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HEALTH TECHNOLOGY BRIEFING
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Diroximel fumarate for relapsing-remitting multiple sclerosis

NIHRIO ID	12021	**NICE ID**	10127
Developer/Company	Biogen Idec Ltd	**UKPS ID**	650499

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

*COMMERCIAL IN CONFIDENCE

SUMMARY

Diroximel fumarate is in clinical development for the treatment of relapsing-remitting Multiple Sclerosis (MS). 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).

Diroximel fumarate is designed to rapidly convert to monomethyl fumarate (MMF) in the body. MMF is known to activate a protein called Nrf2. Among other effects, Nrf2 is thought to have antioxidant properties, and when activated should reduce damage from oxidative stress. In MS, inflammation and oxidative stress contribute to damage to nerve cells and the myelin sheath that insulates nerve fibres. By activating the Nrf2 pathway, diroximel fumarate may reduce or slow the progressive damage to nerve cells. If licensed, diroximel fumarate as an oral formulation may offer an additional treatment option for relapsing-remitting MS with fewer gastrointestinal side effects than currently available therapies.

PROPOSED INDICATION

Relapsing-remitting multiple sclerosis (RRMS).[1,2]

TECHNOLOGY

DESCRIPTION

Diroximel fumarate (BIIB098, ALK 8700) is an investigational, next-generation, oral fumarate. Upon oral administration, diroximel fumarate undergoes rapid pre-systemic conversion to monomethyl fumarate (MMF).[3] MMF is known to activate a protein called Nrf2 which is thought to have antioxidant properties, and therefore reduce or slow the progressive damage to nerve cells.[4] The precise mechanism by which diroximel fumarate works is not well understood, however like dimethyl fumerate (marketed as Tecfidera) which is also a treatment option for RRMS, it is thought to help prevent the degeneration of the myelin sheath that protects the nerve fibres seen in MS patients, without leading to systemic immune suppression.[5]

Diroximel fumarate is in clinical development for the treatment of RRMS (NCT02634307, NCT03093324). Diroximel fumarate is administered orally (as capsules) at a dose of 462 mg twice daily as a monotherapy.[a]

INNOVATION AND/OR ADVANTAGES

Diroximel fumarate offers patients with relapsing form of MS, another treatment choice. Diroximel fumarate undergoes rapid pre-systematic conversion to MMF, which is the active metabolite of dimethyl fumerate (currently approved for treatment of RRMS).[6] Diroximel fumarate has physiochemical properties that are distinct from dimethyl fumerate, and therefore may potentially offer improved gastrointestinal (GI) tolerability. Previous evidence suggests significant GI events for patients while using dimethyl fumerate, which can negatively impact treatment adherence, leading to treatment interruption and discontinuation.[7-11]

Interim clinical trial data testing the safety of diroximel fumarate, has showed low incidence of GI adverse events, with no reports of serious events. During the first month of treatment 0.5% of patients discontinued due to GI adverse events, and there were no serious GI adverse events. For months 0-3, serious adverse events and adverse events-related discontinuation rates were 2.3% and 3.7%.[12]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Diroximel fumarate does not currently have Marketing Authorisation in the UK/EU for any indication.

PATIENT GROUP

DISEASE BACKGROUND

Multiple sclerosis (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.[13]

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.[14]

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).[15]

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.[15]

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 estimates and prevalence data from Mackenzie et al.[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] Assuming the above noted proportion of 85% of people with MS have RRMS[15], the annual incidence of RRMS in England is 3,502.

According the HES data for 2017-18, there were 50,875 admissions, 66,336 bed days and 54,448 finished consultant episodes for multiple sclerosis (ICD10 G35-G37 – Demyelinating diseases (including MS) of the central nervous system).[20]

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.[21]

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 and to reduce the severity of these relapses, however they cannot reverse existing damage. Management of MS symptoms can be overseen by specialist referrals as appropriate.[22,23]

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.[23] The treatments given to manage symptoms may include drug therapies, self-management strategies or different types of therapies.[24]

CURRENT TREATMENT OPTIONS

There are currently eight disease modifying drugs with marketing authorisations for RRMS in the UK, including:[23]

- **Alemtuzumab** (Lemtrada)
- **Beta interferons and glatiramer acetate** (Avonex, Betaferon, Extavia and Copaxone)
- **Cladribine** (Mavenclad)
- **Dimethyl fumarate** (Tecfidera)
- **Fingolimod** (Gilenya)
- **Natalizumab** (Tysabri)
- **Ocrelizumab** (Ocrevus)
- **Teriflunomide** (Aubagio)

PLACE OF TECHNOLOGY

If licensed, diroximel fumarate will offer an additional monotherapy treatment option for patients with RRMS.

