NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING
JULY 2019

Ofatumumab for relapsing multiple sclerosis

NIHRIO ID	3238	**NICE ID**	9680
Developer/Company	Novartis Pharmaceuticals UK Ltd	**UKPS ID**	642657

Licensing and market availability plans	Currently in phase III clinical trials.

*COMMERCIAL IN CONFIDENCE

SUMMARY

Ofatumumab is in clinical development for the treatment of relapsing multiple sclerosis (MS). Multiple sclerosis is an autoimmune disease, meaning the body's own immune cells (which usually fight infection) attack and damage the nerves and brain. This causes a range of issues including problems with walking, balance, memory and thinking as well as pain, tiredness and many other symptoms.

Ofatumumab, taken as an injection under the skin (subcutaneous), reduces the number of B cell lymphocytes, a type of white blood cell which is thought to influence the abnormal immune response that causes the attack on the myelin coating of nerves in MS patients. This is thought to lead to a reduction in the number of these immune cells attacking the myelin sheath that surround and protect the nerves. If licensed, ofatumumab may offer an additional treatment option for patients with relapsing MS. Besides offering the possibility of self-administration by the patient, subcutaneous treatment of ofatumumab can effectively reduce the number of brain lesions without leading to severe depletion of immune B-cells, which is one of the consequences of treatment with intravenous ofatumumab.

PROPOSED INDICATION

Relapsing multiple sclerosis (RMS).[a]

TECHNOLOGY

DESCRIPTION

Ofatumumab (HuMax-CD20) is a human monoclonal antibody,[1] which is a type of drug developed to attack specific targets in the immune system.[2] The exact mode of action by which ofatumumab alters relapse and remission in multiple sclerosis (MS) patients is still uncertain. Ofatumumab is known to target B-cells (a type of immune cell), by binding to the CD20 protein attached to the outside of the cell.[3] Specifically, ofatumumab binds to a distinct epitope of CD20 on the B cell surface, inducing efficient complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity, even when CD20 expression is low.[4-6] This is thought to lead to a reduction in the number of these immune cells attacking the myelin sheath that surround and protect the nerves.[3]

Ofatumumab is in phase III clinical development for the treatment of RMS (ASCLEPIOS II - NCT02792231, ASCLEPIOS I - NCT02792218, NCT03650114). In the extension study (NCT03650114), the dose comprised ofatumumab 20 mg sub-cutaneous (s.c.) injection every 4 weeks, however the revised proposed dosing regimen is three loading doses of 20 mg s.c. weekly followed by maintenance doses of 20 mg s.c. every 4 weeks.[b]

INNOVATION AND/OR ADVANTAGES

At phase II, ofatumumab IV has been shown to reduce the number of B-cell numbers leading to almost complete suppression of new active lesions seen on MRI.[7] Ofatumumab is fully human and could potentially lead to fewer infusion related reaction versus non-fully human compounds. In an additional phase II clinical trial (MIRROR, NCT01457924), ofatumumab was dosed subcutaneously every four weeks rather than via intravenous infusion which presents an additional potential advantage to patients and the healthcare system. The trial imaging showed that all subcutaneous ofatumumab doses demonstrated in the study efficacy (most robust: cumulative doses ≥30 mg/12 wk), with a safety profile consistent with existing ofatumumab data.[6,8] Furthermore, treatment with subcutaneous ofatumumab was seen to effectively reduce the number of brain lesions without leading to severe depletion of immune B-cells, one of the consequences of treatment with intravenous.[9]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Ofatumumab is no longer licensed for any condition in the European Union.[10]

Ofatumumab is in phase II and phase III clinical development for a range of cancers including, follicular lymphoma and acute lymphoblastic leukaemia as well as chronic graft versus host disease. Ofatumumab is also in phase II and phase III clinical development for chronic lymphocytic leukaemia/small lymphocytic lymphoma.[11]

[a] Information provided by Novartis General Medicines on UK PharmaScan.
[b] Information provided by Novartis General Medicines on UK PharmaScan.

