

**NIHR Innovation Observatory  
Evidence Briefing: November 2017****Ponesimod for relapsing-remitting multiple  
sclerosis**

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**LAY SUMMARY**

Multiple Sclerosis (MS) 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. In most people the symptoms of MS follow a 'relapsing and remitting pattern' where the disease relapses (and symptoms worsen) and then remits (where the symptoms improve).

Ponesimod is a drug which works by blocking the signals which allow the body's immune cells to travel to and damage the nerve cells. By preventing the immune cells from damaging the nerves, it is thought this drug will stop the damage which causes MS 'relapses'. In clinical trials it has been shown that ponesimod reduces the number of 'relapses' in people with MS and reduced the amount of damage to the nerves (measured by brain scans) compared to a placebo.

*This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.*

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## TARGET GROUP

Multiple sclerosis – relapsing-remitting multiple sclerosis (RRMS)

## TECHNOLOGY

### DESCRIPTION

Ponesimod (ACT-128800; RG-3477) is a selective sphingosine-1 phosphate type 1 (S1P-1) receptor modulator.<sup>1</sup> The S1P-1 receptor is activated by S1P, an important signalling molecule involved in the migration of lymphocytes from the secondary lymphoid organs (e.g. lymph nodes and spleen) to the periphery. This is important in MS as it is thought that inflammation (caused by lymphocytes and other immune cells) is the primary cause of damage to CNS cells (specifically to the protective myelin sheath which insulates the nerve cells) which is an important factor in the pathogenesis of MS.<sup>2</sup> Ponesimod works as a functional antagonist of the S1P-1 receptor and therefore blocking S1P signalling. This prevents migration of T lymphocytes and their infiltration of peripheral tissues. In the context of MS this is thought to work by blocking lymphocytes from crossing the blood-brain barrier into the CNS and causing damage to myelin sheath.<sup>1</sup>

A S1P-1 receptor modulator, Fingolimod, is currently licenced for the treatment of relapsing remitting MS in the EU.<sup>3</sup> Ponesimod is intended for the treatment of MS and in the phase III clinical trial ponesimod is administered orally at 20mg once daily for approximately 2 years.<sup>4</sup>

Ponesimod does not currently have Marketing Authorisation in the EU for any indication.

## INNOVATION and/or ADVANTAGES

If licensed, ponesimod will offer an additional treatment option for people with relapsing multiple sclerosis with the potential to modify the progression of the disease and prevent relapses of MS symptoms.

## DEVELOPER

Actelion Pharmaceuticals Ltd

## AVAILABILITY, LAUNCH or MARKETING

Ponesimod is currently in phase III clinical trials.

## PATIENT GROUP

### BACKGROUND

Multiple sclerosis (MS) is a neurological disease affecting the central nervous system. 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 CNS. 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.<sup>5</sup>

There are four subgroups of MS: clinically isolated syndrome (CIS), relapsing remitting MS, secondary progressive MS and primary progressive MS. CIS is the first neurological episode in people with MS lasting at least 24 hours caused by demyelination in one or more sites. 80% of people with CIS will develop MS within 10 years.

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. RRMS can be further subcategorised into benign MS (in which patients may have mild symptoms and infrequent relapses over a long time) and rapidly evolving severe relapsing-remitting MS (with two or more disabling relapses occurring in one year).

Secondary progressive MS (SPMS) is a transition from RRMS when relapses become fewer or stop and instead symptoms gradually worsen over a variable length of time. About two thirds of people with RRMS will develop SPMS approximately 15 years after diagnosis. 10-15% people with MS have Primary progressive MS (PPMS), which starts with slow progression of symptoms which gradually worsens with usually few or no relapses. However around 5% of people with MS will have PPMS with relapses called progressive relapsing MS.<sup>6</sup>

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).<sup>7</sup>

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.<sup>8</sup>

## **CLINICAL NEED and BURDEN OF DISEASE**

The MS Society estimates MS prevalence at 89,030 people (164 per 100,000 people) in England in 2013 and incidence of MS at 4,040 people (7 per 100,000) in England in 2013. Assuming the above noted proportion of 85%, the annual incidence of RMS in England is 3,434.<sup>9</sup>

According the HES data for 2016-17, there were 52,199 admissions, 51,338 bed days and 54,732 finished consultant episodes for multiple sclerosis (ICD10 G35.X).<sup>10</sup>

