Product Overview of ENSPRYNG® Subcutaneous Injection 120 mg Syringe

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ENSPRYNG Lifecycle Leader
Chugai Pharmaceutical Co., Ltd.

Prepared: Sep. 2020

Product Outline

ENSPRYNG satralizumab

Therapeutic classification:

pH-Dependent binding humanized anti-interleukin-6 receptor (IL-6R) monoclonal antibody

Product and nonproprietary names:

日本標準商品分類番号　876399

pH依存的結合性ヒト化抗IL-6レセプターモノクローナル抗体　薬価基準収載

生物由来製品、劇薬、処方箋医薬品注)

エンスプリング® 皮下注120mg シリンジ

ENSPRYNG® satralizumab

サトラリズマブ（遺伝子組換え）注

注）注意－医師等の処方箋により使用すること

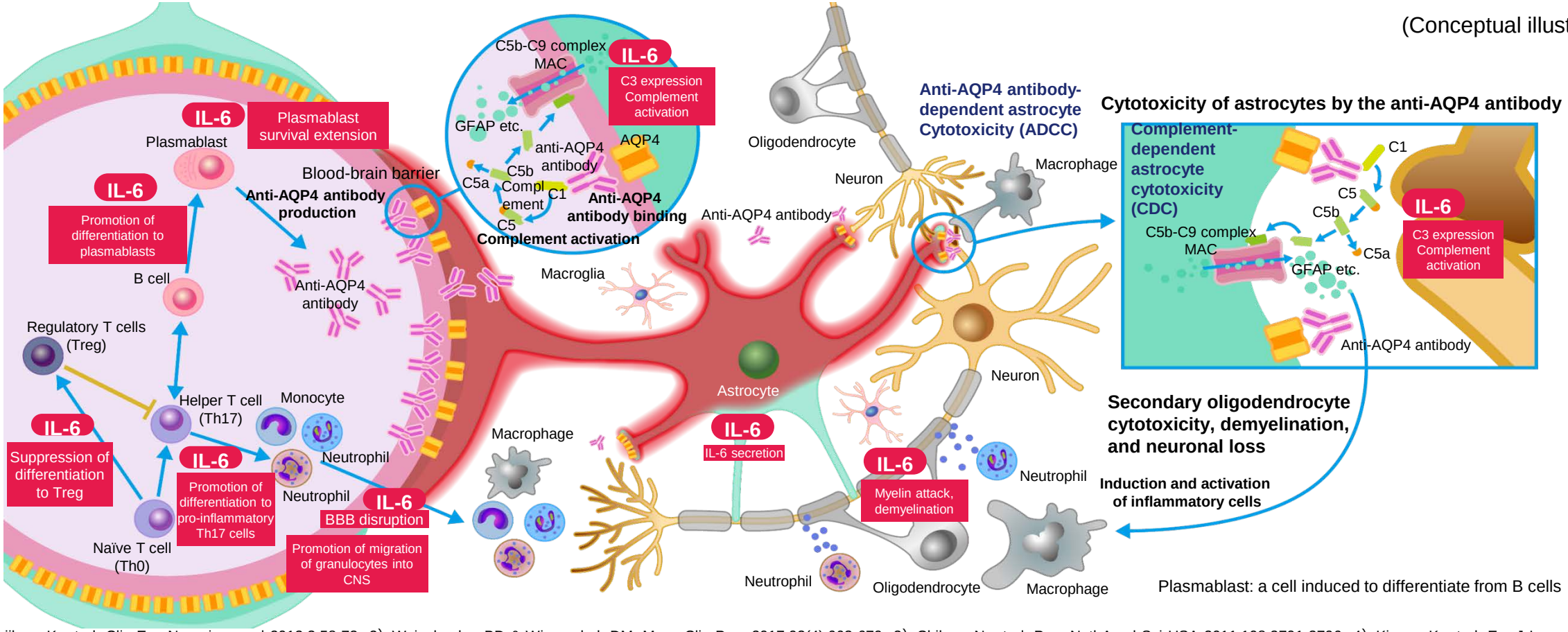
Packaging:

Involvement of IL-6 in the Pathogenesis of Neuromyelitis Spectrum Disorders (NMOSD)

ENSPRYNG satralizumab

IL-6 is known to play a key role in the disease process of NMOSD by extending the survival of plasmablasts that produce anti-aquaporin-4 (AQP4) antibodies

(Conceptual illustration)



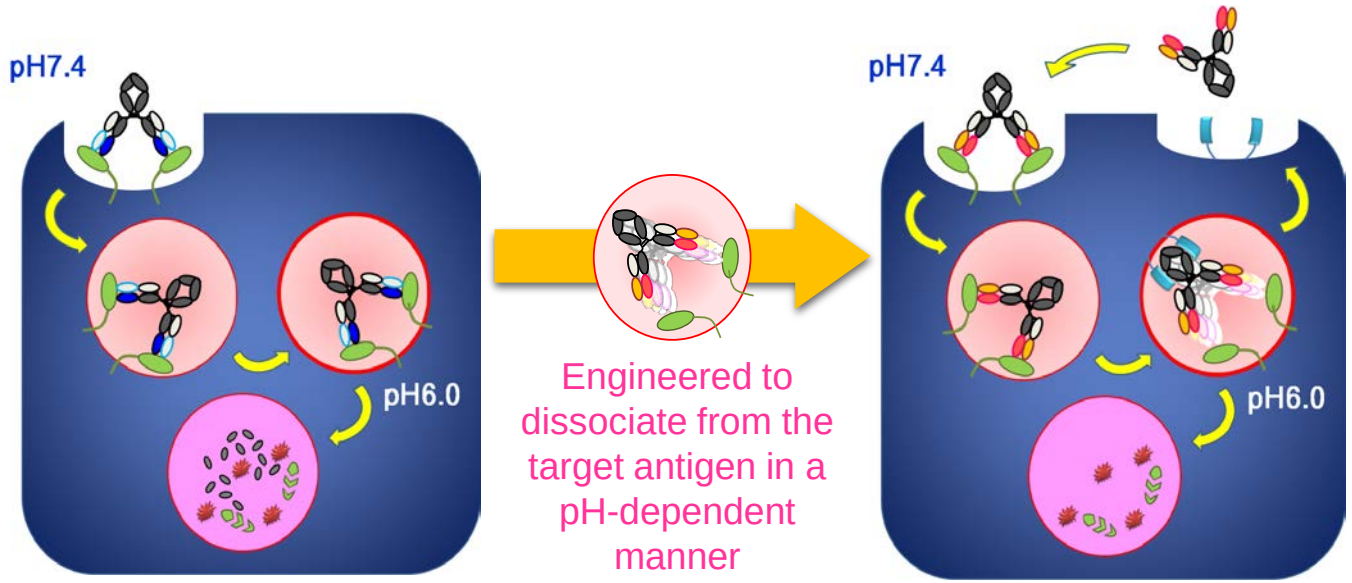
Plasmablast: a cell induced to differentiate from B cells

1）Fujihara K. et al. Clin Exp Neuroimmunol 2012;3:58-73 2）Weinshenker BD & Wingerchuk DM. Mayo Clin Proc 2017;92(4):663-679 3）Chihara N, et al. Proc Natl Acad Sci USA 2011;108:3701-3706 4）Kimura K, et al. Eur J Immunol 2010;40:1830-1835 5）Lin J, et al. Int J Neurosci 2016;126(12):1051-1060 6）Takeshita Y, et al. Neurol Neuroimmunol Neuroinflamm 2017;4:e311 7）Obermeier B, et al. Nat Med 2013;19:1584-1596 8）Erta M, et al. Int J Biol Sci 2012;8:1254-1266 9）Barnum SR, et al. Glia 1996;18:107-117 10）Papadopoulos MC, et al. Nat Rev Neurol 2014;10:493-506 11）Kaplin AJ, et al. J Clin Invest 2005;115:2731−2741 12）Rothhammer V, et al. Semin Immunopathol 2015;37:625-638 13）Uzawa A, et al. Clin Exp Neuroimmunol 2013;4:167-172

Characteristics and Mechanism of Action of ENSPRYNG
-First Application of Chugai's Proprietary Recycling Antibody® Technology-

ENSPRYNG satralizumab

- Recycling antibody® product created by Chugai
- Engineered to dissociate from the antigen (IL-6 receptor) in a pH-dependent manner, allowing the antibody to repeatedly bind to the antigen.



- ✓ Antibodies normally bind to the antigen only once
- ✓ Antibodies are rapidly eliminated after binding to the antigen

- ✓ Designed to repeatedly bind to the antigen
- ✓ This reduces antibody elimination

Nature Biotechnology. 28, 1203-7, 2010

History of the Development of ENSPRYNG

2006	Drug discovery research started
2010	Japanese phase I study started
2013	Fast track designation (US)
2014	Global phase III study started, orphan drug designation (US)
2016	Orphan drug designation (EU)
2018	Breakthrough therapy designation (US)
2019	Regulatory application in Japan, US, EU, and Taiwan
	Orphan drug designation (Japan)
June 2020	Approved in Canada and Japan
July 2020	Approved in Switzerland
August 2020	Approved in the US,
	Listed on the National Health Insurance reimbursement price list and launched in Japan

ENSPRYNG's Contributions to NMOSD treatment

ENSPRYNG is a subcutaneous injection administered every four weeks (or every two weeks up to the fourth week of treatment) for the convenience of patients and healthcare professionals

- **Benefits of a subcutaneous injection every four weeks (for patients)**
  1. For patients who have difficulty visiting the hospital due to physical disability, etc., it is expected to reduce the burden of hospital visits
  2. The simple injection technique reduces the burden on the patient
  3. More convenient for working patients

- **Benefits of a subcutaneous injection every four weeks (for healthcare professionals)**
  1. Shorter consultation times
  2. Less crowded outpatient chemotherapy offices

ENSPRYNG's Indication, Dosage and Administration

ENSPRYNG satralizumab

Indication

Prevention of relapses of neuromyelitis optica spectrum disorders (NMOSD), including neuromyelitis optica (NMO)

Precautions Concerning the Indication

Administer ENSPRYNG to patients with NMOSD, including NMO*

*Should be referred to the "Guidelines for the Management of Multiple Sclerosis and Neuromyelitis Optica, 2017" (Japanese Society of Neurology).

The data showing efficacy for anti-AQP4 antibody-negative patients are limited. ENSPRYNG should be administered to anti-AQP4 antibody-positive patients.

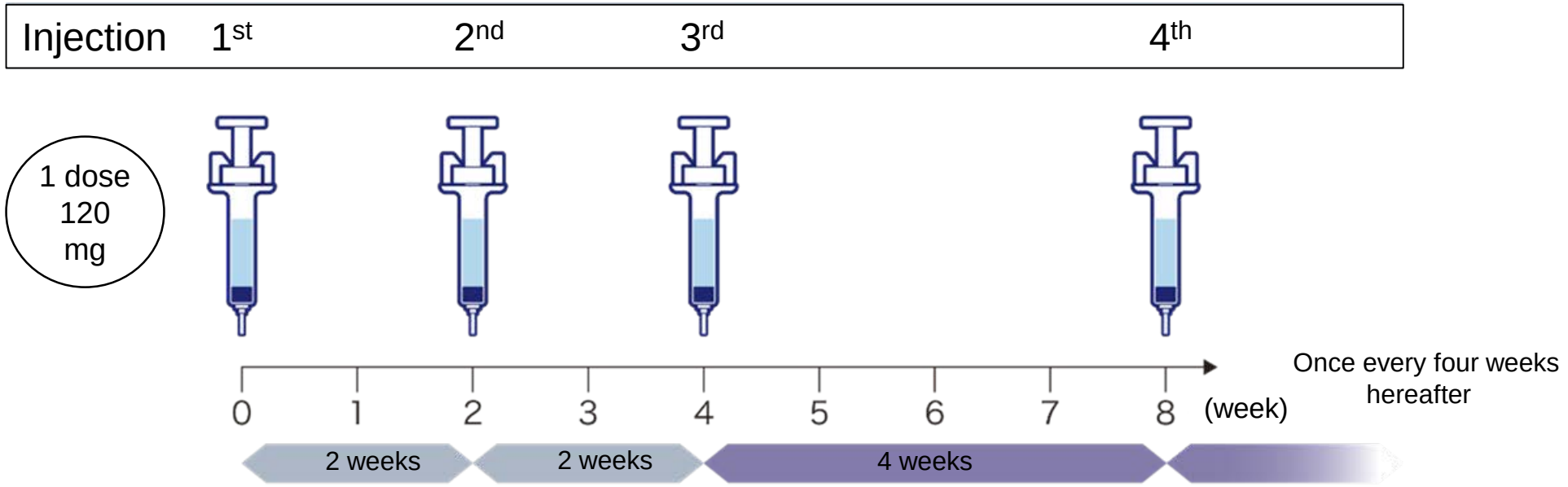
Dosage and Administration

The usual dosage for adults and children is a single dose of 120 mg satralizumab (genetical recombination) administered by subcutaneous injection at weeks 0, 2, and 4, and then once every 4 weeks thereafter.

ENSPRYNG's Dosing Schedule

Illustration of ENSPRYNG's dosing schedule

Usually, a single subcutaneous injection of 120 mg satralizumab is administered by subcutaneous injection at weeks 0, 2, and 4, and then once every 4 weeks thereafter.



Conditions for Approval

ENSPRYNG
satralizumab

1. Formulate and properly implement a risk management plan.

2. Given the very limited sample sizes in clinical trials in Japan, conduct post-marketing all-patient drug use surveillance until data on a certain number of patients has been collected to determine the background information of the patients using the product and to, in the near term, collect data on the safety and efficacy of the product, implementing necessary measures to ensure the appropriate use of the product.

Overview of ENSPRYNG Risk Management Plan

ENSPRYNG satralizumab

1.1 Safety Specification		
[Important identified risks]	[Important potential risks]	[Important missing information]
Infections	Hypersensitivity	None
Neutropenia, leukopenia, and agranulocytosis	Impaired liver function	
Thrombocytopenia	Reactivation of hepatitis B virus	
	Immunogenicity	
	Cardiac disorder	
	Malignancies	
	Intestinal perforation	
	Interstitial pneumonia	
1.2 Efficacy Considerations		
None		

2. Outline of Pharmacovigilance Plan
Regular pharmacovigilance activities
• Collection and evaluation of individual cases • Research reports: Collection and evaluation of publications, etc. • Reports of non-Japanese action plans: Collection and evaluation of information on measures taken outside Japan • Signal detection and evaluation using approaches including data mining techniques for adverse events (including deaths)
Additional pharmacovigilance activities
• Early post-marketing phase vigilance • General drug use surveillance • Post-marketing clinical studies continuing from the Phase III clinical studies in patients with neuromyelitis optica spectrum disorders (including neuromyelitis optica): Study Nos. SA-307JG, JN41468

3. Outline of Plan for Efficacy Studies and Surveillance
None

4. Outline of Risk Minimization Plan
Normal risk minimization activities
• Package insert • Medication guide for patients
Additional risk minimization activities
• Provide information through early post-marketing phase vigilance • Provide reliable information on appropriate use before delivery • Create and disseminate literature for healthcare professionals (Appropriate Use Guide) • Create and disseminate literature for patients (Information for Patients Prescribed ENSPRYNG)

Appropriate Use Guide for ENSPRYNG Syringes for Subcutaneous Injection 120 mg (released June 2020)

Current Status of the Treatment for Neuromyelitis Optica Spectrum Disorders (NMOSD) and Expectations for ENSPRYNG

Kazuo Fujihara

Department of Multiple Sclerosis Therapeutics,
Fukushima Medical University School of Medicine

Disclosure of Conflicts of Interest

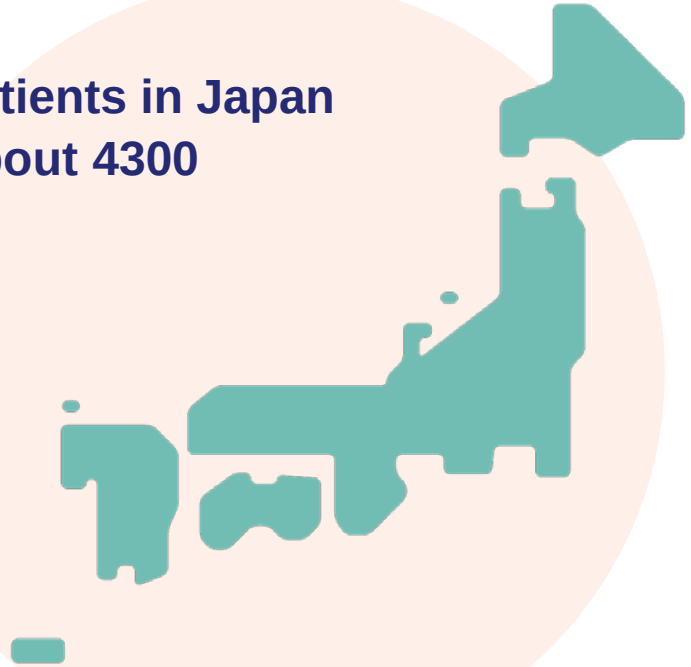
Name of presenter: Kazuo Fujihara
Institution: Department of Multiple Sclerosis Therapeutics, Fukushima Medical University School of Medicine

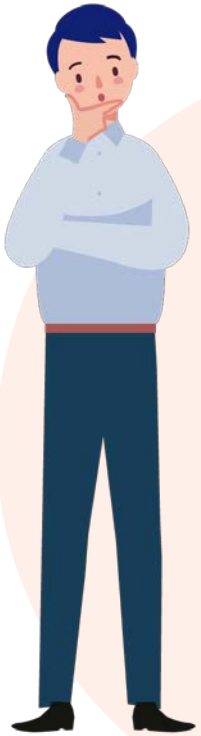
Lecture fee: Chugai, Biogen, Novartis, Alexion
Mitsubishi Tanabe, Bayer Yakuhin, Teijin Pharma, Asahi Kasei Medical
Esai, UCB Japan, Shanghai Roche