PATIENT GROUP

DISEASE BACKGROUND

MS is a neurological disease affecting the central nervous system (CNS). MS is an autoimmune condition and occurs when the body's own immune cells attack and damage the myelin sheath (fatty protein layer) which surrounds and insulates the nerve cells of the central nervous system. This process of myelin destruction is called demyelination. This demyelination causes disruption of the electrical transmissions to and from the brain, causing a slowing or disruption of nervous conduction. Demyelination also causes scarring within the CNS and the symptoms of MS depend on the location and severity of these CNS lesions.[12]

MS can be broadly divided into three main types.[13] Relapsing-remitting MS (RRMS) constitutes the majority of people with MS (with estimates up to 85% of people with MS). People with RRMS will have relapses into MS symptoms, sometimes months or years apart, followed by periods of no symptoms or 'remission'. The severity and symptoms experienced during a relapse can vary between people and between individual relapses.[14] Secondary progressive MS (SPMS) develops in approximately 82% of those with RRMS by 20 years onset.[15] Over time, these patients have fewer or no relapses but their disability increases. As this follows an initial (primary) relapsing remitting phase, this is known as secondary progressive MS.[13] The third main type is primary progressive MS, in which disability increases from the beginning, and it is rare to have any replapses.[13].

Symptoms of MS can vary widely according to where in the CNS damage occurs and commonly may include: fatigue, difficulty walking, vision disturbances, incontinence, numbness and tingling in different parts of the body, muscle stiffness and spasms, reduced balance and co-ordination and problems with cognition (including memory, learning and planning).[16]

As a chronic condition, MS can have impact on everyday life and symptoms such as fatigue and cognitive problems can affect everyday activities. Dealing with the symptoms of MS can be stressful and measures to manage and decrease stress should be taken. Difficulty sleeping is also common and daytime sleepiness can affect work and personal life, so ensuring good sleep is achieved is important.[17]

CLINICAL NEED AND BURDEN OF DISEASE

Using UK estimates and prevalence data from Mackenzie et al. (2014),[18] and population estimates from the Office of National Statistics 2016, the MS Society reporting in 2018 estimates MS prevalence at 90,590 people (164 per 100,000 people), and incidence of MS at 4,120 people (7 per 100,000) in England.[19] If we assume 85% of people have RRMS,[13] the prevalence is estimated to be 77,001 people. The prevalence of SPMS specifically is more difficult to ascertain – a recent systematic review highlighted two UK studies which estimated the prevalence at 57.8 per 100,000 (range 40.9-74.6 per 100,000) people (the large variation could be attributable to SPMS definition, study design or study duration).[20]

According the data from Hospital Episode Statistics for England for 2017-18, there were 48,671 admissions, 49,514 bed days and 51,394 finished consultant episodes for multiple sclerosis (ICD10 G35).[21]

MS is not a terminal condition and only has a small impact of life expectancy (estimated at six to seven years less than the general population) and disability can range greatly from no symptoms to complex disability. MS patients with complex disability may be more at risk of

developing life threatening complications such as respiratory and cardiovascular problems, which usually arise as a result of reduced mobility.[22]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

People who are suspected to have MS will be referred to a consultant neurologist. There are two main approaches to treating MS; disease modifying therapies and management of MS symptoms. Disease modifying therapies, administered by neurologists, aim to reduce the number of relapses experienced, to reduce the severity of these relapses and reduce disability progression and MRI activity. However, they cannot reverse existing damage. Management of MS symptoms can be overseen by specialist referrals as appropriate.[23,24]

The majority of treatment for MS involves the management of MS symptoms. These include cognition, emotional lability, incontinence, mobility and fatigue, oscillopsia, pain and spasticity.[24] The treatments given to manage symptoms may include drug therapies, self-management strategies or different types of therapies.[25]

CURRENT TREATMENT OPTIONS

There are currently eight disease modifying drugs available for use by the NHS in the UK, including:[24]