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.<sup>11</sup>

According to the death registration statistics for England and Wales for 2015, 838 females and 457 males had recorded deaths attributed to multiple sclerosis (ICD10 G35).<sup>12</sup>

## **PATIENT PATHWAY**

## **RELEVANT GUIDANCE**

## **NICE GUIDANCE**

- NICE Technology Appraisal in development. Biotin for treating progressive multiple sclerosis (ID919). Expected publication date 22 August 2018.
- NICE Technology Appraisal in development. Ocrelizumab for treating relapsing multiple sclerosis (ID937). Expected publication date 25 July 2018.
- NICE Technology Appraisal in development. Ocrelizumab for treating primary progressive multiple sclerosis (ID938). Expected publication date 25 July 2018.
- NICE Technology Appraisal in development. Multiple sclerosis – cladribine (ID64). Expected publication date 28 February 2018.
- NICE Technology Appraisal in development. Multiple sclerosis – sativex (ID387). Expected publication date TBC.
- NICE Technology Appraisal in development. Multiple sclerosis (relapsing-remitting) – laquinimod (ID560). Expected publication date TBC.
- NICE Technology Appraisal in development. Multiple sclerosis (primary progressive) – fingolimod (ID62). Expected publication date TBC.
- NICE Technology Appraisal in development. Multiple sclerosis – interferon beta, glatiramer acetate (review TA32) (ID809). Expected publication date TBC.
- NICE Technology Appraisal. Daclizumab for treating relapsing-remitting multiple sclerosis (TA441). April 2017.
- NICE Technology Appraisal. Dimethyl fumarate for treating relapsing-remitting multiple sclerosis (TA320). August 2014.
- NICE Technology Appraisal. Alemtuzumab for treating relapsing-remitting multiple sclerosis (TA312). May 2014.
- NICE Technology Appraisal. Teriflunomide for treating relapsing-remitting multiple sclerosis (TA303). January 2014.
- NICE Technology Appraisal. Fingolimod for the treating of highly active relapsing-remitting multiple sclerosis (TA254). April 2012.
- NICE Technology Appraisal. Natalizumab for the treating of highly active relapsing-remitting multiple sclerosis (TA127). August 2007.
- NICE Technology Appraisal. Beta interferon and glatiramer acetate for the treatment of multiple sclerosis (TA32). January 2002.
- NICE Clinical Guidance. Multiple sclerosis in adults: management (CG186). October 2014.
- NICE Quality Standard. Multiple sclerosis (QS108). January 2016.
- NICE Interventional Procedure Guidance in development. Autologous unmanipulated peripheral blood stem cell therapy for multiple sclerosis (GID-IP1151). Expected publication date TBC.
- NICE Interventional Procedure Guidance. Percutaneous venoplasty for chronic cerebrospinal venous insufficiency for multiple sclerosis (IPG420). March 2012.

## NHS ENGLAND and POLICY GUIDANCE

- 2013/14 NHS Standard Contract for Neurosciences: specialised neurology (adult). D04/S/a.
- 2013/14 NHS Standard Contract for Neurosurgery (adult). D03/S/a.
- NHS England. Clinical Commissioning Policy: Fampridine for Multiple Sclerosis (adults). NHS England/16010/P. July 2016.
- NHS England. Clinical Commissioning Policy: Disease Modifying Therapies for Patients with Multiple Sclerosis (MS). NHS England/D04/P/b. May 2014.
- NHS England. Clinical Commissioning Policy: Fampridine for Multiple Sclerosis (MS). NHCB/D04/PS/c. April 2013.
- NHS England. Clinical Commissioning Policy: Deep Brain Stimulation (DBS) in Movement Disorders. NHSCB/D03/P/b. April 2013.

## OTHER GUIDANCE

- Association of British Neurologists. Revised guidelines for prescribing disease-modifying treatments in multiple sclerosis. 2015.

