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ASIA EDITION

"We're dedicated to Multiple Sclerosis with two approved therapies and Evobrutinib currently in phase 3 trial"

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Rare diseases remain untreatable globally despite major advances in research that have enabled us to understand their molecular basis, as well as legislation that provides regulatory and economic incentives to encourage their development. Rare diseases often lack treatment options and are decades behind in R&D. An important component of addressing this translational gap is the selection of the optimal therapeutic modality to translate advances in rare disease knowledge into potential medicines, such as small molecules, monoclonal antibodies, protein replacement therapies, oligonucleotides, gene and cell therapies, as well as drug repurposing. Global pharma firm, Merck is into development of therapies for one such rare disease, Multiple sclerosis (MS), a chronic inflammatory condition of the central nervous system prevalent in Asia-Pacific. It is the most common non-traumatic, disabling neurological disease in young adults. Like many other rare diseases, MS has received less attention from drug developers because of the smaller market opportunity in this group of patients. In an interaction with BioSpectrum Asia, Liz Henderson, Senior Vice President APAC, Merck Healthcare explains the therapeutic prospects around this rare disease.

Why does multiple sclerosis (MS) deserve attention and investment in APAC for the development of novel treatments?

In my opinion, there can never be too many treatment options for someone with a serious autoimmune disease like MS, because not every treatment works for every patient.

Merck believes that a healthier future deserves a sizable investment. In 2018 our Healthcare business devoted roughly 20 per cent of total sales to R&D activities aimed at discovering and developing new therapies. All of these are integrated in four strategically located and highly connected hubs on three continents: Darmstadt, Boston, Beijing and Tokyo.

What are the latest developments and investments at Merck around MS?

Merck has a long history with MS – we've been developing drugs to treat this disease for over 20 years and we continue to invest heavily in this area of unmet need. The main goal of our drug development programme for MS patients is to help improve their quality of life and delay the progression of the disease. The goal is to reduce the treatment burden, improve adherence, improve care outcomes and make administration easier. We are also fostering debate among the MS community.

In 2017, we received EMA approval for Mavenclad, an oral therapy to treat relapsing MS. This was followed by FDA approval in 2019 for the therapy. Our first product to receive approval was Rebif, 20 years ago, and we have an active neurology and immunology pipeline in lupus and MS with assets in stages 2 and 3 of development.

In addition, we partner with companies with interesting drug candidates which can provide us with strategic additions to our portfolio. Our recent acquisition of Chord Therapeutics allows us to explore the potential of Cladribine in indications beyond MS to generalised myasthenia gravis (gMG) and neuromyelitis optica spectrum disorder (NMOSD). We primarily focus on the molecules we know well and strive to develop their full potential for the benefit of patients.

Furthermore, an earlier initiative called the Grant for Multiple Sclerosis Innovation (GMSI) which supports the advancement of science and medical research in the field of MS. Funding is awarded to early stage research projects, enabling talented and inspiring researchers to advance our understanding of how we predict, diagnose, treat and monitor the progression of this disabling disease.

How do you foresee the opportunities and challenges in the MS treatment sphere?

MS is a complex disease that is difficult to treat. The greatest challenge is around the medical community's understanding of the disease itself – MS symptoms present differently from patient to patient, and responses to therapies vary greatly, making clinical trials challenging.

Therefore, research into biomarkers will open up a lot of possibilities in terms of treatments and response rates. There has been significant progress made in the last decade in the identification of MS biomarkers, and we can now diagnose patients faster, and ensure safe and personalised treatment.

Are there any new pathways that can modulate the immune system in a more targeted way than traditional immuno-suppressant therapies to tackle rare diseases?

For immune mediated disease, our focus is on targeting the innate and adaptive components of the immune system, which means we develop products that aim to inhibit inappropriate immune activation that contributes to the disorder, as well as enhancing immune tolerance, training the body not to react to certain triggers.

In the immune system, there are many complex pathways that can go wrong, which is why so many drugs are being developed by pharmaceutical companies targeting various complex pathways involved in immune dysfunction. For patients with autoimmune diseases, disease-modifying therapies have greatly evolved. Drug discoveries usually start by identifying a specific target, such as inhibiting the Bruton's Tyrosine Kinase (BTK) receptor. Evobrutinib is a BTK inhibitor, developed by Merck and is currently in phase 3 trials for MS.

From a mechanistic perspective, what excites me about this drug is that it is the first and only BTK inhibitor to show a reduction in levels of a key biomarker called blood neurofilament light chain (NfL) levels, indicating neuronal damage and

inflammation in patients with MS. Measurement of this biomarker, especially early on in the disease, can capture the extent of neuroaxonal damage.

While monoclonal antibodies are viewed as a mainstay of treatment for MS because they bind very specifically to large proteins called antigens that can then mediate their effects on specific pathways, BTK inhibitors are much smaller molecules, and are able to enter the central nervous system, which is a property that monoclonal antibodies do not have and thus might have an impact on the disease evolution over time.

Which drugs are in the pipeline for immune-mediated rare diseases? What are Merck's development plans for FY 2023?

In collaboration with Global Business Development, we scout and evaluate external opportunities in immunology, including technologies, preclinical and early clinical assets. In January 2022, we entered an out-licensing agreement for a drug called sprifermin with Trial Spark and High Line Bio, based in New York. Sprifermin is a disease modifying treatment for osteoarthritis (OA) that improves cartilage thickness. The drug is a recombinant form of human fibroblast growth factor 18 and could be the first disease modifying therapy for people with OA.

Across our Neurology and Immunology portfolio, we are also developing drugs to treat lupus, another autoimmune disease that occurs when the body attacks its own cells. Enpatoran is a novel, investigational immune checkpoint inhibitor in development for two different types of lupus, systemic lupus erythematosus (SLE) and cutaneous lupus erythematosus (CLE).

Lupus is a multifactorial autoimmune disease compromising various processes and cell types, including the loss of tolerance to self-nuclear antigens and is driven by Toll Like Receptor (TLR) 7/8 overactivation. TLR’s are a relatively new discovery (1985). They are an important part of our innate immune system and defend us against pathogens. Inhibiting the overactivation of these proteins has recently been identified as a potential target for lupus.

Enpatoran is currently in phase 2 trials and we expect to generate preliminary data soon.

In Neurology and Immunology, we remain dedicated to MS with two approved therapies, and we are focusing on our ongoing phase 3 study of Evobrutinib, which will be out by the end of 2023.

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