- Alemtuzumab (Lamtrada) – recommended (within its marketing authorisation) for treating adults with active RRMS.
- Beta interferons and glatiramer acetate (Avonex, Rebif, Extavia and Copaxone) - recommended for treatment of RRMS and Extavia for MS if the person has RRMS and has had 2 or more relapses within the last 2 years or the person has relapsing SPMS with continuing relapses.
- Cladribine (Mavenclad) – recommended for treating highly active MS in adults if the person has rapidly evolving severe RRMS, that is, at least 2 relapses in the previous year and at least 1 T1 gadolinium-enhancing lesion at baseline MRI, or the patient has RRMS that has responded inadequately to treatment with disease-modifying therapy, defined as 1 relapse in the previous year and MRI evidence of disease activity
- Dimethyl fumarate (Tecfidera) – recommended for the treatment of adults with active RRMS, but not highly active or rapidly evolving severe RRMS.
- Fingolimod (Gilenya) - recommended for the treatment of highly active RRMS in adults if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon.
- Natalizumab (Tysabri) – recommended for the treatment of rapidly evolving severe RRMS (defined by two or more disabling relapses in 1 year, and one or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous MRI).
- Ocrelizumab (Ocrevus) - recommended for treating early primary progressive MS with imaging features characteristic of inflammatory activity in adults
- Teriflunomide (Aubagio) – recommended for treating adults with active RRMS (normally defined as 2 clinically significant relapses in the previous 2 years), if they do not have highly active or rapidly evolving severe RRMS.

PLACE OF TECHNOLOGY

If licensed, ofatumumab will offer an additional monotherapy treatment option for patients with RMS.

CLINICAL TRIAL INFORMATION

Trial	**ASCLEPIOS II, NCT02792231; EudraCT: 2015-005419-33; adults; ofatumumab or teriflunomide placebo vs teriflunomide or ofatumumab placebo; phase III**
Sponsor	Novartis Pharmaceuticals
Status	Ongoing
Source of Information	Trial registry[26,27]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, parallel assignment, quadruple blinded (participant, care provider, investigator, outcomes assessor)
Participants	n=900 (planned); males and females 18-55 yrs; diagnosis of multiple sclerosis (MS); relapsing MS (RRMS or SPMS); at least 1 relapse during the previous 1 yr or 2 relapses during the previous 2 yrs or a positive gadolinium-enhancing MRI scan in previous year; EDSS score of 0 to 5.5.
Schedule	Randomised to receive either experimental ofatumumab subcutaneous injections every 4 weeks or active comparator teriflunomide orally once daily. In order to blind for the different formulations, double-dummy masking will be used i.e. all patients will take injections (containing either active ofatumumab or placebo) and oral capsules (containing either active teriflunomide or placebo).
Follow-up	The maximal treatment duration in the study for an individual patient will be 2.5 years. For patients who complete the core study on study drug and do not enter the extension study will enter the safety follow up period with a minimum of 9 months.
Primary Outcomes	• Annualized relapse rate (ARR) [time frame: up to 2.5 yrs]. ARR is the number of confirmed relapses in a year calculated based on cumulative number of relapses by patient adjusted for time-in-study by patient (ofatumumab versus terifluonmide)
Secondary Outcomes	• Time to 3-month confirmed disability worsening on EDSS [time frame: baseline, every 3 months up to 2.5 years]: a 3-month confirmed disability worsening is an increase from baseline in expanded disability status scale (EDSS) score sustained for at last 3 months. • Time to 6-month confirmed disability worsening on EDSS [time frame: baseline, every 3 months up to 2.5 years]: a 6-month confirmed disability worsening is an increase from baseline in EDSS score sustained for at last 6 months. • Time to 6-month confirmed disability improvement on EDSS [time frame: baseline, every 3 months up to 2.5 years]: a 6-month confirmed disability improvement is a decrease from baseline in EDSS score sustained for at least 6 months. • Number of gadolinium (Gd)-enhancing lesions per MRI scan [time frame: baseline, yearly up to 2.5 years]: total number of Gd-enhancing lesions across all scans per patient adjusted for different number of scans due to variable follow up time in study • Number of new or enlarging T2 lesions on MRI per year (annualized lesion rate) [time frame: baseline, yearly up to 2.5 years]: number of new/enlarging T2 lesions on last available MRI scan compared to baseline adjusted for different time of scans versus baseline due to variable follow up time in study

	• Rate of brain volume loss based on assessments of percentage brain volume change from baseline [time frame: baseline, yearly up to 2.5 years]: percent change from baseline in brain volume loss (BVL) on all MRI scans adjusted for different time of scan versus baseline due to variable follow up time in study
Key Results	Not reported
Adverse effects (AEs)	Not reported
Expected reporting date	Previously reported as May 2019