## CURRENT TREATMENT OPTIONS

There are 2 main approaches to treating MS; disease modifying therapies and management of MS symptoms. Disease modifying therapies for MS aim to reduce the number of relapses experienced and to reduce the severity of these relapses, however they cannot reverse existing damage. There are currently 12 disease modifying drugs available for use by the NHS in the UK, including:<sup>13,14</sup>

- Interferon Beta 1a (Avonex, Betaferon, Extavia, Rebif, Plegridy) – not recommended by NICE for treatment of MS based on balance of clinical and cost effectiveness.
- Glatiramer acetate (Copaxone) - not recommended by NICE for treatment of MS based on balance of clinical and cost effectiveness.
- Teriflunomide (Aubagio) – recommended for the treatment of active RRMS.
- Fingolimod (Gilenya) - recommended for the treatment of highly active (unchanged or increased severe relapses despite Beta interferon treatment) RRMS
- Alemtuzumab (Lemtrada) – recommended only for the treatment of RRMS
- Natalizumab (Tysabri) – recommended only for the treatment of rapidly evolving severe RRMS
- Daclizumab (Zinbryta) – following safety concerns the EMA has restricted the use of Daclizumab to people with highly active relapsing MS who have not responded to other treatments. NICE recommend Daclizumab is used only in those with active relapsing-remitting MS previously treated with disease modifying therapy or in those with rapidly evolving severe RRMS who cannot take Alemtuzumab.
- Dimethyl fumarate (Tecfidera) – recommended for the treatment of RRMS.

The majority of treatment for MS involves the management of MS symptoms. The treatments given to manage symptoms may include drug therapies, self-management strategies or different types of therapies.<sup>15</sup> Treatments provided will depend on the symptom being experienced and may include the following:<sup>15,13</sup>

- Mood:

- Drug therapies: Antidepressants (Fluoxetine, Imipramine and paroxetine)
- Non drug therapies: Cognitive behavioural Therapy (CBT), Mindfulness, Acceptance and commitment therapy (ACT) and counselling
- Incontinence:
  - Drug Therapies: Botox, desmopressin, Imipramine, oxybutynin, tolterodine
  - Non drug therapies: catheters (temporary or permanent)
- Pain:
  - Drug therapies: carbamazepine, clonazepam, gabapentin, imipramine, lamotrigine (not recommended by NICE), phenytoin and pregabalin
  - Non drug therapies: transcutaneous electrical nerve stimulation (TENS)
- Sexual dysfunction (male):
  - Drug therapy: alprostadil, cialis, vardenafil and viagra
- Cognition (including memory): referral to StayingSmart (an online resource providing information of cognitive symptoms of MS and how to deal with it)
- Mobility and function:
  - Drug therapy: fampridine
  - Non drug therapies: exercise, functional electrical stimulation (FES), hippotherapy, therapeutic horse riding, percutaneous endoscopic gastrostomy (PEG), physiotherapy and speech and language therapy.
- Fatigue:
  - Drug therapies: amantadine
  - Non-drug therapies: CBT, exercise, occupational therapy and physiotherapy
- Oscillopsia (visual disturbance characterised by oscillations in the visual field):
  - Drug therapies:
    - First line – gabapentin
    - Second line - memantine
- Spasticity, tremor and co-ordination:
  - Drug therapies:
    - First line therapies - baclofen and gabapentin (individually or in combination)
    - Second and subsequent line therapies - botulinum toxin, carbamazepine, clonazepam, dantrolene sodium, phenol, nabiximols (not recommended by NICE as was not determined as cost effective), tizanidine
  - Non-drug therapies: Exercise, hippotherapy, therapeutic horse riding, physiotherapy TENS, deep brain stimulation and thalamotomy (destruction of part of the thalamus in the brain to stop tremor).

## EFFICACY and SAFETY

<b>Trial</b>	OPTIMUM, NCT02425644, EudraCT-2012-000540-10; ponesimod vs teriflunomide; phase III	OPTIMUM-LT, NCT03232073, EudraCT-2016-004719-10; ponesimod only; phase III extension
<b>Sponsor</b>	Actelion Pharmaceuticals Ltd	Actelion Pharmaceuticals Ltd
<b>Status</b>	ongoing	ongoing – enrolling by invitation
<b>Source of Information</b>	Trial registry <sup>16</sup>	Trial Registry <sup>17</sup>