CLINICAL TRIAL INFORMATION

Trial	EVOLVE-MS-1, NCT02634307; adults aged 18-65; diroximel fumarate (single assignment); phase III
Sponsor	Alkermes, Inc.
Status	Ongoing
Source of Information	Trial registry[2], manufacturer[a], conference poster[25]
Location	EU (not UK), USA, Russia and Serbia
Design	Single group assignment, open label
Participants	n=935 (planned); aged 18-65 yrs; RRMS; neurologically stable with no evidence of relapse within 30 days prior to visit 2
Schedule	Diroximel fumarate capsules (231 mg) taken twice daily for the first week followed by 462 mg (2x 231 mg) twice daily from day 8 for up to 96 wks of treatment.

[a] Information provided by Biogen

Follow-up	Not reported
Primary Outcomes	Safety will be demonstrated by incidence of Adverse Events [Time Frame: up to 96 wks] All enrolled subjects who receive at least one dose of ALKS 8700 will be used in the safety and tolerability analysis
Secondary Outcomes	Not reported
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary and study completion date Dec 2020

Trial	EVOLVE-MS-2, NCT03093324; adults aged 18-65; diroximel fumarate vs dimethyl fumarate; phase III
Sponsor	Alkermes, Inc.
Status	Ongoing
Source of Information	Trial registry[1], poster[3], manufacturer[b]
Location	EU (not UK) and USA
Design	Randomised, parallel assignment, active controlled, quadruple masked
Participants	n=500 (planned); aged 18-65 yrs; RRMS; neurologically stable with no evidence of relapse within 30 days prior to randomisation
Schedule	The study includes a 4-week screening period (including 1 week lead-in period) followed by a 5-week double-blind treatment period with 2 blinded treatment groups. Subjects are randomised into two arms: • **Experimental:** Subjects receive diroximel fumarate capsules (231 mg taken twice daily for the first week followed by 462 mg (2 x 231 mg capsules) twice daily from day 8 onwards), for 5 wks. • **Active comparator:** Subjects receive dimethyl fumarate capsules (one 120 mg capsule twice daily for the first week and 240 mg twice daily from day 8 onwards),for 5 wks.
Follow-up	Not reported
Primary Outcomes	Number of days with GI events using an individual GI symptom scale [Time frame: 5 wks]
Secondary Outcomes	Time frame: 5 wks • Number of days with a GI symptom intensity score using an individual GI symptom scale • Number of days with overall GI symptoms using a global GI symptom scale • Worst GI symptom intensity by week using an individual GI symptom scale • Safety will be measured by incidence of adverse events (AEs)
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary and study completion date Q1 2020

[b] Information provided by Biogen

ESTIMATED COST

The cost of diroximel fumarate 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. 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. Teriflunomide for treating relapsing–remitting multiple sclerosis (TA303). January 2014.
- NICE technology appraisal guidance. Alemtuzumab for treating relapsing–remitting multiple sclerosis (TA312). May 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. *Treatment Algorithm for Multiple Sclerosis Disease-Modifying Therapies (NHS England Reference: 170079ALG)*. London: NHS England; 2019. Available from: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2019/03/Treatment-Algorithm-for-Multiple-Sclerosis-Disease-Modifying-Therapies-08-03-2019-1.pdf.

OTHER GUIDANCE

- NHS England. Manual for Prescribed Specialised Services 2017/18. Chapter 11. Adult specialist neurosciences services. 2017.[26]
- Department of Health. NHS outcomes framework 2016 to 2017: Domains 1–5. 2016.[27]
- Department of Health. The National Service Framework for Long-term Conditions. 2005.[28]

ADDITIONAL INFORMATION

REFERENCES

1 ClinicalTrials.gov. *A Tolerability Study of ALKS 8700 in Subjects With Relapsing Remitting Multiple Sclerosis (RRMS)*. *Trial ID: NCT03093324*. 2017. Status: Ongoing. Available from: https://clinicaltrials.gov/ct2/show/study/NCT03093324?show_locs=Y [Accessed 7th February 2019].

2 ClinicalTrials.gov. *A Study of ALKS 8700 in Adults With Relapsing Remitting Multiple Sclerosis (MS)*. *Trial ID: NCT02634307*. 2015. Status: Ongoing. Available from: https://clinicaltrials.gov/ct2/show/NCT02634307 [Accessed 7th February 2019].

3 Naismith RT, Leigh-Pemberton RA, Claxton AE, Hard ML, Du Y, von Moltke L, et al. *EVOLVE-MS-2: a randomized, double-blind, phase 3 study of the gastrointestinal tolerability of ALKS 8700 versus dimethyl fumarate in relapsing-remitting multiple sclerosis.* 2017. Available from: https://cmsc.confex.com/cmsc/2017/webprogram/Paper4760.html [Accessed 13th February 2019].