Trial	**ASCLEPIOS I, NCT02792218; EudraCT: 2015-005418-31; adults; ofatumumab or teriflunomide placebo vs teriflunomide or ofatumumab placebo; phase III**
Sponsor	Novartis Pharmaceuticals
Status	Ongoing
Source of Information	Trial registry[28,29]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, parallel assignment, quadruple blinded (participant, care provider, investigator, outcomes assessor)
Participants	n=929; males and females aged 18-55 yrs; diagnosis of multiple sclerosis (MS); RMS (RRMS or SPMS); at least 1 relapse during the previous 1 yr or 2 relapses during the previous 2 yrs or a positive gadolinium-enhancing MRI scan in previous year; EDSS score of 0 to 5.5
Schedule	Randomised to receive either experimental ofatumumab subcutaneous injections every 4 weeks or active comparator teriflunomide orally once daily. In order to blind for the different formulations, double-dummy masking will be used i.e. all patients will take injections (containing either active ofatumumab or placebo) and oral capsules (containing either active teriflunomide or placebo).
Follow-up	Patients who complete the core study on study drug and do not enter the extension study will enter the safety follow up period with a minimum of 9 months.
Primary Outcomes	Annualized relapse rate (ARR) [time frame: up to 2.5 years] ARR is the number of confirmed relapses in a year calculated based on cumulative number of relapses by patient adjusted for time-in-study by patient (ofatumumab versus terifluonmide).
Secondary Outcomes	• Time to 3-month confirmed disability worsening on EDSS [time frame: baseline, every 3 months up to 2.5 yrs]: a 3-month confirmed disability worsening is an increase from baseline in EDSS score sustained for at last 3 months. • Time to 6-month confirmed disability worsening on EDSS [time frame: baseline, every 3 mths up to 2.5 yrs]: a 6-month confirmed disability worsening is an increase from baseline in EDSS score sustained for at last 6 months. • Time to 6-month confirmed disability improvement on EDSS [time frame: baseline, every 3 mths up to 2.5 yrs]: a 6-month confirmed

	disability improvement is a decrease from baseline in EDSS score sustained for at least 6 months. • Number of gadolinium (Gd)-enhancing lesions per MRI scan [time frame: baseline, yearly up to 2.5 yrs]: total number of Gd-enhancing lesions across all scans per patient adjusted for different number of scans due to variable follow up time in study • Number of new or enlarging T2 lesions on MRI per year (annualized lesion rate) [time frame: baseline, yearly up to 2.5 yrs]: number of new/enlarging T2 lesions on last available MRI scan compared to baseline adjusted for different time of scans versus baseline due to variable follow up time in study • Rate of brain volume loss based on assessments of percentage brain volume change from baseline [time frame: baseline, yearly up to 2.5 yrs]: percent change from baseline in brain volume loss (BVL) on all MRI scans adjusted for different time of scan versus baseline due to variable follow up time in study.
Key Results	Not reported
Adverse effects (AEs)	Not reported
Expected reporting date	Previously reported as May 2019

Trial	**ALITHIOS, NCT03650114; adults; ofatumumab; phase III extension study**
Sponsor	Novartis Pharmaceuticals
Status	Ongoing
Source of Information	Trial registry[30]
Location	EU (not UK) and USA
Design	Single group assignment (open label)
Participants	n=2010 (planned); males and females 18 yrs and older; must have completed a selected Novartis MS study which dosed ofatumumab 20 mg sc every 4 weeks; written informed consent.
Schedule	Subcutaneous injection of 20 mg ofatumumab every 4 weeks
Follow-up	Follow up for the duration of the study (approximately 5 yrs)
Primary Outcomes	• Proportion of subjects with adverse events • Proportion of subjects with laboratory, vital signs, or electrocardiogram (ECG) results meeting abnormal criteria • Proportion of subjects meeting predefined criteria in Columbia Suicide Severity Rating Scale (C-SSRS) [time frame: up to 5 years]
Secondary Outcomes	• Number of relapse rates per year [time frame: core studies up to 5 yrs from first dose of ofatumumab (depending on if first dose was in the core or in this extension study or comparator randomization)]: ARR time calculated as number of confirmed relapses divided by time in study per year and will also be presented for the entire duration • Patients with confirmed 3 and 6 month disability worsening [time frame: duration of the study, approximately 5 yrs]: a confirmed disability worsening is an increase from baseline in EDSS score sustained for at last 3, or 6 mths. EDSS consists of seven functional systems and an ambulation score that are then combined to determine the EDSS steps (ranging from 0 (normal) to 10 (death due to MS)). The functional systems are visual, brain stem, pyramidal, cerebellar,