<b>Location</b>	17 EU countries including UK, countries in Europe (non-EU) and Asia, USA, Canada and Mexico	USA
<b>Design</b>	Randomised, active controlled, parallel assignment	Non-randomised, open label extension study
<b>Participants</b>	N=1100 (planned); aged 18 to 55 years; multiple sclerosis; relapsing course from onset	N= 800 (planned); aged 18 to 65 years; participants who took part in OPTIMUM study
<b>Schedule</b>	Randomised to 20mg oral ponesimod once daily every morning (active treatment) or 14mg teriflunomide once daily every morning (active control) for 108 weeks.	Single group assignment to 20mg oral ponesimod once daily
<b>Follow-up</b>	Active treatment and follow up until 108 weeks	Active treatment and follow-up for up to 354 weeks
<b>Primary Outcomes</b>	Annual relapse rate (ARR) - baseline to end of treatment (week 108)	<ul style="list-style-type: none"> <li>• Annualized confirmed relapse rate: day 1 in core study (enrolment) to end-of-treatment (EOT) in the extension study - up to 354 wks;</li> <li>• Time from core study randomization to first confirmed relapse: day 1 to 354 wks</li> <li>• Time to first 12-wk confirmed disability accumulation: day 1 to 354 wks</li> <li>• Time to first 24-wk confirmed disability accumulation: day 1 to 354 wks</li> <li>• Patients with absence of relapses: day 1 to 354 wks</li> <li>• Change from baseline in Expanded Disability Status Scale: day 1 to 354 wks</li> <li>• Assessment of no evidence of disease activity (NEDA) status at wk 108 and EOT</li> <li>• Assessment of NEDA status at wk 108 and EOT</li> <li>• Percent change from baseline in brain volume measured by magnetic resonance imaging: day 1 to 354 wks</li> <li>• Cumulative number of combined unique active lesions measured by MRI: day 1 to 354 wks</li> <li>• Determination of number of Gd+ T1 lesions by MRI: day 1 to 354 wks</li> </ul>

		<ul style="list-style-type: none"> <li>• Cumulative number of new or enlarging T2 lesions measured by MRI: day 1 to 354 wks</li> <li>• Assessment of volume of brain lesions measured by MRI: day 1 to 354 wks</li> <li>• Absence of MRI lesions: day 1 to 354 wks</li> <li>• Determination of proportion of Gd+ lesions at baseline evolving to persistent black holes (PBHs): day 1 to 354 wks</li> <li>• Estimation of incidence rates of adverse events (AEs): day 1 to 354 wks</li> <li>• Estimation of incidence rates of treatment-emergent morphological ECG abnormalities: day 1 to 354 wks</li> <li>• Assessment of cardiac rhythms measured by electrocardiogram (ECG) parameters: day 1 to 354 wks</li> <li>• Change from baseline values by visit for cardiac rhythms: day 1 to 354 wks</li> <li>• Change in ECG parameters from pre-dose to selected post-dose assessments: From day 1 to 240 wks</li> <li>• Absolute values and percent change from baseline in forced expiratory volume and forced vital capacity: day 1 to 354 wks</li> <li>• Assessment of treatment-emergent decrease from baseline in forced expiratory volume and forced vital capacity: day 1 to 354 wks</li> <li>• Absolute change from baseline to end-of-study (EOS) versus change from baseline to end-of-treatment (EOT) in forced expiratory volume and forced vital capacity: day 1 to 354 wks</li> </ul>
<p><b>Secondary Outcomes</b></p>	<ul style="list-style-type: none"> <li>• Time to 12-week confirmed disability accumulation (CDA): baseline to wk 108</li> <li>• Percent change in brain volume (PCBV): baseline to wk 108</li> <li>• Time to first confirmed relapse : baseline to wk 108</li> <li>• Cumulative number of combined unique active lesions: baseline to wk 108</li> </ul>	

	• Change from baseline to Week 108 in fatigue-related symptoms	
<b>Key Results</b>	-	-
<b>Adverse effects (AEs)</b>	-	-
<b>Expected reporting date</b>	April 2019	April 2022

