

# Decrease of natalizumab drug levels after switching from intravenous to subcutaneous administration in patients with multiple sclerosis

Alyssa A Toorop <sup>1</sup>, Zoé L E van Kempen <sup>1</sup>, Maurice Steenhuis,<sup>2</sup> Jessica Nielsen,<sup>3</sup> L G F Sinnige,<sup>4</sup> Gert van Dijk,<sup>5</sup> Christiaan M Roosendaal <sup>6</sup>, Edo P J Arnoldus,<sup>7</sup> Elske Hoitsma,<sup>8</sup> Birgit I Lissenberg-Witte,<sup>9</sup> Brigit A de Jong,<sup>1</sup> Bob W van Oosten,<sup>1</sup> Eva M M Strijbis <sup>1</sup>, Bernard M J Uitdehaag,<sup>1</sup> Theo Rispens,<sup>2,10</sup> Joep Killestein,<sup>1</sup> On behalf of the NEXT-MS study group

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/jnnp-2022-330467>).

For numbered affiliations see end of article.

## Correspondence to

Alyssa A Toorop, Department of Neurology, Amsterdam UMC Locatie VUmc, 1081 HV Amsterdam, Noord-Holland, The Netherlands; a.toorop@amsterdamumc.nl

Received 27 September 2022  
Accepted 4 January 2023  
Published Online First 13 January 2023

## ABSTRACT

**Background** Natalizumab is effective in the treatment of multiple sclerosis (MS). In 2021, the European Medicines Agency approved the subcutaneous (SC) variant of natalizumab which can be used instead of intravenous administration. However, the course of drug levels varies between administration routes, and the Food and Drug Administration rejected the request for approval of natalizumab SC for reasons that were not disclosed. Our objective was to evaluate the course of natalizumab trough drug levels in patients who switched from natalizumab intravenous to SC on various treatment intervals.

**Methods** The NEXT-MS trial (N=382) investigates personalised treatment of natalizumab, in which infusion intervals are prolonged based on individual natalizumab trough drug levels. In 2021, an amendment was approved allowing participants to switch from intravenous to SC administration with frequent measurements of natalizumab drug levels and antidrug antibodies (ADAs). Results were compared with linear mixed model analyses.

**Results** Until December 2022, 15 participants switched to SC natalizumab. Natalizumab drug levels with SC administration were on average 55% lower compared with intravenous administration (Exp (estimate) 0.45, 95% CI 0.39 to 0.53,  $p < 0.001$ ), leading to very low trough drug levels in three patients on extended treatment intervals. No natalizumab ADAs were detected during intravenous or SC treatment. None of the participants on natalizumab SC showed evidence of MS disease activity.

**Conclusions** Natalizumab trough drug levels can decrease after switching from natalizumab intravenous to SC administration. We advise to monitor trough drug levels in patients with low natalizumab drug levels during intravenous treatment, patients with higher body mass index or patients on extended treatment intervals who switch to SC administration of natalizumab.

## INTRODUCTION

Natalizumab, a monoclonal antibody used in relapsing remitting multiple sclerosis (MS), reduces inflammation within the central nervous system by

preventing migration of lymphocytes across the blood–brain barrier.<sup>1</sup> In 2006, intravenous natalizumab was approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) in a treatment regimen of 300 mg every 4 weeks. With intravenous administration, natalizumab trough levels are highly variable between patients, while intraindividual trough levels are usually stable.<sup>2</sup> In 2021, the EMA approved the subcutaneous (SC) variant of natalizumab (300 mg every 4 weeks). Trough drug levels prior to redosing were similar between intravenous and SC natalizumab in the DELIVER trial.<sup>3</sup> However, the course of serum natalizumab drug levels, and consequently receptor saturation on lymphocytes, may differ between intravenous and SC administration.<sup>3</sup> The FDA rejected the request for approval of natalizumab SC for reasons that were not disclosed but could be related to insufficient data on pharmacokinetics.

In recent years, extended interval dosing of natalizumab, in which the treatment interval of 4 weeks is prolonged, has gained popularity as this leads to a decreased risk of progressive multifocal leukoencephalopathy.<sup>4</sup> Both retrospective<sup>5–6</sup> and prospective<sup>7–8</sup> studies showed similar efficacy between natalizumab standard interval dosing (4 weeks interval) and extended interval dosing (5–8 weeks interval). When applying extended dosing, it is of importance that natalizumab trough drug levels are maintained above approximately 1–2 µg/mL, as  $\alpha 4$ -integrin receptor desaturation can occur when trough drug levels fall below 1–2 µg/mL, which can lead to rebound disease activity.<sup>9–10</sup> In the PDNMS trial, natalizumab treatment intervals were personalised based on individual natalizumab trough drug levels in 61 patients.<sup>8</sup> In the ongoing follow-up study, the NEXT-MS trial (ClinicalTrials.gov identifier NCT04225312), personalised treatment of natalizumab is studied in a larger group. Since the approval of SC natalizumab, participants in the NEXT-MS trial can switch from natalizumab intravenous to SC administration.

