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Newcastle University

Health Technology Briefing
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Human immunoglobulin with recombinant human hyaluronidase maintenance therapy for treating multifocal motor neuropathy

Company/Developer	Takeda UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

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Licensing and Market Availability Plans

Currently in phase II clinical trials.

Summary

Human immunoglobulin with recombinant human hyaluronidase is currently in development for the maintenance treatment of patients with multifocal motor neuropathy (MMN). MMN is a rare disease that causes damage to the nerves in the arms and legs. The nerve damage is progressive and worsens over time. The cause of MMN is unknown, but it is thought to be due to an abnormal immune response. The main treatment option for MMN is immunoglobulin therapy. Treatment usually does not completely reverse all the symptoms, and those patients who do respond will require repeated treatments to maintain their improvement.

Human immunoglobulin with recombinant human hyaluronidase is a highly purified protein extracted from human plasma (part of the blood). It contains immunoglobulin G (IgG), which is a type of antibody, and works by restoring abnormally low IgG levels to their normal range in the blood. The product also contains recombinant human hyaluronidase, a form of the natural human enzyme, which helps the active substance to disperse under the skin and improve its absorption into the body. Human immunoglobulin with recombinant human hyaluronidase is administered subcutaneously. If licensed, human immunoglobulin with recombinant human hyaluronidase will offer an additional maintenance therapy option for patients with MMN.

Proposed Indication

Treatment of adult patients aged 18 to 90 years with Multifocal Motor Neuropathy (MMN).[1]

Technology

Description

Human immunoglobulin with recombinant human hyaluronidase (TAK-771; HyQvia) is a dual vial unit consisting of one vial of human normal immunoglobulin (Immune Globulin 10% or IG 10%) and one vial of recombinant human hyaluronidase. Human normal immunoglobulin contains mainly immunoglobulin G (IgG) with a broad spectrum of opsonising and neutralising antibodies against infectious agents.[2] The mechanism of action in indications other than replacement therapy is not fully elucidated but includes immunomodulatory effects.[3] Recombinant human hyaluronidase is a soluble recombinant form of human hyaluronidase that increases the permeability of the subcutaneous tissue and facilitates the dispersion and absorption of IG 10%.[2]

Human immunoglobulin with recombinant human hyaluronidase is currently in phase II clinical development for the treatment of patients with MMN. In the phase II clinical trial (NCT02556437), patients received 24 weeks of treatment with conventional subcutaneous (SC) immunoglobulin (subcuvia) followed by 24 weeks of treatment with human immunoglobulin with recombinant human hyaluronidase.[1]

Key Innovation

Treatment of MMN necessitates administration of immunoglobulins (IG) to improve and maintain muscle strength. Subcutaneous immunoglobulin (SCIG) therapy for MMN is equally efficacious to intravenous immunoglobulin (IVIG); may be self-administered and may induce fewer systemic adverse reactions.[4] However, limited SC infusion volumes and reduced bioavailability necessitate multiple infusion sites, more frequent treatment, and dose adjustment to achieve pharmacokinetic equivalence. This is an issue in MMN where relatively high and frequent doses are necessary to maintain long-term improvement of muscle strength.[4]

Recombinant human hyaluronidase (rHuPH20) increases SC tissue permeability and facilitates dispersion and absorption, enabling SC administration of higher (monthly) doses of IG.[4] Human immunoglobulin with recombinant human hyaluronidase could be a favourable option in patients who prefer self-treatment and more independency, and in patients who experience systemic adverse events on IVIG or have difficult intravenous access.[5]

If licensed, human immunoglobulin with recombinant human hyaluronidase will provide an alternative maintenance therapy for patients with MMN.

Regulatory & Development Status

Human immunoglobulin with recombinant human hyaluronidase is currently licensed in the EU/UK for the following indications:[2,3,6]

- Replacement therapy in adults, children and adolescents (0 to 18 years) in:
  - primary immunodeficiency syndromes with impaired antibody production
  - secondary immunodeficiencies in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure or serum IgG level of <4 g/l
- Immunomodulatory therapy in adults, children and adolescents (0 to 18 years) in:

- Chronic inflammatory demyelinating polyneuropathy as maintenance therapy after stabilisation with IVIG.