Facts About Neuromyelitis Optica Spectrum Disorders (NMOSD)

NMOSD is an autoimmune disease (a disease in which the autoantibody mistakenly attacks its own cells) that affects the central nervous system

Patients in Japan
About 4300

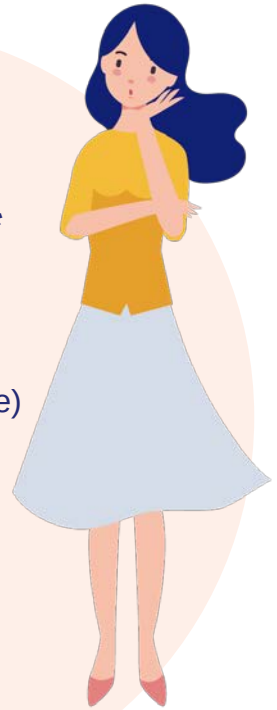




Male-to-female ratio*

1:9

(Male) (Female)



Age at onset

Usually late 30s

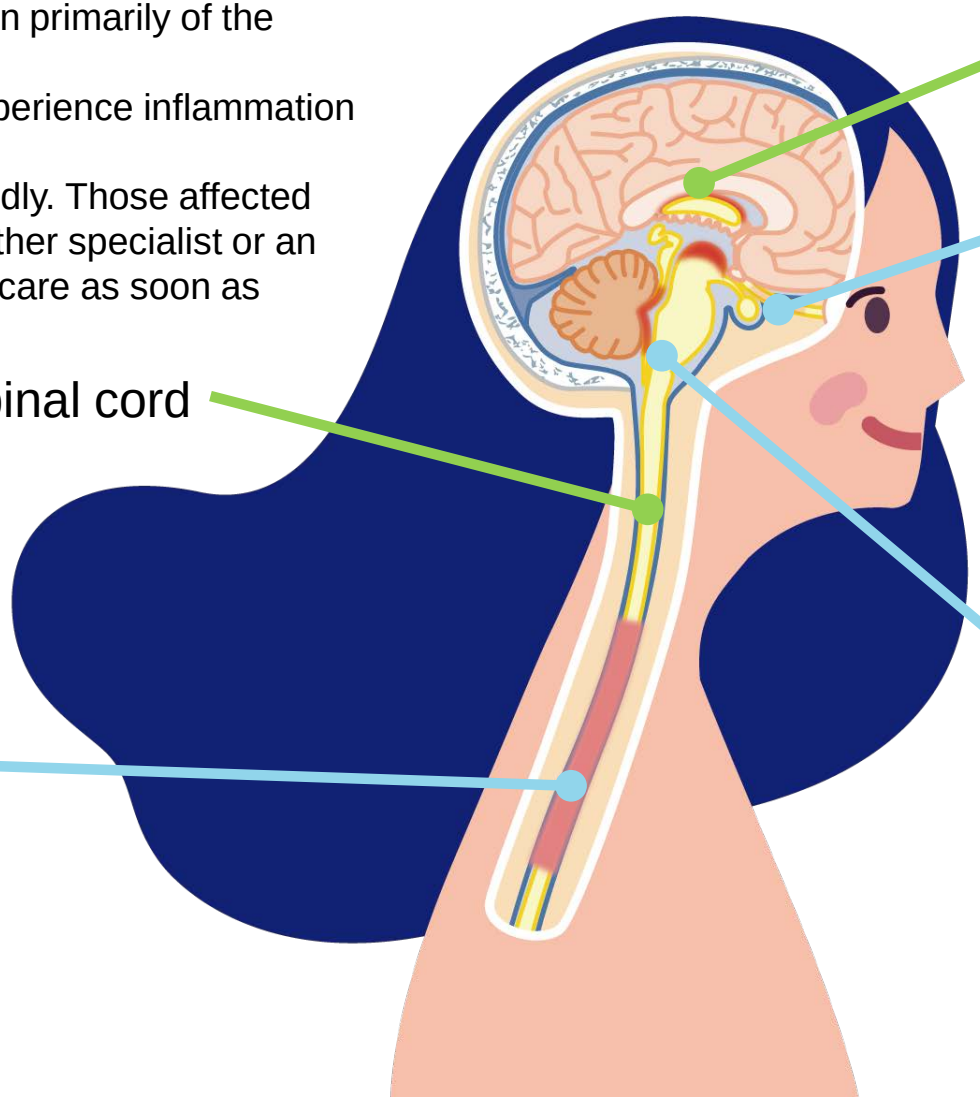
to early 40s

*For anti-AQP4 antibody-positive patients

2017 Guideline for the Treatment of Multiple Sclerosis and Neuromyelitis Optica [in Japanese]. Japanese Society of Neurology, supervising ed.; “Guideline for the Treatment of Multiple Sclerosis and Neuromyelitis Optica” Authoring Committee, ed. Neuromyelitis optica spectrum disorders (supervised by Dr. Ichiro Nakashima, Professor, Department of Geriatric Neurology, Tohoku Medical and Pharmaceutical University School of Medicine)

Facts About Neuromyelitis Optica Spectrum Disorders (NMOSD)

NMOSD is characterized by inflammation primarily of the brain, spinal cord, and optic nerves.
NMOSD varies among patients, who experience inflammation at different sites.
The symptoms of NMOSD progress rapidly. Those affected should seek care with a neurologist or other specialist or an ophthalmologist who offers hospitalized care as soon as possible.



Optic nerve

- Seeing becomes difficult
- Visual field defects occur
- The backs of the eyes hurt, etc.

Spinal cord

- Numbness in the arms and legs and other parts of the body
- Loss of sensation
- Sensation of intense pain, etc.

Brain

- Incessant hiccups
- Nausea and vomiting, etc.

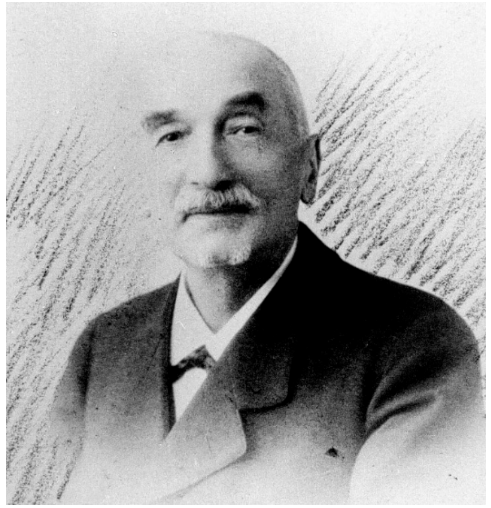
Neuromyelitis optica spectrum disorders (supervised by Dr. Ichiro Nakashima, Professor, Department of Geriatric Neurology, Tohoku Medical and Pharmaceutical University School of Medicine)

Evolution of the Disease Concept of Neuromyelitis Optica Spectrum Disorders (NMOSD)

Once considered a subtype of multiple sclerosis (MS), neuromyelitis optica (NMO) became a disease concept independent from MS with the discovery of the anti-aquaporin-4 (AQP4) antibody.

- **1894** **Devic reports a case of "subacute myelitis with optic neuritis"**
- 1894 Gault (a student of Devic) analyzes the data of 16 cases, proposing the name NMO
- 1907 Acchioté names NMO as Devic's disease

  He defines the condition as a monophasic (non-recurring) severe neuromyelitis optica
- **1990s** **Experts take note of differences from MS as MRI comes into widespread use**
  - Mandler et al., based on 8 autopsies, report oligoclonal IgG band - negative lesions localized to the optic nerves and spinal cord (1993)
  - Based on the data of 71 patients, Wingerchuk et al. propose lesions extending over 3 or more vertebral segments and neurologic symptoms found only in the optic nerve and spinal cord and other diagnostic criteria of NMO (1999)
  - In Japan, the condition is defined as NMO if monophasic, MS if recurrent with brain lesions, and OSMS if lacking brain lesions.
- **2004-05** **Lennon and Tohoku University identify an NMO autoantibody = NMO-IgG = anti-AQP4 antibody**
- 2006 Wingerchuk's diagnostic criteria for NMO
- 2008 The International Panel on the Diagnosis of MS's diagnostic criteria for NMO
- **2015** **Publication of the international consensus diagnostic criteria for neuromyelitis optica spectrum disorders (2015)**



Eugène Devic (1858-1930)

The overarching term NMOSD (Neuromyelitis optica spectrum disorders) is proposed

Latest Approaches: Multiple sclerosis and neuromyelitis optica [In Japanese]. Junichi Kira, supervising ed. Nakayama Shoten, 2015. 2nd printing.

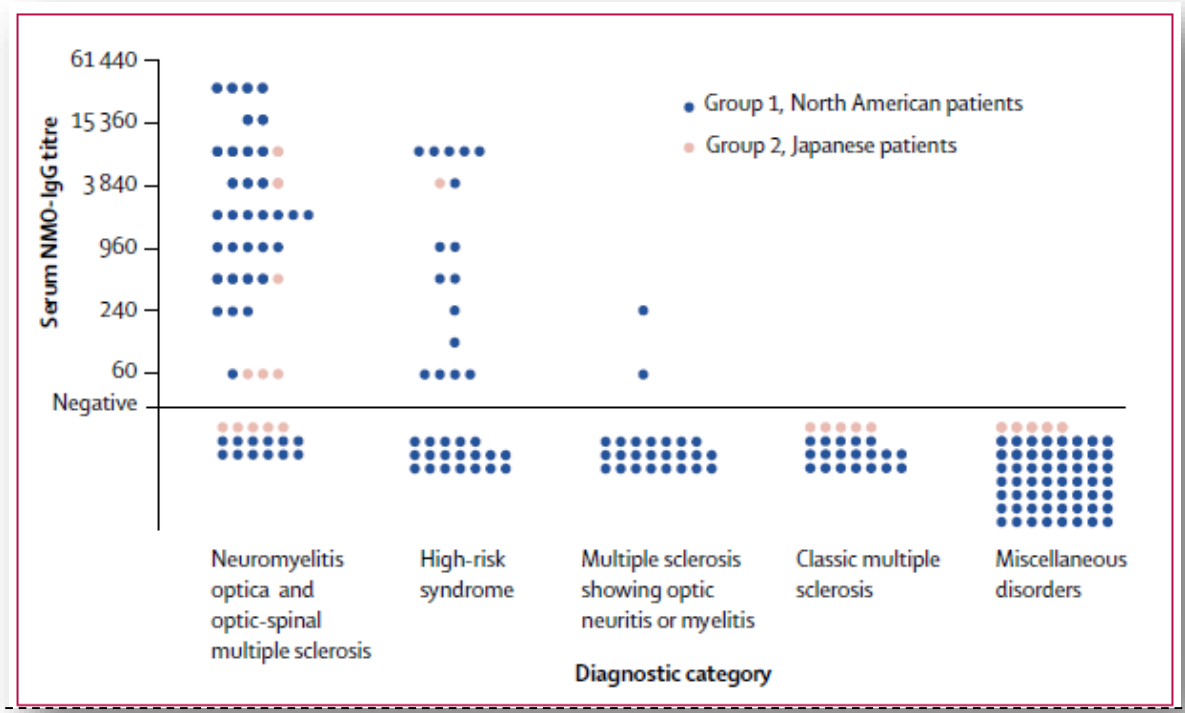
A Neuromyelitis Optica-specific Autoantibody in the Blood (NMO-IgG)

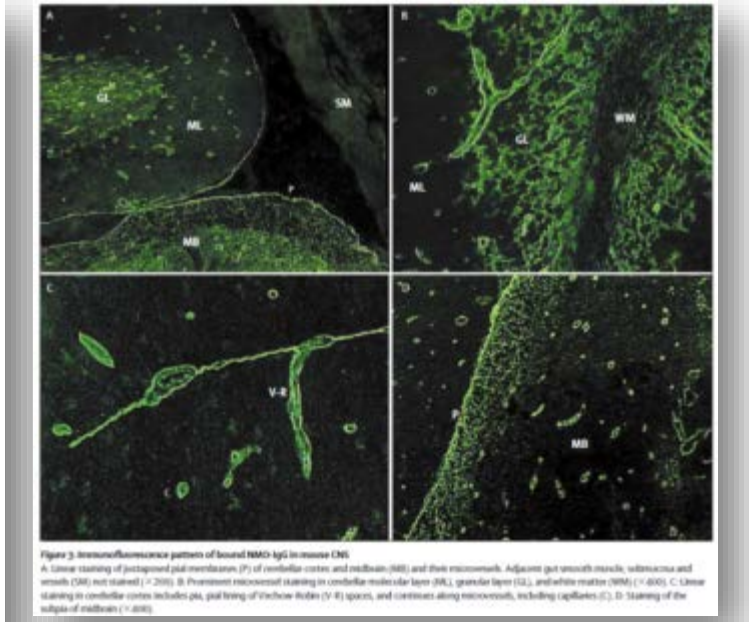
Articles

(The capillaries, pia mater, and subpial tissue
of the brain and spinal cord are stained.)
From the British medical journal *The Lancet* in 2004

A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis

Lancet 2004; 364: 2106–12 Vanda A Lennon, Dean M Wingerchuk, Thomas J Kryzer, Sean J Pittock, Claudia F Lucchinetti, Kazuo Fujihara, Ichiro Nakashima, Brian G Weinshenker





Study summary and methods of assessment:
A clinical diagnosis was made for 102 North American patients with neuromyelitis optica or with syndromes that suggest high risk of the disorder and 22 Japanese patients with optic-spinal multiple sclerosis, after which NMO-IgG was measured using serum samples. The diagnostic classification and serum NMO-IgG concentration are shown above.

How are NMO and MS Related?

	Neuromyelitis optica (NMO)	Multiple sclerosis (MS)
Prevalence in Japan[1)]	3.42 per 100,000 people	7.7 per 100,000 people
Patients in Japan[1)]	4,290 (2012) *	9,900 (2004)
Male-to-female ratio[2)]	**1:9**	1:3
Age of onset[2)]	**30s to 40s** **May affect older people**	20s to 30s Onset is rare in those ≥ 50
Racial and regional differences[2)]	None (tends to be more prevalent in Asia and Latin America)	**More common in Caucasians and high-latitude regions**
Primary lesions[2)]	Bilateral optic neuritis Transverse myelitis	Diffuse (cerebellum, around ventricles)
Relapse frequency and severity[2)]	**1 to 2 times/year, severe**	Mild
Level of disability[2)]	Correlated with relapses	Chronic progressive
Major complications[1,2)]	**Autoimmune diseases** (SjS, SLE, MG, Hashimoto's disease)	None

	Neuromyelitis optica (NMO)	Multiple sclerosis (MS)
Characteristics of visual impairment[2)]	Bilateral impairment, severe Altitudinal hemianopsia	Central scotoma
Characteristics of spinal cord lesions[2)]	**Lesions extend over ≥3 vertebral segments**, bilateral Intense numbness/pain	**Lesions extend less ≤ 2 vertebral segments**, unilateral Sensory/movement disorders
Characteristics of cerebral lesions[2)]	Hiccups/vomiting, diabetes insipidus, Hypersomnia, disturbance of consciousness	Nystagmus, internuclear ophthalmoplegia, cerebellar ataxia, memory impairment, postural tremors, easily fatigued, etc.
Serum anti-AQP4 antibody[2)]	**Positive**	Negative
Spinal fluid OB[2)]	Negative (about 10% positive)	**Positive (about 80%)**
Pleocytosis[2)]	Rare	Common
Neuropathological findings[2)]	Necrotic lesions **(astrocyte cytotoxicity)**	**Demyelination**, gliosis
Prophylactic pharmacotherapy[2)]	**Oral corticosteroids** **(MS drugs exacerbate symptoms)**	Interferon beta, fingolimod, natalizumab, glatiramer acetate

*For NMOSD (Neuromyelitis optica spectrum disorders)
OB: Oligoclonal IgG bands
SjS: Sjögren syndrome
SLE: Systemic lupus erythematosus
MG: Myasthenia gravis

1) 2017 Guideline for the Treatment of Multiple Sclerosis and Neuromyelitis Optica [in Japanese]. Japanese Society of Neurology, supervising ed.; "Guideline for the Treatment of Multiple Sclerosis and Neuromyelitis Optica" Authoring Committee, ed.
2) Latest Approaches: Multiple sclerosis and neuromyelitis optica [In Japanese]. Junichi Kira, supervising ed. Nakayama Shoten, 2015. 2nd printing.

Symptoms: Inflammation of the Optic Nerves

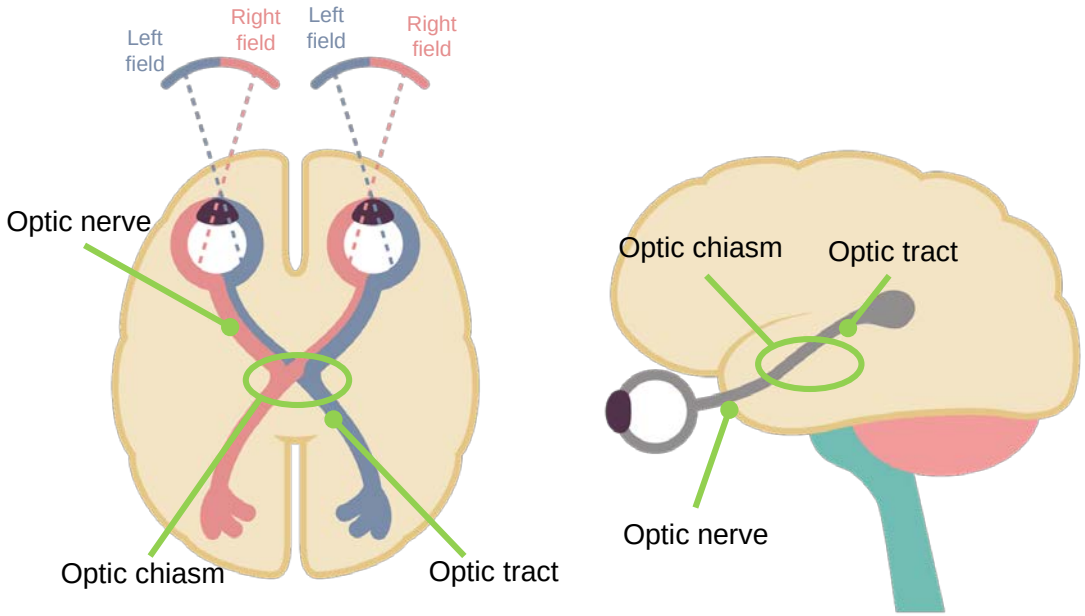
● Symptoms associated with inflammation of the optic nerves ●

Symptoms include rapid decreases in visual acuity and visual field defects.