As there is insufficient data regarding the influence of natalizumab SC on drug levels when switching from intravenous to SC administration,



© Author(s) (or their employer(s)) 2023. No commercial re-use. See rights and permissions. Published by BMJ.

**To cite:** Toorop AA, van Kempen ZL, Steenhuis M, et al. *J Neurol Neurosurg Psychiatry* 2023;**94**:482–486.

especially in extended dosing, we share preliminary data on pharmacokinetics of participants of the NEXT-MS trial who switched from intravenous to SC administration of natalizumab.

## METHODS

### Study protocol

The NEXT-MS trial is an ongoing investigator-initiated multi-centre prospective open-label non-randomised trial (ClinicalTrials.gov identifier NCT04225312) studying personalised intravenous natalizumab treatment (300 mg) in which infusion intervals are adjusted based on individual natalizumab trough drug levels. Patients can participate in three groups: standard interval dosing, extended interval dosing with an aim trough concentration of 10 µg/mL (EID10), and extended interval dosing with a lower aim trough concentration of 5 µg/mL (EID5). Adult patients with MS who received ≥6 natalizumab infusions are included. Trough drug levels are monitored every 1–6 months during extended dosing (more frequent during start of personalised dosing). Treatment intervals are shortened when trough drug levels are <2 µg/mL. In June 2021, an amendment was approved allowing participants to switch to natalizumab SC (300 mg) on their current treatment interval with measurements of natalizumab trough drug levels prior to every injection and natalizumab antidrug antibodies (ADAs) after switching from intravenous to SC. Natalizumab SC was administered by trained healthcare professionals within the participating hospitals of the NEXT-MS trial. Administration was recorded in the electronic patient files. All participants who switched to natalizumab SC until December 2022 with a minimum of one available follow-up blood sample after the switch are described here. Blood samples were analysed centrally at Sanquin Laboratory Amsterdam for measurement of natalizumab drug concentrations and ADA. A cross-linking assay using polyclonal rabbit antinatalizumab fragments and mouse anti-IgG<sub>4</sub> monoclonal antibodies for detection were used as previously reported.<sup>11</sup>

### Statistical analyses

Descriptive data are presented as means with SD, medians with IQR or frequencies with percentages. Natalizumab trough drug levels during intravenous and SC administration were compared using linear mixed effect models, with fixed effect for administration and treatment interval, and random effect for subjects. Ln-transformation was applied to natalizumab drug levels. All statistical analyses were conducted with SPSS statistic software V.28.0 (IBM). Figures were designed in GraphPad Prism V.9.3.1 for Windows (GraphPad software, San Diego, California USA). A p<0.05 was considered statistically significant.

## RESULTS

### Baseline characteristics

Until December 2022, 382 patients were included in the NEXT-MS trial of whom 317 received personalised treatment. Fifteen participants switched from natalizumab intravenous to SC administration with a minimum of one available follow-up blood sample. The main reason for switching to SC administration was difficulty with obtaining intravenous access. Median duration of follow-up after switching to SC administration until last blood sample collection or last available MRI was 6.9 months (IQR 5.0–10.4 months). Patient characteristics and data on natalizumab trough drug levels are described in [table 1](#) and [figure 1](#).

### Natalizumab trough drug levels, ADAs and MS disease activity after switching to natalizumab SC

Natalizumab trough drug levels of 12 out of 15 participants switching from natalizumab intravenous to SC were lower after switching (case 1–5, 7–9, 11, 13–15), resulting in a shorter treatment interval in three participants (case 1, 3 and 4) when trough drug levels were <2 µg/mL ([figure 1](#)). When

