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Newcastle University

Health Technology Briefing
July 2022

Dimethyl fumarate for relapsing remitting multiple sclerosis in people aged 13 years and older

Company/Developer	Biogen

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 27203	NICE ID: 11778	UKPS ID: 665027

Licensing and Market Availability Plans

Currently in phase III/II trials

Summary

Dimethyl fumarate is in clinical development for patients aged 10 -17 years and older with relapsing-remitting multiple sclerosis (RRMS). Multiple Sclerosis (MS) is a chronic condition that affects the brain and spinal cord, it can lead to increased mortality and is one of the most common causes of disability in younger adults. Relapsing and remitting MS is the most common form of MS with 80% of patients diagnosed with this type and is characterised by repeated episodes of new or worsening symptoms which then improve over time but often do not disappear. Symptoms of MS include fatigue, difficulty walking, vision problems, problems controlling bladder, numbness or stiffness, balance and coordination problems, and cognitive impairment, all impairing the quality of life of a person with MS. However, there are no approved pharmacological treatments for paediatric population with RRMS.

Dimethyl fumarate thought to work by activating a protein called nuclear factor (erythroid-derived 2)-like 2 (Nrf2) that regulates certain genes that produce 'antioxidants' involved in protecting cells from damage. However, the mechanism by which dimethyl fumarate exerts therapeutic effects in multiple sclerosis is not fully understood. In the phase III trial, dimethyl fumarate is administered orally. Dimethyl fumarate has been shown to be safe and generally well tolerated for paediatric patients with RRMS. If licensed, dimethyl fumarate will offer an additional treatment option for paediatric patients with RRMS who currently have few effective and well-tolerated therapies available.

Proposed Indication

Treatment of relapsing-remitting multiple sclerosis (RRMS) in patients aged 13 years and older.[1]

Technology

Description

Dimethyl fumarate (FP-187, Skilarence, LAS41008, Tecfidera, BG-12, Fumaderm) is thought to work by activating a protein called nuclear factor (erythroid-derived 2)-like 2 (Nrf2) that regulates certain genes that produce 'antioxidants' involved in protecting cells from damage. However, the mechanism by which dimethyl fumarate exerts therapeutic effects in multiple sclerosis is not fully understood.[1,2]

Dimethyl fumarate is currently in clinical development for treating RRMS in patients aged 10-17 years old.[3] The approved dosage and route of administration of dimethyl fumarate is a starting dose of 120 mg twice a day administered orally as capsules. After 7 days, the dose should be increased to the recommended maintenance dose of 240 mg twice a day.[3]

Key Innovation

Results from phase 3 clinical trials (DEFINE, CONFIRM) and a follow-up study (ENDORSE) have provided good evidence for the efficacy and safety profile of dimethyl fumarate for adult patients with RRMS. Patient-reported outcomes (PROs) assessment revealed stabilisation or improvement in health-related quality of life and work productivity of patients treated with dimethyl fumarate compared to placebo reflecting a higher patient satisfaction to therapy. Being an oral agent with relatively favourable risk versus benefit profile dimethyl fumarate is commonly prescribed first-line agent.[4]

In terms of paediatric populations, first-line injectable therapies for multiple sclerosis in children may be ineffective or not well-tolerated. A study, assessing the effectiveness of oral dimethyl fumarate for paediatric patients with RRMS, suggests that oral dimethyl fumarate is safe and generally well tolerated for these populations.[5] Therefore, if licensed, dimethyl fumarate will offer an additional treatment option for paediatric patients with RRMS who currently have no effective and well-tolerated therapies available.

Regulatory & Development Status

Dimethyl fumarate is already licensed in the EU/UK for the treatment of adult patients with RRMS.[2]

Dimethyl fumarate is in phase III/II clinical development for:[6]

- Acute ischemic stroke
- Intracerebral hemorrhage
- Age-related macular degeneration
- Severe Acute Respiratory Syndrome

Patient Group

Disease Area and Clinical Need

Multiple Sclerosis (MS) is a chronic condition that affects the brain and spinal cord, it can lead to increased mortality and is one of the most common causes of disability in younger adults as it is most commonly diagnosed in people in their 20's, 30's or 40's.[7] MS is an autoimmune condition where the body's own

immune system starts attacking central nervous system (CNS), causing inflammation that damages the myelin sheath protecting the nerve fibres and the nerves themselves, resulting in disruption of signals from the brain.[7,8] Relapsing and remitting MS is the most common form of MS with 80% of patients diagnosed with this type, and is characterised by repeated episodes of new or worsening symptoms which then improve over time but often do not disappear.[7] Active disease is defined as at least two clinically significant relapses occurring within the last 2 years; highly active disease is characterised by an unchanged/increased relapse rate or by ongoing severe relapses compared with the previous year, despite treatment with interferon beta. Rapidly-evolving severe relapsing-remitting MS is defined by two or more disabling relapses in one year, and one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI.[9] Symptoms of MS include fatigue, difficulty walking, vision problems, problems controlling bladder, numbness or stiffness, balance and coordination problems, and cognitive impairment, all impairing the quality of life of a person with MS.[7]