<b>Trial</b>	NCT01006265, EudraCT-2008-006786-92; ponesimod 10mg vs ponesimod 20mg vs ponesimod 40mg vs placebo; phase II	NCT01093326; EudraCT-2009-011470-15; ponesimod 10mg vs ponesimod 20mg vs ponesimod 40mg; phase II extension
<b>Sponsor</b>	Actelion Pharmaceuticals Ltd.	Actelion Pharmaceuticals Ltd.
<b>Status</b>	Completed and published	Ongoing – not recruiting
<b>Source of Information</b>	publication <sup>18</sup> , trial registry <sup>19</sup>	Abstract <sup>20</sup> , Trial registry <sup>21</sup>
<b>Location</b>	15 EU countries including UK, countries in Europe (non-EU) and Asia, USA, Canada and Australia	13 EU countries including UK, countries in Europe (non-EU) and Asia, USA and Canada
<b>Design</b>	Randomised, placebo controlled, parallel assignment	Randomised, parallel assignment extension study
<b>Participants</b>	N=464; aged 18-55 years; diagnosed with multiple sclerosis	n=353; aged 18-55 years; participants who have taken part in the core phase II study (NCT01006265)
<b>Schedule</b>	Randomised to one of four treatment arms: <ol style="list-style-type: none"> <li>1. Ponesimod dose 10mg – oral dose once daily</li> <li>2. Ponesimod dose 20mg – oral dose once daily</li> <li>3. Ponesimod dose 40mg – oral dose once daily</li> <li>4. Placebo – oral dose once daily</li> </ol>	Randomised to one of three treatment arms: <ol style="list-style-type: none"> <li>5. Ponesimod 10mg: 10mg oral dose of ponesimod</li> <li>6. Ponesimod 10mg: 20mg oral dose of ponesimod</li> <li>7. Ponesimod 10mg: 40mg oral dose of ponesimod</li> </ol>
<b>Follow-up</b>	Active treatment for 24 weeks	Not reported
<b>Primary Outcomes</b>	• Cumulative number of new gadolinium-enhancing lesions per patient recorded on four-weekly T1-weighted magnetic resonance imaging (MRI) scans: baseline to 24 wks	<ul style="list-style-type: none"> <li>• Annualized confirmed relapse rate: up to 240 wks</li> <li>• Time to first confirmed relapse: up to 240 wks</li> <li>• Time to 3 mth confirmed disability progression up to end of the study: baseline to 3 mths.</li> <li>• Time to 6 month confirmed disability progression up to end of the study: baseline to 6 mths.</li> </ul>
<b>Secondary Outcomes</b>	• Annualized confirmed relapse rate: 24 weeks	• (Serious) Adverse Events: Through study completion, for approx. 10

	<ul style="list-style-type: none"> <li>•Time to first confirmed relapse: 24 weeks</li> </ul>	years: during Treatment Period (incl. Transition), i.e. study drug administration plus 7 days, and during the Follow up, i.e. from 8 until 30 days (Period 1) or until 90 days (Period 2) after study drug discontinuation.
<b>Key Results</b>	<p>Primary outcome measure was significantly reduced (<math>p=0.0318</math> [10mg ponesimod]; <math>p &lt; 0.0001</math> [20mg ponesimod]; <math>p &lt; 0.0001</math> [40mg ponesimod]) compared to placebo group for all doses of ponesimod with 3.5, 1.1 and 1.4 new gadolinium-enhancing lesions recoded in the 10mg, 20mg and 40mg ponesimod groups respectively compared to 6.2 in the placebo group. Annualised relapse rate was also reduced in the 10mg, 20mg and 40mg ponesimod groups at 0.332, 0.417, 0.251 respectively compared to placebo (0.525).</p>	353 people were recruited to the study. Mean combined (core study plus extension) treatment duration was 115 weeks. Study treatment was discontinued prematurely in 12.5% participants.
<b>Adverse effects (AEs)</b>	<p>The total number of AEs per treatment arm was <math>n=90</math> (74.4%), <math>n=83</math> (76.95%), <math>n=88</math> (77.2%) and <math>n=88</math> (73.9%) in the placebo, 10mg, 20mg, and 40mg ponesimod groups respectively. The most common AEs in the placebo group was headache (<math>n=18</math>), nasopharyngitis (<math>n=17</math>) and upper respiratory tract infection (RTI) (<math>n=11</math>). The most common AEs in the 10mg ponesimod group was nasopharyngitis (<math>n=16</math>), headache (<math>n=15</math>) and dizziness (<math>n=8</math>). The most common AEs in the 20mg ponesimod group was headache (<math>n=15</math>), nasopharyngitis (<math>n=11</math>), upper RTI (<math>N=9</math>) and fatigue (<math>n=9</math>). The most common AEs in the 40mg ponesimod group was dyspnoea (<math>n=17</math>), headache (<math>n=15</math>), nasopharyngitis (<math>n=13</math>) and peripheral oedema (<math>n=13</math>).</p>	AEs with a prevalence above >15% include nasopharyngitis, headache, dyspnoea and upper respiratory tract infection (in any study arm) and cough, dizziness, fatigue, urinary tract infection and increased alanine aminotransferase (in those receiving placebo in core study).
<b>Expected reporting date</b>	July 2011	Study Primary completion date: December 2021

## ESTIMATED COST and IMPACT

### COST

The cost of ponesimod is not yet known.