	sensory, bowel and bladder, and cerebral functions (fatigue contributes). • Patients with confirmed 6, 12 and 24 mth disability improvement and improvement until end of study [time frame: duration of the study, approximately 5 yrs]: confirmed disability improvement is a decrease from baseline in EDSS score sustained for at least 6, 12 or 24 months • Patients with changes in Expanded Disability Status Scale (EDSS) scores [time frame: core studies up to 5 yrs from first dose of ofatumumab (depending on if first dose was in the core or in this extension study or comparator randomization)]: score changes in Expanded Disability Status Scale (EDSS) over time • Changes in and time to 6 mth confirmed worsening of symbol digit modalities test scores [time frame: duration of the study, approximately 5 yrs]: score changes and confirmed 4-point worsening sustained for 6 months in symbol digit modalities test (SDMT) scores The SDMT is a neuropsychological, timed test for sustained attention and concentration. Three versions will be used, alternating at each visit where done. The number of correct responses will be counted for the score. • Changes in the Magnetic Resonance Image (MRI) related to brain volume loss [time frame: core studies up to 5 yrs from first dose of ofatumumab (depending on if first dose was in the core or in this extension study or comparator randomization)]: percent change from baseline in brain volume loss (BVL) • Changes in the MRI related to T2 lesions [time frame: Core studies up to 5 yrs from first dose of ofatumumab (depending on if first dose was in the core or in this extension study or comparator randomization)]: number of new or enlarging T2 lesions • Changes in the MRI related to Gd-enhancing lesions [time frame: Core studies up to 5 yrs from first dose of ofatumumab (depending on if first dose was in the core or in this extension study or comparator randomization)]: total number of Gd-enhancing lesions on all MRI scans adjusted for different time of scan versus follow up time in study • Changes in neurofilament light change serum concentration [time frame: Core studies up to 5 yrs from first dose of ofatumumab (depending on if first dose was in the core or in this extension study or comparator randomization)]: extent of neurofilament light change concentration in blood NfL is a component of the neuronal cytoskeleton and is released into the cerebrospinal fluid and into subsequently blood following neuro-axonal damage
Key Results	Not reported
Adverse effects (AEs)	Not reported
Expected reporting date	Estimated study and primary completion date June 2025

ESTIMATED COST

The cost of ofatumumab is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Ozanimod for treating relapsing multiple sclerosis (GID-TA10299). Expected publication date to be confirmed.
- NICE technology appraisal in development. Multiple sclerosis (relapsing remitting) – laquinimod (GID-TAG337). Expected publication date to be confirmed.
- NICE technology appraisal guidance. Ocrelizumab for treating relapsing–remitting multiple sclerosis (TA533). July 2018.
- NICE technology appraisal guidance. Beta interferons and glatiramer acetate for treating multiple sclerosis (TA527). June 2018.
- NICE technology appraisal guidance. Cladribine tablets for treating relapsing–remitting multiple sclerosis (TA493). December 2017.
- NICE technology appraisal guidance. Dimethyl fumarate for treating relapsing-remitting multiple sclerosis (TA320). August 2014.
- NICE technology appraisal guidance. Alemtuzumab for treating relapsing–remitting multiple sclerosis (TA312). May 2014.
- NICE technology appraisal guidance. Teriflunomide for treating relapsing–remitting multiple sclerosis (TA303). January 2014.
- NICE technology appraisal guidance. Fingolimod for the treatment of highly active relapsing–remitting multiple sclerosis (TA254). April 2012.
- NICE technology appraisal guidance. Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis (TA127). August 2007.
- NICE clinical guideline. Multiple sclerosis in adults: management (CG186). October 2014.
- NICE quality standard. Multiple sclerosis (QS108). January 2016.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. Disease Modifying Therapies for Patients with multiple sclerosis (MS). Clinical commissioning policy reference. June 2019.