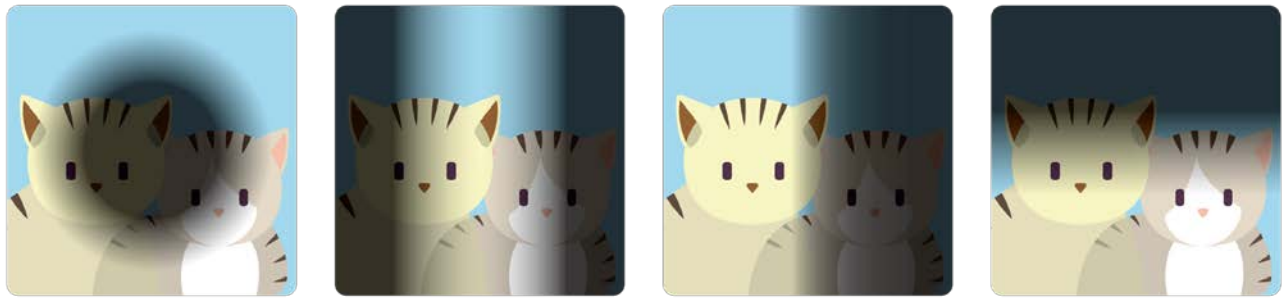
In the span of several hours to several days, blurry vision and difficulty seeing can progress to a level impacting daily activities.
Other symptoms may include visual field defects, the inability to differentiate colors, things appearing bright, and pain at the back of the eyes.

■ Position of the optic nerves and visual field anomalies

Visual field defects vary depending on the location of inflammation.



■ Examples of visual field anomalies



Central scotoma | Bitemporal hemianopsia | Homonymous hemianopsia | Altitudinal hemianopsia

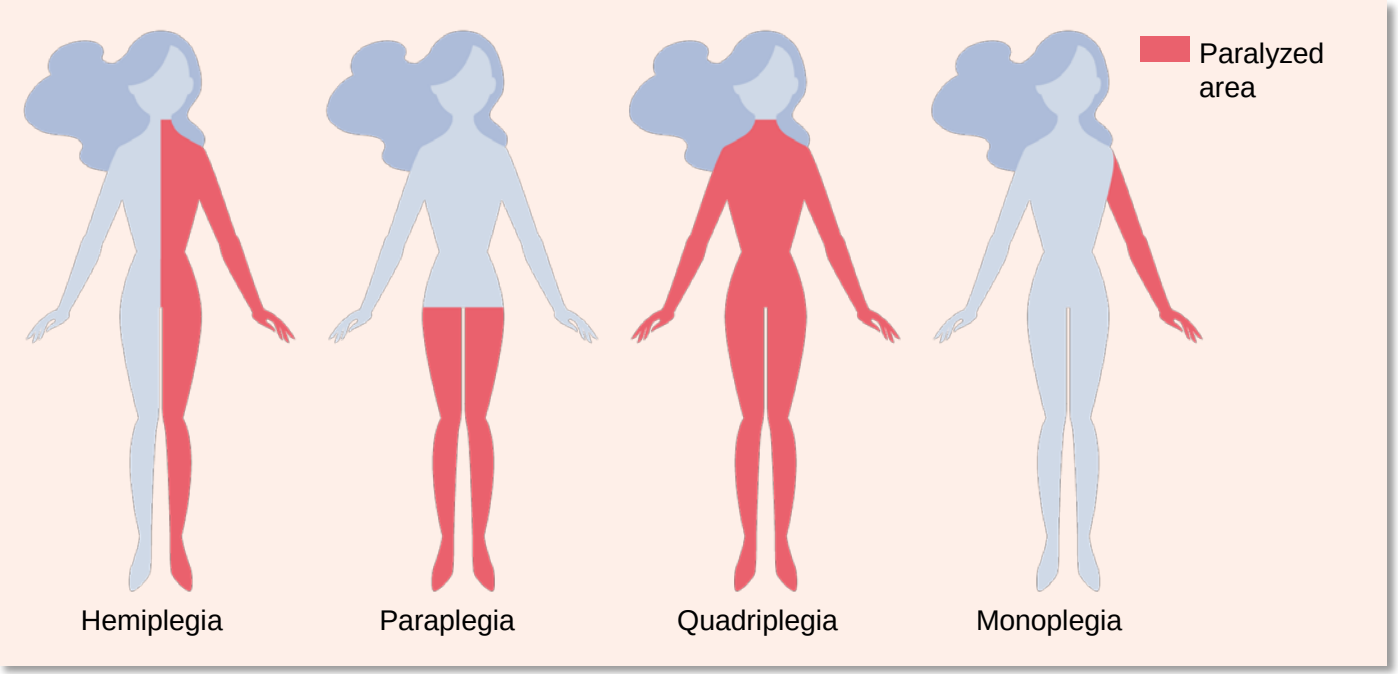
Neuromyelitis optica spectrum disorders (supervised by Dr. Ichiro Nakashima, Professor, Department of Geriatric Neurology, Tohoku Medical and Pharmaceutical University School of Medicine)

Symptoms: Inflammation of the Spinal Cord

● Symptoms associated with inflammation of the spinal cord ●

Symptoms include paralysis and weakness (motor dysfunction) as well as numbness and pain (sensory dysfunction).

One type of movement disorder, paralysis of the arms and legs takes the form of *hemiplegia* (paralysis on one side of the body), *paraplegia* (paralysis of the legs), *quadriplegia* (paralysis of the arms and legs), and *monoplegia* (paralysis of one arm or leg).



These conditions often accompany tingling or lightning-like pain, intense pain when moving, or painful tonic convulsions in which the arms, legs, or abdominals stiffen.

Patients may also have an excretory disorder.
This can involve difficulty urinating or defecating, frequent episodes, a sudden urge to urinate, no relief after urinating, or incontinence.

Neuromyelitis optica spectrum disorders (supervised by Dr. Ichiro Nakashima, Professor, Department of Geriatric Neurology, Tohoku Medical and Pharmaceutical University School of Medicine)

Symptoms: Inflammation of the Brain

● Symptoms associated with inflammation of the brain ●

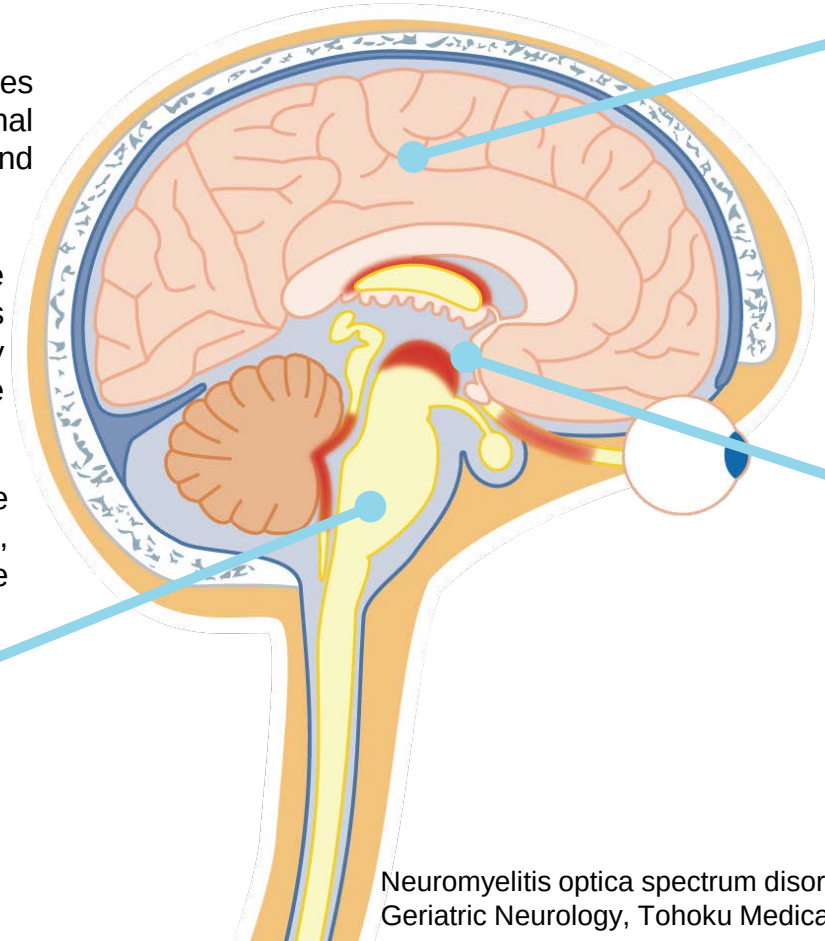
Incessant hiccups, nausea, and sleepiness are characteristic symptoms.

Symptoms vary depending on the part of the brain with inflammation (e.g., hypothalamus, medulla oblongata, cerebrum).

Cerebrum : This is the center of advanced activities in the brain. The cerebrum processes external information to move the body, controlling memories and emotions, and thinking and making decisions.

Hypothalamus : This is the center of the autonomic nervous system. The hypothalamus regulates appetite, sleep, blood pressure, and body temperature. It also secretes hormones that regulate urine volume and cause the expression of breast milk.

Medulla oblongata : This essential part of the brain maintains heart rhythm, breathing, swallowing, and other functions. The center of hiccups is near the medulla oblongata.



Inflammation of the cerebrum

- Unclear thinking
- Poor decision-making and understanding
- Paralysis on one side of the face and body (hemiplegia)
- Left or right visual field defect (homonymous hemianopsia), etc.

Inflammation of the hypothalamus

- Abnormal daytime sleepiness (narcolepsy)
- Production of large amounts of dilute urine (diabetes insipidus)
- Choking caused by difficulty swallowing
- Inability to breathe unassisted, etc.

Inflammation of the medulla oblongata

- Hiccups persist for days or weeks
- Nausea and vomiting, etc.

Neuromyelitis optica spectrum disorders (supervised by Dr. Ichiro Nakashima, Professor, Department of Geriatric Neurology, Tohoku Medical and Pharmaceutical University School of Medicine)

Symptoms: Fatigue and Malaise

Many patients with NMOSD suffer from fatigue and malaise.

Those affected may feel extremely fatigued after moving (exercise fatigue). This involves increasing difficulty moving the body over time when walking or exercising.

Patients may also experience extreme malaise unrelated to their amount of activity.

This may impact daily activities, as those affected feel tired on waking or are unable to move.

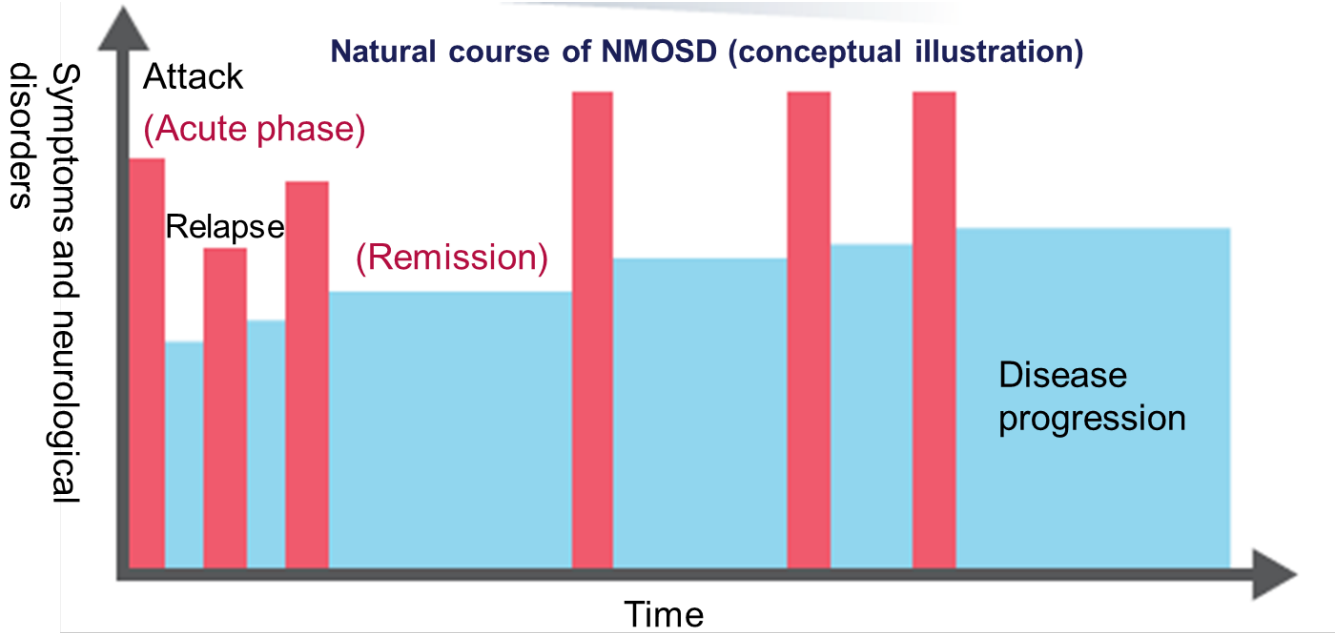
Neuromyelitis optica spectrum disorders (supervised by Dr. Ichiro Nakashima, Professor, Department of Geriatric Neurology, Tohoku Medical and Pharmaceutical University School of Medicine)

Symptoms: Relapses and Course of NMOSD

When untreated, patients often suffer a relapse within a year. The level of disability gradually increases with each relapse.

- Frequency of relapses (when untreated): **1 to 1.5 per year** **(higher than MS)**
- Even a single attack **can blind or leave the patient wheelchair-bound**.
- Characteristics of relapses: Brain syndromes often precede myelitis.
- In relapses, sequelae are common in patients resistant to acute-phase therapy.
- **Pregnancy and delivery: Higher risk of relapse**

*The clinical records and outcomes of 106 anti-AQP4 antibody-positive patients in Japan and the United Kingdom were evaluated.
An unpaired t-test or the Mann-Whitney U test was used to compare the 2 groups. Times to events were compared using the Cox proportional hazards model.



2017 Guideline for the Treatment of Multiple Sclerosis and Neuromyelitis Optica [in Japanese]. Japanese Society of Neurology, supervising ed.; "Guideline for the Treatment of Multiple Sclerosis and Neuromyelitis Optica" Authoring Committee, ed.
Latest Approaches: Multiple Sclerosis and Neuromyelitis Optica [In Japanese]. Jun'ichi Kira, supervising ed. Nakayama Shoten, 2015. 2nd printing.

NMOSD Cases (Case Study)

Case 1: 36-year-old woman

Sudden loss of vision in both eyes (serious optic neuritis)
Three months later, the patient had complete paralysis of the legs, gait inability, sensory disturbance from the sub-abdomen, and urination/defecation disorder (transverse myelitis)
No improvement thereafter.

Case 2: 64-year-old woman

The patient had left optic neuritis when 60. She had 7 relapses (optic neuritis, myelitis, brain lesions) despite subsequent treatment with azathioprine and corticosteroids and was left blind in the left eye and wheelchair bound.

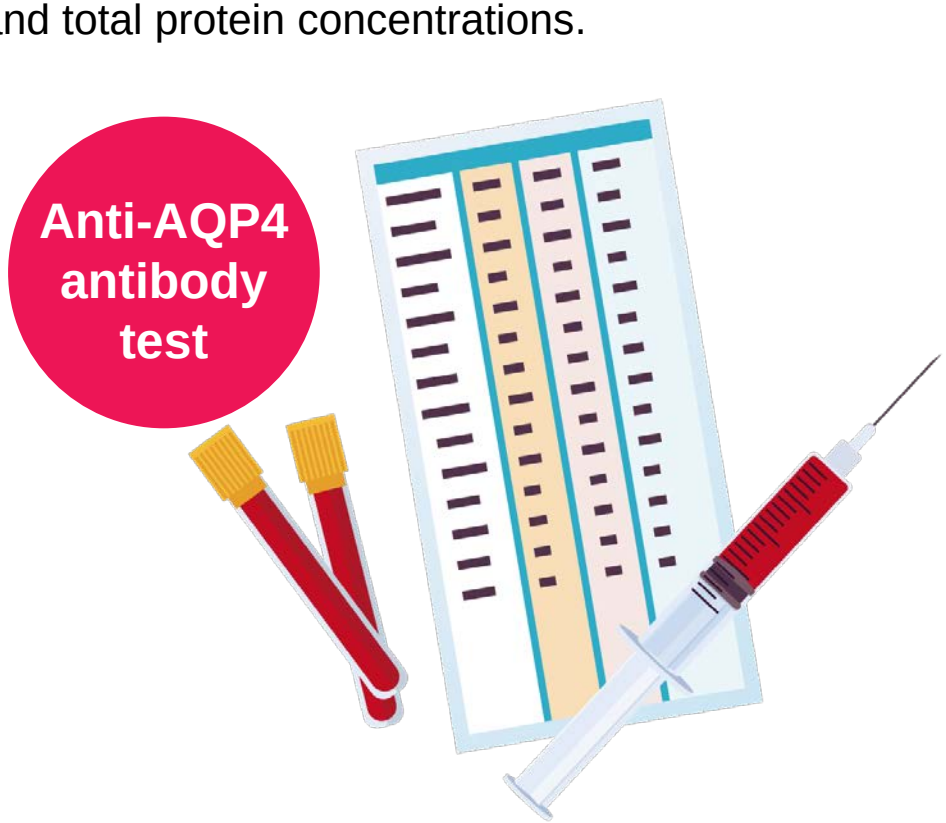
She had intense pain and numbness from the chest down.