### IMPACT – SPECULATIVE

#### IMPACT ON PATIENTS AND CARERS

- |   |  |
|---|--|
| <input type="checkbox"/> Reduced mortality/increased length of survival | <input checked="" type="checkbox"/> Reduced symptoms or disability |
| <input type="checkbox"/> Other  | <input type="checkbox"/> No impact identified                      |

#### IMPACT ON HEALTH and SOCIAL CARE SERVICES

- |   |  |
|---|--|
| <input type="checkbox"/> Increased use of existing services   | <input checked="" type="checkbox"/> Decreased use of existing services: potentially reduced use of services to treat symptoms if the drug induces fewer relapses |
| <input type="checkbox"/> Re-organisation of existing services | <input type="checkbox"/> Need for new services   |
| <input type="checkbox"/> Other                                | <input type="checkbox"/> None identified   |

#### IMPACT ON COSTS and OTHER RESOURCE USE

- |   |  |
|---|--|
| <input type="checkbox"/> Increased drug treatment costs   | <input type="checkbox"/> Reduced drug treatment costs  |
| <input type="checkbox"/> Other increase in costs  | <input checked="" type="checkbox"/> Other reduction in costs: may result in reduced treatment of symptoms if the drug induces fewer relapses |
| <input checked="" type="checkbox"/> Other: <i>uncertain unit cost compared to existing treatments</i> | <input type="checkbox"/> None identified   |

#### OTHER ISSUES

Clinical uncertainty or other research question identified:

