreement (#792532). F. Eftimov, G.J. Wolbink, S.M. van Ham, and T.W. Kuijpers reported a grant from ZonMW for COVID research in patients with autoimmune diseases (ZonMW grants: 10430012010009, 10430022010020, and 10430072010007). The T2B collaboration project is financed by the PPP Allowance made available by Top Sector Life Sciences & Health to Samenwerkende Gezondheidsfondsen (SGF) under project number LSHM18055-SGF to stimulate public-private partnerships and cofinancing by health foundations that are part of the SGF. All other authors report no disclosures relevant to the manuscript. Go to Neurology.org/NN for full disclosures.

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Appendix 1 Authors

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virginia Palomares</td>
<td>Department of Immunopathology, Sanquin Research and Landsteiner Laboratory, Amsterdam UMC, the Netherlands</td>
<td>Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data</td>
</tr>
<tr>
<td>Cabeza, MSc</td>
<td>Department of Neurology and Neurophysiology, Amsterdam Neuroscience, Amsterdam UMC, location AMC, Amsterdam, the Netherlands</td>
<td>Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data</td>
</tr>
<tr>
<td>Laura Y.L. Kummer,</td>
<td>Department of Immunopathology, Sanquin Research and Landsteiner Laboratory, Amsterdam UMC, the Netherlands</td>
<td>Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data</td>
</tr>
<tr>
<td>MD</td>
<td>Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data</td>
<td></td>
</tr>
<tr>
<td>Luuk Wieske, PhD</td>
<td>Department of Hematopoiesis, Sanquin Research and Landsteiner Laboratory, Amsterdam UMC, the Netherlands</td>
<td>Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data</td>
</tr>
<tr>
<td>Ruth R. Hagen, BSc</td>
<td>Department of Neurology and Neurophysiology, Amsterdam Neuroscience, Amsterdam UMC, location AMC, University of Amsterdam, the Netherlands</td>
<td>Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data</td>
</tr>
<tr>
<td>Veronique A.L. Konijn, MSc</td>
<td>Department of Immunopathology, Sanquin Research and Landsteiner Laboratory, Amsterdam UMC, the Netherlands</td>
<td>Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data</td>
</tr>
<tr>
<td>Koos P.J. van Dam, MD</td>
<td>Department of Neurology and Neurophysiology, Amsterdam Neuroscience, Amsterdam UMC, location AMC, University of Amsterdam, the Netherlands</td>
<td>Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data</td>
</tr>
<tr>
<td>Eileen W. Stalman, MD</td>
<td>Department of Neurology and Neurophysiology, Amsterdam Neuroscience, Amsterdam UMC, location AMC, University of Amsterdam, the Netherlands</td>
<td>Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data</td>
</tr>
<tr>
<td>Caroline E. van de Sandt, PhD</td>
<td>Department of Hematopoiesis, Sanquin Research and Landsteiner Laboratory, Amsterdam UMC, the Netherlands; Department of Microbiology and Immunology, University of Melbourne, Peter Doherty Institute for Infection and Immunity, Victoria, Australia</td>
<td>Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data</td>
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<tr>
<td>Laura Boekel, BSc</td>
<td>Amsterdam Rheumatology and Immunology Center, location Reade, Department of Rheumatology, the Netherlands</td>
<td>Drafting/revision of the manuscript for content, and major role in the acquisition of data</td>
</tr>
<tr>
<td>Niels J.M. Verstegen, MSc</td>
<td>Department of Immunopathology, Sanquin Research and Landsteiner Laboratory, Amsterdam UMC, the Netherlands</td>
<td>Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data</td>
</tr>
<tr>
<td>Maurice Steenhuis, PhD</td>
<td>Department of Immunopathology, Sanquin Research and Landsteiner Laboratory, Amsterdam UMC, the Netherlands</td>
<td>Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data</td>
</tr>
<tr>
<td>Theo Rispres, PhD</td>
<td>Department of Immunopathology, Sanquin Research and Landsteiner Laboratory, Amsterdam UMC, the Netherlands</td>
<td>Drafting/revision of the manuscript for content, including medical writing for content, and study concept or design</td>
</tr>
<tr>
<td>Sander W. Tas, PhD</td>
<td>Amsterdam Rheumatology and Immunology Center, Amsterdam UMC, Department of Rheumatology and Clinical Immunology, University of Amsterdam, the Netherlands</td>
<td>Drafting/revision of the manuscript for content, including medical writing for content, and study concept or design</td>
</tr>
<tr>
<td>Gertjan Wolbink, PhD</td>
<td>Department of Immunopathology, Sanquin Research and Landsteiner Laboratory, Amsterdam UMC; Amsterdam Rheumatology and Immunology Center, location Reade, Department of Rheumatology, the Netherlands</td>
<td>Drafting/revision of the manuscript for content, including medical writing for content, and study concept or design</td>
</tr>
<tr>
<td>Joep Killestein, PhD</td>
<td>Department of Neurology, Amsterdam UMC, Vrije Universiteit, the Netherlands</td>
<td>Drafting/revision of the manuscript for content, including medical writing for content, and study concept or design</td>
</tr>
<tr>
<td>Taco W. Kuipers, PhD</td>
<td>Department 32 of Pediatric Immunology, Rheumatology and Infectious Disease, Amsterdam UMC, location AMC; University of Amsterdam, the Netherlands</td>
<td>Drafting/revision of the manuscript for content, including medical writing for content, and study concept or design</td>
</tr>
<tr>
<td>S. Marieke van Ham, PhD</td>
<td>Department of Immunopathology, Sanquin Research and Landsteiner Laboratory, Amsterdam UMC; Swammerdam Institute for Life Sciences, University of Amsterdam, the Netherlands</td>
<td>Drafting/revision of the manuscript for content, including medical writing for content, and study concept or design</td>
</tr>
<tr>
<td>Filip Eftimov, PhD</td>
<td>Department of Neurology and Neurophysiology, Amsterdam Neuroscience, Amsterdam UMC, location AMC; University of Amsterdam, the Netherlands</td>
<td>Drafting/revision of the manuscript for content, including medical writing for content, and study concept or design</td>
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### Appendix 2 Coinvestigators