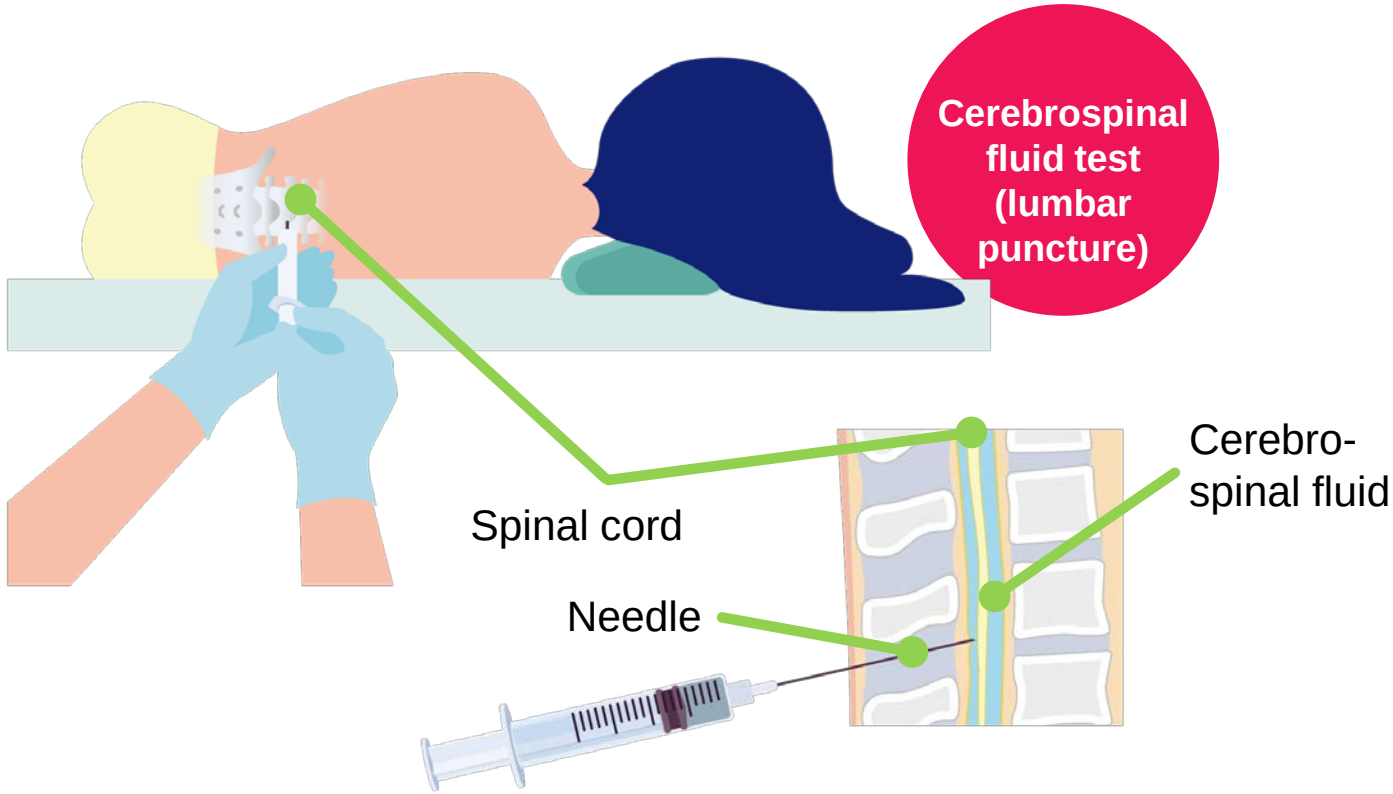
*For indications in Japan, please refer to the latest package insert for each drug.

Testing: Blood Testing (Anti-AQP4 Antibody Test) and Cerebrospinal Fluid Testing

Blood tests are performed to identify the anti-AQP4 antibody responsible for the disease.

Blood tests for the anti-AQP4 antibody are one way to confirm NMOSD.
Since testing can generate a false-negative result depending on when and how it is performed, patients may be retested with another testing procedure.
If more detailed testing is required, a cerebrospinal fluid sample can be collected by lumbar puncture to determine cell counts and total protein concentrations.





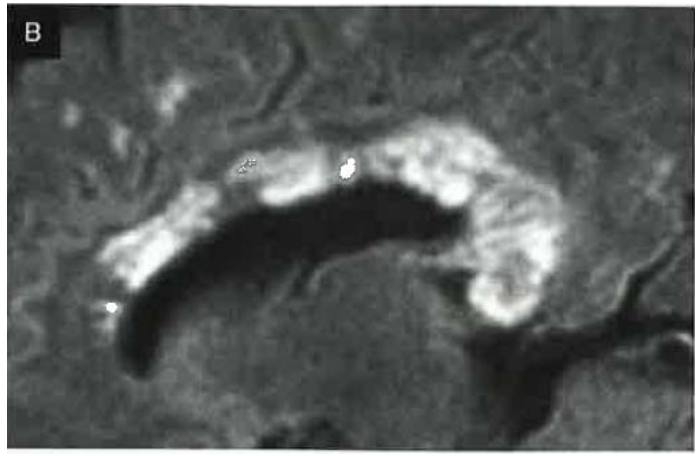
Neuromyelitis optica spectrum disorders (supervised by Dr. Ichiro Nakashima, Professor, Department of Geriatric Neurology, Tohoku Medical and Pharmaceutical University School of Medicine)

Testing: MRI Scans

NMOSD features long spinal cord lesions extending over ≥3 contiguous segments, unlike the ≤1 segment involvement in MS.

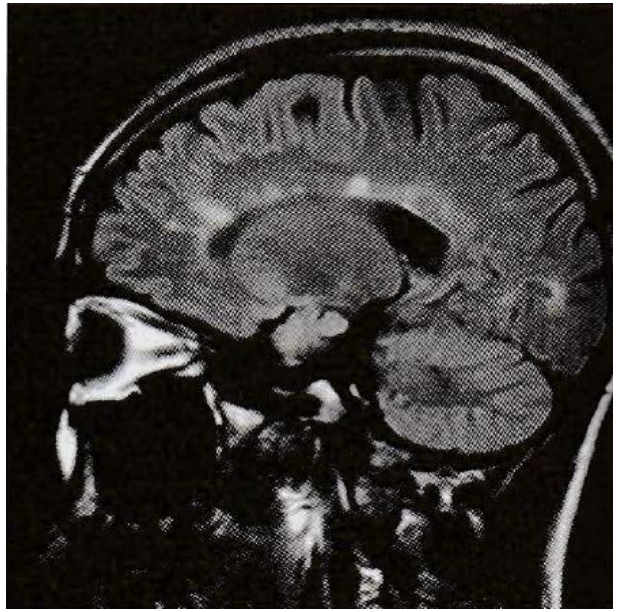
■ Corpus callosum lesions in NMOSD (FLAIR imaging, sagittal)

An edematous lesions cover the entire corpus callosum. The scan shows the periphery with a high-signal intensity and interior with a low-signal intensity marble pattern.
The patient has hypersomnia and disorientation.

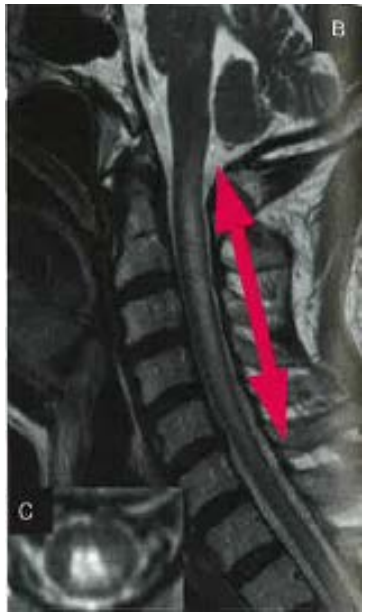


■ Dawson's fingers characteristic of MS (FLAIR imaging, sagittal)

Ovoid lesions along veins run perpendicular to the ventricles.

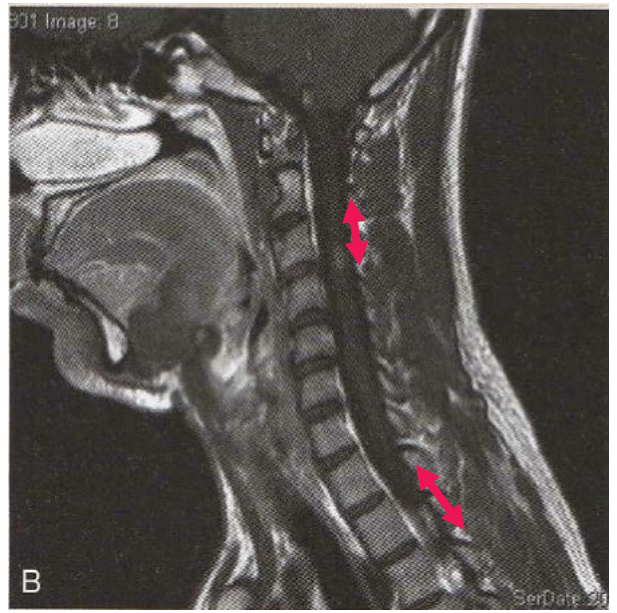


■ Lesion of the cervical spinal cord in NMOSD (T2 weighted, sagittal)



Long lesion running from C3 to C6

■ Active lesion of the cervical spinal cord in MS (Gd-enhanced T1 weighted, sagittal)



Latest Approaches: Multiple sclerosis and neuromyelitis optica [In Japanese]. Jun'ichi Kira, supervising ed. Nakayama Shoten, 2015. 2nd printing.

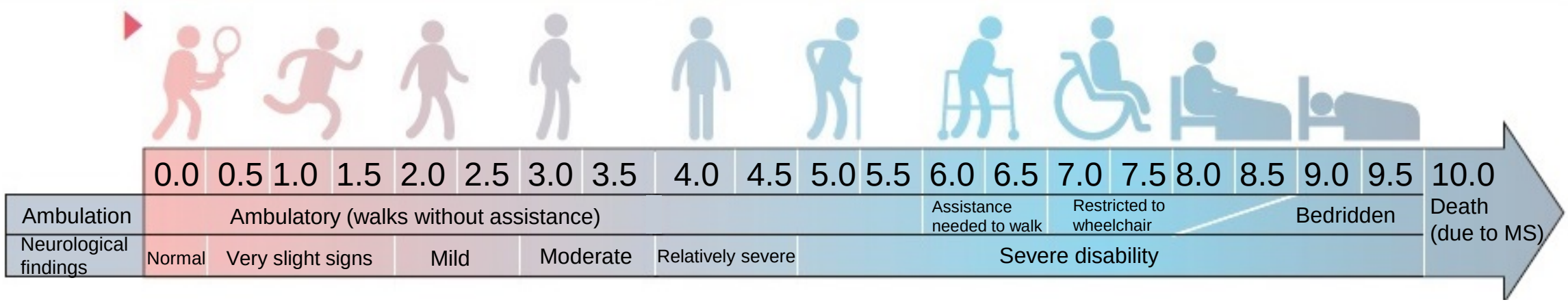
Testing: Expanded Disability Status Scale (EDSS)

There are highly reliable scales for MS, but little evidence supports their use in NMOSD.
Physical disability in NMOSD is currently evaluated with the EDSS, which is used in MS.

- Assessment of physical disability: The Expanded Disability Status Scale (EDSS), or Kurtzke scale

  The EDSS is a scale for assessing disability based on neurological symptoms and is also useful for evaluating symptoms over time.

  Symptoms are scored in 0.5-point increments from 0 (normal) to 10 (death due to MS). In this **scale for evaluating the degree of movement disorders centered on walking function**, those with a score less than 3.5 are fully ambulatory, and those with a score of 5.5 or higher have a walking disorder.



2017 Guideline for the Treatment of Multiple Sclerosis and Neuromyelitis Optica [in Japanese]. Japanese Society of Neurology, supervising ed.; "Guideline for the Treatment of Multiple Sclerosis and Neuromyelitis Optica" Authoring Committee, ed.
Latest Approaches: Multiple Sclerosis and Neuromyelitis Optica [In Japanese]. Jun'ichi Kira, supervising ed. Nakayama Shoten, 2015. 2nd printing.

Diagnosis: International Consensus Diagnostic Criteria for NMOSD (2015)

NMOSD diagnostic criteria for adult patients

NMOSD with aquaporin-4 antibody

1. At least 1 core clinical characteristic
2. Positive test for aquaporin-4 antibody (using best available detection method, cell-based assay strongly recommended)
3. Exclusion of alternative diagnoses

NMOSD without aquaporin-4 antibody or NMOSD with unknown aquaporin-4 antibody status

1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:
   a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome
   b. Dissemination in space (2 or more different core clinical characteristics)
   c. Fulfillment of additional MRI requirements, as applicable
2. Negative tests for aquaporin-4 antibody (using best available detection method), or aquaporin-4 antibody testing unavailable
3. Exclusion of alternative diagnoses

Core clinical characteristics

1. Optic neuritis
2. Acute myelitis
3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
4. Acute brainstem syndrome
5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions

Additional MRI requirements for NMOSD without aquaporin-4 antibody or NMOSD with unknown aquaporin-4 antibody status

1. Acute optic neuritis: requires brain MRI showing (a) normal findings or only nonspecific white matter lesions, OR (b) optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over >1/2 optic nerve length or involving optic chiasm
2. Acute myelitis: requires associated intramedullary MRI lesion extending over ≥3 contiguous segments (LETM) OR ≥3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis
3. Area postrema syndrome: requires associated dorsal medulla/area postrema lesions
4. Acute brainstem syndrome: requires associated periependymal brainstem lesions

NMOSD should not be diagnosed based on only 1 finding or without excluding alternative diagnoses. NMOSD should be diagnosed in overall consideration of the course of clinical symptoms and MRI and test findings.

2017 Guideline for the Treatment of Multiple Sclerosis and Neuromyelitis Optica [in Japanese]. p. 318. Japanese Society of Neurology, supervising ed.; "Guideline for the Treatment of Multiple Sclerosis and Neuromyelitis Optica" Authoring Committee, ed.
Note: "Aquaporin-4 antibody" in the guideline refers to the same antibody as "anti-AQP4 antibody" used in the other slides

Treatment: Treating NMOSD

NMOSD treatment has 3 components: Acute-stage treatment, prevention of relapses, and symptomatic therapy

Purpose of treatment		Main treatment approaches
(1) Alleviating symptoms of acute exacerbations		• Steroid pulse therapy • (If no response) Plasma purification or large-dose immunoglobulin infusion
(2) Preventing relapses and slowing disease progress during remission		• Oral corticosteroids • Immunosuppressants (e.g., azathioprine, mycophenolate mofetil, tacrolimus) • Monoclonal antibodies (eculizumab, satralizumab) • Regular plasma purification or regular immunoglobulin infusions
(3) Symptomatic therapy for sequelae	Spastic paralysis (spasticity)	• Central nervous muscle relaxants (e.g., baclofen)
	Pollakiuria	• Anticholinergic agents
	Dysuria	• α_1 receptor antagonists
	Painful tonic convulsions	• Carbamazepine
	Conservation of motor function	• Rehabilitation

• Patients negative for anti-AQP4 antibody should be treated similarly to antibody-positive patients

*The drugs indicated for neuromyelitis optica spectrum disorders are eculizumab and satralizumab.

*For indications in Japan, please refer to the latest package insert for each drug.

Fujihara K: Neuromyelitis optica (NMO). Diseases Visualized Vol. 7: Brain and nerves [in Japanese]. Medic Media. Adapted from table on p. 328.
Japanese Society of Neurology: 2017 Guideline for the Treatment of Multiple Sclerosis and Neuromyelitis Optica [in Japanese]. 1st ed. Igaku-Shoin Ltd., Tokyo, 2017.