4 Multiple Sclerosis News Today. *BIIB098 (Previously ALKS 8700).* 2016. Available from: https://multiplesclerosisnewstoday.com/alks-8700-multiple-sclerosis/ [Accessed 30th April 2019].

5 Multiple Sclerosis News Today. *FDA asked to approve diroximel fumarate as oral treatment for relapsing MS.* 2018. Available from: https://multiplesclerosisnewstoday.com/2018/12/18/alkermes-biogen-request-fda-approval-of-diroximel-fumarate-for-relapsing-ms/ [Accessed 13th February 2019].

6 Moharregh-Khiabani D, Linker RA, Gold R, Stangel M. Fumaric acid and its esters: an emerging treatment for multiple sclerosis. *Current Neuropharmacology*. 2009;7(1):60-4. Available from: https://doi.org/10.2174/157015909787602788.

7 Fox EJ, Vasquez A, Grainger W, Ma TS, von Hehn C, Walsh J, et al. Gastrointestinal tolerability of delayed-release dimethyl fumarate in a multicenter, open-label Study of patients with relapsing forms of multiple sclerosis (MANAGE). *International journal of MS care*. 2016 Jan-Feb;18(1):9-18. Available from: https://doi.org/10.7224/1537-2073.2014-101.

8 Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *New England Journal of Medicine*. 2012;367(12):1087-97. Available from: https://doi.org/10.1056/NEJMoa1206328.

9 Gold R, Giovannoni G, Phillips JT, Fox RJ, Zhang A, Marantz JL. Sustained effect of delayed-release dimethyl fumarate in newly diagnosed patients with relapsing–remitting multiple sclerosis: 6-year interim results from an extension of the DEFINE and CONFIRM studies. *Neurology and Therapy*. 2016;5(1):45-57. Available from: https://doi.org/10.1007/s40120-016-0042-8.

10 Gold R, Giovannoni G, Phillips JT, Fox RJ, Zhang A, Meltzer L, et al. Efficacy and safety of delayed-release dimethyl fumarate in patients newly diagnosed with relapsing–remitting multiple sclerosis (RRMS). *Multiple Sclerosis Journal*. 2014;21(1):57-66. Available from: https://doi.org/10.1177/1352458514537013.

11 O'Gorman J, Russell HK, Li J, Phillips G, Kurukulasuriya NC, Viglietta V. Effect of aspirin pretreatment or slow dose titration on flushing and gastrointestinal events in healthy volunteers receiving delayed-release dimethyl fumarate. *Clinical Therapeutics*. 2015;37(7):1402-19.e5. Available from: https://doi.org/10.1016/j.clinthera.2015.03.028.

12 Naismith R, Leigh-Pemberton R, Rezendes D, Nangia N, Kandinov B, von Moltke L, et al. EVOLVE-MS-1: a phase 3, open-label, long-term safety study of ALKS 8700 in relapsing-remitting multiple sclerosis (P6.360). *Neurology*. 2018;90(15 Supplement):P6.360. Available from: http://n.neurology.org/content/90/15_Supplement/P6.360.abstract.

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

14 National Multiple Sclerosis Society. *Types of MS.* 2019. Available from: https://www.nationalmssociety.org/What-is-MS/Types-of-MS [Accessed 12th March 2019].
15 MS-UK. *Types of MS*. Colchester: MS-UK; 2019. Available from: http://www.ms-uk.org/sites/default/files/choices_types.pdf.
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 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].
21 Multiple Sclerosis Trust. *Life expectancy.* 2018. Available from: https://www.mstrust.org.uk/a-z/life-expectancy [Accessed 7th February 2019].
22 NHS. *Treatment - Multiple sclerosis.* 2018. Available from: https://www.nhs.uk/conditions/multiple-sclerosis/treatment/ [Accessed 13th February 2019].
23 NICE Pathways. *Multiple sclerosis.* 2019. Available from: https://pathways.nice.org.uk/pathways/multiple-sclerosis [Accessed 7th February 2019].
24 Multiple Sclerosis Trust. *Treatment finder.* 2019. Available from: https://www.mstrust.org.uk/about-ms/ms-treatments/treatment-finder [Accessed 7th February 2019].
25 Naismith R, Claxton A, Leigh-Pemberton R, Du Y, Hard M, von Moltke L, et al. Safety and tolerability of ALKS 8700 in relapsing-remitting multiple sclerosis: Phase 3 open-label study design (EVOLVE-MS-1). *European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS)*. London, UK 2016:P748.
26 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.
27 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.
28 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.

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