

**NIHR Innovation Observatory
Evidence Briefing: August 2017****SA-237 for neuromyelitis optica and neuromyelitis
optica spectrum disorders**

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LAY SUMMARY

Neuromyelitis optica (Devic's disease) is a rare autoimmune disorder (a condition where the immune system attacks itself). It is characterised by the inflammation of the nerve that leads from the eye to the brain, and the spinal cord. Symptoms consist of vision loss, loss of sensation, bladder dysfunction, weakness in limbs and paralysis and most patients tend to have relapsing attacks which can result in permanent brain damage if not treated soon enough.

Neuromyelitis optica is more common in females than males. Currently there are no licensed treatments for this condition, with treatments used for multiple sclerosis often being relied upon. SA-237 is currently in phase III trials for the treatment of neuromyelitis optica and neuromyelitis optica spectrum disorders. It is administered as an injection under the skin and is being developed as both a monotherapy and add-on therapy.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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TARGET GROUP

Neuromyelitis optica (NMO) and NMO spectrum disorders – monotherapy or add-on therapy

TECHNOLOGY

DESCRIPTION

SA-237 is a humanized anti-IL-6 receptor antibody that inhibits cytokines and reduces pro-inflammatory activity. IL-6 is involved in signalling pathways that increase the inflammatory response. IL-6 binds to the soluble and membrane bound IL-6 receptors, preventing IL-6 mediated signalling from activating a number of cells involved in immunological and inflammatory response.

IL-6 deficiency delays the onset and reduces the severity of collagen-induced arthritis, while blocking the IL-6 receptor leads to diminished joint disease. Thus, SA-237 could be effective for the treatment of autoimmune disorders.¹

SA-237 is currently in phase III clinical trials for NMO and NMO spectrum disorders as a monotherapy and as an add-on therapy. It is administered as a subcutaneous injection at a dose of 120 mg/ml, at weeks 0, 2 and 4, and every 4 weeks thereafter.¹

SA-237 does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

Currently there are no approved drugs for NMO, and SA-237, if licensed, will be a viable treatment option for the prevention of relapse and symptom control for this debilitating condition.²

DEVELOPER

Roche Products Ltd and Chugai Pharma

AVAILABILITY, LAUNCH or MARKETING

SA-237 received orphan drug designation in the USA in 2014 and in the EU in 2016, both for NMO.

PATIENT GROUP

BACKGROUND

NMO, also known as Devic's disease, is a rare inflammatory and demyelinating autoimmune disorder of the central nervous system (CNS) characterised by recurrent attacks of optic neuritis and longitudinally extensive transverse myelitis (LETM).³ Patients present with acute loss of vision, loss of sensation, bladder dysfunction, and weakness and paralysis of limbs.⁴ Most patients have relapsing attacks, separated by months or years with partial recovery.⁵ More rarely, the disease course is monophasic, with nearly simultaneous index episodes of optic neuritis and myelitis.⁵

NMO is associated with the presence of aquaporin-4 antibodies (AQP4-Ab) in approximately 70% of cases.⁶ AQP4-Ab positive NMO is more frequently associated with other autoimmune diseases such as myasthenia gravis, systemic lupus erythematosus, Sjogren's syndrome, coeliac disease, and sarcoidosis.⁷ Previously considered a clinical variant of multiple sclerosis, NMO is now regarded as a distinct disease entity.⁷ NMO can be distinguished from multiple sclerosis on the basis of several features, including transverse myelitis presenting with longitudinally extensive spinal cord lesions, a tendency to spare the brain in the early stages of disease, and association with seropositivity for NMO IgG (AQP4-Ab).⁸ The diagnostic criteria for NMO requires a normal MRI brain, transverse myelitis with MRI changes >3 vertebral segments and AQP4 IgG positive.⁹

Sometimes, if these criteria are not met, a diagnosis of NMO spectrum disorders is still given. The 2015 International Panel for NMO Diagnosis criteria for NMO spectrum disorders includes:¹⁰

- At least one core clinical characteristic (optic neuritis, acute myelitis, area postrema syndrome, acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical MRI lesions, or symptomatic cerebral syndrome with NMOSD-typical brain lesions).
- AQP4 IgG positive.
- Exclusion of alternative diagnosis.