Unmet Needs in NMOSD Treatment

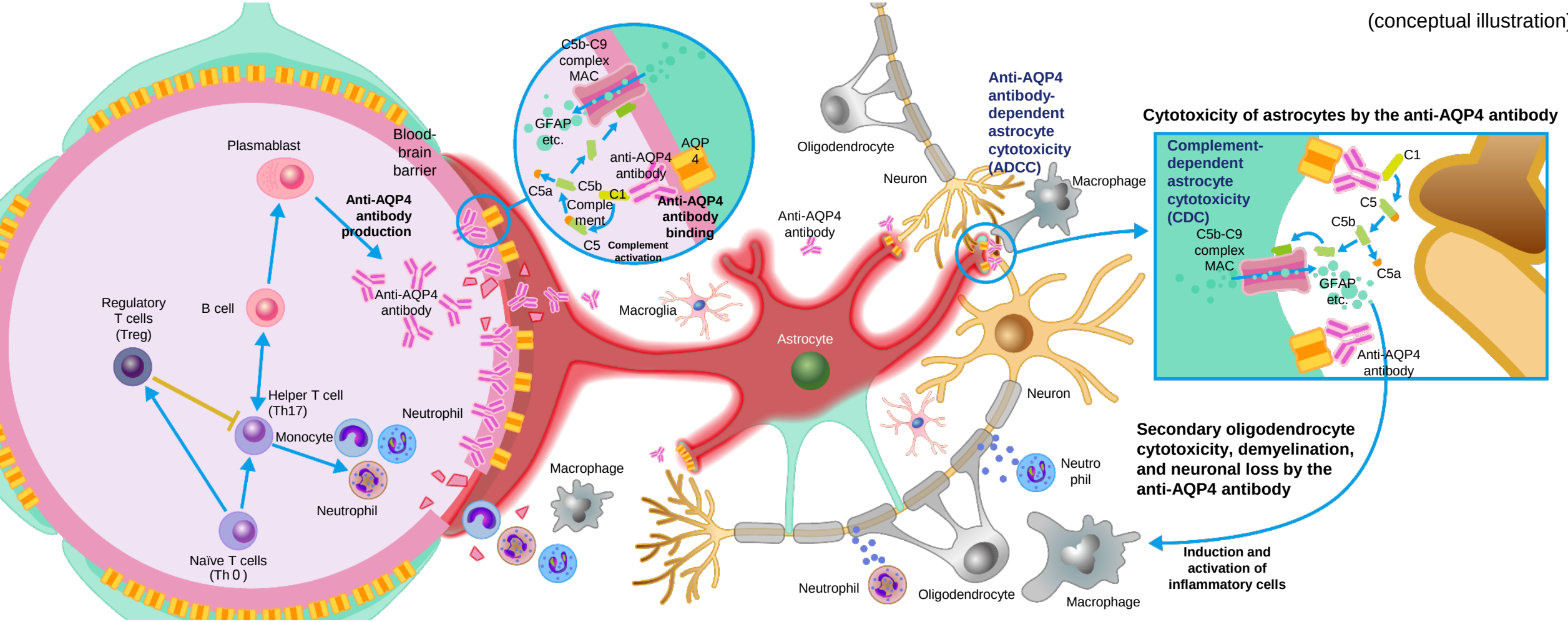
- The lack of indicated treatments has led to a reliance on the off-label use of drugs for treatment
- Suppressing relapses is key to preventing severe disability but it requires the long-term use of fixed-dose corticosteroids
- Although treatment with steroids is effective in controlling relapse in some cases, some patients are refractory, suffering from relapses despite fixed-dose corticosteroid treatment
- Steroids produce many difficult-to-manage adverse events (e.g., infections, osteoporosis, diabetes mellitus, moon face)

The Correlation between IL-6 and NMOSD

Pathophysiology: Anti-AQP4 Antibody and Astrocyte Cytotoxicity

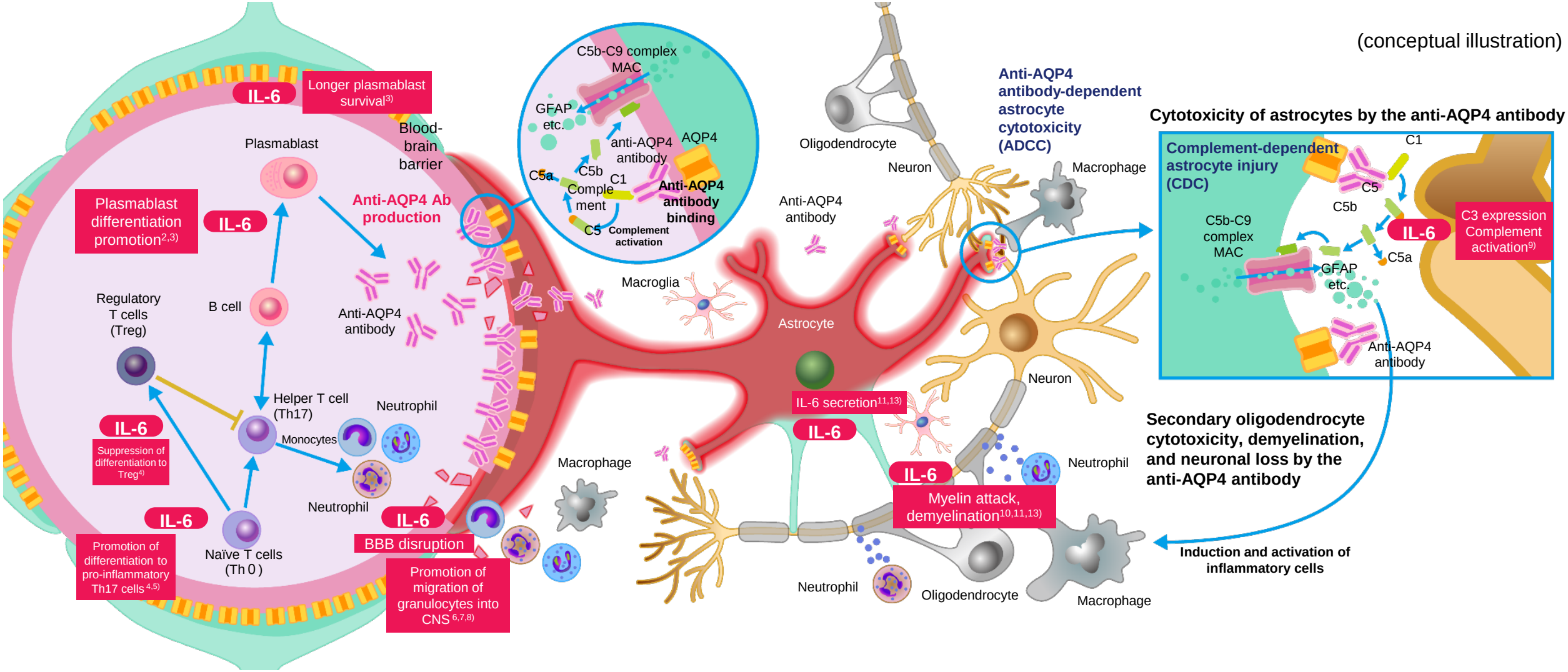
NMOSD is regarded as an autoimmune astrocytopathy, driven by an episode that AQP4-expressing astrocytes are the primary target, which leads to demyelination and neuroaxonal cytotoxicity.

(conceptual illustration)



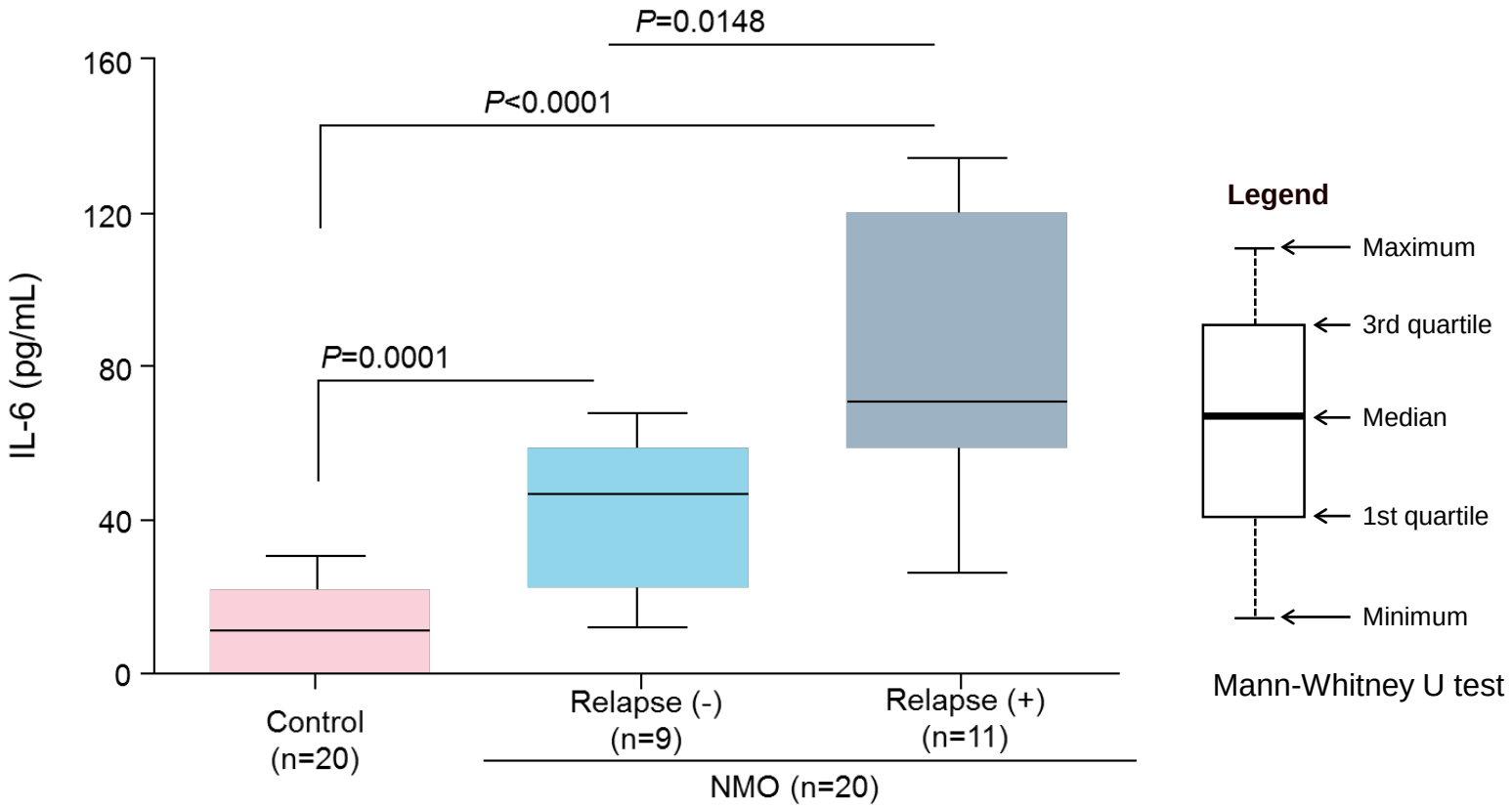
1) Fujihara K. et al. Clin Exp Neuroimmunol 2012;3:58-73, 2) Latest Approaches: Multiple sclerosis and neuromyelitis optica [In Japanese]. Jun'ichi Kira, supervising ed. Nakayama Shoten, 2015. 2nd printing.
3) Papadopoulos MC, et al. Nat Rev Neurol 2014;10:493-506, 4) Basic and Clinical Picture of Multiple Sclerosis (MS) and Neuromyelitis Optica (NMO) [in Japanese]. Fujihara K, ed. Medicine and Drug Journal, published 2012.

Pathophysiology: IL-6 Autoimmune Activation and its Role in Astrocyte cytotoxicity[1)]



1) Fujihara K. et al. Clin Exp Neuroimmunol 2012;3:58-73 2) Weinshenker BD & Wingerchuk DM. Mayo Clin Proc 2017;92(4):663-679 3) Chihara N, et al. Proc Natl Acad Sci USA 2011;108:3701-3706 4) Kimura K, et al. Eur J Immunol 2010;40:1830-1835. 5) Lin J, et al. Int J Neurosci 2016;126(12):1051-1060 6) Takeshita Y, et al. Neurol Neuroimmunol Neuroinflamm 2017;4:e311 7) Obermeier B, et al. Nat Med 2013;19:1584-1596 8) Erta M, et al. Int J Biol Sci 2012;8:1254-1266 9) Barnum SR, et al. Glia 1996;18:107-117 10) Papadopoulos MC, et al. Nat Rev Neurol 2014;10:493-506, some of the authors received consultant fees from Chugai Pharmaceutical Co., Ltd. 11) Kaplin AJ, et al. J Clin Invest 2005;115:2731−2741 12) Rothhammer V, et al. Semin Immunopathol 2015;37:625-638 13) Uzawa A, et al. Clin Exp Neuroimmunol 2013;4:167-172

Pathophysiology: Blood IL-6 Levels and the Frequency of NMO Relapses

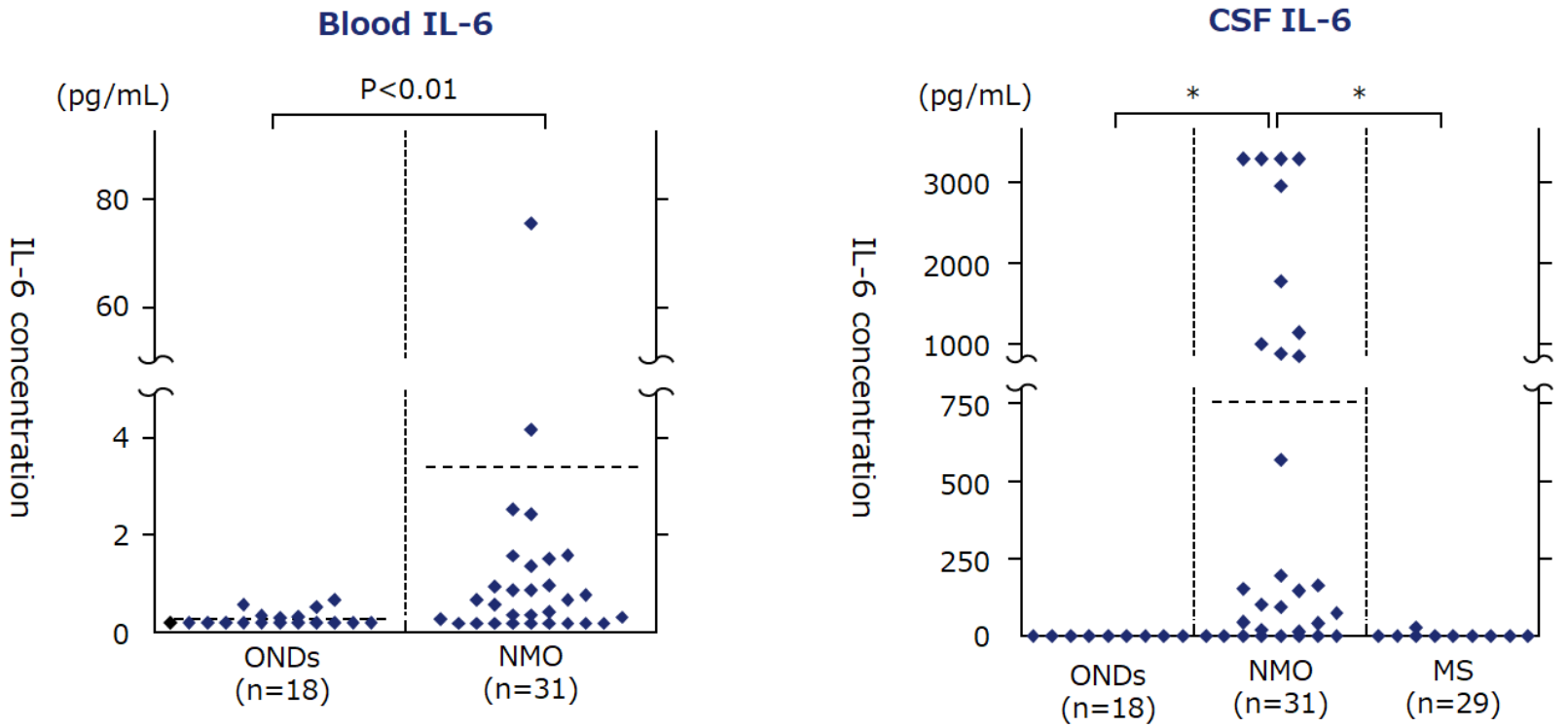


NMO patients with elapses had significantly higher blood IL-6 levels than those without relapses

Study summary and methods of assessment:
In this study, blood samples were collected from 20 patients with relapsing–remitting neuromyelitis optica at the time of clinical remission (baseline) for cell counts and cytokine analysis. Over the following 2 years, relapses and the severity of neuropathy were observed, and the correlations of observations to test values were evaluated. The patients who relapsed during the follow-up period had significantly higher baseline IL-6 levels.
Relative risk analysis revealed that patients with at least the median baseline IL-6 level (58.5 pg/mL) had an 8-fold higher risk of relapse.

Barros PO, et al. Clin Exp Immunol 2016;183:480-489.

Pathophysiology: The Importance of IL-6 in NMO



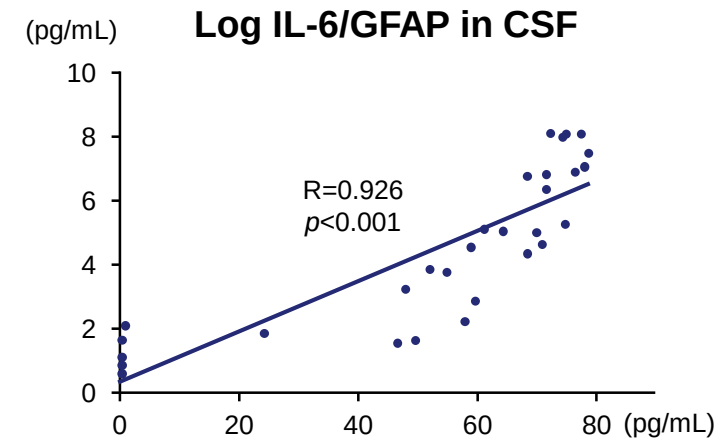
Patients with NMO had higher levels of IL-6 in the serum and cerebrospinal fluid than patients with other diseases

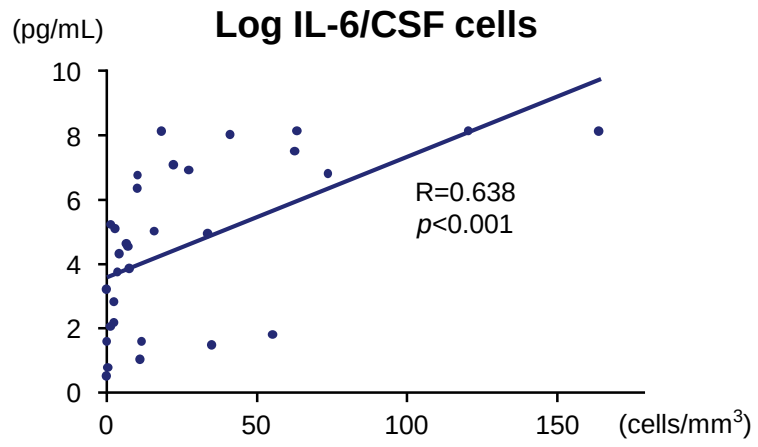
Study summary and methods of assessment:
To evaluate the pathophysiology of NMO and determine the effects of cytokines and chemokines on this disease, levels of 27 cytokines and chemokines and Th17 cell-associated cytokines were measured in the cerebrospinal fluid of 31 patients with anti-AQP4 antibody-positive NMO, 29 patients with MS, and 18 patients with other non-inflammatory neurological disorders (ONDs). (Blood levels of some cytokines and chemokines were also measured.) At the time of sampling, the investigators determined the patients' sex, age, duration of disease, Expanded Disability Status Scale (EDSS) score, whether a longitudinally extensive spinal cord lesion was present, whether serum anti-AQP4 antibody was present by enzyme-linked immunosorbent assay (ELISA), and the status of immunosuppressant therapy. The Mann-Whitney U test was used for inter-group comparisons, and Spearman's rank correlation coefficient was used to evaluate correlations. P<0.05 constituted a significant difference.