OTHER GUIDANCE

- NHS England. Manual for Prescribed Specialised Services 2017/18. Chapter 11. Adult specialist neurosciences services. 2017.[31]
- Department of Health. NHS outcomes framework 2016 to 2017: Domains 1–5. 2016.[32]
- Department of Health. The National Service Framework for Long-term Conditions. 2005.[33]

ADDITIONAL INFORMATION

REFERENCES

1 Österborg A. Ofatumumab, a human anti-CD20 monoclonal antibody. *Expert Opinion on Biological Therapy*. 2010;10(3):439-49. Available from: https://doi.org/10.1517/14712590903586239.

2 Multiple Sclerosis Trust. *Ofatumumab*. 2018. Available from: https://www.mstrust.org.uk/a-z/ofatumumab [Accessed 6th July 2019].

3 Multiple Sclerosis News Today. *Ofatumumab (Arzerra)*. 2019. Available from: https://multiplesclerosisnewstoday.com/ofatumumab-for-multiple-sclerosis/ [Accessed 1st May 2019].

4 Teeling JL, Mackus WJM, Wiegman LJJM, van den Brakel JHN, Beers SA, French RR, et al. The biological activity of human CD20 monoclonal antibodies Is linked to unique epitopes on CD20. *The Journal of Immunology*. 2006;177(1):362-71. Available from: https://doi.org/10.4049/jimmunol.177.1.362.

5 Bleeker WK, Munk ME, Mackus WJM, Van Den Brakel JHN, Pluyter M, Glennie MJ, et al. Estimation of dose requirements for sustained in vivo activity of a therapeutic human anti-CD20 antibody. *British Journal of Haematology*. 2008;140(3):303-12. Available from: https://doi.org/10.1111/j.1365-2141.2007.06916.x.

6 Bar-Or A, Grove RA, Austin DJ, Tolson JM, VanMeter SA, Lewis EW, et al. Subcutaneous ofatumumab in patients with relapsing-remitting multiple sclerosis The MIRROR study. *Neurology*. 2018 May;90(20):E1805-E14. Available from: https://doi.org/10.1212/wnl.0000000000005516.

7 MS Trust. *Ofatumumab*. 2018. Available from: https://www.mstrust.org.uk/a-z/ofatumumab [Accessed 1st May 2019].

8 ClinicalTrials. *Ofatumumab Subcutaneous Administration in Subjects With Relapsing-Remitting Multiple Sclerosis (MIRROR). Trial ID: NCT01457924*. 2011. Status: Completed. Available from: https://clinicaltrials.gov/ct2/show/NCT01457924 [Accessed 6th July 2019].

9 Pena A. *Subcutaneous ofatumumab a safe, effective RRMS therapy at low doses, trial results show*. 2018. Available from: https://multiplesclerosisnewstoday.com/2018/05/23/subcutaneous-ofatumumab-effective-rrms-therapy-low-doses-trial-shows/ [Accessed 6th July 2019].

10 European Medicines Agency. *Arzerra: Withdrawal of the marketing authorisation in the European Union* 2019. Available from: https://www.ema.europa.eu/en/documents/public-statement/public-statement-arzerra-withdrawal-marketing-authorisation-european-union_en.pdf [Accessed 12th June 2019].

11 ClinicalTrials. *Search - ofatumumab (phase II, III)*. 2019. Available from: https://clinicaltrials.gov/ct2/results?term=ofatumumab&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 2nd July 2019].

12 MS-UK. *What is MS?* 2019. Available from: http://www.ms-uk.org/whatisms [Accessed 7th February 2019].

13 Multiple sclerosis Trust. *Types of MS*. 2018. Available from: https://www.mstrust.org.uk/about-ms/what-ms/types-ms [Accessed 2nd July 2019].

14 MS-UK. *Types of MS*. Colchester: MS-UK; 2019. Available from: http://www.ms-uk.org/sites/default/files/choices_types.pdf.

15 Fisniku LK, Brex PA, Altmann DR, Miszkiel KA, Benton CE, Lanyon R, et al. Disability and T2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis. *Brain*. 2008;131(3):808-17. Available from: http://doi.org/10.1093/brain/awm329.

