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Diroximel Fumarate (ALKS 8700 / BIIB0998) For Relapsing-Remitting Multiple Sclerosis

Keywords: Diroximel fumarate, Vumerity™, multiple sclerosis, gastrointestinal tolerability

SUMMARY OF TECHNOLOGY

Diroximel fumarate (ALKS 8700 / BIIB0998) is a novel oral small molecule of fumarate developed for the disease modifying treatment of relapsing-remitting multiple sclerosis (RRMS).[1]

Diroximel fumarate is known to activate a protein called Nrf2, which is thought to have antioxidant properties and has the ability to reduce oxidative stress. It is a prodrug of monomethyl fumarate (MMF), which is also the active metabolite of dimethyl fumarate (DMF, Tecfidera), the current FDA approved oral medication for RRMS. In phase 3 studies of Tecfidera, gastrointestinal adverse effects (AE) were the leading cause of discontinuation of treatment. Diroximel fumarate promises better gastrointestinal tolerability compared to Tecfidera.[1]

The immunomodulatory nature and anti-oxidant properties of diroximel fumarate, like Tecfidera, are expected to help prevent the degeneration of the myelin sheath that protects nerve fibers seen in multiple sclerosis patients, without leading to systemic immune suppression.[1]

Diroximel fumarate (ALKS 8700 / BIIB0998) is a 462 mg capsule, to be taken twice daily. Once inside the body, it is metabolised into an active agent called monomethyl fumarate.[1] Monomethyl fumarate is metabolised via the tricarboxylic cycle to fumarate, glucose and carbon dioxide (CO2) and excreted primarily as exhaled CO2.

Alkermes and Biogen announced the submission of a New Drug Application to U.S. Food and Drug Administration for Diroximel fumarate (Vumerity™) in Multiple Sclerosis on 17 December 2018.[1]

INNOVATIVENESS

Novel, completely new	
Incremental improvement of the existing technology	√
New indication of an existing technology	

DISEASE BURDEN

Multiple sclerosis(MS) is an immune mediated condition of the damage of myelin sheath surrounding the nerve fibers in the central nervous system. Inappropriate inflammatory response to myelin associated autoantigens will result in demyelinating lesions and neurogeneration progressively.

It is uncommon in Malaysia, with prevalence of 2-3 in 100,000.[2] The Multiple Sclerosis Society quotes 1000 sufferers in Malaysia. But the morbidity and mortality is high. Women are three times more prone than men to suffer from MS. They are usually detected at age 20-40 years old. The causes include genetics, environment, and virus. There is no cure for MS but management of MS with pharmaceuticals (subcutaneous/ intramuscular/ intravenous injections, oral, disease modifying drugs), diet, exercise (physiotherapy and occupational therapy) and alternative therapy helps improve symptoms and prevent relapse.[3]

There are 4 subtypes of MS:[3]

1) RRMS : Characterised by unpredictable relapses, which either fade away partial/ completely for months or years. About 85% of MS patients are diagnosed with RRMS.
2) Primary Progressive MS: Characterized by slow accumulation of disabilities, without attacks, but no period of remission in between. About 10% of MS patients are diagnosed with PPMS.
3) Secondary Progressive MS: Follows a diagnosis of RRMS, with relapse and remissions, sometimes with plateaus. But disease begins to progress steadily. About 10-20 years after diagnosis, half of RRMS patients worsen and have increasing levels of disabilities.
4) Progressive Relapsing MS: Rarest condition only occuring in 5% of the diagnosed patients. Relapse with or without recovery and steadily increasing disability from the beginning.

CURRENT OPTIONS FOR PATIENTS

Current oral approved treatment for RRMS is oral dimethyl fumarate (Tecfidera). The Malaysian Clinical Practice Guidelines on Management of Multiple Sclerosis issued in 2015, recommended the use of disease modifying therapy with subcutaneous interferon beta or oral treatment dimethyl fumarate (Tecfidera) as first line for active RRMS. Tecfidera was approved by FDA in 2013 for treatment for RRMS.

POTENTIAL IMPACT OF TECHNOLOGY

Clinical Impact

Two phase 3 studies are currently evaluating ALKS 8700 in patients with RRMS: EVOLVE-MS-1, an open-label long-term efficacy, safety and tolerability study of ALKS 8700, and EVOLVE-MS-2, a 5-week, head-to-head study comparing the gastrointestinal tolerability of ALKS 8700 and DMF.[4]

EVOLVE-MS-1 is a two-year, open-label study to investigate the long-term safety, tolerability and treatment effect of BIIB098 462 mg twice daily in 935 patients with RRMS, at 107 sites across the U.S and Europe, expected to complete in 2020. Interim results were presented at the 2018 American Academy of Neurology Annual Meeting. The annualised relapse rate (ARR) in 570 participants after one year of treatment was 0.16.[4] Inusah et al. in a 2010 study of assessing changes in ARR in RRMS found the mean ARR for the placebo groups was 1.002 compared to the treatment arms with mean ARR of 0.68.[5] In a subset of these individuals, 374 participants with available MRI data, the number of gadolinium-enhancing lesions decreased 80% compared with baseline when they first joined the trial, from a mean 1.5 to 0.3 ($p<0.0001$).[6]

Interim results from 696 patients treated with diroximel fumarate was presented in the annual meeting of Consortium of Multiple Sclerosis Centers (CMSC) in Seattle (May 28–June 1). It was shown that patients treated with prior interferon glatiramer acetate and then diroximel fumarate was associated with significant improvements in radiological and clinical endpoints over one year compared to baseline. The ARR at week 48 dropped by 72% compared to baseline. Additionally, the mean number of gadolinium-enhancing (Gd+) lesions was reduced by 64 percent with diroximel fumarate compared to baseline, and the percentage of patients with no Gd+ lesions at week 48 was 89 percent compared to 74 percent at baseline. Diroximel fumarate demonstrated superiority in tolerability especially with low rates of gastrointestinal (GI) adverse events.[7]

EVOLVE-MS-2 is a 5-week head to head study comparing oral diroximel fumarate 462 mg twice daily and oral dimethyl fumarate 240 mg twice daily, expected to be completed in 2019. The primary outcome will measure the number of days that participants experience gastrointestinal side effects, secondary measures will include other potential side effects. [4]

Cost

No cost information of diroximel fumarate was retrieved. As comparison, Tecfidera is estimated to have a whole sale price of RM4000 per month, with average 40 months maintenance treatment. But it is not registered with the Malaysian National Pharmaceutical Regulatory Agency.

Organisational – no changes identified.

Societal/ethical- None identified.

Safety –
In a phase I clinical trial, randomised and double blinded, involving 35 healthy participants,[8] adverse effect (AE) rates were 45.7% and 54.3% after administration of ALKS 8700 and DMF, respectively; most AEs were mild (all AEs were mild after ALKS 8700 administration). Common AEs (>5%) were flushing, dizziness, and constipation after ALKS 8700 administration and flushing, nausea, and diarrhoea after DMF administration. After the initial three months of treatment with ALKS8700, only 2.3% reported serious AE and 3.7% stopped treatment. [9]

Incidence of GI adverse events over the one year treatment period was 30.9%, generally mild or moderate in severity, appeared within the first month of treatment, and tended to resolve quickly in 89% of patients. Less than 1% (0.7%) had GI adverse events leading to discontinuation.[7]

EVIDENCE

Published Papers:

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