None identified

## REFERENCES

- <sup>1</sup> Multiple Sclerosis News Today. *Ponesimod for RRMS*. Available from: <https://multiplesclerosisnewstoday.com/ponesimod-for-rrms>. [Accessed 09 November 2017].
- <sup>2</sup> Loma I and Heyman R. *Multiple Sclerosis: Pathogenesis and Treatment*. Current Neuropharmacology. (2011) 9; 409-416.
- <sup>3</sup> EMC. *Gilenya 0.5mg hard capsules*. Available from: [https://www.medicines.org.uk/emc/medicine/24443#PHARMACOLOGICAL\\_PROPS](https://www.medicines.org.uk/emc/medicine/24443#PHARMACOLOGICAL_PROPS). [Accessed 09 November 2017]. Last Updated: 30 Jun 2017.
- <sup>4</sup> ClinicalTrials.gov. *Oral Ponesimod Versus Teriflunomide In Relapsing Multiple Sclerosis (OPTIMUM)*. Available from: <https://clinicaltrials.gov/ct2/show/NCT02425644>. [Accessed 09 November 2017]. Last Updated 03 October 2017.
- <sup>5</sup> Multiple Sclerosis UK. *What is MS?* Available from: <http://www.ms-uk.org/whatisms>. [Accessed 09 September 2017].
- <sup>6</sup> Multiple Sclerosis UK. *Choices – Types of MS*. Available from: [http://www.ms-uk.org/sites/default/files/choices\\_types.pdf](http://www.ms-uk.org/sites/default/files/choices_types.pdf). [Accessed 09 November 2017].
- <sup>7</sup> NHS Choices. *Multiple Sclerosis*. Available from: <https://www.nhs.uk/conditions/multiple-sclerosis/#treatments-for-ms>. [Accessed 09 November 2017].
- <sup>8</sup> Multiple Sclerosis Trust. *Living well with MS*. Available from: <https://www.mstrust.org.uk/living-well-ms>. [Accessed 09 November 2017].
- <sup>9</sup> MS Society. *MS in the UK*. Available from: [https://www.mssociety.org.uk/sites/default/files/MS%20in%20the%20UK%20January%202016\\_0.pdf](https://www.mssociety.org.uk/sites/default/files/MS%20in%20the%20UK%20January%202016_0.pdf) [Accessed 09 November 2017]
- <sup>10</sup> NHS Digital. *Hospital Episode Statistics for England. Admitted Patient Care statistics, 2016-17*. Office of National Statistics.
- <sup>11</sup> Multiple Sclerosis trust. *Life Expectancy*. Available from: <https://www.mstrust.org.uk/a-z/life-expectancy>. [Accessed 09 November 2017].
- <sup>12</sup> Office of National Statistics. *Death Registration Summary Statistics, England and Wales, 2015*. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/death-registration-summary-tables-england-and-wales-reference-tables>. [Accessed 09 November 2017].
- <sup>13</sup> NICE Pathways. *Multiple Sclerosis*. Available from: <https://pathways.nice.org.uk/pathways/multiple-sclerosis/multiple-sclerosis-overview#content=view-node:nodes-comprehensive-review>. [Accessed 09 November 2017].
- <sup>14</sup> Multiple Sclerosis Trust. *Disease Modifying drugs*. Available from: <https://www.mstrust.org.uk/understanding-ms/ms-symptoms-and-treatments/disease-modifying-drugs-ms-decisions/disease-modifying>. [Accessed 09 November 2017]
- <sup>15</sup> Multiple Sclerosis Trust. *Treating MS Symptoms*. Available from: <https://www.mstrust.org.uk/understanding-ms/ms-symptoms-and-treatments/treating-ms-symptoms>. [Accessed 09 November 2017]
- <sup>16</sup> ClinicalTrial.gov. *Oral Ponesimod Versus Teriflunomide In Relapsing MULTiple Sclerosis (OPTIMUM)*. Available from: [https://clinicaltrials.gov/ct2/show/study/NCT02425644?show\\_locs=Y#locn](https://clinicaltrials.gov/ct2/show/study/NCT02425644?show_locs=Y#locn). [Accessed 09 November 2017]. Last Updated 03 October 2017.
- <sup>17</sup> ClinicalTrials.gov. *Long-term Extension to Study AC-058B301 to Investigate Safety, Tolerability and Disease Control of Ponesimod 20 mg in Patients With Relapsing Multiple Sclerosis (OPTIMUM-LT)*. Available from: <https://clinicaltrials.gov/ct2/show/NCT03232073>. [Accessed 09 November 2017]. Last Updated 27 July 2017.
- <sup>18</sup> Olsson T, et al. *Oral ponesimod in relapsing-remitting multiple sclerosis: a randomised phase II trial*. J Neurol Neurosurg Psychiatry. 2014 Nov;85(11):1198-208. Available from: <http://jnnp.bmj.com/content/85/11/1198.long>. [Accessed 19 November 2017].
- <sup>19</sup> ClinicalTrials.gov. *Clinical Study to Evaluate the Efficacy, Safety, and Tolerability of ACT-128800 in Patients With Relapsing-remitting Multiple Sclerosis*. Available from:

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[https://clinicaltrials.gov/ct2/show/study/NCT01006265?show\\_locs=Y#locn](https://clinicaltrials.gov/ct2/show/study/NCT01006265?show_locs=Y#locn). [Accessed 09 November 2017].  
Last Updated 4 April 2017.

<sup>20</sup> Possilli, et al. *Maintenance of efficacy, safety and tolerability of ponesimod in patients with relapsing remitting multiple sclerosis: phase II extension study*. European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) Online Library. Volume 34475, 2013. Available from:

<https://onlinelibrary.ectrims-congress.eu/ectrims/2013/copenhagen/34475/carlo.pozzilli.maintenance.of.efficacy.safety.and.tolerability.of.ponesimod.in.html?f=m2>. [Accessed 09 November].

<sup>21</sup> ClinicalTrials.gov. *Clinical Study to Investigate the Long-term Safety, Tolerability, and Efficacy of Ponesimod in Patients With Relapsing-remitting Multiple Sclerosis*. Available from:

[https://www.clinicaltrials.gov/ct2/show/study/NCT01093326?show\\_locs=Y#locn](https://www.clinicaltrials.gov/ct2/show/study/NCT01093326?show_locs=Y#locn). [Accessed 09 November 2017]. Last Updated 19 May 2017.