<table>
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<tr>
<th>Name</th>
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<tr>
<td>Anja ten Brinke, PhD</td>
<td>Department of Immunopathology, Sanquin Research and Landsteiner Laboratory, Amsterdam UMC, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
</tr>
<tr>
<td>Zob L.E. van Kempen, PhD</td>
<td>Department of Neurology, Amsterdam UMC, Vrije Universiteit, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
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<tr>
<td>A.J. vd Kooi</td>
<td>Department of Neurology and Neurophysiology, Amsterdam UMC, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
</tr>
<tr>
<td>J. Raaphorst</td>
<td>Department of Neurology and Neurophysiology, Amsterdam UMC, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
</tr>
<tr>
<td>A.H. Zwinderman</td>
<td>Clinical Research Unit, Amsterdam UMC, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
</tr>
<tr>
<td>M. Lowenberg</td>
<td>Department of Gastroenterology and Hepatology, Amsterdam UMC, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
</tr>
<tr>
<td>A.G. Volkers</td>
<td>Department of Gastroenterology and Hepatology, Amsterdam UMC, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
</tr>
<tr>
<td>G. Dhaens</td>
<td>Department of Gastroenterology and Hepatology, Amsterdam UMC, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
</tr>
<tr>
<td>R.B. Takkenberg</td>
<td>Department of Gastroenterology and Hepatology, Amsterdam UMC, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
</tr>
<tr>
<td>P.I. Spuls</td>
<td>Department of Dermatology, Amsterdam UMC, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
</tr>
<tr>
<td>M.W. Bekkenk</td>
<td>Department of Dermatology, Amsterdam UMC, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
</tr>
<tr>
<td>A.H. Musters</td>
<td>Department of Dermatology, Amsterdam UMC, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
</tr>
<tr>
<td>N.F. Post</td>
<td>Department of Dermatology, Amsterdam UMC, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
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<tbody>
<tr>
<td>A.L. Bosma (continued)</td>
<td>Department of Dermatology, Amsterdam UMC, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
</tr>
<tr>
<td>M.L. Hilhorst</td>
<td>Department of Internal Medicine, Section of Nephrology, Amsterdam UMC, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
</tr>
<tr>
<td>Y. Vegting</td>
<td>Department of Internal Medicine, Section of Nephrology, Amsterdam UMC, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
</tr>
<tr>
<td>F.J. Bemelman</td>
<td>Department of Internal Medicine, Section of Nephrology, Amsterdam UMC, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
</tr>
<tr>
<td>R. de jong</td>
<td>Department of Immunopathology, Sanquin Research and Landsteiner Laboratory, Amsterdam UMC, the Netherlands</td>
<td>Site investigator</td>
<td>Site investigator</td>
</tr>
<tr>
<td>L. Kuijpers</td>
<td>Department of Immunopathology, Sanquin Research and Landsteiner Laboratory, Amsterdam UMC, the Netherlands</td>
<td>Site investigator</td>
<td>Site investigator</td>
</tr>
<tr>
<td>J. van den Diessel</td>
<td>Department of Immunopathology, Sanquin Research and Landsteiner Laboratory, Amsterdam UMC, the Netherlands</td>
<td>Site investigator</td>
<td>Site investigator</td>
</tr>
<tr>
<td>C. Kreher</td>
<td>Department of Immunopathology, Sanquin Research and Landsteiner Laboratory, Amsterdam UMC, the Netherlands</td>
<td>Site investigator</td>
<td>Site investigator</td>
</tr>
<tr>
<td>A. Bos</td>
<td>Department of Immunopathology, Sanquin Research and Landsteiner Laboratory, Amsterdam UMC, the Netherlands</td>
<td>Site investigator</td>
<td>Site investigator</td>
</tr>
<tr>
<td>S. Keijzer</td>
<td>Department of Immunopathology, Sanquin Research and Landsteiner Laboratory, Amsterdam UMC, the Netherlands</td>
<td>Site investigator</td>
<td>Site investigator</td>
</tr>
<tr>
<td>Boogaard</td>
<td>Department of Immunopathology, Sanquin Research and Landsteiner Laboratory, Amsterdam UMC, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
</tr>
<tr>
<td>J. Keijzer</td>
<td>Department of Immunopathology, Sanquin Research and Landsteiner Laboratory, Amsterdam UMC, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
</tr>
<tr>
<td>O. Christianawati</td>
<td>Department of Immunopathology, Sanquin Research and Landsteiner Laboratory, Amsterdam UMC, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
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<tr>
<td>A.E. Voskuyl</td>
<td>Amsterdam Rheumatology and Immunology Center, VU University Medical Center, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
</tr>
<tr>
<td>B. Broens</td>
<td>Amsterdam Rheumatology and Immunology Center, VU University Medical Center, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
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<tr>
<td>A.R. Parrasanchez</td>
<td>Amsterdam Rheumatology and Immunology Center, VU University Medical Center, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
</tr>
<tr>
<td>A. Rutgers</td>
<td>Department of Rheumatology and Clinical Immunology, University Medical Center Groningen, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
</tr>
<tr>
<td>K. de Leeuw</td>
<td>Department of Rheumatology and Clinical Immunology, University Medical Center Groningen, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
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<tr>
<td>B. Horvath</td>
<td>Department of Dermatology, Center for Blistering Diseases, University Medical Center Groningen, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
</tr>
<tr>
<td>J.J.G.M. Verschuuren</td>
<td>Department of Neurology, Leiden University Medical Center, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
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<tr>
<td>A.M. de Ruiter</td>
<td>Department of Neurology, Leiden University Medical Center, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
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<tr>
<td>L. van Oouwerkerk</td>
<td>Department of Rheumatology, Leiden University Medical Center, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
</tr>
<tr>
<td>D. van der Woude</td>
<td>Department of Rheumatology, Leiden University Medical Center, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
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<tr>
<td>C.F. Allaart</td>
<td>Department of Rheumatology, Leiden University Medical Center, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
</tr>
<tr>
<td>Y.K.O. Teng</td>
<td>Centre of Expertise for Lupus, Vascularitis- and Complement-Mediated Systemic Diseases, Department of Nephrology, Leiden, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
</tr>
<tr>
<td>P. van Paassen</td>
<td>Department of Nephrology and Clinical Immunology, Maastricht University Medical Center, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
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Appendix 2 (continued)