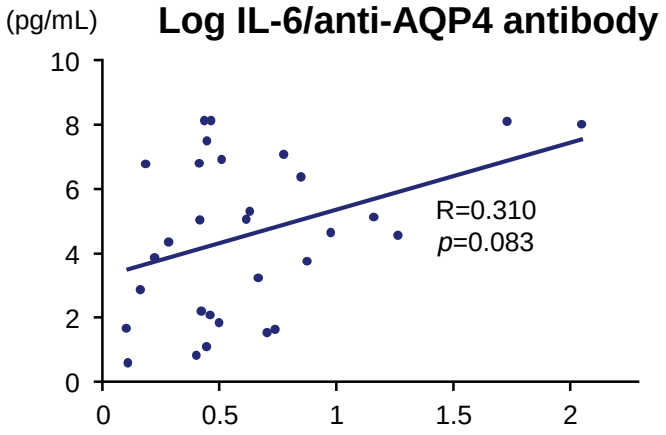
MS: Multiple sclerosis, NMO: Neuromyelitis optica, OND: Other non-inflammatory neurological disorders
*Statistically significant after adjustment for multiple comparison (P<0.05).

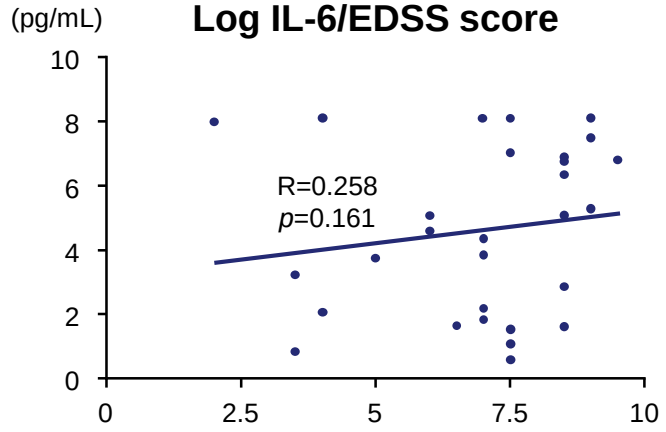
Uzawa A et al.: Mult Scler. 2010; 16(12):1443-1452.

Pathophysiology: The Correlation of CSF IL-6 with Clinical and Test Parameters in NMO





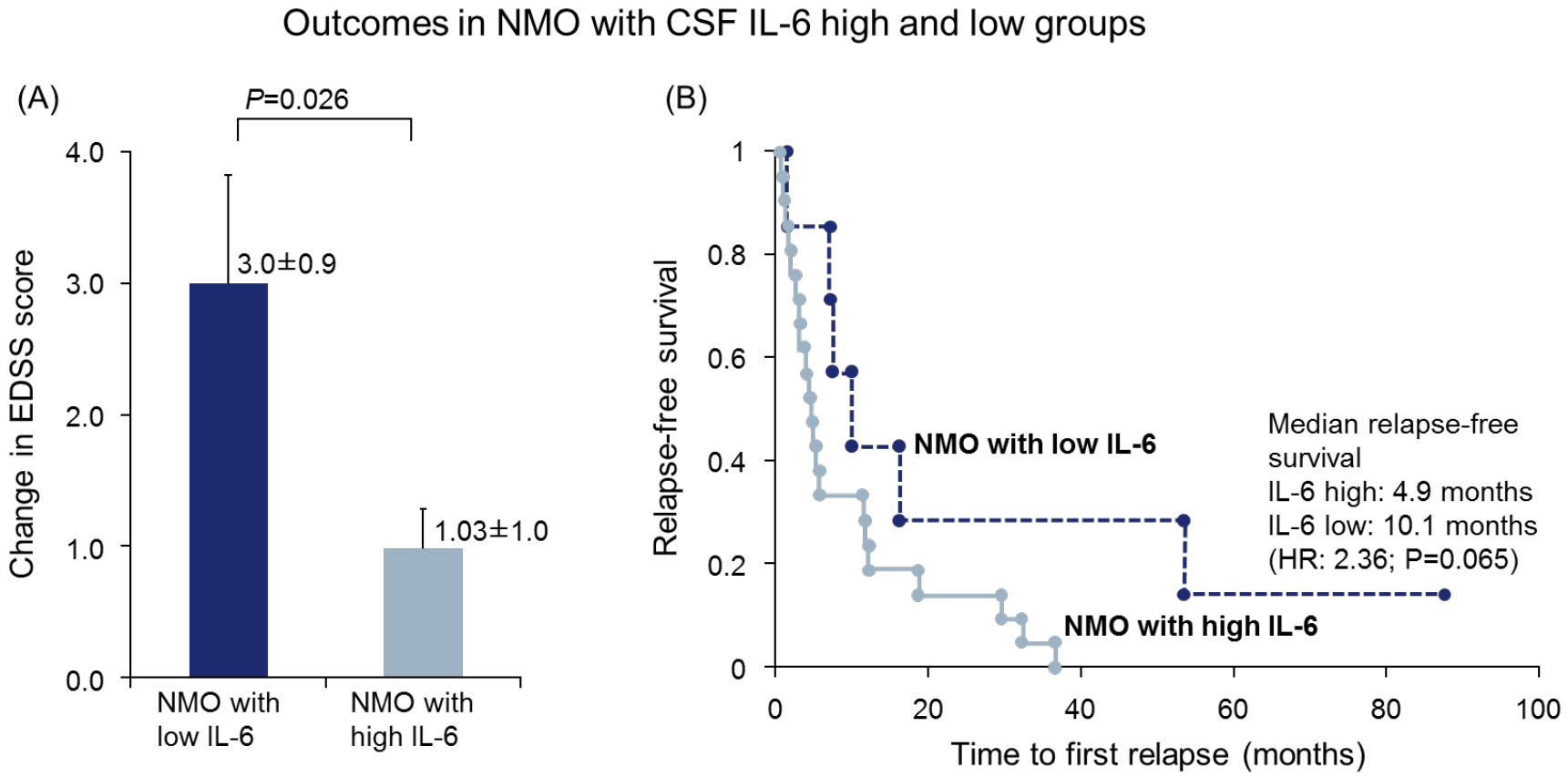




Correlations were tested using Spearman's rank correlation coefficient. P<0.05 constituted statistical significance.

Uzawa A et al., Mult Scler. 2010. 16(12), 1443-1452.

Pathophysiology: CSF IL-6 and NMO Outcomes



Study summary and methods of assessment:
Methods: CSF IL-6 levels, EDSS score improvements, and the rates and durations of relapse-free survival were determined in 28 patients with NMO.
Results: Those with low IL-6 levels achieved significantly better EDSS score improvement than those with high IL-6 levels and tended to have higher/longer relapse-free survival rates and durations.
Statistical analysis: The Mann-Whitney test was used to analyze continuous variables. The log-rank test and Cox proportional hazards model were used to analyze event occurrences.

Uzawa et al., J Neurol Neurosurg Psychiatry. 2012. 83(3) 339-340.

Clinical Data

1. Global Phase III, Double-Blind, Randomized, Parallel-Group Comparative Study

(Combination Therapy, SA-307JG Study)

SAkuraSky

Indications of concomitant drugs (excerpted, see the package inserts for details)
AZA: 1. Prevention of rejection in the following transplants (renal transplants, hepatic transplants, cardiac transplants, and lung transplants); 2. Remission induction and remission maintenance of steroid-dependent Crohn's disease, remission maintenance of steroid-dependent ulcerative colitis; 3. The following treatment-resistant rheumatic diseases [Systemic vasculitis (such as microscopic polyangiitis, Wegener's granulomatosis, polyarteritis nodosa, Churg-Strauss syndrome, and aortitis syndrome), systemic lupus erythematosus (SLE), polymyositis, dermatomyositis, scleroderma, mixed connective tissue disease, and refractory rheumatoid disease]; and 4. Autoimmune hepatitis
MMF: Treatment of refractory rejections after kidney transplant (when the patient does not respond to the existing drugs, or cannot be treated due to adverse drug reactions, and when the rejections are diagnosed as refractory), suppression of rejections after the following organ transplants (kidney, heart, liver, lung and pancreas transplants), lupus nephritis
OCS: Chronic adrenocortical insufficiency (primary, secondary, pituitary-related, iatrogenic), acute adrenocortical insufficiency (adrenal crisis), adrenogenital syndrome, subacute thyroiditis, thyrotoxicosis [thyroid (thyrotoxic) crisis], malignant exophthalmos secondary to a thyroid disease, isolated ACTH deficiency, etc.

4. INDICATIONS
Prevention of relapses of neuromyelitis optica spectrum disorders (NMOSD), including neuromyelitis optica (NMO)
5. PRECAUTIONS CONCERNING INDICATIONS (excerpted)
5.2 There is limited data on the efficacy of ENSPRYNG in patients who are negative for anti-aquaporin-4 (AQP4) antibodies. Administer ENSPRYNG to patients who are positive for anti-AQP4 antibodies.

Study Synopsis

Objectives	To evaluate the efficacy and safety of adding ENSPRYNG to baseline treatment in patients with NMO and NMOSD
Design	Multicenter, placebo-controlled, randomized, double-blind, parallel group study (11 countries, 34 sites)
Study patients	Adolescent (12 to 17 years) and adult (18 to 74 years) patients with NMO/NMOSD*1 Number of patients randomized by the data cutoff for the primary analysis: 83 Efficacy: 83 Safety: 83 for double-blind period and 65 for entire treatment period
Primary endpoint	Time to first relapse*2 (TFR)
Secondary endpoints	○ Major secondary endpoints (reference information) • Change from baseline in Visual Analogue Score (VAS) for pain at Week 24 • Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT) fatigue score at Week 24 ○ Other secondary endpoints Proportion of PDR-free patients, annualized relapse rate, change in Short Form Health Survey 36 (SF-36) Version 2 score, change in EuroQol-5D 3 Level Version (EQ-5D-3L), change in Modified Rankin Scale (mRS) score, change in Zarit Burden Interview (ZBI) score, change in Expanded Disability Status Scale (EDSS) score, change in visual acuity (Snellen chart)
Other endpoints	○ Pharmacodynamics Serum IL-6, sIL-6R, hsCRP levels ○ Pharmacokinetics Serum satralizumab concentration ○ Safety Adverse events [including serious adverse events, adverse events of special interest (AESIs), and selected adverse events], laboratory test values, vital signs, electrocardiography

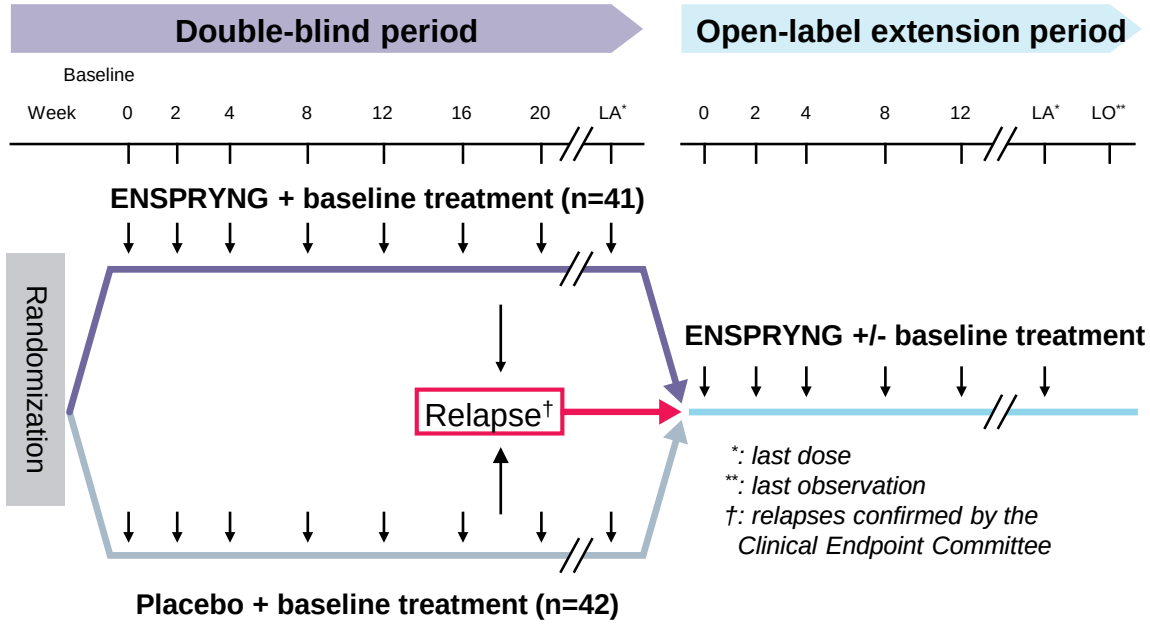
*1 Patients with NMO as defined by 2006 criteria or anti-AQP4 antibody-positive NMOSD patients as defined by 2007 criteria
*2 Protocol-defined relapses confirmed by the Clinical Endpoint Committee

The concomitant drugs used in the study are not approved in Japan for the prevention of NMOSD relapses.
See the first slide describing the study for more information about the indications of the concomitant drugs.
The overall study population includes patients negative for the anti-AQP4 antibody.

Review data as of time of approval of ENSPRYNG Syringes for Subcutaneous Injection 120 mg

Study Synopsis

Administration procedures



The study patients were randomized to ENSPRYNG or placebo at a 1:1 ratio*1. With the baseline treatment*2, ENSPRYNG 120 mg or placebo was administered by subcutaneous injection at Weeks 0, 2, and 4 and Q4W thereafter. Patients who experienced a relapse in the double-blind period*3 or completed the double-blind period were allowed to enter the open-label extension period. In the open-label extension period, all patients received ENSPRYNG 120 mg by subcutaneous injection at Weeks 0, 2, and 4 and Q4W thereafter.

*1 Randomization factors: Baseline annualized relapse rate (1 or >1) and geographic region (Asia or Europe/other)
*2 Patients were allowed to use only 1 of the following 3 baseline treatments:
(1) Azathioprine (AZA) (≤ 3 mg/kg/day)
(2) Mycophenolate mofetil (MMF) (≤ 3000 mg/day)
(3) Oral corticosteroids (OCS) (≤ 15 mg/day prednisolone equivalent)
• Drugs (1), (2), and (3) are not approved in Japan for the prevention of NMOSD relapses.
• Used for at least 8 weeks before the start of treatment.
• Patients 12 to 17 years of age were allowed to use (1) + (3) or (2) + (3) together.
*3 Patients with a protocol-defined relapse (PDR) confirmed by the Clinical Endpoint Committee or patients with receiving acute-phase treatment not constituting a PDR.

The concomitant drugs used in the study are not approved in Japan for the prevention of NMOSD relapses.
See the first slide describing the study for more information about the indications of the concomitant drugs.
The overall study population includes patients negative for the anti-AQP4 antibody.

Review data as of time of approval of ENSPRYNG Syringes for Subcutaneous Injection 120 mg

Patient Characteristics

	ENSPRYNG group (n=41)	Placebo group (n=42)	Total (n=83)
Age			
Mean age (SD)	40.8 (16.1)	43.4 (12.0)	42.1 (14.2)
Number of patients <18 years (%)	4 (9.8%)	3 (7.1%)	7 (8.4%)
≥18	37 (90.2%)	39 (92.9%)	76 (91.6%)
Number of patients by sex (%)			
Male	4 (9.8%)	2 (4.8%)	6 (7.2%)
Female	37 (90.2%)	40 (95.2%)	77 (92.8%)
Number of patients by race/ethnicity (%)			
Japanese	11 (26.8%)	10 (23.8%)	21 (25.3%)
Asian (other than Japanese)	6 (14.6%)	8 (19.0%)	14 (16.9%)
Black/African American	0	2 (4.8%)	2 (2.4%)
Caucasian	24 (58.5%)	21 (50.0%)	45 (54.2%)
Other	0	1 (2.4%)	1 (1.2%)
Baseline ARR			
Mean ARR (SD)	1.48 (0.63)	1.50 (0.60)	1.49 (0.61)
Patients with ARR > 1 (%)	21 (51.2%)	22 (52.4%)	43 (51.8%)

	ENSPRYNG group (n=41)	Placebo group (n=42)	Total (n=83)
Patients with diagnosis (%)			
NMO	33 (80.5%)	28 (66.7%)	61 (73.5%)
NMOSD	8 (19.5%)	14 (33.3%)	22 (26.5%)
Patients anti-AQP4 antibody (%)			
Positive	27 (65.9%)	28 (66.7%)	55 (66.3%)
Negative	14 (34.1%)	14 (33.3%)	28 (33.7%)
Baseline treatment Number of patients (%)			
Azathioprine (AZA)	16 (39.0%)	13 (31.0%)	29 (34.9%)
Mycophenolate mofetil (MMF)	4 (9.8%)	8 (19.0%)	12 (14.5%)
Oral corticosteroids (OCS)	17 (41.5%)	20 (47.6%)	37 (44.6%)
AZA+OCS	3 (7.3%)	0	3 (3.6%)
MMF+OCS	1 (2.4%)	1 (2.4%)	2 (2.4%)
Baseline EDSS			
EDSS mean (SD)	3.83 (1.57)	3.63 (1.32)	3.73 (1.45)
Median weight, kg (range)	57.00 (45.3-99.0)	61.35 (39.4-140.4)	58.40 (39.4-140.4)

SD: Standard deviation, ARR: Annualized relapse rate, EDSS: Expanded Disability Status Scale

The concomitant drugs used in the study are not approved in Japan for the prevention of NMOSD relapses. See the first slide describing the study for more information about the indications of the concomitant drugs. The overall study population includes patients negative for the anti-AQP4 antibody.