NMO is associated with high mortality and morbidity when not diagnosed early and treated adequately.⁶ Relapses usually result in permanent neurologic impairment if not treated in time. Some studies report death in 25 to 30% of patients after a mean of 5 years from onset.¹¹ At five years from onset approximately 60 to 70% of untreated patients have significant visual loss (registered blind) affecting at least one eye.¹¹

Prior to NMO-IgG testing many patients with NMO (>20%) were misdiagnosed with multiple sclerosis, and were subsequently treated with disease-modifying therapies.⁷ Treatment with some of these therapies can result in worsening of NMO disease, with many patients suffering preventable disability and death.⁶

CLINICAL NEED and BURDEN OF DISEASE

NMO affects approximately 0.4 per 10,000 population in the EU, which is equivalent to approximately 2,564 people in the UK.⁴ The worldwide prevalence is estimated to be 1 to 5 per 100,000 people and the median age at onset of NMO is 39 years, with nearly 90% of patients being female.^{5,7}

Hospital episode statistics for 2015/2016 indicate that for NMO there were 546 finished consultant episodes (80% females, 20% males), 406 hospital admissions and 3,095 bed days in England.¹²

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

No guidance identified

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Neuromyelitis Optica Service (Adults and Adolescents). D04/S(HSS)/b.
- NHS England. 2013/14 NHS Standard Contract for Neurosciences: Specialised Neurology (Adult). D04/S/a.
- NHS England. 2013/14 NHS Standard Contract for Specialised Ophthalmology. D12/S/a.

OTHER GUIDANCE

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CURRENT TREATMENT OPTIONS

There is currently no curative treatment for NMO or NMO spectrum disorders.⁴ Management focuses on remission and improvement of relapse-associated symptoms, long term stabilisation of disease course by means of relapse prevention, and symptomatic therapy of residual symptoms.^{7,13}

Disability in NMO and NMO spectrum disorders is attack-related, and relapses require a rapid treatment approach.³ If the symptoms of an NMO or NMO spectrum disorder relapse are not due to infection, treatment with a short course of high dose steroids, such as methylprednisolone, is recommended.⁷ If a patient's condition does not sufficiently improve or the neurological symptoms worsen, therapeutic plasma exchange can be used as rescue therapy.^{5,7}

Following each relapse patients often have incomplete recovery of symptoms and an accumulation of neurological deficits.⁷ Long term immunosuppressive therapies should therefore be initiated immediately upon the diagnosis of NMO to prevent further relapses and disability.¹⁴ First line treatment options include oral prednisolone in combination with azathioprine, mycophenolate mofetil, or methotrexate.^{3,7,13} Following failure of these treatments, second line therapy can include treatment with rituximab, mitoxantrone, or cyclophosphamide.^{3,7,13} Expert opinion states that some patients continue to relapse despite rituximab; currently these patients are treated with IV immunoglobulin, cyclophosphamide and off-label tocilizumab .