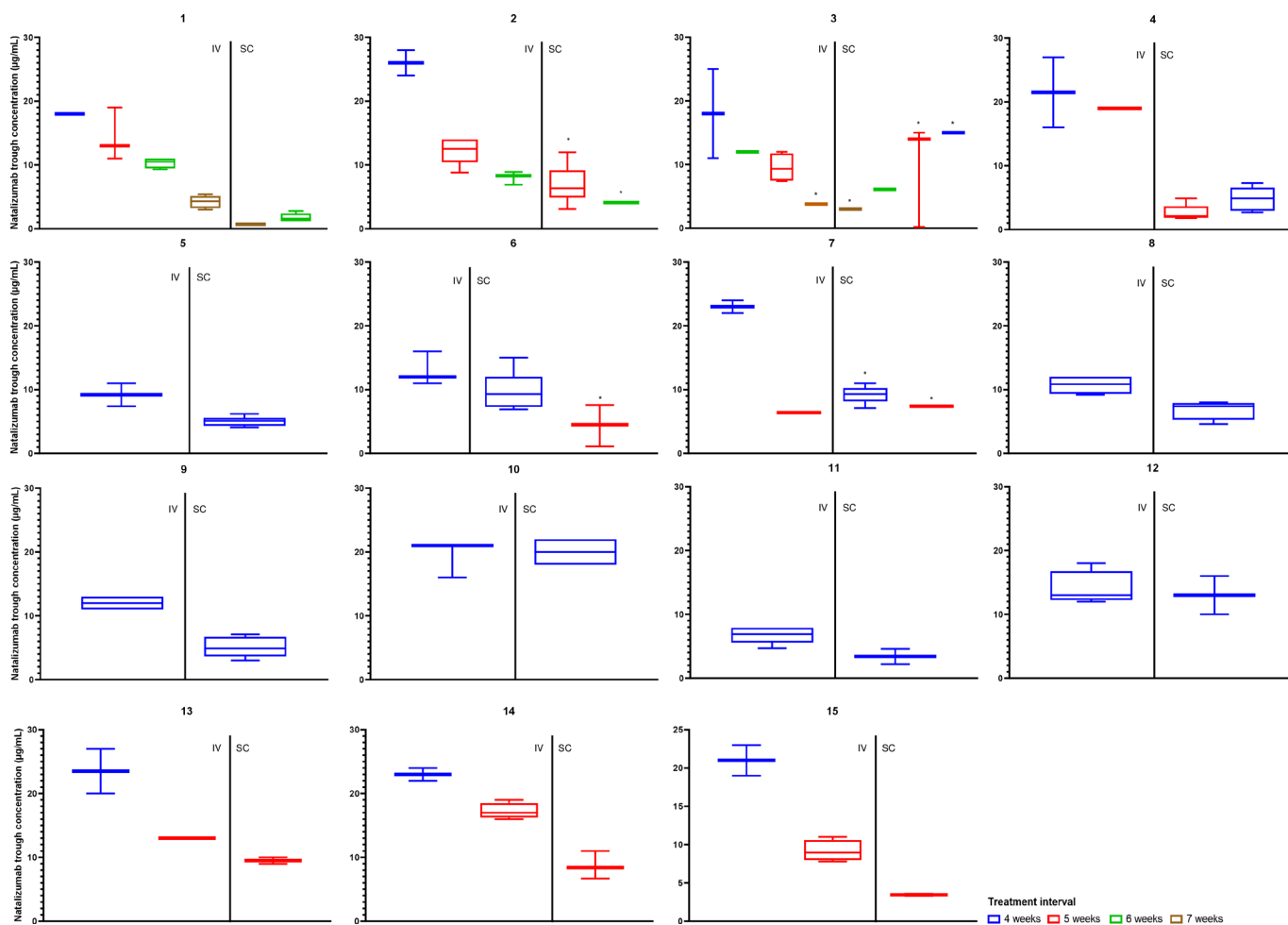
**Table 1** Patient characteristics, study groups and natalizumab ADAs

| Case | BMI (kg/m <sup>2</sup> ) | Duration intravenous treatment (mo) | Duration in study (mo) | Study group | Duration SC treatment (mo) | Duration of radiological FU (mo) | NTZ ADA (intravenous) | NTZ ADA (SC) |
|------|--------------------------|-------------------------------------|------------------------|-------------|----------------------------|----------------------------------|-----------------------|--------------|
| 1    | 33.1                     | 30.1                                | 20.2                   | EID5        | 11.3                       | 9.9                              | <11                   | <11          |
| 2    | 27.4                     | 40.1                                | 16.0                   | EID5        | 10.6                       | 8.0                              | <11                   | <11          |
| 3    | 27.2                     | 17.7                                | 8.9                    | EID5        | 7.4                        | 6.9                              | <11                   | <11          |
| 4    | 30.3                     | 84.1                                | 2.1                    | EID10       | 13.2                       | 13.2                             | <11                   | <11          |
| 5    | 38.1                     | 20.6                                | 2.8                    | EID10       | 10.1                       | 10.1                             | <11                   | <11          |
| 6    | 25.6                     | 11.0                                | 2.7                    | EID10       | 11.8                       | 7.1                              | <11                   | <11          |
| 7    | 32.4                     | 56.7                                | 4.7                    | EID10       | 6.9                        | 5.2                              | <11                   | <11          |
| 8    | 41.6                     | 63.9                                | 16.8                   | EID10       | 5.5                        | NA                               | <11                   | <11          |
| 9    | 33.8                     | 76.4                                | 10.1                   | EID10       | 5.5                        | 1.1                              | <11                   | <11          |
| 10   | 28.3                     | 90.3                                | 20.1                   | SID         | 9.2                        | 5.1                              | <11                   | <11          |
| 11   | 25.0                     | 101.1                               | 17.2                   | EID10       | 5.5                        | 5.5                              | <11                   | <11          |
| 12   | 20.4                     | 91.7                                | 10.3                   | EID10       | 4.6                        | NA                               | <11                   | <11          |
| 13   | 27.4                     | 15.2                                | 6.0                    | EID10       | 3.6                        | NA                               | <11                   | <11          |
| 14   | 24.2                     | 120.7                               | 12.9                   | EID10       | 4.2                        | 4.2                              | <11                   | <11          |
| 15   | 37.3                     | 72.1                                | 13.8                   | EID10       | 2.3                        | NA                               | <11                   | <11          |