Review data as of time of approval of ENSPRYNG Syringes for Subcutaneous Injection 120 mg

Primary Endpoint

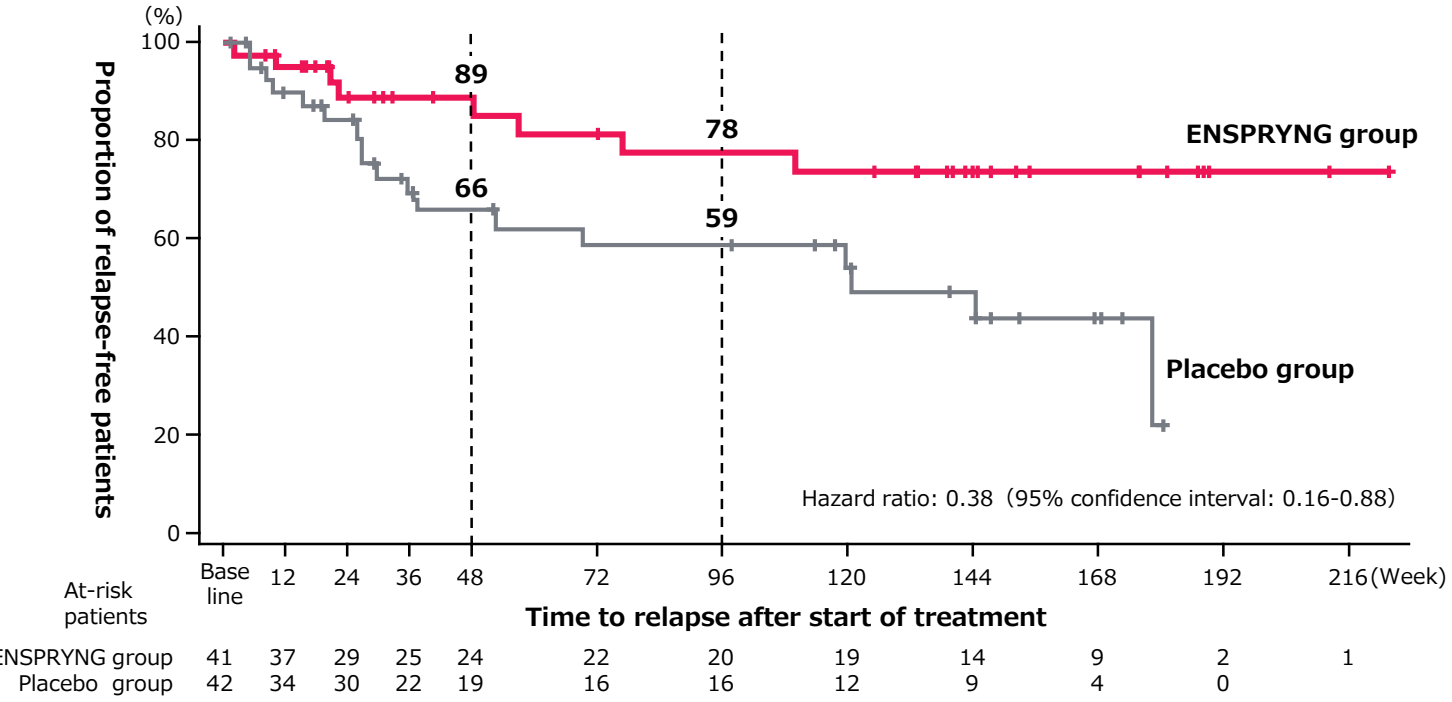
Time to First Relapse*

*Protocol-defined relapses (PDR) confirmed by the Clinical Endpoint Committee

Combination study

The hazard ratio for time to first relapse in the Enspring group relative to the placebo group was 0.38, indicating a superiority (95% confidence interval: 0.16-0.88, P=0.0184, stratified log-rank test). The risk reduction rate was 62%.Relapse during the double-blind period was observed in 8 patients (19.5%) in the Enspring group and 18 patients (42.9%) in the placebo group. The median efficacy evaluation period (range) was 115.1 weeks (10-224 weeks) for the Enspring group and 42.5 weeks (8-185 weeks) for the placebo group.

■ Time to first relapse (ITT population)



At-risk patients

	Base line	12	24	36	48	72	96	120	144	168	192	216(Week)
ENSPRYNG group	41	37	29	25	24	22	20	19	14	9	2	1
Placebo group	42	34	30	22	19	16	16	12	9	4	0	

The concomitant drugs used in the study are not approved in Japan for the prevention of NMOSD relapses.
See the first slide describing the study for more information about the indications of the concomitant drugs.
The overall study population includes patients negative for the anti-AQP4 antibody.

Secondary Endpoint

Proportion of PDR-free patients

The proportion of PDR-free patients during the double-blinded period, the open-label extension period and the entire study were calculated for the each treatment group. The relapse free rates of PDR were analyzed at every 24 weeks after baseline.
The proportion of PDR-free patients at weeks 48 and 96 was 89% and 78% in the ENSPRYNG group, and 66% and 59% in the placebo group, respectively.

Secondary Endpoint

Annualized relapse rate

The relapse episodes for each patient was recorded throughout the whole study. The ARR was calculated as the total number of relapses experienced divided by the person-years at risk for each year of the study period.
The annualized relapse rate based on PDR was 0.11 in the ENSPRYNG group, and 0.32 in the placebo group.

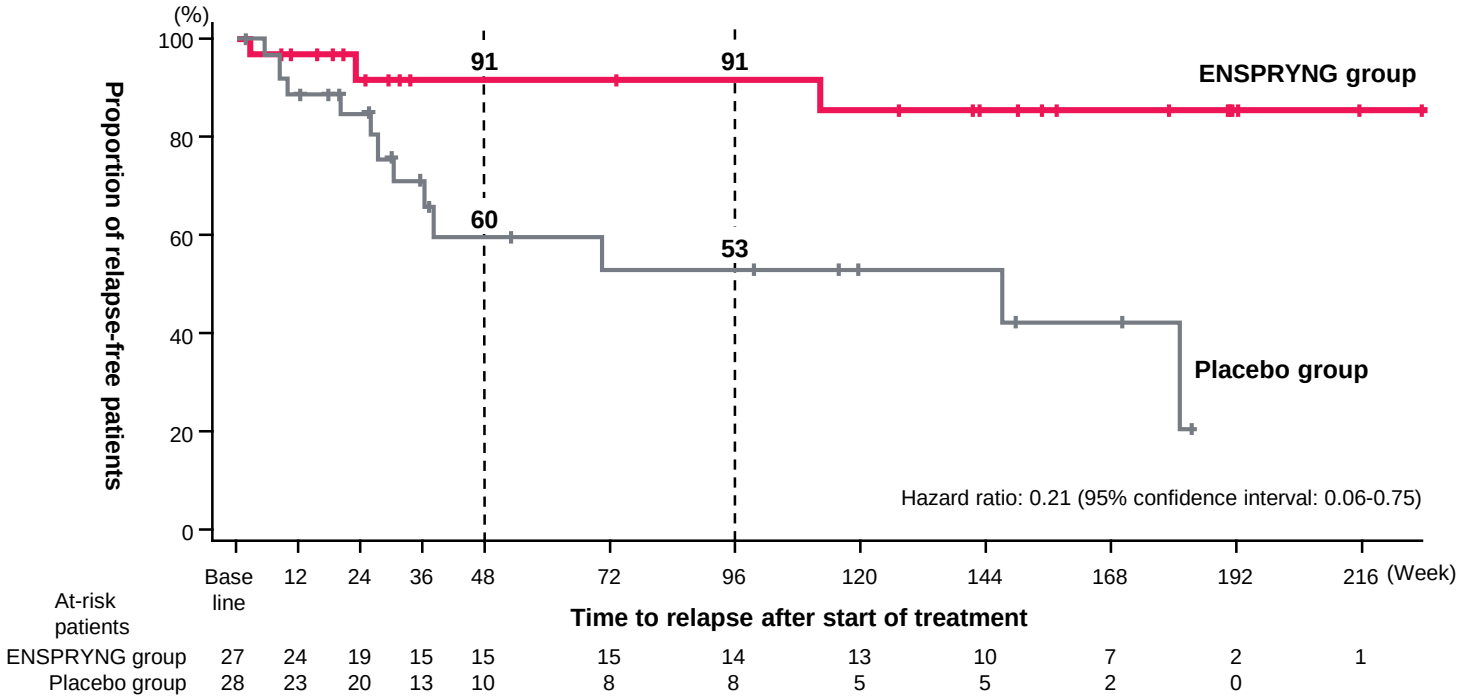
Stratified log-rank test stratified by baseline annualized relapse rate (1 or >1) and geographic region (Asia or Europe/other).
The proportion of PDR-free patients (at Weeks 48 and 96) is a secondary endpoint for the overall population.

Review data as of time of approval of ENSPRYNG Syringes for Subcutaneous Injection 120 mg

Time to First Relapse (Anti-AQP4 Antibody-Positive)

The times to first relapse are shown here. The hazard ratio for the ENSPRYNG group relative to the placebo group was 0.21 (95% confidence interval: 0.06-0.75).

■ Time to first relapse (anti-AQP4 antibody-positive subgroup)



		ENSPRYNG group	Placebo group
Anti-AQP4 antibody-positive patients		27 (10 Japanese)	28 (9 Japanese)
Patients with a relapse (%)		3 (11.1%)	12 (42.9%)
Hazard ratio (95% confidence interval)		0.21 (0.06-0.75)	
Proportion of relapse-free patients	At Week 48 (95% confidence interval)	91% (69.64-97.83)	60% (36.25-77.25)
	At Week 96 (95% confidence interval)	91% (69.64-97.83)	53% (29.34-72.38)

Stratified log-rank test stratified by baseline annualized relapse rate (1 or >1) and geographic region (Asia or Europe/other).
The proportion of PDR-free patients (at Weeks 48 and 96) is a secondary endpoint for the overall population.

The concomitant drugs used in the study are not approved in Japan for the prevention of NMOSD relapses.
See the first slide describing the study for more information about the indications of the concomitant drugs.
The overall study population includes patients negative for the anti-AQP4 antibody.

Review data as of time of approval of ENSPRYNG Syringes for Subcutaneous Injection 120 mg

Subgroup Analysis

Status of PDRs in Japanese and Non-Japanese Subgroups

Combination study

	Overall				Anti-AQP4 antibody-positive subgroup			
	Japanese population		Non-Japanese population		Japanese population		Non-Japanese population	
	ENSPRYNG group	Placebo group	ENSPRYNG group	Placebo group	ENSPRYNG group	Placebo group	ENSPRYNG group	Placebo group
Number of patients	11	10	30	32	10	9	17	19
Patients with a PDR (%)	0	3 (30.0%)	8 (26.7%)	15 (46.9%)	0	3	3 (17.6%)	9 (47.4%)
Hazard ratio* (95% confidence interval)	—		0.51 (0.21-1.24)		—		0.39 (0.10-1.57)	

The concomitant drugs used in the study are not approved in Japan for the prevention of NMOSD relapses.
See the first slide describing the study for more information about the indications of the concomitant drugs.
The overall study population includes patients negative for the anti-AQP4 antibody.

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Safety Evaluation: Double-Blind Period

	ENSPRYNG group (n=41)		Placebo group (n=42)	
Causality	**Total events**	**Causality not ruled out**	**Total events**	**Causality not ruled out**
All adverse events	37 (90.2%)	17 (41.5%)	40 (95.2%)	20 (47.6%)
Serious adverse events	7 (17.1%)	1 (2.4%)	9 (21.4%)	4 (9.5%)
Adverse events leading to withdrawal	3 (7.3%)	2 (4.9%)	5 (11.9%)	2 (4.8%)
Deaths	0	0	0	0

The most common adverse drug reactions in the ENSPRYNG group were leukopenia and injection related reaction each in 5 patients (12.2%) and lymphopenia in 3 patients (7.3%). Leukopenia, lymphopenia, anemia, hypercholesterolemia, and cystitis were each reported in 3 patients (7.1%) in the placebo group.
The serious adverse drug reaction, pneumonia was reported in 1 patient in the ENSPRYNG group. The serious adverse drug reactions reported in the placebo group were leukopenia, uterine polyp, escherichia sepsis, lymphopenia, autoimmune thrombocytopenia, and appendicitis each in 1 patient.
The adverse drug reactions leading to withdrawal were increased ALT and increased AST in 1 patient and neutropenia in 1 patient in the ENSPRYNG group. The adverse drug reactions leading to withdrawal in the placebo group were lymphopenia, autoimmune thrombocytopenia, and leukopenia each in 1 patient.
No deaths were reported in the study.

The concomitant drugs used in the study are not approved in Japan for the prevention of NMOSD relapses.
See the first slide describing the study for more information about the indications of the concomitant drugs.
The overall study population includes patients negative for the anti-AQP4 antibody.

Review data as of time of approval of ENSPRYNG Syringes for Subcutaneous Injection 120 mg

Clinical Data

2. Global Phase III, Double-Blind, Randomized, Parallel-Group Comparative Study

(Monotherapy, SA-309JG Study)

SAkuraStar

4. INDICATIONS
Prevention of relapses of neuromyelitis optica spectrum disorders (NMOSD), including neuromyelitis optica (NMO)
5. PRECAUTIONS CONCERNING INDICATIONS (excerpted)
5.2 There is limited data on the efficacy of ENSPRYNG in patients who are negative for anti-aquaporin-4 (AQP4) antibodies. Administer ENSPRYNG to patients who are positive for anti-AQP4 antibodies.

Study Synopsis

Objectives	To evaluate the efficacy and safety of ENSPRYNG compared with placebo in patients with NMO and NMOSD
Design	Multicenter, placebo-controlled, randomized, double-blind, parallel group comperative study (13 countries, 44 sites)
Study patients	Adult (18 to 74 years) patients with NMO/NMOSD*1 Number of patients randomized by the data cutoff for the primary analysis: 95 Efficacy: 95 Safety: 95 for double-blind period and 80 for entire treatment period
Primary endpoint	Time to first relapse*2 (TFR)
Secondary endpoints	○ Major secondary endpoints (reference information) • Change from baseline in Visual Analogue Score (VAS) for pain at Week 24 • Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT) fatigue score at Week 24 ○ Other secondary endpoints Proportion of PDR-free patients, annualized relapse rate, change in Short Form Health Survey 36 (SF-36) Version 2 score, change in EuroQol-5D 3 Level Version (EQ-5D-3L), change in Modified Rankin Scale (mRS) score, change in Zarit Burden Interview (ZBI) score, change in Expanded Disability Status Scale (EDSS) score, change in visual acuity (Snellen chart), change in Low-contrast Sloan Letter Chart (LCSLC), change in Timed 25-Foot Walk (T25W)
Other Endpoints	○ Pharmacodynamics Serum IL-6, sIL-6R, hsCRP levels ○ Pharmacokinetics Serum satralizumab concentration ○ Safety Adverse events [including serious adverse events, adverse events of special interest (AESIs), and selected adverse events], laboratory test values, vital signs, electrocardiography

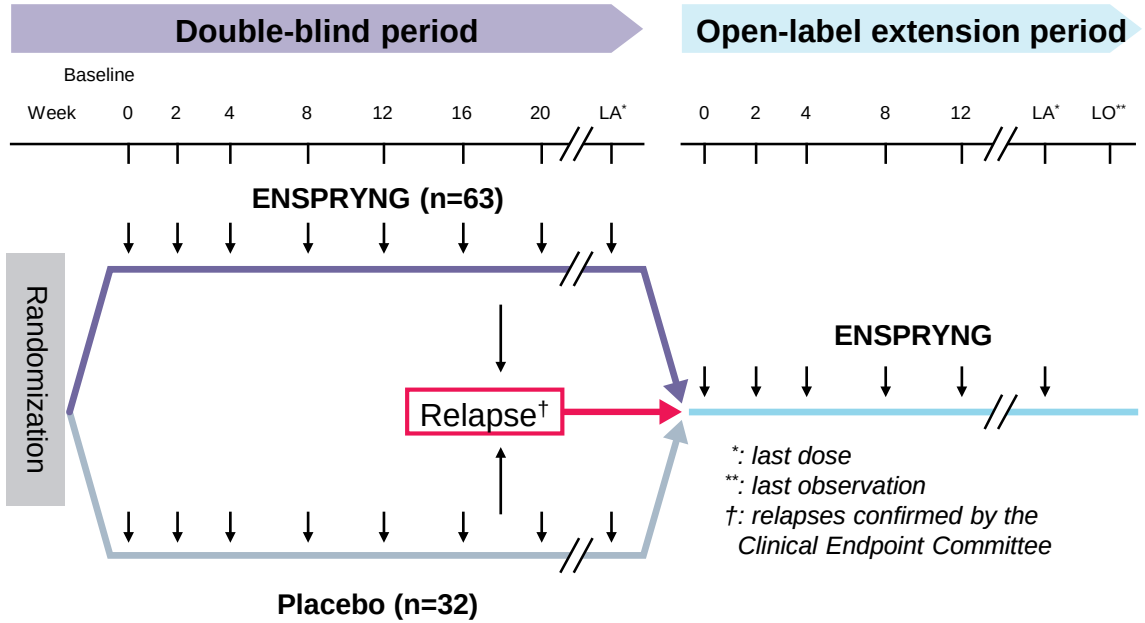
*1 Patients with NMO as defined by 2006 criteria or anti-AQP4 antibody-positive NMOSD patients as defined by 2007 criteria
*2 Protocol-defined relapses (PDR) confirmed by the Clinical Endpoint Committee

The overall study population includes patients negative for the anti-AQP4 antibody.