Each year in the UK over 7,000 people are newly diagnosed with MS, an average prevalence rate of 286 women and 111 men per 100,000 people (2012-17).[10] It is estimated that between 8 and 11 new cases of MS are diagnosed each year in England per 100,000 population.[11] The average life expectancy for patients with MS is 5-10 years lower than the average in the UK.[7] In England (2020-21), there were 47,489 finished consultant episodes (FCE) for MS (ICD-10 code: G35), with 45,308 hospital admissions that resulted in 41,440 day cases and 26,417 FCE bed days.[12] However, the population likely to be eligible to receive dimethyl fumarate could not be estimated from available published sources.

Recommended Treatment Options
NICE recommends Fingolimod for children with MS.[13]

Clinical Trial Information

Trial	**CONNECT; NCT02283853;** Open-Label, Randomized, Multicenter, Multiple-Dose,Active-Controlled, Parallel-Group, Efficacy and Safety Study of BG00012 in Children From 10 to Less Than 18 Years of Age With Relapsing-Remitting Multiple Sclerosis, With Optional Open-Label Extension **Phase III** - Active, not recruiting **Location(s):** 12 EU countries, UK, USA, Canada, Israel and Kuwait **Primary completion date:** September 2025
Trial Design	Randomised, parallel assignment, open-label
Population	N=156; participants 10 to 17 years old who have a diagnosis of RRMS as defined by the revised consensus definition for paediatric RMMS
Intervention(s)	Dimethyl fumarate 240 mg capsule twice daily orally
Comparator(s)	Interferon β-1a 30 µg weekly via intramuscular injection
Outcome(s)	Primary outcome measures • Proportion of Participants Free of New/Newly Enlarging T2 Hyperintense Lesions on Brain MRI Scans [time frame: at week 96] • Number of Participants That Experience Adverse Events (AEs) or Serious Adverse Events (SAEs) [time frame: up to 7 years] • Number of Participants Who Discontinue Study Treatment due to an AE [time frame: up to 7 years]

	See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information

Trial	NCT03870763; A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, 3-Arm, Parallel Group Study in Pediatric Subjects Aged 10 Through 17 Years to Evaluate the Efficacy and Safety of BG00012 and BIIB017 for the Treatment of Relapsing-Remitting Multiple Sclerosis **Phase III** - Active, not recruiting **Location(s):** two EU countries, USA and other countries **Primary completion date:** July 2022
Trial Design	Randomised, parallel assignment, quadruple-blinded, placebo-controlled
Population	N=11; participants 10 to 17 years old who have a diagnosis of RRMS as defined by the revised consensus definition for paediatric MS
Intervention(s)	• Dimethyl fumarate 240 mg capsule twice daily orally and placebo subcutaneous (SC) injection every 2 weeks for up to 96 weeks (2 years) • Peginterferon beta-1a 125 micrograms (µg) SC injection every 2 weeks and placebo capsule twice daily orally for up to 96 weeks (2 years)
Comparator(s)	Placebo SC injection every 2 weeks and placebo capsule twice daily orally for up to 96 weeks
Outcome(s)	Primary outcome measure: time to first relapse [time frame: baseline up to week 96] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Dimethyl fumarate is already marketed in the UK for the treatment of adult patients with RRMS. The prices of a pack of 120-mg tablets (14 tablets per pack) and 240-mg tablets (56 tablets per pack) are £343 and £1373 respectively (excluding VAT; manufacturer's submission). The manufacturer of dimethyl fumarate has agreed a patient access scheme with the Department of Health, with a simple discount applied at the point of purchase or invoice. The level of discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.[14]

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Dimethyl fumarate for treating relapsing-remitting multiple sclerosis (TA320). August 2014.
- NICE quality standard. Multiple sclerosis (QS108). January 2016.
- NICE interventional procedure guidance. Percutaneous venoplasty for chronic cerebrospinal venous insufficiency in multiple sclerosis (IPG640). January 2019.

NHS England (Policy/Commissioning) Guidance

- NHS England. Treatment Algorithm for Multiple Sclerosis Disease-Modifying Therapies (NHS England Reference: 170079ALG). London: NHS England; 2019.
- NHS England. Clinical Commissioning Policy: Disease Modifying Therapies for Patients with Multiple Sclerosis (MS). NHS England/D04/P/b. May 2014.

Other Guidance

- European Committee of Treatment and Research in Multiple Sclerosis (ECTRIMS). Guideline on the pharmacological treatment of people with multiple sclerosis. 2018.[15]
- European Medicines Agency. Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis. 2015.[16]

Additional Information

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