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<th>Name</th>
<th>Location</th>
<th>Role</th>
<th>Contribution</th>
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<tr>
<td>M.H. Busch</td>
<td>Department of Nephrology and Clinical Immunology, Maastricht University Medical Center, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
</tr>
<tr>
<td>P.B. Jallah</td>
<td>Department of Nephrology and Clinical Immunology, Maastricht University Medical Center, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
</tr>
<tr>
<td>E. Brusse</td>
<td>Department of Neurology, Erasmus MC University Medical Center, Rotterdam, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
</tr>
<tr>
<td>P.A. van Doorn</td>
<td>Department of Neurology, Erasmus MC University Medical Center, Rotterdam, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
</tr>
<tr>
<td>A. Baars</td>
<td>Department of Neurology, Erasmus MC University Medical Center, Rotterdam, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
</tr>
<tr>
<td>D. Hijnen</td>
<td>Department of Dermatology, Erasmus MC University Medical Center, Rotterdam, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
</tr>
<tr>
<td>C.R.G. Schreurs</td>
<td>Department of Dermatology, Erasmus MC University Medical Center, Rotterdam, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
</tr>
<tr>
<td>W.L. van der Pol</td>
<td>Brain Center UMC Utrecht, Department of Neurology and Neurosurgery, Utrecht, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
</tr>
<tr>
<td>H.S. Goedee</td>
<td>Brain Center UMC Utrecht, Department of Neurology and Neurosurgery, Utrecht, the Netherlands</td>
<td>Site investigator</td>
<td>Recruitment of patients</td>
</tr>
<tr>
<td>J. de Wit</td>
<td>Centre for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands</td>
<td>Site investigator</td>
<td>Site investigator</td>
</tr>
<tr>
<td>A.C.M. van Els</td>
<td>Centre for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands</td>
<td>Site investigator</td>
<td>Site investigator</td>
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References

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Virginia Palomares Cabeza, Laura Y.L. Kummer, Luuk Wieske, et al.
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