BMI was recorded at baseline of the NEXT-MS trial. Duration intravenous treatment and duration in NEXT-MS trial were calculated until switching to SC administration. Duration of SC treatment was calculated between start of SC treatment and last blood sample collection or last available MRI scan after switching to SC administration. Duration of radiological FU was calculated between start of natalizumab SC and the last available MRI scan after switching to SC administration (median FU 6.9 months, IQR 5.1–9.0 months). Natalizumab ADAs (AE/mL) during intravenous treatment were measured once at baseline of the NEXT-MS trial (<11 AE/mL represents undetectable ADAs). Natalizumab ADAs during SC treatment were measured prior to SC administration on various time points (case 1: +19 wks and +31 wks; case 2: +10 wks, +25 wks, +31 wks and +37.4 wks; case 3: +7 wks +12.7 wks and +18 wks; case 4: +10 wks, +19.1 wks, +23 wks and +27 wks; case 5: +12 wks, +16 wks and +20 wks; case 6: +4 wks, +8.4 wks and +16.3 wks; case 7: +4.1 wks, +8.7 wks, +13.0 wks, +17.7 wks and +22 wks; case 8: +4 wks and +8 wks; case 9: +4 wks and +8 wks; case 10: +12 wks; case 11: +4.1 wks, +20.0 wks; case 12: +8.1 wks, +20.0 wks; case 13: +5.6 wks, +10.4 wks, +15.6 wks; case 14: +10.1 wks, +15.0 wks; case 15: +5 wks, +10.1 wks).

ADAs, anti drug antibodies; BMI, body mass index; EID5, aim trough drug level of 5 µg/mL; EID, extended interval dosing; EID10, aim trough drug level of 10 µg/mL; FU, follow-up; mo, months; NA, not available; NTZ, natalizumab; SC, subcutaneous; SID, standard interval dosing; wks, weeks.

## Multiple sclerosis



**Figure 1** Natalizumab trough drug levels ( $\mu\text{g/mL}$ ) under intravenous and SC administration per participant. Boxplots represent median natalizumab trough drug levels with minimum and maximum concentrations (1–9 samples per boxplot). Colours represent treatment intervals during natalizumab treatment before and after switching to natalizumab SC. Treatment intervals during administration were extended after two measurements on standard interval dosing according to the NEXT-MS trial protocol. Natalizumab concentrations were lower in 12/15 participants after the switch (case 1–5, 7–9, 11, 13–15). \*Adjusted treatment intervals (protocol deviations): case 2: preferred 5 weeks interval during SC treatment and one-time 6 weeks interval due to patient factors; case 3: two-time 7 weeks interval (urinary tract infection and patient factors) and one-time 5 weeks interval due to patient factors with very low drug levels ( $<0.2 \mu\text{g/mL}$ ) with a shortened treatment interval to 4 weeks and 5 weeks thereafter according to the NEXT-MS trial protocol; case 6: three-time 5 weeks interval due to patient factors, illness and herpes labialis; case 7: preferred 4 weeks interval during SC treatment and one-time 5 weeks interval due to patient factors. MS, multiple sclerosis; SC, subcutaneous.

comparing natalizumab trough drug levels between intravenous and SC administration, with treatment interval included as a covariate, natalizumab drug levels with SC administration were on average 55% lower compared with intravenous administration (Exp (estimate) 0.45, 95% CI 0.39 to 0.53,  $p < 0.001$ ). No natalizumab ADAs were detected in any of the participants on natalizumab SC. So far, none of the participants on natalizumab SC showed evidence of radiological or clinical disease activity (table 1).

### DISCUSSION

In our study, trough drug levels of natalizumab decreased after switching to SC administration with a similar dose of 300 mg, leading to very low trough drug levels in three patients. As most natalizumab-treated patients still have high drug levels prior to redosing,<sup>2</sup> switching to SC administration will not lead to subtherapeutic natalizumab levels in the majority of patients. However, in patients with low natalizumab trough drug levels during intravenous treatment, patients on

extended treatment intervals, or patients with higher body mass index (BMI) as higher BMI is associated with lower drug concentrations,<sup>12</sup> a switch from intravenous to SC administration could lead to subtherapeutic natalizumab concentrations and could possibly lead to rebound disease activity.