16 NHS. *Overview - Multiple sclerosis*. 2018. Available from: https://www.nhs.uk/conditions/multiple-sclerosis/#treatments-for-ms [Accessed 7th February 2019].

17 Multiple Sclerosis Trust. *Lifestyle choices*. 2019. Available from: https://www.mstrust.org.uk/life-ms/wellbeing/lifestyle-choices [Accessed 7th February 2019].
18 Mackenzie IS, Morant SV, Bloomfield GA, MacDonald TM, Riordan J. Incidence and prevalence of multiple sclerosis in the UK 1990–2010: a descriptive study in the General Practice Research Database. *Journal of Neurology, Neurosurgery, and Psychiatry*. 2014;85(1):76. Available from: https://doi.org/10.1136/jnnp-2013-305450.
19 MS Society. *MS in the UK*. London: MS Society; 2018. Available from: https://www.mssociety.org.uk/care-and-support/resources-and-publications/publications-search/ms-in-the-uk.
20 Khurana V, Sharma H, Medin J. Estimated prevalence of secondary progressive multiple sclerosis in the USA and Europe: results from a systematic literature search (P2.380). *Neurology*. 2018;90(15 Supplement):P2.380. Available from: http://n.neurology.org/content/90/15_Supplement/P2.380.abstract.
21 NHS Digital. *Hospital Admitted Patient Care Activity, 2017-18 (Diagnosis spreadsheet)*. 2018. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2017-18 [Accessed 7th February 2019].
22 Multiple Sclerosis Trust. *Life expectancy*. 2018. Available from: https://www.mstrust.org.uk/a-z/life-expectancy [Accessed 7th February 2019].
23 NHS. *Treatment - Multiple sclerosis*. 2018. Available from: https://www.nhs.uk/conditions/multiple-sclerosis/treatment/ [Accessed 13th February 2019].
24 NICE Pathways. *Multiple sclerosis*. 2019. Available from: https://pathways.nice.org.uk/pathways/multiple-sclerosis [Accessed 7th February 2019].
25 Multiple Sclerosis Trust. *Treatment finder*. 2019. Available from: https://www.mstrust.org.uk/about-ms/ms-treatments/treatment-finder [Accessed 7th February 2019].
26 ClinicalTrials.gov. *Efficacy and Safety of Ofatumumab Compared to Teriflunomide in Patients With Relapsing Multiple Sclerosis. (ASCLEPIOS II). Trial ID: NCT02792231*. 2016. Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT02792231 [Accessed 1st May 2019].
27 EU Clinical Trials Register. *A randomized, double-blind, double-dummy, parallel-group study comparing the efficacy and safety of ofatumumab versus teriflunomide in patients with relapsing multiple sclerosis. Trial ID: 2015-005419-33*. 2016. Status: Ongoing. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-005419-33/DE [Accessed 6th July 2019].
28 ClinicalTrials.gov. *Efficacy and Safety of Ofatumumab Compared to Teriflunomide in Patients With Relapsing Multiple Sclerosis (ASCLEPIOS I). Trial ID: NCT02792218*. 2016. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT02792218 [Accessed 1st May 2019].
29 EU Clinical Trials Register. *A randomized, double-blind, double-dummy, parallel-group study comparing the efficacy and safety of ofatumumab versus teriflunomide in patients with relapsing multiple sclerosis. Trial ID: 2015-005418-31*. 2016. Status: Ongoing. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-005418-31/GB [Accessed 11th June 2019].
30 ClinicalTrials.gov. *Long-term Safety, Tolerability and Effectiveness Study of Ofatumumab in Patients With Relapsing MS. Trial ID: NCT03650114*. 2018. Status: Completed. Available from: https://clinicaltrials.gov/ct2/show/NCT03650114 [Accessed 1st May 2019].
31 NHS England. *Manual for Prescribed Specialised Services 2017/2018*. London: NHS England; 2017. Available from: https://www.liverpoolccg.nhs.uk/media/3098/48701-pss-manual.pdf.
32 Department of Health. *NHS Outcomes Framework: at-a-glance*. London: Department of Health; 2016. Available from:

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/513157/NHSOF_at_a_glance.pdf.

33 Department of Health. *The National Framework for Long-term conditions*. London: Department of Health; 2005. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/198114/National_Service_Framework_for_Long_Term_Conditions.pdf.

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.