EFFICACY and SAFETY

| | | |
|------------------------------|---|---|
| Trial | NCT02073279, SA-309JG, SA-237 vs placebo; phase III | NCT02028884, SA-307JG, SA-237 vs placebo; phase III |
| Sponsor | Chugai Pharmaceutical | Chugai Pharmaceutical |
| Status | Ongoing | Ongoing |
| Source of Information | Trial registry ¹⁵ and GlobalData ¹ | Trial registry ¹⁶ and GlobalData ¹ |
| Location | 10 EU countries (not incl. UK), USA, Canada and 9 other countries. | 7 EU countries (incl. UK), USA, Japan and Taiwan |
| Design | Randomised, placebo-controlled, double blind study | Randomised, placebo-controlled, double blind study |
| Participants | n=90 (planned); aged 18-74 years; Diagnosed NMO and NMO spectrum disorder; monotherapy | n=70 (planned); aged 12-74 years; , Diagnosed NMO and NMO spectrum disorder; add-on therapy |
| Schedule | Randomised to receive SA-237 at a dose of 120 mg/ml, subcutaneously, at weeks 0, 2 and 4, and every 4 weeks thereafter or placebo where subjects receive subcutaneous comparator at weeks 0, 2 and 4, and every 4 weeks thereafter. | Randomised to receive SA-237 at a dose of 120 mg/ml, subcutaneously, at weeks 0, 2 and 4, and every 4 weeks thereafter or placebo where subjects receive subcutaneous comparator at weeks 0, 2 and 4, and every 4 weeks thereafter. |
| Follow-up | Not reported | Not reported |
| Primary Outcomes | Time to first relapse (time frame: up to approximately 38 months from first patient in) | Time to first relapse - Up to approximately 30 months from first patient in |
| Secondary Outcomes | Annualized relapse rate (time frame: up to approximately 38 months from first patient in); change in visual analogue scale (VAS) score for pain; change in Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue score; change in Short Form generic health survey (SF-36) score; change in EQ-5D score; change in Timed 25-Foot Walk (T25W); proportion of relapse-free patients; annualized relapse rate (ARR); change in modified Rankin Scale (mRS) score; change in Zarit Burden Interview (ZBI) score; change in EDSS score; change in visual acuity (Snellen chart); change in low-contrast visual acuity (Low-contrast Sloan letter chart [LCSLC]) | Annualized relapse rate - Up to approximately 30 months from first patient in; change in visual analogue scale (VAS) for pain; change in Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue; change in Short Form generic health survey score (SF-36); change in EQ-5D; the proportion of relapse-free patients; annualized relapse rate (ARR); change in modified Rankin Scale (mRS); change in Zarit Burden Interview (ZBI); change in Expanded Disability Status Scale (EDSS); change in visual acuity (Snellen chart); pharmacodynamic endpoints: IL-6, soluble IL-6 receptor, high sensitivity C-reactive protein, anti-AQP4 antibodies and plasmablasts; PK endpoints: serum SA237 concentrations; immunogenicity endpoints: Incidence of anti-SA237 antibodies |
| Key Results | - | - |

| | | |
|--------------------------------|--|---|
| Adverse effects (AEs) | - | - |
| Expected reporting date | Study completion date reported as March 2019 | Study completion date reported as June 2020 |

ESTIMATED COST and IMPACT

COST

The cost of SA-237 is not yet known

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

- | | |
|--|--|
| <input type="checkbox"/> Reduced mortality/increased length of survival | <input checked="" type="checkbox"/> Reduced symptoms or disability |
| <input checked="" type="checkbox"/> Other: <i>improved quality of life by reduced relapse rate and by other independent factors like reducing neuropathic pain and fatigue</i> | <input type="checkbox"/> No impact identified |

IMPACT ON HEALTH and SOCIAL CARE SERVICES

- | | |
|--|---|
| <input type="checkbox"/> Increased use of existing services | <input type="checkbox"/> Decreased use of existing services |
| <input checked="" type="checkbox"/> Re-organisation of existing services | <input type="checkbox"/> Need for new services |
| <input type="checkbox"/> Other | <input type="checkbox"/> None identified |

IMPACT ON COSTS and OTHER RESOURCE USE

- | | |
|--|---|
| <input checked="" type="checkbox"/> Increased drug treatment costs | <input type="checkbox"/> Reduced drug treatment costs |
| <input type="checkbox"/> Other increase in costs | <input type="checkbox"/> Other reduction in costs |
| <input checked="" type="checkbox"/> Other: <i>There is expected to be a reduction in drug administration costs of subcutaneous SA-237 compared with other current treatments administered by intravenous</i> | <input type="checkbox"/> None identified |

infusion. There may be an increase in monitoring costs depending on SA-237 safety profile and label requirements.

OTHER ISSUES

- Clinical uncertainty or other research question identified: *Lack of robust evidence supporting clinical benefit of current established management with off label products*
- None identified

INFORMATION FROM

Information was received from Roche Products Ltd

UK PharmaScan ID number 642497

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