So far, none of the participants on natalizumab SC in our study showed evidence of radiological or clinical disease activity. In compliance with the study protocol of the NEXT-MS trial, treatment intervals were shortened in our cohort when trough drug levels fell below  $2 \mu\text{g/mL}$  (cases 1, 3 and 4). It was therefore expected that there was no return of disease activity, as adequate  $\alpha 4$ -integrin receptor saturation is preserved when the treatment interval is adjusted based on trough drug levels.<sup>10</sup>

So far, data on pharmacokinetics of natalizumab SC is described in two trials.<sup>3 13</sup> The DELIVER trial studied natalizumab pharmacokinetics and pharmacodynamics of intramuscular, SC and intravenous administration of natalizumab every 4 weeks in natalizumab-naïve patients.<sup>3</sup> In this trial, the

bioavailability of natalizumab SC was 57%–71% compared with intravenous administration with lower peak serum drug levels (40%).<sup>3</sup> Trough drug levels were 19–40 µg/mL after intravenous administration and 13–34 µg/mL after SC administration.<sup>3</sup> The REFINE trial studied clinically stable patients with relapsing remitting MS switching from intravenous to SC administration of either 300 mg every 4 or 12 weeks, or 150 mg every 4 or 12 weeks.<sup>13</sup> Similar natalizumab trough drug concentrations between SC and intravenous administration were reported with treatment every 4 weeks.<sup>13</sup> However, in both the DELIVER and REFINE trial, natalizumab drug levels were only reported on a group level and not compared intraindividually when switching from intravenous to SC (REFINE trial). Furthermore, in the figures presented in both trials, there seems to be a trend towards lower drug concentrations in the SC study groups compared with the intravenous study groups.<sup>3,13</sup> As the FDA has rejected the request for approval of natalizumab SC, it would be of interest if more data on pharmacokinetics of both studies were disclosed. Currently, another prospective trial on natalizumab SC in standard and extended treatment intervals is ongoing (ClinicalTrials.gov NCT04225312). Hopefully, extensive data on pharmacokinetics and pharmacodynamics will be shared to further clarify the efficacy of SC natalizumab.

Strengths of this study include longitudinal measurements of natalizumab trough drug levels and ADA of individual patients on standard and extended treatment intervals after switching to natalizumab SC in a prospective clinical trial setting. Limitations include intraindividual variations in treatment intervals, short follow-up and low number of cases.

In conclusion, in our cohort of 15 patients switching from intravenous to SC administration, natalizumab trough drug levels decreased in 12 patients. We advise to monitor trough drug levels in patients with low natalizumab drug levels during intravenous treatment, patients with higher BMI or patients on extended treatment intervals who switch to SC administration. Additional longitudinal pharmacokinetic data of SC natalizumab in standard and extended interval dosing regimens are essential.

#### Author affiliations

<sup>1</sup>Department of Neurology, MS Center Amsterdam, Amsterdam UMC Location VUMC, Amsterdam, The Netherlands

<sup>2</sup>Biologics Laboratory, Department of Immunopathology, Sanquin Diagnostic Services, Amsterdam, The Netherlands

<sup>3</sup>Department of Neurology, Ommelander Hospital Groningen, Scheemda, The Netherlands

<sup>4</sup>Department of Neurology, Medical Centre Leeuwarden, Leeuwarden, The Netherlands

<sup>5</sup>Department of Neurology, Canisius Wilhelmina Hospital, Nijmegen, The Netherlands

<sup>6</sup>Department of Neurology, Slingeland Hospital, Doetinchem, The Netherlands

<sup>7</sup>Department of Neurology, Elisabeth-TweeSteden Hospital, Tilburg, The Netherlands

<sup>8</sup>Department of Neurology, Alrijne Hospital, Leiden, The Netherlands

<sup>9</sup>Department of Epidemiology and Data Science, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

<sup>10</sup>Landsteiner Laboratory, Amsterdam UMC Location AMC, Amsterdam, The Netherlands

**Twitter** Eva M M Strijbis @Eef111

**Collaborators** NEXT-MS study group: E.P.J. Arnoldus (Department of Neurology, Elisabeth TweeSteden Hospital, Tilburg, The Netherlands), F. Barkhof (Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam Neuroscience, MS Center Amsterdam, Amsterdam, The Netherlands; Queen Square MS Center, Department of Neuroinflammation, UCL Institute of Neurology, Faculty of Brain Sciences, University College London, UK; and National Institute for Health Research (NIHR) University College London Hospitals (UCLH) Biomedical Research Center, London, UK), W.H. Bouvy (Department of Neurology, Diaconessenhuis Hospital, Utrecht,