Human immunoglobulin with recombinant human hyaluronidase is currently in phase III clinical trials for the treatment of adults with Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP).[7]

Patient Group

Disease Area and Clinical Need

Multifocal motor neuropathy (MMN) is a rare disorder characterised by slowly progressive muscle weakness, primarily of the arms and legs. The disorder is considered to be immune-mediated, which means there is inflammation resulting from abnormal functioning of the immune system and the presence of specific autoantibodies that target a specific protein in the body. The term 'motor' refers to the motor nerves, which are those that carry nerve impulses from the brain to the muscles.[8] Patients frequently develop weakness in their hand(s), resulting in dropping of objects or sometimes inability to turn a key in a lock. The weakness associated with MMN can be recognised as fitting a specific nerve territory. There is essentially no numbness, tingling, or pain. MMN is associated with increased levels of specific antibodies to GM1 (monosialotetrahexosylganglioside), a ganglioside or sugar-containing lipid found in peripheral nerve. Antibodies normally protect individuals from viruses and bacteria but may under certain circumstances bind to and facilitate an immune attack on the peripheral nerve.[9] Other symptoms of MMN may include cramping; involuntary contractions or twitching; and wasting of the affected muscles.[8,10]

It is estimated that over 10 million people in the UK live with a neurological condition which has a significant impact on their lives. Of these people, around 350,000 will require help for most of their daily activities.[11] In England, in 2022-23, there were 20,133 finished consultant episodes (FCE) and 19,709 hospital admissions for other inflammatory polyneuropathies (ICD 10, G61.8) which resulted in 8,732 FCE bed days and 18,827 day cases.[12]

Recommended Treatment Options

The current treatment option for MMN is immunoglobulin therapy, although immunosuppressant drugs are sometimes used.[13,14]

Clinical Trial Information

Trial	NCT02556437; Randomised, Single-blind, Cross-over Study Investigating the Non-inferiority of Efficacy and Safety of HyQvia in Comparison With Conventional Subcutaneous Ig Therapy in Multifocal Motor Neuropathy **Phase II –** Completed **Location:** Denmark **Study completion date:** May 2018
Trial Design	Randomised, single-blind, cross-over assignment
Population	N=18 (actual); subjects aged 18 to 90 years with MMN
Intervention(s)	24 weeks of treatment with conventional SC immunoglobulin followed by 24 weeks of treatment with human immunoglobulin with recombinant human hyaluronidase

Comparator(s)	24 weeks of treatment with human immunoglobulin with recombinant human hyaluronidase followed by 24 weeks of treatment with conventional SC immunoglobulin
Outcome(s)	Changes in isometric muscle strength [Time frame: Evaluation at weeks 0, 12, 24, 36, 48]
Results (efficacy)	The primary study variable, isometric strength, was unchanged, being 100.8% [95% confidence interval (CI) 94.8%–107.1%) in fSCIG (large volume infusion of immunoglobulin G facilitated by pretreatment with hyaluronidase) and 105.9% (95% CI 99.8%–112.0%) in cSCIG (conventional infusion of multiple small dosages). Secondary endpoints of disability, functions, impairments, and quality of life showed no differences between the two treatments.[15]
Results (safety)	Mild and short-lasting generalised side-effects were similar in the two groups, whereas the relative frequency of localised side-effects at the injection site was increased after fSCIG [0.63 (95% CI 0.23–1.00) vs. 0.09 (95% CI 0.00–0.22), P = 0.005]. The preference of the patients favoured fSCIG for two out of five visual analogue scale scores as well as the total mean score of all preferences (P = 0.03).[15]

Trial	**HYMMNE; NCT02885259;** Subcutaneous Immunoglobulin With rHuPH20 in Multifocal Motor Neuropathy **Phase –** Not applicable; Status unknown **Location:** Netherlands **Primary completion date:** December 2017
Trial Design	Open label, single group assignment
Population	N=20 (actual); subjects aged 18 to 99 years with MMN
Intervention(s)	Human immunoglobulin and one vial of recombinant human hyaluronidase (rHuPH20)
Comparator(s)	No comparator
Outcome(s)	Safety measured by anamnesis [Time frame: 1 year]
Results (efficacy)	Overall, no significant differences in muscle strength and disability between fSCIG and IVIg (intravenous immunoglobulin) were found. Treatment with fSCIG was perceived as optimal treatment option by 8 of the 17 patients (47.1%) and they continued with fSCIG after study closure because of improved independence and flexibility to administer treatment.[5]
Results (safety)	Switching to fSCIG reduced the number of systemic adverse events (IVIg 11.6 vs. fSCIg 5.0 adverse events/per person-year, $p < 0.02$), and increased the number of local reactions at the injection site (IVIg 0 vs. fSCIg 3.3 local reactions/per person-year, $p < 0.01$).[5]

Estimated Cost

Normal immunoglobulin is already marketed in the UK:[16]

- a 1.25ml vial (2.5g/25ml) costs £172.50
- a 2.5ml vial (5g/50ml) costs £345
- a 5ml vial (10g/100ml) costs £690
- a 10ml vial (20g/200ml) costs £1,380
- a 15ml vial (30g/300ml) costs £2,070

Relevant Guidance

NICE Guidance

- No relevant NICE guidelines

NHS England (Policy/Commissioning) Guidance

- No relevant NHS England policy/commissioning guidance

Other Guidance

- Stangel M, Gold R, Pittrow D, et al. Treatment of patients with multifocal motor neuropathy with immunoglobulins in clinical practice: the SIGNS registry. Therapeutic Advances in Neurological Disorders. 2016.[14]

Additional Information

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