Review data as of time of approval of ENSPRYNG Syringes for Subcutaneous Injection 120 mg

Study Synopsis

Administration procedures



The study patients were randomized to either ENSPRYNG or placebo at a 2:1 ratio*1. ENSPRYNG 120 mg or placebo was administered by subcutaneous injection at Weeks 0, 2, and 4 and Q4W thereafter. Patients who experienced a relapse in the double-blind period*2 or completed the double-blind period were allowed to enter the open-label extension period. In the open-label extension period, each patient received ENSPRYNG 120 mg by subcutaneous injection at Weeks 0, 2, and 4 and Q4W thereafter.

*1 Randomization factors: Prior treatment for preventing NMOSD relapses (B-cell depleting therapy or immunosuppressant/other), most recent episode before screening (initial or relapse)
*2 Protocol-defined relapses (PDR) confirmed by the Clinical Endpoint Committee

The overall study population includes patients negative for the anti-AQP4 antibody.

Review data as of time of approval of ENSPRYNG Syringes for Subcutaneous Injection 120 mg

Patient Characteristics

	ENSPRYNG group (n=63)	Placebo group (n=32)	Total (n=95)
Age			
Mean age (SD)	45.3 (12.0)	40.5 (10.5)	43.7 (11.7)
Number of patients <65 years (%)	62 (98.4%)	32 (100%)	94 (98.9%)
≥65	1 (1.6%)	0	1 (1.1%)
Number of patients by sex (%)			
Men	17 (27.0%)	1 (3.1%)	18 (18.9%)
Female	46 (73.0%)	31 (96.9%)	77 (81.1%)
Number of patients by race/ethnicity (%)			
American Indian or Alaska Native	2 (3.2%)	0	2 (2.1%)
Asian (other than Japanese)	8 (12.7%)	6 (18.8%)	14 (14.7%)
Black or African American	13 (20.6%)	3 (9.4%)	16 (16.8%)
Caucasian	37 (58.7%)	22 (68.8%)	59 (62.1%)
Other	3 (4.8%)	1 (3.1%)	4 (4.2%)

	ENSPRYNG group (n=63)	Placebo group (n=32)	Total (n=95)
Patients with diagnosis (%)			
NMO	47 (74.6%)	24 (75.0%)	71 (74.7%)
NMOSD	16 (25.4%)	8 (25.0%)	24 (25.3%)
Patients anti-AQP4 antibody (%)			
Positive	41 (65.1%)	23 (71.9%)	64 (67.4%)
Negative	22 (34.9%)	9 (28.1%)	31 (32.6%)
Most recent attack, patients (%)			
Initial	7 (11.1%)	4 (12.5%)	11 (11.6%)
Relapse	56 (88.9%)	28 (87.5%)	84 (88.4%)
Prior treatment, patients (%)			
B-cell depleting therapy	8 (12.7%)	4 (12.5%)	12 (12.6%)
Immunosuppressant/other	55 (87.3%)	28 (87.5%)	83 (87.4%)
Baseline EDSS			
EDSS mean (SD)	3.92 (1.50)	3.66 (1.61)	3.83 (1.54)
Median weight, kg (range)	75.30 (45.7-151.0)	69.00 (42.1-117.3)	72.70 (42.1-151.0)

SD: Standard deviation, EDSS: Expanded Disability Status Scale

The overall study population includes patients negative for the anti-AQP4 antibody.

Review data as of time of approval of ENSPRYNG Syringes for Subcutaneous Injection 120 mg

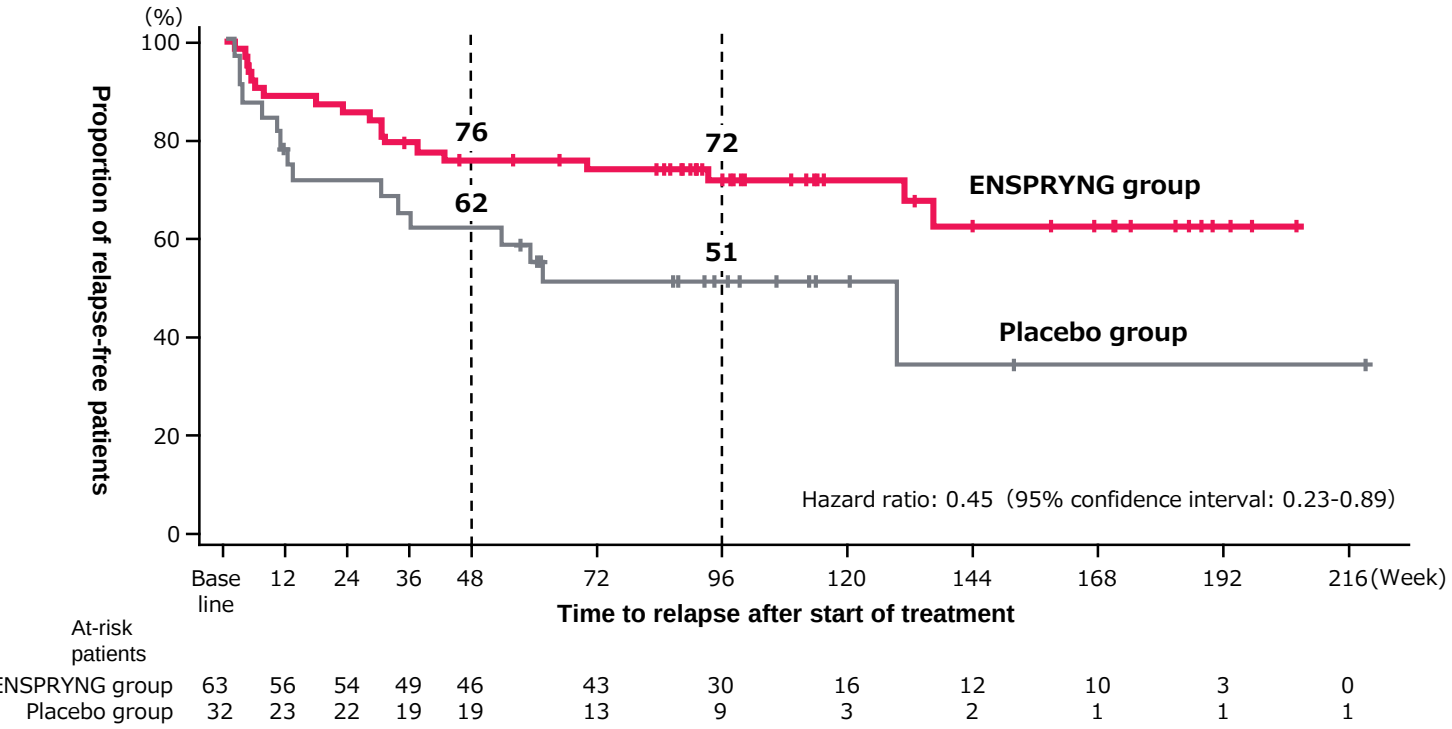
Primary Endpoint

Time to First Relapse*

*Protocol-defined relapses confirmed by the Clinical Endpoint Committee

The hazard ratio for time to first relapse in the Enspring group versus the placebo group was 0.45, indicating a superiority (95% confidence interval: 0.23-0.89, P=0.0184, stratified log-rank test). The risk reduction rate was 55%.Relapse during the double-blind period was observed in 19 patients (30.2%) in the Enspring group and 16 patients (50.0%) in the placebo group. The median efficacy evaluation period (range) was 95.4 weeks (8-205 weeks) in the Enspring group and 60.5 weeks (7-219 weeks) in the placebo group.

■ Time to first relapse (Overall population)



At-risk patients	Base line	12	24	36	48	72	96	120	144	168	192	216(Week)
ENSPRYNG group	63	56	54	49	46	43	30	16	12	10	3	0
Placebo group	32	23	22	19	19	13	9	3	2	1	1	1

The overall study population includes patients negative for the anti-AQP4 antibody.

Secondary Endpoint

Proportion of PDR-free patients

The proportion of PDR-free patients during the double-blinded period, the open-label extension period and the entire study were calculated for the each treatment group. The PDR-free rates were analyzed at every 24 weeks after baseline.
The proportion of PDR-free patients at weeks 48 and 96 was 76% and 72% in the ENSPRYNG group, and 62% and 51% in the placebo group, respectively.

Secondary Endpoint

Annualized relapse rate

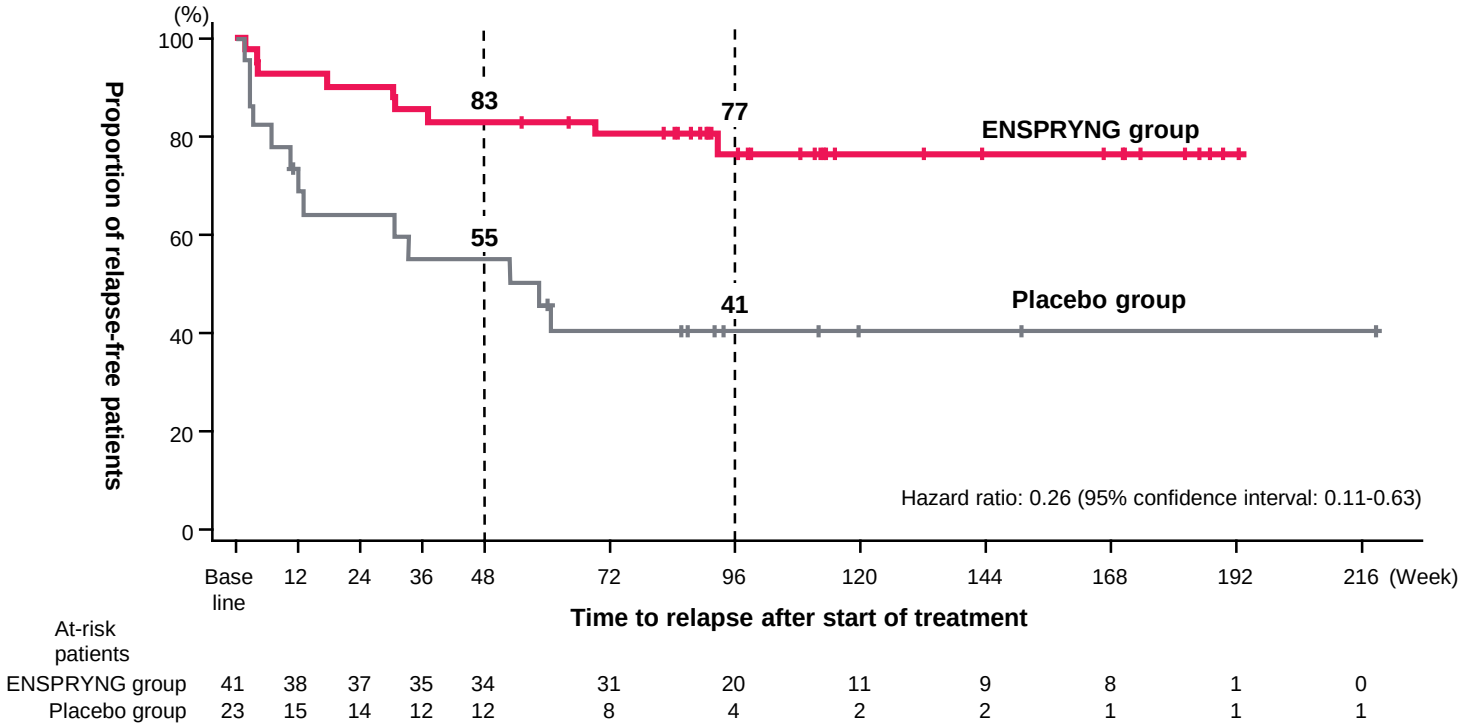
The relapse episodes for each patient was recorded throughout the whole study. The ARR was calculated as the total number of relapses experienced divided by the person-years at risk for each year of the study period.
The annualized relapse rate based on PDR was 0.17 in the ENSPRYNG group, and 0.41 in the placebo group.

Log-rank test stratified by prior treatment for preventing NMOSD relapses (B-cell depleting therapy or immunosuppressant/other) and most recent episode before screening (initial or relapse).
The proportion of PDR-free patients (at Weeks 48 and 96) is a secondary endpoint.

Time to First Relapse (Anti-AQP4 Antibody-Positive Subgroup)

The times to first relapse are shown here. The hazard ratio for the ENSPRYNG group relative to the placebo group was 0.26 (95% confidence interval: 0.11-0.63).

■ Time to first relapse (anti-AQP4 antibody-positive subgroup)



		ENSPRYNG group	Placebo group
Anti-AQP4 antibody-positive patients		41	23
Patients with a relapse (%)		9 (22.0%)	13 (56.5%)
Hazard ratio (95% confidence interval)		0.26 (0.11-0.63)	
Proportion of relapse-free patients	At Week 48 (95% confidence interval)	83% (67.49-91.47)	55% (32.96-73.08)
	At Week 96 (95% confidence interval)	77% (59.22-87.21)	41% (20.76-60.41)

Log-rank test stratified by prior treatment for preventing NMOSD relapses (B-cell depleting therapy or immunosuppressant/other) and most recent episode before screening (initial or relapse).
The proportion of PDR-free patients (at Weeks 48 and 96) is a secondary endpoint.

The overall study population includes patients negative for the anti-AQP4 antibody.

Review data as of time of approval of ENSPRYNG Syringes for Subcutaneous Injection 120 mg

Safety Evaluation: Double-Blind Period

	ENSPRYNG group (n=63)		Placebo group (n=32)	
Causality	**Total events**	**Causality not ruled out**	**Total events**	**Causality not ruled out**
All adverse events	58 (92.1%)	22 (34.9%)	24 (75.0%)	11 (34.4%)
Serious adverse events	12 (19.0%)	2 (3.2%)	5 (15.6%)	1 (3.1%)
Adverse events leading to withdrawal	1 (1.6%)	1 (1.6%)	1 (3.1%)	1 (3.1%)
Deaths	0	0	0	0

The most common adverse reactions in the ENSPRYNG group were injection related reaction in 6 patients (9.5%) and diarrhea in 4 patients (6.3%). The most common adverse reactions in the placebo group were injection related reaction in 5 patients (15.6%) and urinary tract infection in 2 patients (6.3%).
The serious adverse drug reactions, pneumonia and pulmonary sepsis were reported in 1 patient each in the ENSPRYNG group. The serious adverse drug reaction urinary tract infection was reported in 1 patient in the placebo group.
The adverse drug reactions leading to withdrawal in the ENSPRYNG group were pneumonia in 1 patient and systemic lupus erythematosus in 1 patient.
No deaths were reported in the study.

The overall study population includes patients negative for the anti-AQP4 antibody.

Review data as of time of approval of ENSPRYNG Syringes for Subcutaneous Injection 120 mg

Indication/Dosage and Administration

Indication

- **Prevention of relapses of neuromyelitis optica spectrum disorders (NMOSD), including neuromyelitis optica (NMO)**

Precautions Concerning Indication

- **Administer ENSPRYNG to patients with neuromyelitis optica spectrum disorders (NMOSD), including neuromyelitis optica (NMO)***
  ***See the "2017 Guideline for the Treatment of Multiple Sclerosis and Neuromyelitis Optica" published by the Japanese Society of Neurology.**
- **There is limited data on the efficacy of ENSPRYNG in patients who are negative for anti-aquaporin-4 (AQP4) antibodies. Administer ENSPRYNG to patients who are positive for anti-AQP4 antibodies.**

Dosage and Administration

- **The usual dosage for adults and children is a single dose of 120 mg satralizumab (genetical recombination) administered by subcutaneous injection once every 2 weeks for the first three doses, and then once every 4 weeks thereafter.**

Precautions Concerning Dosage and Administration

- **If a scheduled dose is missed, administer ENSPRYNG as soon as possible and then according to the original dosing interval from that point onward.**
- **After administering ENSPRYNG to the patient for a certain period of time, investigate the frequency of relapses. If the patient does not have fewer NMOSD relapses or is otherwise not expected to benefit from taking ENSPRYNG, consider discontinuing the ENSPRYNG treatment.**
- **In pediatric patients, consider the body weight of patients enrolled in clinical studies when determining whether the drug can be administered.**

ENSPRYNG Syringes for Subcutaneous Injection 120 mg package insert (version 2)

Expectation for ENSPRYNG

1. The relapse-preventing effect and safety profile of ENSPRYNG in anti-AQP4 antibody-positive patients were evaluated in two global phase III clinical studies.
2. The convenience by subcutaneous injection every four weeks.
3. Based on the data of a limited number of adolescent users, ENSPRYNG can be used in children.

Conclusion

Progress

1. The concept of this condition as an anti-AQP4 antibody disease has been established, and its pathophysiology has been elucidated.
2. ENSPRYNG and other molecular targeted therapies are now available.

Issues

1. Diagnosis-related considerations

   There are exceptions (e.g., spinal cord lesions in fewer than 3 vertebral segments).

   The precision of anti-AQP4 antibody tests is less than ideal (i.e., there are false positive and false negative results).
2. Measures of disease severity and biomarkers of disease activity are needed.
3. Determining the characteristics of patients who relapse while on a molecular targeted drug and reducing concomitant drugs.
4. Anti-AQP4 antibody-negative NMOSD (e.g., anti-MOG antibody etc.)

Forward-Looking Statements

This presentation may include forward-looking statements pertaining to the business and prospects of Chugai Pharmaceutical Co., Ltd. (the “Company”). These statements reflect the Company’s current analysis of existing information and trends.

Actual results may differ from expectations based on risks and uncertainties that may affect the Company’s businesses.

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