The Netherlands), G.W. van Dijk (Department of Neurology, Canisius Wilhelmina Hospital, Nijmegen, The Netherlands), J.J.J. van Eijk (Department of Neurology, Jeroen Bosch Hospital, 's Hertogenbosch, The Netherlands), M. Eurelings (Department of Neurology, Spaarne Gasthuis, Haarlem, The Netherlands), J. van Genugten (Department of Neurology, Ziekenhuisgroep Twente Hospital, Hengelo, The Netherlands), E. Hoitsma (Department of Neurology, MS Center Alrijne Hospital, Leiden, The Netherlands), E.L.J. Hoogervorst (Department of Neurology, St Antonius Hospital, Utrecht, The Netherlands), B.A. de Jong (Department of Neurology, MS Center Amsterdam, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam Neuroscience, Amsterdam, The Netherlands), N.F. Kalkers (Department of Neurology, OLVG, Amsterdam, The Netherlands), Z.L.E. van Kempen (Department of Neurology, MS Center Amsterdam, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam Neuroscience, Amsterdam, The Netherlands), J. Killestein (Department of Neurology, MS Center Amsterdam, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam Neuroscience, Amsterdam, The Netherlands), M.E. Kloosterziel (Department of Neurology, Wilhelmina Hospital, Assen, The Netherlands), J.J. Kragt (Department of Neurology, Reinier de Graaf Hospital, Delft, The Netherlands), Z.Y.G.J. van Lierop (Department of Neurology, MS Center Amsterdam, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam Neuroscience, Amsterdam, The Netherlands), B.I. Lissenberg-Witte (Department of Epidemiology and Data Science, Amsterdam. University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands), B. Moraal (Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam Neuroscience, MS Center Amsterdam, Amsterdam, The Netherlands), J.P. Mostert (Department of Neurology, Rijnstate Hospital, Arnhem, The Netherlands), C.E.P. van Munster (Department of Neurology, Amphia, Breda, The Netherlands), J. Nielsen (Department of Neurology, Ommelander Hospital, Scheemda, The Netherlands), B.W. van Oosten (Department of Neurology, MS Center Amsterdam, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam Neuroscience, Amsterdam, The Netherlands), T. Rispens (Department of Immunopathology, Sanquin Research, Amsterdam, The Netherlands, and Landsteiner Laboratory, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; Biologics Laboratory, Sanquin Diagnostic Services, Amsterdam, The Netherlands), L.C. van Rooij (Department of Neurology, Maasstad Hospital, Rotterdam, The Netherlands), C.M. Roosendaal (Department of Neurology, Slingeland Hospital, Doetinchem, The Netherlands), L.G.F. Sinnige (Department of Neurology, Medisch Centrum Leeuwarden, Leeuwarden, The Netherlands), E.M.M. Strijbis (Department of Neurology, MS Center Amsterdam, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam Neuroscience, Amsterdam, The Netherlands), A.A. Toorop (Department of Neurology, MS Center Amsterdam, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam Neuroscience, Amsterdam, The Netherlands), B.M.J. Uitdehaag (Department of Neurology, MS Center Amsterdam, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam Neuroscience, Amsterdam, The Netherlands), A. Vennegoor (Department of Neurology, Flevoziekenhuis, Almere The Netherlands), B.H.A. Wokke (Department of Neurology, ErasMS, Erasmus Medical Center, Rotterdam, The Netherlands), E.M.P.E. Zeinstra (Department of Neurology, Isala, Meppel, The Netherlands).

**Contributors** AAT: design and conceptualised study; major role in acquisition of data; analysed and interpreted the data; drafted and revised the manuscript for intellectual content; had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. ZLEVK: design and conceptualised study; interpreted the data; drafted and revised the manuscript for intellectual content. MS: laboratory analyses; interpreted the data; revised the manuscript for intellectual content. JN: major role in acquisition of data; interpreted the data; revised the manuscript for intellectual content. LGFS: major role in acquisition of data; interpreted the data; revised the manuscript for intellectual content. GvD: major role in acquisition of data; interpreted the data; revised the manuscript for intellectual content. CMR: major role in acquisition of data; interpreted the data; revised the manuscript for intellectual content. EPJA: major role in acquisition of data; interpreted the data; revised the manuscript for intellectual content. EH: major role in acquisition of data; interpreted the data; revised the manuscript for intellectual content. BIL-W: analysed and interpreted the data; revised the manuscript for intellectual content. BADJ: interpreted the data; revised the manuscript for intellectual content. BvO: interpreted the data; revised the manuscript for intellectual content. EMS: interpreted the data; revised the manuscript for intellectual content. BMJU: interpreted the data; revised the manuscript for intellectual content. TR: laboratory analyses; interpreted the data; revised the manuscript for intellectual content. JK: design and conceptualised study; interpreted the data; drafted and revised the manuscript for intellectual content.

**Funding** The NEXT-MS study was kindly funded by the Dutch MS Research Foundation (18-1030), the Brain Foundation Netherlands (HA2015.01.05) and Innovation Funds Healthcare insurers (B 18-313/File 3.798).

**Disclaimer** The funding sources had no further involvement in the study.

**Competing interests** AAT: nothing to disclose. ZLEVK: nothing to disclose. MS: nothing to disclose. JN: nothing to disclose. LGFS: nothing to disclose. GvD: nothing to disclose.

to disclose. CMR: nothing to disclose. EPJA: nothing to disclose. EH: has accepted (speaker and congress) fees from Merck Serono, Biogen Idec, Roche, Novartis, Teva and Sanofi Genzyme. BIL-W: nothing to disclose. BADJ: nothing to disclose. BvO: nothing to disclose. EMS: nothing to disclose. BMJU: received research support and/or consultancy fees from Biogen Idec, Genzyme, Merck Serono, Novartis, Roche, Teva and Immunic Therapeutics. TR: received funding for research from Genmb; received consulting fees from Novartis. JK: received research grants for multicentre investigator initiated trials DOT-MS trial, ClinicalTrials.gov Identifier: NCT04260711 (ZonMW) and BLOOMS trial (ZonMW and Treatmeds), ClinicalTrials.gov Identifier: NCT05296161; received consulting fees for F. Hoffmann-La Roche, Biogen, Teva, Merck, Novartis and Sanofi/Genzyme (all payments to institution); reports speaker relationships with F. Hoffmann-La Roche, Biogen, Immunic, Teva, Merck, Novartis and Sanofi/Genzyme (all payments to institution); adjudication committee of MS clinical trial of Immunic (payments to institution only).

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and was approved by VUMC Ethics committee number 2019.552. Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Research data will be shared anonymously on reasonable request from any qualified investigator.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

#### ORCID iDs

Alyssa A Toorop <http://orcid.org/0000-0002-7196-9826>

Zoé L E van Kempen <http://orcid.org/0000-0001-9557-5381>

Christiaan M Roosendaal <http://orcid.org/0000-0001-7998-5225>

Eva M M Srijbis <http://orcid.org/0000-0001-6705-5864>

#### REFERENCES

- Polman CH, O'Connor PW, Havrdova E, *et al.* A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006;354:899–910.
- van Kempen ZLE, Leurs CE, Witte BI, *et al.* The majority of natalizumab-treated MS patients have high natalizumab concentrations at time of re-dosing. *Mult Scler* 2018;24:805–10.
- Plavina T, Fox EJ, Lucas N, *et al.* A randomized trial evaluating various administration routes of natalizumab in multiple sclerosis. *J Clin Pharmacol* 2016;56:1254–62.
- Ryerson LZ, Foley J, Chang I, *et al.* Risk of natalizumab-associated PML in patients with MS is reduced with extended interval dosing. *Neurology* 2019;93:10.1212/WNL.0000000000008243–62.
- Yamout BI, Sahraian MA, Ayoubi NE, *et al.* Efficacy and safety of natalizumab extended interval dosing. *Mult Scler Relat Disord* 2018;24:113–6.
- Bomprezzi R, Pawate S. Extended interval dosing of natalizumab: a two-center, 7-year experience. *Ther Adv Neurol Disord* 2014;7:227–31.
- Foley JF, Defer G, Ryerson LZ, *et al.* Comparison of switching to 6-week dosing of natalizumab versus continuing with 4-week dosing in patients with relapsing-remitting multiple sclerosis (nova): a randomised, controlled, open-label, phase 3B trial. *Lancet Neurol* 2022;21:608–19.
- van Kempen ZLE, Hoogervorst ELJ, Wattjes MP, *et al.* Personalized extended interval dosing of natalizumab in MS: a prospective multicenter trial. *Neurology* 2020;95:e745–54.
- Derfuss T, Kovarik JM, Kappos L, *et al.*  $\alpha$ 4-integrin receptor desaturation and disease activity return after natalizumab cessation. *Neurol Neuroimmunol Neuroinflamm* 2017;4:e388.
- van Kempen ZLE, Toorop AA, Sellebjerg F, *et al.* Extended dosing of monoclonal antibodies in multiple sclerosis. *Mult Scler* 2022;28:2001–9.
- Rispens T, Leeuwen Avan, Vennegoor A, *et al.* Measurement of serum levels of natalizumab, an immunoglobulin G4 therapeutic monoclonal antibody. *Anal Biochem* 2011;411:271–6.
- Zhovtis Ryerson L, Li X, Goldberg JD, *et al.* Pharmacodynamics of natalizumab extended interval dosing in MS. *Neurology - Neuroimmunology Neuroinflammation* 2020;7:e672.
- Trojano M, Ramió-Torrentà L, Grimaldi LM, *et al.* A randomized study of natalizumab dosing regimens for relapsing-remitting multiple sclerosis. *Mult Scler* 2021;27:2240–53.

## Supplementary appendix

### The NEXT-MS study group:

| <b>Name</b>        | <b>Affiliation</b>  |
|--------------------|---|
| E.P.J. Arnoldus    | Department of Neurology, Elisabeth TweeSteden Hospital, Tilburg, The Netherlands  |
| F. Barkhof         | Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam Neuroscience, MS Center Amsterdam, Amsterdam, the Netherlands; Queen Square MS Center, Department of Neuroinflammation, UCL Institute of Neurology, Faculty of Brain Sciences, University College London, UK; and National Institute for Health Research (NIHR) University College London Hospitals (UCLH) Biomedical Research Center, London, UK |
| W.H. Bouvy         | Department of Neurology, Diakonessenhuis Hospital, Utrecht, The Netherlands   |
| G.W. van Dijk      | Department of Neurology, Canisius Wilhelmina Hospital, Nijmegen, The Netherlands  |
| J.J.J. van Eijk    | Department of Neurology, Jeroen Bosch Hospital, 's Hertogenbosch, The Netherlands   |
| M. Eurelings       | Department of Neurology, Spaarne Gasthuis, Haarlem, The Netherlands   |
| J. van Genugten    | Department of Neurology, Ziekenhuisgroep Twente Hospital, Hengelo, The Netherlands  |
| E. Hoitsma         | Department of Neurology, MS Center Alrijne Hospital, Leiden, The Netherlands  |
| E.L.J. Hoogervorst | Department of Neurology, St Antonius Hospital, Utrecht, The Netherlands   |
| B.A. de Jong       | Department of Neurology, MS Center Amsterdam, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam Neuroscience, Amsterdam, The Netherlands  |
| N.F. Kalkers       | Department of Neurology, OLVG, Amsterdam, The Netherlands   |
| Z.L.E. van Kempen  | Department of Neurology, MS Center Amsterdam, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam Neuroscience, Amsterdam, The Netherlands  |

|                       |  |
|-----------------------|--|
| J. Killestein         | Department of Neurology, MS Center Amsterdam, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam Neuroscience, Amsterdam, The Netherlands   |
| M.E. Kloosterziel     | Department of Neurology, Wilhelmina Hospital, Assen, The Netherlands   |
| J.J. Kragt            | Department of Neurology, Reinier de Graaf Hospital, Delft, The Netherlands   |
| Z.Y.G.J. van Lierop   | Department of Neurology, MS Center Amsterdam, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam Neuroscience, Amsterdam, The Netherlands   |
| B.I. Lissenberg-Witte | Department of Epidemiology and Data Science, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands  |
| B. Moraal             | Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam Neuroscience, MS Center Amsterdam, Amsterdam, the Netherlands.   |
| J.P. Mostert          | Department of Neurology, Rijnstate Hospital, Arnhem, The Netherlands   |
| C.E.P. van Munster    | Department of Neurology, Amphia, Breda, The Netherlands  |
| J. Nielsen            | Department of Neurology, Ommelander Hospital, Scheemda, The Netherlands  |
| B.W. van Oosten       | Department of Neurology, MS Center Amsterdam, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam Neuroscience, Amsterdam, The Netherlands   |
| T. Rispens            | Department of Immunopathology, Sanquin Research, Amsterdam, The Netherlands, and Landsteiner Laboratory, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; Biologics Laboratory, Sanquin Diagnostic Services, Amsterdam, The Netherlands |
| L.C. van Rooij        | Department of Neurology, Maasstad Hospital, Rotterdam, The Netherlands   |
| C.M. Rosendaal        | Department of Neurology, Slingeland Hospital, Doetinchem, The Netherlands  |
| L.G.F. Sinnige        | Department of Neurology, Medisch Centrum Leeuwarden, Leeuwarden, The Netherlands   |

|                   |  |
|-------------------|--|
| E.M.M. Strijbis   | Department of Neurology, MS Center Amsterdam, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam Neuroscience, Amsterdam, The Netherlands |
| A.A. Toorop       | Department of Neurology, MS Center Amsterdam, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam Neuroscience, Amsterdam, The Netherlands |
| B.M.J. Uitdehaag  | Department of Neurology, MS Center Amsterdam, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam Neuroscience, Amsterdam, The Netherlands |
| A. Vennegoor      | Department of Neurology, Flevoziekenhuis, Almere The Netherlands   |
| B.H.A. Wokke      | Department of Neurology, ErasMS, Erasmus Medical Center, Rotterdam, The Netherlands  |
| E.M.P.E. Zeinstra | Department of Neurology, Isala, Meppel, The Netherlands  |